Clinical Practice Guidelines for the Screening, Diagnosis, and Outpatient Management of Type 2 Diabetes Mellitus among Filipino Adults:

Part 2b - Guidelines for the Management of Type 2 Diabetes Mellitus



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Disclaimer and Contact Information

This clinical practice guideline is primarily intended for physicians, especially primary care providers, general practitioners, general medicine or family and community medicine specialists rather than subspecialists. Like most other guidelines it is intended to provide specific evidence-based guidance but is not intended to substitute for sound clinical judgment when faced with individual decisions, especially in consideration of a patient or client's values, needs and preferences. Although adherence to the recommendations is encouraged by the stakeholder organizations and by the Department of Health (DOH), there are many clinical situations when the recommendations may not always apply and thus, clinicians must always exercise their best judgment in individualized decision-making always of course, upholding the patient's welfare and best interests.

The contents of the recommendations could also potentially be used by decision makers for purposes other than primarily intended, which is patient care; some of these examples may include resource allocation and the prioritization of goods or services for health. As such, the recommendations may not always be the best.

This CPG is intended to cover only the most common type of diabetes mellitus, that is Type 2 diabetes mellitus (T2DM) as well as the most common setting where they are seen, and this in the outpatient clinics. It does not provide recommendations for in-patient management, as well as for other forms of diabetes such as Type 1 DM or gestational diabetes. It is also not intended to be comprehensive and focuses on clinical questions where there may be variability in practice or where controversies may exist in the use of tests and treatments.

The specific considerations are always in the context of the Philippines and whenever possible, issues of equity were pointedly included in the discussions of the recommendations.

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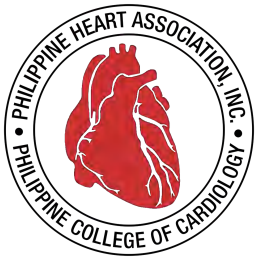
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Executive Summary

Diabetes mellitus is a growing public health challenge in the Philippines, with increasing prevalence and delayed diagnosis leading to complications. This Clinical Practice Guideline (CPG) on the Screening and Diagnosis of Type 2 Diabetes Mellitus (T2DM) provides evidence-based recommendations for early detection and timely intervention. It primarily targets adults aged 18 years and older in outpatient settings, guiding general practitioners, specialists, and policymakers. This guideline does not cover Type 1 diabetes, gestational diabetes, or inpatient management. This CPG addresses three key areas: (1) screening for pre-diabetes and T2DM, (2) diagnosis of T2DM, and (3) screening for macrovascular and microvascular complications.

This CPG was developed following a rigorous methodology involving systematic review of existing guidelines using the ADAPTE framework and/or de novo systematic reviews. The GRADE approach was used to assess the quality of evidence and determine the strength of the recommendations. This guideline was developed through a multi-sectoral approach, ensuring representation from medical societies, primary care providers, endocrinologists, nephrologists, cardiologists, policymakers, and patient advocacy groups. The Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) led the initiative in collaboration with the Department of Health (DOH), the Philippine College of Physicians (PCP), Philippine Heart Association (PHA), Philippine Society of Nephrology (PSN), Philippine Academy of Family Physicians (PAFP), and other key stakeholders. Patients were actively involved in the consensus panel, clinical outcomes prioritization, and focus group discussions to ensure that their perspectives were considered. This guideline was independently developed by the PCEDM and collaborating organizations, with no direct influence from pharmaceutical companies or commercial entities.

This CPG recommends practical strategies for implementation across various healthcare settings which includes the following: (1) dissemination through professional societies, DOH, and academic institutions, (2) promoting the use of the screening algorithms in primary care, (3) integration of the recommendations into DOH's Universal Health Care framework and PhilHealth reimbursement policies, and (4) public awareness campaigns to promote early screening and diabetes prevention. Furthermore, addressing the identified limitations such as the availability of some tests (e.g., HbA1c in certain regions), need for cost-effectiveness analysis of screening interventions in the Philippine setting, and variability in access to diabetes care is needed.

Chapter 1. Background

Introduction

The prevalence of diabetes mellitus has been steadily rising since the late 1990s, when it was around 4.0%. By 2008, it had increased to 4.8% and reached approximately 8.0% by 2018.[1] More alarming than these numbers is the high prevalence of pre-diabetes (impaired fasting glucose, FBS 100 to 125 mg/dL) at 26.0% in 2018. When considering both types of dysglycemia, the prevalence is approximately one-third of the adult population 20 years and older.

Compounding this rising prevalence of diabetes mellitus is the pervasive problem of poor glycemic control. Between 1998 to 2008, the DiabCare Philippines survey estimated only about 15.0% of patients in outpatient clinics in the Philippines had an HbA1c level below 7.0%.[2] In this same survey, which examined a cohort of patients with established diabetes (mean duration: 9.0 ± 6.0 years), complications were already common: 45.0% had neuropathy, 16.0% had microalbuminuria, and 20.1% had non-proliferative retinopathy. Severe late eye complications included photocoagulation in 7.4% of patients and proliferative diabetic retinopathy in 8.3%. Finally, 10.7% reported a history of angina pectoris while 4.7% had experienced a stroke.

Even among newly diagnosed cases, complications within one year are also already prevalent, indicating poor screening and late identification of both diabetes and its complications. A 2009 study in Manila found that among persons newly diagnosed with Type 2 diabetes mellitus (T2DM), 20.0% already had peripheral neuropathy, 42.0% had proteinuria, and 12.0% had diabetic retinopathy.[3]

Several initiatives can help improve diabetes care by addressing both systemic challenges and needs of individual patients. One key initiative is the development of clinical (practice) guidelines, which forms part of an evidence-based toolkit that has the potential to improve both the process of care and patient outcomes.[4]

It is therefore in this spirit of quality improvement in the way that care is delivered, and of improving the lives of persons with diabetes that this clinical practice guideline has been conceptualized and developed. The first multi-sectoral guideline on diabetes mellitus in the Philippines, UNITE for Diabetes CPG for the Diagnosis and Management of Diabetes, was published in 2013. Since its development, it has been integrated into the Department of Health (DOH) Primary Care National Formulary and has been used to inform decisions and priorities at various levels of healthcare, such as the DOH medicine access programs.

An update to the 2013 CPG is essential due to significant developments in diabetes care, including several new medications, expanded indications for existing treatments, and evolving public health policies locally and internationally. Advocacy efforts from public health organizations including the World Health Organization (WHO) have had a direct impact on the care of persons with diabetes, such as warnings on alcohol, cigarette smoking and vape, and artificial sweeteners.

Scope and Purpose of the CPG

This updated CPG intends to support the implementation of Universal Health Care (UHC) by providing evidence-based recommendations for improving diabetes care delivery. It focuses on the management of adult patients with T2DM–the most prevalent type of diabetes.

This CPG primarily covers clinical questions that are relevant for the outpatient management of adults with T2DM and does not include recommendations for pediatric patients or inpatient settings. The key topics include:

Part 1:

1. Screening for Prediabetes and T2DM
2. Diagnosis of T2DM
3. Screening for Complications

Part 2:

4. Prevention of T2DM and Prediabetes
5. Non-pharmacologic Management of T2DM
6. Pharmacologic Treatment of T2DM
7. Cardiovascular Risk Reduction in T2DM
8. Vaccination and Adjunctive Therapies

For purposes of this CPG, adults are defined as individuals 18 years and older, including older age groups. However, this CPG does not cover pregnant women with diabetes as the recommendations for this subgroup are typically different in many aspects, from screening, diagnosis, to pharmacologic treatment. Outpatient settings include hospital outpatient departments or doctors' clinics, various diabetes clinics (hospital-based, mall-based, or stand-alone), workplace clinics, and local health centers where many more persons with diabetes are being seen.

End users and settings

The primary intended users of this CPG are physicians who are in general practice, general medicine or family medicine specialists, Family Medicine and Internal Medicine residents-in-training and even medical students (as part of preparation for general practice). The recommendations can also be used by subspecialists who are managing persons with T2DM, including but not limited to endocrinologists, nephrologists, neurologists, or cardiologists.

Although the guidelines are intended for clinical use, some of the content may also be used to guide administrators, policymakers, and public/private health sector leaders for the procurement of medications, planning of health programs and priorities for persons with diabetes, or formulating diabetes screening strategies for at-risk populations.

Stakeholder Involvement

The organizations involved in developing this clinical practice guideline were intentionally identified to adequately represent the interests of persons with diabetes or at risk for diabetes. These organizations represent primary care physicians (general practice, family medicine, general medicine, or physicians in

occupational health settings) as well as subspecialists managing patients with complex cases or complications. The representatives of these organizations were involved in the guideline development through these mechanisms: (1) serving as members of the Steering Committee and/or Consensus Panel; (2) developing, reviewing, and approving clinical questions as well as identifying and prioritizing clinical outcomes; and (3) reviewing, revising, and disseminating the draft guidelines through the organizations.

The involvement of lay persons with diabetes was three-fold: (1) representation in the consensus voting panel with active involvement during the discussions; (2) determination of outcomes and importance of clinical outcomes through focus group discussions with members of a lay diabetes club; (3) prioritization of the herbal products or dietary supplements which will be included in the recommendations through direct interaction with the members of an online diabetes group. These processes were intentionally done so that the voice of persons with diabetes is well heard, ensuring that their perspectives are reflected in the guideline.

Chapter 2. Guideline Development Methodology

Overview

This clinical practice guideline was developed following the prescribed methodology of the DOH.[5] Following international recommendations, this guideline development followed 4 main phases or steps: (1) guideline preparation, (2) evidence synthesis, (3) evidence to decision (EtD), and (4) dissemination and evaluation. This manuscript will cover the first 3 phases and outline plans for dissemination and evaluation.

Phase 1 involves guideline preparation with three main steps: (1) organization of the guideline development teams, (2) formulation of clinical questions, and (3) search and retrieval of literature, appraisal of validity and applicability of literature by the evidence review experts (technical working group). *Phase 2* involves synthesizing and assessing the certainty of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In this phase, draft recommendations are prepared and an initial strength of recommendation is identified. *Phase 3* involves EtD, where the evidence and the draft recommendations are presented by the EREs followed by a discussion and deliberation by the expert panel. The final recommendation, along with the corresponding strength of the recommendation, is decided by the expert panel by consensus building. Finally, *Phase 4* will involve presentations of the CPG in various meetings of medical societies, publication, providing online access to the guideline and its tools, and evaluation of its impact on the way that we care for people with diabetes.

Phase 1: Guideline Preparation

Organization of the Guideline Development Teams

The Guideline Development Teams are composed of the Steering Committee (SC), Technical Working Group/Evidence Review Experts (EREs), the Consensus Panel (CP), and the external Conflict of Interest Review Committee (COIRC).

Steering Committee (SC)

The Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) is the lead organization for this Clinical Practice Guideline (CPG), having volunteered to develop it in collaboration with the Department of Health (DOH). The Steering Committee is headed by the PCEDM Officers and includes representatives from the Philippine College of Physicians (PCP), the Philippine Heart Association (PHA), and the Philippine Society of Nephrology (PSN). These organizations represent specialists in internal medicine, cardiology, and nephrology, all of whom are frequently consulted in the management of diabetes and its complications.

Evidence Review Experts (EREs)

The organization of the evidence review experts (EREs) is unique because each team was organized from the training core of the various endocrinology fellowship programs of the PCEDM. They were joined by technical experts or methodologists with specific training on clinical epidemiology, guideline development, health technology assessment, and research methods, all of whom were also PCEDM

members. The representatives from the training institutions underwent three training workshops to improve their skills and knowledge on guideline development: (1) guideline development using GRADE approach, the ADAPTE process, and the AGREE tool for appraising CPGs; (2) formulating clinical questions; (3) assessing risk of bias for various clinical questions with focus on using diagnostic tests, systematic reviews with meta-analyses. These workshops were conducted by the Asia Pacific Center on Evidence-Based Medicine and the National Institutes of Health. Convened by the PCEDM, the EREs were tasked with reviewing existing CPGs, summarizing evidence, and drafting evidence-based recommendations.[5]

Consensus Panel (CP)

The members of the consensus panel were identified and invited by the SC as key stakeholders who are either experts in the field of diabetes, target CPG users, advocates for diabetes prevention and management, and persons with diabetes. Major diabetes organizations were represented, such as the PCEDM, Philippine Center for Diabetes Education Foundation, Inc. (PCDEFI), and Diabetes Philippines, alongside non-voting representatives from the Department of Health (DOH) and PhilHealth. Other organizations included the Philippine College of Physicians (PCP), Philippine Heart Association (PHA), Philippine Society of Nephrology (PSN), Philippine Academy of Family Physicians (PAFP), Philippine College of Occupational Medicine (PCOM), and the Philippine Society of General Internal Medicine (PSGIM).

Lay representation came from the Philippine Alliance of Patient Organizations (PAPO), the Chinese General Hospital and Medical Center Diabetes Club, and the St. Luke's Medical Center-Quezon City Diabetes Club, with at least one person with diabetes attending each consensus panel meeting.

The SC, EREs, and CP collaborated to develop and finalize clinical questions and prioritize critical outcomes, ensuring that stakeholders' values, including those of lay participants, were incorporated into the PICO questions. The consensus panel also reviewed evidence summaries, voted on draft recommendations, and finalized the CPG recommendations. A technical facilitator moderated the meetings to guide the consensus process.

Conflict of Interest Review Committee (COIRC)

Finally, COIRC reviewed possible conflicts of interest of all the participants involved in the development of this guideline. They are external to the various organizations and were contracted by the SC to provide an unbiased evaluation of the possible financial/material and intellectual or various types of conflicts of interest of the CP, EREs and the SC.

However, the COIRC was not engaged early enough in the project but evaluated the conflicts of interest while the remaining questions on pharmacotherapy and vaccinations have not yet been presented to the expert panel. Despite this oversight, this CPG incorporated several mitigating strategies to try to address the conflicts of interest.

Strategies to address conflicts of interest

Before the recommendations were developed:

1. Each of the members of the various panels (SC, EREs, CP) accomplished disclosure of conflicts of interest forms at the beginning of the project to individually evaluate any potential or actual conflicts which may introduce biases during the development of the recommendations. The standard form provided by the DOH was used and the declarations extended back up to 4 years prior to the start of their involvement in this project. They were also asked to submit their curriculum vitae for evaluation by the COIRC.

2. Rather than an individual output of the guideline developer or ERE, the recommendations were the collective work of the group of 3 to 4 persons comprising the group. The output of each training institution was then presented to the bigger group of EREs comprising the technical working group of the PCEDM so that any biases that could have been introduced into the recommendation still also be addressed.

    a. Those who are noted to have COI were assigned to the topics where they have direct or potential conflicts of interest.
    b. Each of the EREs, most of whom have some form of primary or secondary COI, were paired up with other members of the team who have no or minimal COI.
    c. Each of the EREs presented their work to their team to minimize COI as the other members of the team can check the work and ensure that there are no biases that are introduced. Subsequently, the statements were again presented in the larger group of EREs for comments and refinement to ensure that the process or methodology of guideline development was followed, including checking for any introduction of biases.

2. The oversight committee then gave their recommendations as to whether or not members of the CPG development process need to be removed. These were treated as recommendations rather than direct actions.

3. Those who can divest the sources of their conflicts of interest were asked to do so and these were noted.

During the CPG Development:

4. The clinical questions and recommendations were sent to the expert panel before each consensus meeting so that those who had major conflicts of interest (especially the advisory boards of pharmaceutical companies or speakers for products or who owned stocks in hospitals) could identify their conflicts and request their organization to provide a replacement who does not have COI.
5. At the beginning of each meeting, and with each recommendation that was going to be discussed, a declaration of conflicts of interest was called by the facilitator. If anyone in the consensus panel had significant conflicts, they were not allowed to vote. Since the topics were known ahead of time, the organizations that were represented were allowed to change their representative to the voting panel in case the regular representative had conflicts of interest.

6. External review of conflicts of interest– while this was not done early on because of the idea that declaration and management of conflicts is sufficient, this external review was done prior to the discussions on pharmacologic therapy and vaccination.

Generally, these were the strategies used in this CPG to manage conflicts of interest:

1. **Disclosure:** public disclosure of all potential & actual COIs before the start of the project and before each panel meeting.
2. **Divestment:** resignation from any positions that may cause COI or divestment of financial interests; this was identified as a strategy and the technical facilitator did not lecture on any of the topics that were tackled in the guidelines.
3. **Recusal:** several of the members of the expert panel recused themselves from participation in both the discussions and voting after declaring major conflict of interest. Those who participated in discussions always stated their COI and always recused themselves from voting.
4. **Monitoring the output** (draft recommendations) of the EREs by the steering committee, the technical facilitator and the other EREs within their team and the bigger group to ensure that biases are not introduced;
5. **Modification of the plan for development of the recommendations:** e.g. when one of the EREs within the team are assigned to a question where they have COI, then their assignments were revised by the team.
6. **Change of personnel:** Some of the members of the SC were replaced due to significant COI.

On **Annex A**, are some of the tools used by the group and the COIRC for addressing conflicts of interest.

Development of clinical questions

The clinical questions framework was based on the UNITE for Diabetes Practice Guidelines (2013). While many original questions were retained, the significant time gap necessitated the development of additional, relevant questions. These were formulated by the SC, EREs, and technical or content experts in diabetes, then circulated to the CP for review and revision. The complete list of clinical questions can be found in **Annex B**.

Selection and Rating of Critical Outcomes

Important clinical outcomes were likewise identified and prioritized, and these were also reviewed by the expert panel including (lay) persons with diabetes plus persons with diabetes other than the representatives in the expert panel for greater inclusivity. This was done through focus group discussions with members of a lay diabetes club in one of the endocrine training hospitals in Manila.

Although the outcomes were identified mainly by the SC, technical experts on diabetes, EREs and the expert (consensus) panel, persons with diabetes were asked for additional outcomes and their relative importance. These were rated using the GRADE categories of importance. The clinical outcomes were rated numerically on a 1-to-9 scale following the GRADE categories, where a score of 7-9 is critical; 4 -6 important; and 1- 3, of limited importance. According to GRADE, ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered most important and help to resolve or clarify disagreements.[6]

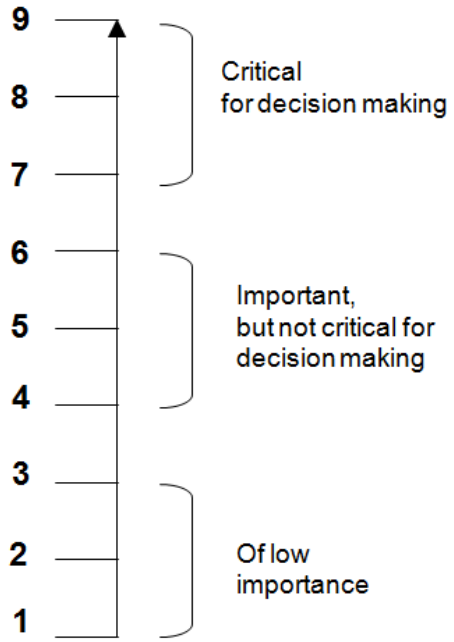


Figure 1. Interpretation of the numerical ranking for critical outcomes.[6]

Table 2 lists the outcomes rated as critical for formulating the guideline recommendations. Since typically only 7 outcomes per intervention/test are suggested, questions on therapeutics involves only outcomes #2 to #9. For diagnostic test questions, only outcomes #1 to #4 were assessed. Safety in pregnancy (#8) was only included whenever applicable for questions related to pharmacologic interventions.

Table 1. Interpretation of the numerical ranking for critical outcomes

Outcomes	Score	Importance
1. Diagnostic accuracy (for tests)	9	Critical
2. Glycemic control	9	Critical
3. Microvascular complications	9	Critical
4. Macrovascular complications*	9	Critical
5. Hypoglycemia	9	Critical
6. ADRs especially Hepatotoxicity or Nephrotoxicity	8	Critical
7. Safety in Pregnancy	8	Critical
8. Quality of Life	7	Critical
9. Weight (loss/gain)	7	Critical

For questions that involve the cardiovascular outcomes of drugs (#4), macrovascular complications are further broken down into the following outcomes:

Table 2. Interpretation of the numerical ranking for critical outcomes

Outcomes	Score	Importance
1. Total mortality	9	Critical
2. Cardiovascular death	9	Critical
3. Fatal and non-fatal myocardial infarction	9	Critical
4. Stroke or cerebrovascular disease	9	Critical
5. Major adverse cardiovascular events (MACE)	7	Critical
6. Coronary revascularization	6	Important

Funding and Independence Statement

This Clinical Practice Guideline (CPG) development project was funded by the Philippine College of Endocrinology, Diabetes, and Metabolism (PCEDM), which served as the lead organization in collaboration with the Department of Health (DOH). The development process was overseen by a Steering Committee led by PCEDM Officers, with representation from the Philippine College of Physicians (PCP), the Philippine Heart Association (PHA), and the Philippine Society of Nephrology (PSN). These organizations collectively contributed their expertise in internal medicine, cardiology, and nephrology—fields integral to the management of diabetes and its complications.

While PCEDM provided financial support and administrative coordination, it did not have exclusive authority over the development of the guideline. The content was determined through a consensus-driven process involving all participating organizations, ensuring a balanced, multidisciplinary, and evidence-based approach. The funding body had no influence on the recommendations, which were formulated based on the best available evidence and expert consensus.

To ensure transparency and safeguard the integrity of the guideline development process, all members of the development group—including the Steering Committee, Oversight Committee, Consensus Panel, and Technical Working Group—were required to complete a Declaration of Conflict of Interest (COI) form prior to their participation. The form required disclosure of any financial or intellectual conflicts of interest within the past four years.

An independent COI Oversight Committee reviewed all declarations, classified the nature and severity of each conflict, and advised the Steering Committee on the appropriate level of participation. The following classifications and management strategies were used:

1. **Allowed / Acceptable** – No relevant financial or intellectual conflicts of interest were identified. Full participation, including voting, was permitted.

2. **Manageable B (Broadcast)** – Typically applies to intellectual conflicts of interest (e.g., affiliations with relevant organizations, positions of leadership, authorship of related publications). Members were allowed to vote but were required to declare these conflicts during en banc meetings and relevant discussions.

3. **Manageable C** – Applied to individuals with both intellectual and limited financial conflicts of interest. These members could contribute to discussions as resource persons but were not allowed to vote on recommendations. Examples include representatives from implementing government agencies or the funding organization. Specific terms of participation were determined by the Oversight Committee, based on the clinical question.

4. **Disqualified** – Applied when an individual had significant financial and intellectual conflicts that could compromise objectivity. These individuals were not permitted to participate in the guideline development process.

This rigorous process for managing conflicts of interest reinforces the editorial independence of the guideline and ensures that the recommendations made in this document are unbiased, evidence-informed, and aligned with the best interests of Filipino patients and healthcare providers.

Management of Conflicts of Interest (COI) in the Steering Committee

The management of conflicts of interest (COI) for the steering committee was guided by principles of transparency, accountability, and integrity. To ensure full disclosure, all COIs of steering committee members were publicly broadcasted. This process allowed stakeholders to be informed of any potential competing interests, fostering trust in the committee's deliberations.

Notably, the overall chair had no conflicts of interest, reinforcing the impartiality of the group's oversight and coordination. Beyond disclosure, the committee implemented additional safeguards to uphold credibility. Any decisions made by the steering committee underwent further vetting to assess the potential perception of bias. This ensured that any concerns related to conflicts were identified and mitigated appropriately. However, it was important to note that the steering committee did not directly formulate recommendations. Instead, the final recommendations were developed by the consensus panel—an independent, multi-stakeholder body composed of experts representing diverse perspectives and disciplines. The consensus panel's decisions were grounded in a rigorous evaluation of the best available evidence and guided by explicit value judgments, ensuring a balanced and methodologically sound approach.

Justification for COI Management Approach

1. **Ensuring Transparency and Public Trust** – Public disclosure of COIs promoted openness, allowing stakeholders to assess any potential influences on decision-making. This aligned with international best practices for governance in evidence-based policymaking, as recommended by organizations such as the WHO, GRADE Working Group, and ICMJE.

2. **Strengthening Decision Integrity** – The absence of COI in the overall chair reinforced neutrality, ensuring that the committee's processes remained free from undue influence. Additionally, the independent vetting of decisions served as a safeguard against perceived bias.

3. **Alignment with Best Practices in Guideline Development** – The separation of roles between the steering committee and the consensus panel adhered to global standards for managing conflicts in clinical and policy guidelines. The presence of a diverse, multi-stakeholder consensus panel with a multiplicity of viewpoints further minimized the risk of any single interest disproportionately influencing the recommendations.

4. **Commitment to Rigorous, Evidence-Based Decision-Making** – The consensus panel formulated recommendations based on systematic evidence synthesis, explicitly weighing benefits, harms, feasibility, and acceptability. This structured approach mitigated the potential impact of conflicts of interest by ensuring that recommendations were primarily driven by empirical data and established value judgments.

5. **Enhancing Credibility and Adoption** – By implementing COI management strategies that exceeded standard disclosure requirements, the process enhanced the legitimacy of the final recommendations. This, in turn, increased stakeholder confidence and facilitated broader adoption of the recommendations in practice.

By employing a multi-layered approach to COI management—including disclosure, vetting, independent decision-making, and diverse stakeholder representation—the committee upheld the highest standards of integrity, ensuring that the recommendations were both scientifically robust and ethically sound.

Steering Committee

No.	Name	Area of Expertise	Affiliation	Sex	Summary of disclosures or other relevant interest
1	Ma. Encarnita C. Blanco-Limpin, MD, FPCP, FPSCCM, FPSSM	Internal Medicine, Pulmonary Medicine, Critical Care Medicine	Philippine Heart Center	F	Acceptable (A) No relevant financial or intellectual conflicts of interest. Full participation allowed.
2	Jude Erric Cinco MD, FPCP, FPCC, FPSCCM, FAsCC, FESC, FACC	Cardiology and Critical Care Medicine	Philippine Heart Association; The Medical City	M	Manageable B Received honoraria as a speaker, module creator, or key opinion leader for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Biomedis, Corbridge, Delex, Getz, JustRight, LRI Therapharma, Novartis, Philcare Pharma, Pfizer, and Sanofi (2018–present).
3	Roberto C. Tanchanco, MD, MBA, FPCP, FPSN, FISN	Internal Medicine, Nephrology	Ateneo de Manila University School of Medicine and Public Health ; Philippine Society of Nephrology	M	Manageable B Received honoraria for speaking engagements from AstraZeneca (2021–present) and MSD (prior to 2020).
4	Marichel D. Pile-Coronel, MD, FPCP, FPSN	Internal Medicine- Adult Nephrology	Philippine Society of Nephrology	F	Manageable B Received honoraria for speaking engagements related to Dapagliflozin (Forxiga) from AstraZeneca (2021–2022), and for Vildagliptin (Galvus) and Sacubitril/Valsartan (Entresto) from Novartis (2019–2022).
5	Carolyn Narvacan-Montano, MD, FPCP, FPCEDM	Endocrinology, Diabetes and Metabolism	Makati Medical Center	F	Manageable B Served as a speaker for Sanofi Aventis, Novo Nordisk, Boehringer Ingelheim, and Gx Philippines.
6	Daveric Pagsisihan, MD, FPCP, FPCEDM	Endocrinology, Diabetes and Metabolism	De La Salle Medical and Health Sciences Institute	M	Manageable B Served on the advisory board of Eli Lilly (2018–2019). Sub-investigator in clinical trials sponsored by Sanofi Aventis (2017–2020). Received travel grants from Corbridge, Natrapharm, LRI Therapharma, and Servier Philippines (2017–present). Holds shared stocks in Gentri Medical Center, Dasmariñas City Medical Center, and Asia Medic Family Hospital. Receives income as a member of a pharmacy corporation (2022–present).

Technical Working Group

Question	Specific Assignments	Decision/Management	Assessments/Remarks
Prevention Q4. Should we recommend non-pharmacologic methods (LSM) for preventing diabetes among those with risk factors for diabetes or pre-diabetes?			
Q 4.1 Should we recommend dietary interventions?	Daphne Gayle Galang	A - Allowed – participation with no constraints	
	Ma. Cecilia G. Gonzales	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
	Maria Jocelyn C. Isidro	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
	Aimee Andag-Silva	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q 4.2 Should we recommend physical activity and exercise?	Aimee Andag-Silva	A - Allowed – participation with no constraints	
	Daphne Gayle Galang	A - Allowed – participation with no constraints	
	Maria Jocelyn C. Isidro	A - Allowed – participation with no constraints	
Q 4.3 Should we recommend limitation of alcohol intake?	Aimee Andag-Silva	A - Allowed – participation with no constraints	
	Daphne Gayle Galang	A - Allowed – participation with no constraints	
Q 4.4. Should we recommend sleep hygiene	Aimee Andag-Silva	A - Allowed – participation with no constraints	
	Daphne Gayle Galang	A - Allowed – participation with no constraints	
Q 4.5. Smoking cessation	Ma. Cecilia G. Gonzales	A - Allowed – participation with no constraints	

Question	Specific Assignments	Decision/Management	Assessments/Remarks
Prevention Q5. Should we recommend pharmacologic therapy (metformin, pioglitazone, SGLT-2 inhibitors, acarbose, orlistat, DPP4-inh, GLP-1 RAs) among adults with pre-diabetes?			
Metformin and Pioglitazone Acarbose and Orlistat SGLT-2 inhib and GLP-1/ GIP agonists	Aimee Andag-Silva	D- Disallowed – participation is not allowed (Metformin Pioglitazone; SGLT-2 inhib and GLP-1/ GIP agonists)	Merck Serono Global (Glucophage XR); pioglitazone LRI/ Therapharma; Astrazeneca (Forxiga, Xigduo, Q-tern); Novo Nordisk (Ryzodeg, Ozempic, Rybelsius)
	Aimee Andag-Silva	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
	Olivia P. Roderos	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
	Antonio L. Faltado Jr.	D- Disallowed – participation is not allowed (SGLT-2 inhib and GLP-1/ GIP agonists)	SGLT2i speaker Astrazeneca (Forxiga, Xigduo, Q-tern); Investor (120,000 PhP) at Zure Rx Pharmacy (2022-present)
Mgt Q6.0 Among persons with T2DM, should we recommend non-pharmacologic methods (LSM)?			
Q 6.1 Should we recommend dietary interventions for glucose control, weight management and overall cardiovascular health? Done	Rebecca Lim-Alba	D- Disallowed – participation is not allowed	Novo Nordisk Has stocks (50,000 PhP) in Promedica Pharma (food supplements and nutriceuticals), Exact Check Lab, Accuserve Lab, Intercon Lab (2016-present) Proprietor (30,000 PhP) of Accuserve plus, Mediscount Pharmacy (2017-present)
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	

Question	Specific Assignments	Decision/Management	Assessments/Remarks
Q 6.2 Should we recommend physical activity and exercise for glucose control, weight management and overall cardiovascular health? What are the specific recommendations? [type, duration, frequency, targets]	Rebecca Lim-Alba	D- Disallowed – participation is not allowed	
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q 6. 3 Should we recommend limitation of alcohol intake? Done	Lora Tan Tin-hay	A - Allowed – participation with no constraints	
Q 6.4. Should we recommend non-nutritive sweeteners (aspartame, sucralose, stevia) for glycemic control and weight loss? Done	Lora Tan Tin-hay	A - Allowed – participation with no constraints	
Q 6.5 Should we recommend KD and intermittent fasting for weight loss and glycemic control?	Daphne Gayle Galang	A - Allowed – participation with no constraints	
Mgt Q7. Among persons with T2DM, should we recommend glycemia-targeted or diabetes-specific formulas			
Q 7.1 for weight management?	Lora Tan Tin-Hay	D- Disallowed – participation is not allowed	LRI-Therapharma (2018-2022); GlucoBest
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q7.2 for glucose control?	Lora Tan Tin-Hay	D- Disallowed – participation is not allowed	LRI-Therapharma (2018-2022); GlucoBest
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Mgt Q8. Among persons with T2DM, should we recommend bariatric surgery for weight loss and glycemic control? What are the specific indications for bariatric surgery?	Rebecca Lim-Alba	D- Disallowed – participation is not allowed	Novo Nordisk

Question	Specific Assignments	Decision/Management	Assessments/Remarks
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Mgt Q 9. Among adults with T2 DM, should we recommend metformin as the preferred first line antidiabetic agent?			
Mgt Q 9.1. Among adults with T2 DM, should we recommend metformin as the preferred first line antidiabetic agent as monotherapy? [specify cut-off HbA1c or FBS]	Anna Elvira S. Arcellana	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Janumet
	Roy Raoul Felipe	D- Disallowed – participation is not allowed	Med Choice
Mgt Q 9.2. Among adults with T2 DM, should we recommend metformin as the preferred first line antidiabetic agent as the base drug for combination therapy?	Anna Elvira S. Arcellana	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Janumet
	Roy Raoul Felipe	D- Disallowed – participation is not allowed	Med Choice
Q 10.1 Among adults with T2DM, should we recommend initial oral combination therapy for an HbA1c > 9%? HbA1c > 10% ? FBS > 250mg/dL?	Gabriel V. Jasul Jr.	D- Disallowed – participation is not allowed	Novo Nordisk
	Anna Angelica Macalalad-Josue	D- Disallowed – participation is not allowed	Degludec
Q10.2 Among adults with T2DM, should we recommend initial injectable therapy combined with oral agents/ s for an HbA1c > 9%? HbA1c > 10% ? FBS > 250mg/dL?			
10.2.1 Basal Insulin	Gabriel V. Jasul Jr.	D- Disallowed – participation is not allowed	Novo Nordisk
	Anna Angelica Macalalad-Josue	D- Disallowed – participation is not allowed	Degludec
10.2.2 GLP-1 mimetics or agonists	Gabriel V. Jasul Jr.	D- Disallowed – participation is not allowed	Novo Nordisk
	Anna Angelica Macalalad-Josue	D- Disallowed – participation is not allowed	Degludec
Q 11.1 Among adults with T2DM on metformin, should we recommend SU/DPP4- inh/SGLT-2 inhibitors/TZD/alpha-glucosidase	Karla Kristine S. Fernando	D- Disallowed – participation is not allowed	TReceived travel meeting sponsorship (100,000 PhP/meeting) from Novo Nordisk, Natrapharm (2019)

Question	Specific Assignments	Decision/Management	Assessments/Remarks
inhibitors after failure to achieve glycemic targets?			Received honoraria as part of speakers' bureau (10,000 to 25,000 PhP/lecture) from Boehringer, Astra, Novo Nordisk, Sanofi, MSD (2018-2022)
	Harold Henrison C. Chiu	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
	Sahra O. Paragas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q 11.2 Among adults with T2DM on 2-3 oral agents and with HbA1c above target, should we recommend injectable therapy (basal insulin or GLP-1 receptor agonists)?	Karla Kristine S. Fernando	D- Disallowed – participation is not allowed	TReceived travel meeting sponsorship (100,000 PhP/meeting) from Novo Nordisk, Natrapharm (2019) Received honoraria as part of speakers' bureau (10,000 to 25,000 PhP/lecture) from Boehringer, Astra, Novo Nordisk, Sanofi, MSD (2018-2022)
	Anna Elvira Arcellana	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Janumet
	Katherine Anne C. Banal	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Received honoraria for speaking engagements for FGDs from Sanofi, Servier, Astrazeneca (2018-2021)
Mgt Q12. Among adults with T2DM and specific disease conditions, should we recommend specific oral antidiabetic agents or injectables?			
12.1 Cirrhosis/chronic liver disease 12.2 Chronic kidney disease, ESRD on dialysis 12.4 NAFLD	Ma. Cecille Anonuevo-Cruz	D- Disallowed – participation is not allowed	Receives honoraria as Advisory Board Member (50,000 PhP) from Zuellig-Lilly, now ZP Therapeutics (2019-present)

Question	Specific Assignments	Decision/Management	Assessments/Remarks
12.5 TB [with recommendations from TB consensus] 12.6 Obese 12.7 Elderly & those with risks for hypoglycemia 12.8 Prior stroke or CVD			Received research grant as primary investigator (279,145.75 PhP) from Servier Philippines (2019) Received sponsorship for conventions (120,000 PhP) from Servier Philippines, Astrazeneca, MSD, Boehringer Ingelheim, LRI-Therapharma (2018-2021) Received honoraria as member of speakers' bureau (600,000 PhP) from Servier Philippines, Novo Nordisk, Zuellig-Lilly (now ZP Therapeutics) MSD, Astrazeneca, Getz Pharma, LRI-Therapharma (2018-2022) Part of group investment (100,000 PhP) in ZureRx, Tanauan, Batangas (2020)
	Mark David Francisco	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Mgt Q14. Among persons with T2DM, should we recommend the following herbal medications and supplements?			
14.1 Chromium	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
14.2 Ampalaya [Momordica]	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
14.3 Serpentina	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor	

Question	Specific Assignments	Decision/Management	Assessments/Remarks
		constraints (e.g., – COIs declared aloud during panel discussions);	
14.4 Vitamin B complex	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
14.5 Insulin Plant	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Mgt Q15. Among adults with T2DM, should we recommend the following tests for monitoring glycemic control?			
Q15.1 FBS, HbA1c	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Has hospital stocks (450.000 PhP) in Great Valley Medical Center (still under construction) (2021-present)
Q15.2 1,5-anhydroglucitol test (Glycomark)	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q15.3 Fructosamine	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q15.4 SMBG	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q15.5 CGM	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor	

Question	Specific Assignments	Decision/Management	Assessments/Remarks
		constraints (e.g., – COIs declared aloud during panel discussions);	
Mgt Q16. Among adults diagnosed with diabetes, should we recommend the following glycemic targets?			
Q 16.1 FBS < 100 mg/dL (or 110)	Elaine C. Cunanan	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q 16.2 HbA1c < 7.0%, < 6.5%	Erick Mendoza	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q 16.3 SMBG pre-breakfast < 110 mg/dL (< 100 mg/dL), 1 hr-post-prandial < 140 mg/dL	Aurora G. Macaballug	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	Has hospital stocks (500,000 PhP) in Las Pinas Doctors Hospital, Medical Center Muntinlupa (2010-present)
Q17.1 Among persons with T2DM, should we recommend ASA or clopidogrel for primary prevention of CV events?	Jeremy Jones F. Robles	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q17.2 Among persons with T2DM with ASCVD or previous acute coronary syndrome, should we recommend ASA and/ clopidogrel for secondary prevention of CV events?	Waynila Lim-Cuizon	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q18. Among persons with Type 2 DM and hypertension, should we recommend low dose combination drugs for the control of hypertension? [RAS blocker + CCB, RAS blocker + HCTZ] [From Philippine CPG on Hypertension]	Cecilia A. Jimeno	D- Disallowed – participation is not allowed	Sanofi - Irbesartan
Q19.1 Among persons with Type 2 DM and dyslipidemia, should we recommend	Cecilia A. Jimeno	D- Disallowed – participation is not allowed	Sanofi - generic STATIN; Member of the technical review board of the UP NIH FDA

Question	Specific Assignments	Decision/Management	Assessments/Remarks
statins for primary prevention of CV events? [from Phil CPG ON Dyslipidemia]			and Board Member of the Philippine Lipid and Atherosclerosis Society
Q 19.2 Among persons with Type 2 DM and dyslipidemia, should we recommend fibrates for primary prevention of CV events? [from Phil CPG ON Dyslipidemia]	Cecilia A. Jimeno	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q20.1 Among adults with T2DM and established atherosclerotic cardiovascular disease (ASCVD), should we recommend SGLT-2 inhibitors?	Waynila Lim-Cuizon	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Q20.2 Among adults with T2DM and established atherosclerotic cardiovascular disease (ASCVD), should we recommend GLP-1 Receptor agonists in combination with metformin? [from Philippine consensus recommendations]	Celito A. Tamban	A - Allowed – participation with no constraints	
Vac Q21.1 Among adults with T2DM, should we give influenza vaccine yearly for the prevention of respiratory tract infections?	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	
Vac Q21.2 Among adults with T2DM, should we give pneumococcal vaccination for the prevention of hospitalization from bacterial pneumonia?	Mia Fojas	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);	

Expert Panel or Consensus Panel

Name	COI Declaration	COI Assessment
Dr. Maria Rosario Sylvia Uy	Nothing to disclose	A - Allowed – no constraints
Dr. Charisse Banaag	Nothing to disclose	A - Allowed – no constraints
Dr. Bernice Ong-Dela Cruz	Nothing to disclose	A - Allowed – no constraints
Dr. Rowena Roselle P. Blanco-Santos	Nothing to disclose	A - Allowed – no constraints
Ms. Agnes Angelo Aquino	Nothing to disclose	A - Allowed – no constraints

Name	COI Declaration	COI Assessment
Ms. Zenaida Velasco	NDAP, expert lectures on nutrition	For questions on diet and nutrition - B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); All other questions: A - Allowed – no constraints
Dr. Gerald B. Natanauan	Nothing to disclose	A - Allowed – no constraints
Dr. Cynthia H. Manabat	Receives honorarium as Advisory Board member of Boehringer Ingelheim, Novo Nordisk, Sanofi, Zuellig-Lilly (2018–2022) Receives fees for equipment/travel to meetings from Boehringer Ingelheim, Cathay YSS, Corbridge, Kaufmann, LRI-Therapharma, Natrapharm, Novo Nordisk, Sanofi, Servier, Westmont, Zuellig-Lilly (2018–2022) Receives honorarium as Lecturer for Boehringer Ingelheim, Cathay YSS, Corbridge, Kaufmann, LRI-Therapharma, Natrapharm, Novo Nordisk, Sanofi, Servier, Westmont, Zuellig-Lilly (2018–2022) Secretary of the Board, Philippine Center for Diabetes Education Foundation (NGO) (2018–present)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (e.g., DPP4, SGLT2, GLP1RA)
Ms. Ma. Regina Rosario 'Gina' Javier	Board of Trustee, RAINBOW Camp Foundation Philippines, Inc. Member of Philippine Alliance of Patients Organizations	B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);
Dr. Waynila Lim-Cuizon	Received honoraria for RTDs on Gliclazide (SU) MR, Gemigliptin (DPP4) from GX Pharma, Med Choice (2020-2021)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Monica Therese Cating-Cabral	Travel meetings paid by LRI-Therapharma (March 2019) Received honoraria for speaking engagements from AstraZeneca, Johnson & Johnson, Novo Nordisk, Sanofi, Medtronic (November 2019 – October 2022)	Manageable B for non-pharmacologic intervention questions D – disallowed for pharmacologic, diagnostic, and screening questions

Name	COI Declaration	COI Assessment
	Board of Trustee, Philippine College of Endocrinology, Diabetes and Metabolism a. Holds stocks in Makati Medical Center b. Holds stocks in Rinon Care Pharma, Inc.	
Dr. Walid Amil	Receives honorarium as Advisory Board member of Boehringer Ingelheim Receives honorarium as Speaker for LRI-Therapharma, Servier, AstraZeneca, Novartis, and Boehringer Ingelheim (2018–2022) Board Member, Hospital de Zamboanga, Zamboanga City (2018–present) Treasurer, Philippine Heart Association (2020–present) Holds stocks in hospitals and a diagnostic laboratory	Manageable B for non-pharmacologic intervention questions D – disallowed for pharmacologic/treatment, diagnostic, and screening questions
Dr. Rebecca Lim-Alba	Received honoraria for lectures/RTDs from Abbott, Astra, Boehringer Ingelheim, LRI, Menarini, MSD, Novo Nordisk, and Westmont (2018–2022) Has stocks in Promedica Pharma, Exact Check Lab, Accuserve Lab, and Intercon Lab (2016–present) Proprietor of Accuserve Plus and Mediscount Pharmacy (2017–present) Vice Chair, Filipino-Chinese Charitable Foundation Receives honoraria for lectures on SGLT2 inhibitors, novel insulin, and GLP-1 agonists from Astra, Boehringer Ingelheim, Novo Nordisk, Menarini, and MSD (2017–present)	Manageable B for non-pharmacologic intervention questions D – disallowed for pharmacologic/treatment, diagnostic, and screening questions
Dr. Jerome R. Barrera	Received honoraria as Advisory Board member of Eli Lilly (2019 only) Received airfare, accommodation, and registration for conventions from Sanofi, Natrapharm, Cathay, Getz Pharma, Scigen, Corbridge, Kauffman, AstraZeneca, GX Pharma (2018–2022) Received honoraria for CME lectures from GX Pharma, Sanofi Aventis, Eli Lilly, Novo Nordisk, Getz Pharma, Multicare, Scigen Pharma, Cathay, Novartis, Servier, Boehringer, AstraZeneca, Merck, Abbott, Nestlé (2018–2022) Received stock fees from Healthwise Laboratory and Rite Drug Pharmacy (2021–2022)	Manageable B for non-pharmacologic intervention questions D – disallowed for pharmacologic/treatment, diagnostic, and screening questions

Name	COI Declaration	COI Assessment
	Board of Trustee, Philippine College of Endocrinology, Diabetes and Metabolism	
Dr. Ma. Theresa M. Chua-Agcaoili	Sponsored in conventions by Boehringer Ingelheim Receives honoraria for lectures on SGLT-2 and GLP-1 round table discussions from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk Member of the Medical Advisory Council for Ayala Healthcare	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Elizabeth Angelica Lapid-Roasa	Receives honoraria for module development from Boehringer Ingelheim (2017–present) and AstraZeneca	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Katherine Anne C. Banal	Received honoraria for speaking engagements for FGDs from Sanofi, Servier, Astrazeneca (2018-2021)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Richard Henry Tiongco	Receives honoraria for speaking engagements from Boehringer-Ingelheim and Astrazeneca (2020-2022)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor

Name	COI Declaration	COI Assessment
	Director II, Philippine Heart Association (non-stock, non-profit organization)	constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Erick Mendoza	Vice President, Philippine Thyroid Association (2022–present) Received honoraria for lectures/RTDs from Sanofi (2018–2022), Novo Nordisk (2020–2022), AstraZeneca (2019–2021), Boehringer Ingelheim (2021–2022), and GX International (2021–2022) Speaker for Lantus, Toujeo, Apidra, Soliqua (2018–2022); Tresiba, Ryzodeg (2020–2022); Forxiga, Xigduo (2019–2021); Jardiance and Jardiance Duo (2021–2022); Zemiglo (2021–2022)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Endrik H. Sy	Government employee with private clinic connected to a pharmacy and diagnostic laboratory	For screening and diagnostic questions - D- Disallowed – participation is not allowed For other questions, B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);
Dr. Michael L. Villa	Receives honoraria for speaking engagements from Novo Nordisk, Unilab, Servier (2019–2022), AstraZeneca, and Abbott	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)

Name	COI Declaration	COI Assessment
Dr. Jeremy Jones F. Robles	Speaker AZ, Abbott	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Franklin Guillano	Founding members of Tagum Global Medical Center in Tagum City. It is a member of ACE GROUP of Hospitals. Part ownership of 3 dialysis centers in Davao region under the Nephro group of companies.	For screening and diagnostic questions - D- Disallowed – participation is not allowed Manageable B for non-pharmacologic intervention questions For other questions, B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions);
Dr. Reynaldo Rosales	Receives honoraria as Medical Advisory Board member of Novo Nordisk (1 year) Receives honoraria for speaking engagements from Novo Nordisk, Boehringer Ingelheim, Sanofi, and Nestlé Health Science Board of Director, Diabetes Philippines	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Grace K. de los Santos	Receives honoraria as adviser and for speaking engagements from AstraZeneca, Boehringer Ingelheim, Corbridge, LRI-Therapharma, Menarini, Merck, Novartis, Novo Nordisk, OEP, and Sanofi (2019–present)	For screening and diagnostic questions B - Broadcast - Manageable with minor constraints – there are COIs: participation is allowed with minor constraints (e.g., – COIs declared aloud during panel discussions); Manageable B for non-pharmacologic intervention questions

Name	COI Declaration	COI Assessment
		D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)
Dr. Aurora G. Macaballug	Received travel sponsorship from LRI/Therapharma, Natrapharm, and Corbridge (2018–2019) Received honoraria for speaking engagements from AstraZeneca, MSD, Novo Nordisk, Zuellig/Eli Lilly, Boehringer Ingelheim, LRI, Natrapharm, and Sandoz (2018, 2019, 2020, 2022) Has hospital stocks in Las Piñas Doctors Hospital and Medical Center Muntinlupa (2010–present) Advisory Board Member for dulaglutide, Zuellig Secretary, Philippine College of Endocrinology, Diabetes and Metabolism Head of Advocacy, Philippine College of Endocrinology, Diabetes and Metabolism	For screening and diagnostic questions - D- Disallowed – participation is not allowed Manageable B for non-pharmacologic intervention questions D – Disallowed for questions on pharmacologic therapy (DPP4, SGLT2, GLP1RA)

Phase 2: Evidence synthesis

The technical experts and the EREs, working with the SC decided on two main frameworks for guideline development. The first is to use ADAPTE in order to make use of the evidence in existing and updated guidelines that have similar clinical questions to inform the current guideline development, and the second is to use GRADE for many of the de-novo clinical questions.

ADAPTE framework

A systematic literature search for existing CPGs was done using MEDLINE through PubMed (https://pubmed.ncbi.nlm.nih.gov/). The initial search strategy and the results are summarized in Table 3. A team of four (4) EREs then refined the search in order to have an optimal output.

Table 3. Literature search on MEDLINE

Search number	Query	Search Details	Results
3	(#2) AND (("2017"[Date - Publication] : "3000"[Date - Publication]))	"guideline"[Publication Type] AND ("diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Terms] OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields])) AND 2017/01/01:3000/12/31[Date - Publication]	78
2	("guideline"[Publication Type]) AND (#1)	"guideline"[Publication Type] AND ("diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Terms] OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]))	361
1	(((Type 2 diabetes mellitus[MeSH Terms]) OR (diabetes mellitus, type 2[MeSH Terms])) OR (diabetes mellitus, Type 2)) OR (Type 2 diabetes mellitus)	"diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]	163,540

Additional guidelines were identified from cross-referencing and consultation with the rest of the EREs, which yielded a total of 86 reports after deduplication.

Eligibility criteria for guidelines

The team of four EREs then applied the following eligibility criteria to identify CPGs eligible for inclusion and further appraisal using AGREE (Table 5). From the initial 86 guidelines, the list was then narrowed to 26 with the following distribution: (a) general guidelines (n=13), (b) specific guidelines on pharmacologic therapy (n=9), and (c) guidelines specifically tackling complications (n=4).

Table 4. Eligibility criteria for guidelines included for adaptation

Inclusion criteria	Exclusion criteria
1. Guideline must be about diabetes in the outpatient setting 2. General guidelines covering the entire scope of diabetes with focus on those which include the management of Type 2 diabetes in an outpatient setting 3. Published (in text or online) since the details of the review must be available 4. Written in English or with English translation 5. Published in the last five years (2017- onwards) to ensure that evidence base is current. In case that the guideline has an update, then both the original guideline and the update will be retrieved and reviewed. 6. Only evidence-based guidelines will be included (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence) 7. Only national and/or international guidelines will be included (see exclusion #2)	1. For duplicate guidelines (e.g., update or revision of previous guidelines), reviewers will only consider the most recent guidelines 2. Guidelines commissioned by or published by HMO's will not be included since the intent and the use of these guidelines is different from the intended users of this guideline 3. Guidelines for special situations which may be unique to the western population will not be included e.g., care of institutionalized patients, homeless, nursing homes, etc. 4. Guidelines written by a single author not on behalf of an organization; in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input. 5. Guidelines published without references – as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations

Appraisal of Guideline Quality

The EREs were divided into teams according to their training institutions, and the 26 guidelines then underwent appraisal using the AGREE II tool. While there are no specific guidelines for the "cut-off" or passing scores in the AGREE instrument, the EREs decided on the following criteria:

1. Both of the reviewers have to have at least a final score of five (5) and answer YES (or yes with Modification) that they will use the guideline, and for the
2. Rigour criteria to have at least a score of 70.0% and higher

After applying AGREE, the final list of guidelines was narrowed to 15 as follows: (a) general guidelines (n=8); (2) specific guidelines on pharmacologic therapy (n=4); and (3) guidelines specifically tackling complications (n=3). The final list of the 15 included guidelines is listed in Annex C. These guidelines were used as the source of the evidence base.

De novo Systematic Reviews

Whenever the listed CPGs were not able to provide direct evidence or address the same guideline question, de novo systematic reviews and meta-analysis were performed. Aside from cross-referencing from the international guidelines, systematic literature search was done for online databases including MEDLINE via PubMed https://pubmed.ncbi.nlm.nih.gov/, Google Scholar, as well as COCHRANE database (https://www.cochranelibrary.com/central and https://www.cochranelibrary.com/cdsr/reviews). Local databases such as HERDIN and the PCEDM list of researches were also reviewed for studies relevant to the clinical question. A separate search strategy was done to obtain cost-effectiveness studies or similar studies on the treatment of Type diabetes.

Systematic Literature Search

Keywords for the systematic literature search were derived from the PICO (Population, Intervention/Exposure, Comparison, Outcomes) framework for each clinical question, utilizing both MeSH terms and free-text searches. When necessary, EREs contacted authors of relevant studies, including local research, to obtain copies or clarify study details for appraisal. Search strategies for each clinical question are detailed in the subsequent chapter.

For diagnostic questions, the included studies comprised cross-sectional (simple or criterion-referenced), cohort, case-control studies, and diagnostic systematic reviews and meta-analyses. For therapy-related questions, the review incorporated observational studies (cohorts and case-control), randomized controlled trials (RCTs), systematic reviews, meta-analyses, and network meta-analyses.

Quality Assessment Of Studies Included In The Review

Individual studies, including RCTs, diagnostic accuracy studies, and studies on harm, were evaluated using appraisal guides tailored to each study type.[7] The QUADAS tool[8] was applied for assessing the quality of diagnostic accuracy studies, while the Newcastle-Ottawa Scale[9] was used for evaluating non-randomized clinical and observational studies.

Evidence Synthesis Using GRADE Approach

The primary framework for developing this CPG is GRADE, a widely used tool for both grading the quality of evidence and formulating recommendations. GRADE offers a transparent, systematic approach for summarizing evidence and making clinical practice recommendations.[10-12]

The process of guideline development begins with formulating clinical questions in the PICO format, which includes the population that the question applies to, the two or more alternatives (the comparison), and the outcomes that matter most to those faced with the decision.[13] The best estimates of treatment effects are determined for each outcome, ideally through systematic reviews and meta-analyses.[14] The EREs then rate the certainty of evidence for each outcome. An overall GRADE quality (or certainty) rating is given to the body of evidence, taking into account the lowest quality of evidence from outcomes critical to decision-making. The quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation.[14]

GRADE classifies evidence into four levels of certainty (Table 5): very low, low, moderate, and high. For intervention or pharmacologic treatment questions, evidence from randomized controlled trials starts as high quality, while evidence from observational studies starts as low quality due to potential residual confounding.

Table 5. GRADE Categories of Certainty of Evidence

Certainty of Evidence	Interpretation
Very low ⨁◯◯◯	The true effect is probably markedly different from the estimated effect [the estimate of the effect is very uncertain].
Low ⨁⨁◯◯	The true effect might be markedly different from the estimated effect [further research is very likely to have an important impact].

Certainty of Evidence	Interpretation
Moderate ⊕⊕⊕◯	The true effect is probably close to the estimated effect [further research is likely to have an important impact].
High ⊕⊕⊕⊕	The authors have a lot of confidence that the true effect is similar to the estimated effect [further research is unlikely to change our confidence in the estimate of the effect].

After determining the baseline certainty of evidence (e.g. high for data from RCTs), the certainty can be rated up or down based on various domains. Certainty can be rated down for the following reasons: serious risk of bias (as obtained from appraisal of individual studies), imprecision, inconsistency, indirectness, and publication bias. Conversely, certainty can be upgraded in the presence of a large magnitude of effect, dose-response gradient, or when confounding is deemed to have no effect on the results.

As GRADE is used to rate the body of evidence at the outcome level rather than the study level, EREs must make a judgement about whether the risk of bias in the individual studies is sufficiently large that their confidence in the estimated treatment effect is lower. Imprecision is rated down if the 95% confidence interval (CI) suggests that clinical decisions might differ depending on whether the true effect lies at the upper or lower CI.[15] Similarly, certainty may be downgraded if evidence comes from only a few small studies or if there are few events.[16] Inconsistency across the studies involves evaluating the similarity of point estimates and the overlap of their confidence intervals, usually through statistical tests for heterogeneity (e.g., the I^2 and chi-squared test).[17] Indirectness involves comparing the included studies with the population, intervention, or outcomes of interest for the guideline question. Certainty can be rated down if the populations or patients studied are different from those for whom the recommendations apply (e.g., no Filipinos or even Asians are included in the studies, or when the interventions studied are different than the real outcomes, the outcome in the studies is a surrogate for a different outcome).[18] For publication bias, inferences are made about the missing evidence. Visual methods such as the funnel plot in meta-analyses and various statistical methods are helpful in detecting publication bias. In assessing publication bias, consider the following: what is the study design (experimental vs. observational), study size (small studies vs. large studies), lag bias (early publication of positive results), search strategy (was it comprehensive?) and asymmetry in the funnel plot.[19]

Phase 3: Evidence-to-Decision

Generating recommendations

GRADEpro online software (https://www.gradepro.org) online was used to generate the Summary of Findings (SoF) tables for each outcome. The EREs present the SoF tables to the expert panel, summarizing the results for each of the relevant outcomes and giving an over-all certainty of evidence. An Evidence to Decision (EtD) framework was used to process the evidence to develop recommendations, which takes into consideration several domains that contribute to the strength of the recommendation (Table 7).

Resource Implications and Sources of Cost Information

Resource use was one of the criteria explicitly considered by the Consensus Panel within the GRADE Evidence-to-Decision framework for every guideline question. Cost information was sought through a

structured, stepwise inquiry conducted by the Evidence Review Experts and the Technical Working Group.

First, published economic evaluations relevant to each guideline question were sought, including cost-effectiveness, cost-utility, cost-minimization, and budget impact analyses. Searches were conducted in MEDLINE via PubMed, the Cochrane Library, HERDIN, and Google Scholar, combining the clinical search strategy for each PICO question with an economic evaluation filter. Health technology assessments published by the Philippine Health Technology Assessment Council and by international health technology assessment agencies were also reviewed for relevance to the Philippine setting.

Second, where published economic evaluations were unavailable, of limited quality, or not applicable to the local context, the direct acquisition costs of the intervention and its alternatives were obtained. Local medicine prices were retrieved from the Department of Health Philippine Drug Price Reference Index, the Philippine National Formulary, published retail price listings of major local pharmacy chains, and the Philippine Pharmaceutical Directory. Prices were expressed in Philippine pesos and, where they varied across manufacturers, preparations, or retail outlets, the observed range was reported rather than a single figure. The availability of each intervention through PhilHealth benefit packages, Department of Health medicine access programs, and local government unit procurement was also determined, since access mechanisms materially affect the cost actually borne by Filipino patients.

Third, the cost information compiled for each guideline question was presented to the Consensus Panel in the evidence summaries under a dedicated heading, alongside the estimates of desirable and undesirable effects and the certainty of evidence and was available to panel members before and during deliberation.

The Consensus Panel used this information to inform the resource use domain of the Evidence-to-Decision framework. Cost did not by itself determine the direction of any recommendation. It informed judgments on the strength of recommendations, the framing of remarks concerning access and affordability, and the identification of lower-cost alternatives where these were supported by acceptable evidence, as reflected in the conditional recommendation for gliclazide MR in resource-limited settings. Formal economic evaluation was not undertaken as part of this guideline. The cost figures presented reflect prices prevailing at the time of guideline development and are subject to change; they are intended to support contextual judgment rather than to serve as definitive pricing guidance.

Determining The Direction Strength Of Recommendations

During the consensus meetings, the wording of the recommendations as well as the strength of each recommendation was determined by the panel by considering the domains that are given in Table 6. A strong recommendation means that the panel is *"confident that the desirable effects of adherence to a recommendation outweighs the undesirable effects,"* while a weak recommendation means that the *"desirable effects of adherence to a recommendation probably outweigh the undesirable effect"* but the panel cannot say so with confidence.

Table 6. Domains that contribute to the strength of a recommendation

Domain	Comment
Balance between desirable and undesirable outcomes (trade-offs) e.g. prevention of complications of diabetes versus adverse effects of drugs, taking into account: - Best estimates of the magnitude of effects on desirable & undesirable outcomes - Importance of outcomes (estimated typical values and preferences).	The larger the differences between desirable and undesirable outcomes, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a weak recommendation warranted.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Confidence in values and preferences, and their variability	The greater the variability in values and references, or uncertainty about typical values and preferences, the more likely a weak recommendation is made.
Resource use.	The higher the cost of an intervention (the more resources consumed), the less likely a strong recommendation is warranted.

Source: Schünemann H, Brożek J, Guyatt G, and OxmanA (eds). GRADE Handbook. October 2013.

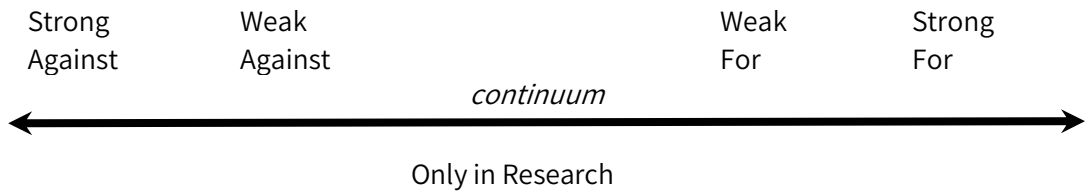


Figure 2. Strength of recommendation: a continuum divided into categories

Consensus Process

The recommendation for each question and the strength of each recommendation were determined through voting. A consensus decision was reached if 75% of all CP members agreed. In case that consensus was not reached in the first voting, questions and discussion were encouraged. Afterwards, another round of voting was done and if still, no consensus is reached after voting, then the recommendation is tabled for discussion at the next meeting. Evidence-based recommendations were based on input arrived at by consensus in the en banc discussions. The recommendations presented by the evidence-based reviewers were moved forward and revised depending on the decision of the consensus panel during voting.

In cases where direct evidence is lacking and the consensus panel deems it necessary that a statement be articulated regarding the intervention in question, a good practice statement is included. A good practice statement implies that there is general agreement that the intervention will do more good than harm.

Modified Delphi Consensus Process for Question on Initial Oral Combination Therapy in Adults with Type 2 Diabetes Mellitus

Rationale and Overview

During the en banc consensus meetings, Question 3 on *"Among adults with type 2 diabetes mellitus, should we recommend oral combination therapy for an HbA1c of >9% or FBS >250 mg/dL as initial treatment?"*) was reviewed by the Evidence Review Experts (EREs) but could not be taken up for deliberation and voting within the available meeting time. To resolve this question without convening an additional face-to-face session, the Steering Committee (SC) elected to obtain the consensus of the Consensus Panel (CP) through a modified Delphi process conducted online.

The modified Delphi method is an established, structured technique for reaching group consensus through iterative rounds of anonymous, independent judgment interspersed with controlled feedback. It is well suited to guideline development because it preserves the equal weighting of each panelist's vote, reduces the dominance effects that can arise in live discussion, and produces an auditable record of both votes and their justifications. The process retained the same Evidence-to-Decision (EtD) framework, the same voting panel, and the same decision rules used for questions resolved during the en banc, so that the recommendation arising from Q3 is methodologically consistent with the remainder of the guideline.

Participants

The voting panel for the modified Delphi comprised the same Consensus Panel members constituted for this guideline, representing the participating professional societies, government agencies (non-voting), and lay persons with diabetes. Panelists retained the voting eligibility determined by the Conflict of Interest (COI) Review Committee: members classified as *Allowed/Acceptable* or *Manageable B (Broadcast)* were permitted to vote, while those classified as *Manageable C* or *Disqualified* participated only as resource persons or were excluded from voting, respectively. A declaration of conflicts of interest relevant to Q3 was solicited at the start of the process, and panelists with significant conflicts on this question were asked to recuse themselves from voting, consistent with the COI management strategy applied throughout the guideline.

The EREs assigned to Q3 served as non-voting facilitators, and a technical facilitator/methodologist administered the survey, compiled results, and prepared the anonymized feedback between rounds. Individual votes were confidential; only aggregated, de-identified results were shared with the panel.

Evidence Base Provided to Panelists

Prior to voting, each panelist was given access to the full evidence summary for Q3 and a recorded presentation of the evidence delivered by the assigned EREs. The evidence summary followed the standard format used throughout the guideline and included the PICO question, the GRADE evidence profile with the certainty of evidence for each critical outcome, and the draft recommendation with its initial strength. Panelists were instructed to review these materials before, or refer to them while, completing the survey. The key findings presented for Q3 were the effect estimates for glycemic efficacy (achievement of target HbA1c and mean HbA1c reduction) and safety outcomes (adverse effects and hypoglycemia) comparing initial oral combination therapy with oral monotherapy, each accompanied by its GRADE certainty rating.

The Consensus Instrument

The consensus instrument was an online questionnaire (Google Forms) structured around the DOH–NIH Evidence-to-Decision (EtD) framework for questions on therapy. The instrument operationalized the same EtD domains used in the en banc so that the online judgments mapped directly onto the EtD worksheet. For each domain, the instrument presented (a) an explanatory statement of the domain and the corresponding research evidence for Q3, (b) a structured judgment vote using the response options specified in the DOH–NIH EtD worksheet, and (c) a required free-text field in which the panelist recorded the justification for that judgment. The seven EtD domains assessed were:

- **Balance of effects** — the trade-off between desirable and undesirable effects;
- **Resources required** — the magnitude of costs of the intervention;
- **Cost-effectiveness** — whether cost-effectiveness favored the intervention or the comparator;
- **Values** — the importance of, or uncertainty and variability in, how patients value the main outcomes;
- **Equity** — the anticipated impact on health equity;
- **Acceptability** — acceptability to key stakeholders; and
- **Feasibility** — feasibility of implementation.

Following the domain judgments, panelists cast their overall vote on the **direction** (recommend or suggest, for, or against) and the **strength** (strong or conditional/weak) of the recommendation, recorded their assessment of the overall certainty of evidence, and provided an overall written justification. Panelists additionally rated their level of agreement with the draft recommendation as worded on a 9-point scale (1 = strongly disagree to 9 = strongly agree) and could propose alternative wording or additional conditions. Requiring a written justification for every judgment ensured that the basis for each vote was documented and available for panel review, preserving the transparency of the deliberative process that would ordinarily occur during en banc discussion.

Conduct of the Delphi Rounds

The modified Delphi was conducted over iterative rounds as follows:

1. **Round 1.** The survey link, together with the evidence summary and recorded presentation, was circulated to all eligible panelists. Panelists reviewed the evidence and independently and privately registered their domain judgments, overall direction and strength votes, agreement rating, and written justifications.
2. **Analysis and feedback.** The technical facilitator collated the responses and, for each EtD domain and for the overall vote, computed the distribution of judgments and the proportion of agreement. An anonymized summary—including the vote distribution and the de-identified justifications, with particular attention to outlying or dissenting views—was prepared for circulation to the panel.
3. **Subsequent round(s).** Items that did not reach the pre-specified consensus threshold in Round 1 were returned to the panel for re-voting in light of the aggregated results and accompanying justifications. Panelists could revise or maintain their positions; those maintaining a position outside the emerging consensus were encouraged to articulate their reasoning. Rounds continued until consensus was reached or until further rounds were judged unlikely to change the distribution of votes.

4. **Resolution.** Any item remaining unresolved after the planned rounds was scheduled for brief synchronous discussion and a final vote by the Consensus Panel, using the same EtD worksheet and decision rules.

Definition of Consensus

Consensus was defined a priori. For the direction and strength of the recommendation, consensus was reached when at least **75.0%** of eligible voting panelists selected the same direction of recommendation. For agreement with the draft recommendation as worded, consensus was defined as at least 75% of panelists providing a rating of 7 to 9 on the 9-point agreement scale, with no more than 15% providing a rating of 1 to 3. Where these thresholds were not met, the item proceeded to a further round or to synchronous resolution as described above. The threshold was fixed before the first round and applied uniformly.

The table below summarizes the decision rule applied to each vote.

Vote	Consensus threshold	If not met
Direction of recommendation	≥75% selecting the same direction (for/against)	Advance to next Delphi round
Strength of recommendation	Majority of those in the consensus direction	Discussed in next round / en banc
Agreement with draft wording	≥75% rating 7–9 and ≤15% rating 1–3	Reword using panel suggestions; re-vote

Data Handling and Formulation of the Final Recommendation

Survey responses were exported and analyzed descriptively. For each domain and for the overall recommendation, results were expressed as frequencies and percentages of the eligible votes cast; free-text justifications were compiled verbatim and thematically grouped to inform the panel feedback and the final EtD documentation. Once consensus was reached, the direction, strength, and certainty of the recommendation were transcribed onto the DOH–NIH EtD worksheet for Q3, and the recommendation statement was finalized to reflect the agreed wording and any conditions specified by the panel. The completed EtD worksheet, the round-by-round vote distributions, and the consensus outcome were retained as part of the guideline's documentation to ensure the transparency and reproducibility of the process.

Note. This modified Delphi process was adopted specifically for questions reviewed by the EREs but not deliberated during the en banc meetings. It preserves the EtD framework, voting panel, COI eligibility rules, and consensus thresholds used elsewhere in the guideline, and differs only in that judgments were elicited asynchronously and anonymously through iterative online rounds rather than in a single synchronous session.

Table 7. Summary of Recommendations

No.	Recommendations	Certainty	Strength
Pharmacologic Therapy			
Q1. Should we use metformin as first-line glucose-lowering agent (i.e., monotherapy or base drug for combination therapy) among adult patients with type 2 diabetes mellitus?			
1	Recommendation 1. We recommend metformin as the preferred initial pharmacological agent for type 2 diabetes if it is not contraindicated and is tolerated among adults with T2DM.	Moderate	Strong
2	Recommendation 2. We recommend metformin as the base drug when combining with other glucose-lowering agents among adults with T2DM.	Moderate	Strong
3	Recommendation 3. We recommend that initial therapy be based on individual treatment considerations among those with contraindications or intolerance to metformin or based on their specific profile (CHF, ASCVD, CKD).	Low	Strong
Q2. Should we use sulfonylureas, DPP4-inhibitors, SGLT2 inhibitors, thiazolidinediones, GLP-1 receptor agonists and basal insulin among adults with T2DM on metformin after failure to achieve glycemic targets?			
4	Recommendation 4. We recommend any of the oral anti-diabetes medications may be used as a second-line agent among patients with T2DM on metformin after failure to achieve glycemic targets.	Moderate	Strong
5	Recommendation 5. We recommend the addition of SGLT2 inhibitor as the initial choice of second-line oral agent* among patients with T2DM after failure to achieve glycemic targets. **Remarks: SGLT2 inhibitors have been shown to reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality. They also improve health-related quality of life for patients with these conditions. Additionally, SGLT2 inhibitors slow*	Moderate	Strong

No.	Recommendations	Certainty	Strength
	the progression of chronic kidney disease and reduce the risk of end-stage kidney disease in individuals with type 2 diabetes.		
6	Recommendation 6. We recommend a GLP-1 receptor agonist or insulin therapy as add-on therapy among patients with T2DM on metformin after failure to achieve glycemic targets.	High	Strong
7	Recommendation 7. We recommend the addition of a GLP-1 receptor* agonist as the initial injectable therapy as second-line agent among patients with T2DM on metformin after failure to achieve glycemic targets. **Remarks:* *GLP-1 RAs have been shown to reduce the risk of stroke, cardiovascular events, and all-cause mortality. They also decrease the progression of macroalbuminuria, promote weight loss, and improve health-related quality of life.*	Moderate	Strong
8	Recommendation 8. We recommend the use of SGLT2 inhibitors, and GLP-1 receptor agonists among patients with T2DM with chronic kidney disease.	High	Strong
9	Recommendation 9. We suggest the use of sulfonylureas, specifically gliclazide MR*, in resource-limited settings among patients with T2DM with chronic kidney disease. *Remarks:* **Gliclazide MR may help reduce the incidence of end-stage renal disease in patients with type 2 diabetes, particularly in settings with limited healthcare resources.*	Low	Weak
10	Recommendation 10. We recommend the use of SGLT2 inhibitors among patients with T2DM who are taking metformin and have heart failure.	High	Strong

No.	Recommendations	Certainty	Strength
11	Recommendation 11. We recommend against the use of thiazolidinediones among patients with T2DM who are taking metformin and have heart failure. *Remarks:* *This recommendation is based on evidence indicating that thiazolidinediones may increase the risk of exacerbating heart failure in patients with type 2 diabetes.*	Very Low	Strong
12	Recommendation 12. We recommend the use of GLP-1 receptor agonists among patients with T2DM who are at high risk for stroke or have a previous history of stroke.	High	Strong
13	Recommendation 13. We recommend the use of either semaglutide* or dulaglutide* among patients with T2DM who are at high risk for stroke or have a previous history of stroke *Remarks:* *Both semaglutide and dulaglutide have been shown to reduce non-fatal and total stroke in patients with type 2 diabetes.*	High	Strong
14	Recommendation 14. We recommend the use of GLP-1 receptor agonist semaglutide 1 mg for weight reduction in patients with T2DM and obesity. *Remarks: semaglutide 1 mg and Liraglutide 3 mg demonstrated the greatest magnitude of weight reduction among GLP-1 receptor agonists in patients with type 2 diabetes and obesity.*	High	Strong
15	Recommendation 15. We recommend the use of GLP-1 receptor agonist liraglutide 3 mg for weight reduction in patients with T2DM and obesity. *Remarks: semaglutide 1 mg and Liraglutide 3 mg demonstrated the greatest magnitude of weight reduction among GLP-1 receptor agonists in patients with type 2 diabetes and obesity.*	Low	Strong

No.	Recommendations	Certainty	Strength
16	Recommendation 16. We suggest against the use of sulfonylureas, thiazolidinediones, and insulin among patients with obesity and T2DM. *Remarks:* *Sulfonylureas, thiazolidinediones, and insulin are associated with a higher risk of weight gain in patients with obesity and type 2 diabetes, which is why their use is discouraged in this population*	Moderate	Weak
17	Recommendation 17. We recommend against the use of sulfonylureas and thiazolidinediones among patients with T2DM who are at high risk for hypoglycemia	Low	Strong
18	Recommendation 18. We recommend the use of insulin analogues* (such as glargine U100, glargine U300, and degludec U100) in patients with T2DM requiring insulin. *Remarks:* *Insulin analogues have been shown to reduce the risk of hypoglycemia, particularly nocturnal hypoglycemia, compared to other insulin preparations*	Moderate	Strong
Q3. Should we recommend initial oral combination therapy for adults with T2DM with HbA1c >9% or fasting blood sugar (FBS) >250 mg/dL?			
19	Recommendation 19. We recommend oral combination therapy as initial treatment among adults with type 2 diabetes mellitus who have an HbA1c >9% or FBS >250 mg/dL, provided they have no signs or symptoms of ketosis or metabolic decompensation and type 1 diabetes mellitus is not suspected.	Moderate	Strong
Q4. Should we recommend initial combination of injectable therapy combined with oral agent/s for adults with T2DM with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?			

No.	Recommendations	Certainty	Strength
20.	Recommendation 20. We recommend basal insulin therapy in combination with oral glucose-lowering agent/s among adults with T2DM with HbA1c > 9% or fasting blood sugar > 250 mg/dL.	Moderate	Strong
21	Recommendation 21. We recommend the use of glucagon-like peptide-1 (GLP-1) receptor agonists in combination with oral glucose-lowering agent/s among adults with T2DM with HbA1c >9% or fasting blood sugar >250 mg/dL, who have established atherosclerotic cardiovascular disease or are at high cardiovascular risk.	Moderate	Strong
Q5. Should we recommend add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target?			
22	Recommendation 22. We recommend the use of GLP-1 receptor agonist therapy, basal insulin therapy, OR fixed-ratio combination as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target, following careful consideration of patient-centered factors to further individualize treatment regimens.	Moderate	Strong
23	Recommendation 23. In resource-limited settings where cost is a major consideration, we recommend the use of basal insulin as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target.	Moderate	Strong
Herbal medications and Supplements			
Q6. Should we recommend the use of *Momordica charantia* [Ampalaya] among adults with T2DM?			

No.	Recommendations	Certainty	Strength
24	Recommendation 24. We neither recommend for nor against the use of *Momordica charantia* for glycemic control among persons with diabetes. There is no clear evidence that *Momordica charantia* can improve glycemic control among adults with T2DM at this time.	Very Low	Weak
Q7. Should we recommend the use of Chromium picolinate among adults with T2DM?			
25	Recommendation 25. We do not recommend the use of Chromium picolinate or any other Chromium preparation among adults with T2DM.	Very Low	Strong
Q8. Should we recommend the use Andrographis paniculata (Serpentina) among adults with T2DM?			
26	Recommendation 26. We do not recommend the use of *Andrographis paniculata* (Serpentina)* for glycemic control of adults with T2DM. **Remarks: Published studies are mostly in preclinical, phase I or II, searching for its role in the treatment of a lot of other chronic illnesses, including viral infections.*	Very Low	Strong
Q9. Should we recommend the routine use of vitamin B12 (methylcobalamin or cyanocobalamin) supplementation among adults with T2DM on metformin?			
27	Recommendation 27. We neither recommend for nor against supplementation with methylcobalamin / Vitamin B12 among adults with T2DM on metformin.	Very Low	Weak
Q10. Should we recommend the use of *Costus igneus* (Insulin Plant) among adults with T2DM?			
28	Recommendation 28. We recommend against the use of *Costus igneus* (Insulin plant) among adults with T2DM.	Very Low	Strong

No.	Recommendations	Certainty	Strength
Monitoring and Treatment Targets			
Q11. Should we recommend a fasting plasma glucose (FPG) target of 80 to 130 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?			
29	Recommendation 29. We suggest a general fasting plasma glucose (FPG) goal of 80 to 130 mg/dL to approximate the target HbA1c of <7% among nonpregnant adults with T2DM.	Low	Weak
Q12. Should we recommend an HbA1c target of <7% for glycemic control among nonpregnant adults with T2DM?			
30	Recommendation 30. We recommend an HbA1c goal of <7% using an NGSP-certified method among nonpregnant adults with T2DM as long as it can be safely achieved without significant hypoglycemia.	High	Strong
31	Recommendation 31. We recommend a less stringent HbA1c goal of <8% among nonpregnant adults with T2DM and a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications or severe comorbid conditions.	High	Strong
32	Recommendation 32. We recommend an individualized HbA1c goal taking into account life expectancy, disease duration, presence or absence of complications, comorbid conditions, risk for hypoglycemia and other social determinants of health such as patient support and resources.	High	Strong
Q13. Should we recommend self-monitoring of blood glucose (SMBG) targets of fasting capillary plasma glucose of 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose of <180 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?			

No.	Recommendations	Certainty	Strength
33	Recommendation 33. We suggest a fasting capillary plasma glucose target of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and a 2-hour postprandial capillary plasma glucose target of <180 mg/dL (<10.0 mmol/L) in order to achieve an HbA1c of <7.0% among nonpregnant adults with T2DM.	Low	Weak
Vaccination and Adjunctive Therapies			
Q14. Should we give influenza vaccines annually among adults with T2DM?			
34	Recommendation 34. We recommend routinely giving the influenza vaccine annually to adults with T2DM, ideally from February to June each year before the start of the rainy season in the Philippines (per DOH guidance)	Moderate	Strong
Q15. Should we give pneumococcal vaccines annually among adults with T2DM?			
35	Recommendation 35. We recommend routinely giving both types of pneumococcal vaccine to all adults with T2DM, in the following order: PCV13 or PCV15, followed by PPSV23 after at least 8 weeks (up to a maximum of 1 year). *Remarks:* ● *For adults who have already received PPSV23, they may receive PCV13 or PCV15 after 1 year.* ● *PPSV23 is given every 5 years until the age of 65.* ● *When a second PPSV23 dose is used, no additional pneumococcal vaccines are recommended until at least age 65 years.* ● *For adults aged ≥65 years: one PPSV23 dose only.*	Low	Strong
T2DM and specific disease conditions			

No.	Recommendations	Certainty	Strength
Q16. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and concomitant tuberculosis?			
36	Recommendation 36. We recommend optimization of glycemic control generally using metformin as background therapy in patients with T2DM and concomitant active TB. In the absence of studies, we recommend combined oral anti-diabetes agents or insulin with background metformin therapy.	Low	Strong
37	Recommendation 37. We recommend the use of insulin in patients with severe hyperglycemia (glycosylated hemoglobin [HbA1c] >10% or fasting plasma glucose [FPG] >300 mg/dL), or in the presence of weight loss and other symptoms of hyperglycemia.	Low	Strong
38	Recommendation 38. We suggest referral to diabetes clinics for structured care programs for optimization of glycemic control.	Low	Weak
Q17. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)?			
39	Recommendation 39. We recommend GLP-1 RAs as adjunctive therapy among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD).	Moderate	Strong
40	Recommendation 40. We recommend pioglitazone as adjunctive therapy among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)	Low	Strong
Q18. Should we recommend specific oral antidiabetic agents or injectable therapies to prevent the occurrence of stroke or its recurrence among adults with type 2 diabetes mellitus and established cardiovascular disease?			
41	Recommendation 41. We suggest the use of GLP1RAs* among individuals with type 2 diabetes mellitus with established cardiovascular disease.	Low	Weak

No.	Recommendations	Certainty	Strength
	**Refers to GLP-1 receptor agonists with demonstrated cardiovascular benefit, specifically dulaglutide or semaglutide.*		
Q19. Should we use specific oral antidiabetic agents or injectable therapies among adults with T2DM and obesity?			
42	Recommendation 42. We recommend the use of a GLP-1 receptor agonist as an adjunct to diet and exercise among adults with T2DM and obesity	Moderate	Strong
43	Recommendation 43. In selecting oral glucose-lowering therapies among adults with T2DM and obesity, we suggest the use of agents that may contribute to weight loss such as metformin and/or SGLT2 inhibitors.	Low	Weak
Q20. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and chronic kidney disease (CKD) or end-stage renal disease (ESRD) on dialysis?			
44	Recommendation 44. We recommend the use of SGLT2 inhibitors among adults with T2DM and CKD with an estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m^2.	High	Strong
	Adults with type 2 diabetes mellitus and end-stage renal disease (ESRD) on dialysis should be referred for specialist care for individualized management.	Good Practice Statement	
Q21. Should we recommend specific oral antidiabetic agents or injectables among adults with T2DM and cirrhosis or chronic liver disease (CLD)?			
45	Recommendation 45. We suggest the use of metformin and/or sulfonylureas as the initial treatment(s) among adults with T2DM and cirrhosis	Low	Weak

No.	Recommendations	Certainty	Strength
46	Recommendation 46. We suggest the use of insulin in patients with severe hyperglycemia [glycosylated hemoglobin (HbA1C) >10% or fasting plasma glucose (FPG) >300 mg/dL] among adults with T2DM and cirrhosis	Low	Weak

Chapter 3. Evidence and Recommendations

A. Management (Pharmacologic therapy) for Diabetes Mellitus

Guideline Question 1. Should we use metformin as first-line glucose-lowering agent (i.e., monotherapy or base drug for combination therapy) among adult patients with type 2 diabetes mellitus?

Recommendation 1. We recommend metformin as the preferred initial pharmacological agent for type 2 diabetes if it is not contraindicated and is tolerated among adults with type 2 diabetes mellitus

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 2. We recommend metformin as the base drug when combining with other glucose-lowering agents among adults with type 2 diabetes mellitus.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 3. We recommend that initial therapy be based on individual treatment considerations among those with contraindications or intolerance to metformin or based on their specific profile (CHF, ASCVD, CKD).

Certainty of Evidence: Low
Strength of recommendation: Strong

Guideline Panel Considerations/Statements

- The panel agreed that metformin should be the preferred initial pharmacologic therapy for most patients, given its well-established glycemic efficacy, absence of weight gain and hypoglycemia, favorable tolerability profile, and low cost. In addition, the panel noted that metformin has no known adverse cardiovascular effects and is associated with a reduction in cardiovascular events.
- The panel emphasized that the choice of first-line therapy should be individualized, taking into account the presence of comorbidities, patient-centered factors (such as preferences, tolerability, and risk of adverse effects), and overall management needs. In most patients, initial management should include metformin in combination with comprehensive lifestyle modification.

Background

In initiating pharmacologic treatment for type 2 diabetes, several factors are considered when selecting the optimal agent as first-line monotherapy. Glycemic efficacy of the agent is a primary consideration. The impact on cardiovascular outcomes is also a crucial factor in treatment selection. Other factors critical in decision-making include the risk of adverse effects (i.e., weight gain and hypoglycemia), presence of cardiovascular benefit, and cost of treatment. [1]

Metformin, a biguanide, is widely used as a first-line agent due to its effectiveness and safety. It acts as an insulin sensitizer by inhibiting hepatic gluconeogenesis and increasing peripheral glucose uptake in the tissues. [2] The evidence reviewers examined the use of metformin as a first-line or initial agent as monotherapy in type 2 diabetes mellitus and explored the use of metformin as the base drug in combination with other therapies.

Summary of the Evidence

This review comprised 204 randomized controlled trials. The trials included adults with type 2 diabetes mellitus, both with low and high cardiovascular risks. In these studies, metformin was compared to placebo, other oral agents, or injectables. Outcomes assessed were the magnitude of HbA1c reduction, cardiovascular mortality and morbidity, weight change, hypoglycemia and other adverse effects. The included studies were deemed to be generally low risk of bias, with considerable heterogeneity and some imprecision. Heterogeneity resulted from differences in the population groups studied, as well as variation in the dose of metformin and comparator used, and outcomes assessed. [3,4]

Efficacy outcomes

Metformin as Monotherapy

Data on the efficacy of metformin as monotherapy was largely derived from an updated systematic review and meta-analysis by Maruthur et al. in 2016 [3], and a network meta-analysis by Tsapas et al. in 2020 [4].

The network meta-analysis [4] demonstrated that metformin was effective in reducing HbA1c compared to placebo, with an effect estimate of -0.92% (95% CI -1.07 to -0.77%) based on moderate certainty of evidence. The overall efficacy of metformin was superior to all oral hypoglycemic agents except for oral semaglutide and canagliflozin. The GLP-1 agonists and insulins, on the other hand, were found to be superior to metformin in terms of HbA1c lowering among patients who were drug naïve. All treatments reduced HbA1c level compared with placebo, with mean differences ranging from -1.48% (95% CI -2.15% to -0.81%) for subcutaneous semaglutide to 0.60% (95% CI -0.75% to -0.46%) for DPP-4 inhibitors. This is based on a moderate certainty of evidence. All treatments reduced HbA1c level to a similar extent with metformin, except for DPP-4 inhibitors (MD, 0.32%, 95% CI 0.17% to 0.46%), which were also inferior to liraglutide, subcutaneous semaglutide, pioglitazone, and sulfonylureas in terms of the outcome of glycemic efficacy [4].

The meta-analysis by Maruthur et al. (2016) also reflected the use of metformin as monotherapy. There were no significant between group differences in hemoglobin A1c with metformin versus sulfonylureas, and the strength of evidence was graded as high. Twenty-three studies mildly favored metformin as

monotherapy vs. thiazolidinediones (MD = -0.04, 95% CI -0.11 to 0.03, high strength of evidence) and 6 studies overwhelmingly favored metformin vs. DPP-4 inhibitors (MD = -0.43, 95% CI -0.55 to -0.31, high strength of evidence).[3]

In addition to glycemic efficacy, metformin was found to have a favorable effect on weight, with therapy initiation not resulting in weight gain. In a meta-analysis of six randomized controlled trials involving 2,774 patients, compared to DPP-4 inhibitors, metformin was found to result in modest weight loss, with an effect estimate of -1.3 kg/m2 (95% CI -1.6 to -1.0), with a high certainty of evidence.[4] Indeed, the potential of metformin therapy to induce weight loss was demonstrated in these trials.

In terms of cardiovascular endpoints, two randomized controlled trials demonstrated that metformin monotherapy was associated with lower rates of long-term (at least 2 years of observation) cardiovascular mortality compared to sulfonylurea treatment (RR= 0.6 to 0.7 across studies with a moderate strength of evidence). No significant differences were found between metformin and sulfonylurea in terms of CVD morbidity (RR = 0.7 to 1.6 across two studies) and all-cause mortality (RR = 0.5 to 1.0 across two studies).[3] Likewise, in the meta-analysis of Tsapas *et al*, metformin monotherapy did not demonstrate any significant effect on all-cause mortality and other cardiovascular outcomes.[4]

Metformin as Base Therapy in Combination with Other Agents

The efficacy of metformin as a base drug when considering combination anti-hyperglycemic therapy for more optimal glycemic control was explored in the meta-analysis of Maruthur et al. All metformin-based combination therapies exhibited a greater extent of HbA1c reduction than monotherapy with metformin. The combination therapy of metformin and sulfonylurea exhibited the highest potency in terms of HbA1c reduction, with an effect estimate of 0.94 (95% CI 0.68 to 1.19) with a high strength of evidence. Also, evidence showed that combining metformin with a GLP-1 agonist resulted in a higher reduction in HbA1c than adding a DPP-4 inhibitor to metformin (effect estimate 0.65, 95% CI 0.54 to 0.75), with a moderate strength of evidence (Figure 2).[3] The meta-analysis of Tsapas et al. echoed the viability of metformin-based combination therapy in attaining glycemic control. Therapeutic regimens that combined metformin with insulin or GLP-1 receptor agonists yielded the highest extent of HbA1c reduction.[4]

For the outcome of body weight, favorable effects in terms on body weight were seen when metformin was combined with SGLT-2 inhibitor or GLP-1 agonist.[3]

Cardiovascular outcomes were analyzed in the meta-analysis of Tsapas et al. For patients on metformin monotherapy, no significant differences in terms of cardiovascular outcomes were detected. Participants on metformin-based background therapy were stratified according to low and high cardiovascular risk in the analysis. In the cohort of patients with low cardiovascular risk, no significant differences in groups with metformin as base therapy in combination with other drugs across drug classes and placebo in terms of cardiovascular death, stroke, hospitalization for heart failure and stroke. For the outcome of all-cause mortality, GLP-1 receptor agonists were found to be associated with decreased odds of this deleterious outcome compared to placebo (OR = 0.64, 95% CI 0.45 to 0.91). Likewise, GLP-1 receptor agonists and SGLT-2 inhibitors were both found to be associated with lower rates of myocardial infarction versus placebo (Figure 5). In the cohort of patients with increased

cardiovascular risk, combining metformin with oral semaglutide, empagliflozin or liraglutide resulted in lower all-cause mortality and cardiovascular death. Subcutaneous semaglutide and dulaglutide were also associated with lower rates of stroke.[4]

The selection of agents to add to metformin is guided by the clinical profile and the presence of particular conditions such as atherosclerotic cardiovascular disease, congestive heart failure, and chronic kidney disease. Agents that are associated with improved cardiovascular outcomes (GLP-1 receptor agonists, SGLT-2 inhibitors) are preferred in such scenarios.

Safety outcomes

Hypoglycemia is the most significant adverse effect of glycemic lowering therapy. For all treatments, there was no difference versus placebo or metformin in the incidence of severe hypoglycemia based on 59 studies featuring 24,479 patients. [4] When metformin-based combination therapy was utilized, those who used sulfonylureas, basal bolus insulin regimens, and pre-mixed insulins had elevated odds of developing severe hypoglycemia. [4] Similarly, the work of Maruthur et al. detected less incidents of severe hypoglycemia when metformin monotherapy was used compared to sulfonylurea monotherapy. Sulfonylurea treatment was associated with higher rates of severe hypoglycemia compared to metformin monotherapy with a high strength of evidence (OR = 9.0, 95% CI 4.9 to 16.4 for normal renal function, OR = 6.0, 95% CI 3.8 to 9.5 for those with impaired kidney function). In terms of combination therapy employing metformin as the base agent, combinations involving basal or premixed insulin were associated with higher rates of hypoglycemia compared to combinations using GLP-1 receptor agonists.[3]

Gastrointestinal side effects may be prominent adverse outcomes of metformin therapy. Nausea, vomiting and diarrhea were the most common adverse effects reported, and such side effects were found in patients who were using metformin as monotherapy and in combination with other agents. Metformin combined with a GLP-1 receptor agonist resulted in higher rates of gastrointestinal side effects compared to the use of metformin alongside with DPP-4 inhibitors or thiazolidinediones. [3]

Overall Certainty of Evidence

Overall certainty of evidence was downgraded to moderate due to the marked heterogeneity across the randomized controlled trials in terms of the characteristics of the populations investigated. Included studies for all outcomes have a low risk of bias.

Other considerations

Metformin is considered to be affordable in the Philippine setting, with the price of the 500 mg tablet preparation ranging from Php 3.50 to 18.25. It is also available in most local health centers with government financing.

Guideline Question 2. Should we use sulfonylureas, DPP4-inhibitors, SGLT-2 inhibitors, thiazolidinediones, GLP1-RA, and basal insulin among adults with T2DM on metformin after failure to achieve glycemic targets?

Recommendation 4. We recommend any of the oral anti-diabetes medications (i.e., sulfonylureas, DPP4-inhibitors, SGLT-2 inhibitors, thiazolidinediones) may be used as a second-line agent among patients with T2DM on metformin after failure to achieve glycemic targets.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 5. We recommend the addition of an SGLT2 inhibitor as the initial choice of second-line oral agent* among patients with T2DM after failure to achieve glycemic targets.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Remarks:
- *SGLT2 inhibitors have been shown to reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality.*
- *SGLT2 inhibitors also improve health-related quality of life for patients with these conditions.*
- *Additionally, SGLT2 inhibitors slow the progression of chronic kidney disease and reduce the risk of end-stage kidney disease in individuals with type 2 diabetes.*

Recommendation 6. We recommend a GLP-1 receptor agonist or insulin therapy as second-line injectable therapy among patients with T2DM on metformin after failure to achieve glycemic targets.

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 7. We recommend the addition of a GLP-1 receptor* agonist as the initial choice of second-line injectable agent among patients with T2DM on metformin after failure to achieve glycemic targets.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Remarks:
- *GLP-1 RAs have been shown to reduce the risk of stroke, cardiovascular events, and all-cause mortality.*
- *They also decrease the progression of macroalbuminuria, promote weight loss, and improve health-related quality of life.*

Recommendation 8. We recommend the use of SGLT2 inhibitors, and GLP-1 receptor agonists among patients with T2DM with chronic kidney disease.

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 9. We suggest the use of sulfonylureas, specifically gliclazide MR*, in resource-limited settings among patients with T2DM with chronic kidney disease.

Certainty of Evidence: Low
Strength of recommendation: Weak

Remarks: *Gliclazide MR may help reduce the incidence of end-stage renal disease in patients with T2DM, particularly in settings with limited healthcare resources.*

Recommendation 10. We recommend the use of SGLT2 inhibitors among patients with T2DM who are taking metformin and have heart failure.

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 11. We recommend against the use of thiazolidinediones among patients with T2DM who are taking metformin and have heart failure.

Certainty of Evidence: Very Low
Strength of recommendation: Strong

Remarks: *This recommendation is based on evidence indicating that thiazolidinediones may increase the risk of exacerbating heart failure in patients with type 2 diabetes.*

Recommendation 12. We recommend the use of GLP-1 receptor agonists among patients with T2DM who are at high risk for stroke or have a previous history of stroke.

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 13. We recommend the use of either semaglutide or dulaglutide* among patients with T2DM who are at high risk for stroke or have a previous history of stroke.

Certainty of Evidence: High
Strength of recommendation: Strong

Remarks: *Both semaglutide and dulaglutide have been shown to reduce non-fatal and total stroke in patients with type 2 diabetes.*

Recommendation 14. We recommend the use of GLP-1 receptor agonist semaglutide 1 mg for weight reduction in patients with T2DM and obesity.

Certainty of Evidence: High
Strength of recommendation: Strong

Remarks: *Semaglutide 1 mg and Liraglutide 3 mg demonstrated the greatest magnitude of weight reduction among GLP-1 receptor agonists in patients with type 2 diabetes and obesity.*

Recommendation 15. We recommend the use of GLP-1 receptor agonist liraglutide 3 mg for weight reduction in patients with T2DM and obesity.

Certainty of Evidence: Low
Strength of recommendation: Strong

Remarks: *Semaglutide 1 mg and Liraglutide 3 mg demonstrated the greatest magnitude of weight reduction among GLP-1 receptor agonists in patients with type 2 diabetes and obesity.*

Recommendation 16. We suggest against the use of sulfonylureas, thiazolidinediones, and insulin among patients with obesity and T2DM.

Certainty of Evidence: Moderate
Strength of recommendation: Weak

Remarks: *Sulfonylureas, thiazolidinediones, and insulin are associated with a higher risk of weight gain in patients with obesity and type 2 diabetes, which is why their use is discouraged in this population*

Recommendation 17. We recommend against the use of sulfonylureas and thiazolidinediones among patients with T2DM who are at high risk for hypoglycemia.

Certainty of Evidence: Low
Strength of recommendation: Strong

Recommendation 18. We recommend the use of insulin analogues* (such as glargine U100, glargine U300, degludec U100, and detemir) in patients with T2DM requiring insulin.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Remarks: *Insulin analogues have been shown to reduce the risk of hypoglycemia, particularly nocturnal hypoglycemia, compared to other insulin preparations*

Background

Type 2 diabetes is a chronic and progressive disease requiring regular monitoring and adjustment of medications to maintain good glycemic control. Metformin is frequently used as the first-line treatment for most patients with type 2 diabetes because of its established long-term safety as well as its glucose-lowering efficacy and affordability. However, some patients may not be controlled by metformin alone, or may eventually experience metformin monotherapy failure in the course of their diabetes. In the ADOPT trial, the cumulative prevalence of metformin monotherapy failure was 21% after 5 years of follow up.[1] In a retrospective cohort study by Weiss et al[2], 32.9% of patients in a US database experienced secondary metformin monotherapy failure. With the increasing number of available anti-diabetes medications, it is important to choose the most appropriate, effective, and beneficial drug to add to metformin, taking into consideration not just glucose control, but prevention of diabetes complications as well.

We systematically searched for systematic reviews and network meta-analyses (NMA) of randomized controlled trials that examined the effects of anti-diabetes medications among patients with type 2 diabetes on background metformin therapy to enable consideration of direct, indirect, and mixed treatment comparisons of the different drug classes. The initial search yielded 303 articles with 20 full text articles retrieved for review. One of the NMAs was excluded from this review because of lack of evaluation for certainty of evidence. Hence, 5 out of 6 NMAs were assessed as having low risk of bias after critical appraisal and were included in this review.

Summary of the Evidence

Five (5) systematic reviews and network meta-analyses of RCTs on various anti-diabetic interventions for 1,081,954 patients with T2DM (Table 8) were utilized. These NMAs investigated basal insulins like NPH, glargine, and degludec (n = 44 RCTs; 23,699 participants) for hypoglycemia outcomes (overall, nocturnal, and severe); GLP-1 receptor agonists such as liraglutide, semaglutide, and dulaglutide (n = 76 RCTs; 39,246 participants) for body weight outcomes, both with a minimum follow-up of 12 weeks (Dehghani, 2023; Yao 2023) and a broad range of glucose-lowering agents including SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, TZDs, and other agents (n = 816 RCTs; 471,038 participants) for health-related quality of life (HrQOL) and body weight outcomes over at least 24 weeks. (Shi, 2023) Sim and colleagues synthesized findings from 38 RCTs (n = 227,497 patients with T2DM on metformin-based regimens) for macrovascular and microvascular outcomes, adverse events, and hypoglycemia, while Tsapas et al. pooled the results from 453 RCTs (n = 320,474 participants) to determine the effects of various glucose-lowering therapies, such as metformin, sulfonylureas, pioglitazone, and newer agents, on glycemic control (HbA1c reduction) for over at least 24 weeks. (Tsapas, 2020) These studies recruited adults with T2DM who are insulin-naïve and on background metformin therapy.

These studies provide a moderate-to-high certainty of evidence for efficacy and low certainty of evidence for safety.

Table 8. Characteristics of include systematic reviews and network meta-analysis

Author, year	Population	Intervention	Comparator/s	Outcomes (considered in this review)	Follow up duration	Number of Trials	Number of Participants
Dehghani, 2023	adults with T2DM, insulin-naïve and on OGLDs) or already on insulin	basal insulins (NPH, ILPS, glargine, 100 U/mL (IGlar-100); glargine, 300 U/mL (IGlar-300); detemir (IDet); degludec, 100 U/mL (IDeg-100); degludec, 200 U/mL (IDeg-200); and thrice-weekly degludec (IDeg-3TW).	Other basal insulins	Hypoglycemia Nocturnal hypoglycemia Severe hypoglycemia	12 weeks or longer	44	23,699
Haiqiang Yao, 2023	adults with T2DM who received GLP-1RA	Tirzepatide, orforglipron, Semaglutide, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, retatrutide, and CagriSema (semaglutide with cagrilintide), PEG-loxenatide, Mazdutide, Efpeglenatide, ITCA 650	placebo or any GLP-1RA drug	Body weight	12 weeks or longer	76	39 246
Qingyang Shi,2023	adults with T2DM	SGLT-2 inhibitors, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, TZD, sulfonylureas, metformin, α-glucosidase inhibitors, meglitinides, insulins, dual GIP/GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists	Standard treatments Active comparators	HrQOL Body weight	24 weeks or longer	816	471,038

Author, year	Population	Intervention	Comparator/s	Outcomes (considered in this review)	Follow up duration	Number of Trials	Number of Participants
Sim, 2022	adults with type 2 diabetes.on metformin as background therapy	biguanides, insulin, glinides, sulphonylureas, alpha-glucosidase inhibitors, glitazones, amylin analogues, glucagon-like peptide 1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter- 2 inhibitors (SGLT2i), and dopamine-2 agonists	placebo, standard care or active comparator	Macrovascular and microvascular outcomes Adverse events Hypoglycemia	any	38*	227,497
Tsapas, 2020	adults with type 2 diabetes	metformin, sulfonylureas, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, SGLT-2 inhibitors, basal insulin, basal–bolus insulin regimens (including basal-plus insulin), premixed insulins, a-glucosidase inhibitors, meglitinides	placebo, standard care or active comparator	Hba1c reduction	24 weeks or longer	453	320,474

Efficacy outcomes

Glycemic control

Glycemic control remains the cornerstone in the management of diabetes. The locally available oral anti-diabetes medications other than metformin, namely sulfonylureas, thiazolidinediones (TZD), DPP4 inhibitors, and SGLT2 inhibitors, shows efficacy in HbA1c reduction. In the NMA[3] these drugs reduced HbA1c by 0.5 to 0.6% more compared to placebo when added to metformin. Among injectable agents, basal insulin and GLP-1 receptor agonists (GLP-1RA) were both effective in reducing Hba1c among patients with type 2 diabetes mellitus compared to placebo.[3]

Macrovascular and microvascular complications

Most guidelines recommend shifting from a glucocentric approach to a patient-centered approach in managing diabetes, considering comorbidities as well as patient's values, preferences, and lifestyle. Diabetes has long been established as a major risk factor for cardiovascular and renal disease. It is

estimated that 50.0% of patients with diabetes will eventually develop heart failure as a complication,[4] while 58.0% of patients will develop chronic kidney disease.[5] Thus, aside from glycemic control, it is also important to look at other aspects of the disease such as cardiovascular and renal outcomes. The recent years have seen the emergence of newer anti-diabetes medications with potential for cardiovascular and renal protection.

Among Filipinos, diabetes is the most common cause of chronic kidney disease. Diabetic kidney disease is frequently characterized by albuminuria with or without reduction of eGFR, and these are independent risk factors for end stage renal disease, cardiovascular disease, and death.[6,7] Several large, randomized studies such as UKPDS,[8] ADVANCE,[9] ACCORD,[10] and VADT[11] have shown that glycemic control can delay progression of albuminuria and decline of eGFR. The cardiovascular outcome trials (CVOTs) of SGLT2 inhibitors and GLP-1RA have shown improvement in renal endpoints beyond glycemic control in patients with diabetes. The EMPA-KIDNEY,[12] DAPA-CKD,[13] and CREDENCE[14] trials are large clinical trials of SGLT2 inhibitors that look at the cardiovascular and renal outcomes of patients with diabetes and established kidney disease. These trials showed significant reduction in renal composite endpoints, including renal death and progression to end stage renal disease. Large clinical trials on GLP1 RAs such as LEADER[15] (liraglutide) and SUSTAIN-6[16] (semaglutide) also showed reduced risk of new or worsening nephropathy. However, the population for these 2 studies were not selected primarily for CKD and the renal endpoint were examined as secondary outcomes.

Heart failure is a major cause of morbidity and mortality in patients with diabetes and cardiovascular disease. Earlier CVOTs of SGLT2 inhibitors showed benefits on cardiovascular outcomes and mortality in patients with diabetes, including reduced risk of hospitalization for heart failure. Some of the recent SGLT2i trials focused on patients with established heart failure, with or without diabetes. The results of such studies, namely DAPA-HF,[17] EMPEROR-Preserved,[18] EMPEROR-Reduced,[19] and DELIVER[20] trials consistently showed a significant reduction in the composite outcome of hospitalization for heart failure or cardiovascular death.

The results of the NMA by Sim[21] further confirmed the cardiovascular and renal benefits with SGLT2 inhibitors. Based on high certainty of evidence, SGLT2 inhibitors have consistently been shown to lower the risk of hospitalization for heart failure, improve renal outcomes (including reduction in albuminuria, doubling of creatinine, GFR decline and progression to end stage renal disease), and reduce all-cause mortality (Appendix E Table 2.4B). SGLT2 inhibitors have also been associated with lower incidence of serious adverse events[21] and improved health-related quality of life[22] (Appendix E Table 2.4C and Table 2.4D). The recommended eGFR cut off for the use of dapagliflozin and empagliflozin is 20 mL/min/1.73m^2. For canagliflozin and luseogliflozin, the recommended eGFR cut off is 30 mL/min/1.73m^2.

Among injectable agents, GLP-1RA has been found to reduce risk for all-stroke and all-cause mortality, while having little or no difference in combined fatal and non-fatal MI, and hospitalization for heart failure compared to that of placebo[21] (Appendix E Table 2.4B). The use of GLP-1RA was also associated with a significant reduction on the risk of macroalbuminuria but with little or no effects on other renal outcomes (Appendix E Table 2.4C).

In addition, sulfonylureas may also reduce the risk for end stage renal disease (Appendix E Table 2.4C) based on low certainty of evidence[21]. However, data on the effects of sulfonylurea on renal outcome came only from the ADVANCE[10] trial which used gliclazide MR in the intensive glucose lowering arm. Hence, sulfonylureas may also be considered for those with CKD especially in resource limited settings.

TZDs have been associated with an increased risk of heart failure. In the PROActive Trial,[23] a prospective outcome study in patients with type 2 diabetes and pre-existing macrovascular disease, 5.7% of the patients in the pioglitazone group were reported with heart failure leading to hospitalization compared with 4.1% of placebo group (p 0.007). Similarly, the NMA by Sim[21] suggests an increased risk in hospitalization for heart failure (RR 1.49; 1.2,1.87) with TZDs compared to placebo based on very low certainty of evidence. Thus, we suggest avoiding the use of TZDs in patients with pre-existing heart failure, especially if the options for other anti-diabetes agents are available.

Safety outcomes

Adverse effects and hypoglycemia

Among the anti-diabetes medications, insulin, TZD, and sulfonylureas were associated with increased risk for hypoglycemia based on low certainty of evidence (Table 9). The NMA by Dehghani[24] compared the effects of all basal insulin with NPH among patients with type 2 diabetes not controlled on oral anti-diabetes medications or those who were already on insulin. All basal insulin analogues (degludec U100, detemir, glargine U100 and glargine U300) significantly reduced the risk of hypoglycemia including nocturnal hypoglycemia compared to NPH (Table 9). Among the basal insulin analogues, degludec was associated with a reduction in severe hypoglycemia based on low certainty of evidence[24]

In terms of adverse effects, insulin treatment was associated with adverse events leading to discontinuation of treatment albeit based on very low certainty of evidence[21]. DPP-4i increased the risk of acute pancreatitis (low certainty). SGLT2i were associated with increased risk of genital infection, volume depletion (high certainty), and probably increased the risk for amputation and ketoacidosis (moderate certainty). TZD was associated with increased risk in fractures (moderate certainty). GLP-1RA probably increased the risk of gastrointestinal side effects leading to treatment discontinuation (low certainty).[21,22]

Table 9. Effects of various basal insulin on hypoglycemia compared to NPH

252 RCTs 261,559 Participants	**Degludec U100**	**Detemir**	**Glargine U100**	**Glargine U300**
Overall/Any hypoglycemia	0.52 (0.37,0.73) ⊕⊕◯◯	0.55 (0.42,0.70) ⊕⊕⊕⊕	0.75 (0.63,0.90) ⊕⊕⊕◯	0.65 (0.51,0.81) ⊕⊕⊕⊕
Nocturnal hypoglycemia	0.32 (0.22,0.45) ⊕⊕⊕◯	0.44 (0.34,0.56) ⊕⊕⊕◯	0.58 (0.48,0.69) ⊕⊕⊕◯	0.57 (0.45,0.71) ⊕⊕⊕◯
Severe hypoglycemia	0.28 (0.13,0.59) ⊕⊕◯◯	0.69 (0.41,1.16) ⊕⊕⊕⊕	0.74 (0.53,1.02) ⊕⊕⊕◯	0.59 (0.35,1.00) ⊕⊕◯◯

Health Related Quality of Life (HrQOL) and Body Weight

SGLT-2 inhibitors and GLP-1RA were shown to improve HrQOL, but did not reach the threshold for minimal important differences, suggesting no to little effects[22](Appendix E Table 2.4E).

In terms of body weight, the use of GLP-1RA and SGLT2 inhibitors consistently showed weight reduction (Table 10).[21] However, among the GLP-1RA, the magnitude of benefit seems to be drug specific. Hence, we looked at the NMA by Yao who compared the effects of GLP-1RAs with placebo or other GLP-1RA. Among the GLP-1RAs, semaglutide and liraglutide showed significant reductions in body weight based on high and moderate certainty of evidence, respectively. The magnitude of weight reduction also showed a dose response gradient with higher doses of semaglutide 1mg and liraglutide 3mg resulting in greater weight loss (Appendix E Table 2.4F).

Table 10. Effects of various GLP-1RA on body weight

Total studies: 76 RCTS **Total Participants: 39,246**	**Relative effect** **(95% CrI)**	**Certainty of the evidence** **(GRADE)**
Dulaglutide 1.5mg	MD -0.7 (-1.56, 0.02)	⊕⊕◯◯ LOW
Liraglutide 1.8mg	MD -1.96 (-2.69,-1.22)	⊕⊕◯◯ LOW[d]
Liraglutide 3mg	MD -3.9 (-5.98,-1.81)	⊕⊕◯◯ LOW
Lixisenatide	MD -0.32 (-1.51,0.87)	⊕⊕◯◯ LOW
Semaglutide (injectable) 1mg	MD -3.62 (-4.47, -2.77)	⊕⊕⊕⊕ HIGH
Semaglutide (injectable) 0.5mg	MD -3.09 (-4.21, -1.97)	⊕⊕⊕⊕ HIGH

Certainty of Evidence

The certainty of evidence across the included studies varied depending on the outcomes and interventions assessed. High-certainty evidence supported the effectiveness of GLP-1 receptor agonists and SGLT-2 inhibitors in reducing HbA1c levels, improving cardiovascular and renal outcomes, and lowering all-cause mortality in patients with Type 2 Diabetes Mellitus (T2DM). These drug classes were consistently associated with significant benefits, such as reduced hospitalization for heart failure and improved health-related quality of life (HrQOL). Moderate-certainty evidence was observed for other interventions like DPP-4 inhibitors, TZDs, and sulfonylureas in their impact on glycemic control and some cardiovascular outcomes. However, TZDs were linked to an increased risk of heart failure hospitalization, a finding with very low-certainty evidence due to variability in study designs and limited data.

For adverse events, the evidence certainty ranged from moderate to very low. SGLT-2 inhibitors demonstrated high-certainty evidence for a lower incidence of serious adverse events, whereas TZDs were associated with moderate-certainty evidence for an increased risk of fractures. Hypoglycemia risk with insulin and sulfonylureas was supported by low to moderate certainty. Body weight reduction with GLP-1 receptor agonists was backed by high-certainty evidence, particularly with semaglutide and

liraglutide. Overall, the recommendations in the document rely on a mix of high to moderate-certainty evidence for efficacy, while adverse events and risks are generally supported by lower-certainty evidence due to study limitations.

Other considerations

Cost

In a local study on the cost of treatment for diabetes, the development of complications from poor diabetes control was found to result in significantly high direct medical cost[25]. As such improving control and reducing the risk for diabetes related complications may reduce the financial burden of diabetes among Filipino patients. Among the locally available anti-diabetes medications, recent HTA evaluation[26] for dapagliflozin for type 2 diabetes mellitus concluded that due to the potential of its potential to avert the cost of dialysis and hospitalization due to heart failure, dapagliflozin has a favorable cost estimation. In addition, dapagliflozin was also evaluated for its cost utility as an add-on medication in heart failure with reduced ejection fraction (HFrEF). In this study, they found that adding dapagliflozin to standard treatment for HFpEF was deemed cost-effective using the perspective of the Philippine public healthcare provider.[27]

Table 11. Cost of locally available anti-diabetes medications

Medication	Generic	Generic Price	Innovator Price
SULFONYLUREAS	Glibenclamide	5.75 php/tab	20.75 php/tab
	Glipizide	16.00 php/tab	30.75 php/tab
	Gliclazide 30 mg	6.75 php/tab	-
	Gliclazide 60 mg	12.50 php/tab	31.00 php/tab
	Gliclazide 80 mg	7.50 php/tab	
	Glimepiride 2 mg	11.50 php/tab	19.75 php/tab
DDP-IV INHIBITORS	Gemigliptin 50mg	-	52.00 php/tab
	Linagliptin	-	55.75php/tab
	Sitagliptin 25 mg	-	46.00 php/tab
	Sitagliptin 50 mg	33 php/tab	53.00 php/tab
	Sitagliptin 100 mg	35 php/tab	65.25 php/tab
	Teneligliptin 20mg	-	23.50 php/tab
	Vildagliptin 50	-	29.00 php/tab
GLP1 RECEPTOR AGONISTS	Dulaglutide		1565/pen/week
	Liraglutide 1.8mg	-	3,381php/pen 10,143php/month
	Semaglutide	-	7,650 php/pen/month
SGLT2 INHIBITORS	Canagliflozin 100mg	-	53.50 php/tab

Medication	Generic	Generic Price	Innovator Price
	Canagliflozin 100mg	-	87.50 php/tab
	Dapagliflozin	35 php/tab	44.00 php/tab
	Empagliflozin 10mg, 25mg	-	55.25
	Luseogliflozin 2.5mg	-	29.75
	Luseogliflozin 5mg	-	31.75
THIAZOLIDINEDIONE	Pioglitazone 15mg	12-23 php/tab	67
	Pioglitazone 30mg	12-34 php/tab	105

Insulin (Basal or Premix)	Cost in PhP
Insulin Degludec U100	
Insulin Degludec 100units/ml 3 ml PEN	763
Insulin Detemir	
Human InsulinLevemir Flexpen 3 ml	691
Insulin Glargine U300	
Insulin Glargine U300 450units/PEN	1,450
Insulin Glargine U100	
Insulin Glargine U100 100 units/ml 3ml PEN	744 to 1,254.00
Insulin Glargine 100units/ml 3 ml VIAL	517
Insulin Isophane	
Isophane Human Insulin Isophane 100 IU 10ml VIAL	660 to 1452
Human Insulin Recombinant 100units/ml 3ml PEN	578 to 674
Premix insulin	
Human Insulin Recombinant 100units/ml 3ml PEN	578
Human Insulin Recombinant 100units/ml 10 ml Vial	1,250.00
Protaminated insulin Lispro 100 iu/ml 3 ml pen	477 to 510

Patient's Values and Preference, Equity, Acceptability, And Feasibility

When treating patients with type 2 diabetes, health care professionals must also take into consideration the values and preferences that are important to patients when making treatment decisions about their care. In 2021, a systematic review and meta-analysis[28] evaluated the values, preferences, and burden of treatment that patients must consider when initiating a GLP-1RA or a SGLT2 inhibitor and included 17

studies with 7,296 patients. The review found no studies on the preference of SGLT2-inhibitors. When choosing a medication, drug attributes that patients consider the most include the following[28]:

- Oral administration and lesser frequency of side effects (preferring DPP4 inhibitor over GLP-1RA)
- Type of delivery system and dosing frequency (preferring GLP-1RA over insulin glargine, the latter requiring also self-monitoring of blood glucose)
- Weight change (preferring to pay more for GLP-1RA over insulin glargine)
- Changing injection frequency from daily to weekly (preferring once-weekly GLP-1RA over daily GLP-1RA or daily insulin)

Guideline Question 3. Should initial injectable therapy combined with oral agent/s be recommended for among adults with type 2 diabetes mellitus (T2DM) with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?

Recommendation 19. We recommend basal insulin therapy in combination with oral glucose-lowering agent/s among adults with T2DM with HbA1c > 9% or fasting blood sugar > 250 mg/dL.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Background and Summary of the Evidence

A key challenge in managing newly diagnosed type 2 diabetes mellitus is achieving glycemic control in a timely manner. Early attainment of glycemic control measured by individualized HbA1c targets is paramount because of the progressive nature of diabetes mellitus. The glycosylated hemoglobin (HbA1c) level is not only a marker of glycemic control, but of cardiovascular risk. Higher HbA1c levels are associated with an increased risk for diabetes-related complications. Avoiding long-standing hyperglycemia is a treatment goal in order to prevent deleterious sequelae such as diabetic nephropathy, neuropathy, retinopathy, and cardiovascular events. It has been demonstrated that there are lower success rates of achieving durable glycemic control when monotherapy with an oral agent is utilized for patients with a baseline HbA1c of > 8%. Previous studies have shown that adding a second agent to metformin can decrease HbA1c by 0.64 to 0.97%.1 The use of combination therapy enables the utility of multiple mechanisms surrounding the pathophysiology of diabetes mellitus to be addressed at the same time.2 Utilizing a person-centered approach by taking into account the clinical profile, individualized risk assessment and socioeconomic factors is crucial in the selection of the most appropriate therapeutic regimen.

Summary of the Evidence

Characteristics of Included Studies

Glycemic Lowering Efficacy

The studies included in this analysis consisted of randomized controlled trials with relatively large sample sizes representing populations of adult persons with type 2 diabetes mellitus who were mostly treatment-naïve and without diabetes-related complications yet, with high baseline HbA1c. In the trials, dual therapy with oral agents comprised the intervention arm, while monotherapy with an oral agent, mostly metformin, served as the control. Glucose lowering efficacy, as measured by the odds ratio of achieving the target HbA1c or the change in HbA1c from the baseline, was the relevant outcome of interest. The studies were generally of good quality, with a low risk of bias, but notable heterogeneity because of differences in population characteristics and treatment duration.

Table 12. Characteristics of Included Studies

Number of Studies	Design	Population	Intervention	Comparator	Outcomes	Quality
20 N = 11,478 [3]	RCTs	Adult patients with newly diagnosed or drug-naïve type 2 diabetes mellitus	Dual therapy with gliclazide and metformin; saxagliptin /sitagliptin /alogliptin/ linagliptin and metformin; and empagliflozin/ canagliflozin and metformin; pioglitazone and metformin; repaglinide and metformin	Monotherapy with oral agent	Glucose lowering efficacy (odds ratio of achieving target HbA1c)	Generally low risk of bias, heterogeneity was apparent, diverse population, variable treatment duration
2 N= 1160 [4]	RCTs	Adult patients with type 2 diabetes mellitus	Dual therapy with linagliptin and metformin	Monotherapy with metformin	Glucose lowering efficacy (HbA1c reduction), odds ratio of achieving HbA1c of 6.5%, adverse effects of treatment such as hypoglycemia	Low risk of bias, included studies had relatively short duration of treatment
4 N= 3749 [5]	RCTs	Adult patients with treatment-naïve type 2 diabetes mellitus	Dual therapy with SGLT2 inhibitor	Monotherapy with oral agent	Glucose lowering efficacy (change in HbA1c from baseline), adverse events	Generally low risk of bias, sample sizes of included RCTs relatively large, with notable heterogeneity
21 N= 11,484 [6]	RCTs	Adult patients with type 2 diabetes mellitus	Dual therapy with glimepiride/glyburide and metformin; saxagliptin /sitagliptin /alogliptin/ linagliptin and metformin; and empagliflozin/ canagliflozin and metformin; pioglitazone/rosiglitazone and metformin; colsevelam and metformin; miglitol and metformin	Monotherapy with oral agent	Glucose lowering efficacy (HbA1c reduction), adverse effects of treatment	Generally low risk of bias, heterogeneity because of diverse population, includes a study with a long duration of follow-up

Summary of Findings

Various randomized controlled studies have demonstrated a higher odds ratio of achieving HbA1c targets with oral combination therapy than with monotherapy. For the metaanalysis of 20 randomized trials by Kelly et al, all forms of combination therapy with metformin (with sulfonylurea, DPP4-inhibitor, SGLT2 inhibitor, and TZD) yielded a greater HbA1c reduction than monotherapy with metformin alone. However, the study was downgraded for indirectness due to significant heterogeneity among the populations in the trials.[3] In the pooled analysis of dual therapy with linagliptin and metformin vs. metformin of Qian et al, the odds ratio of achieving an HbA1c of ≤ 6.5% was greater for the combination therapy. The trial was downgraded for imprecision because the sample size does not fully

meet the optimal information size powered enough for the outcome. The follow-up time was also relatively short.[4] In the meta-analysis of Miller et al of the combination of SGLT2 inhibitor vs. monotherapy alone, it was found that combination therapy resulted in a significant decrease of HbA1c for baseline. Downgrading for inconsistency was done because of a few inconsistent results in trials, likely stemming from heterogeneity.[5] The metaanalysis of 36 studies by Cai et al likewise demonstrated that all forms of combination therapy resulted to better glycemic efficacy than monotherapy alone, with mostly similar risks of hypoglycemia. However, the study was downgraded due to indirectness emanating from marked heterogeneity in the study populations and use of some interventions not currently available in the setting of the population of interest (ex. miglitol, rosiglitazone).[6]

Table 13. Summary of findings table with critical outcomes

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Glycemic efficacy (Odds of achieving HbA1c of ≤7.5%)	20 RCTs[3] N = 11,478	OR 1.33 (p = 0.003)	1.20 to 1.47	Benefit	Moderate
Glycemic efficacy (Odds of achieving HbA1c of ≤6.5%) (Linagliptin + Metformin vs. Metformin monotherapy)	2 RCTs[4] N = 1160	OR 2.84 (p = <0.0001)	1.87 to 4.32	Benefit	Moderate
Glycemic efficacy (Mean change of HbA1c from baseline) (SGLT2i + Metformin vs. Metformin monotherapy)	4 RCTs[5] N = 3749	MD -0.55%	-0.67 to -0.43	Benefit	Moderate
Glycemic efficacy (HbA1c reduction from baseline) (Cai 2018)	36 RCTs[6] N = 11,484	WMD -0.44% (p<0.001)	-0.57 to -0.31	Benefit	Moderate

Safety Profile

Data have shown that the use of combination therapy did not result to any serious adverse effects. Rates of hypoglycemia when compared to monotherapy were similar (p>0.05).[6]

Overall Certainty of Evidence

The available evidence was derived from four meta-analyses of randomized controlled trials comparing initial oral combination therapy with monotherapy in adults with type 2 diabetes mellitus who were predominantly treatment-naïve and without established diabetes-related complications: Kelly et al. (20 RCTs; N = 11,478), Lv et al. (2 RCTs; N = 1,160), Milder et al. (4 RCTs; N = 3,749), and Cai et al. (36 RCTs; N = 11,484) — all assessed as generally low risk of bias, with notable heterogeneity attributable to differences in population characteristics and treatment duration. All four critical outcomes, each addressing glycemic lowering efficacy, were rated as moderate certainty. The odds of achieving HbA1c <7.5% (OR 1.33, 95% CI 1.20–1.47) was downgraded for indirectness attributed to heterogeneity in patient characteristics, as was the odds of achieving HbA1c <6.5% (OR 2.84, 95% CI 1.87–4.32), while the reduction in HbA1c from baseline at 24–26 weeks (MD −0.55%, 95% CI −0.67 to −0.43) was downgraded for inconsistency among trial results. HbA1c reduction from baseline at 16–50 weeks (MD −0.44%, 95% CI −0.57 to −0.31) was likewise downgraded for indirectness, reflecting both heterogeneity in patient characteristics and the inclusion of agents not currently available in the local setting. The overall certainty of the evidence — driven by the lowest certainty among critical outcomes — is moderate, limited principally by between-study heterogeneity in populations and treatment duration and by the use of comparators not reflective of current local practice.

Other Considerations

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 4. Should initial injectable therapy combined with oral agent/s be recommended for among adults with type 2 diabetes mellitus (T2DM) with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?

Recommendation 20. We recommend basal insulin therapy in combination with oral glucose-lowering agent/s among adults with T2DM with HbA1c > 9% or fasting blood sugar > 250 mg/dL.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 21. We recommend the use of glucagon-like peptide-1 (GLP-1) receptor agonists in combination with oral glucose-lowering agent/s among adults with type 2 diabetes mellitus with HbA1c > 9% or fasting blood sugar > 250 mg/dL, who have established atherosclerotic cardiovascular disease or are at high cardiovascular risk.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Background and Summary of the Evidence

The choice of initial therapy for type 2 diabetes mellitus is highly influenced by the level of fasting blood sugar or HbA1c upon diagnosis. A high HbA1c level, at more than 9% or 10%, underscores the urgency to attain glycemic control in a timely manner to reduce the risk of developing diabetes-related complications. Such cohort of patients would benefit from intensified glycemic control at the outset.

Basal Insulin in Combination with Oral Agents

Several studies looked into the impact of early initiation of insulin therapy in combination with one or several oral agents in patients with marked hyperglycemia. One meta-analysis and one observational prospective study explored the effect of timely use of basal insulin therapy on glycemic control. Two randomized controlled trials investigated the effect of initiating basal insulin therapy to achieve optimal glycemic control on microvascular and macrovascular outcomes.

Characteristics of Included Studies

Eleven studies comparing the use of basal insulin with oral agents alone explored the outcome of HbA1c reduction while one randomized controlled trial looked into the incidence of microvascular outcomes.

Table 14. Characteristics of included studies comparing basal insulin with oral agents and oral agents only

Basis	Population	Comparator	Outcomes	Quality
11 RCTs N = 2,171	Adult patients with uncontrolled type 2 diabetes mellitus (mean baseline HbA1c 8.77%)	Oral agents only (metformin or SU) early in treatment	HbA1c reduction, percentage achieving HbA1c ≤ 7.0%, weight gain and hypoglycemic events	Generally, of good quality, heterogeneity noted, majority of participants were Caucasian
1 RCT N = 12, 537	Men and women aged 50 years or older with type 2 diabetes on not more than one oral glucose-lowering drug with either a prior cardiovascular event or at high risk of vascular disease	Standard care	Incidence of microvascular outcomes	Low risk of bias, heterogeneity

Summary of Findings

The meta-analysis of Fonseca et al showed that the use of basal insulin reduced HbA1c by 2.0% for those not on OAD or on a single OAD and by 1.7% for those on 2 OADs. In the ORIGIN trial, it was demonstrated that the use of basal insulin led to a decrease in HbA1c of 0.33%, and this led to a 10% reduction in cardiovascular events.

Table 15. Summary of findings: basal insulin basal insulin with oral agents versus oral agents only

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
HbA1c reduction after 24 weeks (%)	11 RCTs N= 2,171	-2.0% for 0/1 OAD vs. -1.7% 2 OAD OR = 0.261	-0.057 to 0.580	Equivalent	Moderate
Incidence of primary microvascular composite outcome of kidney and eye disease	1 RCT N = 12,537	HbA1c ≥ 6.4%: HR 0.90	0.81 to 0.99	Benefit	Moderate

Adverse Effects of Basal Insulin

Hypoglycemia is the most significant adverse effect of basal insulin therapy. In the meta-analysis of Fonseca et al, the incidence of symptomatic hypoglycemia, in terms of event rate per subject year were as follows: 4.05 for those without or only on a single OAD, 7.18 for those on 2 OADs, while the incidence of severe symptomatic hypoglycemia is 0.01 and 0.06 event rate per subject year for those without or only on a single OAD, and on 2 OADs respectively.

GLP-1 Receptor Agonists and Oral Agents

Characteristics of Included Studies

Thirty-one studies dealt with the outcome of HbA1c reduction while 8 studies investigated the outcome of cardiovascular events in terms of MACE.

Table 16. Characteristics of included studies comparing GLP-1 receptor agonists with oral agents and oral agents only

Basis	Population	Comparator	Outcomes	Quality
31 RCTs N = 23, 061	Adult patients with mean HbA1c ≥7.8%	Oral agents alone	Change in HbA1c	Generally low risk of bias, with heterogeneity, Asian population
8 RCT N = 60, 080	Adult patients with type 2 diabetes with mean HbA1c range from 7.3-8.7%	Oral agents alone	Incidence of MACE	Generally low risk of bias, heterogeneity in characteristics of participants

Summary of Findings

Based on the meta-analysis of Yeh et al, the use of GLP-1 receptor agonists resulted in a reduction of 0.99% in HbA1c. The administration of a GLP-1 receptor agonist also led to a 14% reduction in the risk of major cardiovascular events.

Table 17. Summary of findings: GLP-1 receptor agonists with oral agents versus oral agents only

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in HbA1c (%)	31 RCTs N = 23, 061	-0.99%	-1.17 to -0.82	Benefit	Moderate
Incidence of MACE	8 RCTs N = 60, 080	HR 0.86	0.80 to 0.93, p < 0.0001	Benefit	Moderate

A retrospective study by Tran et al involving 151 patients found that the addition of GLP-1 receptor agonist to the treatment regimen of patients with HbA1c of 9% or greater lead to a 2.1 reduction in HbA1c (95% CI -2.3 to -1.8, p < 0.001).

Adverse Effects of GLP-1 Receptor Agonists

Gastrointestinal side effects were the most common adverse effects associated with GLP-1 receptor agonist administration. Nausea, vomiting, constipation, and diarrhea were the most common side effects. The most common side effect is nausea, which can occur in about half of patients. Such an adverse effect is dose dependent. For instance, the probability of developing nausea for liraglutide 1.2 mg per day is lower (OR = 2.16) compared to the 1.8 mg dose (OR = 3.19).

Overall Certainty of the Evidence

The available evidence was derived from two parallel comparisons. For basal insulin versus oral agents alone, the evidence comprised the Fonseca et al. meta-analysis of 11 RCTs (N = 2,171; mean baseline HbA1c 8.77%) — assessed as generally good quality with heterogeneity noted in a predominantly Caucasian population — and the ORIGIN trial (1 RCT, N = 12,537) — assessed as low risk of bias with heterogeneity. For GLP-1 receptor agonists versus oral agents alone, the evidence comprised the Yeh et al. meta-analysis of 31 RCTs (N = 23,061; mean HbA1c 7.8%) and an 8-RCT meta-analysis (N = 60,080;

mean HbA1c 7.3 to 8.7%) cited in the source, both rated as generally low risk of bias with heterogeneity. Across all four critical outcomes, risk of bias and inconsistency were judged not serious.

All four critical outcomes were rated as moderate certainty. The odds of reaching HbA1c ≤7.0% with basal insulin (11 RCTs; OR 0.261) was downgraded for imprecision, attributed to heterogeneous populations. The incidence of the primary microvascular composite outcome with basal insulin (1 RCT; HR 0.90, 95% CI 0.81 to 0.99) was downgraded for indirectness, as the included population had good baseline glycemic control (HbA1c ≥6.4%). Change in HbA1c with GLP-1 receptor agonists (31 RCTs; MD −0.99%, 95% CI −1.17 to −0.82) and incidence of MACE (8 RCTs; HR 0.86, 95% CI 0.80 to 0.93) were each downgraded for imprecision attributed to marked heterogeneity. The overall certainty of the evidence — driven by the lowest certainty among critical outcomes — is moderate, primarily limited by between-study heterogeneity in populations and indirectness in the ORIGIN trial population for the microvascular outcome.

Other Considerations

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 5. Should we recommend add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target?

Recommendation 22. We recommend the use of GLP-1 receptor agonist therapy, basal insulin therapy, OR fixed-ratio combination as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target, following careful consideration of patient-centered factors to further individualize treatment regimens.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 23. In resource-limited settings where cost is a major consideration, we recommend the use of basal insulin as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target.

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Background

Several studies have shown that glycemic control is associated with lower rates of microvascular and long-term cardiovascular complications.[1] A multifaceted approach is prudent in the management of type 2 diabetes among patients with 2–3 oral agents and with HbA1c above target. The shift to injection therapy, after failure of oral antidiabetic agents, is often considered as a difficult step by both the patient with type 2 diabetes and the physician, a situation that may lead to clinical inertia.[1] Two options may be considered, either starting insulin therapy with a preference for basal insulin analogues or adding a glucagon-like peptide-1 receptor agonist (GLP-1 RA). Each option has its advantages and disadvantages.

Incretin mimetics (glucagon-like peptide-1 receptor agonists) and the glucose-dependent insulinotropic polypeptide [GIP]/GLP-1 receptor co-agonist tirzepatide, and insulin are highly effective injectable treatments for stages of type 2 diabetes which can no longer be successfully managed by diet, exercise and conventional oral glucose-lowering medications (e.g., metformin, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulphonylureas and thiazolidinediones).[1] In a network meta-analysis of 453 trials assessing glucose-lowering medications from nine drug classes, the greatest reductions in HbA1c were seen with insulin regimens and GLP-1 RA.[1]

In 2019, the ADA-EASD consensus report was released which recommended that GLP-1 RA therapy should be considered in people with type 2 diabetes with specific profiles (comorbidities, obesity) when no contraindications are present prior to initiation of insulin therapy, as they allow lower glycemic

targets to be reached with a lower injection burden and lower risk of hypoglycemia and weight gain than with insulin alone.[1] GLP-1 receptor agonists generally have favorable effects on weight reduction and low risk for hypoglycemia. However, it has been established that the cost of GLP-1 receptor agonists is restrictive, particularly in low-resource settings. In specific circumstances, insulin may be the preferred agent for glucose lowering, specifically in the setting of severe hyperglycemia (HbA1c >10%, particularly when associated with weight loss or ketonuria/ketosis, and with acute glycemic dysregulation during hospitalization, surgery, or acute illness), and in underweight patients. A combination of the two approaches is also possible, with the recent commercialization of fixed-ratio specialties combining a basal insulin analogue and a GLP-1 RA.[2]

Summary of the Evidence

Basal insulin versus Oral Anti-Diabetics (OADs)

In a meta-analysis of 11 RCTs conducted by Fonseca et al wherein they employed standard of care and they evaluated the benefits of initiating insulin at an earlier versus later treatment stage, although there was no difference in mean endpoint HbA1c between groups, patients taking 0/1 oral antidiabetic (OAD) at baseline showed a significantly greater decrease in HbA1c from baseline to week 24 compared with the group on 2 OADs (p = 0.0198).[3] Outcomes measured included Hba1c reduction after 24 weeks. The characteristics of included studies are summarized below.

Characteristics of Included Studies

Table 18. Characteristics of included studies comparing basal insulin and oral anti-diabetics

Basis	Population	Comparator	Outcomes	Quality
11 RCTs N = 2,171	Adult patients with uncontrolled type 2 diabetes mellitus (Mean baseline HbA1c 8.77%)	Oral agents only (metformin or SU) early in treatment	HbA1c reduction, percentage achieving HbA1c ≤ 7.0%, weight gain and hypoglycemic events	Good quality, heterogeneity noted, (participants mostly Caucasian)

Efficacy Outcomes

Table 19. Summary of findings: basal insulin versus oral anti-diabetics

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
HbA1c reduction after 24 weeks (%)	11 RCTs N= 2,171	-2.0% for 0/1 OAD vs. -1.7% 2 OAD OR = 0.261	-0.057 to 0.580, *P* = 0.108	Equivalent	Moderate

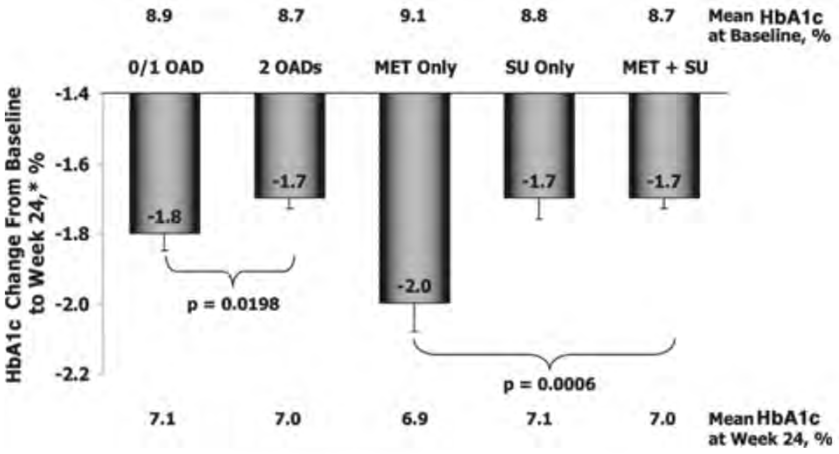


Figure 2. Change in HbA1c from baseline to week 24 by number and type of OAD at baseline (0/1 or 2; MET only, SU only, or both MET and SU). p Values were calculated from an analysis of variance model with study and baseline OAD class as factors and baseline HbA1c as a covariate. MET, metformin; OAD, oral antidiabetic drug; SU, sulfonylurea. *Least squares mean.

Figure 3. Change in HbA1c from baseline to week 24 by number and type of OAD at baseline (adopted from reference)

For the pooled analysis, patients on 0/1 OAD and those on metformin monotherapy at baseline had the largest 24-week reductions in HbA1c following the addition of insulin glargine (0.44 U/kg). Of patients failing MET/SU monotherapy and MET + SU in combination, 68.1, 50.4 and 56.4% achieved HbA1c ≤ 7.0%, respectively (P = 0.0006). Additionally, in the same study, weight gain was noted to be lowest when basal insulin was added to metformin, and patients on 0/1 OAD at baseline had significantly less symptomatic hypoglycemia when basal insulin was added than those on 2 OADs (P= 0.0007).[3]

Safety Outcomes

Adverse Effects of Basal Insulin

Hypoglycemia is the most significant adverse effect of basal insulin therapy. In the meta-analysis of Fonseca et al, the incidence of symptomatic hypoglycemia, in terms of event rate per subject year were as follows: 4.05 for those without or only on a single OAD, 7.18 for those on 2 OADs, while the incidence of severe symptomatic hypoglycemia is 0.01 and 0.06 event rate per subject year for those without or only on a single OAD, and on 2 OADs respectively.[3]

GLP-1 Receptor Agonist Therapy vs Oral Agents Alone

The latest consensus algorithm for the management of T2D jointly issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2019 recommends GLP-1 receptor agonists (GLP-1RA) as the first injectable therapy, before basal insulin, in most patients with T2D, although basal insulin remains an established approach for patients with high HbA1c levels (> 97 mmol/mol [> 11%]) and symptoms of hyperglycemia or hypercatabolism) [2]. To date, only one other guideline (Canadian Clinical Practice Guidelines) has considered this in their algorithm, wherein they recommend liraglutide as add-on to metformin when the priority is clinical cardiovascular disease.

GLP-1 agonists, mainly liraglutide and semaglutide, show a significant reduction in the incidence of major cardiovascular events, as shown in Liraglutide Effect and Action in Diabetes: Evaluation of

Cardiovascular Outcome Results (LEADER) trial (n= 9,340), and in the Trial to Evaluate Cardiovascular and Other Long- term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) (n= 3,297). These may be taken into consideration when selecting a glucose lowering drug in patients with established CVD where most of these benefits were observed.

Characteristics of Included Studies

In the RCTs analyzed by Yeh et al and Sattar et al, thirty-one studies dealt with the outcome of HbA1c reduction, while 8 studies investigated the outcome of cardiovascular events in terms of MACE, respectively.[4,5]

Table 20. Characteristics of included studies comparing GLP-1 receptor agonist versus oral agents

Basis	Population	Comparator	Outcomes	Quality
31 RCTs N = 23, 061	Adult patients with mean HbA1c ≥7.8%	Oral agents alone	Change in HbA1c	Most studies with low risk of bias, with high heterogeneity, Asian population
8 RCTs N = 60, 080	Adult patients with type 2 diabetes with mean HbA1c range from 7.3-8.7% (8.9% for the AMPLITUDE-O study)	Oral agents alone	Incidence of MACE	Generally low risk of bias, heterogeneity in characteristics of participants

Efficacy and Safety Outcomes

Based on the meta-analysis of Yeh et al, the use of GLP-1 receptor agonist resulted in a reduction of 0.99% in HbA1c in type 2 DM patients. The administration of a GLP-1 receptor agonist also led to a pooled body weight reduction of -4.05 kg (-3.14% in type 2 DM patients and -5.77% in overweight/obese patients) .[4]

Table 21. Summary of findings: GLP-1 receptor agonist versus oral agents

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in HbA1c (%)	31 RCTs N = 23, 061 (Yeh et al)	-0.99% in type 2 patients	-1.17 to -0.82 p < 0.001	Benefit	Moderate
Body weight reduction	31 RCTs N = 23, 061 (Yeh et al)	-4.05 kg (-5.02 kg, -3.09 kg) in the random-effects model and -2.04 kg (-2.16 kg, -1.92 kg) in the fixed-effect model	-3.84 to -2.44 p < 0.001	Benefit	Moderate
Incidence of MACE	8 RCTs N = 60, 080 (Sattar et al)	HR 0.86 (3P-MACE reduced by 14%)	0.80 to 0.93, p < 0.0001	Benefit	Moderate

Based on the meta-analysis of Yeh et al, the use of GLP-1 receptor agonist resulted in a reduction of 0.99% in HbA1c.[3] Based on the meta-analysis of Sattar et al, the administration of a GLP-1 receptor agonist also led to a 14% reduction in the risk of major cardiovascular events.[4]

GLP-1 Receptor Agonist Therapy versus Basal Insulin

Characteristics of Included Studies

In the attempt to answer the question on which injectable therapy should be initiated if Hba1c is still above target despite being on 2-3 oral antidiabetic agents, a study done by Nauck et al in 2022 was done to assess the comparative efficacy, safety and tolerability of injectable incretin-based glucose lowering medications (IBGLMs) versus basal insulin treatment in patients with type 2 diabetes mellitus.[6]

In a study by Longato et al, GLP-1 receptor agonist therapy was compared with basal insulin for cardiovascular protection among patients with type 2 diabetes mellitus (n= 330, 193)[7]. The study compared two cohorts of 4063 patients each, who initiated GLP-1RA or BI after an average of 2.5 other diabetes drug classes (metformin, sulfonylureas, DPP4 inhibitors, SGLT2 inhibitors), and 15% had a baseline history of cardiovascular disease.[7]

Table 22. Characteristics of included studies comparing GLP-1 receptor agonist and basal insulin

Number of Studies	Design and Study Duration	Population	Comparator	Outcomes	Quality
20 RCTs N= 11,843 (Nauck et al)	RCT ≥ 12 weeks duration	Adult patients with mean Hba1c of 8.3-8.4% +/- 0.9-1 % despite being on Met ± SU/TZD/ SGLT2i	Insulin Glargine/Detemir/ Degludec VS Exenatide/Liraglutide/ Dulaglutide/ Semaglutide/ Tirzepatide	Primary endpoint: Change in Hba1c vs baseline Secondary endpoints: -Reduction in FPG vs baseline -Reduction in body weight vs baseline	Good
1 retrospective cohort N= 330, 193 (Longato et al)	Observational study, Median follow up ≥ 24 months	Adult patients newly treated with GLP-1RA or basal insulin with mean Hba1c of 7.7-8.3 (+/- 0.8-1.1%) on Metformin +/- SU/DPP4 inhibitor	Insulin Glargine/ Detemir/Degludec VS exenatide/liraglutide/ lixisenatide, dulaglutide)	Primary endpoint: 3P-MACE Secondary endpoints: 3P-MACE components, hospitalization for heart failure, revascularizations, and adverse events	Low quality, high risk of bias and imprecision (retrospective study)

Efficacy and Safety Outcomes

Table 23. Summary of findings: GLP-1 receptor agonist therapy versus basal insulin

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in Hba1c	20 N= 11,843 (Nauck et al)	0.5%	0.46-0.53 (*P* < 0.001)	Benefit	Moderate
Change in body weight	20 N= 11,843 (Nauck et al)	4.6 kg	4.5- 4.7 kg (*P* < 0.001)	Benefit	Moderate
Rate of hypoglycemia	20 N= 11,843 (Nauck et al)	0.56	0.32-1.00 *(P* = 0.052)	Benefit	Moderate
3P-MACE	1 N= 330, 193 (Longato et al)	HR 0.59	0.50–0.71; *(P* < 0.001)	Benefit	Moderate

In comparison with basal insulin, IBGLMs lowered serum Hba1c by 0.48 (0.45-0.52%), an effect that was driven by pooled long-acting GLP- 1RAs (ΔHbA1c 0.25%) and the only GIP/GLP-1 receptor co-agonist, tirzepatide (pooled doses; ΔHbA1c 0.90%) while short-acting GLP- 1RAs were equally effective compared with basal insulin (P = 0.90) [6]. All IBGLM sub-groups achieved significantly lower body weight versus insulin treatment (4.6 kg), in particular tirzepatide (12.0 kg). IBGLMs significantly reduced hypoglycemia and blood pressure and improved lipid variables, however, IBGLM treatment was associated with more nausea, vomiting and diarrhea and study medication discontinuation, underscoring the fact that the tolerability and high cost of GLP-1 receptor agonists are important limitations to their use.[6]

In the meta-analysis by Longato et al, after a median follow-up of 24 months in the intention-to-treat analysis, 3P-MACE occurred less frequently in the GLP-1RA cohort (HR versus BI 0.59; 95% CI 0.50–0.71; p < 0.001).[7] All secondary cardiovascular endpoints (individual components of 3P-MACE: myocardial infarction, stroke, or all-cause death; hospitalization for heart failure (HHF), hospitalization for any cardiovascular disease (CVD), and revascularization procedures) were also significantly in favor of GLP-1RA..[7] The relative reduction in hazard among patients who initiated a GLP-1RA versus a BI was particularly strong for stroke and mortality (exceeding 50%) but was statistically significant and clinically relevant also for MI and HHF.[7]

For the adverse events, severe hypoglycemia occurred less frequently after initiation of GLP-1RA than after initiation of basal insulin (32 versus 50 events, HR 0.56, p = 0.052).[6]

GLP-1 Receptor Agonists versus Fixed Ratio Combination versus Basal Insulin

Two fixed-ratio combinations of GLP-1 RA with basal insulin analogs are available: insulin degludec plus liraglutide (IDegLira) and insulin glargine plus lixisenatide (iGlarLixi).[1] The combination of basal insulin with GLP-1 RA results in greater glycemic lowering efficacy than the mono-components, with less weight

gain and lower rates of hypoglycemia than with intensified insulin regimens, and better gastrointestinal tolerability than with GLP-1 RA alone.[8] In studies of people with type 2 diabetes inadequately controlled on basal insulin or GLP-1 RA, switching to a fixed- ratio combination of basal insulin and GLP-1 RA demonstrated significant improvements in blood glucose levels and achievement of glycemic goals with fewer hypoglycemic events than with basal insulin alone .[8]

Greater reductions in HbA1c from baseline (8.1% [65 mmol/mol]) were achieved with iGlarLixi compared with iGlar and Lixi (21.6%, 21.3%, 20.9%, respectively), reaching mean final HbA1c levels of 6.5% for iGlarLixi versus 6.8% for insulin glargine and 7.3% for lixisenatide, respectively (both P < 0.0001). More subjects reached target HbA1c <7% with iGlarLixi (74%) versus iGlar (59%) or Lixi (33%) (P < 0.0001 for all).[8]

Mean body weight decreased with iGlarLixi (20.3 kg) and Lixi (22.3 kg) and increased with iGlar (+1.1 kg, difference 1.4 kg, P < 0.0001). Documented symptomatic hypoglycemia (< 70 mg/dL) was similar with iGlarLixi and iGlar (1.4 and 1.2 events/patient-year) and lower with Lixi (0.3 events/ patient-year). iGlarLixi improved postprandial glycemic control versus iGlar and demonstrated considerably fewer nausea (9.6%) and vomiting (3.2%) events than Lixi (24% and 6.4%, respectively).[8]

Characteristics of Included Studies

In a network meta-analysis of 29 RCTs conducted by Visolyi et al, they compared the efficacy and safety of fixed- ratio combinations (FRCs) of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and basal insulins.

Table 24. Characteristics of included studies: fixed ratio combinations of GLP-1 RA versus basal insulin

Number of Studies	Design and Study Duration	Population	Comparator	Outcomes	Quality
29 (N= 23,605) (Visolyi et al)	RCTs (≥24 weeks or 24-104 weeks)	Adult patients with type 2 diabetes mellitus with mean Hba1c of 8% **with inadequate glycemic control or Hba1c ≥ 7.5% despite being treated for at least 3 months with metformin +/- 2nd OAD*	Basal insulin or GLP-1 RA (IGlarLixi as reference treatment)	Mean difference in Hba1c, weight gain, hypoglycemia	Low risk of bias, with heterogeneity, included Asian populations

The results showed that the effect of the fixed combination of insulin degludec and liraglutide (IDegLira) and basal insulins was similar to that of iGlarLixi (reference treatment) on fasting glucose, whereas GLP-1RAs had lower efficacy than iGlarLixi. Weight gain was lower with GLP-1RAs and IDegLira than with iGlarLixi (reference) and higher with basal insulins. There was an approximately 0.72 kg difference ($P < 0.05$) in weight gain between the FRCs, favoring IDegLira. GLP-1RAs were associated with a 2.1- to 3.4 kg smaller weight increase, whereas basal insulins had >1 kg greater weight increase compared with iGlarLixi (all $P < 0.05$). Incident hypoglycemia was least frequent with GLP-1RAs, followed by the FRCs (IDegLira -OR, 0.78; 95% CI, 0.39 to 1.57, iGlarLixi (reference), and was most frequently seen with basal insulins.

Efficacy and Safety Outcomes

Table 25. Summary of findings: fixed ratio combinations of GLP-1 RA versus basal insulin

Outcomes	Basis Number of RCTs and N)	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in Hba1c	29 (N= 23,605)	-0.10	-0.3 to 0.10	Equivalent	Moderate
Change in weight	29 (N= 23,605)	-0.72	-1.35 to -0.09	Benefit	Moderate
Rate of hypoglycemia	29 (N= 23,605)	0.78	0.39 to 1.57	Equivalent	Moderate

Certainty of Evidence

The available evidence was derived from four parallel comparisons. For basal insulin versus oral agents alone, the evidence comprised the Fonseca et al. meta-analysis of 11 RCTs (N = 2,171; mean baseline HbA1c 8.77%) — assessed as generally good quality with heterogeneity noted in a predominantly Caucasian population. For GLP-1 receptor agonists versus oral agents alone, the evidence comprised the Yeh et al. meta-analysis of 31 RCTs (N = 23,061; mean HbA1c 7.8%) and an 8-RCT meta-analysis (N = 60,080; mean HbA1c 7.3 to 8.7%) cited in the source — both rated as generally low risk of bias with heterogeneity. For GLP-1 receptor agonist therapy versus basal insulin, the evidence comprised the Nauck et al. head-to-head meta-analysis of 20 RCTs (N = 11,843; mean HbA1c 8.3 to 8.4%) — rated as good quality — and the Longato et al. retrospective cohort (1 study, N = 330,193) — rated as low quality with high risk of bias and imprecision. For fixed-ratio combinations versus basal insulin or GLP-1 receptor agonists, the evidence comprised the Visolyi et al. network meta-analysis of 29 RCTs (N = 23,605; mean HbA1c 8%) — rated as low risk of bias with heterogeneity and inclusive of Asian populations.

Across the GRADE-rated outcomes, certainty was High for the Nauck et al. head-to-head comparisons: achievement of HbA1c <7% with short-acting and long-acting GLP-1 RA versus basal insulin (5 and 16 RCTs, respectively), and the corresponding outcomes for any hypoglycemia, weight reduction, nausea, vomiting, and diarrhea — no domain downgrades were applied. Certainty was Moderate for the odds of reaching HbA1c ≤7.0% with basal insulin (Fonseca et al., 11 RCTs; downgraded for imprecision attributed to heterogeneous populations); for the microvascular composite outcome from the ORIGIN trial (1 RCT; downgraded for indirectness, as the included population had HbA1c ≥6.4%); for the change in HbA1c, MACE, and weight with GLP-1 RA versus oral agents (each downgraded for imprecision attributed to marked heterogeneity); and for the three Visolyi et al. fixed-ratio combination outcomes — HbA1c reduction, weight change, and incident hypoglycemia — each downgraded for imprecision attributed to heterogeneous populations. Certainty was Low for the three Longato et al. cardiovascular outcomes (all-cause death, myocardial infarction, and stroke), each derived from a single retrospective cohort and downgraded to low per the source on that basis. As stated in the source, the overall certainty of the evidence was moderate, limited by risk of bias, inconsistency, indirectness, and imprecision; the cardiovascular evidence from the Longato cohort sits at low certainty owing to its observational, single-study design.

Other considerations

Cost

Cost of medications is a barrier and should be given due consideration when choosing treatment options. There were no local cost-effectiveness studies found on the use of GLP-1 agonists versus basal insulin or FRCs among adult Filipinos with Type 2 Diabetes Mellitus on 2–3 oral hypoglycemic agents with serum HbA1c above target. There were no cost-effectiveness studies found for low-resource settings/populations similar to the Philippines as well. The estimated cost for pharmacologic therapy with basal insulin is PHP 61.70–96.67 per day and the cost of locally available GLP-1 RA therapy ranges from PHP 112.60–255.00 per day (see table below). Semaglutide costs PHP 255 per day (computation of which was based on locally available dose of 0.5–1 mg SC once weekly).

Table 26. Cost of locally available injectable therapies (from source document)

Product	Price
Liraglutide 6 mg/mL, 3 mL pen	PHP 112.60 / day · PHP 3,380.00 / month
Liraglutide 6 mg/mL, 3 mL pen	PHP 211.59 / day · PHP 6,347.75 / month
Semaglutide 0.5 mg	PHP 255.00 / day · PHP 7,650.00 / month
Semaglutide 1 mg	PHP 255.00 / day · PHP 7,650.00 / month
Dulaglutide 0.75 mg/0.5 mL pen	PHP 208.60 / day · PHP 6,260.00 / month
Dulaglutide 1.5 mg/0.5 mL pen	PHP 208.60 / day · PHP 6,260.00 / month
Insulin glargine 3.64 mg/100U/mL 3 mL pen	PHP 61.70 / day · PHP 1,851.00 / month (basal insulin requirement assumed at 20 units daily)
Insulin glargine 100 IU/mL 3 mL pen	PHP 83.60 / day · PHP 2,508.00 / month (basal insulin requirement assumed at 20 units daily)
Insulin levemir	PHP 46.10 / day · PHP 1,383.00 / month (basal insulin requirement assumed at 20 units daily)
Insulin degludec	PHP 50.87 / day · PHP 1,526.00 / month (basal insulin requirement assumed at 20 units daily)
Insulin glargine U300	PHP 96.67 / day · PHP 2,900.00 / month (basal insulin requirement assumed at 20 units daily)
Insulin Glargine + Lixisenatide	PHP 109.20 / day · PHP 3,276.50 / month

Patient's Values and Preference, Equity, Acceptability, and Feasibility

There were no local studies found on patients' values, preferences, acceptability, feasibility or other perspectives on the use of GLP-1 agonists versus basal insulin or FRCs among adult Filipinos with Type 2 Diabetes Mellitus on 2–3 oral hypoglycemic agents with serum HbA1c above target.

Guideline Question 6. Should we recommend the use Momordica charantia [Ampalaya] among adults with T2DM?

Recommendation 24. We neither recommend for nor against the use of Momordica charantia for glycemic control among persons with diabetes. There is no clear evidence that Momordica charantia can improve glycemic control among persons with diabetes at this time.

Certainty of Evidence:	Very Low
Strength of recommendation:	Weak

Background

Bitter melon (Momordica charantia) is frequently cited as an alternative for lowering blood glucose levels in persons with type 2 diabetes mellitus. Capsules containing this herb have been made available to the public. There is a need to present evidence regarding its efficacy and safety.

Summary of the Evidence

Nine randomized controlled trials (RCT's) fulfilled the inclusion criteria, with a total of 624 subjects included in the analysis. (Appendix B). All studies included only adults who were newly-diagnosed with type 2 diabetes, where 7 studies included those previously treated with oral antihyperglycemic agents, whose glycosylated hemoglobin values ranged from 6.5 to 10%. Momordica charantia were given in capsule form, wherein 7 studies contained dried fruit pulp or fruit juice, while 1 used dried leaves from the Makiling variety (Amargozin brand), and 1 used dried fruits and seeds (Charantia brand). Dosages ranged from 1.2 to 6.0 grams per day. The shortest study duration was 4 hours, whereas the longest was 16 weeks. Of the 9 RCT's, Momordica charantia was compared to placebo in 6 trials, metformin in 2 trials and glibenclamide in 1 trial.

There were serious risks of bias from 5 RCTs due to limitations in random sequence generation, allocation concealment, and blinding of participants and outcome assessors.

Efficacy Outcomes

Table 27. Summary of findings: Effect of Momordica charantia vs. placebo in fasting blood glucose and glycosylated hemoglobin A1c

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in FBS (mmol/L)	2 RCT's[3,5] N=39	0.31	-1.99 to 2.61	Inconclusive	Very Low
Mean and SD of FBS from baseline to end of study	3 RCT's [2,6,7] N=149	John 2003 – no significant change in FBS between MC at 6g/day (n=26) vs Placebo (n=24) at the end of 4 weeks Suthar 2016a – for the MC 1.2g/d group (n=62) fbs decreased by 21.89 mg/dL vs an added 2.12 mg/dL in the placebo group (n=17). (p= 0.013) at the end of 90 days Cortez-Navarrete 2018 – no significant change in FBS between MC 2g/d (n=10) vs Placebo (n=10) at the end of 12 weeks		Inconclusive	Very low
Change in A1c (%)	2 RCT's[3,5] N=39	0.28	0.03 to 0.54	Inconclusive	Very low
Mean and SD of A1c from baseline to end of study	RCT's[6,7] N=99	Suthar 2016a – for the MC group (n=62) A1c decreased by 0.78 vs 0.2 in placebo (n=17) (p=0.066) at the end of 90 days Cortez-Navarrete 2018 – at the end of 12 weeks, mean A1c from the MC group (n=10) decreased by 0.7% vs placebo (n=10) by 0.5% (p<0.05)		Inconclusive	Very low

Comparing M. charantia with placebo, changes in fasting blood glucose, the effect estimate from 2 RCTs [3,5] was 0.31 mmol/L (95% CI: -1.99 to 2.61). Means and standard deviations from 3 RCTs[2,6,7], showed no significant changes in fasting blood glucose for the M. charantia at 6 grams per day[2] and 2 grams per day[7] trials, and a significant decrease by 21.89 mg/dL in the M. charantia at 1.2 grams per day[6] at the end of 90 days. The 2 RCTs with showed an A1c change of 0.28 (95% CI: 0.03, 0.54), whereas for the other 2 RCTs that had incalculable effect estimates, the A1c decreased significantly by 0.7 to 0.78%.

Table 28. Summary of findings: Effect of Momordica charantia vs. placebo in postprandial blood glucose

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Mean and SD of Postprandial blood sugar from baseline to end of study	2 RCT's [4,6] N=99	Lim 2010 – post prandial blood glucose for the MC (100 mg/kg, n=10) increased by 30.8 mg/dL vs. Placebo (n=10) at 43.3 mg/dL. (p=0.821) Suthar 2016a – decrease in post prandial blood glucose for MC 1.2 g/d (n = 62) was 44.95 mg/dL and Placebo (n = 17) was 7.06 mg/dL at the end of 90 days (*P* = 0.002)		Inconclusive	Very low

Of the two RCTs that analyzed postprandial glucose, only the trial with 1.2 grams per day of M. charantia showed a significant decrease in postprandial blood glucose by 44.95 mg/dL. Both RCTs had inconclusive results with very low certainty of evidence.

Table 29. Summary of findings: Effect of Momordica charantia vs. oral antihyperglycemic agents

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Change in **FBS** vs Metformin 1g/d	2 RCT's [8,9] N=103	12.89	6.72 to 19.7	Metformin better	Low
Mean change in **A1c** from baseline to week 15 vs Metformin 1g	1 RCT [9] N=109	0.35	0.07 to 0.63	Inconclusive	Very low
Mean change in **FBS** from baseline to week 10	1 RCT [10] N=60	MC group 4g/day (n=31) fbs decreased by 15.2 mg/dL Glibenclamide 5 mg/day (n=29) fbs decreased by 26.5 mg/dL		Inconclusive	Very low
Mean change in **PPS** after glucose load from baseline to week 10	1 RCT [10] N=60	MC group 4g/day (n=31) pps decreased by 6.3 mg/dL Glibenclamide 5 mg/day (n=29) pps decreased by 26.2 mg/dL		Glibenclamide better	Low

For the studies that compared M. charantia with metformin, fasting blood glucose improved with Metformin; whereas the changes in glycosylated hemoglobin A1c were not significant. Comparing M. charantia at 4 grams per day with glibenclamide 5 mg/day showed inconclusive results regarding fasting blood glucose, and that the latter produced better postprandial blood sugar results by week 10.

Safety outcomes

There were no clinically relevant shifts in the laboratory parameters in all treatment arms for those that recorded transaminase levels and creatinine. Only gastrointestinal symptoms, specified as diarrhoea, flatulence, constipation and nausea were mentioned as adverse events in the M. charantia group, but this did not lead to any dropouts in any of the studies.

Table 30. Safety Outcomes and Momordica charantia

	Number of Events in M. charantia	n	**Number of Events in Placebo**	**n**	
Diarrhea	4	20	1	20	Dans 2007
	5	19	0	19	Trakoon-osot 2013
Flatulence	8	19	2	19	Trakoon-osot 2013
Constipation	1	12	2	12	Cortez 2018
Nausea	2	12	1	12	Cortez 2018
Total (%)	**20 (24.4%)**	**82**	**6 (7.3%)**	**82**	

Certainty of evidence

The certainty of evidence is very low due to serious risks of bias, indirectness and imprecision. Dosages were inconsistent, with differing preparations of M. charantia. The RCT's that showed effect sizes also resulted in wide confidence intervals in terms of glycemic control.

Other Considerations

Cost

The recommended dose for Momordica charantia that was studied and available locally was 100 mg/kg/day.[4] For a 50 kg individual, it will be 500 mg/cap at 10 capsules per day or 5 grams of M. charantia per day.

There are currently 117 FDA registered Momordica charantia products (as FOOD), 20 of which contain plain Momordica charantia (without other herbs).[1] A 500 mg capsule costs from PhP 4.75 to 9.00.
For a 50 kg individual, the cost of M. charantia would be PhP 47.50 per day.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

1

Guideline Question 7. Should we use Chromium picolinate for glycemic control among adults with type 2 diabetes mellitus?

Recommendation 25. We do not recommend the use of Chromium picolinate (or any other Chromium preparation) among adults with T2DM as there is insufficient evidence to recommend its use.

Certainty of Evidence:	Very Low
Strength of recommendation:	Strong

Background

Some studies have shown that people with type 2 diabetes have lower blood levels of chromium than those without the disease. Chromium is an essential mineral that appears to have a beneficial role in the regulation of insulin action and its effects on carbohydrate, protein and lipid metabolism. Chromium is an important factor for enhancing insulin activity. Although the precise mechanism for this activity has not been identified, scientists have proposed that chromium binds to an oligopeptide to form chromodulin, a low-molecular-weight, chromium-binding substance that binds to and activates the insulin receptor to promote insulin action.

In 2001, the Food and Nutrition Board (FNB) of the National Academies of Sciences, Engineering, and Medicine considered chromium to be an essential nutrient based on its effects on insulin action. However, recent research has suggested that although chromium might have benefits at pharmacologic amounts (e.g., in the hundreds of mcg), it is not an essential mineral because an absence or deficiency of chromium does not produce abnormalities that can be reversed with the addition of chromium. Capsules are available in drug stores, mentioned in Brewer's yeast, as a diabetes mellitus supplement. There is a need to present evidence regarding its efficacy in diabetes.

Summary of the Evidence

Seven randomized controlled trials were included in this review, comprising adults with type 2 diabetes — 1 trial in newly diagnosed drug-naive patients, 5 in patients on oral antidiabetic agents (OAD), and 1 in patients on insulin. The intervention was Chromium picolinate (CrPic) given at the lowest dose of 3.82 to 19.8 µg in 1 study and 200 µg to 1000 µg in the remaining 6 studies, over a treatment period of 4 to 24 weeks. The comparator was placebo in 6 studies and glipizide 5 mg in 1 study. Outcomes assessed were improvement in fasting blood sugar (FBS), postprandial blood sugar (PPS), and HbA1c; one study assessed adverse events. Six of the 7 RCTs had serious to very serious risks of bias; 1 had low risk of bias.

Efficacy Outcomes

Chromium picolinate versus placebo — fasting blood glucose

For mean difference in FBS (mg/dL), a pooled analysis of 2 RCTs (N = 96) yielded an effect estimate of −19.5 (95% CI −25.41 to −13.58) — interpreted as Chromium picolinate with glipizide better than glipizide alone; certainty of evidence very low.

For change in mean FBS across 4 RCTs (N = 252): Anderson 1997 reported FBS decrease of 50.4 mg/dL with CrPic versus 21.6 mg/dL with placebo; Ghosh 2002 reported FBS decrease of 9 mg/dL with CrPic versus increase of 7.3 mg/dL with placebo; Ahmad 2016 reported FBS decrease of 12.43 mg/dL with CrPic versus 6.32 mg/dL with placebo; Iqbal 2009 reported FBS increase of 4.68 mg/dL with CrPic versus decrease of 0.72 mg/dL with placebo. Of these 4 RCTs, only Anderson 1997 showed a significant change in FBS after 16 weeks of treatment with 19.2 µmol CrPic. Overall interpretation: inconclusive; certainty very low.

Chromium picolinate versus placebo — HbA1c

For change in A1c, a pooled analysis of 3 RCTs (N = 159) yielded an effect estimate of −0.5 (95% CI −0.74 to −0.25) — interpretation inconclusive; certainty very low.

For change in mean A1c across 4 RCTs (N = 252): Anderson 1997 reported A1c decrease of 2.1% with CrPic versus 0.4% with placebo; Ghosh 2002 reported no change in A1c with CrPic versus increase of 0.7% with placebo; Ahmad 2016 reported A1c decrease of 1.48% with CrPic versus 1.64% with placebo; Iqbal 2009 reported A1c increase of 0.08% with CrPic versus 0.05% with placebo. Of these 4 RCTs, only Anderson 1997 showed a significant change in A1c after 16 weeks of treatment with 19.2 µmol CrPic. Overall interpretation: inconclusive; certainty very low.

Chromium picolinate versus placebo — postprandial blood sugar

For change in mean PPS across 2 RCTs (N = 152): Anderson 1997 reported PPS decrease of 75.6 mg/dL with CrPic versus 21.6 mg/dL with placebo; Ghosh 2002 reported PPS decrease of 36 mg/dL with CrPic versus no change with placebo. Of these 2 RCTs, only Anderson showed a significant change in FBS after 16 weeks of treatment with 19.2 µmol CrPic [source attributes the significance comment to FBS, as transcribed]. Overall interpretation: inconclusive; certainty very low.

Safety outcomes

No significant changes in AST, ALT, or creatinine were noted across 3 RCTs comparing CrPic with placebo. In Ahmad 2016, no change in ALT was observed in either CrPic or placebo arms. In Anderson 1997, no general toxicity was reported in either arm. In Ghosh 2002, no changes were noted in hemoglobin level, total and differential leukocyte counts, platelet count, serum urea, creatinine, ALT, or alkaline phosphatase activity in either arm.

Table 31. Summary of Findings: CrPic vs Placebo

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Mean Difference in FBS (mg/dL)	2 RCTs N = 96	−19.5	−25.41 to −13.58	Chromium better than placebo *(CrPic with Glipizide over Glipizide alone)*	Very Low
Change in Mean FBS	4 RCTs N = 252	Anderson 1997 FBS decreased by 50.4 mg/dL for CrPic; 21.6 mg/dL for placebo Ghosh 2002 FBS decreased by 9 mg/dL for CrPic; increased by 7.3 mg/dL for placebo Ahmad 2016 FBS decreased by 12.43 mg/dL for CrPic; decreased by 6.32 mg/dL for placebo Iqbal 2009 FBS increased by 4.68 mg/dL for CrPic; decreased by 0.72 mg/dL for placebo Out of all 4 RCTs only Anderson showed a significant change in FBS after 16 weeks of treatment with 19.2 µmol CrPic.	—	Inconclusive	Very Low
Change in A1c	3 RCTs N = 159	−0.5	−0.74 to −0.25	Inconclusive	Very Low
Change in Mean A1c	4 RCTs N = 252	Anderson 1997 A1c decreased by 2.1% for CrPic; 0.4% decreased for placebo Ghosh 2002 A1c with no change for CrPic; increased by 0.7% for placebo Ahmad 2016 A1c decreased by 1.48% for CrPic; decreased by 1.64% for placebo Iqbal 2009 A1c increased by 0.08% for CrPic; increased by 0.05% for placebo Out of all 4 RCTs only Anderson showed a significant change in A1c after 16 weeks of treatment with 19.2 µmol CrPic.	—	Inconclusive	Very Low

Certainty of Evidence

The overall certainty of evidence is very low. Across all efficacy outcomes the source rates the certainty as Very Low, attributable to risk of bias, inconsistency (different dosages and chromium preparations), indirectness, and imprecision (small populations, wide confidence intervals).

Other considerations

Cost

As of 04 May 2023, locally available chromium picolinate preparations were priced as follows: Chromium picolinate (Healthy Options brand) 200 µg, 100 capsules at PhP 799.00 — equivalent to PhP 7.99 per capsule, or PhP 39.95 per day at 5 capsules per day; 21st Century Chromium Picolinate (iHerb) 200 µg, 100 tablets at PhP 222.30 — equivalent to PhP 2.22 per tablet, or PhP 11.10 per day at 5 tablets per day.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 8. Should we recommend the use Andrographis paniculata (Serpentina) among adults with T2DM?

Recommendation 26. We do not recommend the use of Andrographis paniculata (Serpentina)* for glycemic control of adults with T2DM.

Certainty of Evidence: Very Low
Strength of recommendation: Strong

****Remarks**: Published studies are mostly in preclinical, phase I or II, searching for its role in the treatment of a lot of other chronic illnesses, including viral infections.*

Background

Andrographis paniculata, commonly known as serpentina, sinta, or King of Bitters, is a medicinal herb commonly growing among the tropical countries in Asia. It is traditionally used as treatment for inflammation, upper respiratory tract infection, diabetes, hypertension, flu, diarrhea, and liver problems. Extracts from this plant have been documented to exhibit antimicrobial, anti-inflammatory, and antioxidant activities.

Capsules containing this herb have been made available to the public and are also mixed with FDA-registered ampalaya capsules as food and advertised as supplements for diabetes. Andrographis paniculata is also featured on PCHRD's website. There is a need to present evidence regarding its efficacy.

Summary of the Evidence

Two studies — 1 randomized controlled trial and 1 open-label clinical trial — were included for the use of Andrographis paniculata in glycemic control, with a total of 55 individuals analyzed.

Characteristics of Included Studies

Two studies met the inclusion criteria, with a total of 55 participants. One open-label clinical trial (Agarwal 2005, Malaysia, N = 20) included adults aged 35 to 70 years with type 2 diabetes mellitus, A1c 7 to 10%, and FPG 7 to 15 mmol/L; the intervention was 600 mg capsules of dried leaves of Andrographis paniculata titrated up to 1.8 g daily (300 mg/cap, 2 capsules with breakfast as add-on to current treatment; if FPG > 7 mmol/L during follow-up the dose was increased to 3 capsules BID) for 12 weeks, with no separate control arm — outcomes were assessed against baseline. One randomized double-blind placebo-controlled crossover trial (Tarigan 2022, Indonesia, N = 35) included adults with prediabetes by oral glucose tolerance test; the intervention was a 550 mg "Sambiloto" capsule given for 2 weeks then crossed over to placebo. Outcomes assessed by Agarwal 2005 were fasting blood sugar, AST, ALT, creatinine, urine glucose, and urine protein; outcomes assessed by Tarigan 2022 were GLP-1, fasting insulin, 2-hour postprandial insulin, homeostasis model assessment of insulin resistance (HOMA-IR), fasting blood glucose, 2-hour postprandial blood glucose, glycated albumin, and DPP-4 before and after the intervention. Agarwal 2005 was assessed as high risk of bias; Tarigan 2022 was assessed as low risk of bias overall.

Table 32. Characteristics of included studies

Author / Year	Study Design (RoB)	Country	N	Population	Intervention	Control	Outcomes
Agarwal 2005 (Malaysian Journal of Medical Sciences, 2005;12(1):13-19)	Open-label clinical trial (RoB: High)	Malaysia	20	Adults with T2DM, 35 to 70 yo; A1c 7 to 10%; FPG 7 to 15 mmol/L	600 mg capsule of dried leaves of A. paniculata titrated up to 1.8 g daily (300 mg/cap, 2 caps with breakfast; increased to 3 caps BID if FPG > 7 mmol/L); 12 weeks	(no separate control arm - baseline comparison)	FBS, AST, ALT, creatinine; urine glucose; urine protein
Tarigan 2022 (Evidence-Based Complementary and Alternative Medicine 2022; Article ID 1535703, 7 pp.)	Randomized double-blind placebo-controlled crossover trial (RoB: Low)	Indonesia	35	Adults with prediabetes by OGTT	550 mg "Sambiloto" capsule for 2 weeks then crossover	Placebo	GLP-1; fasting insulin; 2-h postprandial insulin; HOMA-IR; fasting blood glucose; 2-h postprandial blood glucose; glycated albumin; DPP-4

Summary of Findings

In the open-label clinical trial of dried leaves of Andrographis paniculata in adults with type 2 diabetes (Agarwal 2005), from baseline to 12 weeks, fasting blood sugar showed a change of 0.48 mmol/L (% difference 4.71, $p > 0.05$); HbA1c showed a change of 0.47% (% difference 5.46, $p < 0.01$); fasting insulin showed a change of 2.34 IU/L (% difference 20.93, $p < 0.003$).

In the randomized double-blind placebo-controlled crossover trial of Sambiloto (Andrographis paniculata) in adults with prediabetes by OGTT (Tarigan 2022), mean (SD) changes from baseline were: fasting blood glucose -4.0 (15.4) mg/dL; 2-hour postprandial blood glucose +6.5 (35.5) mg/dL; fasting insulin 0 (-30 to -14.8) mU/L.

Across all assessed outcomes, the interpretation per source was inconclusive and the certainty of evidence was very low.

Table 33. Summary of Findings: Andrographis paniculata, baseline to end of study

Outcome	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
FBS (mmol/L)	1 CT (Agarwal 2005); N = 20; 12 weeks	0.48 mmol/L (% difference 4.71, $p > 0.05$)	—	Inconclusive	Very Low

Outcome	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
A1c	1 CT (Agarwal 2005); N = 20; 12 weeks	0.47% (% difference 5.46, p < 0.01)	—	(not specified in source)	Very Low
Fasting insulin (IU/L)	1 CT (Agarwal 2005); N = 20; 12 weeks	2.34 (% difference 20.93, p < 0.003)	—	(not specified in source)	Very Low
Fasting blood glucose (mg/dL), mean (SD)	1 RCT (Tarigan 2022); N = 35	-4.0 (15.4)	—	Inconclusive	Very Low
2-h postprandial glucose (mg/dL), mean (SD)	1 RCT (Tarigan 2022); N = 35	+6.5 (35.5)	—	(not specified in source)	Very Low
Fasting insulin (mU/L), mean (SD)	1 RCT (Tarigan 2022); N = 35	0	-30 to -14.8	(not specified in source)	Very Low

Certainty of Evidence

The overall certainty of evidence is very low. The open-label trial (Agarwal 2005) had very serious risk of bias (no allocation concealment, no randomization, non-blinding). The randomized trial (Tarigan 2022) had low risk of bias overall, with blinding of outcome assessors not specified. Indirectness and imprecision were judged serious; inconsistency was low. Across all outcomes the source-rated certainty of evidence was Very Low.

Other considerations

Cost

No local cost-effectiveness studies were found on the use of Serpentina among adult Filipinos with type 2 diabetes mellitus. No cost-effectiveness studies were found for low-resource settings or populations similar to the Philippines either.

Table 34. Traceable Price Table

Product / pack	Pack size	Price (PHP)	Per capsule	Source
Natural Herbs Serpentina Capsules (No Brand)	100 caps	PHP 199.00 (promo; list PHP 480)	**PHP 1.99**	Lazada PH
Organic Serpentina Capsules + free refill (Nature's Elements)	100 caps	PHP 418.00	**PHP 4.18**	Shopee (via BigGo)
Serpentina Capsules (JMJ Herbal Products)	100 caps	PHP 350.00 (out of stock)	**PHP 3.50**	Lazada PH
Amazing Food Supplement Serpentina 500 mg (FDA-registered)	100 caps + 30 free	PHP 482.00 (typical listing)	**approx. PHP 3.71**	Lazada PH (Lazmall)
Organic Herb Serpentina 400-500 mg, Buy 2 Get 1	230 caps (2x100 + 30)	PHP 700.00 (typical bundle)	**approx. PHP 3.04**	Organic Health Pharma

Note: Prices observed on listings retrieved on the dates noted in references; promotional prices are volatile and may differ at time of reading.

Derived course-cost estimates

- At ~PHP 3.50/capsule, 2 capsules/day: ~PHP 7/day, ~PHP 210/month.
- At ~PHP 3.50/capsule, 3 capsules/day: ~PHP 10.50/day, ~PHP 315/month.
- At ~PHP 1.99/capsule (cheapest listing), 2 capsules/day: ~PHP 4/day, ~PHP 120/month.

Course-cost figures are author-derived from the per-capsule prices and label dosing; they are arithmetic illustrations, not observed prices.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 9. Should we recommend the routine use of vitamin B12 (methylcobalamin or cyanocobalamin) supplementation among adults with T2DM on metformin?

Recommendation 27. We neither recommend for nor against supplementation with methylcobalamin / Vitamin B12 among adults with T2DM on metformin.

Certainty of Evidence:	Very Low
Strength of recommendation:	Weak

Background

Currently there are no studies indicating a direct link between diabetes and Vitamin B12 deficiency. However, it has been established that long-term metformin use may lead to B12 deficiency. The American Diabetes Association recommends to consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy.

Metformin is thought to induce malabsorption of vitamin B-12 and intrinsic factor in the ileum, an effect that can be reversed by increasing calcium intake. The consequences of clinically important decreases in vitamin B-12 concentrations - such as macrocytic anaemia, neuropathy, and mental changes - can be profound. There is no consensus on the issue of whether "asymptomatic" vitamin B-12 deficiency should be treated.

Supporting evidence on metformin and B12 deficiency: the Diabetes Prevention Program Outcomes Study (Aroda 2016, post-hoc analysis) reported a 13% increased risk of B12 deficiency per year of total metformin use, with greater prevalence of anemia at a mean of 5 years after randomization and B12 deficiency seen even in the absence of anemia; peripheral neuropathy was a significant clinical consequence of B12 deficiency, higher among those on metformin. De Jager 2010 found that long-term treatment with metformin in patients with type 2 diabetes receiving insulin increases the risk of vitamin B-12 deficiency, resulting in higher levels of homocysteine, with the negative effect of metformin on vitamin B-12 concentrations increasing over time.

Summary of the Evidence

Five randomized controlled trials were found on the use of Vitamin B12 supplementation among adult individuals being treated for type 2 diabetes, with a total of 641 subjects analyzed. Of the 5 RCTs, all individuals were already on oral antidiabetic agents - 1 study included patients on Metformin alone, and 4 studies included patients on different oral antidiabetic agents.

Characteristics of Included Studies

All included studies included only adults who were diagnosed with type 2 diabetes. One study included older individuals (>60 years old) who were already on Metformin for at least 4 years (Didangelos 2021); 4 studies included persons with diabetes on oral antidiabetic agents other than Metformin alone, 2 of which specified older individuals aged >60 to >70 years old (Didangelos 2021; Kwok 2016/2017), and 2 specified adults more broadly (Satapathy 2020; Sharma 2021; Talaei 2009). Vitamin B12 was given at a

dose of 500 µg to 1500 µg per orem per day, ranging from 8 weeks to 52 weeks (1 year); Vitamin B12 was also given intramuscularly at 2000 µg twice weekly for 12 weeks (Talaei 2009). Control groups were placebo (Didangelos 2021; Kwok 2016/2017), Vitamin B12 added to folic acid or folic acid alone (Satapathy 2020), Vitamin B12 added to pregabalin or duloxetine (Sharma 2021), or compared to nortriptyline alone (Talaei 2009). Pertinent outcomes were improvement in cognition (Kwok 2016/2017), improvement in painful neuropathy score (Didangelos 2021; Sharma 2021; Talaei 2009), and improvement in metabolic parameters (Satapathy 2020). Three of the 5 studies were assessed as having serious risks of bias (common issues on imprecision and indirectness); 2 had low risks of bias.

Table 35. Characteristics of included studies

Author / Year	Study Design	Country	N	Population	Intervention	Control	Outcomes
Didangelos et al. 2021	RCT, Double-blind	Greece	90	T2DM >60 yo on Metformin for at least 4 years; with peripheral and autonomic DN; B12 <400 pmol/L	Methylcobalamin 1000 µg/day x 1 year	Placebo	Cardiovascular autonomic reflex tests (CARTs); neuropathy tests (MNSIQ, MNSIE, DQoL, SNAP, SNCV, VPT, MCR, PI, postural hypotension, pain score; ESCF, ESCH)
Kwok et al. 2017	RCT	Hong Kong	271	T2DM >70 yo; B12 150 to 300 pmol/L	Methylcobalamin 1000 µg/day x 27 months; N = 137 (116 on Metformin)	Placebo; N = 134 (111 on Metformin)	Clinical Dementia Rating; Neuropsychological test battery Z-scores
Satapathy et al. 2020	RCT, open label	India	80	T2DM 30 to 65 yo on stable doses of oral antihyperglycemic agents (Metformin and/or SU)	(A) folic acid 5 mg (18); (B) methylcobalamin 500 µg od (19); (C) folic acid + methylcobalamin (19); x 8 weeks	Oral antidiabetic agents alone (19)	Change in A1c, lipid profile, FBS, plasma insulin, HOMA-IR, homocysteine, adiponectin, TNF-alpha, IL-6, hsCRP
Sharma et al. 2021	RCT	India	100	T2DM with painful diabetic neuropathy	(B) Pregabalin 150 mg + methylcobalamin (29); (C) Duloxetine 60 mg + methylcobalamin (29); x 12 weeks	(A) Methylcobalamin 1500 µg/day (26)	Vibration sensation (tuning fork test); pressure sensation (monofilament test); thermal sensation (thermo-tube test); VAS score
Talaei et al. 2009	RCT, single-blind	Iran	100	T2DM >3 years; A1c <10.5	B12 2000 µg IM 2x a week x 3 months	Nortriptyline 10 mg p.o. at night	Pain, tingling, paresthesia; position, vibration, pinprick; FBS, A1c, NCV

Summary of Findings

The effects of Vitamin B12 supplementation among persons with diabetes on oral antihyperglycemic agents in terms of cognition, painful neuropathies, and improvement of metabolic parameters were inconclusive.

For improvement in pain score (3 RCTs): Didangelos 2021 reported $p < 0.001$ for methylcobalamin 1000 µg vs placebo in pain score, SNCV, SNAP, ESCF, vibration perception, MNSIQ, and QoL, with no significant difference in cardiovascular autonomic reflex tests (CARTs) and MNSIE; Sharma 2021 reported the lowest improvement in vibration perception, pressure sensation, and thermal sensitivity, and the lowest decrease in VAS score, in the methylcobalamin-alone arm; Talaei 2009 reported significant improvement in pain, tingling, and paresthesias ($p < 0.001$) but non-significant change in position, vibration, and pinprick versus nortriptyline. Overall interpretation: inconclusive; combination of methylcobalamin + duloxetine more efficacious in Sharma 2021; B12 intramuscular better than nortriptyline in mostly small myelinated nerve fibers (except pinprick) in Talaei 2009. Certainty: very low.

For improvement in cognition (1 RCT, Kwok 2016/2017): no significant difference in clinical dementia scores (CDR) or neuropsychological test battery Z-scores (NTB); methylcobalamin 1000 µg not better than placebo. Interpretation: inconclusive. Certainty: very low.

For improvement in metabolic parameters (1 RCT, Satapathy 2020): methylcobalamin 500 µg/day x 8 weeks - mean change from baseline A1c −1.2% (95% CI −3.2 to −0.4, $p = 0.043$); HOMA2-IR −1.3 (95% CI −2.1 to −0.25, $p < 0.001$). Methylcobalamin 500 µg/day + folic acid - A1c −1.5 (95% CI −2.5 to −0.6, $p = 0.02$); HOMA2-IR −1.5 (95% CI −2.0 to −0.4). Lipid profile showed no significant difference among all groups. Other parameters of inflammation with significant changes were homocysteine, adiponectin, TNF-alpha, and IL-6 for both methylcobalamin 500 µg/day and methylcobalamin with folic acid. Interpretation: inconclusive; methylcobalamin 500 µg/day with folic acid improves A1c and insulin resistance but not plasma glucose and lipid profile. The overall certainty of evidence is very low.

Table 36. Summary of findings: Vitamin B12 supplementation in adults with type 2 diabetes

Outcome	Basis	Effect Estimate / Findings	Interpretation	Certainty of Evidence
Improvement in pain score	3 RCTs (Didangelos 2021; Sharma 2021; Talaei 2009)	Didangelos 2021: $p < 0.001$ for MC 1000 µg vs placebo in pain score, SNCV, SNAP, ESCF, vibration perception, MNSIQ, QoL; no significant difference in CARTs, MNSIE. Sharma 2021: vibration perception, pressure sensation, thermal sensitivity - lowest improvement with MC alone; decrease in VAS score - lowest on MC alone. Talaei 2009: pain, tingling, and paresthesias with significant improvement ($p < 0.001$); position, vibration, pinprick - NS vs nortriptyline.	Inconclusive. Combination of MC + duloxetine more efficacious; B12 IM better than nortriptyline in mostly small myelinated nerve fibers (except pinprick).	Very Low

Outcome	Basis	Effect Estimate / Findings	Interpretation	Certainty of Evidence
Improvement in cognition	1 RCT (Kwok 2016/2017)	No significant difference in clinical dementia scores (CDR) or neuropsychological test battery Z-scores (NTB).	Inconclusive. MC 1000 µg not better than placebo.	Very Low
Improvement in metabolic parameters	1 RCT (Satapathy 2020)	MC 500 µg/day x 8 weeks: A1c −1.2% (95% CI −3.2 to −0.4, p = 0.043); HOMA2-IR −1.3 (95% CI −2.1 to −0.25, p < 0.001). MC 500 µg/day + folic acid: A1c −1.5 (95% CI −2.5 to −0.6, p = 0.02); HOMA2-IR −1.5 (95% CI −2.0 to −0.4). Lipid profile no significant difference. Significant changes in homocysteine, adiponectin, TNF-alpha, IL-6 for both MC and MC + folic acid.	Inconclusive. MC 500 µg/day with folic acid improves A1c and insulin resistance but not plasma glucose and lipid profile.	Very Low

Abbreviations: MC = methylcobalamin; SNCV = sural nerve conduction velocity; SNAP = sural nerve action potential (amplitude); ESCF / ESCH = electrochemical skin conductance in feet / hands; MNSIQ / MNSIE = Michigan Neuropathy Screening Instrument Questionnaire / Examination; CARTs = cardiovascular autonomic reflex tests; QoL = Quality of Life; VAS = visual analogue scale; NCV = nerve conduction velocity; HOMA-IR = homeostasis model assessment of insulin resistance; CDR = Clinical Dementia Rating; NTB = neuropsychological test battery.

Safety outcomes

All 5 RCTs mentioned the lack of adverse events in all treatment arms with the use of Vitamin B12 per orem or intramuscularly at the doses administered.

Certainty of Evidence

The certainty of evidence is very low due to serious risks of bias, indirectness, and imprecision. Dosages and presentation of Vitamin B12 were inconsistent across studies. The only RCT that showed a significant effect on any outcome was performed on individuals given methylcobalamin 500 µg/day with folic acid (Satapathy 2020). Across the body of evidence, 3 of 5 RCTs had serious risks of bias and 2 had low risk of bias; certainty was rated Very Low across all outcomes.

Other considerations

Cost

Vitamin B12 (methylcobalamin) is available in the Philippines as a registered drug in oral and intramuscular formulations. Per the DOH Drug Price Reference Index (DPRI) 2022, a 500 µg/tab methylcobalamin tablet costs PhP 13.20, and a 500 mcg/mL, 1 mL solution-for-injection ampule costs PhP 321.75. At a typical oral dose of 1000 µg/day, the cost is approximately PhP 26.40 per day or PhP 792 per 30-day month. At an intramuscular dose of 2000 µg twice weekly (per Talaei 2009 protocol), the cost is approximately PhP 1,287 per dose or PhP 2,574 per week (PhP 10,296 per month). There are no published cost-effectiveness studies on the use of Vitamin B12 supplementation for the management of

type 2 diabetes mellitus among adult Filipinos; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Table 37. Locally available Vitamin B12 (methylcobalamin) preparations (DPRI 2022)

Preparation	Unit price (PhP)	Typical dose	Cost per day (PhP)	Cost per month (PhP)
Methylcobalamin 500 µg/tab (per os)	13.20 per tablet	1000 µg/day (2 tablets/day)	26.40	792.00
Methylcobalamin 500 mcg/mL, 1 mL Solution for Injection ampule (intramuscular)	321.75 per ampule (source notes 1,287 per dose; 4 ampules per dose)	2000 µg IM twice weekly (per Talaei 2009)	(per dose: 1,287; per week: 2,574)	10,296.00

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 10. Should we use *Costus igneus* (Insulin Plant) for glycemic control among adults with T2DM?

Recommendation 28. We recommend against the use of *Costus igneus* (Insulin plant) among adults with T2DM.

Certainty of Evidence:	Very Low
Strength of recommendation:	Strong

Background

Costus igneus, commonly known as Insulin Plant in India, belongs to the family Costaceae. Consumption of the leaves are believed to lower blood glucose levels, and diabetics who consumed the leaves of this plant did report a fall in their blood glucose levels. It is popular in social media. There is a need to present evidence regarding its efficacy (Shetty 2010, International Journal of Ayurveda Research 1(2):100-102).

Summary of the Evidence

No randomized controlled trials were found on the use of Costus igneus (Insulin Plant) in humans with type 2 diabetes mellitus. One preclinical study (in-vitro and in-vivo in mice; Joshi 2013) and one in-vivo toxicology study in mice (Hardikar 2016) were included. Evidence for the efficacy of Costus igneus or Costus pictus for glycemic control in humans is lacking.

Characteristics of Included Studies

Two preclinical studies were included. Joshi 2013 (India) was an in-vitro and in-vivo study evaluating an insulin-like protein (ILP) purified from the leaf extract of Costus igneus. The in-vitro arm used RIN5f insulin-responsive cell line (10^4 cells/well in a 24-well plate, with baseline 500 mM glucose added with fetal bovine serum), at ILP doses of 25, 50, and 100 µg. The in-vivo arm used streptozotocin-induced diabetic mice (3 mg/25 g STZ in citrate buffer pH 4.5, intraperitoneal; glucose 2 g/kg body weight orally), with intervention 50 µg oral ILP and 50 µg intraperitoneal ILP; subcutaneous insulin 2 U/25 g body weight served as positive control. In-vitro outcomes were the amount of glucose utilized by cells from 0 to 180 minutes; in-vivo outcomes were glucose reduction at 30, 60, 90, 120, and 150 minutes.

Hardikar 2016 (India) was an in-vivo toxicology study in 4 streptozotocin-induced diabetic mice, orally given ILP at 8 mg/kg (i.e. 1.43 mM/kg body weight) — 4-fold the usual dose (2 mg/kg from previous studies) — for 21 days. The outcome was histologic analysis of the pancreas, adipose tissue, kidney, heart, and liver. Per the source, no evidence of harm in tissues was reported.

Table 38. Characteristics of included studies

Author / Year (citation)	Study Design	Country	N	Population	Intervention	Control	Outcomes
Joshi 2013 (Biochemical and Biophysical Research Communications 436(2013):278-282) - Orally active hypoglycemic protein from Costus igneus N. E. Br.: An in vitro and in vivo study	In-vitro and in-vivo	India	N/A	In-vitro: RIN5f (insulin-responsive cell line). In-vivo: streptozotocin-induced diabetic mice (3 mg/25 g STZ in citrate buffer pH 4.5, intraperitoneal; glucose 2 g/kg BW orally).	Insulin-like protein (ILP) purified from leaf extract. In-vitro: 25, 50, 100 µg. In-vivo: 50 µg oral ILP and 50 µg intraperitoneal ILP.	In-vitro: baseline 500 mM glucose added in 10^4 cells/well of 24-well plate with fetal bovine serum. In-vivo: insulin 2 U/25 g body weight subcutaneous as positive control.	In-vitro: amount of glucose utilized by cells from 0 to 180 min. In-vivo: glucose reduction at 30, 60, 90, 120, 150 min.
Hardikar 2016 (http://dx.doi.org/10.1016/j.phytochem.2016.02.001) - Elucidation of hypoglycemic action and toxicity studies of insulin-like protein from Costus igneus	In-vivo (toxicology)	India	N/A	4 streptozotocin-induced diabetic mice.	ILP given orally at 8 mg/kg (1.43 mM/kg body weight) - 4-fold usual dose (2 mg/kg from previous studies) for 21 days.	(none)	Histologic analysis of pancreas, adipose tissue, kidney, heart, and liver.

Summary of Findings

Joshi 2013 reported results for ILP versus insulin in mice (figures presented in source slide 5); the source does not provide a tabulated effect estimate for Insulin Plant glycemic outcomes in a tabular Summary-of-Findings format. Hardikar 2016 reported no evidence of harm in pancreas, adipose tissue, kidney, heart, and liver tissues at the 8 mg/kg dose over 21 days.

From the earlier EAMC/UPPGH Sep 2022 draft (background context only): Gireesh 2009 reported that Costus pictus leaf extract significantly increased glucose-induced insulin secretion at 0.5 mg/mL in in-vitro human pancreatic islet cells. Pareek 2010 reported that ethanolic extract of Costus pictus leaf showed no direct peripheral action on GLUT4 translocation and glucose uptake at 300 µg/mL, comparable with insulin and metformin.

Safety outcomes

Per Hardikar 2016 (in-vivo mouse toxicology, ILP 8 mg/kg orally for 21 days), there was no evidence of harm in histologic analysis of the pancreas, adipose tissue, kidney, heart, and liver.

In rodents, acute toxicity studies showed that administration of aqueous extract 1 g/kg body weight/day for 30 days produced no effect on general behavior and all animals survived. However, a study using the methanolic extract of C. igneus indicated toxicity at 250 mg/kg body weight. Palmitic acid was found in the stem, leaf, and rhizome oils of C. pictus (Jose & Reddy 2010); palmitic acid is known to induce damage in healthy adult rat cardiomyocytes and is a precursor for the development of coronary heart diseases. Based on these preclinical findings, the earlier draft concluded that the use of C. pictus leaves for treatment may cause serious cardiac diseases and may not be recommended for persons with diabetes.

Certainty of Evidence

The overall certainty of evidence is very low. No randomized controlled trials in humans were identified; the available evidence base comprises preclinical in-vitro and in-vivo studies in rodent models only, which carry serious indirectness for human clinical decision-making.

Other considerations

Cost

There are no published cost-effectiveness studies on the use of Costus igneus (Insulin Plant) for the management of type 2 diabetes mellitus among adult Filipinos; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found assessing patient's values or preferences regarding this topic.

Guideline Question 11. Should we recommend a fasting plasma glucose (FPG) target of 80 to 130 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

Recommendation 29. We suggest a general fasting plasma glucose (FPG) goal of 80 to 130 mg/dL to approximate the target HbA1c of <7% among nonpregnant adults with T2DM.

Certainty of Evidence: Low
Strength of recommendation: Weak

Background

Fasting plasma glucose (FPG), although used in the diagnosis of diabetes mellitus, is not a well-studied measure of long-term glycemic control. None of the guidelines mentioned a laboratory-measured fasting plasma glucose target for glycemic control. Actual FPG targets that lead to the reduction in clinical outcomes have not been specifically defined. For monitoring in low-resource settings where HbA1c is not immediately available, fasting plasma glucose may be the most readily available test to predict probability of achieving good glycemic control.

FPG cannot be used as the basis of glycemic control alone. It has use in conjunction with other parameters in monitoring glycemic variability and risk of hypoglycemia. It is not used in clinical trials as the primary metric to correlate with glycemic control and development of complications. However, fasting plasma glucose may be checked in certain situations such as immediate monitoring of response to therapy, determination of the risk for hypoglycemia, and investigation of discordant levels of BGM and HbA1c.

Summary of the Evidence

Two meta-analyses formed the evidence base: a meta-analysis of 7 studies correlating FPG with HbA1c, and a meta-analysis assessing the effects of reduction of FPG and postprandial plasma glucose (PPG) on cardiovascular outcomes in randomized controlled trials (Monami et al. 2013). Supporting evidence was drawn from Ketema and Kibret (2015), a meta-analysis of 14 studies estimating the relative contribution of FPG and PPG to overall hyperglycemia, and the international A1C-Derived Average Glucose (ADAG) study in 507 adults with type 1, type 2, or no diabetes.

Characteristics of Included Studies

The primary evidence base for FPG-HbA1c correlation was the meta-analysis of Monami et al. (2013), which included 7 studies correlating fasting plasma glucose and HbA1c in adult populations. A second meta-analysis (Monami et al. 2013) assessed the effect of FPG and PPG reduction on cardiovascular outcomes in trials with a between-group FPG or PPG difference of greater than 1 mmol/L (18 mg/dL). Supporting evidence included Ketema and Kibret (2015) - a meta-analysis of 14 studies estimating relative contributions of FPG and PPG to overall hyperglycemia - and the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between HbA1c and frequent blood glucose monitoring and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes.

The Cochrane risk of bias tool was used to assess the included RCTs; risks of bias were judged low and certainty of evidence moderate to high.

Summary of Findings

In the meta-analysis of 7 studies (Ketema and Kibret 2015), the Pearson correlation coefficient of FPG and HbA1c was 0.61 (95% CI 0.48 to 0.72), indicating a moderate positive correlation. The correlation coefficient was significantly greater in those who had FPG > 120 mg/dL. The well-powered studies in this meta-analysis correlate an FPG level of 130 mg/dL to the HbA1c target of 7%. In a meta-analysis of 14 studies that estimated the relative contribution of FPG and PPG to overall hyperglycemia, the pooled correlation coefficient (r) of FPG with HbA1c was 0.61 (P < 0.001, 95% CI 0.48 to 0.72), while PPG had a pooled correlation coefficient of 0.68 (P < 0.001, 95% CI 0.56 to 0.75).

In the meta-analysis assessing the effects of FPG and PPG reduction on cardiovascular outcomes, the Mantel-Haenszel Odds Ratio (MH-OR) for trials with a between-group FPG difference greater than 1 mmol/L (18 mg/dL) produced a significantly lower all-cause mortality (MH-OR 0.90, 95% CI 0.81 to 0.99, P = 0.03) and cardiovascular mortality (MH-OR 0.86, 95% CI 0.76 to 0.97, P = 0.012), with no significant effect on the incidence of major cardiovascular events. In contrast, the MH-OR for cardiovascular events, all-cause and cardiovascular mortality in trials with a between-group PPG difference greater than 1 mmol/L was not significantly different from controls.

Based on the international A1C-Derived Average Glucose (ADAG) study, the average blood glucose levels at premeal, postmeal, and bedtime had a strong correlation (r = 0.92) with the specified HbA1c levels. Most guidelines used FPG values that correlate best with the recommended HbA1c target of <7%. Based mainly on expert opinion, the majority of these guidelines recommend an FPG or preprandial capillary blood glucose range of 80 to 130 mg/dL (4.4 to 7.2 mmol/L).

Table 38. Estimated average glucose (eAG) at premeal, postmeal, and bedtime against specified HbA1c levels (from the international A1C-Derived Average Glucose study)

HbA1c (%)	mg/dL (95% CI)	mmol/L (95% CI)
5	97 (76 to 120)	5.4 (4.2 to 6.7)
6	126 (100 to 152)	7.0 (5.5 to 8.5)
7	154 (123 to 185)	8.6 (6.8 to 10.3)
8	183 (147 to 217)	10.2 (8.1 to 12.1)
9	212 (170 to 249)	11.8 (9.4 to 13.9)
10	240 (193 to 282)	13.4 (10.7 to 15.7)
11	269 (217 to 314)	14.9 (12.0 to 17.5)
12	298 (240 to 347)	16.5 (13.3 to 19.3)

Table 39. Summary of evidence: effect of fasting plasma glucose reduction on cardiovascular outcomes (Monami et al. 2013; trials with a between-group difference of FPG greater than 1 mmol/L [18 mg/dL])

Outcome	No. of studies	Effect Estimate (OR)	95% CI	Certainty of Evidence
Major cardiovascular events	13 RCTs	0.950	0.818 to 1.105	Moderate
All-cause mortality	8 RCTs	0.904	0.825 to 0.991	Moderate
Cardiovascular mortality	8 RCTs	0.857	0.760 to 0.967	Moderate

Certainty of Evidence

For the RCTs, the risks of bias were low and the certainty of evidence was moderate to high. The draft recommendation classifies the overall certainty for the FPG goal recommendation as Low, reflecting the indirect nature of using a correlation-based target rather than a directly trial-tested clinical endpoint.

Other considerations

Cost

Fasting plasma glucose (FPG) is a routinely available laboratory test in the Philippines. The cost of FPG varies from PhP 100 to PhP 500 depending on the healthcare facility. FPG is readily available in most primary care facilities and in all secondary and tertiary facilities. There are no published cost-effectiveness studies on the use of an FPG target of 80 to 130 mg/dL to approximate an HbA1c target of <7% among adult Filipinos with type 2 diabetes mellitus; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find any study that addressed the patient's values or preferences.

Guideline Question 12. Should we recommend an HbA1c target of <7% for glycemic control among nonpregnant adults with T2DM?

Recommendation 30. We recommend an HbA1c goal of <7% using an NGSP-certified method among nonpregnant adults with T2DM as long as it can be safely achieved without significant hypoglycemia

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 31. We recommend a less stringent HbA1c goal of <8% among nonpregnant adults with T2DM and a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications or severe comorbid conditions.

Certainty of Evidence: High
Strength of recommendation: Strong

Recommendation 32. We recommend an individualized HbA1c goal taking into account life expectancy, disease duration, presence or absence of complications, comorbid conditions, risk for hypoglycemia and other social determinants of health such as patient support and resources.

Certainty of Evidence: High
Strength of recommendation: Strong

Background

Glycosylated hemoglobin A1c (HbA1c) is the most widely used laboratory test to monitor glycemic control. It is the parameter that has been used to demonstrate the benefits on microvascular and macrovascular outcomes in clinical trials. It is the primary endpoint for the demonstration of glycemic-lowering efficacy for new diabetes drugs.

The National Glycohemoglobin Standardization Program (NGSP), established by DCCT investigators, has succeeded in standardizing more than 99 percent of the assays used in the United States to the DCCT standard. The differences in HbA1c across ethnic groups are so small (approximately 0.3 to 0.4 percentage-point difference) that they will not significantly modify the association between HbA1c and diabetes-related complications.

Pooled analyses of large landmark RCTs (ACCORD, ADVANCE, Kumamoto, UGDP, UKPDS, VACSDM, VADT, PROACTIVE) comparing intensive versus standard glycemic control among patients with type 2 diabetes were synthesized. Long-term follow-up of the UKPDS cohort (recently diagnosed individuals with DMT2) was also considered.

Summary of the Evidence

Characteristics of Included Studies

The evidence base comprises the large landmark RCTs of intensive versus standard glycemic control in adults with type 2 diabetes. Studies pooled in the included meta-analyses encompassed populations from a wide range of disease duration and complication status, with end-of-trial HbA1c attained averaging 6.9% in the intensive arm and 8.3% in the standard arm. Risk of bias across the body of evidence was judged Not Serious; certainty was judged High for microvascular and key macrovascular outcomes and Moderate for severe hypoglycemia (with considerable heterogeneity noted).

Table 40. HbA1c levels attained at the end of the large landmark trials comparing intensive versus standard glycemic control

Trial	Year	N	Mean age (years)	Study duration (years)	Intensive arm end-of-trial HbA1c	Standard arm end-of-trial HbA1c
ACCORD	2010	10,251	62.2	3.7	6.3%	7.6%
ADVANCE	2008	11,140	66	5	6.49%	7.24%
Kumamoto	1995	110	49	6	7.1%	9.4%
UGDP	1982	414	52.7	12	NC	NC
UKPDS	1998	3,867	54	10	7.5%	8.4%
VACSDM (Veteran Affairs 1995)	1995	153	60.1	2	7.1%	9.2%
VADT	2009	1,791	60.4	5.6	6.9%	8.4%
PROACTIVE	2005	5,238	62	3	7.0%	7.6%
Mean (across trials)	—	—	—	—	6.9%	8.3%

Source-derived table. Adapted from Sun S, Hisland L, Grenet G, Gueyffier F, Cornu C, Jaafari N, Boussageon R. Reappraisal of the efficacy of intensive glycaemic control on microvascular complications in patients with type 2 diabetes: A meta-analysis of randomised control-trials. Therapie. 2022 Jul-Aug;77(4):413-423.

Summary of Findings

In pooled studies comparing more with less intensive glucose control among patients with type 2 diabetes, a modest reduction in HbA1c of 0.9% significantly reduced the risk of microvascular complications, especially that of kidney and eye events. The primary renal outcome of new or worsening nephropathy was reduced by 25%, and the progression of retinopathy was reduced by 20%.

Unlike the robust evidence for microvascular complications, there was a borderline non-significant reduction in composite cardiovascular outcomes, nonfatal stroke, and peripheral arterial disease. However, pooled results showed that intensive treatment was associated with a significant reduction in non-fatal myocardial infarction. There was no significant difference between the intensive and standard therapy groups for all-cause mortality and cardiovascular mortality. Considerable heterogeneity suggests that the effect of intensive therapy was not uniform across studies; however, subgroup analysis by risk of bias and length of study did not show statistically significant differences between subgroups. In the pooled results, intensive glycemic control led to a significantly greater risk for severe hypoglycemia compared with the standard, although heterogeneity among studies was substantial.

In summary, lowering HbA1c to below or around 7% has been shown to significantly reduce microvascular complications (approximately 15 to 20% risk reduction). Hence, most guidelines recommend an HbA1c goal of <7% for nonpregnant adults. Long-term follow-up of the UKPDS cohorts

(recently diagnosed individuals with DMT2) suggests that HbA1c targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease.

Table 41. Summary of Findings: Effects of intensive versus standard glycemic control on microvascular outcomes

Outcome	Number of studies	Intensive (n/N)	Conventional (n/N)	Risk Ratio (95% CI)	Certainty of Evidence
Composite microvascular outcomes	3 RCTs	1331/13770	1312/11830	0.88 (0.81 to 0.95)	High
New or worsening nephropathy	9 RCTs	3414/14755	3522/13174	0.76 (0.70 to 0.9)	High
Retinopathy	9 RCTs	1033/11027	886/8324	0.79 (0.70 to 0.9)	High
Neuropathy	7 RCTs	4284/11738	4101/10251	0.97 (0.92 to 1.03)	High

Table 42. Summary of Findings: Effects of intensive versus standard glycemic control on severe hypoglycemia

Outcome	No. of studies	Intensive (n/N)	Conventional (n/N)	Odds Ratio (95% CI)	Certainty of Evidence
Severe hypoglycemia	11 RCTs	1121/16988	414/15671	1.74 (1.06 to 2.85)	Moderate

Table 43. NNT or NNH of statistically significant clinical outcomes (pooled across the landmark trials)

Clinical outcome	Event rate (Intensive)	Event rate (Standard)	Pooled RR or OR (95% CI)	ARR	NNT / NNH
Composite microvascular outcomes	9.7% (1331/13770)	11% (1312/11830)	0.88 (0.81 to 0.95)	1.3	77 (NNT)
New or worsening nephropathy	23.1% (3414/14755)	26.7% (3522/13174)	0.76 (0.70 to 0.9)	3.6	28 (NNT)
Retinopathy	9.37% (1033/11027)	10.6% (886/8324)	0.79 (0.70 to 0.9)	1.27	81 (NNT)
Neuropathy	36.5% (4284/11738)	40% (4101/10251)	0.97 (0.92 to 1.03)	NA	NA
Composite macrovascular complications	9.2% (1337/14471)	10.3% (1325/12884)	0.92 (0.82 to 1.03)	NA	NA
Nonfatal MI	4.5% (814/18110)	4.9% (787/16012)	0.83 (0.75 to 0.92)	0.4	250 (NNT)
Nonfatal stroke	2.9% (520/17564)	3.1% (486/15658)	0.87 (0.68 to 1.11)	NA	NA
Peripheral arterial disease	4.5% (587/12978)	5.1% (555/10884)	0.97 (0.83 to 1.15)	NA	NA
Cardiovascular mortality	5.1% (956/18597)	4.3% (699/16383)	1.16 (0.95 to 1.42)	NA	NA
All-cause mortality	9.4% (1760/18654)	8.4% (1376/16415)	1.03 (0.93 to 1.13)	NA	NA
Severe hypoglycemia	6.6% (1121/16988)	2.6% (414/15671)	1.74 (1.06 to 2.85)	3.9	25 (NNH)

All guidelines, directly or indirectly, recommend individualization or personalization of HbA1c targets on the basis of discussion of benefits and harms, preferences and determinants of health.

Table 43. Recommended HbA1c targets from the different guidelines

	General target	Less stringent target	More stringent target
ADA	<7% (w/o significant hypoglycemia)	<8% (w/ specific risk factors)	
AACE	<6.5% (if can be safely achieved)	7 to 8% (w/ specific risk factors)	
NICE	7% (on drugs associated with hypoglycemia)		6.5% (newly diagnosed on single drug)
ACP	7-8%		
SIGN	7%		6.5% (at diagnosis)
Malaysia	6.6-7%	7.1-8.0%	6.0-6.5%
Japan	<7% (normoglycemia)	<8% (difficult intensification)	<6% (prevent most complications)

Certainty of Evidence

For the RCTs, the risk of bias was low and the certainty of evidence was high for microvascular outcomes (composite, nephropathy, retinopathy, neuropathy) and moderate for severe hypoglycemia.

Other considerations

Cost

HbA1c testing is a standard of care for diabetes monitoring in the Philippines. The cost of HbA1c varies from PhP 400 to PhP 2,000 depending on the healthcare facility. HbA1c is readily available in secondary and tertiary care facilities. There are no published cost-effectiveness studies on the use of an HbA1c target of < 7% among adult Filipinos with type 2 diabetes mellitus; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find any study that addressed the patient's values or preferences.

Guideline Question 13. Should we recommend self-monitoring of blood glucose (SMBG) targets of fasting capillary plasma glucose of 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose of <180 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

Recommendation 33. We suggest a fasting capillary plasma glucose target of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and a 2-hour postprandial capillary plasma glucose target of <180 mg/dL (<10.0 mmol/L) in order to achieve an HbA1c of <7.0% among nonpregnant adults with T2DM.

Certainty of Evidence:	Low
Strength of recommendation:	Weak

Background

Several outcome studies have mainly shown HbA1c to be the primary predictor of diabetes complications. However, HbA1c is a measure of chronic glycemic levels over months and does not provide information that can be useful for immediate and short-term decisions. Real-time self-monitoring of capillary blood glucose through finger prick can be a valuable tool for this purpose. HbA1c measurement encompasses a component of both fasting plasma glucose (FPG) and postprandial glucose (PPG); hence, FPG and PPG could provide different and independent contributions to long-term outcomes.

Summary of the Evidence

Evidence on SMBG targets is drawn from: (1) a meta-analysis assessing the effects of FPG and PPG reduction on cardiovascular outcomes in randomized controlled trials (Monami et al. 2013), (2) studies correlating mean glucose values with HbA1c in type 1 and type 2 diabetes, (3) a meta-analysis of 14 studies (Ketema and Kibret 2015) estimating the relative contribution of FPG and PPG to overall hyperglycemia, (4) a continuous glucose monitoring (CGM) study correlating 2-hour PPG with HbA1c (Wei et al. 2014), (5) a study of forced intensified antihyperglycemic treatment in 164 participants with HbA1c not at target (≥7.5%) defining FPG and PPG thresholds for HbA1c <7%, and (6) the international A1C-Derived Average Glucose (ADAG) study in 507 adults (83% non-Hispanic White) with type 1, type 2, or no diabetes.

Characteristics of Included Studies

The evidence base comprises meta-analyses of RCTs assessing the impact of FPG and PPG reduction on cardiovascular outcomes (Monami et al. 2013), correlation meta-analyses (Ketema and Kibret 2015, 14 studies), and physiologic-correlation studies including the international ADAG study (Nathan et al. 2008) in 507 adults across type 1 diabetes, type 2 diabetes, and no diabetes; a CGM study (Wei et al. 2014); and a forced-titration study in 164 participants with type 2 diabetes and HbA1c ≥7.5%. For the RCTs assessed, the risks of bias were low and the certainty of evidence was moderate. The recommended SMBG targets are derived primarily from expert opinion across major guidelines (ADA, Canadian, IDF, Japan, Malaysian) using FPG and PPG values that correlate best with the recommended HbA1c target of <7%.

Summary of Findings

In the meta-analysis assessing the effects of FPG and PPG reduction on cardiovascular outcomes (Monami et al. 2013), trials with a between-group FPG difference greater than 1 mmol/L (18 mg/dL) produced a significantly lower all-cause mortality (MH-OR 0.90, 95% CI 0.81 to 0.99, P = 0.03) and cardiovascular mortality (MH-OR 0.86, 95% CI 0.76 to 0.97, P = 0.012), with no significant effect on the incidence of major cardiovascular events. In contrast, the MH-OR for cardiovascular events, all-cause mortality, and cardiovascular mortality in trials with a between-group PPG difference greater than 1 mmol/L was not significantly different from controls.

Mean glucose values correlate with HbA1c in both type 1 and type 2 diabetes. When HbA1c values are higher, the major contributor is FPG, but as HbA1c approaches 7.0%, there is a greater contribution from PPG values. In a meta-analysis of 14 studies that estimated the relative contribution of FPG and PPG to overall hyperglycemia, the pooled correlation coefficient (r) of FPG with HbA1c was 0.61 (P < 0.001, 95% CI 0.48 to 0.72), while the pooled correlation coefficient between PPG and HbA1c was 0.68 (P < 0.001, 95% CI 0.56 to 0.75). A study using continuous glucose monitoring (CGM) demonstrated that a 2-hour PPG <8.0 mmol/L (144 mg/dL) correlates best with an HbA1c <7.0%. In a study of forced intensified antihyperglycemic treatment in 164 participants with type 2 diabetes with HbA1c not at target (≥7.5%), achievement of HbA1c <7.0% was associated with an FPG target of <5.5 mmol/L (100 mg/dL) in 64% of participants, and a PPG target of <7.8 mmol/L (140 mg/dL) in 94% of participants. Based on the international A1C-Derived Average Glucose (ADAG) study, the average blood glucose levels at premeal, postmeal, and bedtime had a strong correlation (r = 0.92) with the specified HbA1c levels.

The actual FPG and PPG targets that lead to the reduction in clinical outcomes have not yet been specifically defined. Most guidelines used FPG and PPG values that correlate best with the recommended HbA1c target of <7%. Based mainly on expert opinion, the majority of these guidelines recommend an FPG or preprandial CBG range of 80 to 130 mg/dL (4.4 to 7.2 mmol/L), and a postprandial target of <180 mg/dL (<10 mmol/L) based on the ADAG study which showed the upper range of 185 mg/dL to correlate with an HbA1c of 7%.

It is reasonable to check postprandial glucose in individuals who have premeal glucose values within target but the HbA1c values are still above target.

Table 44. Estimated average glucose (eAG) at premeal, postmeal, and bedtime against specified HbA1c levels (international A1C-Derived Average Glucose study)

HbA1c (%)	mg/dL (95% CI)	mmol/L (95% CI)
5	97 (76 to 120)	5.4 (4.2 to 6.7)
6	126 (100 to 152)	7.0 (5.5 to 8.5)
7	154 (123 to 185)	8.6 (6.8 to 10.3)
8	183 (147 to 217)	10.2 (8.1 to 12.1)
9	212 (170 to 249)	11.8 (9.4 to 13.9)
10	240 (193 to 282)	13.4 (10.7 to 15.7)
11	269 (217 to 314)	14.9 (12.0 to 17.5)
12	298 (240 to 347)	16.5 (13.3 to 19.3)

Table 45. Recommended SMBG targets by most guidelines to meet HbA1c target of <7%

SMBG Glycemic Targets	ADA (Grade E)	Canadian (Grade B, Level 2)	IDF (evidence level not mentioned)	Japan (evidence level not mentioned)	Malaysian (Grade B)
FPG / preprandial	80 to 130 mg/dL (4.4 to 7.2 mmol/L)	72 to 126 mg/dL (4 to 7 mmol/L)	<110 mg/dL (<6 mmol/L)	<130 mg/dL (<7.2 mmol/L)	80 to 126 mg/dL (4.4 to 7 mmol/L)
Postprandial	Peak, 1 to 2 h postprandial; <180 mg/dL (<10 mmol/L)	2 h postprandial; 90 to 180 mg/dL (5 to 10 mmol/L)	<180 mg/dL (<10 mmol/L)	2 h postprandial; <180 mg/dL (<10 mmol/L)	80 to 153 mg/dL (4.4 to 8.5 mmol/L)

Table 46. GRADE evidence profile - FPG reduction (more intensive vs less intensive FPG reduction; Monami et al. 2013)

Outcome	No. of studies	Effect (OR; 95% CI)	Certainty
Major cardiovascular events	13 RCTs	OR 0.950 (0.818 to 1.105)	Moderate (⊕⊕⊕○)
All-cause mortality	8 RCTs	OR 0.904 (0.825 to 0.991)	Moderate (⊕⊕⊕○)
Cardiovascular mortality	8 RCTs	OR 0.857 (0.760 to 0.967)	Moderate (⊕⊕⊕○)

Table 47. GRADE evidence profile - PPG reduction (more intensive vs less intensive PPG reduction; Monami et al. 2013)

Outcome	No. of studies	Effect (OR; 95% CI)	Certainty
Major cardiovascular events	5 RCTs	OR 0.898 (0.509 to 1.583)	Moderate (⊕⊕⊕○)
All-cause mortality	8 RCTs	OR 1.082 (0.751 to 1.557)	Moderate (⊕⊕⊕○)
Cardiovascular mortality	4 RCTs	OR 1.608 (0.631 to 4.094)	Moderate (⊕⊕⊕○)

Table 48. Summary of glycemic target recommendations for most nonpregnant adults with diabetes

Parameter	Target
HbA1c	<7.0%
Fasting or preprandial capillary blood glucose	80 to 130 mg/dL (4.4 to 7.2 mmol/L)
2-hour postprandial capillary blood glucose	<180 mg/dL (<10.0 mmol/L)

Certainty of Evidence

For the RCTs, the risks of bias were low and the certainty of evidence was moderate across the FPG and PPG reduction outcomes from the Monami et al. 2013 meta-analysis. The actual FPG and PPG targets that lead to reductions in clinical outcomes have not yet been specifically defined; the recommended SMBG targets are derived primarily from expert opinion across guidelines using glucose values that correlate best with the recommended HbA1c target of <7%.

Other considerations

Cost

Self-monitoring of blood glucose (SMBG) requires a glucose meter and capillary blood glucose test strips. Per-strip costs and meter ownership vary widely across the Philippine market; capillary blood glucose testing is widely accessible in primary, secondary, and tertiary care settings. There are no published cost-effectiveness studies on the use of specific SMBG targets (fasting / preprandial 80 to 130 mg/dL and 2-hour postprandial <180 mg/dL) among adult Filipinos with type 2 diabetes mellitus; no

cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find any study that addressed the patient's values or preferences.

Similar to HbA1c, SMBG goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, advanced microvascular or macrovascular complications, hypoglycemia unawareness, and individual patient considerations.

Guideline Question 14. Should we give influenza vaccine annually among adults with T2DM?

Recommendation 34. We recommend routinely giving the influenza vaccine annually to adults with T2DM, ideally from February to June each year before the start of the rainy season in the Philippines (per DOH guidance)

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Background

Hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens; persons with diabetes are therefore known to be more susceptible to infections.[1]

Influenza is associated with more severe complications among persons with diabetes, including higher odds of hospitalization, intensive care unit (ICU) admission, and mortality compared with individuals without diabetes.[2] In the Philippines, the influenza season spans June to December, coinciding with the humid and rainy months. Based on the Department of Health (DOH) influenza-like illness surveillance for January to September 2023, Influenza A H1N1 was the most common circulating strain at 30%, followed by SARS-CoV-2 at 28% and Influenza B at 18.3%. The DOH recommends getting a flu shot from February to June each year, before the start of the rainy season.

Summary of the Evidence

One meta-analysis[2] of observational studies, was utilized for the influenza arm of the review. No randomized controlled trials were identified.

Characteristics of Included Studies

The included evidence base is a single meta-analysis of observational studies. Dicembrini et al. (2023, Italy) pooled 13 observational studies on the effectiveness of influenza vaccination, with a total of 1,080,619 adults with diabetes mellitus (516,628 vaccinated and 563,991 unvaccinated), with data through May 31, 2022. Included studies were predominantly retrospective cohorts (n = 8) and case-control studies (n = 5); included patients were adults with diabetes mellitus, the majority above 50 years of age. Risk of bias of included studies was appraised using the Newcastle-Ottawa Scale (NOS), with the included studies generally rated as good quality. Outcomes assessed in the meta-analysis were hospitalizations, ICU admissions, and mortality.

Table 49. Characteristics of the included studies

Author / Year (citation)	Study Design	N (vaccinated / unvaccinated)	Population	Intervention	Comparator	Outcomes
Dicembrini et al, 2023	Meta-analysis of observational studies (no RCTs); 13 studies (8 retrospective cohorts, 5 case-control)	1,080,619 (vaccinated 516,628 / unvaccinated 563,991)	Adults with diabetes mellitus; majority >50 years old	Influenza vaccination	Unvaccinated	Hospitalizations ICU admissions, mortality

Summary of Findings

Influenza vaccination among persons with diabetes was associated with a reduction in the overall hospitalization rate of approximately 23%, and a reduction of 37% for hospitalizations specifically for influenza or pneumonia.[2] A diagnosis of diabetes mellitus was associated with a significantly higher odds of hospitalization due to influenza or pneumonia compared with individuals without diabetes; a significantly higher odds of ICU admission; and significantly higher mortality for influenza in comparison to non-diabetic individuals (5 studies reported adjusted odds ratios for mortality in the general population). For these outcomes among vaccinated persons with diabetes specifically, none of the included studies reported data on ICU admission, glycemic control, or cardiovascular mortality.

Table 50. Summary of findings on influenza vaccination effectiveness in adults with type 2 diabetes (from Dicembrini et al. 2023)

Outcome	Effect (relative reduction)
Overall hospitalization rate (vaccinated vs unvaccinated PWD)	approximately 23%
Hospitalization for influenza or pneumonia (vaccinated vs unvaccinated PWD)	37%
ICU admission (among vaccinated PWD)	Not reported in included studies
Glycemic control (among vaccinated PWD)	Not reported in included studies
Cardiovascular mortality (among vaccinated PWD)	Not reported in included studies
All-cause mortality (general population, DM vs non-DM)	DM associated with significantly higher mortality for influenza

Safety outcomes

Safety of vaccines used for routine immunization in the United States was reviewed by Gidengil C et al. in 2021.

Certainty of Evidence

The certainty of evidence for influenza vaccination in persons with diabetes was rated as moderate. Downgrades were considered for risk of bias (observational designs only), inconsistency across studies (variation in vaccine doses and preparations), imprecision (small populations and wide confidence intervals in some outcomes), and indirectness (variation in vaccine formulations and uncertainty about the intervention administered at the peak of the influenza season).

Other considerations

Cost

Influenza vaccine is registered and available in the Philippines. Based on the Department of Health Drug Price Reference Index (DPRI) 2023, the influenza polyvalent vaccine 0.5 mL suspension for injection in a pre-filled syringe is priced at a lowest of PhP 550.00, DPRI median PhP 600.00, and highest of PhP 650.00. There are no published cost-effectiveness studies on the use of influenza vaccination among adult Filipinos with type 2 diabetes mellitus; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either. The economic burden of community-acquired pneumonia among Filipino adults has been characterized in a local cost-of-illness study (Bernadette A et al., Value Health Reg Issues 2015;6:118-125).

Table 51. Local price of influenza vaccine (DPRI 2023)

Product	Lowest (PhP)	DPRI Median (PhP)	Highest (PhP)
Influenza Polyvalent 0.5 mL suspension for injection, pre-filled syringe	550.00	600.00	650.00

Guideline Question 15. Should we give pneumococcal vaccine annually among adults with T2DM?

Recommendation 35.
We recommend routinely giving both types of pneumococcal vaccine to all adults with T2DM, in the following order: PCV13 or PCV15, followed by PPSV23 after at least 8 weeks (up to a maximum of 1 year).

Certainty of Evidence: Low
Strength of recommendation: Strong

Remarks:

- *For adults who have already received PPSV23, they may receive PCV13 or PCV15 after 1 year.*
- *PPSV23 is given every 5 years until the age of 65.*
- *When a second PPSV23 dose is used, no additional pneumococcal vaccines are recommended until at least age 65 years.*
- *For adults aged ≥65 years: one PPSV23 dose only.*

Background

Hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens; persons with diabetes are therefore known to be more susceptible to infections.

Adults with diabetes are up to three times more likely to contract pneumonia compared with healthy adults of the same age group, and adult patients with diabetes older than 65 years are up to three times more likely to contract pneumonia compared with younger patients. Pneumonia is the second most common cause of hospitalization in persons with diabetes; the incidence of hospitalization due to pneumonia is three times higher in adult patients with diabetes compared with healthy adults. Streptococcus pneumoniae is among the most commonly identified pathogens for pneumonia in patients with diabetes.[1-4]

Streptococcus pneumoniae bacteria are serotyped based on the polysaccharides in the outer capsule of the bacteria. Serotypes vary in how common they are and in the proportion of pneumococcal disease they cause; available pneumococcal vaccines target different sets of serotypes.

Summary of the Evidence

One systematic review and meta-analysis[5] was utilized for the pneumococcal arm, with a supporting vaccine-effectiveness review.[6]

Characteristics of Included Studies

The included evidence base is a single systematic review and meta-analysis of observational studies. Marques Antunes et al. (2021, Portugal) pooled 7 cohort studies (3 prospective and 4 retrospective), with a total of 163,756 participants. No randomized controlled trials were found. The included population was

not restricted to persons with diabetes - it comprised adults with previous clinically established cardiovascular disease, unequivocally documented cardiovascular disease on imaging, diabetes mellitus with target organ damage, severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2), or a calculated 10-year SCORE of >10%. The intervention was vaccination with PPSV23 or PCV compared with no vaccination. The primary outcome was all-cause mortality; secondary outcomes included cardiovascular mortality, acute myocardial infarction, death from acute myocardial infarction, ischemic cerebrovascular events (stroke, transient ischemic attack), death from stroke, and major adverse cardiac events (MACE). Three of the 7 included studies had serious risk of bias.

A supporting vaccine-effectiveness review by Dunne et al. (2023) evaluated 9 studies, all from high-income countries, comparing PPV23 and PCV13 against vaccine-type pneumococcal pneumonia, pneumococcal pneumonia or severe pneumococcal disease (IPD or pneumococcal pneumonia), and all-cause pneumonia or lower respiratory tract infection. None of the 9 studies evaluated invasive pneumococcal disease alone.

Table 52. Characteristics of the included studies

Author / Year	Study Design	Country	No. of studies (N)	Population	Intervention	Comparator	Outcomes
Marques Antunes et al., 2021	Systematic review and meta-analysis of observational studies (no RCTs found); 7 cohort studies (3 prospective, 4 retrospective)	Portugal	7 studies (163,756)	Adults with previous clinically established CVD; documented CVD on imaging; T2DM with target organ damage; severe CKD (eGFR <30 mL/min/1.73 m^2); or 10-year SCORE >10%	PPSV23 or PCV vaccination	Unvaccinated	All-cause mortality (primary); CV mortality, acute MI, death from acute MI, ischaemic cerebrovascular events, death from stroke, MACE (secondary)
Dunne et al., 2023	Vaccine-effectiveness review (supporting)	High-income countries	9 studies	Adults	PPV23, PCV13, or sequential PCV13/PPV23	Unvaccinated	Vaccine-type pneumococcal pneumonia; pneumococcal pneumonia or severe pneumococcal disease; all-cause pneumonia or LRTI

Summary of Findings

Pooled results from 5 studies enrolling a total of 163,756 participants showed a significant decrease in all-cause mortality with pneumococcal vaccination (HR 0.78, 95% CI 0.73 to 0.83) without statistically significant heterogeneity (χ^2 test P = 0.21; I^2 = 32%). Pneumococcal vaccination was associated with a

22% decrease in all-cause mortality in patients with cardiovascular disease or at very high cardiovascular risk (Marques Antunes et al. 2021).

Across the studies included in the Dunne et al. (2023) review, vaccine effectiveness against vaccine-type pneumococcal pneumonia ranged from 2 to 6% for PPV23 and from 41 to 71% for PCV13. Vaccine effectiveness against pneumococcal pneumonia or severe pneumococcal disease (invasive pneumococcal disease or pneumococcal pneumonia) ranged from −10 to 11% for PPV23, 40 to 79% for PCV13, and 39 to 83% for sequential PCV13/PPV23. Vaccine effectiveness against all-cause pneumonia or lower respiratory tract infection ranged from −8 to 3% for PPV23 and 9 to 12% for PCV13. None of the studies evaluated invasive pneumococcal disease alone.

Table 53. Summary of findings: pneumococcal vaccination - all-cause mortality[5]

Outcome	Basis	Effect Estimate	95% CI	Heterogeneity	Interpretation	Certainty
All-cause mortality	5 studies; N = 163,756 (pooled from 7-study review)	HR 0.78 (22% decrease)	0.73 to 0.83	χ^2 P = 0.21; I^2 = 32% (no statistically significant heterogeneity)	Benefit	Very Low (per source review's own assessment)

Table 54. Vaccine effectiveness ranges by vaccine type (Dunne et al. 2023; 9 studies from high-income countries)

Outcome category	PPV23	PCV13	Sequential PCV13 / PPV23
Vaccine-type pneumococcal pneumonia	2 to 6%	41 to 71%	—
Pneumococcal pneumonia or severe pneumococcal disease (IPD or pneumococcal pneumonia)	−10 to 11%	40 to 79%	39 to 83%
All-cause pneumonia or lower respiratory tract infection	−8 to 3%	9 to 12%	—
Invasive pneumococcal disease alone	Not evaluated in any included study	Not evaluated	Not evaluated

Safety outcomes

Safety of vaccines used for routine immunization was reviewed by Gidengil C et al.[7]

Certainty of Evidence

The certainty of evidence for pneumococcal vaccination was rated as Low. Three of the included studies had serious risk of bias. The pooled estimate for all-cause mortality was assessed at very low confidence owing to limitations of study design and risk of bias.[5] Additional downgrades were considered for inconsistency (variation in doses and preparations), imprecision (wide confidence intervals around some pooled estimates), and indirectness (the included population was not restricted to persons with diabetes mellitus alone).

Other considerations

Cost

Pneumococcal vaccines are registered and available in the Philippines. Based on the Department of Health Drug Price Reference Index (DPRI) 2023[8], pneumococcal conjugate vaccine in a multi-dose vial costs PhP 2,561.47 (lowest) to PhP 3,970.19 (highest), with a DPRI median of PhP 2,850.00; pneumococcal polyvalent vaccine 25 mcg/0.5 mL, 0.5 mL single-dose vial, costs PhP 1,935.00 (lowest) to PhP 2,098.00 (highest), with a DPRI median of PhP 2,016.50. There are no published cost-effectiveness studies on the use of pneumococcal vaccination among adult Filipinos with type 2 diabetes mellitus; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either. The economic burden of community-acquired pneumonia among Filipino adults has been characterized in a local cost-of-illness study.[9]

When both pneumococcal vaccines are administered, PCV is given before PPSV23 because this sequence provides the best immune response to both vaccines; subjects who received PPSV23 as the initial dose had lower antibody responses after subsequent administration of PCV13 than those who received PCV13 as the initial dose followed by a dose of PPSV23.

Table 55. Local price of pneumococcal vaccines (DPRI 2023).

Product	Lowest (PhP)	DPRI Median (PhP)	Highest (PhP)
Pneumococcal Conjugate Vaccine, multi-dose vial	2,561.47	2,850.00	3,970.19
Pneumococcal Polyvalent vaccine 25 mcg/0.5 mL, 0.5 mL single-dose vial	1,935.00	2,016.50	2,098.00

Guideline Question 16. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and concomitant tuberculosis?

Recommendation 36. We recommend optimization of glycemic control generally using metformin as background therapy in patients with T2DM and concomitant active TB. In the absence of studies, we recommend combined oral anti-diabetes agents or insulin with background metformin therapy.

Certainty of Evidence: Low
Strength of recommendation: Strong

Recommendation 37. We recommend the use of insulin in patients with severe hyperglycemia (glycosylated hemoglobin [HbA1c] >10% or fasting plasma glucose [FPG] >300 mg/dL), or in the presence of weight loss and other symptoms of hyperglycemia.

Certainty of Evidence: Low
Strength of recommendation: Strong

Recommendation 38.
We suggest referral to diabetes clinics for structured care programs for optimization of glycemic control.

Certainty of Evidence: Low
Strength of recommendation: Weak

Background

Diabetes mellitus affects host immunity, leading to an increased propensity for infections including tuberculosis (TB). Diabetes has been found to be associated with a two- to four-fold higher risk of active and latent tuberculosis. It has also been found to affect the presentation of TB: compared to those without DM, patients with DM were more likely to have extensive parenchymal lesions, cavitations and lower lung field opacity. Even with TB treatment, DM was associated with higher risk of poor outcomes including relapse, risk of development of multi-drug resistant TB (MDR-TB), and death. In a population-based study in Taiwan, the independent risk factors for mortality in patients with DM and TB were male gender, age 60 years or older, and the presence of hypertension and heart failure. Inadequate glycemic control has also been associated with an increased susceptibility to TB and worse TB outcomes; TB-associated inflammation also aggravates hyperglycemia, making glycemic control challenging in active TB. A cross-sectional study of comorbidities in patients with TB in the Philippines found a 9.2% prevalence of diabetes (95% CI 7.0 to 11.8), of whom 52% were previously undiagnosed. The global prevalence of DM among TB patients is estimated at 15.4%.

Recognizing the increase in diabetes-tuberculosis comorbidity globally, the World Health Organization and the International Union Against Tuberculosis and Lung Disease (The Union) developed a collaborative framework to guide individuals caring for patients with TB and diabetes and national programs in creating a coordinated response at clinical and organizational levels. Screening for diabetes should be done in all patients with TB, and screening for active TB should be recommended in newly-diagnosed DM and established DM in areas with high TB prevalence rates.

Glycemic goals during anti-TB treatment

The general glycemic goal of HbA1c <7% is recommended by the American Diabetes Association (ADA) for most non-pregnant adults. During anti-TB treatment, TB-associated inflammation causing hyperglycemia, drug interactions with anti-TB medications, and varying dietary intake and physical activity make glycemic control more challenging to achieve. In situations where the risks of treatment outweigh the benefit of intensive glucose control, including the presence of significant comorbidities, a less stringent goal, such as HbA1c <8%, may be more appropriate.

Achievement of glycemic goals will generally entail more frequent blood glucose monitoring. The Union guidance recommends monitoring frequency depending on the severity of DM: with baseline HbA1c <8%, fasting blood glucose (FBG) may be retested after three months; with higher baseline HbA1c, FBG may be done every one to two weeks until achievement of acceptable control. Enhanced diabetes management in a pay-for-performance program (P4P) in Taiwan showed better outcomes in patients with DM and TB under P4P. In a prospective study in eastern China, compared to patients with consistently normal glycemic trajectories, treatment failure was more likely in patients with transient hyperglycemia (AOR 4.20, 95% CI 1.57 to 11.25), glycemic instability (AOR 5.98, 95% CI 2.0 to 17.87), or diabetes (AOR 6.56, 95% CI 2.22 to 19.35). Conversely, treatment of diabetes was associated with a higher likelihood of completing treatment for TB and achieving cure (OR 1.82, 95% CI 1.20 to 2.77).

Antidiabetes medications in TB

There is no clear evidence on the most appropriate medication for glycemic control in TB. Older drug classes - specifically metformin, sulfonylureas, and insulin - have been recommended because of their extensive experience and availability. Thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1 RA) have limited data on superior efficacy in patients with TB and DM, and may not be available in most resource-limited settings.

With the known advantages of wide availability, broad experience, low cost, low hypoglycemia risk, and cardiovascular benefit, metformin remains as the initial choice for glucose control in T2DM. Concomitant use of rifampicin, a potent hepatic enzyme inducer, did not result in any clinically significant changes in metformin's glucose-lowering effect, renal clearance, or tubular secretion. The disadvantages of metformin are generally its gastrointestinal adverse effects and limited use in patients with deteriorating renal function. Sulfonylureas are also recommended as add-on therapy in patients who have not achieved glycemic control with metformin; advantages include wide availability, relatively low cost, and extensive experience, while known drug interactions with rifampicin and the risk of hypoglycemia are potential disadvantages. Insulin initiation is recommended if weight loss and other symptoms of hyperglycemia are present, or with blood glucose levels ≥300 mg/dL or HbA1c >10%. Insulin has also been recommended as treatment for diabetes in patients with TB in cases of severe hyperglycemia,

because of its unlimited efficacy. The disadvantages of insulin are its relative cost compared with oral medications, requirement for injection and proper storage, risk of hypoglycemia, and need for self-monitoring of blood glucose via personal glucometers - which adds cost to treatment in resource-limited settings.

Summary of the Evidence

The search strategy for clinical practice guidelines (CPG) did not yield any eligible publications. A search for indirect evidence was conducted for the management of type 2 diabetes and pulmonary tuberculosis. The search yielded one meta-analysis on the effect of oral antidiabetic drugs (OADs) on the risk of development of active TB, TB recurrence, and mortality. One randomized trial on the effect of a structured clinical algorithm on glycemic control in patients with TB and diabetes for the outcomes of glycemic control, hypoglycemia, and mortality was included for its value in general practice.

Characteristics of Included Studies

Two main bodies of evidence were utilized. The first was the Meregildo-Rodriguez et al. (2022) meta-analysis, which included 2 RCTs and 16 observational studies published until 31 August 2022 (sourced from MEDLINE/PubMed, Google Scholar, Scopus, ScienceDirect, EMBASE, Web of Science, and Cochrane Library). The OADs analyzed included metformin (MET), sulfonylureas (SU), meglitinides (MEG), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI), DPP-4 inhibitors, and SGLT2 inhibitors. The included population was patients newly- or previously-diagnosed with type 2 diabetes; outcomes included development of active TB, TB recurrence, mortality, and sputum culture conversion. Significant heterogeneity was noted across studies ($I^2 > 90\%$, $P < 0.05$) and possible publication bias was identified against studies that did not find a significant association between OADs and TB outcomes.

1. The second body of evidence was the Ruslami et al. (2021) RCT (Indonesia) on a structured clinical algorithm on glycemic control. The trial assessed the use of a package of structured counseling, clinical monitoring, and algorithm-based adjustment of diabetes treatments compared with routine care in patients with DM and TB. Baseline HbA1c was ≥11.0% in both groups. The trial was conducted in 150 randomized participants. Risk of bias was evaluated using the Cochrane RoB2 tool for the RCT and AMSTAR-2 for the meta-analysis.

Table 56. Summary of results from the Meregildo-Rodriguez 2022 meta-analysis: effect of oral antidiabetic drugs on tuberculosis outcomes (selected included studies)

Study (year, design, country)	Participants	Exposure	Control	Outcome	Effect (95% CI)
Padmapriydarsini 2022, RCT, India	Newly diagnosed TB culture-positive, non-DM, ≥18 yrs (n = 322)	Standard ATT + MET 1 g/day	Standard ATT	Time to sputum culture conversion during 8 weeks ATT	HR 0.8 (0.624 to 1.019) for median time to sputum conversion
Heo 2021, RCS, South Korea	Newly-diagnosed T2DM (n = 76,973)	MET	Non-use of MET	Development of TB within 2 years of index date	HR 1.17 (0.75 to 1.83) for MET and prevention of TB
Lee YJ 2018, RCS, South Korea	TB culture-positive, DM and non-DM (n = 499)	MET	Non-use of MET	Sputum culture conversion after 2 months; TB recurrence	**DM only:** OR 2.69 (0.92 to 7.95) for sputum culture conversion; OR 1.92 (0.42 to 8.76) for TB recurrence
Degner 2018, RCS, Taiwan	TB culture-confirmed, DM and non-DM, ≥13 yrs, on ATT (n = 2,416)	MET within 30 days of starting ATT	Non-use of MET	Mortality in DM on ATT within 6 months	**DM only**: HR 0.56 (0.39 to 0.82) for MET and mortality
Lin HF 2017, RCS, Taiwan	Newly-diagnosed T2DM (n = 22,256)	MET, SU, TZD, AGI	Non-use of agents	Risk of TB in 2 years	**DM only:** HR 0.52 (0.43 to 0.62) for MET; HR 0.76 (0.63 to 0.92) for SU; HR 0.75 (0.61 to 0.93) for TZD; HR 0.55 (0.44 to 0.67) for AGI
Lin SY 2018, RCS, Taiwan	T2DM (n = 29,028)	MET	Non-use of MET	Risk of TB in 12 years	**Active TB:** RR 0.24 (0.18 to 0.32) for MET; RR 1.82 (1.25 to 2.64) for SU; RR 1.36 (1.04 to 1.79) for MEG; RR 1.79 (1.35 to 2.37) for TZD; RR 1.36 (1.05 to 1.77) for AGI
Lin KH 2020, CCS, Taiwan	DM ≥20 yrs, TB and non-TB (n = 7,780)	Different OADs	Non-use of agents	Risk of TB in 11 years	**TB**: RR 1.032 (0.887 to 1.200) low-dose MET; RR 0.904 (0.732 to 1.117) high-dose MET; RR 1.154 (0.955 to 1.338) SU;

Study (year, design, country)	Participants	Exposure	Control	Outcome	Effect (95% CI)
					RR 0.960 (0.809 to 1.138) MEG; RR 0.810 (0.693 to 0.942) AGI; RR 0.927 (0.789 to 1.087) TZD
Lee MC 2018, RCS, Taiwan	Newly-diagnosed DM (n = 88,866)	MET	Non-use of MET	Risk of TB ≥8 years	**Active TB**: RR 0.84 (0.74 to 0.96) all subjects; RR 0.83 (0.72 to 0.97) high-dose MET
Lee MC 2019, RCS, Taiwan	TB close contacts, DM (n = 5,846)	MET	Non-use of MET	Risk of TB in 2 years	**Incident TB**: HR 0.73 (0.54 to 0.98) for MET; HR 0.66 (0.49 to 0.88) for low-dose MET; HR 0.59 (0.14 to 2.48) for high-dose MET
Pan SW 2018, RCS, Taiwan	T2DM (n = 40,179)	MET	MET <60 cDDD	Risk of TB in 6.1 years	HR 0.337 (0.169 to 0.673) for MET vs SU users
Tseng 2018, RCS, Taiwan	Newly-diagnosed T2DM (n = 423,949)	MET	Never MET user	Risk of TB ≥72 months	**TB:** HR 0.552 (0.493 to 0.617) for MET vs never MET user
Al-Shaer 2018, RCS, Qatar	PTB, poorly controlled DM (n = 103)	MET	Non-use of MET	Time to negative smears in 4 months	Time to sputum smear conversion: OR 0.12 (0.03 to 0.45)
Park S 2019, RCS, South Korea	T2DM ≥60 yrs (n = 12,582)	MET	SU	Risk of TB in 11 years	**TB:** HR 0.74 (0.58 to 0.95) MET vs SU; HR 0.63 (0.44 to 0.91) males vs females
Fu CP 2021, RCS, Taiwan	T2DM (n = 9,750)	MET	Non-use of MET	Risk of TB in 1.8 to 2.8 years	**TB:** HR 0.54 (0.3 to 0.99) for MET vs non-use MET
Chen HH 2020, RCS, Taiwan	DM >20 yrs (n = 12,798)	DPP-4i	Non-use of DPP-4i	Risk of TB in 5 years	**TB:** HR 1.04 (0.57 to 1.92) for DPP-4i vs non-use of DPP-4i
US FDA 2010, RCT, USA	DM (n = 7,827)	DPP-4i (SAXA)	Non-use of DPP-4i	Risk of TB up to 929 days	**TB:** RR 1.5790 (1.5526 to 1.6059) for DPP-4i
Su WJ 2018, RCS, Taiwan	T2DM and matched controls (n = 47,740)	MET	SU	Risk of TB in 8 years	**TB:** RR 0.328 (0.174 to 0.625) for MET vs SU initiators
Bailey CJ 2012, Phase 3 RCT (multi-country)	T2DM (n = 282)	DAPA (1, 2.5, 5 mg)	Placebo	Risk of TB in 28 weeks	**TB:** RR 1.0313 (0.0425 to 25.0080)

Table adapted from Meregildo-Rodriguez et al. 2022. Abbreviations: AGI = alpha-glucosidase inhibitor; ATT = anti-TB therapy; cDDD = cumulative defined daily dose; CCS = case-control study; CI = confidence interval; DAPA = dapagliflozin; DM = diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; MEG = meglitinide; MET = metformin; OAD = oral antidiabetic drug; RCS = retrospective cohort study; RCT = randomized controlled trial; SAXA = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Summary of Findings

From the Meregildo-Rodriguez 2022 meta-analysis: in patients newly- or previously-diagnosed with diabetes, metformin use was associated with a decreased risk of developing active tuberculosis by 40% (RR 0.60, 95% CI 0.47 to 0.77). Metformin was not shown to have any effect on sputum culture conversion in either DM or non-DM patients (RR 0.70, 95% CI 0.20 to 2.47). The studies on metformin and latent TB infection were not deemed to be good-quality studies. Mortality risk and metformin was investigated only in one study (Degner 2018), which showed a reduction by 44% (HR 0.56, 95% CI 0.39 to 0.82). DPP-4 inhibitor use increased the risk of active TB by 43% (RR 1.43, 95% CI 1.02 to 2.02). There were no associated increased risks of TB with the use of sulfonylureas (RR 1.14, 95% CI 0.82 to 1.60), meglitinides (RR 1.12, 95% CI 0.80 to 1.58), thiazolidinediones (RR 1.06, 95% CI 0.69 to 1.63), or alpha-glucosidase inhibitors (RR 0.84, 95% CI 0.54 to 1.31). The risk of TB with SGLT2i was only investigated in one study. There were no studies on the use of these other OADs on latent TB infection and mortality. There was significant heterogeneity of the studies ($I^2 > 90\%$, $P < 0.05$) and possible publication bias against studies that did not find significant association between OADs and TB outcomes. From the Ruslami 2021 RCT[38] in Indonesia (N = 150, baseline HbA1c ≥11.0% in both groups): the structured clinical algorithm effected a larger reduction in HbA1c in the intervention group compared with control (adjusted mean difference 1.82%, 95% CI 0.82 to 2.83, $P < 0.001$). There were more hypoglycemic events in the intervention group (35.0% versus 11.8%, $P = 0.002$). There were two deaths in the intervention group and none in the control group.

Table 57. Summary of findings: structured clinical algorithm on glycemic control in DM and TB

Critical Outcome	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Glycemic control at month 3 (defined as reaching target HbA1c <8%)	1 RCT (N = 150)	OR 2.08 (1.05 to 4.14)	Benefit	High
Glycemic control at month 6 (defined as reaching target HbA1c <8%)	1 RCT (N = 150)	OR 3.21 (1.58 to 6.51)	Benefit	High
Mortality	1 RCT (N = 150)	Not estimable	Inconclusive	Low
Hypoglycemia	1 RCT (N = 150)	HR 2.94	Inconclusive	High
Adverse events	1 RCT (N = 150)	HR 1.23	Inconclusive	Moderate

Certainty of Evidence

One RCT[38] had high certainty for glycemic control outcomes at months 3 and 6, and for hypoglycemia (the effect-size confidence interval for hypoglycemia was inconclusive despite the high certainty); mortality outcome was rated low certainty (not estimable); adverse events Moderate certainty. For the In the meta-analysis[19] of mostly observational studies, the body of evidence had significant heterogeneity ($I^2 > 90\%$) and possible publication bias; the Draft Recommendation overall is rated Low certainty by the source panel.

Other considerations

Cost

Locally available antidiabetic drug classes for use in T2DM with concomitant TB include biguanides (metformin), sulfonylureas, thiazolidinediones, DPP-4 inhibitors, alpha-glucosidase inhibitors, SGLT2 inhibitors, and insulin (human and analogues). Metformin, sulfonylureas, and human insulins are

available free of charge to PhP 30, PhP 28.25, and PhP 1,257 respectively under the Department of Health's Free Basic Medicine Assistance Program. There are no published cost-effectiveness studies on the use of specific antidiabetic agents for glycemic control among adult Filipinos with type 2 diabetes mellitus and concomitant tuberculosis; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Table 58. Cost of commonly used antidiabetes drugs in the Philippines

Drug Class	Price Range
Biguanide (Metformin)	Free* to PhP 30.00 per tablet
Sulfonylurea	Free* to PhP 28.25 per tablet
Thiazolidinedione (Pioglitazone)	PhP 12.75 to 30.00 per tablet
Dipeptidyl peptidase-4 inhibitor	PhP 23.50 to 53.00 per tablet
Alpha-glucosidase inhibitor (Acarbose)	PhP 7.10 to 11.65 per tablet
Sodium-glucose cotransporter 2 inhibitor	PhP 29.75 to 87.50 per tablet
Human insulins	Free* to PhP 1,257.00 per vial
Insulin analogues	PhP 517.00 to 1,650 per pen or vial

*Free for medications under the Free Basic Medicine Assistance Program of the Department of Health.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find any dedicated studies on patient values, preferences, equity, acceptability, or feasibility for antidiabetic agent selection in T2DM patients with concomitant TB. Considerations on availability of medications and social determinants of health are noted in the Research Gaps section.

Guideline Question 17. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)?

Recommendation 39. We recommend glucagon-like peptide-1 receptor agonist (GLP-1 RA) as adjunctive therapy among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD).

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 40. We recommend pioglitazone as adjunctive therapy among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)

Certainty of Evidence: Low
Strength of recommendation: Strong

Background

MASLD consists of a spectrum of hepatic disorders, from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, development of hepatocellular carcinoma, and liver-related mortality.[1] Obesity, insulin resistance, and type 2 diabetes are the major drivers of the pathogenesis of NAFLD.[2] MASLD is present in more than 70% of individuals with type 2 DM.[3] MASLD also negatively impacts type 2 DM in terms of related adverse clinical outcomes, including cardiovascular and chronic kidney diseases.

MASLD and type 2 DM have a bidirectional relationship.[4] Type 2 DM promotes MASLD progression to cirrhosis and elevates the risk of liver-related and all-cause mortality by two- to threefold. The presence of MASLD was associated with a twofold increased risk of developing type 2 diabetes, with a greater risk with more severe hepatic steatosis and fibrosis.[5]

The ADA recommends a general glycemic goal of HbA1c <7% in non-pregnant adults.[6] In patients with biopsy-proven MASLD, each 1% increase in HbA1c in the year preceding liver biopsy was independently associated with a 15% higher odds of harboring more severe stages of liver fibrosis, highlighting the effect of glycemia on fibrosis progression.[7]

Lifestyle modification, particularly weight reduction, remains the cornerstone in the management of MASLD. A dose-response relationship between percentage weight loss and overall improvement in liver histology has been reported; weight loss of ≥7 to 10% was required to achieve NASH resolution and improvement in hepatic fibrosis.[8] No pharmacologic agents are currently approved for treating MASLD or specifically NASH. Some antidiabetes medications should be prioritized for use in type 2 DM with MASLD, particularly those with NASH and significant fibrosis, in view of hepatic benefits or weight-reducing properties beyond HbA1c lowering. Pioglitazone and glucagon-like peptide-1 receptor agonists

(GLP-1 RA) have been recommended by the ADA as adjunctive therapy to lifestyle modifications for weight loss.[9]

Summary of the Evidence

A systematic search was conducted via PubMed, Cochrane Library, and HERDIN Plus. The search for clinical practice guidelines (CPG) did not yield any eligible publications. A search for indirect evidence yielded: (1) two randomized controlled trials[10-11] (combined n = 371) on patients with BMI ≥25 kg/m^2 evaluating the effect of GLP-1 RA on histological parameters (NASH resolution, no hepatocyte ballooning, no worsening of liver fibrosis); and (2) one meta-analysis (Musso 2017; n = 371) on patients with biopsy-proven NASH evaluating improvement in advanced fibrosis on liver biopsy (fibrosis stage F3 to F4 to F0 to F2).

Characteristics of Included Studies

The evidence base for GLP-1 RA in MASLD comprises two RCTs.[10-11] In patients with BMI ≥25 kg/m^2 with biopsy-proven NASH, evaluating GLP-1 RA versus placebo on histological parameters of NASH resolution, hepatocyte ballooning, worsening of liver fibrosis, mortality, and serious adverse events. Risk of bias was appraised using the Cochrane Risk of Bias tool.

The evidence base for pioglitazone in NAFLD comprises the meta-analysis[12] of 8 studies with post-treatment histological features of the liver. The proportion of patients with diabetes in each study ranged from 0 to 70%. Rosiglitazone was used in 3 of the 8 studies (n = 201); total N across the meta-analysis was 698. The meta-analysis assessed improvement in advanced fibrosis and NASH resolution.

Table 59. Characteristics of included studies for GLP-1 RA in MASLD

Study (author / year / citation)	Design	N	Population	Intervention	Comparator	Outcomes
Armstrong MJ et al. Lancet. 2016;387:679-690	RCT	Part of combined n = 371	BMI ≥25 kg/m^2 with biopsy-proven NASH	GLP-1 RA (liraglutide)	Placebo	NASH resolution, hepatocyte ballooning, worsening of liver fibrosis, mortality, serious adverse events
Newsome PN et al. N Engl J Med. 2021;384:113-124	RCT	Part of combined n = 371	BMI ≥25 kg/m^2 with biopsy-proven NASH	GLP-1 RA (semaglutide)	Placebo	NASH resolution, hepatocyte ballooning, worsening of liver fibrosis, mortality, serious adverse events

Table 60. Characteristics of the included meta-analysis for pioglitazone in MASLD

Study (author / year / citation)	Design	N (total)	Population	Intervention	Comparator	Outcomes
Musso G et al. JAMA Intern Med. 2017;177:633-640	Meta-analysis of 8 studies with post-treatment histological features	698 (n = 201 with rosiglitazone in 3 of 8 studies); proportion of patients with diabetes in each study ranged 0 to 70%	Adults with biopsy-proven NASH	Pioglitazone (and rosiglitazone in some included studies)	Placebo / standard care	Improvement in advanced fibrosis (F3 to F4 → F0 to F2); NASH resolution

Summary of Findings

From the GLP-1 RA evidence base (Armstrong 2016 and Newsome 2021 RCTs), pooled effect estimates from the source GRADE appraisal were:

- Resolution of MASLD / NASH (2 RCTs, n = 275): RR 2.80 (95% CI 1.63 to 4.81) - Benefit; certainty of evidence Moderate.
- Mortality (2 RCTs, n = 371): RR 1.01 (95% CI 0.04 to 24.61) - Inconclusive; certainty of evidence Very Low.
- Serious adverse events (2 RCTs, n = 371): RR 1.73 (95% CI 0.86 to 3.48) - Inconclusive; certainty of evidence Moderate.

For pioglitazone (Musso 2017 meta-analysis), source slides 14 to 17 reference forest plots for improvement in advanced fibrosis and NASH resolution; the per-outcome pooled effect estimates were displayed graphically and were not transcribed as text in the source slide deck.

Table 61. Summary of GRADE appraisal: GLP-1 RA versus placebo in MASLD[10-11]

Outcome	Basis (no. of studies; total N)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Resolution of MASLD / NASH	2 RCTs (n = 275)	RR 2.80 (1.63 to 4.81)	Benefit	Moderate
Mortality	2 RCTs (n = 371)	RR 1.01 (0.04 to 24.61)	Inconclusive	Very Low
Serious adverse events	2 RCTs (n = 371)	RR 1.73 (0.86 to 3.48)	Inconclusive	Moderate

Certainty of Evidence

Per the source: certainty of evidence was Moderate for resolution of MASLD / NASH with GLP-1 RA; Very Low for mortality; and Moderate for serious adverse events. For pioglitazone, the draft recommendation rates certainty as Low (indirectness). Review indicates that the meta-analysis may be indirect because of the population (i.e., not all studies enrolled patients with type 2 diabetes; the Musso 2017 meta-analysis included studies in which the proportion of patients with diabetes ranged from 0 to 70%).

Other considerations

Cost

Locally available antidiabetic drug classes relevant to T2DM with MASLD include biguanides (metformin), sulfonylureas, thiazolidinediones (including pioglitazone, the agent of interest for MASLD), DPP-4 inhibitors, alpha-glucosidase inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin (human and analogues). Metformin, sulfonylureas, and human insulins are available free of charge to PhP 30.00, PhP 28.25, and PhP 1,257.00 respectively under the Department of Health's Free Basic Medicine Assistance Program. There are no published cost-effectiveness studies on the use of pioglitazone or GLP-1 receptor agonists specifically as adjunctive therapy for MASLD among adult Filipinos with type 2 diabetes mellitus; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Table 62. Cost of commonly used antidiabetes drugs in the Philippines (as of 16 February 2024)

Drug Class	Price Range
Biguanide (Metformin)	Free* to PhP 30.00 per tablet
Sulfonylurea	Free* to PhP 28.25 per tablet
Thiazolidinedione (Pioglitazone)	PhP 12.75 to 30.00 per tablet
Dipeptidyl peptidase-4 inhibitor	PhP 23.50 to 53.00 per tablet
Alpha-glucosidase inhibitor (Acarbose)	PhP 7.10 to 11.65 per tablet
Sodium-glucose cotransporter 2 inhibitor	PhP 29.75 to 87.50 per tablet
Glucagon-like peptide-1 receptor agonist	PhP 1,565.00 to 6,347.00 per pen
Human insulins	Free* to PhP 1,257.00 per vial
Insulin analogues	PhP 517.00 to 1,650 per pen or vial

*Free for medications under the Free Basic Medicine Assistance Program of the Department of Health.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find dedicated studies on patient values, preferences, equity, acceptability, or feasibility for antidiabetic agent selection in T2DM patients with NAFLD.

Guideline Question 18. Should we recommend specific oral antidiabetic agents or injectable therapies to prevent the occurrence of stroke or its recurrence among adults with type 2 diabetes mellitus and established cardiovascular disease?

Recommendation 41. We suggest the use of GLP-1 receptor agonists (GLP-1 RAs)* among individuals with type 2 diabetes mellitus with established cardiovascular disease.

Certainty of Evidence: Low
Strength of recommendation: Weak

**Refers to GLP-1 receptor agonists with demonstrated cardiovascular benefit, specifically dulaglutide or semaglutide.*

Background

Some older antihyperglycemic agents (e.g., sulfonylureas, rosiglitazone) have been associated with an increased risk of stroke or did not protect against stroke. In recent years, however, randomized controlled trials on non-insulin antihyperglycemic agents have demonstrated cardiovascular safety, with some agents even showing evidence on stroke prevention (Ghosh-Swaby OR et al. Lancet Diabetes Endocrinol. 2020 May;8(5):418-435).

Per the source materials, glycemic control and glucose-lowering drugs or strategies are now known to significantly decrease the risk of atherosclerotic major adverse cardiovascular events (RR 0.92, 95% CI 0.89 to 0.95, P < 0.0001), with significant reductions in risk for cardiovascular death (RR 0.92, 95% CI 0.87 to 0.97, P = 0.004), all-cause mortality (RR 0.94, 95% CI 0.90 to 0.98, P = 0.004), fatal and non-fatal myocardial infarction (RR 0.92, 95% CI 0.88 to 0.96, P = 0.0002), and fatal and non-fatal stroke (RR 0.93, 95% CI 0.89 to 0.98, P = 0.006). The American Diabetes Association (Diabetes Care, January 2024 Standards of Care) has recommended that in people with type 2 diabetes and established ASCVD or indicators of high cardiovascular risk, an SGLT2 inhibitor or GLP-1 receptor agonist with proven cardiovascular benefit should be considered.

Summary of the Evidence

Seventeen randomized controlled trials were included for the comparison of antihyperglycemic agents on stroke outcomes in adults with type 2 diabetes mellitus, mostly with established cardiovascular disease.

Characteristics of Included Studies

Seventeen RCTs comprised the evidence base, spanning four drug classes. Four DPP-4 inhibitor RCTs were identified (TECOS - sitagliptin, N = 14,671; CARMELINA - linagliptin, N = 6,979; SAVOR-TIMI 53 - saxagliptin, N = 16,492; EXAMINE - alogliptin, N = 5,380). Four SGLT2 inhibitor RCTs (DECLARE-TIMI 58 - dapagliflozin, N = 17,160; EMPA-REG OUTCOME - empagliflozin, N = 7,020; VERTIS-CV - ertugliflozin, N = 8,246; CANVAS - canagliflozin, N = 10,142). One thiazolidinedione RCT (PROactive - pioglitazone, N = 5,238). Eight GLP-1 receptor agonist RCTs (ELIXA - lixisenatide, N = 6,068; LEADER - liraglutide, N = 9,340; SUSTAIN-6 - semaglutide, N = 2,735; EXSCEL - exenatide, N = 14,752; Harmony Outcomes - albiglutide, N = 9,463; PIONEER 6 - oral semaglutide, N = 3,183; REWIND - dulaglutide, N = 9,901; AMPLITUDE-O -

efpeglenatide, N = 4,076). The included population was adults with type 2 diabetes mellitus, mostly with established cardiovascular disease; comparator was placebo or standard of care / existing therapy (including metformin); stroke (fatal or non-fatal) was assessed as part of MACE composite endpoints in most trials. Overall risk of bias across the included trials was rated Not Serious.

Table 63. Characteristics of included CVOT trials (DPP-4 inhibitors)

Trial / Author	Country	N	Population	Duration	Intervention	Control	Primary Outcome
TECOS - Green JB et al. N Engl J Med. 2015 Jul 16;373(3):232-42.	USA	14,671 (Sita 7,332 / Placebo 7,339)	T2DM and established cardiovascular disease	3 yrs	Sitagliptin	Placebo	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
CARMELINA - Rosenstock J et al. JAMA. 2019 Jan 1;321(1):69-79.	USA	6,979 (Lina 3,494 / Placebo 3,485)	T2DM, HbA1c 6.5% to 10.0%, high CV and renal risk	2.2 yrs	Linagliptin	Placebo	Time to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke
SAVOR-TIMI 53 - Scirica BM et al. N Engl J Med. 2013 Oct 3;369(14):1317-26.	USA	16,492 (Saxa 8,280 / Placebo 8,212)	T2DM, A1c 6.5% to 12.0%, history of established CVD or multiple vascular risk factors	2.1 yrs	Saxagliptin 2.5 to 5 mg	Placebo	Composite of CV death, nonfatal MI, or nonfatal ischemic stroke
EXAMINE - White WB et al. N Engl J Med. 2013 Oct 3;369(14):1327-35.	USA	5,380 (Alo 2,679 / Placebo 2,701)	T2DM and either acute MI or unstable angina requiring hospitalization within the previous 15 to 90 days	18 mos	Alogliptin	Placebo	Composite of death from CV causes, nonfatal MI, or nonfatal stroke

Table 64. Characteristics of included CVOT trials (SGLT2 inhibitors and pioglitazone)

Trial / Author	Country	N	Population	Duration	Intervention	Control	Primary Outcome
DECLARE-TIMI 58 - Wiviott SD et al. N Engl J Med. 2019;380(4):347-357.	USA	17,160 (Dapa 8,582 / Placebo 8,578)	T2DM with or at risk for atherosclerotic CVD	4.2 years	Dapagliflozin	Placebo	Composite of MACE - CV death, MI, or ischemic stroke
EMPA-REG OUTCOME - Zinman B et al. N Engl J Med. 2015;373(22):2117-2128.	USA	7,020 (Empa 4,687 / Placebo 2,333)	T2DM with established CVD	3.1 years	Empagliflozin	Placebo	Composite of death from CV causes, nonfatal MI (excluding silent MI), or nonfatal stroke

VERTIS-CV - Cannon CP et al. N Engl J Med. 2020 Oct 8;383(15):1425-1435.	USA	8,246 (Ertu 5,499 [5 mg 2,752; 15 mg 2,747] / Placebo 2,572)	T2DM and atherosclerotic CVD	3.5 years	Ertugliflozin 5 or 15 mg	Placebo	MACE - composite of death from CV causes, nonfatal MI, or nonfatal stroke
CANVAS - Neal B et al. N Engl J Med. 2017 Aug 17;377(7):644-657.	Australia	10,142 (Cana 5,795 / Placebo 4,347)	T2DM (A1c ≥7.0% and ≤10.5%); ≥30 yo with symptomatic atherosclerotic CVD, or ≥50 yo with 2+ CV risk factors	188.2 weeks (3.92 years)	Canagliflozin	Placebo	Composite of death from CV causes, nonfatal MI, or nonfatal stroke
PROactive - Dormandy JA et al. Lancet. 2005 Oct 8;366(9493):1279-89.	UK	5,238 (Pio 2,605 / Placebo 2,633)	T2DM with evidence of macrovascular disease	34.5 month (2.88 years)	Pioglitazone 15 to 45 mg	Placebo	Composite of all-cause mortality, nonfatal MI (incl. silent MI), stroke, ACS, endovascular/surgical intervention, or amputation above ankle

Table 65. Characteristics of included CVOT trials (GLP-1 receptor agonists)

Trial / Author	Country	N	Population	Duration	Intervention	Control	Primary Outcome
ELIXA - Pfeffer MA et al. N Engl J Med. 2015 Dec 3;373(23):2247-57.	USA	6,068 (Lixi 3,034 / Placebo 3,034)	T2DM with MI or hospitalization for unstable angina within previous 180 days	25 months	Lixisenatide (10 µg/day initial, titrated to max 20 µg/day)	Placebo	CV death, MI, stroke, or hospitalization for unstable angina
LEADER - Marso SP et al. N Engl J Med. 2016 Jul 28;375(4):311-22.	USA	9,340 (Lira 4,668 / Placebo 4,672)	T2DM and high CV risk	3.8 years	Liraglutide 1.8 mg or max tolerated dose	Placebo	First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
SUSTAIN-6 - Marso SP et al. N Engl J Med. 2016 Nov 10;375(19):1834-1844.	USA	2,735 (Sema 1,648 / Placebo 1,649)	T2DM with established CVD, CKD, or both	104 weeks (2.2 years)	Semaglutide	Placebo	First occurrence of CV death, nonfatal MI, or nonfatal stroke
EXSCEL - Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239.	UK	14,752 (Exe 7,356 / Placebo 7,396); 70% with previous CVE	T2DM, with or without previous CVD	3.2 years	Exenatide 2 mg once weekly	Placebo	First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
Harmony Outcomes - Hernandez AF et al. Lancet. 2018 Oct 27;392(10157):1519-1529.	USA	9,463 (Alb 4,731 / Placebo 4,732)	T2DM and CVD	1.5 years	Albiglutide 30 to 50 mg (based on glycemic response and tolerability)	Placebo	First occurrence of CV death, MI, or stroke
PIONEER 6 - Husain M et al. N Engl J Med. 2019 Aug 29;381(9):841-851.	Canada	3,183 (Sema 1,591 / Placebo 1,592)	T2DM; aged ≥50 yrs with established CVD/CKD, or aged ≥60 yrs with CV risk factors only	15.9 months	Oral semaglutide (target 14 mg once daily)	Placebo	First occurrence of MACE: death from CV causes, nonfatal MI, or nonfatal stroke
REWIND - Gerstein HC et al. Lancet. 2019 Jul 13;394(10193):121-130.	Canada	9,901 (Dula 4,949 / Placebo 4,952)	Aged ≥50 yrs with T2DM with previous CV event or CV risk factors	5.4 years	Dulaglutide 1.5 mg once weekly	Placebo	First occurrence of composite endpoint of nonfatal MI, nonfatal stroke, or death from CV causes
AMPLITUDE-O - Gerstein HC et al. N Engl J Med. 2021 Sep 2;385(10):896-907.	Canada	4,076 (Efpe 2,717 / Placebo 1,359)	T2DM and either history of CVD or current CKD (eGFR 25.0 to 59.9	1.81 years	Efpeglenatide	Placebo	First MACE - composite of nonfatal MI, nonfatal stroke, or death from CV or

Trial / Author	Country	N	Population	Duration	Intervention	Control	Primary Outcome
			mL/min/1.73 m^2) plus at least one other CV risk factor				undetermined causes

Summary of Findings

For the outcome of fatal or nonfatal stroke (per source slide 19):

- DPP-4 inhibitors (4 RCTs, N = 43,522): effect estimate 1.01 (95% CI 0.88 to 1.15) - Inconclusive.
- Pioglitazone (1 RCT, N = 5,238): 0.81 (95% CI 0.65 to 1.06) - Inconclusive.
- SGLT2 inhibitors (3 RCTs, N = 32,426): 1.06 (95% CI 0.94 to 1.21) - Inconclusive.
- SGLT2 inhibitor (CANVAS subgroup, canagliflozin only): event rate per 1,000 patient-years 7.9 (canagliflozin) vs 9.6 (placebo); effect estimate 0.67 (95% CI 0.52 to 0.87) - Favours canagliflozin.
- GLP-1 receptor agonists (8 RCTs, N = 60,100): 0.84 (95% CI 0.76 to 0.93) - Favours GLP-1 RA.

Across all five comparisons, certainty of evidence was rated Low (per source slide 19).

Table 66. Summary of findings: fatal or nonfatal stroke in adults with T2DM and established CVD

Intervention	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
DPP-4 inhibitors	4 RCTs; N = 43,522	1.01	0.88 to 1.15	Inconclusive	Low
Pioglitazone	1 RCT; N = 5,238	0.81	0.65 to 1.06	Inconclusive	Low
SGLT2 inhibitors	3 RCTs; N = 32,426	1.06	0.94 to 1.21	Inconclusive	Low
SGLT2 inhibitor (CANVAS subgroup - canagliflozin)	1 RCT; N = 10,142; Canagliflozin 7.9 vs Placebo 9.6 per 1,000 patient-years	0.67	0.52 to 0.87	Favours canagliflozin	Low
GLP-1 receptor agonists	8 RCTs; N = 60,100	0.84	0.76 to 0.93	Favours GLP-1 RA	Low

Note: Low certainty rating reflects publication bias (industry-sponsored trials) and indiectness (stroke evaluated as part of MACE composite endpoints rather than as a primary outcome)

Certainty of Evidence

The overall certainty of evidence across all assessed antidiabetic drug classes for the outcome of fatal or nonfatal stroke was Low. The downgrade reflects publication bias (most included CVOTs were industry-sponsored), indirectness (stroke was evaluated as part of MACE composite endpoints in most trials rather than as a primary outcome), and clinical heterogeneity in baseline CV risk across trials.

Other Considerations

Cost

Locally available antidiabetic agents relevant to stroke prevention in T2DM include DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists. Per the source cost reference (South Star Drug website, January 2024), unit costs and monthly costs are summarized in the table below. None of these medications were included in the most recent Department of Health Drug Price Reference Index (DPRI 2023). There are no published cost-effectiveness studies on the use of these antidiabetic agents specifically for stroke prevention among adult Filipinos with type 2 diabetes mellitus and established cardiovascular disease; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Table 67. Locally available antidiabetic agents and monthly cost (source: South Star Drug, January 2024)

Drug class / Agent	Cost per unit (PhP)	Units per day or per month	Monthly cost (PhP, 30 days)
DPP-4i - Sitagliptin	56.25	1 per day	1,687.50
DPP-4i - Saxagliptin	56.00	1 per day	1,680.00
DPP-4i - Vildagliptin	29.00	2 per day	1,740.00
DPP-4i - Linagliptin	44.00	1 per day	1,320.00
SGLT2i - Dapagliflozin	44.00	1 per day	1,320.00
SGLT2i - Empagliflozin 10 mg	53.75	1 per day	1,612.50
SGLT2i - Empagliflozin 25 mg	55.25	1 per day	1,657.50
SGLT2i - Canagliflozin 100 mg	53.60	1 per day	1,608.00
SGLT2i - Canagliflozin 300 mg	87.50	1 per day	2,625.00
GLP-1 RA - Liraglutide 6 mg/3 mL (Victoza), 1.8 mg/day	3,173.83	3 units per month	9,521.48
GLP-1 RA - Dulaglutide 1.5 mg/0.5 mL	1,565.00	4 units per month	6,260.00
GLP-1 RA - Semaglutide 0.5 mg and 1 mg	7,880.00	1 unit per month	7,880.00

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find dedicated studies on patient values, preferences, equity, acceptability, or feasibility for the use of antidiabetic agents in stroke prevention in T2DM.

Guideline Question 19. Should we use specific oral antidiabetic agents or injectables among adults with T2DM and obesity?

Recommendation 42. We recommend the use of a GLP-1 receptor agonist as an adjunct to diet and exercise among adults with T2DM and obesity

Certainty of Evidence: Moderate
Strength of recommendation: Strong

Recommendation 43. In selecting oral glucose-lowering therapies among adults with T2DM and obesity, we suggest the use of agents that may contribute to weight loss such as metformin and/or SGLT2 inhibitors.

Certainty of Evidence: Low
Strength of recommendation: Weak

Background

Obesity is a co-morbidity usually associated with type 2 diabetes mellitus and is a risk factor for its development, with about 80 to 90% of persons with type 2 diabetes being overweight or obese. Reduction in body weight has been demonstrated to have an impact on decreasing morbidity and mortality rates. Therefore, pharmacologic agents that produce both optimal glycemic control and weight loss are preferred for persons afflicted with type 2 diabetes and obesity.[1]

A review of the impact of injectable agents on weight loss and glycemic control on patients with type 2 diabetes mellitus and obesity was conducted. Injectable agents in the form of GLP-1 receptor agonists were found to produce the most significant extent of weight reduction, in line with the target 5 to 10% of weight loss.[2] Examples of GLP-1 receptor agonists that have been associated with notable weight reduction are semaglutide, liraglutide, and dulaglutide. The target of GLP-1 receptor agonists are both central and peripheral mechanisms influencing changes in weight such as appetite, dietary habits, and blood sugar management. Various modes of action such as the slowing down of gastric emptying, decrease in gastrointestinal motility, and insulin resistance are responsible for producing the weight reduction seen in GLP-1 receptor agonist therapy.

The presence of obesity in an individual with type 2 diabetes can influence the choice of the oral antidiabetic agent to be given. In this type of patient profile, a drug that is efficacious in terms of glycemic control and at the same time does not cause weight gain - or, better yet, leads to weight loss - is ideal. Among the oral antidiabetic agents, biguanides in the form of metformin and sodium-glucose cotransporter 2 inhibitors (SGLT2-i) are not associated with weight gain and were observed to result in some degree of weight loss.

Summary of the Evidence

Four primary meta-analyses formed the evidence base for the comparison: Vosoughi et al. (2022) for GLP-1 receptor agonists vs placebo, Tsapas et al. (2021) network meta-analysis for comparative efficacy across glucose-lowering medications, Pu et al. (2020) for metformin, and Cheong et al. (2022) for SGLT2 inhibitors.[2-6] Additional safety meta-analyses were utilized for GLP-1 RA, metformin GI adverse events[7] and SGLT2-i adverse events and infection[8-10].

Characteristics of Included Studies

The meta-analysis of Vosoughi et al. included 17,183 patients who had overweight and obesity with or without type 2 diabetes mellitus from 22 placebo-controlled randomized trials which had data on the proportion of patients achieving greater than or equal to 5% or 10% weight loss. Asian individuals were included in the populations studied and the cut-off of BMI > 23 kg/m^2 was utilized for inclusion. Trials included had a follow-up period of at least 12 weeks and generally low risk of bias.

A network meta-analysis performed by Tsapas et al. included 407 randomized controlled trials with 264,578 subjects with type 2 diabetes. Almost all of the trials included patients with mean BMI in the overweight or obese range. The majority of the studies had a median duration of follow-up of 26 weeks, and were of moderate to high quality.

A meta-analysis of 21 trials (11 randomized controlled trials and one case-control study) by Pu et al. included adults with overweight and obesity and investigated the effect of metformin on weight loss, measured by the reduction in BMI compared to placebo or lifestyle modification alone. Participants in the trials were mostly Asian patients. Mean BMI of the participants ranged from 26 kg/m^2 to 41 kg/m^2. The trials exhibited an overall low risk of bias, with some degree of imprecision and heterogeneity.
For SGLT2 inhibitors, a meta-analysis (Cheong et al.) consisting of 116 trials investigated the effect of these agents in terms of reducing weight or BMI. Majority of the trials included patients with type 2 diabetes. Overall, the risk of bias across trials was low, but significant heterogeneity was observed.

Table 68. Characteristics of included meta-analyses for injectable agents.

Number of Studies	Design	Population	Comparator	Outcomes	Quality
22 (N = 17,183) - Vosoughi et al. 2022	RCT	Patients with overweight and obesity with or without T2DM	Placebo	Proportion of participants achieving ≥5% or ≥10% loss of body weight compared to baseline	Acceptable risk of bias, with considerable heterogeneity and imprecision
424 (N = 276,336) - Tsapas et al. 2021 (network MA)	RCT	Patients with T2DM, mostly with overweight or obesity	Other antidiabetic medications	Change in body weight (kg)	Generally low risk of bias, with acceptable heterogeneity and imprecision

Table 69. Characteristics of included meta-analyses for oral agents

Number of Studies	Design	Population	Comparator	Outcomes	Quality
21 (N = 1,004) - Pu et al. 2020	RCTs, case control	Adults with overweight and obesity	Placebo or lifestyle modification	Reduction in BMI with metformin use	Generally low risk of bias, imprecision and heterogeneity observed
116 (N = 98,497) - Cheong et al. 2022	RCTs	Adults taking SGLT2i	Placebo	Reduction in weight and BMI	Generally low risk of bias, significant heterogeneity

Summary of Findings

Efficacy outcomes

Administration of a GLP-1 receptor agonist resulted in significant weight loss compared to placebo. In the meta-analysis of Vosoughi et al., weight loss of at least 5% from baseline was seen in 50.2% of patients treated with GLP-1 receptor agonist and 17.1% of patients on placebo (OR 5.03, 95% CI 3.00 to 6.32). Weight loss of at least 10% from baseline was seen in 17.5% of patients given GLP-1 receptor agonist compared with only 3.1% on placebo (OR 5.31, 95% CI 3.90 to 7.22). The greatest proportion of at least 5% weight loss from baseline was seen in the group treated with semaglutide at a dose of 2.4 mg (OR 8.32, 95% CI 4.59 to 15.09). Even at a dose of less than 2.4 mg, semaglutide administration still resulted in a considerable proportion of the group experiencing at least 5% weight loss (OR 7.1, 95% CI 4.6 to 10.95).

Among 21 glucose-lowering therapies belonging to nine different drug classes, subcutaneous semaglutide was found to reduce body weight to the greatest extent (WMD −3.80 kg, 95% CI −4.46 to −3.14). Significant reductions in body weight were also observed for the other GLP-1 receptor agonists: liraglutide WMD −2.37 kg (95% CI −2.75 to −1.98) and dulaglutide WMD −0.80 kg (95% CI −1.41 to 0.19). Metformin use was observed to result in modest reductions in BMI (WMD −0.98 kg/m^2; 95% CI −1.25 to −0.72) in the meta-analysis of Pu et al. Subgroup analysis revealed that patients on more than 1500 mg/day of metformin exhibited a greater degree of decrease in BMI from baseline (WMD −1.01 kg/m^2; 95% CI −1.29 to −0.73).

Patients treated with sodium/glucose cotransporter 2 inhibitors likewise demonstrated significant reduction in weight (WMD −1.79 kg, 95% CI −1.93 to −1.66) and BMI (WMD −0.71 kg/m^2, 95% CI −0.94 to −0.47).

When compared to other antidiabetic agents, the network meta-analysis showed that metformin and SGLT2-i resulted in weight loss but to a lesser extent than GLP-1 receptor agonists. Sodium-glucose cotransporter 2 inhibitors produced a greater degree of weight loss compared with metformin: empagliflozin WMD −0.92 kg (95% CI −2.41 to −1.43), canagliflozin WMD −1.83 kg (95% CI −2.42 to −1.23), dapagliflozin WMD −1.82 kg (95% CI −2.23 to −1.41) versus metformin WMD −0.62 kg (95% CI −1.00 to −0.25).

Table 70. Summary of evidence: injectable agents (GLP-1 receptor agonists) for weight loss in T2DM and obesity

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
≥5% weight loss	22 RCTs; N = 17,183 (Vosoughi et al.)	GLP-1: 50.2%; Placebo: 17.1%; OR 5.03	3.00 to 6.32	Benefit	Moderate
≥10% weight loss	22 RCTs; N = 17,183 (Vosoughi et al.)	GLP-1: 17.5%; Placebo: 3.1%; OR 5.31	3.90 to 7.22	Benefit	Moderate
Change in body weight (kg) - Semaglutide SC	407 RCTs; N = 264,578 (Tsapas et al.)	WMD −3.80 kg	−4.46 to −3.14	Benefit	High
Change in body weight (kg) - Liraglutide	407 RCTs; N = 264,578 (Tsapas et al.)	WMD −2.37 kg	−2.75 to −1.98	Benefit	High
Change in body weight (kg) - Dulaglutide	407 RCTs; N = 264,578 (Tsapas et al.)	WMD −0.80 kg	−1.41 to −0.19	Benefit	High

Table 71. Summary of evidence: oral agents (metformin and SGLT2 inhibitors) for weight loss / BMI reduction in T2DM and obesity

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Reduction in BMI (kg/m^2) with metformin	21 RCTs / case-control; N = 1,004 (Pu et al.)	WMD −0.98	−1.25 to −0.72	Benefit	Moderate
Reduction in weight (kg) with SGLT2-i	114 RCTs; N = 98,398 (Cheong et al.)	WMD −1.79	−1.93 to −1.66	Benefit	Low
Reduction in BMI (kg/m^2) with SGLT2-i	15 RCTs; N = 1,237 (Cheong et al.)	WMD −0.71	−0.94 to −0.47	Benefit	Moderate
Reduction in weight (kg) - SGLT2-i agent-level (Cheong et al.; 116 RCTs; N = 98,497)	Empagliflozin WMD −0.92; Canagliflozin WMD −1.83; Dapagliflozin WMD −1.82; Metformin (comparator) WMD −0.62	Empa: −2.41 to −1.43 (see note above); Cana: −2.42 to −1.23; Dapa: −2.23 to −1.41; Metformin: −1.00 to −0.25	—	Benefit	High

Safety outcomes

Glucagon-like peptide 1 agonists have been found to have an excellent safety profile. A meta-analysis by Wu et al. demonstrated that GLP-1 RA administration was not associated with an elevated risk of incident arrhythmias in patients with diabetes and obesity. No significant association was found between the use of GLP-1 RA and the incidence of atrial fibrillation (RR 0.97, 95% CI 0.83 to 1.12; P = 0.65) or atrial flutter (RR 0.83, 95% CI 0.59 to 1.17; P = 0.96). The most common adverse events associated with GLP-1 RA therapy are gastrointestinal in nature, with nausea and vomiting occurring most frequently. In the meta-analysis by Vosoughi et al., liraglutide at a dose of more than 1.8 mg was found to have the highest risk of discontinuation due to adverse events (SUCRA 28.3), while dulaglutide at a dose of less than 1.5 mg was the least likely to be discontinued due to symptoms of nausea and vomiting.

Oral antidiabetic agents are generally deemed safe with a low risk of untoward events. Metformin use is associated with gastrointestinal adverse events such as abdominal pain, bloating, nausea, vomiting, and diarrhea, seen in about 20%, and leading to discontinuation of treatment in about 5% of patients. In the meta-analysis of Nabrdalik et al., metformin therapy was significantly associated with a higher incidence of abdominal pain (RR 1.491, 95% CI 1.211 to 1.836; P = 0.0001), diarrhea (RR 2.445, 95% CI 1.656 to 3.609; P = 0.0001), and nausea (RR 1.641, 95% CI 1.169 to 2.302; P = 0.0004). The extended-release formulation has been observed to be associated with lower rates of bloating and diarrhea compared with the immediate-release formulation.

Sodium-glucose cotransporter 2 inhibitors have been assessed to have a good safety profile. In the meta-analysis of Qiu et al. involving 9 trials, treatment with SGLT2-i was significantly associated with a reduced risk of atrial fibrillation (RR 0.78), heart failure (RR 0.74), and acute kidney injury (RR 0.72). In a meta-analysis of randomized controlled trials involving 50,880 patients, there was no increased probability of urinary tract infection with SGLT2-i (RR 1.03, 95% CI 0.96 to 1.11, I^2 0%); however, there was an increase in genital infections (RR 3.37, 95% CI 2.89 to 3.93, I^2 0%). A meta-analysis involving Japanese participants from 19 RCTs found no significant difference between SGLT2-i and placebo for urinary tract infection (RR 0.78, 95% CI 0.47 to 1.31; P = 0.35) or genital infection (RR 1.30, 95% CI 0.65 to 2.58; P = 0.46).

Certainty of Evidence

For the injectable agents: the 22 randomized controlled trials in Vosoughi et al. had a low risk of bias, but marked heterogeneity in population characteristics, type and dose of GLP-1 agonist, and duration of observation was observed; the certainty of evidence was therefore downgraded to Moderate. For the change in body weight outcome from Tsapas et al., the 407 randomized controlled trials had a low risk of bias and no serious issues, so the certainty of evidence was assessed as High.

For the oral agents: for the reduction of BMI with metformin, the 21 studies in Pu et al. had low risk of bias but heterogeneity among the different population groups was noted; certainty of evidence was Moderate. For SGLT2 inhibitors, 114 trials assessing weight reduction had significant heterogeneity across populations, resulting in the certainty of evidence being downgraded to Low; whereas the 116-trial assessment of BMI reduction had no serious risk of bias and certainty of evidence was deemed High.

Other considerations

Cost

The cost of injectables may present a barrier to access. Among the oral agents, metformin is the most affordable and is usually available at local health centers. There are no published cost-effectiveness studies on the use of GLP-1 receptor agonists or SGLT2 inhibitors specifically for the management of type 2 diabetes mellitus and obesity among adult Filipinos; no cost-effectiveness studies were identified for low-resource settings or populations comparable to the Philippines either.

Table 72. Locally available antidiabetic agents with weight-loss potential (unit price and monthly cost)

Medication	Unit Price (PhP)	Cost per Month (PhP)
Metformin (2000 mg)	3.50 to 18.25	420 to 2,190
Empagliflozin (25 mg)	55.25	1,657.50
Canagliflozin (300 mg)	87.50	2,625

Medication	Unit Price (PhP)	Cost per Month (PhP)
Dapagliflozin (10 mg)	44	1,230
Semaglutide (1 mg)	6,990	6,990
Dulaglutide (1.5 mg)	1,565	6,260
Liraglutide (6 mg/mL)	3,380	6,760

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found in terms of patient's values and preferences for such agents that could be utilized for diabetes and obesity.

Guideline Question 20. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and chronic kidney disease (CKD) or end-stage renal disease (ESRD) on dialysis?

Recommendation 44. We recommend the use of SGLT2i among adults with T2DM and CKD with an estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m^2.

Certainty of Evidence: High
Strength of recommendation: Strong

Good Practice Statement:
Adults with type 2 diabetes mellitus and end-stage renal disease (ESRD) on dialysis should be referred for specialist care for individualized management.

Background

The prevalence of diabetes as a cause of CKD has increased substantially over the past three decades. Individuals with diabetes and CKD are at risk for acute diabetes-related complications (hypoglycemia, ketoacidosis), chronic diabetes-related complications (retinopathy, neuropathy, foot complications), kidney failure with a need for dialysis or transplantation, and cardiovascular complications (myocardial infarction, ischemia, arrhythmia, heart failure).[1]

Management of DM in patients with CKD is challenging: many antidiabetic agents are contraindicated in advanced CKD, and others require dose adjustments due to increased risk of drug toxicity as a result of reduced renal excretion.[2] End-stage renal disease (ESRD) is a condition that predisposes to other problems: a higher risk of lactic acidosis related to metformin use (prompting cautious use in patients with progressively declining renal function), and a higher risk of hypoglycemia due to impaired regulation of gluconeogenesis and reduced insulin clearance.[3-5]

Summary of the Evidence

Glycemic Goals in CKD

The ADA states that glycemic targets must be individualized.[6] An HbA1c goal for many non-pregnant adults of <7% without significant hypoglycemia is appropriate; less stringent HbA1c goals may be more appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. The ADA also advises deintensification of diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals.

HbA1c can be confounded by CKD. Elevated serum urea concentrations or metabolic acidosis usually lead to increased levels, while anemia, shortened erythrocyte lifespan, blood transfusions, and protein-energy wasting (malnutrition-cachexia syndrome) may lead to lower levels. Data from continuous glucose monitoring show that glucose values are significantly lower on dialysis days than on non-dialysis days despite similar energy intake.[7-12]

KDIGO 2022 Recommendation Framework

The Kidney Disease: Improving Global Outcomes (KDIGO) recommends that blood glucose management of patients with type 2 diabetes (T2D) and CKD should involve lifestyle therapy, and first-line treatment with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), with additional medications as needed for glycemic control.[2] In patients with T2D, CKD and an eGFR ≥30 mL/min/1.73 m^2, metformin is recommended [Grade 1B]; metformin is inexpensive, generally well-tolerated, and effectively lowers blood glucose. In patients with T2D, CKD and eGFR ≥30 mL/min/1.73 m^2, an SGLT2i is recommended [Grade 1A]; SGLT2i have been demonstrated to confer benefits in reducing the risks of CKD and cardiovascular disease. In patients with T2D and CKD who have not yet achieved their individualized glycemic goals with metformin and SGLT2i, or are unable to use metformin and SGLT2i, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) is recommended [Grade 1B]; GLP-1RA have been demonstrated to confer benefits in reducing cardiovascular events, particularly in patients with atherosclerotic cardiovascular disease, and they also have the potential to prevent the onset of severely increased albuminuria and delay eGFR decline.

Until additional studies become available, SGLT2i are not recommended for kidney transplant patients.

Characteristics of Included Studies

The systematic search via PubMed, Cochrane Library and HERDIN Plus identified one CPG on diabetes management in chronic kidney disease (KDIGO 2022). Indirect evidence included one meta-analysis (23 RCTs, total N = 41,359) on the effect of DPP-4 inhibitors on renal outcomes in patients on dialysis (Bae 2019); two retrospective cohort studies (total N = 3,868) on use of anti-diabetic drugs in dialysis patients (Hsiao 2016; Ou 2021); and one RCT (N = 51) on the effect of dose adjustment of once-daily insulin on blood glucose and hypoglycemic events on dialysis days.[13]

Table 73. Dose adjustment of insulin in type 2 DM on hemodialysis[13]

PICO element	Detail
P	T2D on hemodialysis 3× weekly with stable once-daily insulin dose for 3 months
E	25% reduction of insulin dose
C	Standard insulin dose (with crossover after 2 weeks)
O	Pre-, 2-hour intra-, 3-hour intra-, post-dialysis blood glucose; hypoglycemia (plasma glucose <70 mg/dL)

Reduced insulin administration by 25% on the day of dialysis resulted in sustained glycemic control and stable plasma glucose levels, and fewer hypoglycemic-related symptoms (verbatim from source slide 23).

Dose adjustment for antihyperglycemic drugs in CKD

Because of reduced renal excretion, many antidiabetic drugs are contraindicated or require dose adjustments to prevent hypoglycemia. Metformin is contraindicated in patients with eGFR <30 mL/min/1.73 m^2. SGLT2i have low hypoglycemic effect in patients with impaired renal function. DPP-4 inhibitors demonstrated favorable safety profile and very low risk of hypoglycemia. Due to adverse effects (fluid retention) with thiazolidinediones, caution should be exercised in case of advanced renal dysfunction associated with ineffective diuresis. Insulin use is considered safe in patients with CKD, but there are no guidelines.

Table 74. Dose adjustment for antihyperglycemic drugs in CKD

Drug class	Medication	Recommendation
Biguanides	Metformin	Contraindicated if GFR <30 mL/min/1.73 m^2
SGLT2 inhibitors	Empagliflozin	Initiate if eGFR ≥20 mL/min/1.73 m^2. Continue until dialysis or transplant.
	Canagliflozin	—
	Dapagliflozin	—
Second-generation sulfonylureas	Glyburide	Avoid use
	Glimepiride	Start cautiously in GFR <15 mL/min/1.73 m^2
	Glipizide	No dose adjustment
	Gliclazide	No dose adjustment
Alpha-glucosidase inhibitors	Acarbose	Hypoglycemia
GLP-1 RA	Lixisenatide	Limited data for severe CKD. Not recommended with eGFR <15 mL/min/1.73 m^2.
	Liraglutide	Limited data for severe CKD
	Semaglutide (injection)	Limited data for severe CKD
	Dulaglutide	Use with eGFR >15 mL/min/1.73 m^2
Thiazolidinediones	Pioglitazone	No dose adjustment
Meglitinides	Repaglinide	Start cautiously in GFR <15 mL/min/1.73 m^2
DPP-4 inhibitors	Sitagliptin	Lower dosage
	Vildagliptin	Lower dosage
	Saxagliptin	Lower dosage
	Alogliptin	Lower dosage
	Linagliptin	No dose adjustment
Insulins	—	Dose adjustment based on patient response

Table shows agents available in the Philippines. Adapted from Gembillo G et al. Int J Mol Sci. 2021;22:4824 and KDIGO Diabetes Work Group. Kidney Int. 2022;102(Suppl 5S):S1–127.

Summary of Findings — DPP-4 inhibitor renal outcomes[10]

In a systematic review and meta-analysis of 23 randomized controlled trials (reported in 19 publications) involving 41,359 patients with type 2 diabetes, DPP-4 inhibitors were compared with placebo or other antidiabetic agents across surrogate and hard kidney outcomes. For albuminuria outcomes, DPP-4 inhibitors reduced the risk of incident microalbuminuria (RR 0.89; 95% CI, 0.80 to 0.98) and macroalbuminuria (RR 0.77; 95% CI, 0.61 to 0.97) and increased the rate of regression of albuminuria (RR 1.22; 95% CI, 1.10 to 1.35), with negligible statistical heterogeneity (I^2 = 0.0%, 1.3%, and 0.0%, respectively), although the authors noted these estimates were largely driven by a single large trial (SAVOR-TIMI 53). For the hard outcome, DPP-4 inhibitors did not reduce the risk of end-stage renal disease (RR 0.93; 95% CI, 0.76 to 1.14; I^2 = 0.0%), and overall change in urine albumin-to-creatinine ratio did not differ between groups (P = 0.150) amid substantial heterogeneity (I^2 = 67.9%). DPP-4 inhibitors were associated with a small but statistically significant decline in eGFR (WMD, −1.11 mL/min/1.73 m^2; 95% CI, −1.78 to −0.44), the clinical importance of which the authors considered uncertain. Confidence in these estimates is tempered by three author-acknowledged limitations: kidney outcomes were not prespecified endpoints in most included trials, roughly 40% of trials carried possible selection or attrition bias, and few studies contributed to the albuminuria and ESRD analyses.

Certainty of Evidence

For all-cause mortality (retrospective cohort studies on antidiabetic drug use in dialysis patients), the quality of the evidence is very low — downgraded due to inconsistency (different exposure period/duration of treatment, different dialysis modalities, concomitant treatments), indirectness (unspecified causes of death, different baseline characteristics, different dialysis modalities), and imprecision. Studies included had high methodological and clinical heterogeneity.

Other considerations

Cost

The cost of commonly used anti-diabetes drugs in the Philippines is shown below (as of 16 February 2024, verbatim from source slide 24).

Table 75. Cost of commonly used anti-diabetes drugs in the Philippines (as of 16 February 2024)

Drug Class	Price Range
Biguanide (Metformin)	Free* to PHP 30.00 per tablet
Sulfonylurea	Free* to PHP 28.25 per tablet
Thiazolidinedione (Pioglitazone)	PHP 12.75 to 30.00 per tablet
Dipeptidyl peptidase-4 inhibitor	PHP 23.50 to 53.00 per tablet
Alpha-glucosidase inhibitor (Acarbose)	PHP 7.10 to 11.65 per tablet
Sodium-glucose cotransporter 2 inhibitor	PHP 29.75 to 87.50 per tablet
Glucagon-like peptide-1 receptor agonist	PHP 1,565.00 to 6,347.00 per pen
Human insulins	Free* to PHP 1,257.00 per vial
Insulin analogues	PHP 517.00 to 1,650 per pen/vial

*For medications under the Free Basic Medicine Assistance Program of the Department of Health.

There is no published Philippine cost-effectiveness analysis specific to the use of any individual anti-diabetes class in patients with type 2 diabetes mellitus and CKD or ESRD on dialysis. Pricing reflects current local retail ranges; out-of-pocket cost may be substantially lower for patients qualifying for the DOH Free Basic Medicine Assistance Program.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

We did not find dedicated studies on Patient's Values and Preference, Equity, Acceptability, and Feasibility among adults with T2DM and CKD or ESRD.

Guideline Question 21. Should we recommend specific oral antidiabetic agents or injectables among adults with T2DM and cirrhosis or chronic liver disease (CLD)?

Recommendation 45. We suggest the use of metformin and/or sulfonylureas as the initial treatment(s) among adults with T2DM and cirrhosis

Certainty of Evidence: Low
Strength of recommendation: Weak

Recommendation 46. We suggest the use of insulin in patients with severe hyperglycemia [glycosylated hemoglobin (HbA1C) >10% or fasting plasma glucose (FPG) >300 mg/dL] among adults with T2DM and cirrhosis

Certainty of Evidence: Low
Strength of recommendation: Weak

Background

Diabetes and liver cirrhosis have a bidirectional pathophysiologic association. In the presence of both conditions, insulin resistance in the adipose and muscle tissues, the compensatory hyperinsulinemia by the pancreas, in addition to reduced hepatic insulin clearance, all contribute to further dysregulation of glucose metabolism.[1] A recent literature review of liver outcomes in patients with cirrhosis has shown that the presence of diabetes increased the risk of hepatic encephalopathy, variceal hemorrhage, variceal rebleeding, hepatocellular carcinoma and adverse outcomes in liver transplantation. Uncontrolled diabetes was found to be associated with increased risk of bacterial infections.[2]

Summary of the Evidence

Glycemic Goals

The general glycemic goal of HbA1c <7% is recommended by the American Diabetes Association (ADA) for most non-pregnant adults.[3] In situations where the risks of treatment outweigh the benefit of intensive glucose control, a less stringent goal, such as HbA1c <8% may be more appropriate, as recommended by the ADA.[4-5]

Anti-diabetes Medications

There is no clear evidence on the most appropriate medication for glycemic control in chronic liver disease and cirrhosis. Anti-diabetes medications in chronic liver disease have not been extensively studied. Because of the role of the liver as the primary site for metabolism of most medications, those with liver cirrhosis may also have decreased metabolism of anti-diabetes drugs.[6-8] The recommendations are mostly based on pharmacokinetic and drug safety studies.

Characteristics of Included Studies

The drug-class characteristics drawn from Tsapas A et al.[9], Williams Textbook of Endocrinology 14th edition[10] and ADA Standards of Care[11]. The figures below are transcribed verbatim and reflect general T2DM efficacy and safety considerations.

Table 76. Characteristics of anti-diabetes drug classes

Drug class / agent	HbA1c reduction, drug-naive %	HbA1c reduction, with background metformin %	Adverse events / other considerations
Metformin	0.92	—	Bloating, abdominal discomfort, diarrhea; very rarely, lactic acidosis. Associated with vitamin B12 deficiency and worsening of neuropathic symptoms. Contraindicated if eGFR <30 mL/min/1.73 m^2.
Sulfonylureas (second generation)	0.86	0.57	Caution in patients at risk for hypoglycemia. Glibenclamide generally not recommended in CKD.
Thiazolidinediones (Pioglitazone)	0.89	0.60	Fluid retention, edema, heart failure, weight gain. Generally not recommended in patients with renal impairment and heart failure due to fluid retention.
DPP-4 inhibitors	0.60	0.53	Joint pain, bullous pemphigoid. Although causality of pancreatitis has not been established, discontinue if with suspicion of pancreatitis.
SGLT2 inhibitors	0.81 to 1.02	0.51 to 0.63	Increased risk of genital mycotic infections. Rarely: DKA, necrotizing fasciitis of the perineum; discontinue if suspected.
GLP-1 RA	1.29 to 1.48	0.80 to 1.33	Gastrointestinal side effects. Although causality of pancreatitis has not been established, discontinue if with suspicion of pancreatitis.
Basal insulin	1.12	0.71	Hypoglycemia, weight gain, injection site discomfort; rarely, lipoatrophy and lipohypertrophy. May require more frequent self-monitoring of blood glucose.
Premixed insulin	1.03	0.89	Hypoglycemia, weight gain, injection site discomfort; rarely, lipoatrophy and lipohypertrophy. May require more frequent self-monitoring of blood glucose.

Certainty of Evidence

The overall certainty of evidence is low. The evidence was downgraded primarily for indirectness, as the included studies were largely drawn from populations not restricted to adults with type 2 diabetes mellitus and cirrhosis or chronic liver disease (CLD), and for imprecision arising from small sample sizes and wide confidence intervals around the pooled estimates. Limitations in study design (risk of bias) and variation across interventions and outcomes (inconsistency) further reduced confidence in the estimates.

Other considerations

Cost

The cost of commonly used anti-diabetes drugs in the Philippines is shown below.

Table 77. Cost of commonly used anti-diabetes drugs in the Philippines

Drug Class	Price Range
Biguanide (Metformin)	Free* to PHP 30.00 per tablet
Sulfonylurea	Free* to PHP 28.25 per tablet
Thiazolidinedione (Pioglitazone)	PHP 12.75 to 30.00 per tablet
Dipeptidyl peptidase-4 inhibitor	PHP 23.50 to 53.00 per tablet
Alpha-glucosidase inhibitor (Acarbose)	PHP 7.10 to 11.65 per tablet
Sodium-glucose cotransporter 2 inhibitor	PHP 29.75 to 87.50 per tablet

Drug Class	Price Range
Human insulins	Free* to PHP 1,257.00 per vial
Insulin analogues	PHP 517.00 to 1,650 per pen/vial

*For medications under the Free Basic Medicine Assistance Program of the Department of Health.

There is no published Philippine cost-effectiveness analysis specific to the use of any individual anti-diabetes class in patients with type 2 diabetes mellitus and cirrhosis or chronic liver disease. Pricing reflects current local retail ranges; out-of-pocket cost may be substantially lower for patients qualifying for the DOH Free Basic Medicine Assistance Program.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies directly addressing patient values and preferences, equity, acceptability, or feasibility were found for the use of specific oral antidiabetic agents or injectable therapies among adults with type 2 diabetes mellitus and cirrhosis or chronic liver disease.

Chapter 4. Application and Implementation

External review

The Clinical Practice Guideline (CPG) manuscript **underwent** a structured external review process. This process **involved** the engagement of external reviewers representing end-users, stakeholders, or technical experts who **performed** a comprehensive review of the draft manuscript. The external review **focused** on evaluating methodological rigor, local applicability, and general usability. The following review process **was implemented**:

1. **Methodological Review** – A clinical epidemiologist or guideline methodology expert **assessed** the methodological rigor and reporting quality of the CPG using the AGREE-II checklist (non-scored version).
2. **Content Expert Review** – A content expert / clinician **evaluated** the technical soundness and relevance of the recommendations using the AGREE-REX checklist, focusing on clinical validity and applicability.
3. **Non-Content Expert Review** – A clinician without specialized expertise in the topic area **provided** feedback to ensure the recommendations were clear, applicable, and user-friendly for broader audiences.

External reviewers also **provided** their feedback using a structured template that **addressed** the following aspects for each recommendation:

- General response to the guideline as a whole
- Specific comments or feedback on individual recommendations
- Assessment of completeness in terms of search and synthesis of the evidence base
- Evaluation of the acceptability of the recommendation statement, including justification for agreement or disagreement
- Suggestions for alternative recommendation statements, if applicable
- Comments on the rationale behind the recommendation, such as consensus issues, trade-offs between benefits and harms, cost considerations, patient preferences, availability, and feasibility
- Feedback on the implementability of the recommendations

Feedback from the external reviewers **was consolidated** and **deliberated upon** by the Steering Committee (SC) and Overall Technical Lead. A consensus-based approach **was followed** to address all comments and ensure relevant feedback **was incorporated** into the final manuscript. After resolving all identified issues, the Technical Writer **prepared** the final version of the manuscript, integrating approved revisions. This final draft **was submitted** to the DOH National Practice Guidelines Program for further review and approval.

Dissemination

The CPG was submitted to the Department of Health (DOH) National Practice Guideline Clearinghouse for review, assessment, and approval. The DOH, PCEDM, and other collaborating organizations will promote the use and adoption of these recommendations nationwide through publications, lectures, and various forms of communication targeting relevant stakeholders.

Dissemination efforts will include presentations at conferences and stakeholder meetings, submission for publication in both local and international journals, and availability of the guideline through the official platforms of the Philippine College of Endocrinology, Diabetes, and Metabolism and the Compendium of DOH-Approved Clinical Practice Guidelines (https://doh.gov.ph/dpcb/doh-approved-cpg/).

The DOH will distribute copies of the CPG to the Philippine Health Insurance Corporation, health maintenance organizations, and pharmaceutical partners. Additionally, the guideline will be presented during medical society conferences and annual conventions. Endorsed copies will also be sent to medical schools and libraries to support integration into training curricula, with the collaboration of faculty members and department heads from relevant medical specialties.

Implementation strategies

To facilitate the nationwide uptake of the newly developed guidelines for screening and diagnosis of diabetes and pre-diabetes, implementation tools will be developed either de novo or adapted from existing resources. Protocols, algorithms, and care pathways will be designed to be culturally relevant, ensuring accessibility and practicality across diverse local settings. The Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM), in collaboration with the Department of Health (DOH), will employ a comprehensive implementation and monitoring strategy that includes capacity-building, system support, and performance tracking mechanisms.

Implementation tools will be developed de novo or adapted from existing resources. These include:

1) Standardized protocols, algorithms, and care pathways tailored to the Philippine context, designed to be relevant across diverse local settings including primary care and community health stations.
2) Educational resources, including training modules, presentation slides, and case studies.
3) Digital platforms (e.g., interactive websites, mobile-accessible portals) for dissemination of tools, continuing education, and updates.

In partnership with government agencies, academic institutions, local governments, and professional societies, the PCEDM aims to promote widespread access and uptake of the CPG through medical societies, webinars, CME programs, and facility-based rollouts.

Availability of Implementation Tools

In accordance with the AGREE II checklist, the guideline development process considers the availability of practical implementation tools that support the application of recommendations in clinical practice. As part of this consideration, existing implementation-oriented guideline materials developed in other health systems, such as those from Canada (https://guidelines.diabetes.ca/cpgrefguide), were identified as reference examples that illustrate how clinical practice guidelines may be operationalized at the point of care.

These materials do not replace the full guideline document but are designed to translate recommendations into concise, actionable formats, including algorithms, tables, targets, and safety prompts. While direct transferability cannot be assumed, these tools demonstrate established

approaches used internationally and may serve as models for potential adoption or adaptation to the Philippine context, taking into account local epidemiology, health system capacity, and resource availability.

The 2025 Canadian Clinical Practice Guidelines Quick Reference Guide provides an example of how guideline recommendations are accompanied by embedded implementation tools to facilitate screening, diagnosis, management, monitoring, and patient safety. The following section enumerates and describes these actual implementation tools as examples of approaches used in other countries.

Examples of Implementation Tools Used in Other Settings (Canadian Experience)

1. Screening and Diagnostic Algorithms

The 2025 Canadian Clinical Practice Guidelines Quick Reference Guide includes structured screening and diagnostic pathways that specify:

- Eligibility for screening based on age and risk category
- Recommended screening intervals for different risk strata
- Diagnostic thresholds and confirmatory testing strategies using A1C, fasting plasma glucose, OGTT, or random plasma glucose

These pathways function as clinical decision support tools that promote consistency in screening and diagnosis and may inform locally adapted algorithms.

2. Risk-Based Screening Tools

The document references the use of a validated diabetes risk calculator (e.g., CANRISK) to guide screening decisions. This reflects the incorporation of risk stratification tools within guideline implementation and provides an example of how risk-based screening approaches may be operationalized using validated instruments.

3. Treatment Targets as Monitoring and Audit Tools

The 2025 Canadian Clinical Practice Guidelines Quick Reference Guide presents explicit treatment targets, including:

- A1C targets tailored to patient characteristics (e.g., frailty, hypoglycemia risk, life expectancy)
- Fasting and post-prandial blood glucose targets
- Continuous glucose monitoring (CGM) metrics such as time in range, time below range, and glycemic variability

These targets function as monitoring and audit reference points, supporting evaluation of practice alignment with guideline recommendations.

4. Pharmacotherapy Pathways Linked to Comorbidities

Structured guidance is provided for pharmacologic management based on the presence of comorbid conditions such as atherosclerotic cardiovascular disease, chronic kidney disease, and heart failure. This represents a prescribing support tool that translates recommendations into clinically actionable treatment pathways.

5. Dose Adjustment Tables Based on Kidney Function
The 2025 Canadian Clinical Practice Guidelines Quick Reference Guide includes tabulated dose recommendations and restrictions for antihyperglycemic agents according to estimated glomerular filtration rate (eGFR). These tables function as medication safety tools that support appropriate dosing and monitoring in patients with impaired kidney function.

6. Safety and Sick-Day Management Guidance
In the 2025 Canadian Clinical Practice Guidelines Quick Reference Guide, practical guidance is provided on sick-day management, including hydration advice and temporary withholding of specific medication classes during acute illness or dehydration risk. These elements serve as patient safety and self-management support tools that may be adapted for local patient education and clinical protocols.

7. Checklists for Special Populations
The 2025 Canadian Clinical Practice Guidelines Quick Reference Guide includes structured guidance for specific populations, such as individuals planning pregnancy, outlining glycemic targets, medication adjustments, screening requirements, and referral considerations. This functions as a checklist-style implementation tool for managing defined clinical scenarios.

Collectively, these examples illustrate that actual implementation tools are embedded within guideline materials used in other countries, providing concrete models for operationalizing recommendations. While these tools are not prescriptive for local use, they demonstrate approaches that may be considered for adoption or adaptation in the Philippine context, consistent with AGREE II principles on applicability, feasibility, and implementation support.

The PCEDM will also offer training on monitoring and auditing techniques to healthcare providers and encourage benchmarking against national and international standards to drive continuous improvement. Standardized reporting requirements will be established to promote adherence to evidence-based practices, particularly in facilities implementing diabetes screening programs.

To ensure ongoing refinement and alignment with clinical practice needs, the PCEDM plans to implement robust feedback mechanisms. Feedback will be gathered through online surveys, email correspondence, and dedicated feedback forms, allowing healthcare professionals to provide comments, suggestions, and share their experiences. These insights will be invaluable for the continuous improvement of the guidelines and their practical application in real-world settings.

Criteria to Assess Implementation and Adherence

To assess implementation and adherence to the CPG recommendations, the following key performance indicators (KPIs) and operational definitions may be used. These indicators are derived from strong recommendations and key steps in the screening and diagnostic process:

Indicator	Operational Definition	Level of Measurement
% of adults ≥40 years screened for diabetes	Numerator: Adults ≥40 years screened using FBG or HbA1c within the last 3 years; Denominator: All adults ≥40 years seen in outpatient settings	Facility-level
% of patients with impaired FBG who received confirmatory testing (OGTT or HbA1c)	Numerator: Patients with FBG 100–125 mg/dL who underwent OGTT/HbA1c; Denominator: All patients with impaired FBG	Individual-level
% of new T2DM diagnoses based on recommended tests	Numerator: Patients diagnosed with T2DM using FBG, 2h-OGTT, or HbA1c; Denominator: All newly diagnosed patients with T2DM	Facility-level
% of primary care providers trained on the CPG	Numerator: Providers who completed CPG training; Denominator: All target providers in participating regions	Regional/national

These indicators may be refined through pilot testing and finalized in consultation with the DOH.

Evaluation of Impact

The PCEDM, in coordination with academic partners, will assess the real-world impact of guideline adoption through both qualitative and quantitative approaches. Impact may be evaluated through:

- Trends in early detection rates of diabetes and pre-diabetes
- Changes in HbA1c values or diagnostic delays pre- vs post-CPG dissemination
- Provider adherence to recommended screening pathways
- Reduction in missed or delayed diagnoses
- Patient outcomes and satisfaction (through surveys or interviews)

Tools and Resources to Support Implementation

To improve adherence and uptake, the Task Force will develop and disseminate:

- Quick reference guides and decision aids tailored to primary care settings
- Training modules and webinars for clinicians on how to implement key recommendations
- Patient education materials (e.g., leaflets, posters, digital content) in both English and Filipino
- EMR-integrated prompts and order sets based on CPG pathways

Equity, Acceptability, and Feasibility Assessment

Initial and ongoing evaluations of the equity, acceptability, and feasibility of the CPG across diverse healthcare settings (rural vs urban, public vs private) will be conducted through key informant interviews and focus group discussions with:

- Frontline healthcare workers
- Patients and caregivers

- Local health system administrators

Findings will inform revisions to future versions of the guideline and highlight areas requiring targeted implementation support.

Monitoring, Auditing, and Feedback Mechanisms

The PCEDM will offer training on monitoring, evaluation, and audit techniques to healthcare providers, enabling self-assessment and benchmarking. Recommended strategies include:

- Use of audit templates for facility-level review of screening practices
- Annual or bi-annual benchmarking reports aligned with national targets
- Development of a CPG implementation dashboard for internal quality improvement

A set of standardized reporting requirements may be developed for programs and institutions conducting systematic diabetes screening, in alignment with DOH monitoring protocols.

Feedback and Continuous Improvement

Robust feedback mechanisms will be integrated to support iterative refinement of both guideline content and implementation strategies. Channels include:

- Anonymous online feedback forms embedded in training platforms
- Periodic surveys targeting healthcare professionals and program implementers
- Stakeholder consultations and key informant interviews to identify barriers and enablers

Findings from the feedback process will be reviewed annually and used to inform guideline updates and improvements in implementation support.

Facilitators and barriers to application or compliance to the recommendations

After discussions with the multistakeholder group throughout the CPG development process, information on the types of facilitators and barriers emerged. Additional feedback was sought from other key stakeholders through dialogues or external communications. These methods included identifying facilitators (e.g., government support for medications and services, advocacy group activities) and barriers (e.g., out-of-pocket healthcare payments, availability of specific machines/laboratory tests/reagents). This information influenced the value judgments of the consensus panel during discussions and the formulation of recommendation statements and the strength of each recommendation.

Monitoring and evaluation

The Task Force will distribute an annual questionnaire to identify best practices among relevant stakeholders regarding the screening and diagnosis of diabetes and pre-diabetes. Monitoring the use of this clinical practice guideline may also serve as a topic for research by interested parties. For monitoring and auditing, the CPG group will use the final strength of recommendation to establish key performance indicators. Recommendations classified as “Strong Recommendation” will serve as the primary indicators. These indicators will be identified once the strength of recommendations has been finalized for each guideline review question.

Specific operational definitions for measuring the criteria will be aligned with the recommended standards outlined in the DOH Manual for CPG Development. These definitions will also be determined following consultations with the Department of Health (DOH), as local literature on these measurements is currently limited.

Frequency and Interval of Monitoring and Audit

- Routine monitoring of guideline uptake and implementation may be undertaken as part of existing quality assurance and clinical audit activities at the facility, institutional, or program level.
- Audit of adherence to selected key recommendations, particularly those rated as strong recommendations, may be conducted periodically, such as annually or biennially, depending on local capacity, data availability, and alignment with institutional audit cycles.
- Feedback from end users (e.g., primary care physicians, specialists, and other stakeholders) may be collected on an ongoing basis, particularly during the early phases of dissemination, to identify barriers to implementation and areas requiring clarification or contextualization.
- Findings from monitoring and audit activities are intended to inform quality improvement initiatives and guide refinements in dissemination strategies.

Chapter 5. Updating of the Clinical Practice Guideline

The recommendations in this CPG are considered valid until the emergence of new evidence or contextual developments that materially alter the balance of benefits and harms, the certainty of evidence, or the feasibility of implementation for any guideline question. Under Administrative Order No. 2023-0002 (Institutionalization of the Expanded National Practice Guidelines Program), DOH-approved CPGs carry a validity period of five years, after which updating by the lead developer is required. Consistent with the DOH–PhilHealth Manual for Clinical Practice Guideline Development, the Steering Committee (SC), together with the evidence review experts (EREs) and the Consensus Panel (CP), set the expiration date of this guideline and finalized the plan for its updating at the close of the development process.

The expiration date of this CPG is **three years from date of publication (e.g., 2029)**, which is earlier than the five-year DOH validity period, reflecting the pace at which evidence in the management of type 2 diabetes mellitus is expected to change.

Updating is not a separate or abbreviated exercise. Any revision of a recommendation follows the same methodological standards applied in the original development of this CPG — systematic search, critical appraisal, GRADE certainty assessment, Evidence-to-Decision deliberation, and formal voting by a multistakeholder Consensus Panel operating under the same conflict-of-interest (COI) safeguards described in Chapter 2.

Triggers for Updating

An update of all or part of this CPG will be initiated when any of the following conditions is identified:

1. **New evidence.** Publication of adequately powered randomized controlled trials, high-quality systematic reviews or meta-analyses, network meta-analyses, or long-term outcome or safety data that could plausibly change the direction, strength, or certainty of an existing recommendation, or that address a question for which evidence was previously judged insufficient.
2. **New or reclassified health technologies.** Registration by the Philippine Food and Drug Administration of new pharmacologic agents, formulations, devices, or diagnostic assays relevant to the management of type 2 diabetes mellitus; withdrawal or restriction of a currently recommended agent; or the emergence of biosimilars, generics, or fixed-dose combinations that materially change availability or cost.
3. **Policy, financing, or access shifts.** Changes in PhilHealth benefit packages, outpatient benefit or Konsulta provisions, the Philippine National Formulary, DOH administrative orders or service delivery guidelines, Health Technology Assessment Council appraisals, or procurement and supply arrangements that affect the applicability or implementability of a recommendation.
4. **New safety signals.** Post-marketing surveillance findings, regulatory advisories, or pharmacovigilance reports indicating harms not accounted for in the original evidence base.
5. **Equity and health system considerations.** Evidence of widening disparities in access to recommended interventions, or findings from monitoring and evaluation (M&E) and end-user

feedback indicating consistent implementation barriers, misinterpretation, or non-adoption of specific recommendations.

6. **Substantial revision of high-quality international guidelines.** Material changes in source guidelines that met the AGREE II inclusion criteria used in this CPG (Annex C), or in other guidelines subsequently appraised as eligible, that warrant local reassessment and contextualization.
7. **Identified errors or ambiguities.** Errata, internal inconsistencies, or clarifications raised by end users, external reviewers, or the DOH National Practice Guidelines Program (NPGP).

Updating Mechanisms

Routine review cycle. This CPG will undergo comprehensive review and, where indicated, revision every three years, counted from the date of DOH NPGP approval. This interval is shorter than the five-year validity period prescribed under AO 2023-0002 and is adopted deliberately: the volume of new trial evidence, newly registered agents, and changes in formulary and benefit coverage relevant to the management of type 2 diabetes mellitus is such that a five-year interval risks the guideline falling out of step with practice. Should the three-year review determine that no revision is warranted, the finding is documented and the guideline is reaffirmed, with the next review scheduled accordingly and the DOH five-year validity period unaffected.

Annual evidence surveillance. In the intervening years, the Technical Working Group (TWG) of the PCEDM, acting under the direction of the SC, will conduct annual horizon scanning to detect any of the triggers listed above. Surveillance does not automatically result in revision; it results in a documented determination for each guideline question.

Interim or rapid focused update. Where a trigger is judged urgent — particularly a new safety signal, a regulatory withdrawal, or a practice-changing trial affecting a Strong recommendation — the SC, in consultation with the DOH NPGP, may initiate a focused update of the affected recommendations at any time, without waiting for the routine cycle.

Evidence Surveillance: How New Evidence Will Be Identified

The SC will designate, from among the EREs and TWG members, a surveillance team with a nominated lead. The team is responsible for executing the annual scan and preparing the Evidence Surveillance Report.

Search re-execution. The search strategies documented for each guideline question in Annex E — including database, MeSH and free-text terms, and filters — are retained as the standing search protocol. At each surveillance round, these strategies are re-run without modification, restricted by publication or entry date to the period beginning on the closing date of the most recent search for that question. Where a strategy is found to have been insufficiently sensitive, it is revised, the revision is documented, and the search is re-run in full rather than date-limited.

Sources scanned. Surveillance covers the same sources used in the original evidence synthesis, supplemented by regulatory, policy, and trial-registry sources (Table 1).

Table 1. Sources scanned during annual evidence surveillance.

Domain	Sources scanned
Bibliographic databases	MEDLINE via PubMed; Cochrane CENTRAL and Cochrane Database of Systematic Reviews; Google Scholar
Local evidence	HERDIN Plus; PCEDM registry of researches; theses and registry outputs from endocrinology training institutions
Ongoing and unpublished studies	ClinicalTrials.gov; WHO International Clinical Trials Registry Platform; conference proceedings of major diabetes and endocrine societies
Guidelines	Source guidelines previously appraised with AGREE II (Annex C) and their subsequent editions; newly published international and regional guidelines
Regulatory and safety	Philippine Food and Drug Administration registrations and advisories; international regulatory safety communications
Policy and financing	DOH administrative orders and circulars; PhilHealth circulars and benefit package issuances; Philippine National Formulary; Health Technology Assessment Council appraisal outputs
Implementation feedback	Monitoring and evaluation returns, audit findings, and end-user feedback collected under Chapter 4

Screening and appraisal. Titles and abstracts retrieved through surveillance are screened independently by two reviewers against the original eligibility criteria for the corresponding PICO question, with disagreements resolved by discussion or by referral to a third reviewer. Newly identified guidelines are appraised with AGREE II using the same inclusion thresholds applied in this CPG (an overall score of at least 5 from both appraisers with an affirmative recommendation for use, and a Rigour of Development domain score of at least 70%). Newly identified primary studies and systematic reviews are appraised using the instruments appropriate to their design, as used in this CPG.

Triage and determination. For each guideline question, the surveillance team assigns one of the statuses in Table 2.

Table 2. Triage of guideline questions following annual evidence surveillance.

Status	Basis	Action
Current	No new eligible evidence, or new evidence consistent with and not adding materially to the existing body	No action; status documented and carried to the next cycle
Monitor	New evidence identified but of insufficient size, quality, or directness to alter the recommendation; or ongoing trials with anticipated completion	Re-examined at the next surveillance round; flagged if interim results emerge
Update indicated	New evidence, safety signal, technology, or policy change with reasonable likelihood of altering the direction, strength, or certainty of the recommendation	Referred to the SC with a summary of the signal and a proposed scope of work
Urgent	Safety signal, regulatory withdrawal, or restriction affecting a currently recommended intervention	Immediate referral to the SC and DOH NPGP for interim update

Reporting. The surveillance team submits an annual Evidence Surveillance Report to the SC, containing the dates and yields of re-run searches, the appraisal outcomes for newly identified evidence, the status assigned to each guideline question with justification, and a recommended scope of update. The report is retained as part of the guideline documentation and is made available to the DOH NPGP on request.

Determining the Scope of the Update

On receipt of the Evidence Surveillance Report, the SC, in consultation with the DOH NPGP, determines the scope of work (Table 3).

Table 3. Scope of update and corresponding process.

Scope	Applies when	Process
No revision	All questions assessed as Current or Monitor	Status documented; publication date of next review reaffirmed
Editorial correction	Typographical errors, clarifications, or formatting corrections with no change in meaning	Issued as an erratum by the SC and Technical Writer; no CP deliberation required
Focused (partial) update	One or more specific recommendations affected	Full methodological process applied to the affected questions only; unaffected recommendations are carried forward unchanged with their original evidence base and date of last search stated
Full revision	Multiple domains affected, the scope or clinical questions require reformulation, or the routine three-year cycle has elapsed	Complete re-execution of the guideline development process, including review of the guideline scope, clinical questions, and critical outcomes

Where a focused update or full revision is indicated, the SC — together with the EREs and CP — will prepare an update protocol specifying the guideline questions to be revisited, the search and appraisal methods, the composition of the update group, the COI management plan, and the quality indicators to be used for monitoring and evaluating the updated recommendations. Consistent with the DOH–PhilHealth Manual for CPG Development, this protocol will be submitted to the DOH for approval before the update is implemented.

Recommendations carried forward without revision will be explicitly labeled as such, with the date of the last evidence search retained, so that end users can distinguish reaffirmed from revised recommendations.

Convening the Update Group

Steering Committee. The SC is reconstituted for each update. Continuity is maintained by retaining a proportion of members from the preceding cycle to preserve institutional memory, while incorporating new members to broaden expertise and mitigate entrenchment. The SC retains an overall chair without relevant conflicts of interest, consistent with the arrangement used in the original development of this CPG.

Evidence review experts and Technical Working Group. EREs are drawn from the endocrinology training institutions and the PCEDM technical working group, and are organized into teams of three to four members per question, as in the original development. Each ERE team is paired to include members with no or minimal conflicts of interest, and each team's output is presented first within the team and then to the larger group of EREs for methodological review before it reaches the CP. A methodologist or clinical epidemiologist is retained to oversee search execution, appraisal, GRADE application, and Evidence-to-Decision documentation.

Consensus Panel. The CP is reconvened as a multistakeholder body reflecting the same composition principles applied in the original development, with organizations formally requested to nominate representatives for the update. Representation will include, at a minimum:

- Diabetes and endocrine organizations — the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM), the Philippine Center for Diabetes Education Foundation, Inc. (PCDEFI), and Diabetes Philippines
- Allied medical and specialty societies relevant to the scope of the questions under review — including but not limited to the Philippine College of Physicians, the Philippine Society of General Internal Medicine, the Philippine Academy of Family Physicians, the Philippine Heart Association, the Philippine Society of Nephrology, and the Philippine College of Occupational Medicine, with additional societies invited where the questions under review require their expertise
- Lay and patient representation — the Philippine Alliance of Patient Organizations and hospital-based diabetes clubs, with at least one person living with diabetes present at each consensus meeting
- Non-voting representatives of the DOH and PhilHealth, participating as resource persons on policy, financing, and implementation

Facilitation and documentation. A technical facilitator without conflicts of interest on the topics under review moderates all consensus meetings, calls declarations of interest, and administers voting. A Technical Writer prepares the revised manuscript and maintains the change log.

Convening procedure. Once the SC approves the scope of the update, letters of invitation and terms of reference are issued to the participating organizations, specifying the questions to be deliberated, the expected number of meetings, and the COI requirements. Evidence summaries, GRADE evidence profiles, and draft recommendation statements are circulated to CP members in advance of each meeting, as in the original process.

Managing Conflicts of Interest During the Update

The COI process is re-executed in full for every update; declarations made during the original development do not carry over.

1. **Declaration.** All members of the SC, ERE/TWG, and CP complete the standard DOH Declaration of Conflict of Interest form before any participation, disclosing financial and intellectual interests covering the four years preceding their involvement in the update, and submit an updated curriculum vitae.
2. **Independent review.** An external Conflict of Interest Review Committee (COIRC), contracted by the SC and independent of the participating organizations, reviews all declarations and curricula vitae before the first consensus meeting of the update — correcting the timing limitation acknowledged in the original development — and classifies each participant as Allowed/Acceptable, Manageable B (Broadcast), Manageable C, or Disqualified, in accordance with the definitions used in this CPG.
3. **Terms of participation.** Members classified as Manageable B may vote but must declare their interests at each en banc meeting and before each affected recommendation. Members classified

as Manageable C may participate in discussion as resource persons but may not vote. Members classified as Disqualified do not participate.

4. **Advance circulation and substitution.** Because the questions to be deliberated are circulated in advance, organizations whose designated representative holds a disqualifying interest on a given question may nominate an alternate representative for that session.
5. **Meeting-level declaration and recusal.** At the start of each meeting, and again before each recommendation is deliberated, the technical facilitator calls for declarations. Members with significant conflicts on the recommendation under discussion recuse themselves from voting; where they contribute to discussion, the conflict is stated on the record.
6. **Process safeguards.** ERE assignments are structured so that reviewers are not assigned to questions in which they hold direct conflicts; draft outputs are cross-checked within and across ERE teams and monitored by the SC, technical facilitator, and methodologist; divestment or resignation from conflicting positions is requested where feasible; and members of the SC with significant conflicts are replaced.
7. **Transparency.** All declarations and their classifications are documented and published with the updated guideline, using the tools in Annex A.

Evidence Synthesis and Recommendation Development for the Update

Updated recommendations are developed using the identical methodology described in Chapter 2:

- Clinical questions are expressed in PICO format, with the population component specified in full; questions may be reformulated where new interventions, comparators, or outcomes have emerged.
- Critical outcomes are re-reviewed and, where the evidence base or stakeholder priorities have shifted, re-rated on the GRADE 1-to-9 scale, with input from persons living with diabetes.
- Evidence is drawn first from source guidelines meeting the AGREE II thresholds; where these do not provide direct evidence, de novo systematic reviews are conducted, with PRISMA flow diagrams updated to reflect records identified in the surveillance period.
- Risk of bias is assessed with the instruments appropriate to study design, and certainty of evidence is assessed using GRADE, with evidence profiles prepared for each critical outcome.
- Evidence-to-Decision considerations — balance of benefits and harms, certainty of evidence, values and preferences, resource use, equity, acceptability, and feasibility in the Philippine setting — are documented for each recommendation.
- Where a revised body of evidence does not change the previous conclusion, the recommendation is reaffirmed and labeled with the new search date; where it does, the recommendation, its strength, and its certainty rating are revised accordingly.

Consensus Process for the Update

The consensus process for updated recommendations is identical to that used in the original guideline. Each recommendation and its strength are determined by voting, with consensus reached when at least 75% of all voting CP members agree. If consensus is not reached on the first ballot, clarification and discussion are encouraged and a second round of voting is held; if consensus is still not reached, the

recommendation is tabled for deliberation at a subsequent meeting. Where direct evidence is lacking but the panel judges that a statement is necessary, a good practice statement may be issued, reflecting general agreement that the intervention will do more good than harm. Voting results, declared conflicts, recusals, and the substance of dissenting views are recorded in the minutes and reflected in the justification accompanying each recommendation.

Revised drafts undergo the same external review process applied to the original manuscript — methodological review using the AGREE II checklist, content expert review using AGREE-REX, and non-content expert review for clarity and usability — before submission to the DOH NPGP.

Documentation, Version Control, and Dissemination of Updates

- Each update is issued with a version number and date, and is accompanied by a summary of changes identifying, for every guideline question, whether the recommendation was reaffirmed, revised, retired, or newly added, together with the reason for the change and the date of the last evidence search.
- Superseded recommendations are archived rather than deleted, so that the evolution of the guideline is traceable.
- Approved updates are submitted to the DOH NPGP and disseminated through the DOH Compendium of Clinical Practice Guidelines, PCEDM and partner society platforms and scientific meetings, peer-reviewed publication, and derivative products including quick reference guides, decision aids, patient education materials, and electronic medical record prompts.
- End users are notified of interim updates through the same channels, with clear identification of which recommendations have changed.
- Updated versions will be resubmitted to the DOH NPGP for AGREE II appraisal, and must meet the threshold of at least 75% in the domains of Rigour of Development and Editorial Independence required for inclusion in the Compendium of DOH-Approved Clinical Practice Guidelines.

Sustainability and Accountability

- Post-publication surveillance is conducted continuously to identify emerging evidence and practice gaps, with formal reporting to the SC on an annual basis.
- The SC and TWG ensure continuity by designating a standing update team responsible for evidence surveillance, liaison with the DOH NPGP, and coordination of update activities between cycles.
- Accountability for initiating updates rests with the SC; the DOH independently assesses the continuing relevance and applicability of this guideline and may direct an update at any time.
- Resource requirements for updating — including database access, surveillance and appraisal work, COIRC engagement, consensus panel meetings, external review, and dissemination — are incorporated into the guideline's sustainability plan and included in funding requests to the DOH and partner organizations, with the same editorial independence safeguards applied to the original development.
- Findings from monitoring and evaluation and end-user feedback are formally considered in scoping each update, so that revisions address implementation barriers as well as evidence gaps.

Access to the guideline

The guideline will be publicly accessible through official websites of healthcare societies and through the Compendium of DOH-Approved Clinical Practice Guidelines (https://doh.gov.ph/dpcb/doh-approved-cpg/). The evidence base and final manuscript will be made accessible through both print and electronic media platforms managed by the DOH, the PCEDM, and other contributing organizations.

Recommendations for future research

There is a paucity of data for most aspects of diabetes in the country. Available epidemiology data pertains mainly to the prevalence of the condition. The following have been identified as the research gaps:

Screening

- The cost-effectiveness of screening based on each risk factor for developing diabetes and the long-term follow-up of people screened with the clinical risk score questionnaire in the Philippines.
- The identification of prevalent risk factors in people diagnosed with diabetes during national health surveys to monitor changes in the population's risk profile.
- The optimal frequency for screening diabetes using fasting blood sugar levels.

Diagnosis

- The utility of 1-hour post-75-gram glucose load in diagnosing glucose intolerance in non-pregnant adults.
- The accuracy of HbA1c testing in the Philippines given the lack of standardization of reporting of results, that is, the lack of indicating the specific laboratory assay used and specifying if the methodology used is certified by the National Glycohemoglobin Standardization Program (NGSP).
- The correlation of HbA1c with plasma glucose in the Philippines.
- The validity of point-of-care HbA1c kits.
- An adequately powered cross-sectional study comparing the accuracy of CBG with OGTT.
- An adequately powered cross-sectional study among patients in geographically inaccessible and disadvantaged areas comparing the accuracy of CBG using the government-issued glucometers with OGTT.
- Validated studies to assess the commonly used criterion of random plasma glucose ≥200 mg/dL (≥11.1 mmol/L) when classic hyperglycemic symptoms are present.

Screening for Complications

- The lack of prevalence data on microvascular complications (neuropathy, nephropathy, and retinopathy) and diabetes-related cardiovascular diseases, including among newly diagnosed people with diabetes.
- The diagnostic accuracy of retinal photograph interpretation by non-ophthalmologist credentialed personnel.
- The most accurate among the existing eGFR calculators for Filipino adults with chronic kidney disease.

- The optimal monitoring frequency for albumin:creatinine ratio and serum creatinine.
- The accuracy of microalbumin test and urine protein-creatinine ratio.
- The optimal cut-off for the Semmes-Weinstein monofilament test that would predict foot ulceration and amputation.

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Guideline Question 5. Should we recommend add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target?

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Guideline Question 11. Should we recommend a fasting plasma glucose (FPG) target of 80 to 130 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

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Guideline Question 13. Should we recommend self-monitoring of blood glucose (SMBG) targets of fasting capillary plasma glucose of 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose of <180 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

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Guideline Question 16. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and concomitant tuberculosis?

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Annex A. Tools for Assessing Conflicts of Interest

Primary:	Relates to company products in the same therapeutic areas.
Secondary:	Relates to products in other therapeutic areas.
Major:	Huge potential impact on panel decisions.
Minor:	Small impact on panel decisions.
Direct:	Immediate economic returns (e.g. payments)
Indirect:	Delayed material returns (e.g. academic promotions)
Personal:	Arises from a relationship with a person.
Institutional:	Arises from a relationship with an institution.
Financial:	Leads to gains in a material sense.
Intellectual:	Leads to gains in terms of academic status, recognition, or popularity.
Financial:	Leads to material/financial gain.
Non financial:	Leads to intellectual and other gains.

Annex B: Clinical Questions

A. Management (Pharmacologic therapy) for Diabetes Mellitus

Guideline Question 1. Use of Metformin as first-line glucose-lowering agent

Q1. Should we use metformin as first-line glucose-lowering agent (i.e., monotherapy or base drug for combination therapy) among adult patients with type 2 diabetes mellitus?

Q1.1. Should we use metformin monotherapy as first-line glucose-lowering agent among adult patients with type 2 diabetes mellitus?	
P	Adult patients with type 2 diabetes mellitus
I	Metformin monotherapy as first-line glucose-lowering agent
C	Non-metformin use or other glucose-lowering agents
O	Efficacy and safety

Q1.2. Should we use metformin as base drug in combination therapy as the first-line glucose-lowering treatment among adults with type 2 diabetes mellitus?	
P	Adult patients with type 2 diabetes mellitus
I	Metformin as base drug for combination as the first-line glucose-lowering agent
C	Non-metformin use or other glucose-lowering agents
O	Efficacy and safety

Guideline Question 2. Use of second-line agents among adults with T2DM on metformin after failure to achieve glycemic targets

Q2. Should we use sulfonylureas, DPP4-inhibitors, SGLT-2 inhibitors, thiazolidinediones, GLP1-RA and basal insulin among adults with T2DM on metformin after failure to achieve glycemic targets?

Q2.1. Should we use sulfonylureas among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	Sulfonylureas as a glucose-lowering agent
C	Non-sulfonylurea use or other glucose-lowering agents
O	Efficacy and safety

Q2.2. Should we use DPP4-inhibitors among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	DPP4-inhibitors as a glucose-lowering agent
C	Non-DPP4i use or other glucose-lowering agents
O	Efficacy and safety

Q2.3. Should we use SGLT-2 inhibitors among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	SGLT2 inhibitors as a glucose-lowering agent
C	Non-SGLT2i use or other glucose-lowering agents
O	Efficacy and safety

Q2.4. Should we use thiazolidinediones among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	Thiazolidinediones as a glucose-lowering agent
C	Non-thiazolidinediones use or other glucose-lowering agents
O	Efficacy and safety

Q2.5. Should we use GLP1-RA among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	GLP1-RA as a glucose-lowering agent
C	Non-GLP1-RA use or other glucose-lowering agents
O	Efficacy and safety

Q2.6. Should we use basal insulin among adults with T2DM on metformin after failure to achieve glycemic targets?	
P	Among adults with T2DM on metformin after failure to achieve glycemic targets
I	Basal insulin as a glucose-lowering agent
C	Non-basal insulin use or other glucose-lowering agents
O	Efficacy and safety

Guideline Question 3. Use of initial oral combination therapy among adults with T2DM and marked hyperglycemia

Q3. Among adults with type 2 diabetes mellitus (T2DM), should initial oral combination therapy be recommended for patients with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?	
P	Among adults with type 2 diabetes mellitus (T2DM) presenting with marked hyperglycemia (HbA1c > 9% or fasting blood sugar > 250 mg/dL)
I	Initial oral combination therapy (two oral glucose-lowering agents, e.g., metformin combined with a second oral agent)
C	Oral monotherapy (e.g., metformin alone) or stepwise intensification without initial combination therapy
O	Glycemic control (HbA1c reduction, achievement of glycemic targets), time to glycemic control, hypoglycemia, weight change, adverse events, treatment adherence, and treatment discontinuation

Guideline Question 4. Use of initial injectable therapy combined with oral agent/s among adults with T2DM and marked hyperglycemia

Q4. Among adults with type 2 diabetes mellitus (T2DM), should initial injectable therapy combined with oral agent/s be recommended for patients with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?	
P	Among adults with type 2 diabetes mellitus (T2DM) presenting with marked hyperglycemia (HbA1c > 9% or fasting blood sugar > 250 mg/dL)
I	Initial injectable therapy (e.g., basal insulin or GLP-1 receptor agonist), combined with oral glucose-lowering agent/s
C	Oral glucose-lowering agent/s alone or stepwise intensification without initial injectable therapy
O	Glycemic control (HbA1c reduction, achievement of glycemic targets), time to glycemic control, hypoglycemia, weight change, adverse events, treatment adherence, and treatment discontinuation

Guideline Question 5. Add-on injectable therapy among adults with T2DM on 2–3 oral agents and with HbA1c above target

Q5. Should we recommend add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target?

Q5.1. Should we recommend basal insulin as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target?	
P	Adults with T2DM on 2–3 oral agents and with HbA1c above target
I	Basal insulin as an add-on injectable, combined with oral glucose-lowering agent/s
C	Continued oral glucose-lowering agent/s alone or other add-on injectable options
O	Efficacy and safety

Q5.2. Should we recommend GLP-1 receptor agonist therapy as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target?	
P	Adults with T2DM on 2–3 oral agents and with HbA1c above target
I	GLP-1 receptor agonist as an add-on injectable, combined with oral glucose-lowering agent/s
C	Continued oral glucose-lowering agent/s alone or other add-on injectable options
O	Efficacy and safety

Q5.3. Should we recommend fixed-ratio combination therapy as an add-on injectable, in combination with oral glucose-lowering agent/s, among adults with T2DM on 2–3 oral agents and with HbA1c above target?	
P	Adults with T2DM on 2–3 oral agents and with HbA1c above target
I	Fixed-ratio combination (basal insulin plus GLP-1 receptor agonist) as an add-on injectable, combined with oral glucose-lowering agent/s
C	Continued oral glucose-lowering agent/s alone or other add-on injectable options
O	Efficacy and safety

Guideline Question 6. Use of Momordica charantia (Ampalaya) among adults with T2DM

Q6. Should we recommend the use of Momordica charantia [Ampalaya] among adults with T2DM?	
P	Adults with T2DM
I	Momordica charantia (Ampalaya)
C	Placebo, no Momordica charantia
O	Efficacy and safety

Guideline Question 7. Use of Chromium picolinate among adults with T2DM

Q7. Should we use Chromium picolinate for glycemic control among adults with type 2 diabetes mellitus?	
P	Adults with T2DM
I	Chromium picolinate (or any other chromium preparation)
C	Placebo, no chromium
O	Efficacy and safety

Guideline Question 8. Use of Andrographis paniculata (Serpentina) among adults with T2DM

Q8. Should we recommend the use of Andrographis paniculata (Serpentina) among adults with T2DM?	
P	Adults with T2DM
I	Andrographis paniculata (Serpentina)
C	Placebo, no Andrographis paniculata
O	Efficacy and safety

Guideline Question 9. Routine vitamin B12 supplementation among adults with T2DM on metformin

Q9. Should we recommend the routine use of vitamin B12 (methylcobalamin or cyanocobalamin) supplementation among adults with T2DM on metformin?	
P	Adults with T2DM on metformin
I	Routine vitamin B12 (methylcobalamin or cyanocobalamin) supplementation
C	No supplementation or placebo
O	Efficacy and safety

Guideline Question 10. Use of Costus igneus (Insulin Plant) among adults with T2DM

Q10. Should we use Costus igneus (Insulin Plant) for glycemic control among adults with T2DM?	
P	Adults with T2DM
I	Costus igneus (Insulin Plant)
C	Placebo, no Costus igneus
O	Efficacy and safety

Guideline Question 11. Fasting plasma glucose (FPG) target among nonpregnant adults with T2DM

Q11. Should we recommend a fasting plasma glucose (FPG) target of 80 to 130 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?	
P	Nonpregnant adults with T2DM
I	Fasting plasma glucose (FPG) target of 80 to 130 mg/dL
C	Other or no specified FPG target
O	Approximation of the HbA1c target of <7% (glycemic control) and safety

Guideline Question 12. HbA1c target for glycemic control among nonpregnant adults with T2DM

Q12. Should we recommend an HbA1c target of <7% for glycemic control among nonpregnant adults with T2DM?	
P	Nonpregnant adults with T2DM
I	HbA1c target of <7%
C	Other or less stringent HbA1c targets
O	Glycemic control, microvascular and macrovascular complications, hypoglycemia, and safety

Guideline Question 13. Self-monitoring of blood glucose (SMBG) targets among nonpregnant adults with T2DM

Q13. Should we recommend self-monitoring of blood glucose (SMBG) targets of fasting capillary plasma glucose of 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose of <180 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?	
P	Nonpregnant adults with T2DM
I	SMBG targets (fasting capillary plasma glucose 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose <180 mg/dL)
C	Other or no specified SMBG targets
O	Approximation of the HbA1c target of <7% (glycemic control) and safety

Guideline Question 14. Annual influenza vaccination among adults with T2DM

Q14. Should we give influenza vaccine annually among adults with T2DM?	
P	Adults with T2DM
I	Annual influenza vaccination
C	No influenza vaccination
O	Efficacy and safety (influenza infection, hospitalization, mortality, adverse events)

Guideline Question 15. Pneumococcal vaccination among adults with T2DM

Q15. Should we give pneumococcal vaccine annually among adults with T2DM?	
P	Adults with T2DM
I	Pneumococcal vaccination (PCV13/PCV15 and PPSV23)
C	No pneumococcal vaccination
O	Efficacy and safety (pneumococcal disease, hospitalization, mortality, adverse events)

Guideline Question 16. Glucose-lowering therapy among adults with T2DM and concomitant tuberculosis

Q16. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and concomitant tuberculosis?	
P	Adults with T2DM and concomitant (active) tuberculosis
I	Specific oral antidiabetic agents or injectable therapies (e.g., metformin as background therapy, combined oral agents or insulin)
C	Other glucose-lowering agents or no specific agent
O	Efficacy and safety (glycemic control and tuberculosis treatment outcomes)

Guideline Question 17. Glucose-lowering therapy among adults with T2DM and MASLD

Q17. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)?	
P	Adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)
I	Specific oral antidiabetic agents or injectable therapies (e.g., GLP-1 receptor agonists, pioglitazone)
C	Other glucose-lowering agents or no specific agent
O	Efficacy and safety (glycemic control and hepatic outcomes)

Guideline Question 18. Glucose-lowering therapy for stroke prevention among adults with T2DM and established cardiovascular disease

Q18. Should we recommend specific oral antidiabetic agents or injectables to prevent the occurrence of stroke or its recurrence among adults with T2DM and established cardiovascular disease?	
P	Adults with T2DM and established cardiovascular disease
I	Specific oral antidiabetic agents or injectables (e.g., GLP-1 receptor agonists with demonstrated cardiovascular benefit)
C	Other glucose-lowering agents or no specific agent
O	Prevention of stroke occurrence or recurrence, and safety

Guideline Question 19. Glucose-lowering therapy among adults with T2DM and obesity

Q19. Should we use specific oral antidiabetic agents or injectables among adults with T2DM and obesity?	
P	Adults with T2DM and obesity
I	Specific oral antidiabetic agents or injectables (e.g., GLP-1 receptor agonists, metformin, SGLT2 inhibitors)
C	Other glucose-lowering agents or no specific agent
O	Efficacy and safety (glycemic control and weight loss)

Guideline Question 20. Glucose-lowering therapy among adults with T2DM and CKD or ESRD on dialysis

Q20. Should we recommend specific oral antidiabetic agents or injectables among adults with T2DM and chronic kidney disease (CKD) or end-stage renal disease (ESRD) on dialysis?	
P	Adults with T2DM and chronic kidney disease (CKD) or end-stage renal disease (ESRD) on dialysis
I	Specific oral antidiabetic agents or injectables (e.g., SGLT2 inhibitors)
C	Other glucose-lowering agents or no specific agent
O	Efficacy and safety (glycemic control and renal outcomes)

Guideline Question 21. Glucose-lowering therapy among adults with T2DM and cirrhosis or chronic liver disease (CLD)

Q21. Should we recommend specific oral antidiabetic agents or injectables among adults with T2DM and cirrhosis or chronic liver disease (CLD)?	
P	Adults with T2DM and cirrhosis or chronic liver disease (CLD)
I	Specific oral antidiabetic agents or injectables (e.g., metformin and/or sulfonylureas, insulin)
C	Other glucose-lowering agents or no specific agent
O	Efficacy and safety (glycemic control and hepatic outcomes)

Annex C: Final List of Guidelines Appraised with AGREE II

1. Ivers NM, Jiang M, Alloo J, et al. Diabetes Canada 2018 clinical practice guidelines: Key messages for family physicians caring for patients living with type 2 diabetes. Can Fam Physician. 2019;65(1):14-24. https://www.cfp.ca/content/65/1/14.long [**Diabetes Canada Family Medicine]**

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3. Lipsombe L, Booth G, Butalia S, Dasgupta K, et al. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. Can J Diabetes 44 (2020): 575-591. **[Diabetes Canada Main Guidelines Update 2020: Pharmacologic Therapy]**

4. Riddle, MC (editor). American Diabetes Association. *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S1-S257. doi: 10.2337/dc21-S006. PMID: 33298417. [whenever an update is available, the latest guideline is also accessed. Diabetes Care. 2023 Jan; 46 (Suppl 1):S1-onwards]

5. UK National Institute for Health and Care Excellence (NICE). Type 2 Diabetes in Adults: Management (NICE Guideline) 2015 (updated 2020). www.nice.org.uk/guidance/ng136 . **[UK NICE]**

6. Scottish Intercollegiate Guideline Network. *SIGN 116: Management of diabetes*. Edinburgh: SIGN; 2017. (SIGN Guidelines No. 116). [**Scotland SIGN]**

7. International Diabetes Federation. Recommendations For Managing Type 2 Diabetes In Primary Care, 2017. www.idf.org/managing-type2-diabetes. **[IDF Primary Care]**

8. Araki E, Goto A, Kondo T et al. Japanese Clinical Practice Guideline for Diabetes 2019. J Diabetes Investig Vol. 11 No. 4 July 2020 [**Japan Diabetes Society]**

9. Chan Siew Pheng et al. Managaement of Type 2 Diabetes Mellitus (6th edition**) [Malaysian Endocrine and Metabolic Society]**

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12. Scottish Intercollegiate Guidelines Network. Scottish Intercollegiate Guideline Network. *Pharmacological management of glycaemic control in people with type 2 diabetes*. Edinburgh: SIGN; 2017. (SIGN Guidelines No. 154) [**Scottish Intercollegiate Guidelines Network]**

13. Schorr SG, Hammes HP, Müller UA, Abholz HH, Landgraf R, Bertram B. The Prevention and Treatment of Retinal Complications in Diabetes. Dtsch Arztebl Int. 2016 Dec 2;113(48):816-823. doi: 10.3238/arztebl.2016.0816. [**German Medical Association]**

14. Hooper P, Boucher MC, Cruess A, Dawson KG, et al. Excerpt from the Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol. 2017 Nov;52 Suppl 1:S45-S74. doi: 10.1016/j.jcjo.2017.09.027. [**Canadian Ophthalmological Society].**

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Annex D. Guidelines Used in the Hypertension Recommendations

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5. Malaysian Endocrine & Metabolic Society, Ministry of Health Malaysia, Academy of Medicine Malaysia, Persatuan Diabetes Malaysia. Clinical practice guidelines: management of type 2 diabetes mellitus (6th edition). http://www.moh.gov.my. December 2020. [**Malaysia]**

6. Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings (Revised Edition October 2018) . https://www.fhb.gov.hk **[Hongkong]**

7. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, Osawa H, Taguchi A, Tanziawa Y, Tobe K, Yoshioko N. Japanese Clinical Practice Guideline for Diabetes 2019. J Diabetes Investig. 11 (4): 1020-1076. 24 May 2020. **[Japan]**

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10. Tobe SW, Stone JA, Anderson T, Bacon S, Cheng AY, Daskalopoulou SS, Ezekowitz JA, Gregoire JC, Gubitz G, Jain R, Keshavjee K, Lindsay P, L'Abbe M, Lau DC, Leiter LA, O'Meara E, Pearson GJ, Rabi DM, Sherifali D, Selby P, Tu JV, Wharton S, Walker KM, Hua-Stewart D, Liu PP. Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE) guideline for the

prevention and management of cardiovascular disease in primary care: 2018 update. CMAJ : Canadian Medical Association Journal. 2018 Oct 9; 190(40): E1192-E1206. **[Canada Harmonized Guidelines for Primary Care]**

Annex E: Detailed Methods and Results of Evidence Syntheses

A. Management (Pharmacologic therapy) for Diabetes Mellitus

Guideline Question 1. Use of Metformin as first-line glucose-lowering agent

Should we use metformin as first-line glucose-lowering agent (i.e., monotherapy or base drug for combination therapy) among adult patients with type 2 diabetes mellitus?

Q1.1. Methods

A comprehensive search of various databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted by the reviewers following the PRISMA guidelines from inception to December 7, 2023. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The search was targeted towards randomized controlled trials that evaluated the effect of metformin monotherapy on all-cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety. Search terms utilized include “diabetes mellitus”, “metformin”, “monotherapy”, “3-point MACE”, “macrovascular outcomes”, “glycemic control”, “HbA1c reduction”. Studies with a low risk of bias were selected.

Q1.2. Search strategy

Database	Search Strategy/ Search Terms	Date and Time of Search	Results	
			Yield	Eligible
MEDLINE via PubMed	((("Metformin"[Mesh] OR metformin[tiab]) AND ("Diabetes Mellitus, Type 2"[Mesh] OR type 2 diabetes[tiab])) AND ("Randomized Controlled Trial"[Publication Type] OR randomized controlled trial[tiab] OR RCT[tiab])) AND ("Monotherapy"[Mesh] OR monotherapy[tiab]) AND ("Mortality"[Mesh] OR mortality[tiab] OR "Cardiovascular Diseases"[Mesh] OR cardiovascular[tiab] OR "Microvascular Complications"[Mesh] OR microvascular[tiab] OR "Hemoglobin A, Glycosylated"[Mesh] OR HbA1c[tiab] OR "Hypoglycemia"[Mesh] OR hypoglycemia[tiab] OR "Body Weight"[Mesh] OR weight[tiab])) AND ("2000/01/01"[Date - Publication] : "2023/12/31"[Date - Publication])	December 7, 2023	204	204

Q1.3. Characteristics of the Included Studies and risk of bias

# of Studies	Design	Population	Comparator	Outcomes	Quality
204	RCTs	Adults with Type 2 diabetes, both with low and high cardiovascular risks	Metformin vs. placebo other oral agents or injectables	HbA1c reduction, cardiovascular mortality and morbidity, weight change, hypoglycemia, other adverse effects	Generally low risk of bias, high heterogeneity, imprecision

Q1.4. Results

Forest plots

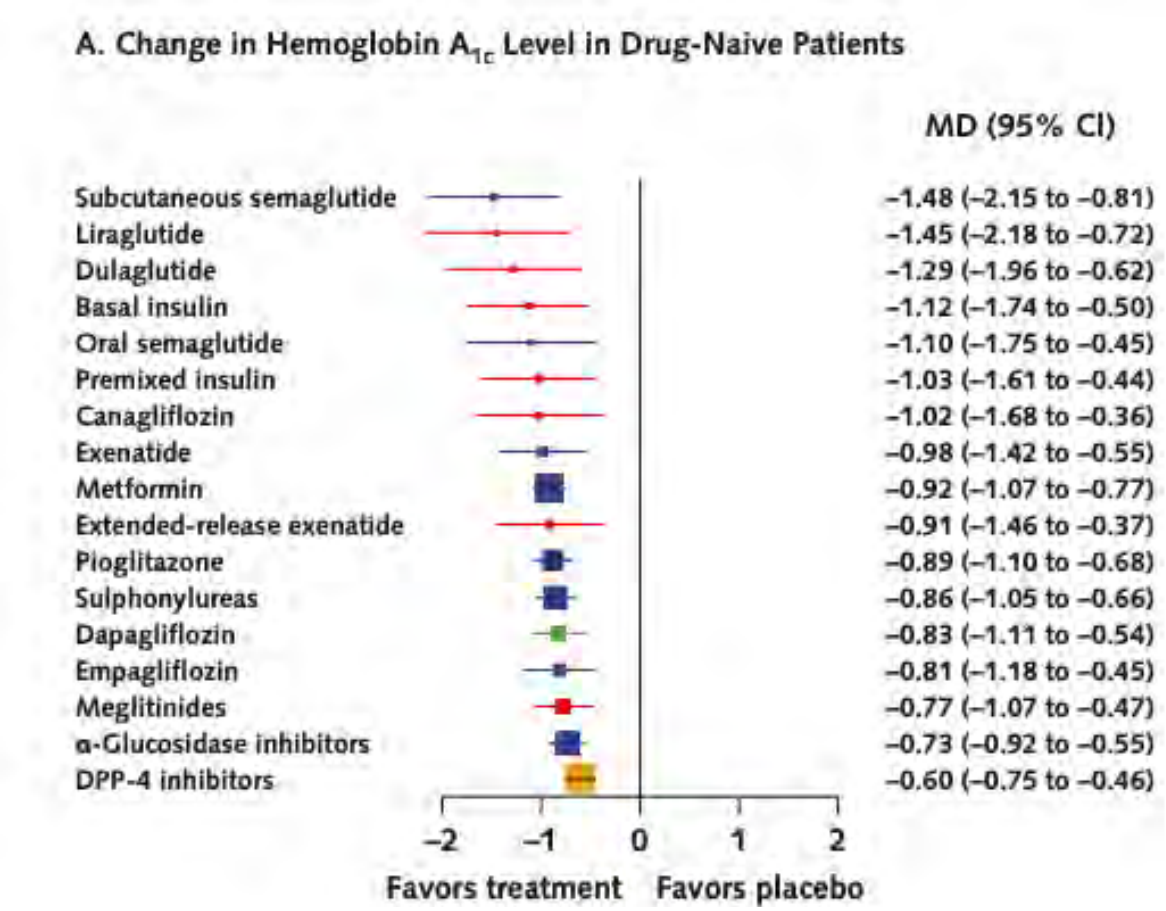


Figure 1. Network meta-analysis result for the outcome of glycemic efficacy of the different anti-diabetic agents for drug-naïve patients. *(Adapted from Tsapas et al., 2020)*

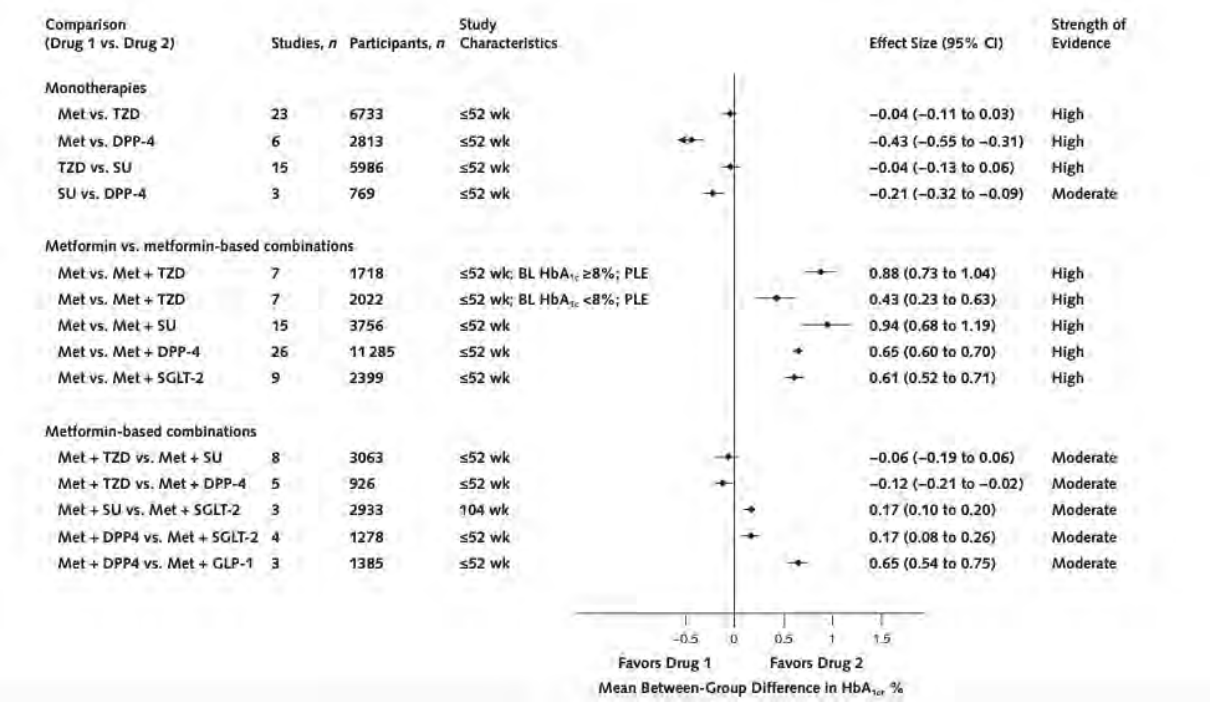


Figure 2. Pooled results of comparisons of metformin monotherapy and combination therapies in terms of HbA1c reduction. (Adapted from Maruthur et al., 2016)

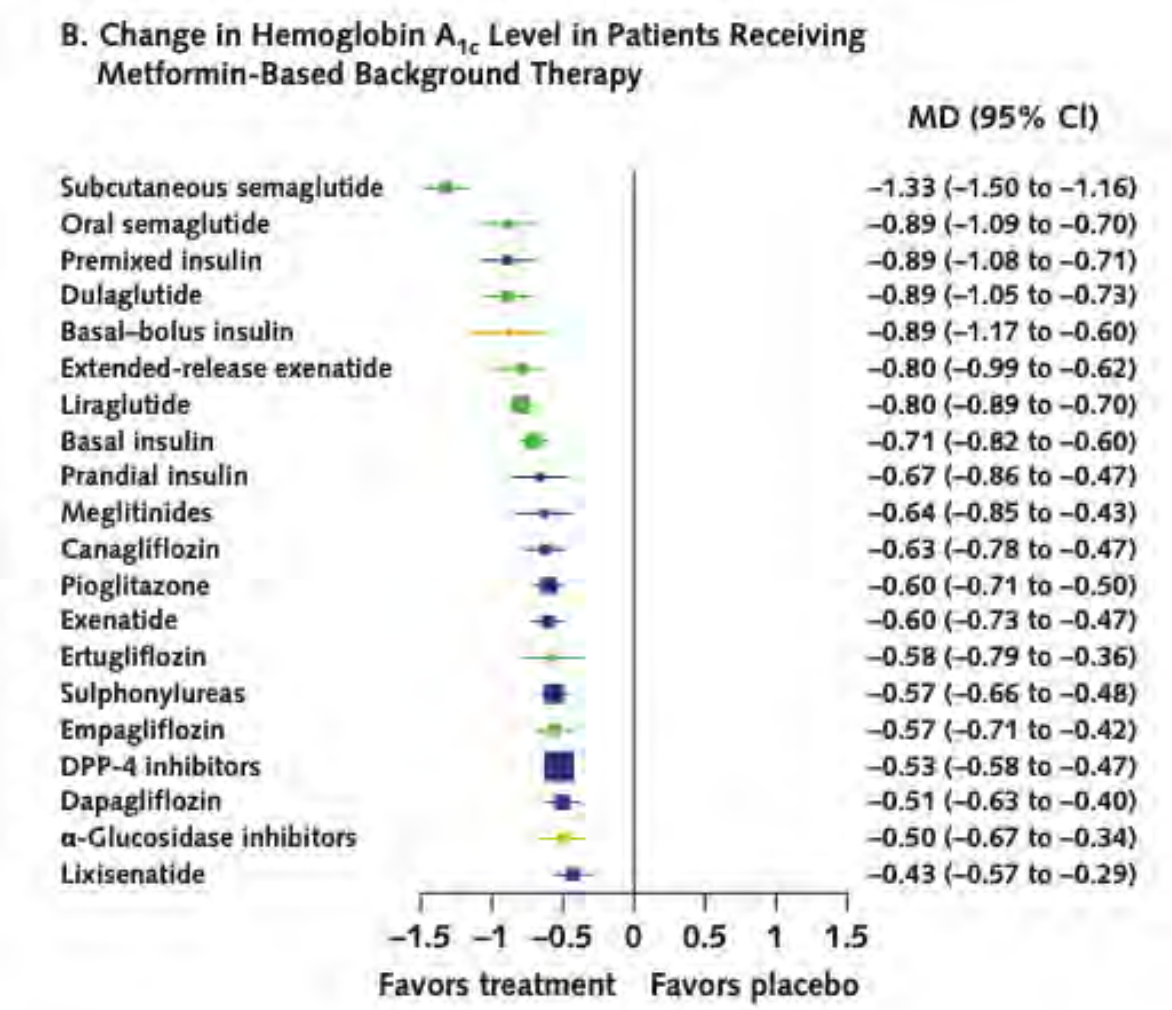
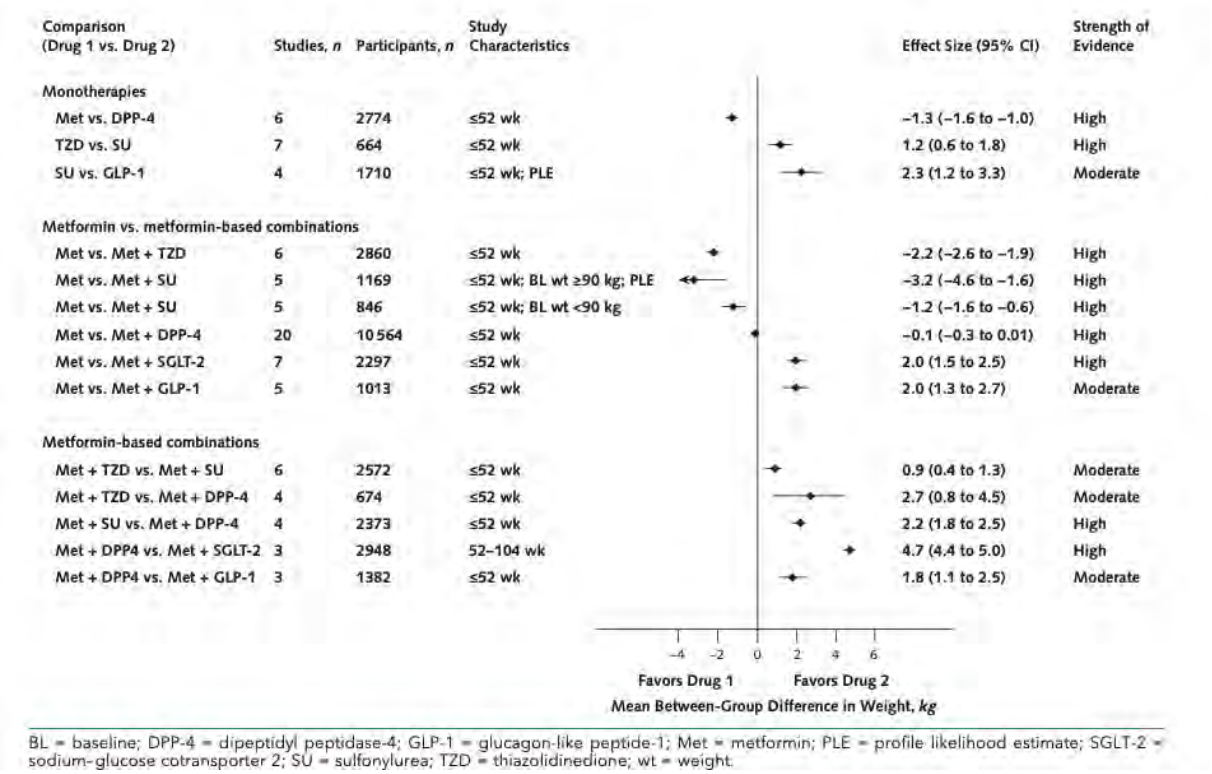


Figure 3. Network meta-analysis result for the outcome of glycemic efficacy of combination therapies using metformin as base therapy. *(Adapted from Tsapas et al., 2020)*



BL = baseline; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; PLE = profile likelihood estimate; SGLT-2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione; wt = weight.

Figure 4. Pooled results of comparisons of metformin monotherapy and combination therapies in terms of the outcome of change in weight *(Adapted from Maruthur et al, 2016)*

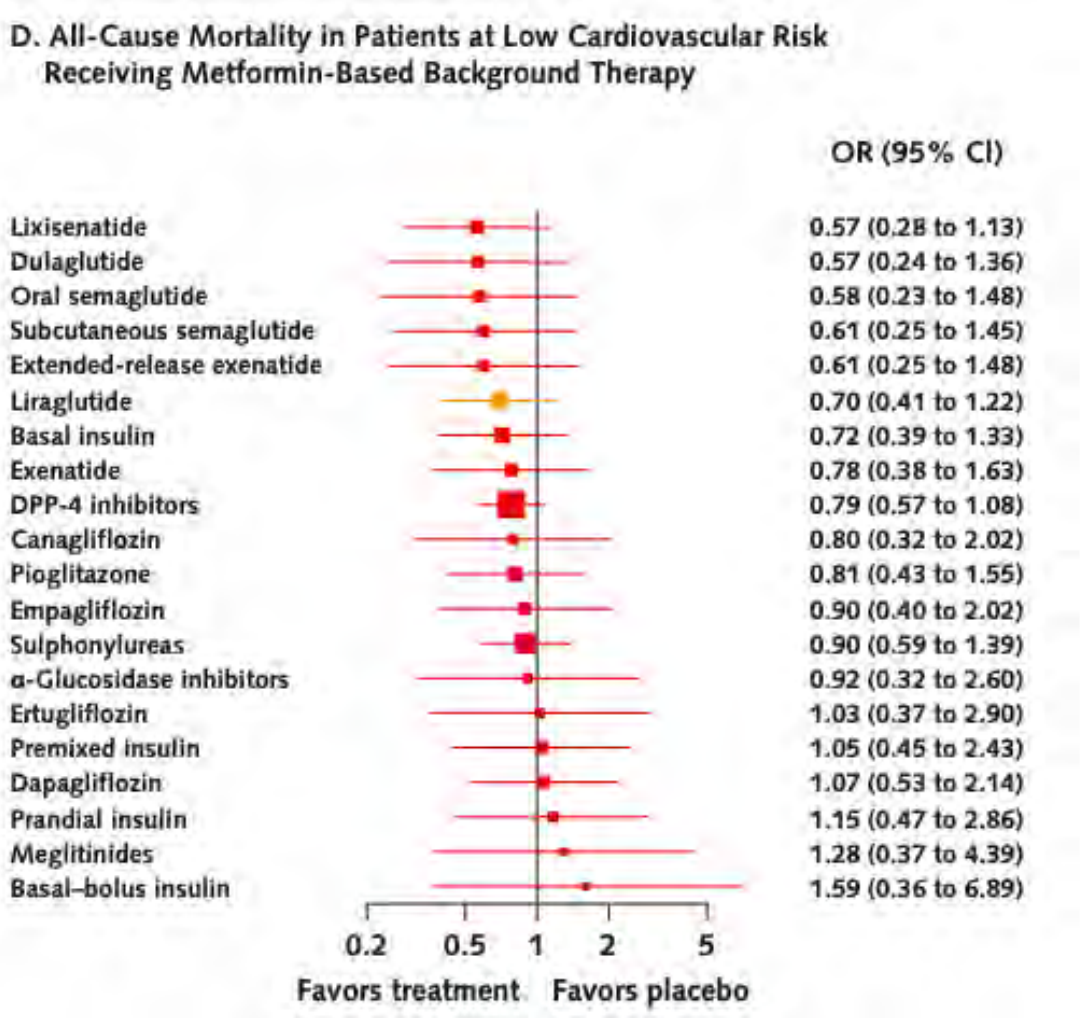


Figure 5. Network meta-analysis results for all-cause mortality for different agents for patients at low cardiovascular risk. *(Adapted from Tsapas et al, 2020)*

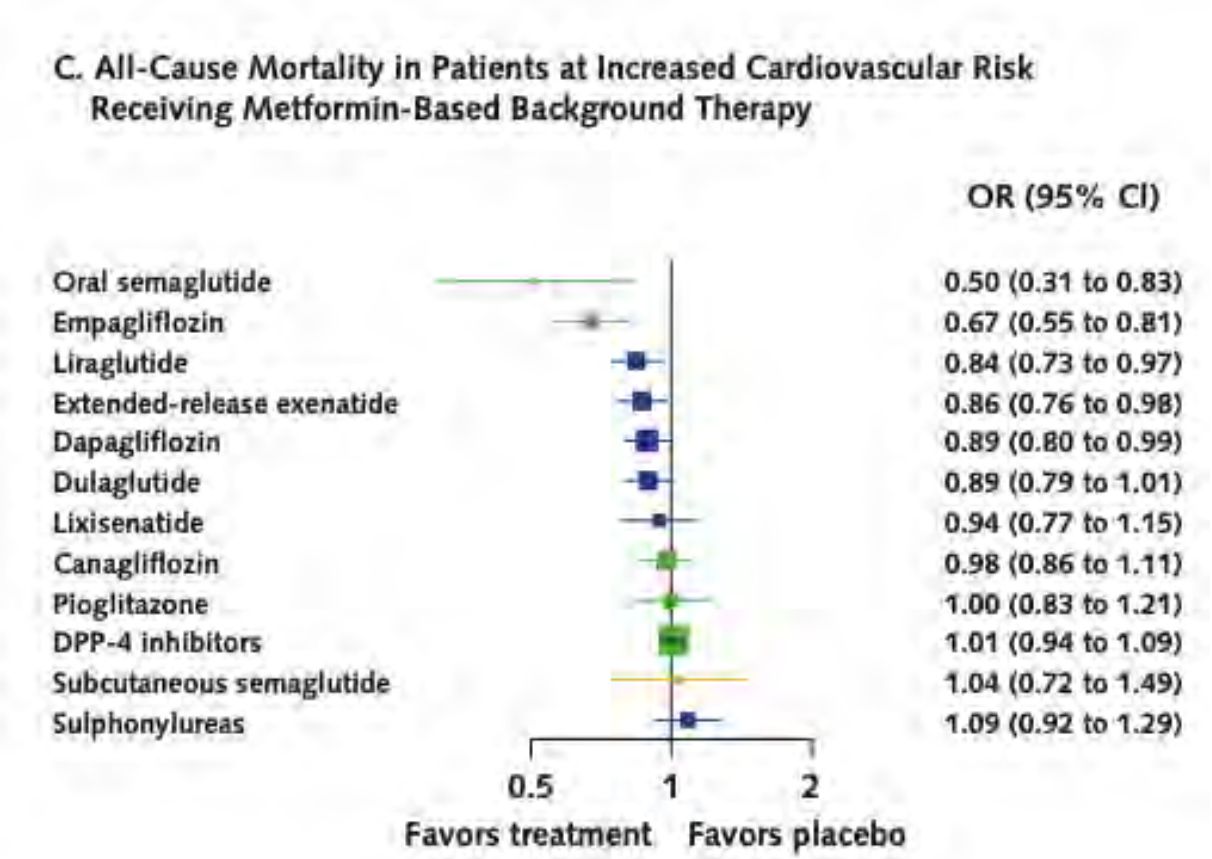


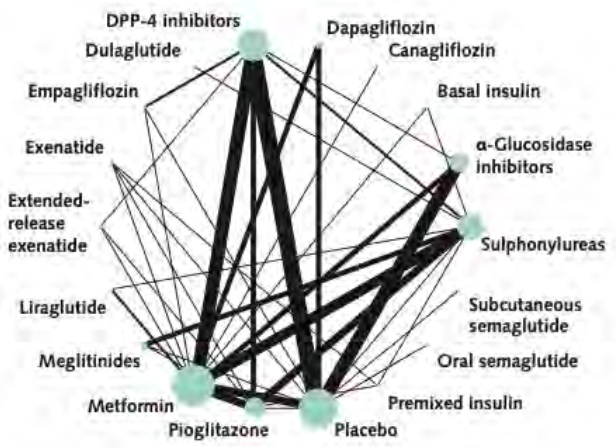
Figure 6. Network meta-analysis results for all-cause mortality for different agents for patients at increased cardiovascular risk. (Adapted from Tsapas et al, 2020)

Q1.6. GRADE Evidence Profile

GRADE Certainty of Evidence for Network Meta-analysis (Different Interventions Compared to Placebo)

BENEFITS

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes



Patient or population: Adults with type 2 diabetes

Interventions: Subcutaneous semaglutide, liraglutide, dulaglutide, basal insulin, oral semaglutide, premixed insulin, canagliflozin, metformin, pioglitazone, sulphonylureas, dapagliflozin, empagliflozin, α-glucosidase inhibitors, DPP-4 inhibitors

Comparator (reference): placebo

Outcome: change in HbA1c level

Setting: Outpatient setting

Total studies: 134 RCT **Total Participants**: 41,862 patients	**Relative effect (95% CI)**	**Anticipated absolute effect (95% CI)**		**Certainty of Evidence**	**Ranking**	**Interpretation of findings**
		Without intervention	**With intervention**			
Subcutaneous semaglutide	-		MD -1.48 (–2.15 to –0.81)	⊕⊕⊕◯ MODERATE	1	-
Liraglutide	-		MD –1.45 (–2.18 to –0.72)	⊕⊕⊕◯ MODERATE	2	-
Dulaglutide	-		MD –1.29 (–1.96 to –0.62)	⊕⊕⊕◯ MODERATE	3	-
Basal insulin	-		MD –1.12 (–1.74 to –0.50)	⊕⊕⊕◯ MODERATE	4	-
Oral semaglutide	-		MD –1.10 (–1.75 to –0.45)	⊕⊕⊕◯ MODERATE	5	-
Premixed insulin	-		MD –1.03 (–1.61 to –0.44)	⊕⊕⊕◯ MODERATE	6	-

Canagliflozin	-		MD –1.02 (–1.68 to –0.36)	⊕⊕⊕◯ MODERATE	7	-
Metformin	-		MD –0.92 (–1.07 to –0.77)	⊕⊕⊕◯ MODERATE	9	-
Pioglitazone	-		MD –0.89 (–1.10 to –0.68)	⊕⊕⊕◯ MODERATE	11	-
Sulfonylureas	-		MD –0.86 (–1.05 to –0.66)	⊕⊕⊕◯ MODERATE	12	-
Dapagliflozin	-		MD –0.83 (–1.11 to –0.54)	⊕⊕⊕◯ MODERATE	13	-
Empagliflozin	-		MD –0.81 (–1.18 to –0.45)	⊕⊕⊕◯ MODERATE	14	-
α-glucosidase inhibitors	-		MD –0.73 (–0.92 to –0.55)	⊕⊕⊕◯ MODERATE	16	-
DPP-4 inhibitors	-		MD –0.60 (–0.75 to –0.46)	⊕⊕⊕◯ MODERATE	17	-

Q1.7. Recommendations from other groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
American Diabetes Association (2023)	"Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality. Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits."[5]	Strong recommendation
Diabetes Association of the Republic of China Taiwan (2018)	"Biguanide (metformin) is the preferred initial pharmacological agent for type 2 diabetes if it is not contraindicated and is tolerated."[6]	Strong recommendation
Korean Diabetes Association (2021)	"Metformin is recommended as a first-line glucose-lowering agent in patients with T2DM and is maintained as long as there are no contraindications or intolerable side effects based on a general recommendation from an RCT. If metformin is contraindicated or intolerable as the initial treatment, then another class of antihyperglycemic agent can be used depending on the clinical situation based on an expert consensus. As an initial therapy for newly diagnosed patients with an HbA1c level ≤ 7.5%, metformin monotherapy is recommended."[7]	Strong recommendation
American Diabetes Association and European Association for the Study of Diabetes (2018)	"Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes. It remains the preferred option for initiating glucose-lowering medication in type 2 diabetes and should be added to lifestyle measures in newly diagnosed patients. Because of its high efficacy in lowering HbA1c, good safety profile, and low cost, metformin remains the first-	Strong recommendation

	line medication for the management of type 2 diabetes."[8]	
American College of Physicians (2017)	"Based on a strong recommendation, moderate-quality of evidence, ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. Metformin is effective in reducing glycemic levels, is associated with weight loss and fewer hypoglycemic episodes, and is cheaper than most other pharmacologic agents. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification. The American College of Physicians recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered based on a weak recommendation with moderate-quality evidence."[9]	Strong recommendation

Guideline Question 2. Combination after failure of oral agents

Should we use sulfonylureas, DPP4- inhibitors, SGLT-2 inhibitors, thiazolidinediones, GLP1-RA and basal insulin among adults with T2DM on metformin after failure to achieve glycemic targets?

Q2.1. Methods

A comprehensive search of various databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted by the reviewers following the PRISMA guidelines from inception to December 7, 2023. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The search was targeted towards randomized controlled trials that evaluated the effect of second-line agents (sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, thiazolidinediones, GLP-1 receptor agonists, and basal insulin) added to metformin among adults with T2DM who failed to achieve glycemic targets, on all-cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety. Search terms utilized include "diabetes mellitus", "metformin", "sulfonylureas", "DPP-4 inhibitors", "SGLT-2 inhibitors", "thiazolidinediones", "GLP-1 receptor agonists", "basal insulin", "3-point MACE", "macrovascular outcomes", "glycemic control", "HbA1c reduction". Studies with a low risk of bias were selected.

Q2.2. Search strategy

Search number	Query	Results
5	(network[Title/Abstract]) AND ((((((systematic review*[Title]) OR (meta analys*[Title])) OR (metaanalys*[Title])) AND ((((((((search*[Title]) OR (strateg*[Title])) OR (filter[Title/Abstract])) OR (filters[Title/Abstract])) OR (retrieve*[Title])) OR (identif*[Title])) OR (locat*[Title])) OR (find*[Title])) OR ((indexing[Title] OR indexed[Title]))))) OR ((review*[Title]) AND (((search*[Title]) OR (review*[Title])) OR (filter*[Title]))))) AND (((((diabetes mellitus, type 2[MeSH Terms]) OR (NIDDM)) OR ((Non insulin* AND depe*) OR (Noninsulin* AND depe*) OR (Non insulin depe*))) OR ((Type II diabet*) OR (Type 2 diabet*) OR (diabet* type 2) OR (diabet* type II))))	303
4	network[Title/Abstract]	589,705
3	(((((systematic review*[Title]) OR (meta analys*[Title])) OR (metaanalys*[Title])) AND ((((((((search*[Title]) OR (strateg*[Title])) OR (filter[Title/Abstract])) OR (filters[Title/Abstract])) OR (retrieve*[Title])) OR (identif*[Title])) OR (locat*[Title])) OR (find*[Title])) OR ((indexing[Title] OR indexed[Title]))))) OR ((review*[Title]) AND (((search*[Title]) OR (review*[Title])) OR (filter*[Title]))))) AND (((((diabetes mellitus, type 2[MeSH Terms]) OR (NIDDM)) OR ((Non insulin* AND depe*) OR (Noninsulin* AND depe*) OR (Non insulin depe*))) OR ((Type II diabet*) OR (Type 2 diabet*) OR (diabet* type 2) OR (diabet* type II)))	11,223
2	((((systematic review*[Title]) OR (meta analys*[Title])) OR (metaanalys*[Title])) AND ((((((((search*[Title]) OR (strateg*[Title])) OR (filter[Title/Abstract])) OR (filters[Title/Abstract])) OR (retrieve*[Title])) OR (identif*[Title])) OR (locat*[Title])) OR (find*[Title])) OR ((indexing[Title] OR indexed[Title]))))) OR ((review*[Title]) AND (((search*[Title]) OR (review*[Title])) OR (filter*[Title]))))	773,050
1	(((diabetes mellitus, type 2[MeSH Terms]) OR (NIDDM)) OR ((Non insulin* AND depe*) OR (Noninsulin* AND depe*) OR (Non insulin depe*))) OR ((Type II diabet*) OR (Type 2 diabet*) OR (diabet* type 2) OR (diabet* type II))	355,119

Q2.3. Characteristics of the Included Studies

Table 2.3 Characteristics of included systematic reviews and network meta-analyses

Author, year	Population	Intervention	Comparator/s	Outcomes (considered iin this review	Follow up duration	Number of Trials	Number of Participants
Dehghani, 2023	adults with T2DM, insulin-naïve and on OGLDs) or already on insulin	basal insulins (NPH, ILPS, glargine, 100 U/mL (IGlar-100); glargine, 300 U/mL (IGlar-300); detemir (IDet); degludec, 100 U/mL (IDeg-100); degludec, 200 U/mL (IDeg-200); and thrice-weekly degludec (IDeg-3TW).	Other basal insulins	Hypoglycemia Nocturnal hypoglycemia Severe hypoglycemia	12 weeks or longer	44	23,699
Haiqiang Yao, 2023	adults with T2DM who received GLP-1RA	Tirzepatide, orforglipron, Semaglutide, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, retatrutide, and CagriSema (semaglutide with cagrilintide), PEG-loxenatide, Mazdutide, Efpeglenatide, ITCA 650	placebo or any GLP-1RA drug	Body weight	12 weeks or longer	76	39 246
Qingyang Shi,2023	adults with T2DM	SGLT-2 inhibitors, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, TZD, sulfonylureas, metformin, α-glucosidase inhibitors, meglitinides, insulins, dual GIP/GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists	Standard treatments Active comparators	HrQOL Body weight	24 weeks or longer	816	471,038

Sim, 2022	adults with type 2 diabetes.on metformin as background therapy	biguanides, insulin, glinides, sulphonylureas, alpha-glucosidase inhibitors, glitazones, amylin analogues, glucagon-like peptide 1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter- 2 inhibitors (SGLT2i), and dopamine-2 agonists	placebo, standard care or active comparator	Macrovascular and microvascular outcomes Adverse events Hypoglycemia	any	38*	227,497
Tsapas, 2020	adults with type 2 diabetes	metformin, sulfonylureas, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, SGLT-2 inhibitors, basal insulin, basal–bolus insulin regimens (including basal-plus insulin), premixed insulins, a-glucosidase inhibitors, meglitinides	placebo, standard care or active comparator	Hba1c reduction	24 weeks or longer	453	320,474

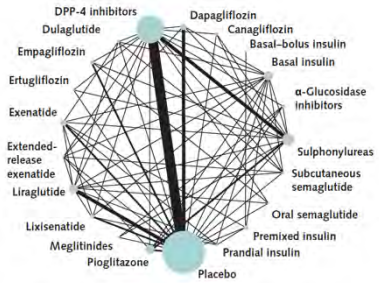
*reported at least one cardiovascular or renal outcome recruited more than 1000 participants

Q2.4. GRADE Evidence Profile

Appendix Table 2.4A: GRADE Summary of Findings on the effects of add-on therapy on Hba1c reduction

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: HBA1C REDUCTION
Setting: Inpatient and outpatient
Reference: Tsapas et al, 2020



Hba1c reduction

Total studies: 252 RCTS Total Participants: 261,559	Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
DPP4i	MD -0.52 (-0.58, -0.46)	⊕⊕⊕◯ MODERATE	NA	DPP4 treatment probably reduces Hba1c
TZD	MD -0.60 (-0.71, -0.50)	⊕⊕⊕◯ MODERATE	NA	TZD treatment probably reduces Hba1c
GLP-1RA	MD -0.77 (-0.84, -0.71)	⊕⊕⊕⊕ HIGH	NA	GLP-1RA treatment reduces Hba1c
Insulin (Basal)	MD -0.72 (-0.83, -0.61)	⊕⊕⊕⊕ HIGH	NA	Insulin treatment reduces Hba1c
SGLT2i	MD -0.55 (-0.62, -0.47)	⊕⊕⊕◯ MODERATE	NA	SGLT2i treatment probably reduces Hba1c
Sulfonylureas	MD -0.57 (-0.66, -0.48)	⊕⊕⊕◯ MODERATE	NA	Sulfonylurea treatment probably reduces Hba1c

Appendix Table2.4B: Summary of findings on the effects of add-on therapy on macrovascular outcomes

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: All MI (fatal and non-fatal MI)
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



All MI (fatal and non-fatal MI)

Total studies: 21 Total Participants: 174,373	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				

DPP4i 44175 (4 RCTs)	78 per 1,000	78 per 1,000 (69 to 88)	0 fewer per 1,000 (9 fewer to 10 more)	RR 1.00 (0.89 to 1.13)	⊕⊕⊕⊕ HIGH	4	DPP4i treatment makes little or no difference on all MI.
TZD 6544 (2 RCT)	78 per 1,000	81 per 1,000 (57 to 115)	3 more per 1,000 (21 fewer to 37 more)	RR 1.04 (0.73 to 1.48)	⊕◯◯◯ VERY LOW [a,b,c]	7	TZD treatment has uncertain effect on all MI.
GLP-1RA 60080 (8 RCTs)	78 per 1,000	72 per 1,000 (65 to 78)	6 fewer per 1,000 (12 fewer to 0 fewer)	RR 0.92 (0.84 to 1.00)	⊕⊕⊕⊕ HIGH	2	GLP-1RA treatment makes little or no difference on all MI.
Insulin 12537 (1 RCT)	78 per 1,000	80 per 1,000 (65 to 99)	2 more per 1,000 (12 fewer to 21 more)	RR 1.03 (0.84 to 1.27)	⊕⊕⊕◯ MODERATE [b]	8	Insulin treatment probably makes little or no difference on all MI.
SGLT2i 36827 (4 RCTs)	78 per 1,000	72 per 1,000 (64 to 81)	6 fewer per 1,000 (14 fewer to 3 more)	RR 0.92 (0.82 to 1.04)	⊕⊕⊕⊕ HIGH	3	SGLT2i treatment makes little or no difference on all MI.
Sulfonylureas 11140, (1 RCT)	78 per 1,000	79 per 1,000 (66 to 95)	1 more per 1,000 (12 fewer to 17 more)	RR 1.01 (0.85 to 1.22)	⊕⊕⊕◯ MODERATE [b]	5	Sulfonylureas treatment probably makes little or no difference on all MI.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: All Stroke
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



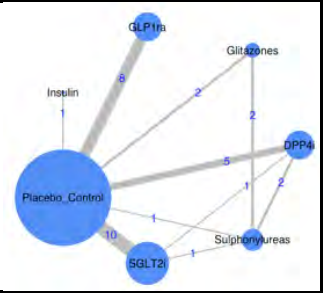
All stroke

Total studies: 22 Total Participants: 177,396	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 44,175 (4 RCTs)	45 per 1,000	44 per 1,000 (38 to 50)	1 fewer per 1,000 (7 fewer to 5 more)	RR 0.97 (0.84 to 1.12)	⊕⊕⊕⊕ HIGH	4	DPP4i treatment makes little or no difference on all stroke.
TZD 11,782 (3 RCTs)	45 per 1,000	36 per 1,000 (28 to 45)	9 fewer per 1,000 (17 fewer to 0 fewer)	RR 0.80 (0.63 to 1.01)	⊕◯◯◯ VERY LOW [a,e]	2	TZD treatment has uncertain effect on all stroke.
GLP-1RA 57,865 (8 RCTs)	45 per 1,000	39 per 1,000 (34 to 43)	6 fewer per 1,000 (11 fewer to 2 fewer)	RR 0.86 (0.76 to 0.96)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment reduces all stroke.
Insulin 12,537 (1 RCT)	45 per 1,000	47 per 1,000 (38 to 57)	2 more per 1,000 (7 fewer to 12 more)	RR 1.04 (0.85 to 1.27)	⊕⊕⊕◯ MODERATE [b]	8	Insulin treatment probably makes little

							or no difference on all stroke.
SGLT2i 36,827 (4 RCTs)	45 per 1,000	46 per 1,000 (40 to 53)	1 more per 1,000 (5 fewer to 8 more)	RR 1.02 (0.89 to 1.17)	⊕⊕⊕⊕ HIGH	7	SGLT2i treatment makes little or no difference on all stroke.
Sulfonylureas 11,140 (1 RCT)	45 per 1,000	45 per 1,000 (38 to 54)	0 fewer per 1,000 (7 fewer to 9 more)	RR 1.01 (0.84 to 1.21)	⊕⊕⊕◯ MODERATE [b]	6	Sulfonylurea treatment probably makes little or no difference on all stroke.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: All-cause mortality
Setting: Inpatient and outpatient
Reference: Sim et. al 2021

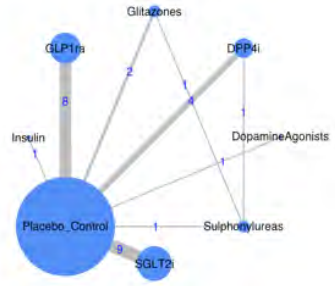


All-cause mortality

Total studies: 33 Total Participants: 218,469	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 53,436 (7 RCTs)	127 per 1,000	125 per 1,000 (115 to 136)	1 fewer per 1,000 (11 fewer to 9 more)	RR 0.99 (0.91 to 1.07)	⊕⊕⊕⊕ HIGH	5	DPP4i treatment makes little or no difference on all-cause mortality
TZD 14,810 (4 RCTs)	127 per 1,000	118 per 1,000 (101 to 137)	9 fewer per 1,000 (25 fewer to 10 more)	RR 0.93 (0.80 to 1.08)	⊕◯◯◯ VERY LOW [a,e]	3	TZD treatment has uncertain effect on all-cause mortality
GLP-1RA 60,080 (8 RCTs)	127 per 1,000	113 per 1,000 (104 to 120)	14 fewer per 1,000 (23 fewer to 6 fewer)	RR 0.89 (0.82 to 0.95)	⊕⊕⊕⊕ HIGH	2	GLP-1RA treatment reduces all-cause mortality
Insulin 12,537 (1 RCT)	127 per 1,000	125 per 1,000 (109 to 143)	1 fewer per 1,000 (18 fewer to 16 more)	RR 0.99 (0.86 to 1.13)	⊕⊕⊕◯ MODERATE [b]	4	Insulin treatment probably makes little or no difference on all-cause mortality
SGLT2i 66,466 (12 RCTs)	127 per 1,000	110 per 1,000 (103 to 118)	16 fewer per 1,000 (24 fewer to 9 fewer)	RR 0.87 (0.81 to 0.93)	⊕⊕⊕⊕ HIGH	1	SGLT2i treatment reduces all-cause mortality
Sulfonylureas 11140, pwr:5% (1 RCT)	127 per 1,000	125 per 1,000 (111 to 142)	1 fewer per 1,000 (15 fewer to 15 more)	RR 0.99 (0.88 to 1.12)	⊕⊕⊕◯ MODERATE [b]	6	Sulfonylureas treatment probably makes little or no difference on all-cause mortality

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: Hospitalization for heart failure
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



Hospitalization for heart failure

Total studies: 28 Total Participants: 209,712	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 49,555 (5 RCTs)	76 per 1,000	81 per 1,000 (73 to 90)	5 more per 1,000 (3 fewer to 14 more)	RR 1.07 (0.96, 1.19)	⊕⊕⊕⊕ HIGH	7	DPP4i treatment makes little or no difference on hospitalization for heart failure.
TZD 11,782 (3 RCTs)	76 per 1,000	113 per 1,000 (91 to 142)	37 more per 1,000 (15 more to 66 more)	RR 1.49 (1.2, 1.87)	⊕◯◯◯ VERY LOW [a,h]	8	TZD treatment has uncertain effect on hospitalization for heart failure.
GLP-1RA 60080, (8 RCTs)	76 per 1,000	68 per 1,000 (62 to 76)	8 fewer per 1,000 (14 fewer to 0 fewer)	RR 0.9 (0.82, 1)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment makes little or no difference on hospitalization for heart failure.
Insulin 12,537 (1 RCT)	76 per 1,000	68 per 1,000 (57 to 83)	8 fewer per 1,000 (19 fewer to 7 more)	RR 0.9 (0.75, 1.09)	⊕⊕⊕◯ MODERATE [b]	4	Insulin treatment probably makes little or no difference on hospitalization for heart failure.
SGLT2i 61,548 (9 RCTs)	76 per 1,000	54 per 1,000 (49 to 58)	22 fewer per 1,000 (27 fewer to 17 fewer)	RR 0.71 (0.65, 0.77)	⊕⊕⊕⊕ HIGH	1	SGLT2i treatment reduces hospitalization for heart failure.
Sulfonylureas 11,140 (1 RCT)	76 per 1,000	71 per 1,000 (60 to 85)	5 fewer per 1,000 (16 fewer to 9 more)	RR 0.94 (0.79, 1.12)	⊕⊕⊕◯ MODERATE [b]	5	Sulfonylureas treatment probably makes little or no difference on hospitalization for heart failure.

Explanations

a. Very serious risk of bias: Contributions from low Rob comparisons are more than 50%

b. Serious indirectness: Single-connected nodes and evaluation of transitivity is unclear

c. Very serious indirectness: Mixed population with history of cardiovascular disease and nil history of cardiovascular disease

d. Serious imprecision: Wide confidence interval for network meta-analysis

e. Serious imprecision: Wide confidence interval for direct evidence

f. Contributing direct evidence of low/very low quality

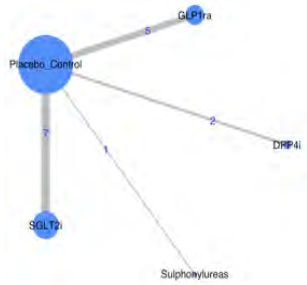
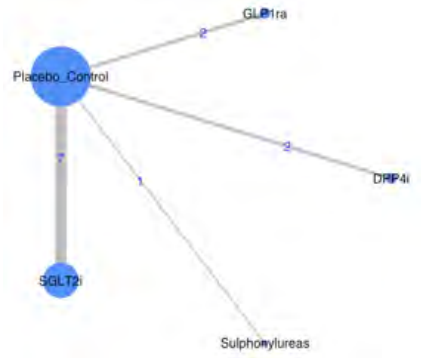
g. Serious indirectness: Serious intransitivity as indirect evidence for this comparison goes through first order loop via trials with population without history of cardiovascular disease

h. Very serious imprecision: Very wide confidence interval for direct evidence

i. Very serious imprecision: Very wide confidence interval for network meta-analysis

j. Contributing evidence of moderate quality

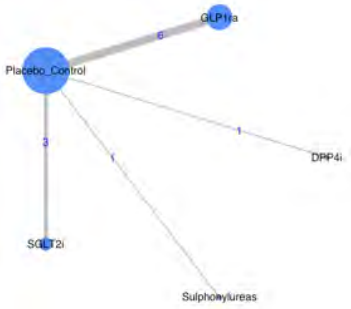
Appendix Table2.4C. Summary of findings on the effects of add-on therapy on microvascular outcomes (renal and retinopathy)

BENEFITS							
Patient or population: Patients with type 2 diabetes on background metformin therapy Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas Comparison: Placebo_Control Outcome: End stage renal disease Setting: Inpatient and outpatient Reference: Sim et. al 2021							
End stage renal disease							
Total studies: 15 Total Participants: 127,252	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 23,471 (2 RCTs)	19 per 1,000	18 per 1,000 (13 to 25)	1 fewer per 1,000 (6 fewer to 6 more)	RR 0.95 (0.69 to 1.31)	⊕⊕⊕⊕ HIGH	4	DPP4i treatment makes little or no difference on end stage renal disease.
GLP-1RA 42,766 (5 RCTs)	19 per 1,000	16 per 1,000 (12 to 20)	3 fewer per 1,000 (7 fewer to 1 more)	RR 0.83 (0.63 to 1.07)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment makes little or no difference on end stage renal disease.
SGLT2i 49875, pwr:100% (7 RCTs)	19 per 1,000	12 per 1,000 (10 to 15)	6 fewer per 1,000 (9 fewer to 4 fewer)	RR 0.66 (0.52 to 0.81)	⊕⊕⊕⊕ HIGH	2	SGLT2i treatment reduces end stage renal disease.
Sulfonylureas 11140, pwr:99% (1 RCT)	19 per 1,000	6 per 1,000 (2 to 15)	12 fewer per 1,000 (16 fewer to 3 fewer)	RR 0.34 (0.13 to 0.82)	⊕⊕◯◯ LOW [c,d]	1	Sulfonylureas treatment may reduce end stage renal disease.
BENEFITS							
Patient or population: Patients with type 2 diabetes on background metformin therapy Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas Comparison: Placebo_Control Outcome: Renal death Setting: Inpatient and outpatient Reference: Sim et. al 2021							
Renal death							

Total studies: 12 Total Participants: 108,576	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 23,471 (2 RCTs)	2 per 1,000	3 per 1,000 (1 to 15)	1 more per 1,000 (1 fewer to 14 more)	RR 1.82 (0.33 to 9.57)	⊕◯◯◯ VERY LOW [e,f]	5	DPP4i treatment has uncertain effect on renal death.
GLP-1RA 24,092 (2 RCTs)	2 per 1,000	2 per 1,000 (1 to 9)	1 more per 1,000 (1 fewer to 7 more)	RR 1.31 (0.31 to 5.53)	⊕◯◯◯ VERY LOW [e,g]	4	GLP-1RA treatment has uncertain effect on renal death.
SGLT2i 49,873 (7 RCTs)	2 per 1,000	1 per 1,000 (0 to 2)	1 fewer per 1,000 (1 fewer to 1 more)	RR 0.50 (0.15 to 1.33)	⊕◯◯◯ VERY LOW [d,g]	1	SGLT2i treatment has uncertain effect on renal death.
Sulfonylureas 11,140 (1 RCT)	2 per 1,000	1 per 1,000 (0 to 8)	0 fewer per 1,000 (1 fewer to 7 more)	RR 0.84 (0.14 to 5.12)	⊕◯◯◯ VERY LOW [c,d,f]	2	Sulfonylurea treatment has uncertain effect on renal death.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: Macroalbuminuria
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



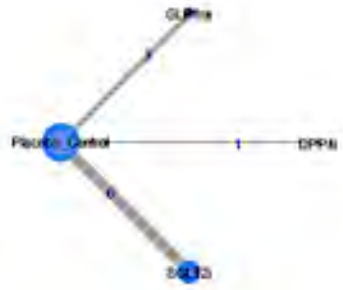
Macroalbuminuria

Total studies: 11 Total Participants: 83,924	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 11,476 (1 RCT)	106 per 1,000	80 per 1,000 (53 to 120)	27 fewer per 1,000 (53 fewer to 14 more)	RR 0.75 (0.50 to 1.13)	⊕⊕⊕◯ MODERATE [c]	3	DPP4i treatment probably makes little or no difference on macroalbuminuria.
GLP-1RA 46,169 (6 RCTs)	106 per 1,000	81 per 1,000 (68 to 96)	26 fewer per 1,000 (38 fewer to 11 fewer)	RR 0.76 (0.64 to 0.90)	⊕⊕⊕⊕ HIGH	4	GLP-1RA treatment reduces macroalbuminuria.
SGLT2i 15,139 (3 RCTs)	106 per 1,000	67 per 1,000 (51 to 84)	39 fewer per 1,000 (55 fewer to 22 fewer)	RR 0.63 (0.48 to 0.79)	⊕⊕⊕◯ MODERATE [d]	1	SGLT2i treatment probably reduces macroalbuminuria.
Sulfonylureas 11,140 (1 RCT)	106 per 1,000	74 per 1,000 (49 to 113)	32 fewer per 1,000 (57 fewer to 6 more)	RR 0.70 (0.46 to 1.06)	⊕⊕⊕◯ MODERATE [c]	2	Sulfonylureas treatment probably makes little or no

							difference on macroalbuminuria.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: Doubling of serum creatinine
Setting: Inpatient and outpatient
Reference: Sim et. al 2021

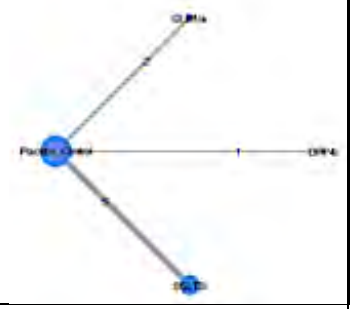


Doubling of serum creatinine

Total studies: 10 Total Participants: 67,085	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 16,492 (1 RCT)	46 per 1,000	51 per 1,000 (31 to 82)	5 more per 1,000 (15 fewer to 36 more)	RR 1.10 (0.68 to 1.78)	⊕⊕⊕◯ MODERATE [c]	4	DPP4i treatment probably makes little or no difference on doubling of serum creatinine.
GLP-1RA 18,700 (3 RCTs)	46 per 1,000	48 per 1,000 (35 to 71)	2 more per 1,000 (11 fewer to 24 more)	RR 1.05 (0.76 to 1.53)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment makes little or no difference on doubling of serum creatinine.
SGLT2i 31,893 (6 RCTs)	46 per 1,000	29 per 1,000 (22 to 35)	18 fewer per 1,000 (24 fewer to 11 fewer)	RR 0.62 (0.48 to 0.77)	⊕⊕⊕⊕ HIGH	1	SGLT2i treatment reduces doubling of serum creatinine.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: Decline in eGFR
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



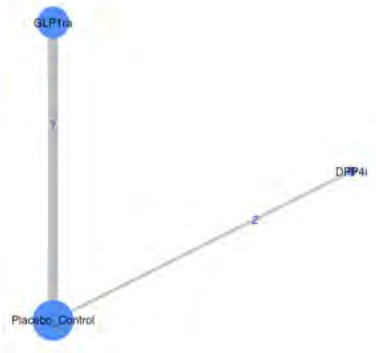
Decline in eGFR

Total studies: 8 Total Participants: 68,259	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 6,979 (1 RCT)	61 per 1,000	67 per 1,000 (48 to 94)	6 more per 1,000 (14 fewer to 33 more)	RR 1.09 (0.78 to 1.53)	⊕⊕⊕◯ MODERATE [c]	4	DPP4i treatment probably makes little

							or no difference on decline in eGFR.
GLP-1RA 22,826 (2 RCTs)	61 per 1,000	50 per 1,000 (39 to 63)	12 fewer per 1,000 (23 fewer to 2 more)	RR 0.81 (0.63 to 1.03)	⊕⊕⊕⊕ HIGH	2	GLP-1RA treatment makes little or no difference on decline in eGFR.
SGLT2i 38,454 (5 RCTs)	61 per 1,000	36 per 1,000 (30 to 44)	25 fewer per 1,000 (31 fewer to 18 fewer)	RR 0.59 (0.49 to 0.71)	⊕⊕⊕⊕ HIGH	1	SGLT2i treatment reduces decline in eGFR.

BENEFITS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: Retinopathy
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



Retinopathy

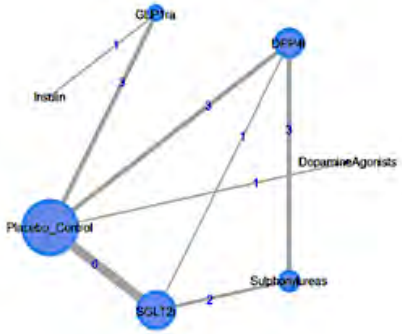
Total studies: 9 Total Participants: 75,612	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 21,650 (2 RCT)	46 per 1,000	49 per 1,000 (31 to 72)	3 more per 1,000 (15 fewer to 26 more)	RR 1.07 (0.68 to 1.57)	⊕⊕◯◯ LOW [j]	2	DPP4i treatment may make little or no difference on retinopathy.
GLP-1RA 53962 (7 RCTs)	46 per 1,000	49 per 1,000 (40 to 62)	4 more per 1,000 (6 fewer to 16 more)	RR 1.08 (0.87 to 1.36)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment makes little or no difference on retinopathy.

Explanations
a. Serious indirectness: Serious intransitivity as indirect evidence for this comparison goes through first order loop via trials with population without history of cardiovascular disease
b. Contributing evidence of moderate quality
c. Serious indirectness: Single-connected nodes and evaluation of transitivity is unclear
d. Serious imprecision: Wide confidence interval for direct evidence
e. Very serious imprecision: Very wide confidence interval for direct evidence
f. Very serious imprecision: Very wide confidence interval for network meta-analysis
g. Serious imprecision: Wide confidence interval for network meta-analysis
h. Very serious imprecision: Very wide confidence interval for indirect evidence
i. Serious inconsistency: High heterogeneity
j. Very serious imprecision: Very wide confidence interval for direct evidence

Appendix Table2.4D. Summary of findings on the effects of add-on therapy on hypoglycemia and adverse events

HARMS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: ADVERSE EVENTS (Any)
Setting: Inpatient and outpatient
Reference: Sim et. al 2021

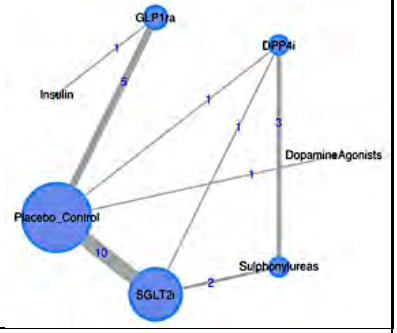


Adverse event (Any)

Total studies: 20 Total Participants: 86,528	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 23805, (6 RCTs)	829 per 1,000	820 per 1,000 (771 to 862)	8 fewer per 1,000 (58 fewer to 33 more)	RR 0.99 (0.93 to 1.04)	⊕⊕⊕◯ MODERATE [d]	2	DPP4i treatment probably makes little or no difference on any adverse event.
GLP-1RA 19782 (4 RCTs)	829 per 1,000	878 per 1,000 (829 to 986)	50 more per 1,000 (0 fewer to 157 more)	RR 1.06 (1.00 to 1.19)	⊕⊕⊕◯ MODERATE [e]	6	GLP-1RA treatment probably makes little or no difference on any adverse event.
Insulin (Indirect evidence)	829 per 1,000	796 per 1,000 (696 to 961)	33 fewer per 1,000 (133 fewer to 133 more)	RR 0.96 (0.84 to 1.16)	⊕⊕◯◯ LOW [f,g]	1	Insulin treatment may make little or no difference on any adverse event.
SGLT2i 39,871 (9 RCTs)	829 per 1,000	820 per 1,000 (787 to 862)	8 fewer per 1,000 (41 fewer to 33 more)	RR 0.99 (0.95 to 1.04)	⊕⊕⊕⊕ HIGH	3	SGLT2i treatment makes little or no difference on any adverse event.
Sulfonylureas (Indirect evidence)	829 per 1,000	837 per 1,000 (779 to 895)	8 more per 1,000 (50 fewer to 66 more)	RR 1.01 (0.94 to 1.08)	⊕◯◯◯ VERY LOW [f,h]	5	Sulfonylureas treatment has uncertain effect on any adverse event.

HARMS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: ADVERSE EVENTS (Treatment discontinuation)
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



Adverse event Treatment discontinuation)

Total studies: 24	Anticipated absolute effects* (95% CrI) over 5 years			Certainty of the	SUCRA ranking	Interpretation of findings

Total Participants: 112591	Without intervention	With intervention	Difference	Relative effect (95% CrI)	evidence (GRADE)		
DPP4i 17164 (4 RCT)	163 per 1,000	141 per 1,000 (98 to 205)	21 fewer per 1,000 (65 fewer to 42 more)	RR 0.87 (0.60 to 1.26)	⊕⊕◯◯ LOW [b,i]	2	DPP4i treatment may make little or no difference on adverse event leading to treatment discontinuation.
GLP-1RA 27041 (6 RCTs)	163 per 1,000	213 per 1,000 (166 to 276)	50 more per 1,000 (3 more to 114 more)	RR 1.31 (1.02 to 1.70)	⊕◯◯◯ VERY LOW [e,i,j]	6	GLP-1RA treatment has uncertain effect on adverse event leading to treatment discontinuation.
Insulin (Indirect evidence)	163 per 1,000	34 per 1,000 (8 to 102)	128 fewer per 1,000 (154 fewer to 60 fewer)	RR 0.21 (0.05 to 0.63)	⊕◯◯◯ VERY LOW [f,h,k]	1	Insulin treatment has uncertain effect on adverse event leading to treatment discontinuation.
SGLT2i 65,316 (13 RCT)	163 per 1,000	169 per 1,000 (141 to 202)	7 more per 1,000 (21 fewer to 39 more)	RR 1.04 (0.87 to 1.24)	⊕◯◯◯ VERY LOW [e,j,i]	5	SGLT2i treatment has uncertain effect on adverse event leading to treatment discontinuation.
Sulfonylureas (Indirect evidence)	163 per 1,000	164 per 1,000 (112 to 241)	2 more per 1,000 (50 fewer to 78 more)	RR 1.01 (0.69 to 1.48)	⊕⊕◯◯ LOW [h,i]	4	Sulfonylureas treatment may make little or no difference on adverse event leading to treatment discontinuation.

HARMS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: SERIOUS ADVERSE EVENTS
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



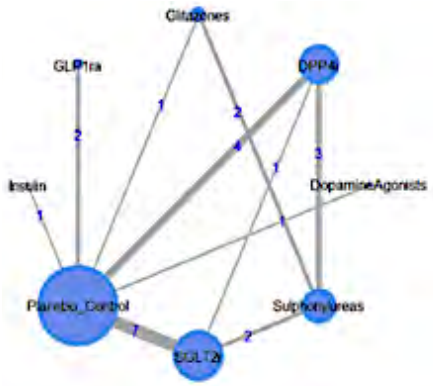
Serious adverse event

Total studies: 29 Total Participants: 142,554	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 23824, pwr:86% (6 RCT)	502 per 1,000	477 per 1,000 (447 to 513)	25 fewer per 1,000 (55 fewer to 10 more)	RR 0.95 (0.89 to 1.02)	⊕⊕⊕◯ MODERATE [d]	4	DPP4i treatment probably makes little or no

							difference on serious adverse event.
TZD 8266, pwr:31% (2 RCT)	502 per 1,000	482 per 1,000 (442 to 533)	20 fewer per 1,000 (60 fewer to 30 more)	RR 0.96 (0.88 to 1.06)	⊕⊕⊕◯ MODERATE [b]	6	TZD treatment probably makes little or no difference on serious adverse event.
GLP-1RA 37,681 (6 RCTs)	502 per 1,000	482 per 1,000 (452 to 502)	20 fewer per 1,000 (50 fewer to 0 fewer)	RR 0.96 (0.90 to 1.00)	⊕⊕⊕⊕ HIGH	5	GLP-1RA treatment makes little or no difference on serious adverse event.
Insulin (Indirect evidence)	502 per 1,000	432 per 1,000 (241 to 749)	70 fewer per 1,000 (261 fewer to 246 more)	RR 0.86 (0.48 to 1.49)	⊕◯◯◯ VERY LOW [f,h,i]	3	Insulin treatment has uncertain effect on serious adverse event.
SGLT2i 69,713 (14 RCT)	502 per 1,000	467 per 1,000 (447 to 482)	35 fewer per 1,000 (55 fewer to 20 fewer)	RR 0.93 (0.89 to 0.96)	⊕⊕⊕⊕ HIGH	1	SGLT2i treatment reduces serious adverse event.
Sulfonylureas (Indirect evidence)	502 per 1,000	487 per 1,000 (447 to 533)	15 fewer per 1,000 (55 fewer to 30 more)	RR 0.97 (0.89 to 1.06)	⊕◯◯◯ VERY LOW [f,h]	7	Sulfonylureas treatment has uncertain effect on serious adverse event.

HARMS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo Control
Outcome: HYPOGLYCEMIA (Any)
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



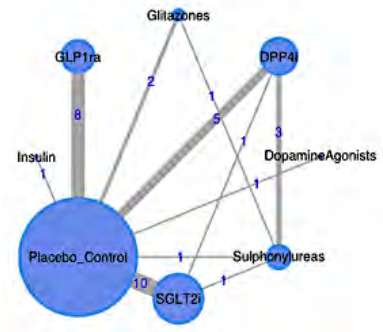
Hypoglycemia (Any)

Total studies: 24 Total Participants: 123,413	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 40,316, pwr:3% (7 RCT)	311 per 1,000	311 per 1,000 (252 to 370)	0 fewer per 1,000 (59 fewer to 59 more)	RR 1.00 (0.81 to 1.19)	⊕⊕◯◯ LOW [d,e]	1	DPP4i treatment may make little or no difference on any hypoglycaemia.
TZD 10,363, pwr:100% (3 RCT)	311 per 1,000	475 per 1,000 (354 to 658)	165 more per 1,000 (43 more to 348 more)	RR 1.53 (1.14 to 2.12)	⊕⊕⊕◯ MODERATE [b]	6	TZD treatment probably increases any hypoglycaemia.
GLP-1RA 15,403, pwr:13% (2 RCTs)	311 per 1,000	317 per 1,000 (233 to 432)	6 more per 1,000 (78 fewer to 121 more)	RR 1.02 (0.75 to 1.39)	⊕⊕⊕◯ MODERATE [j]	4	GLP-1RA treatment probably makes little or no difference on any hypoglycaemia.
Insulin 12,537 (1 RCT)	311 per 1,000	705 per 1,000 (463 to 1000)	394 more per 1,000 (152 more to 770 more)	RR 2.27 (1.49 to 3.48)	⊕⊕◯◯ LOW [b,i]	7	Insulin treatment may increase any hypoglycaemia.

SGLT2i 41,724 (10 RCTs)	311 per 1,000	314 per 1,000 (267 to 373)	3 more per 1,000 (43 fewer to 62 more)	RR 1.01 (0.86 to 1.20)	⊕⊕⊕⊕ HIGH	3	SGLT2i treatment makes little or no difference on any hypoglycaemia.
Sulfonylureas (Indirect evidence)	311 per 1,000	1000 per 1,000 (1000 to 1000)	1323 more per 1,000 (988 more to 1795 more)	RR 5.26 (4.18 to 6.78)	⊕⊕◯◯ LOW [f,g]	8	Sulfonylureas treatment may increase any hypoglycaemia.

HARMS

Patient or population: Patients with type 2 diabetes on background metformin therapy
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Placebo_Control
Outcome: HYPOGLYCEMIA (SEVERE)
Setting: Inpatient and outpatient
Reference: Sim et. al 2021



Hypoglycaemia (Severe)

Total studies: 34 Total Participants: 218,282	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	With intervention	Difference				
DPP4i 54,987 (8 RCTs)	37 per 1,000	39 per 1,000 (27 to 56)	1 more per 1,000 (10 fewer to 19 more)	RR 1.04 (0.73 to 1.51)	⊕⊕⊕⊕ HIGH	5	DPP4i treatment makes little or no difference on any hypoglycaemia.
TZD 12,713 (3 RCTs)	37 per 1,000	49 per 1,000 (25 to 98)	12 more per 1,000 (13 fewer to 60 more)	RR 1.31 (0.66 to 2.62)	⊕◯◯◯ VERY LOW [i,m]	6	TZD treatment has uncertain effect on any hypoglycaemia.
GLP-1RA 60064, pwr:65% (8 RCTs)	37 per 1,000	33 per 1,000 (25 to 45)	4 fewer per 1,000 (13 fewer to 8 more)	RR 0.90 (0.66 to 1.22)	⊕⊕⊕⊕ HIGH	3	GLP-1RA treatment makes little or no difference on any hypoglycaemia.
Insulin 12,537 (1 RCT)	37 per 1,000	119 per 1,000 (54 to 265)	82 more per 1,000 (16 more to 227 more)	RR 3.19 (1.44 to 7.11)	⊕⊕◯◯ LOW [b,i]	7	Insulin treatment may increase any hypoglycaemia.
SGLT2i 63,771 (12 RCTs)	37 per 1,000	33 per 1,000 (24 to 44)	4 fewer per 1,000 (13 fewer to 7 more)	RR 0.88 (0.65 to 1.19)	⊕⊕⊕⊕ HIGH	2	SGLT2i treatment makes little or no difference on any hypoglycaemia.
Sulfonylureas 11,140 (1 RCT)	37 per 1,000	188 per 1,000 (115 to 349)	150 more per 1,000 (78 more to 312 more)	RR 5.04 (3.09 to 9.39)	⊕◯◯◯ VERY LOW [b,i,l]	8	Sulfonylureas treatment has uncertain effect on any hypoglycaemia.

Explanations

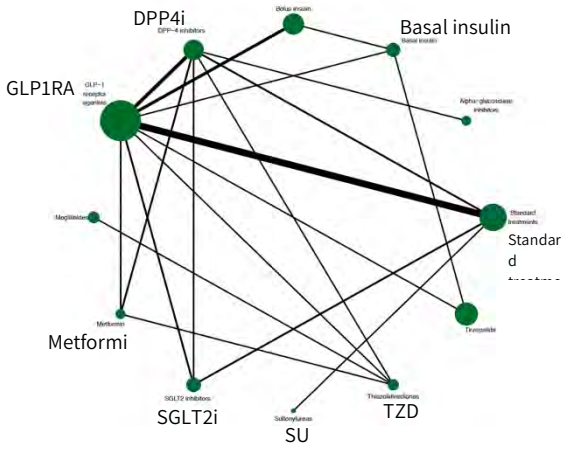
a. Very serious risk of bias: Contributions from low Rob comparisons are more than 50%
b. Serious indirectness: Single-connected nodes and evaluation of transitivity is unclear
c. Very serious indirectness: Mixed population with history of cardiovascular disease and nil history of cardiovascular disease
d. Serious indirectness: Mixed population with history of cardiovascular disease and nil history of cardiovascular disease
e. Serious inconsistency: High heterogeneity
f. Serious indirectness: Serious intransitivity as indirect evidence for this comparison goes through first order loop via trials with population without history of cardiovascular disease
g. Contributing evidence of moderate quality

h. Contributing direct evidence of low/very low quality
i. Serious imprecision: Wide confidence interval for network meta-analysis
j. Serious imprecision: Wide confidence interval for direct evidence

Appendix Table 2.4E. Summary of findings on the effects of add-on therapy on Health-related qualiy of life (HrQOL) and body weight

BENEFITS

Patient or population: Patients with type 2 diabetes
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Standard treatment
Outcome: HrQOL
Setting: Inpatient and outpatient
Reference: Qingyang, 2023

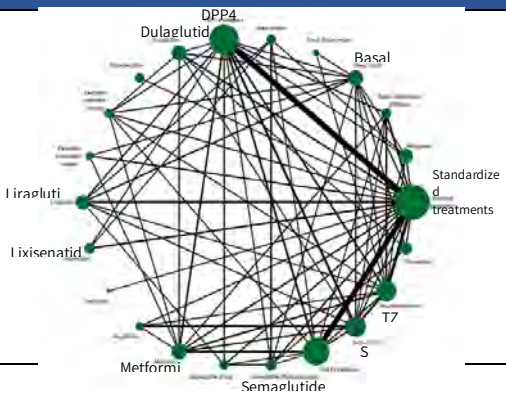


Health-related Quality of Life

Total studies: 33 RCTS Total Participants: =18 588	Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
DPP4i	SMD 0.03 (-0.12 to 0.17)	⊕⊕⊕◯ MODERATE	NA	DPP4 treatment probably makes little or no difference on HrQOL
TZD	SMD 0.20 (-0.13 to 0.52)	⊕⊕◯◯ LOW	NA	TZD treatment may make little or no difference on HrQOL
GLP-1RA	SMD 0.17 (0.07 to 0.27)	⊕⊕⊕◯ MODERATE	NA	GLP-1RA treatment probably improves HrQOL
Insulin (Basal)	SMD -0.00 (-0.25 to 0.24)	⊕◯◯◯ VERY LOW	NA	Insulin treatment has uncertain effect on HrQOL
SGLT2i	SMD 0.30 (0.10 to 0.49)	⊕⊕⊕◯ MODERATE	NA	SGLT2i treatment probably improves HrQOL
Sulfonylureas	SMD 0.23 (-0.19 to 0.64)	⊕⊕◯◯ LOW	NA	Sulfonylurea treatment may make little or no difference on HrQOL

BENEFITS

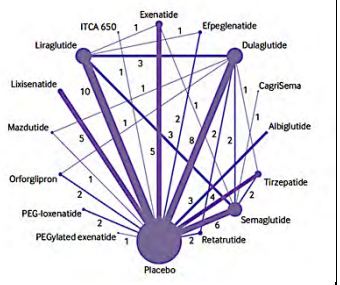
Patient or population: Patients with type 2 diabetes
Intervention: DPP4i, TZD, GLP-1RA, Insulin, SGLT2i, Sulfonylureas
Comparison: Standard treatment
Outcome: Body weight
Setting: Inpatient and outpatient
Reference: Qingyang, 2023



BODY WEIGHT				
Total studies: 531 Total Participants: 279,118	Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
DPP4i	MD 0.28 (0.11 to 0.46)	⊕⊕⊕◯ MODERATE	NA	DPP4 treatment probably makes little or no difference on weight
TZD	MD 2.81 (2.55 to 3.07)	⊕⊕⊕◯ MODERATE	NA	TZD treatment probably results in weight gain
GLP-1RA				
Dulaglutide	MD -1.40 (-1.93 to -0.88)	⊕⊕⊕⊕ HIGH	NA	Dulaglutide treatment results in weight loss
Liraglutide	MD -2.21 (-2.58 to -1.85)	⊕⊕⊕◯ MODERATE	NA	Liraglutide treatment probably results in weight loss
Lixisenatide	MD -0.83 (-1.40 to -0.26)	⊕⊕⊕⊕ HIGH	NA	Lixisenatide treatment results in weight loss
Semaglutide (injectable)	MD -4.62 (-5.22 to -4.03)	⊕⊕⊕◯ MODERATE	NA	SGLT2i treatment probably results in weight loss
Insulin (Basal)	MD 2.15 (1.74 to 2.56)	⊕⊕⊕◯ MODERATE	NA	Insulin treatment probably results in weight gain
SGLT2i	MD -1.98 (-2.18 to -1.78)	⊕⊕⊕⊕ HIGH	NA	SGLT2i treatment results in weight loss
Sulfonylureas	MD 1.78 (1.50 to 2.06)	⊕⊕⊕◯ MODERATE	NA	Sulfonylurea treatment probably results in weight gain

NA – not available

Appendix Table 2.4F. Summary of findings on the effects of various GLP-1 receptor agonists at varying doses on body weight

BENEFITS				
Patient or population: Patients with type 2 diabetes Intervention: GLP-1RA Comparison: Placebo Outcome: BODY WEIGHT Setting: Inpatient and outpatient Reference: Haiqiang Yao, 2023				
Total studies: 76 RCTS Total Participants: 39,246	Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
Dulaglutide 1.5mg	MD -0.7 (-1.56, 0.02)	⊕⊕◯◯ LOW[a,d]	10	Dulaglutide treatment may make little or no difference onweight loss
Liraglutide 1.8mg	MD -1.96 (-2.69,-1.22)	⊕⊕◯◯ LOW[d]	8	Liraglutide 1.8mg treatment may result in weight loss
Liraglutide 3mg	MD -3.9 (-5.98,-1.81))	⊕⊕◯◯ LOW[d]	8	Liraglutide 3mg treatment may result in weight loss

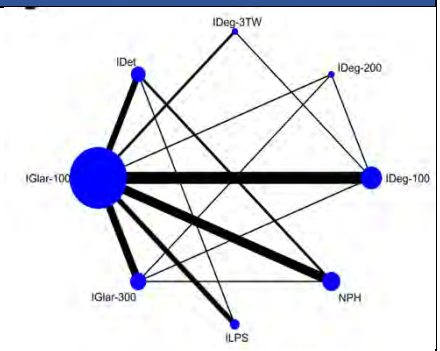
Lixisenatide	MD -0.32 (-1.51,0.87)	⊕⊕◯◯ LOW[a,c]	12	Lixisenatide treatment may make little or no difference onweight loss weight loss
Semaglutide (injectable) 1mg	MD -3.62 (-4.47, -2.77	⊕⊕⊕⊕ HIGH	5	Semaglutide 1mg results in weight loss
Semaglutide (injectable) 0.5mg	MD -3.09 (-4.21, -1.97)	⊕⊕⊕⊕ HIGH	5	Semaglutide 0.5mg results in weight loss

Explanations
a -some concerns within-study bias
b – some concerns with imprecision
c- major concern with imprecision
d – major concerns with heterogeneity

Appendix Table 2.4G. Summary of findings on the effects of the different basal insulins on hypoglycemia compared to NPH

BENEFITS

Patient or population: Patients with type 2 diabetes, insulin-naïve and on oral anti-diabetes medications, or already on insulin
Intervention: BASAL INSULINS (GLARGINE U100, GLARGINE U300, DEGLUDEC U100, DETEMIR)
Comparison: NPH
Outcome: HYPOGLYCEMIA, NOCTURNAL HYPOGLYCEMIA
Setting: Inpatient and outpatient
Reference: Denghani et al, 2024



Total studies: 44 RCTS Total Participants: 23,699	Anticipated absolute effects* (95% CrI) over 5 years			Relative effect (95% CrI)	Certainty of the evidence (GRADE)	SUCRA ranking	Interpretation of findings
	Without intervention	Without intervention	Without intervention				
Overall/Any hypoglycemia = 43 RCTs							
Degludec U100	320 per 1000	154 fewer per 1,000 (202 fewer to 86 fewer)	166 fewer per 1,000 (118 fewer to 234 fewer)	0.52 (0.37,0.73)	⊕⊕◯◯ LOW	NA	Degludec U100 may reduce hypoglycemia
Detemir	320 per 1000	144 fewer per 1,000 (186 fewer to 96 fewer)	176 fewer per 1,000 (134 fewer to 224 fewer)	0.55 (0.42,0.70)	⊕⊕⊕⊕ HIGH	NA	Detemir reduces hypoglycemia
Glargine U100	320 per 1000	80 fewer per 1,000 (118 fewer to 32 fewer)	240 fewer per 1,000 (202 fewer to 288 fewer)	0.75 (0.63,0.90)	⊕⊕⊕◯ MODERATE	NA	Glargine U100 probably reduces hypoglycemia
Glargine U300	320 per 1000	112 fewer per 1,000	208 fewer per 1,000	0.65 (0.51,0.81)	⊕⊕⊕⊕ HIGH	NA	Glargine U300 reduces hypoglycemia

		(157 fewer to 61 fewer)	(163 fewer to 259 fewer)				
Nocturnal hypoglycemia = 40 RCTs							
Degludec U100	223 per 1000	152 fewer per 1,000 (174 fewer to 123 fewer)	71 fewer per 1,000 (49 fewer to 100 fewer)	0.32 (0.22,0.45)	⊕⊕⊕◯ MODERATE	NA	Degludec U100 probably reduces hypoglycemia
Detemir	223 per 1000	125 fewer per 1,000 (147 fewer to 98 fewer)	98 fewer per 1,000 (76 fewer to 125 fewer)	0.44 (0.34,0.56)	⊕⊕⊕◯ MODERATE	NA	Detemir probably reduces hypoglycemia
Glargine U100	223 per 1000	94 fewer per 1,000 (116 fewer to 69 fewer)	129 fewer per 1,000 (107 fewer to 154 fewer)	0.58 (0.48,0.69)	⊕⊕⊕◯ MODERATE	NA	Glargine U100 probably reduces hypoglycemia
Glargine U300	223 per 1000	96 fewer per 1,000 (123 fewer to 65 fewer)	127 fewer per 1,000 (100 fewer to 158 fewer)	0.57 (0.45,0.71)	⊕⊕⊕◯ MODERATE	NA	Glargine U300 probably reduces hypoglycemia
Severe hypoglycemia = 35 RCTs							
Degludec U100	612 per year	439 fewer per 1,000 (531 fewer to 250 fewer)	173 fewer per 1,000 (81 fewer to 362 fewer)	0.28 (0.13,0.59)	⊕⊕◯◯ LOW	NA	Degludec U100 may reduce severe hypoglycemia
Detemir	612 per year	189 fewer per 1,000 (360 fewer to 98 more)	423 fewer per 1,000 (252 fewer to 514 more)	0.69 (0.41,1.16)	⊕⊕⊕⊕ HIGH	NA	Detemir make little or no difference o
Glargine U100	612 per year	159 fewer per 1,000 (287 fewer to 12 more)	453 fewer per 1,000 (325 fewer to 600 more)	0.74 (0.53,1.02)	⊕⊕⊕◯ MODERATE	NA	Glargine U100 probably make little or no difference o
Glargine U300	612 per year	250 fewer per 1,000 (397 fewer to 0 fewer)	75 fewer per 1,000 (215 fewer to 612 fewer)	0.59 (0.35,1.00)	⊕⊕◯◯ LOW	NA	Glargine U300 may make little or no difference o

Q2.5. Recommendations from Other Groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
AACE consensus statement: Comprehensive Type 2 Diabetes Mellitus Management Algorithm 2023 Update	Metformin should be initiated if there is no contraindication. Persons with a history of hypoglycemia, at high risk of hypoglycemia and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, TZD, or DPP-4i. For recently diagnosed individuals with T2D and an A1C ≥7.5%, early combination therapy may also be considered, usually with metformin combined with another agent that does not cause hypoglycemia, particularly a GLP-1 RA, SGLT2i, or DPP-4i. For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use. For many persons with T2D, access and cost are barriers to receiving newer antihyperglycemic agents. In this situation, a TZD, SU, or glinide would be the more economical choices.	Strong Strong
The American Diabetes Association "Standards of Care in Diabetes" 2024	In adults with Type 2 Diabetes Mellitus and established or high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk (e.g., sodium-glucose cotransporter 2 inhibitor and /or glucagon-like peptide 1 receptor agonist for glycemic management and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. In adults with type 2 diabetes who have heart failure (HF) - with either reduced or preserved ejection fraction, and SGLT2 inhibitor is recommended, for glycemic management and prevention of HF hospitalizations. In adults with type 2 diabetes who have CKD – with confirmed estimated glomerular filtration rate of 20-	Strong

	60mL/min/1.73m^2 and/or albuminuria, an SGLT2 inhibitors should be used for minimizing progression of CKD, reduction in cardiovascular events, and reduction in hospitalizations for HF; however, the glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min per 1.73m^2. In adults with type 2 diabetes and advanced CKD (eGFR <30mL/min per 1.73m^2), a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if there is evidence of ongoing catabolism – unexpected weight, if symptoms of hyperglycemic are present, or when A1c or blood glucose levels are very high – A1c >10% or blood glucose >/= 300 mg/dL. In adults with type 2 diabetes, a GLP1 RA including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin. If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP1-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. In adults with diabetes and cost-related barriers, consider use of lower-cost medications for glycemic management – metformin, sulfonylureas, TZD, and human insulin, within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects.	

Guideline Question 3.

Should we recommend initial oral combination therapy for adults with T2DM with HbA1c >9% or fasting blood sugar (FBS) >250 mg/dL?

Q3.1. Methods and search strategy

A comprehensive search of various databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted by the reviewers following the PRISMA guidelines from inception to December 7, 2023. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The search was targeted towards randomized controlled trials that evaluated the effect of initial oral combination therapy (two oral glucose-lowering agents) compared with oral monotherapy among adults with T2DM and HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL, on all-cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety. Search terms utilized include "diabetes mellitus", "oral antidiabetic agents", "metformin", "sulfonylurea", "DPP-4 inhibitors", "SGLT2 inhibitors", "oral combination therapy", "dual therapy", "monotherapy", "HbA1c > 9%", "fasting blood sugar", "glycemic control", "HbA1c reduction". Studies with a low risk of bias were selected.

Q3.2 GRADE Evidence Profile and Forest Plots

Question: Initial oral combination therapy compared to monotherapy with oral agent for persons with type 2 diabetes mellitus with HbA1c >9%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initial oral combination therapy	monotherapy with oral agent	Relative (95% CI)	Absolute (95% CI)		
Odds ratio of achieving HbA1c <7.5% (follow-up: mean 24 weeks; assessed with: odds ratio)												
37	randomised trials	not serious	not serious	serious[a]	not serious	none	5958	5520	-	OR **1.33 higher** (1.2 higher to 1.47 higher)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Odds ratio of achieving HbA1c <6.5% (follow-up: mean 24 weeks; assessed with: OR)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	289	291	-	OR **2.84 higher** (1.87 higher to 4.32 higher)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Reduction of HbA1c from baseline (follow-up: range 24 weeks to 26 weeks; assessed with: HbA1c)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initial oral combination therapy	monotherapy with oral agent	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	serious[b]	not serious	not serious	none	1470	916	-	MD **0.55 HbA1c lower** (0.67 lower to 0.43 lower)	⨁⨁⨁◯ Moderate[b]	CRITICAL
HbA1c reduction from baseline (follow-up: range 16 weeks to 50 weeks; assessed with: HbA1c)												
36	randomised trials	not serious	not serious	serious[a,c]	not serious	none	5736	5748	-	MD **0.44 HbA1c lower** (0.57 lower to 0.31 lower)	⨁⨁⨁◯ Moderate[b]	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Heterogeneity in patient characteristics
b. inconsistency among some trial results, heterogeneity
c. indirectness in terms of treatment used
d. Heterogeneity in duration of follow-up

Q3.3 Recommendations from other guidelines:

Group or Agency	Recommendation	Strength of Recommendation/Certainty/Quality of Evidence
American Diabetes Association	Early, aggressive, and often combination therapy is recommended for patients with type 2 diabetes presenting with an HbA1c >10%.[7]	A
Diabetes Canada	In people with type 2 diabetes with A1C ≥1.5% above target, antihyperglycemic agents should be initiated concomitantly with healthy behaviour interventions, and consideration could be	A

Group or Agency	Recommendation	Strength of Recommendation/Certainty/Quality of Evidence
	given to initiating combination therapy with 2 agents.[8]	

Q3.4 Research Gaps and Recommendations:

There is a need for more research on the impact of oral combination therapy vs. metformin on long-term outcomes, such as the incidence of diabetes-related complications and cardiovascular events. Cost-effectiveness studies on the impact of overcoming therapeutic inertia with the timely use of oral combination therapy would also be ideal.

Summary of Panel Justifications by EtD Domain

Balance of effects. Panel support rested on the demonstrated superiority of dual therapy for glycemic control — one panelist citing the effect estimates directly (OR 1.33 for achieving HbA1c <7.5%; OR 2.84 for ≤6.5%) — alongside early intensification of therapy, prevention of target organ damage with specific reference to the kidney, preservation of pancreatic function, and avoidance of clinical inertia. The single judgment of "probably favors the intervention" was qualified by the need to individualize therapy according to pathophysiologic, racial, and ethnic variation in drug responsiveness and diagnostic limitations, while one panelist noted that the evidence presented did not identify which specific combination achieved the greatest reduction in HbA1c.

Resources required and cost-effectiveness. The majority judgment of moderate upfront cost reflected the prescription of two agents rather than one, considered offset by the availability of generic preparations and fixed-dose combinations, with cost-effectiveness judgments based on anticipated downstream savings — avoidance of microvascular and macrovascular complications, hospitalization, dialysis, and therapeutic inertia — rather than formal economic evaluation, and one panelist citing cardiovascular and chronic kidney disease benefit with SGLT2 inhibitors in other populations as indirect support. Two panelists explicitly noted the absence of economic data, one observing that no cost studies were presented and another indicating that the judgment might be revised toward cost-saving should more objective data become available.

Values. Panelists reporting little or no important variability reasoned that patients generally accept additional medication when the rationale is adequately explained and that oral combination therapy is preferred over insulin, while those reporting important variability described a trade-off between rapid and durable glycemic control and considerations of medication burden, cost, adverse effects, and treatment complexity. One panelist further distinguished between blue-collar and informal workers, for whom limited insurance coverage and absence of paid medical leave contribute to financial

concern and treatment-related stress at diagnosis, and salaried workers, who are less constrained by cost but prefer single-pill regimens.

Equity. This domain received the largest proportion of unfavorable judgments, with barriers including exclusion of most SGLT2 inhibitors from UHC, PhilHealth, and Yakap coverage; limited stocking of combination preparations in government pharmacies; out-of-pocket expenditure where medications are not covered; and limited benefit to geographically isolated and disadvantaged areas. Panelists reporting increased equity noted that three oral agents suitable for initial combination are included in the PhilHealth and DOH formulary, that generic preparations, low-cost fixed-dose combinations, and Yakap subsidies could improve access among lower-income groups, and that early organ protection may be of greatest benefit to informal workers conditional on prioritization of affordable single-pill generic combinations, while one anticipated no impact given available generic equivalents and two noted that recent patent expiries have increased affordability.

Acceptability and feasibility. No unfavorable judgments were recorded in either domain, with acceptability attributed to consistency with international guidelines, limited anticipated resistance among patients and clinicians, and the role of shared decision-making in addressing pill burden and cost — two panelists conditioning acceptability on adequate explanation of the expected benefit. Feasibility was attributed to the availability of oral agents as single-pill and fixed-dose combinations, applicability across levels of care from workplace clinics and primary care facilities to tertiary hospitals, and the absence of any requirement for specialized infrastructure or additional training, subject to two conditions: sustained government support through UHC and PhilHealth programs, and adequate support from relevant stakeholders.

Justifications for conditional/weak judgments. Of the three panelists voting for a conditional strength, one cited variability in values and context while acknowledging the intervention to be well supported with respect to safety, superiority, and long-term glycemic durability, and a second cited variability in patient preferences and socioeconomic barriers to access, particularly among blue-collar and informal workers, together with the need for individualized care and shared decision-making to ensure affordability and adherence. The third provided no explicit rationale beyond the statement that better initial control results in fewer complications.

Guideline Question 4.

Should initial injectable therapy combined with oral agent/s be recommended for among adults with type 2 diabetes mellitus (T2DM) with HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL?

Q4.1. Methods and search strategy

A comprehensive search of various databases such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials was conducted by the reviewers following the PRISMA guidelines from inception to December 7, 2023. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The search was targeted towards randomized controlled trials that evaluated the effect of initial combination of injectable therapy with oral agent/s among adults with T2DM and HbA1c > 9% or fasting blood sugar (FBS) > 250 mg/dL, on all-cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety. Search terms utilized include "diabetes mellitus", "injectable therapy", "insulin", "GLP-1 receptor agonists", "oral antidiabetic agents", "combination therapy", "HbA1c > 9%", "fasting blood sugar", "3-point MACE", "macrovascular outcomes", "glycemic control", "HbA1c reduction". Studies with a low risk of bias were selected.

Q4.2. GRADE Evidence Profile and Forest Plots

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	basal insulin	oral agents alone	Relative (95% CI)	Absolute (95% CI)		
Odds of reaching HbA1c </= 7.0% (follow-up: mean 24 weeks)												
11	randomised trials	not serious	not serious	not serious	serious[a]	none	1478/2171 (68.1%)	849/2171 (39.1%)	**OR 0.261** (-0.057 to 0.580)	**248 fewer per 1,000** (from 429 fewer to 120 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of primary microvascular composite outcome (follow-up: mean 2 years; assessed with: HR)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	718/3720 (19.3%)	726/3666 (19.8%)	**HR 0.90** (0.81 to 0.99)	**18 fewer per 1,000** (from 34 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

Explanations

a. heterogeneous populations

b. included patients with good glycemic control (HbA1c >/= 6.4%)

Question: GLP-1 receptor agonists compared to oral agents alone for patients with type 2 diabetes with HbA1c > 9%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP-1 receptor agonists	oral agents alone	Relative (95% CI)	Absolute (95% CI)		
Change in HbA1c (follow-up: mean 38.1 weeks)												
31	randomised trials	not serious	not serious	not serious[a]	serious[b]	none	12319	10742	-	MD **0.99 % lower** (1.17 lower to 0.82 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of MACE (follow-up: range 1.3 years to 5.4 years; assessed with: HR)												
8	randomised trials	not serious	not serious	not serious	serious[b]	none	3137/30694 (10.2%)	3429/29386 (11.7%)	HR 0.86 (0.80 to 0.93)	**15 fewer per 1,000** (from 22 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference

Explanations

a. mean HbA1c of patients >/= 7.8%, included patients without diabetes
b. marked heterogeneity

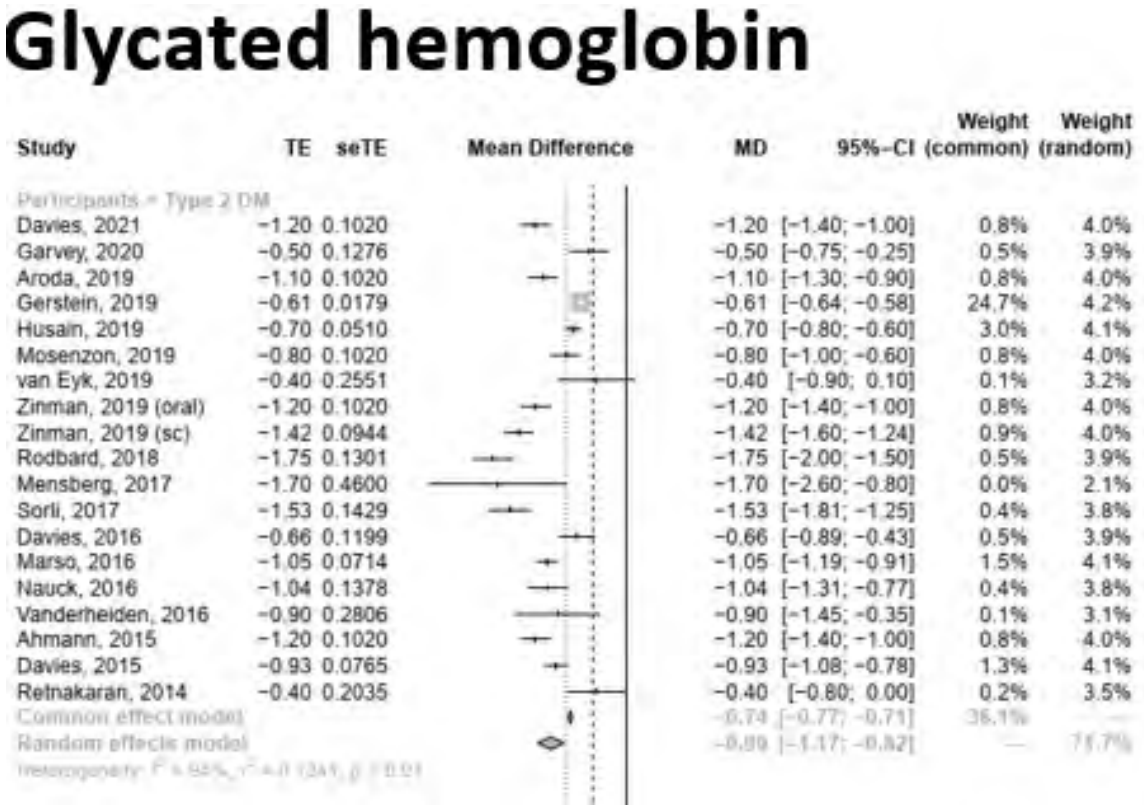
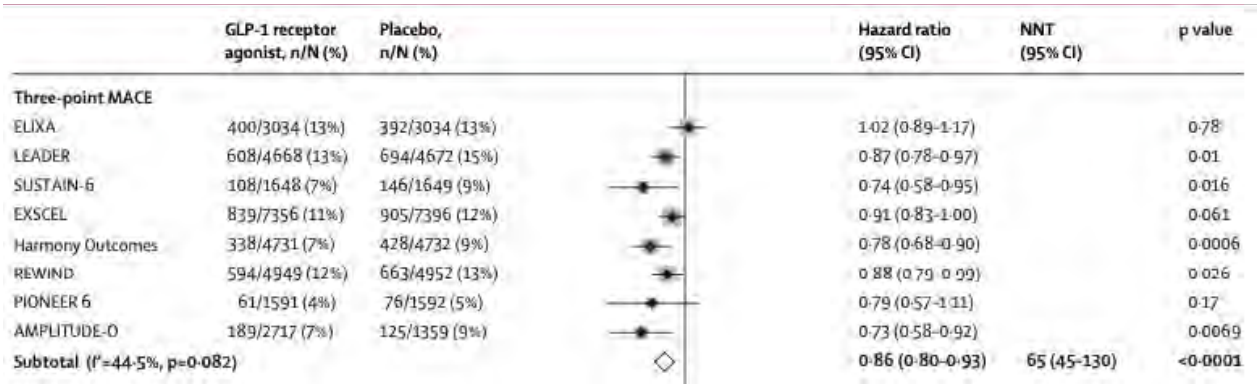


Fig 1. HbA1c reduction with use of GLP-1 RA (adopted from Yeh et al)



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I²=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**

Fig 2. Incidence of MACE with GLP-1 RA use (adopted from Sattar et al)

Q4.3. Recommendations from other groups

Group or Agency	Recommendation	Strength of Recommendation/Certainty/Quality of Evidence
American Diabetes Association	Initiate basal insulin for A1C > 10, blood glucose > 300 mg/dL, or who are symptomatic of hyperglycemia For patients with type 2 diabetes who have atherosclerotic cardiovascular disease or are at high risk for it or who have kidney disease or heart failure, either a GLP-1 receptor agonist or an SGLT-2 inhibitor with demonstrated cardiovascular benefit with or without metformin is recommended, independent of the hemoglobin A1c level	A
American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)	In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) is the first injectable therapy in most cases.	A
American Association of Clinical Endocrinologists	Initiate insulin therapy for HbA1c > 9%	A
Korean Diabetes Association 2017	Insulin can be used as an initial treatment at the diagnosis of type 2 diabetes in the presence of metabolic	E

	decompensation and/or glycosylated hemoglobin >9.0% and/or symptomatic hyperglycemia.	
East African Diabetes Study Group	In T2DM patients, with regards to achieving glycemic goals, insulin is considered alone or in combination with oral agents when HbA1c is ≥ 7.5% (≥ 58 mmol/mol); and is essential for treatment in those with HbA1c ≥ 10% (≥ 86 mmol/mol), when diet, physical activity, and other antihyperglycemic agents have been optimally used	B

Q4.4 Research Gaps and Recommendations:

There is a need for more research on using the threshold of fasting blood sugar level of more than 250 mg/dl for initiating basal insulin therapy or adding GLP-1 receptor agonist treatment. This is relevant in the local setting since fasting blood sugar is the readily available laboratory exam in the geographically isolated and disadvantaged areas. Local data on the impact of early initiation of injectables in the setting of marked hyperglycemia are needed. Cost-effectiveness studies on the impact of overcoming therapeutic inertia with the timely use of injectables would also be optimal.

Guideline Question 5.

Should we recommend add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target?

Q5.1. Methods and Search strategy

From January to April 2024, a systematic review of literature was conducted by five independent reviewers. A targeted search strategy was employed to identify relevant clinical practice guidelines (CPGs) on the stepwise approach to the management of type 2 diabetes mellitus, specifically the use of add-on injectable therapy (basal insulin, GLP-1 receptor agonists, or fixed-ratio combination therapy) among adults with T2DM on 2–3 oral agents and with HbA1c above target, from international databases, including MEDLINE/PubMed, National Guidelines Clearinghouse, Guideline International Network, and National Institute for Clinical Evidence. Additional searches of other databases and medical specialty websites were also performed by the Technical Working Group (TWG) to find articles not covered by the primary search. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

Q5.2 Characteristics of the Included Studies

Basal insulin vs. OADs — Fonseca et al. (2011):

# of Studies	Design	Population	Comparator	Outcomes	Quality
11 (N = 2,171)	Randomized controlled trials (RCTs)	Adult patients with uncontrolled type 2 diabetes mellitus (Mean baseline HbA1c 8.77%)	Oral agents only (metformin or SU) early in treatment	HbA1c reduction, percentage achieving HbA1c ≤7.0%, weight gain and hypoglycemic events	Good quality, heterogeneity noted (participants mostly Caucasian)

GLP-1 RA vs. oral agents alone — Yeh et al. and Sattar et al.:

# of Studies	Design & Duration	Population	Comparator	Outcomes	Quality
31 (N = 23,061) — Yeh et al.	RCT, >38 weeks	Adult patients with mean HbA1c 7.8%	Oral agents alone	Change in HbA1c	Most studies with low risk of bias, with high heterogeneity, Asian population
8 (N = 60,080) — Sattar et al.	RCT	Adult patients with type 2 diabetes with mean HbA1c range from 7.3–8.7% (8.9%	Oral agents alone	Incidence of MACE	Generally low risk of bias, heterogeneity in characteristics of participants

# of Studies	Design & Duration	Population	Comparator	Outcomes	Quality
		for the AMPLITUDE-O study)			

GLP-1 RA vs. basal insulin — Nauck et al. and Longato et al.:

# of Studies	Design & Duration	Population	Comparator	Outcomes	Quality
20 (N = 11,843) — Nauck et al.	RCT >12 weeks duration	Adult patients with mean HbA1c of 8.3–8.4% ± 0.9–1% despite being on Met + SU/TZD/SGLT2i	Insulin Glargine/Detemir/Degludec vs Exenatide/Liraglutide/Dulaglutide/Semaglutide/Tirzepatide	Primary endpoint: Change in HbA1c vs baseline. Secondary: reduction in FPG vs baseline; reduction in body weight vs baseline.	Good
1 (N = 330,193) — Longato et al.	Retrospective, single-nature study; Median follow-up >24 months	Adult patients newly treated with GLP-1RA or basal insulin with mean HbA1c of 7.7–8.3 (±0.8–1.1%) on Metformin ± SU/DPP4 inhibitor	Insulin Glargine/Detemir/Degludec vs exenatide/liraglutide/lixisenatide/dulaglutide	Primary: 3P-MACE. Secondary: 3P-MACE components, hospitalization for heart failure, revascularizations, and adverse events.	Low quality, high risk of bias and imprecision (retrospective study)

GLP-1 RA vs. FRC vs. basal insulin — Visolyi et al.:

# of Studies	Design & Duration	Population	Comparator	Outcomes	Quality
29 (N = 23,605) — Visolyi et al.	RCTs (>24 weeks or 24–104 weeks)	Adult patients with type 2 diabetes mellitus with mean HbA1c of 8% *with inadequate glycemic control or HbA1c >7.5% despite being treated for at least 3 months with metformin ± 2nd OAD	Basal insulin or GLP-1 RA (iGlarLixi as reference treatment)	Mean difference in HbA1c, weight gain, hypoglycemia	Low risk of bias, with heterogeneity, included Asian populations

Q5.3 Assessment of Risk of Bias

Per the source document: most studies had overall low risk of bias with high heterogeneity. The Longato et al. (2021) retrospective study was rated as low quality with high risk of bias and imprecision.
<INSERT HERE — per-domain Cochrane RoB (or AMSTAR/ROBIS) judgments for each included systematic review and individual study>

Q5.4. Results

Summary of effects — basal insulin vs. oral agents alone (Fonseca et al.):

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
HbA1c reduction after 24 weeks (%)	11 RCTs · N = 2,171	−2.0% for 0/1 OAD vs −1.7% for 2 OAD; OR = 0.261	−0.057 to 0.580; p = 0.108	Equivalent	Moderate

Summary of effects — GLP-1 RA vs. oral agents alone (Yeh et al., Sattar et al.):

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Change in HbA1c (%)	31 RCTs · N = 23,061 (Yeh et al.)	−0.99% in type 2 patients	−1.17 to −0.82; p < 0.001	Benefit	Moderate
Body weight reduction	31 RCTs · N = 23,061 (Yeh et al.)	−4.05 kg (−5.02, −3.09) random-effects; −2.04 kg (−2.16, −1.92) fixed-effect	−3.84 to −2.44; p < 0.001	Benefit	Moderate

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Incidence of MACE	8 RCTs · N = 60,080 (Sattar et al.)	HR 0.86 (3P-MACE reduced by 14%)	0.80 to 0.93; p < 0.0001	Benefit	Moderate to High

Summary of effects — GLP-1 RA vs. basal insulin (Nauck et al., Longato et al.):

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Change in HbA1c	20 RCTs · N = 11,843 (Nauck et al.)	0.5%	0.46–0.53; p < 0.001	Benefit	Moderate
Change in body weight	20 RCTs · N = 11,843 (Nauck et al.)	4.6 kg	4.5–4.7 kg; p < 0.001	Benefit	Moderate
Rate of hypoglycemia	20 RCTs · N = 11,843 (Nauck et al.)	0.56	0.32–1.00; p = 0.052	Benefit	Moderate
3P-MACE	1 study · N = 330,193 (Longato et al.)	HR 0.59	0.50–0.71; p < 0.001	Benefit	Moderate

Summary of effects — FRC vs. basal insulin or GLP-1 RA (Visolyi et al.):

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Change in HbA1c	29 RCTs · N = 23,605	−0.10	−0.3 to 0.10	Equivalent	Moderate
Change in weight	29 RCTs · N = 23,605	−0.72	−1.35 to −0.09	Benefit	Moderate
Rate of hypoglycemia	29 RCTs · N = 23,605	0.78	0.39 to 1.57	Equivalent	Moderate

Q5.5. GRADE Evidence Profile

GRADE summary-of-findings (key outcomes transcribed from source GRADE tables):

Basal Insulin vs. Oral Anti-Diabetic Agents — Bibliography: Fonseca V et al. Diabetes Obes Metab. 2011;13(9):814-22.

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
Odds of reaching HbA1c ≤7.0%	11	randomised trials	imprecision: serious; RoB / inconsistency /	OR 0.261 (−0.057 to 0.580); 248 fewer per 1,000 (429	Moderate

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
(follow-up: mean 24 weeks)			indirectness: not serious	fewer to 120 fewer); basal insulin 1478/2171 (68.1%) vs OADs 849/2171 (39.1%)	
Incidence of primary microvascular composite outcome (follow-up: mean 2 years; assessed with HR)	1	randomised trials	indirectness: serious; RoB / inconsistency / imprecision: not serious	HR 0.90 (0.81 to 0.99); 18 fewer per 1,000 (34 fewer to 2 fewer); basal insulin 718/3720 (19.3%) vs OADs 726/3666 (19.8%)	Moderate

Explanations from source: (a) heterogeneous populations; (b) included patients with good glycemic control (HbA1c ≥6.4%).

GLP-1 RAs vs. Oral Anti-Diabetic Agents — Bibliography: Yeh TL et al. PLoS One 2023;18(1):e0278685; Sattar N et al. Lancet Diabetes Endocrinol 2021;9(10):653–662.

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
Change in HbA1c (follow-up: mean 38.1 weeks)	31	randomised trials	imprecision: serious	MD 0.99% lower (1.17 lower to 0.82 lower); GLP-1 RA 12,319 vs OADs 10,742	Moderate
Incidence of MACE (follow-up: range 1.3–5.4 years; assessed with HR)	8	randomised trials	imprecision: serious	HR 0.86 (0.80 to 0.93); 15 fewer per 1,000 (22 fewer to 8 fewer); GLP-1 RA 3137/30,694 (10.2%) vs OADs 3429/29,386 (11.7%)	Moderate
Weight (follow-up: mean 38.1 weeks; assessed with kg)	31	randomised trials	imprecision: serious	MD 3.23 kg lower (3.86 lower to 2.59 lower); GLP-1 RA 12,319 vs OADs 10,742	Moderate

Explanations from source: (a) mean HbA1c of patients ≥7.8%, included patients without diabetes; (b) marked heterogeneity.

GLP-1 RAs vs. FRCs vs. Basal Insulin — Bibliography: Visolyi GÁ et al. Can J Diabetes 2023;47(4):368-377.

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
HbA1c reduction (%) (follow-up: 24–104 weeks)	29	randomised trials	imprecision: serious	MD 0.1% lower (0.3 lower to 0.1 higher); FRC 3,549 vs basal insulin or GLP-1 RA 20,056	Moderate
Weight Change (follow-up: 24–104 weeks; kg)	29	randomised trials	imprecision: serious	MD 0.72 kg lower (1.35 lower to 0.09 lower); FRC 3,549 vs 20,056	Moderate
Incident Hypoglycemia (follow-up: 24–104 weeks)	29	randomised trials	imprecision: serious	OR 0.78 higher (0.39 higher to 1.57 higher); FRC 3,549 vs 20,056	Moderate

Explanation from source: (a) heterogeneous populations.

GLP-1 RA vs. Basal Insulin (glycemic control among T2DM with failure on OADs) — Bibliography: Nauck MA et al. Diabetes Obes Metab. 2023;25(5):1361-1371.

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
Short-acting GLP1RA vs Basal insulin — Achievement of Target HbA1c <7% (follow-up: 25–52 weeks; proportion)	5	randomised trials	none (not serious across all domains)	OR 0.92 (0.69 to 1.23) NS; 21 fewer per 1,000 (89 fewer to 52 more); GLP1RA 157/366 (42.9%) vs basal insulin 171/380 (45.0%)	High
Long-acting GLP1RA vs Basal insulin — Achievement of Target HbA1c <7% (follow-up: 25–52 weeks; proportion)	16	randomised trials	none	OR 1.90 (1.41 to 2.54) favoring GLP-1 RA; 159 more per 1,000 (85 more to 228 more); GLP1RA 1893/3526 (53.7%) vs basal insulin 1016/2415 (42.1%)	High
Any hypoglycemia (all GLP1RA + tirzepatide vs basal insulin; 25–52 weeks; event rate)	20	randomised trials	none	Not estimable; GLP1RA 20/100 (20.0%) vs basal	High

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
				insulin 40/100 (40.0%)	
Weight reduction (all GLP1RA + tirzepatide vs basal insulin)	20	randomised trials	none	MD 4.6 kg lower (4.7 lower to 4.4 lower)	High
Nausea (all GLP1RA vs basal insulin; 25–52 weeks; event rate)	14	randomised trials	none	RR 6.1 (4.9 to 7.4); 142 more per 1,000 (109 more to 178 more); GLP1RA 925/4719 (19.6%) vs basal insulin 99/3553 (2.8%)	High
Vomiting (all GLP1RA vs basal insulin; 25–52 weeks; event rate)	12	randomised trials	none	RR 3.7 (2.8 to 4.8); 54 more per 1,000 (36 more to 76 more); GLP1RA 316/4061 (7.8%) vs basal insulin 63/3140 (2.0%)	High
Diarrhea (all GLP1RA vs basal insulin; 25–52 weeks; event rate)	11	randomised trials	none	RR 2.6 (2.1 to 3.1); 70 more per 1,000 (48 more to 92 more); GLP1RA 554/4590 (12.1%) vs basal insulin 138/3150 (4.4%)	High

GLP-1 RA vs. Basal Insulin (CV protection among T2DM patients) — Bibliography: Longato E et al. Cardiovasc Diabetol. 2021;20:222.

NB (from source): certainty of evidence downgraded to LOW due to retrospective nature, single study only.

Outcome	# studies	Design	Certainty downgrade	Effect	Certainty
All-cause death (follow-up: median 24 months)	1	observational study	Source: strong association; all plausible residual confounding would reduce the demonstrated effect	RR 0.42 (0.30 to 0.59); 86 fewer per 1,000 (104 fewer to 61 fewer); GLP1RA 49/786 (6.2%) vs basal insulin 117/791 (14.8%)	Low
Myocardial infarction (median 24 months)	1	observational study	Source: all plausible residual confounding would reduce the demonstrated effect	RR 0.77 (0.61 to 0.97); 49 fewer per 1,000 (84 fewer to 6 fewer); GLP1RA 128/774 (16.5%) vs basal insulin 166/774 (21.4%)	Low
Stroke (median 24 months)	1	observational study	Source: strong association; all plausible residual confounding would reduce the demonstrated effect	RR 0.44 (0.31 to 0.62); 74 fewer per 1,000 (91 fewer to 50 fewer); GLP1RA 45/782 (5.8%) vs basal insulin 103/781 (13.2%)	Low

Q5.6 GRADE Tables

Q5.6.1 Question: Basal Insulin VS Oral Anti Diabetic Agents among T2DM patients

Bibliography: Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab. 2011 Sep;13(9):814-22. doi: 10.1111/j.1463-1326.2011.01412.x. PMID: 21481127; PMCID: PMC3170705.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	basal insulin	oral agents alone	Relative (95% CI)	Absolute (95% CI)		
Odds of reaching HbA1c </= 7.0% (follow-up: mean 24 weeks)												
11	randomised trials	not serious	not serious	not serious	serious[a]	none	1478/2171 (68.1%)	849/2171 (39.1%)	**OR 0.261** (-0.057 to 0.580)	**248 fewer per 1,000** (from 429 fewer to 120 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of primary microvascular composite outcome (follow-up: mean 2 years; assessed with: HR)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	718/3720 (19.3%)	726/3666 (19.8%)	**HR 0.90** (0.81 to 0.99)	**18 fewer per 1,000** (from 34 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

Explanations

a. heterogeneous populations

b. included patients with good glycemic control (HbA1c >/= 6.4%)

Q5.6.2 Question: GLP1-RAs VS Oral Anti Diabetic Agents among T2DM patients with hba1c >9%

Bibliography:

(1) Yeh TL, Tsai MC, Tsai WH, Tu YK, Chien KL. Effect of glucagon-like peptide-1 receptor agonists on glycemic control, and weight reduction in adults: A multivariate meta-analysis. PLoS One. 2023 Jan 25;18(1):e0278685. doi: 10.1371/journal.pone.0278685. PMID: 36696429; PMCID: PMC9876280

(2) Sattar, N., Lee, M. M. Y., Kristensen, S. L., Branch, K. R. H., Del Prato, S., Khurmi, N. S., … Gerstein, H. C. (2021). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. The Lancet Diabetes & Endocrinology, 9(10), 653–662. doi:10.1016/s2213-8587(21)00203-5.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP-1 receptor agonists	oral agents alone	Relative (95% CI)	Absolute (95% CI)		
Change in HbA1c (follow-up: mean 38.1 weeks)												
31	randomised trials	not serious	not serious	not serious[a]	serious[b]	none	12319	10742	-	MD **0.99 % lower** (1.17 lower to 0.82 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of MACE (follow-up: range 1.3 years to 5.4 years; assessed with: HR)												
8	randomised trials	not serious	not serious	not serious	serious[b]	none	3137/30694 (10.2%)	3429/29386 (11.7%)	**HR 0.86** (0.80 to 0.93)	**15 fewer per 1,000** (from 22 fewer to 8 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Weight (follow-up: mean 38.1 weeks; assessed with: kg)												
31	randomised trials	not serious	not serious	not serious	serious[b]	none	12319	10742	-	MD **3.23 kg lower** (3.86 lower to 2.59 lower)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference

Explanations

a. mean HbA1c of patients >/= 7.8%, included patients without diabetes

b. marked heterogeneity

Q5.6.3 Question: GLP1-RAs VS Basal Insulin VS FRCs among T2DM patients with Hba1c >9%

Bibliography: Visolyi GÁ, Domján BA, Svébis MM, Péterfi A, Lovász BD, Mészáros S, Horváth VJ, Tabák ÁG. Comparison of Efficacy and Safety of Commercially Available Fixed-Ratio Combinations of Insulin Degludec/Liraglutide and Insulin Glargine/Lixisenatide: A Network Meta-analysis. Can J Diabetes. 2023 Jun;47(4):368-377. doi: 10.1016/j.jcjd.2023.03.002. Epub 2023 Mar 22. PMID: 36963632.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FRC	basal insulin or GLP-1 RA	Relative (95% CI)	Absolute (95% CI)		
HbA1c reduction (%) (follow-up: range 24 weeks to 104 weeks)												
29	randomised trials	not serious	not serious	not serious	serious[a]	none	3549	20056	-	MD **0.1 % lower** (0.3 lower to 0.1 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Weight Change (follow-up: range 24 weeks to 104 weeks; assessed with: kg)												
29	randomised trials	not serious	not serious	not serious	serious[a]	none	3549	20056	-	MD **0.72 kg lower** (1.35 lower to 0.09 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Incident Hypoglycemia (follow-up: range 24 weeks to 104 weeks)												
29	randomised trials	not serious	not serious	not serious	serious[a]	none	3549	20056	-	OR **0.78 higher** (0.39 higher to 1.57 higher)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. heterogeneous populations

Q5.6.4 Question: GLP1RA compared to Basal Insulin in glycemic control among T2DM with failure on OADs

Author(s): Nauck MA, Mirna AE, Quast DR

Bibliography: Nauck MA, Mirna AEA, Quast DR. Meta-analysis of head-to-head clinical trials comparing incretin-based glucose-lowering medications and basal insulin: An update including recently developed glucagon-like peptide-1 (GLP-1) receptor agonists and the glucose-dependent insulinotropic polypeptide/GLP-1 receptor co-agonist tirzepatide. Diabetes Obes Metab. 2023 May;25(5):1361-1371. doi: 10.1111/dom.14988. Epub 2023 Feb 8. PMID: 36700380.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsis-tency	Indirectness	Imprecision	Other consid e-rations	GLP1-RA	Basal Insulin	Relative (95% CI)	Absolute (95% CI)		
Short-acting GLP1RA vs Basal insulin Achievement of Target HBA1c <7% (follow-up: range 25 weeks to 52 weeks; assessed with: proportion)												
5	randomized trials	not serious	not serious	not serious	not serious	none	157/366 (42.9%)	171/380 (45.0%)	**OR 0.92** (0.69 to 1.23) **NS**	**21 fewer per 1,000** (from 89 fewer to 52 more)	⊕⊕⊕⊕ High	CRITICAL
Long-acting GLP1RA vs Basal insulin Achievement of Target HBA1c <7% (follow-up: range 25 weeks to 52 weeks; assessed with: Proportion)												
16	randomized trials	not serious	not serious	not serious	not serious	none	1893/3526 (53.7%)	1016/2415 (42.1%)	**OR 1.90** (1.41 to 2.54) **Favoring GLP-1 RA**	**159 more per 1,000** (from 85 more to 228 more)	⊕⊕⊕⊕ High	CRITICAL
Any Hypoglycemia (all GLP1RA plus Tirzepatitde vs Basal Insulin) (follow-up: range 25 weeks to 52 weeks; assessed with: event rate)												
20	randomized trials	not serious	not serious	not serious	not serious	none	20/100 (20.0%)	40/100 (40.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Weight reduction (all GLP1RA plus Tirzepatide vs Basal Insulin) (assessed with: change in weight)												
20	randomized trials	not serious	not serious	not serious	not serious	none			-	MD **4.6 kg lower** (4.7 lower to 4.4 lower)	⊕⊕⊕⊕ High	IMPORTANT
Nausea (all GLP1RA vs Basal Insulin) (follow-up: range 25 weeks to 52 weeks; assessed with: event rate)												
14	randomized trials	not serious	not serious	not serious	not serious	none	925/4719 (19.6%)	99/3553 (2.8%)	**RR 6.1** (4.9 to 7.4)	**142 more per 1,000** (from 109 more to 178 more)	⊕⊕⊕⊕ High	IMPORTANT
Vomiting (all GLP1RA vs Basal Insulin) (follow-up: range 25 weeks to 52 weeks; assessed with: event rate)												
12	randomized trials	not serious	not serious	not serious	not serious	none	316/4061 (7.8%)	63/3140 (2.0%)	**RR 3.7** (2.8 to 4.8)	**54 more per 1,000** (from 36 more to 76 more)	⊕⊕⊕⊕ High	IMPORTANT

Diarrhea (all GLP1RA vs Basal Insulin) (follow-up: range 25 weeks to 52 weeks; assessed with: event rate)

11	randomized trials	not serious	not serious	not serious	not serious	none	554/4590 (12.1%)	138/3150 (4.4%)	**RR 2.6** (2.1 to 3.1)	**70 more per 1,000** (from 48 more to 92 more)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Q5.6.5 Question: GLP1RA compared to Basal Insulin for CV protection among T2DM patients
Bibliography: Longato, E., Di Camillo, B., Sparacino, G. *et al.* Cardiovascular outcomes after initiating GLP-1 receptor agonist or basal insulin for the routine treatment of type 2 diabetes: a region-wide retrospective study. *Cardiovasc Diabetol* **20**, 222 (2021). https://doi.org/10.1186/s12933-021-01414-3

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP1 RA	Basal Insulin	Relative (95% CI)	Absolute (95% CI)		
All-cause death (follow-up: median 24 months; assessed with: event rate)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	49/786 (6.2%)	117/791 (14.8%)	**RR 0.42** (0.30 to 0.59)	**86 fewer per 1,000** (from 104 fewer to 61 fewer)	⨁ LOW	CRITICAL
Myocardial infarction (follow-up: median 24 months; assessed with: event rate)												
1	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	128/774 (16.5%)	166/774 (21.4%)	**RR 0.77** (0.61 to 0.97)	**49 fewer per 1,000** (from 84 fewer to 6 fewer)	⨁ LOW	CRITICAL
Stroke (follow-up: median 24 months; assessed with: event rate)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP1 RA	Basal Insulin	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	45/782 (5.8%)	103/781 (13.2%)	**RR 0.44** (0.31 to 0.62)	**74 fewer per 1,000** (from 91 fewer to 50 fewer)	⊕ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

NB Certainty of evidence downgraded to low due to retrospective nature, single study only.

Q6.6 Recommendations from other groups

Group (Year)	Recommendation	Strength / Certainty
American Diabetes Association (ADA) Standards of Care (2024)	Initiate basal insulin for A1C > 10%, blood glucose > 300 mg/dL, or who are symptomatic of hyperglycemia. For patients with type 2 diabetes who have atherosclerotic cardiovascular disease or are at high risk for it or who have kidney disease or [cell text truncated in source — see originating guideline for full text].	Grade A
American Diabetes Association–European Association for the Study of Diabetes (ADA-EASD) Consensus Report (2019)	In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. Glucagon-like peptide 1 receptor agonists (GLP-1 RA) [cell text truncated in source — see originating guideline for full text].	Grade A
Diabetes Canada Clinical Practice Guidelines (2020)	A GLP-1RA should be considered as add-on therapy to improve glycemic control with weight loss before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared with single or mu [cell text truncated in source — see originating guideline for full text].	Grade A, level IA (additional ratings include Grade D, consensus; Grade B, level I; Grade A, level IA — preserved as in source)
National Institute for Health and Care Excellence (NICE) (2015)	In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see recommendation 1.6.25) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either: triple thera [cell text truncated in source — see originating guideline for full text].	Grade A
American Association of Clinical Endocrinologists (AACE)	Initiate insulin therapy for HbA1c > 9%.	Grade A

Q6.7 Research Gaps and Recommendations

There are currently no local studies on patients' values and preferences, equity, acceptability, and feasibility of the use of GLP-1 agonists versus the use of basal insulin or fixed-ratio combination therapy. The evidence review did not address whether patients who are already taking insulin and have stable HbA1c levels should switch to another medication. The choice of treatment should largely account for the tolerability and side-effect profiles of medications, complexity of the medication plan and the individual's capacity to implement it given the accessibility, cost, and availability of medication [2].

Guideline Question 6. Should we recommend the use Momordica charantia [Ampalaya] among adults with T2DM?

Q6.1. Methods

A search was done (date of last search: April 15, 2023) through MEDLINE, Cochrane Central, UpToDate Society Guideline Links, and Google Scholar using the combined MeSH and keyword search on Momordica charantia and diabetes. A filter was placed to include only clinical trials, RCTs, reviews, and meta-analyses. Only studies with Momordica charantia in capsule or tablet forms were included, with the following outcomes: glycemic control in terms of glycosylated hemoglobin, fasting blood glucose, and 2-hour postprandial glucose. For adverse reactions, those with results on transaminases, creatinine, and urinary albumin-to-creatinine ratio were noted. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

To assess the risk of bias, the studies on efficacy were evaluated for randomization, allocation concealment, blinding of participants, other personnel and assessors, and completeness of data presented, using the Cochrane Risk of Bias tool v.1.

Q6.2. Search strategy

PubMed search strings used in the source (selected lines from Appendix A; full search history preserved in source):

Search term(s)	Filter(s)	Yield
("diabetes"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR variants) AND ("momordica charantia"[MeSH Terms] OR variants)	Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review	28
("diabetes" + variants) only	Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review	67,599
("diabetes" + variants) only	Clinical Trial, Meta-Analysis, Randomized Controlled Trial	59,833
diabetes	Clinical Trial, Meta-Analysis	59,833
diabetes	Clinical Trial	47,753
diabetes (no filter)	—	926,373
momordica charantia (no filter)	—	1,333

Q6.3A. Characteristics of the Included Studies

Momordica charantia versus placebo (selected included trials, Appendix B):

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
John AJ, 2003	RCT	India	N = 50 (Tx 26 / C 24)	Adults with T2DM (FBS 140–200 mg/dL; PPS 200–300 mg/dL)	Dried fruit of MC, 2 g TID after meals (6 g/day)	Placebo	SMD from baseline to 4 weeks: FBS, PPS, Fructosamine, ADRs
Dans 2007	RCT	Philippines	N = 40 (20 per arm)	Adults, newly diagnosed T2DM or poorly controlled T2DM, A1c 7 to 9%	Fruits and seeds of MC (Charantia brand), 2 tabs TID (3 g/day)	Placebo	SMD from baseline to 12 weeks: A1c, FBS, Tchol, BMI, Crea, AST, ALT, Na, K, ADRs
Lim 2010 (MOCHA-DM)	RCT	Philippines	N = 40 (10 per group)	Adults with T2DM, 21 to 65 yo, newly diagnosed, drug-naive or no oral AHA for 3 mos, A1c 6.5 to 9, FBS 126 to 205 mg/dL	MC tablets from dried ampalaya leaves (Makiling variety, Amargozin), 500 mg/tablet, at 60, 80, or 100 mg/kg/day	Placebo	Change in glucose and insulin from baseline and after 15m, 30m, 1h, 2h, 4h
Trakoon-osot 2013	RCT	Thailand	N = 38	Adults with T2DM, A1c ≥6.5%	Dried fruit pulp of MC, 6 g/day	Placebo	SMD from baseline to 16 weeks: A1c, FPG, UACR
Suthar 2016a (Glycebal)	RCT, open label	India	N = 85 (3:1 T:C, 64 Tx / 21 placebo)	Adults with T2DM on at least 1 oral AHA	Dried fruit juice powder of MC in capsules, 400 mg/cap, 1 cap 30 min pre-	Placebo	Mean change from baseline to 90 days in FBS, A1c

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
					breakfast + 2 caps 30 min pre-supper (1.2 g/day)		
Cortez-Navarrete 2018	RCT	Mexico	N = 24	Adults with newly diagnosed T2DM (<5 years)	Dried powder of fruit pulp from China, 2 g/day, 500 mg/cap, 2 caps pre-breakfast and pre-supper	Placebo	SMD from baseline to 12 weeks: FBS, A1c; others: crea, AST, ALT, lipid profile, insulin

Q6.3B Momordica charantia versus oral antihyperglycemic agents (selected included trials):

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
Fuangchan 2011	RCT	Thailand	N = 129 (MC 0.5 g 31; MC 1 g 30; MC 2 g 29; Met 1 g 30)	Adults with newly diagnosed T2DM, FPG ≥126 mg/dL or 2-h post-OGTT ≥200 mg/dL (ADA 2006)	Dried powder of unripe fruit pulp, 500 mg/cap; 3 groups: 1 cap/day (0.5 g), 2 caps/day (1.0 g), 4 caps/day (2.0 g)	Metformin 1 g/day	Mean changes after 4 weeks in: FPG, 2h PPG (75 g OGTT), Fructosamine
Suthar 2016b (PDM01 1011 vs Met)	RCT, open label	India	N = 123 (2:1 T:C, 83 Tx / 40 C)	Adults with T2DM, drug-naive for 3 months, FPG 110 to 250 mg/dL,	Dry juice powder from unripe green fruits of MC, 400 mg/cap, 1 cap before meals 2× daily	Metformin 1 g/day (500 mg/tab, 1 tab during/after meals 2× daily)	Mean change from baseline to 15 weeks in FPG, A1c

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
				A1c 7 to 10%			
Rahman 2015	RCT	Pakistan	N = 95 (MC 2 g 30; MC 4 g 31; Glibenclamide 29)	Adults with T2DM, FPG 126 to 240 mg/dL	Freeze-dried juice powder from unripe MC, 1000 mg/cap; T1 2 g/day, T2 4 g/day	Placebo; Glibenclamide 5 mg; Powdered roasted rice (vs MC); Lactose (vs Gliben)	Mean differences from baseline to 10 weeks in FPG, A1c, plasma sialic acid, BP, lipids, atherogenic index

Q6.4. Assessment of Risk of Bias

Cochrane Risk of Bias tool v.1 was used. Of the 9 RCTs, 6 studies were found to have serious risks of bias (with common issues in randomization, allocation concealment, and blinding of participants and outcome assessors), while 3 had low risk of bias.

Q6.5. Results

A. Summary of evidence — Momordica charantia versus placebo:

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Change in FBS (mmol/L)	2 RCTs (Dans 2007; Trakoon-osot 2013); N = 39	0.31	−1.99 to 2.61	Inconclusive	Very Low
Mean and SD of FBS from baseline to end of study	3 RCTs (John 2003; Suthar 2016a; Cortez-Navarrete 2018); N = 149	John 2003: no significant change in FBS between MC 6 g/day (n = 26) vs Placebo (n = 24) at 4 weeks. Suthar 2016a: MC 1.2 g/day (n = 62) FBS decreased by 21.89 mg/dL vs +2.12 mg/dL in placebo (n = 17), p = 0.013, at 90 days. Cortez-Navarrete 2018: results for MC 2 g/day (n = 12) vs placebo (n = 12) at 12 weeks.	—	Inconclusive	Very low
Change in A1c (%)	2 RCTs; N = 39	0.28	0.03 to 0.54	Inconclusive	Very low
Mean and SD of A1c from baseline to end of study	2 RCTs (Suthar 2016a; Cortez-Navarrete 2018); N = 99	Suthar 2016a: MC (n = 62) A1c decreased by 0.78 vs 0.2 in placebo (n = 17), p = 0.066, at 90 days. Cortez-Navarrete 2018: at 12 weeks, mean A1c from MC group (n = 10) decreased by 0.7% vs placebo (n = 10) by 0.5%, p < 0.05.	—	Inconclusive	Very low
Mean and SD of postprandial blood sugar from baseline to end of study	2 RCTs (Lim 2010; Suthar 2016a); N = 99	Lim 2010: PPG for MC (100 mg/kg, n = 10) increased by 30.8 mg/dL vs placebo (n = 10) at 43.3 mg/dL, p = 0.821. Suthar 2016a: decrease in PPG for MC 1.2 g/day (n = 62) was 44.95 mg/dL and placebo (n = 17) was 7.06 mg/dL at end of study.	—	Inconclusive	Very low

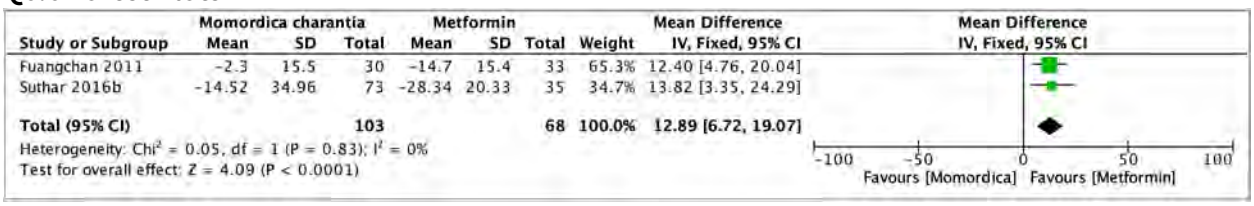
B. Summary of evidence — Momordica charantia versus oral antihyperglycemic agents:

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Change in FBS vs Metformin 1 g/day	2 RCTs (Fuangchan 2011; Suthar 2016b); N = 103	12.89	6.72 to 19.7	Metformin better	Low
Mean change in A1c from baseline to week 15 vs Metformin 1 g	1 RCT (Suthar 2016b); N = 109	0.35	0.07 to 0.63	Inconclusive	Very low
Mean change in FBS from baseline to week 10	1 RCT (Rahman 2015); N = 60	MC group 4 g/day (n = 31): FBS decreased by 15.2 mg/dL. Glibenclamide 5 mg/day (n = 29): FBS decreased by 26.5 mg/dL.	—	Inconclusive	Very low
Mean change in PPS after glucose load from baseline to week 10	1 RCT (Rahman 2015); N = 60	MC group 4 g/day (n = 31): PPS decreased by 6.3 mg/dL. Glibenclamide 5 mg/day (n = 29): PPS decreased by 26.2 mg/dL.	—	Glibenclamide better	Low

C. Adverse events (from source):

Adverse event	M. charantia (events)	M. charantia (n)	Placebo (events)	Placebo (n)	Source
Diarrhea	4	20	1	20	Dans 2007
Diarrhea	5	19	0	19	Trakoon-osot 2013
Flatulence	8	19	2	19	Trakoon-osot 2013
Constipation	1	12	2	12	Cortez 2018
Nausea	2	12	1	12	Cortez 2018
Total (%)	20 (24.4%)	82	6 (7.3%)	82	—

Q6.6 Forest Plots



Q6.7. Recommendations from other groups

There are no guidelines that have included Momordica charantia as treatment for type 2 diabetes.

Q6.8. Research Gaps and Recommendations

As of April 2023, no ongoing studies were seen in clinicaltrials.gov.

- Given the currently available published studies, there is still a need for well-designed trials that would determine the part of the plant and optimal dose of M. charantia that would provide the optimal glycemic control.
- It would also be prudent to find out the percentage of charantin from the extracts that would be able to produce the desired effects.
- Once these are determined, larger randomized controlled trials should be performed.
- There is also a lack of long-term safety data.
- Quality of life was not in any of the outcomes.

Guideline Question 7. Should we recommend the use Chromium picolinate among adults with T2DM?

Q7.1. Methods

A search was conducted through PubMed and supplemented by handsearching, with date of last search 04 May 2023. PubMed was queried using combined MeSH and keyword search on chromium picolinate and diabetes; filters were applied for Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review, and age groups (Adolescent 13–18 years; Adult 19+ years; Young Adult 19–24 years). The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. Risk of bias of included studies was appraised.

Q7.2. Search strategy

PICO framework

Element	Definition
Population	Adults with type 2 diabetes — newly diagnosed drug-naive (1 study), T2DM on OAD (5 studies), T2DM on insulin (1 study)
Intervention	Chromium picolinate; lowest dose 3.82 to 19.8 µg (1 study), 200 µg to 1000 µg (6 studies); duration 4 to 24 weeks
Comparator	Placebo (6 studies) or Glipizide 5 mg (1 study)
Outcomes	Improvement in FBS, PPS, A1c; adverse events (1 study)

PubMed search history (verbatim from source PubMedSearchHistory CSV, 04 May 2023):

#	Query	Filters	Yield
1	diabetes	(none)	927,189
2	chromium	(none)	45,309
3	chromium picolinate	(none)	1,291
4	#1 AND #2	(none)	1,040
5	#3 AND #4	(none)	157
6	#1 AND #3	(none)	183
7	#1 AND #3	Adult: 19+ years	42
8	#1 AND #3	Adolescent: 13–18 years	5
9	#1 AND #3	Adolescent 13–18; Adult 19+	43

#	Query	Filters	Yield
10	#1 AND #3	Adolescent 13–18; Adult 19+; Young Adult 19–24	43
11	#1 AND #3	RCT + age filters	24
12	#1 AND #3	Meta-Analysis, RCT + age filters	25
13	#1 AND #3	Meta-Analysis, RCT, Systematic Review + age filters	25
14	#1 AND #3	Clinical Trial, Meta-Analysis, RCT, Systematic Review + age filters	27 (final yield)

Q7.3 Characteristics of the Included Studies

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
Anderson 1997 (Diabetes 47, Nov 1997, 1786–1791)	RCT, double blind	China	N = 155 (50 placebo / 53 for 3.85 / 52 for 19.2)	T2DM, 35 to 65 yo, on OHA, FBS 7.2 to 15.5 mmol/L, A1c 8 to 12%	1) 1.92 µmol CrPic BID (3.85); 2) 9.6 µmol CrPic BID (19.2)	Placebo	Baseline and after 4 months (16 weeks): FBS, 75 g OGTT, A1c
Ghosh 2002 (J Nutr Biochem 2002;13:690–697)	Double blind, placebo controlled, cross-over	India	N = 50 (cross-over)	T2DM on Oral AHA or diet controlled; adults	400 µg CrPic/day (200 µg BID)	Placebo	Baseline then monthly up to 12 weeks; 4-week wash-off then cross-over for 12 weeks: FBS, A1c, Insulin, Lipids, Chromium
Kleefstra 2006 (Diabetes Care 2006;29(3):521–525)	RCT, double blind, placebo controlled	Netherlands	N = 36 (Placebo 17; 500 µg 14; 1000 µg 15)	Adults <75 yo, T2DM, insulin requiring >50 U/day, A1c >8%	1) 500 µg CrPic; 2) 1000 µg CrPic	Placebo	Baseline and at 3 and 6 months (24 weeks): A1c, BP, Lipids, Chromium
Martin 2006 (Diabetes Care	RCT	USA	N = 29 (Placebo 12;	Adult T2DM on Glipizide 5 mg, FBS	1000 µg CrPic (500 µg bid) + Glipizide	Placebo + Glipizide	Baseline and 24 weeks: FBS, A1c, Insulin, Lipids, Weight

Author / Year	Study Design	Country	No. of pts	Population	Intervention	Control	Outcomes
2006;29:1826–1832)			CrPic 17)	125 to 170 mg/dL			
Iqbal 2009 (Metab Syndr Relat Disord 2009;7(2):143–150)	RCT	USA	N = 63 (Placebo 30; CrPic 33)	Adults with T2DM on OADs, 18 to 75 yo, FBS 6.1 to 7	1000 µg CrPic (500 µg bid)	Placebo	Baseline and 16 weeks: FBS, A1c, Lipids, BMI, BP
Paiva 2015 (J Trace Elem Med Biol 2015;32:66–72)	RCT, single blind	Brazil	N = 71 (C 39; CrPic 32)	Adults with T2DM on OADs, A1c >7%	600 µg CrPic	Placebo	Baseline and 16 weeks: FBS, PPS, A1c
Ahmad 2016 (J Food Nutr Res 2016;4(8):535–542)	RCT	Pakistan	N = 37/52 (Control 13/26; CrPic 22/26)	T2DM newly diagnosed, 40 to 65 yo	200 µg Chromium picolinate	Placebo	Baseline and 30 days (4 weeks): FBS, A1c, AEs

Q7.4. Assessment of Risk of Bias

Six of the 7 RCTs had serious to very serious risks of bias, and 1 RCT had low risk of bias.

Q7.5. Results

A. Summary of evidence — Chromium picolinate vs. placebo:

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
Mean Difference in FBS (mg/dL)	2 RCTs; N = 96	−19.5	−25.41 to −13.58	Chromium better than placebo (CrPic with Glipizide over Glipizide alone)	Very Low
Change in Mean FBS	4 RCTs; N = 252	Anderson 1997: FBS decreased by 50.4 mg/dL for CrPic; 21.6 mg/dL for placebo. Ghosh 2002: FBS decreased by 9 mg/dL for CrPic; increased by 7.3 mg/dL for placebo. Ahmad 2016: FBS decreased by 12.43 mg/dL for	—	Inconclusive	Very Low

Outcome	Basis	Effect Estimate	95% CI	Interpretation	Certainty
		CrPic; decreased by 6.32 mg/dL for placebo. Iqbal 2009: FBS increased by 4.68 mg/dL for CrPic; decreased by 0.72 mg/dL for placebo. Of all 4 RCTs, only Anderson showed a significant change in FBS after 16 weeks of treatment with 19.2 µmol CrPic.			
Change in A1c	3 RCTs; N = 159	−0.5	−0.74 to −0.25	Inconclusive	Very Low
Change in Mean A1c	4 RCTs; N = 252	Anderson 1997: A1c decreased by 2.1% for CrPic; 0.4% decreased for placebo. Ghosh 2002: A1c with no change for CrPic; increased by 0.7% for placebo. Ahmad 2016: A1c decreased by 1.48% for CrPic; decreased by 1.64% for placebo. Iqbal 2009: A1c increased by 0.08% for CrPic; increased by 0.05% for placebo. Of all 4 RCTs, only Anderson showed a significant change in A1c after 16 weeks of treatment with 19.2 µmol CrPic.	—	Inconclusive	Very Low
Change in Mean PPS	2 RCTs; N = 152	Anderson 1997: PPS decreased by 75.6 mg/dL for CrPic; 21.6 mg/dL for placebo. Ghosh 2002: PPS decreased by 36 mg/dL for CrPic; no change for placebo. Of 2 RCTs, only Anderson showed a significant change in FBS [source wording] after 16 weeks of treatment with 19.2 µmol CrPic.	—	Inconclusive	Very Low

B. Safety — Chromium picolinate vs. placebo

Outcome assessed	Chromium picolinate	Placebo	Source
Change in ALT	none	none	Ahmad 2016
General toxicity	None	none	Anderson 1997
Hemoglobin level, total and differential leukocyte counts, platelet count, serum urea, creatinine, ALT, alkaline phosphatase activity	None	none	Ghosh 2002

No significant changes in AST, ALT, and Creatinine were noted in 3 RCTs comparing CrPic with placebo.

Q7.6 GRADE Evidence Profile

Question: Chromium compared to placebo for Type 2 diabetes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chromium**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
fasting blood glucose (follow-up: range 4 weeks to 25 weeks; assessed with: FBS; scale from 80 to 200)												
22	randomised trials	serious [a]	serious [b]	not serious	serious	strong association — all plausible residual confounding would reduce the demonstrated effect	743	747	—	**MD 19 lower** (36.15 lower to 1.85 lower)	⨁⨁⨁◯ **Moderate**	**IMPORTANT**
glycemic control (follow-up: range 4 weeks to 25 weeks; assessed with: HbA1c)												
22	randomised trials	serious	serious	not serious	serious	strong association — all plausible residual confounding would reduce the demonstrated effect	743	747	—	**MD 0.71 lower** (1.19 lower to 0.23 lower)	⨁⨁⨁◯ **Moderate**	**IMPORTANT**

CI: confidence interval; **MD:** mean difference

Explanations

a. more than half of the included RCTs had either no allocation concealment or it was uncertain. Outcome assessment were mostly non-blinded.

b. formulations were varied, as well as dosages.

Q7.7. Recommendations from other groups

In its 2010 diabetes guidelines, the American Diabetes Association concluded that because studies have not definitively shown that chromium supplementation benefits people with diabetes or obesity, the association cannot recommend such supplementation. This determination was based on conflicting evidence from poorly controlled or uncontrolled studies.

Similarly, the American Diabetes Association concluded in its 2015 position statement that evidence is insufficient to support the routine use of supplements containing chromium and other micronutrients for glycemic control in people with diabetes. Additional research is needed to determine whether specific populations (e.g., ethnic background, obesity status, baseline insulin sensitivity, and medication use) might be more likely than others to benefit from chromium supplementation.

Per the source speaker notes, the UK Food Standards Agency announced on 24 January 2005, based on the balance of scientific evidence, that there is "no need to avoid chromium picolinate." The update stemmed from conclusions reported by the Committee on Mutagenicity, which conducted a year-long comprehensive scientific review of chromium picolinate's safety.

<INSERT HERE — verbatim full-text recommendations from each guideline group's originating document>

Q7.8. Research Gaps and Recommendations

- Dosage uncertainty: only one study (Martin 2006) addressed this directly, where 1000 µg CrPic was compared with glipizide 5 mg.
- Among individuals with type 2 diabetes, is there a subset that would have chromium deficiency with whom this supplement might work?
- Insulin resistant only — or insulin deficient?
- Toxicologic studies are needed.
- No ongoing RCT in clinicaltrials.gov as of 04 May 2023.

Guideline Question 8. Should we recommend the use Andrographis paniculata (Serpentina) among adults with T2DM?

Q8.1. Methods

A search was conducted through PubMed/MEDLINE and supplemented by handsearching. PubMed was queried using combined MeSH and keyword search on Andrographis paniculata and diabetes; filters were applied for Clinical Trial, Systematic Review, Review, and Randomized Controlled Trial. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The risk of bias of included studies was appraised.

Q8.2. Search strategy

#2 and #3	Randomized Controlled Trial, Review	(("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields])) AND (randomizedcontrolledtrial[Filter] OR review[Filter])	10
#2 and #3	Review	(("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields])) AND (review[Filter])	9
#2 and #3		("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields])	75
#2 and #3	Systematic Review	(("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields])) AND (systematicreview[Filter])	0

#2 and #3	Clinical Trial	(("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields])) AND (clinicaltrial[Filter])	1
andrographis paniculata		"andrographis paniculata"[MeSH Terms] OR ("andrographis"[All Fields] AND "paniculata"[All Fields]) OR "andrographis paniculata"[All Fields]	1,132
diabetes		"diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]	927,959

Q8.3. Research Gaps and Recommendations

No ongoing studies related to diabetes in clinicaltrials.gov as of the date of the source review.

Guideline Question 9. Should we recommend the routine use of vitamin B12 (methylcobalamin or cyanocobalamin) supplementation among adults with T2DM on metformin?

Q9.1. Methods

A search was conducted (date of last search: May 15, 2023) through MEDLINE, Cochrane Central, UpToDate Society Guideline Links, and Google Scholar using the combined MeSH and keyword search on Vitamin B12 / Vitamin B12 supplementation / cobalamin / mecobalamin and diabetes. Filters were applied for meta-analysis, clinical trial, randomized clinical trial, systematic review, and age groups adults 19+ and adolescents 13 to 18 years. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. Risk of bias of included studies was appraised.

Q9.2. Search strategy

A. PubMed search history

#	Query	Yield
1	vitamin b12 supplementation	401
2	mecobalamin	61
3	mecobalamin supplementation	9
4	diabetes	32,765
5	#1 or #2 or #3 and #4	47
6	cobalamin	737
7	#1 or #2 or #3 or #6 AND #4	97
8	#1 or #2 or #3 or #6 AND #4 (with filters)	97 (final yield)

B. Search Yield Screened

Search number	Query	Search Details	Results
8	#1 or #2 or #3 or #6 AND #4	((((("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("cobalamine"[All Fields] OR "cobalamines"[All Fields] OR "vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR "cobalamin"[All Fields] OR "cobalamins"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND (("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	97
7	#1 or #2 or #3 or #6 AND #4	((((("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("cobalamine"[All Fields] OR "cobalamines"[All Fields] OR "vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR "cobalamin"[All Fields] OR "cobalamins"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND (("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	97
6	cobalamin	("cobalamine"[All Fields] OR "cobalamines"[All Fields] OR "vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR "cobalamin"[All Fields] OR "cobalamins"[All Fields]) AND ((meta-	737

		analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	
5	#1 or #2 or #3 and #4	((((("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms]))) OR (("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND (("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND (("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND ("adolescent"[MeSH Terms] OR "adult"[MeSH Terms])))) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	47
4	diabetes	("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	32,765
3	mecobalamin supplementation	(("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields])) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	9
2	mecobalamin	("mecobalamin"[Supplementary Concept] OR "mecobalamin"[All Fields] OR "mecobalamine"[All Fields]) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	61
1	vitamin b12 supplementation	(("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields])) AND ((meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (adolescent[Filter] OR alladult[Filter]))	401

Q9.3. Recommendations from other groups

Group	Recommendation	Strength of Recommendation / Certainty
American Diabetes Association (ADA): Standards of Care in Diabetes (2023), p. S44	Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Source also notes higher risk for vitamin B12 deficiency (<150 pmol/L) at 4.3 years of metformin use, from the HOME (Hyperinsulinaemia: the Outcome of its Metabolic Effects) study.	Screening - B
Toronto Consensus Panel on Diabetic Neuropathy (2011) - Painful diabetic peripheral neuropathy: Consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev. 2011;27:629-638.	No mention of B12, mecobalamin, or methylcobalamin.	(not applicable)
Toronto Consensus Panel on Diabetic Neuropathy (2011) - Cardiovascular autonomic neuropathy in diabetes: Clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011;27:639-653.	No mention of B12, mecobalamin, or methylcobalamin.	(not applicable)
Guidelines on diabetic neuropathy from Canada	Did not mention supplementation with Vitamin B12 nor with methylcobalamin.	(not applicable)

Q9.4. Research Gaps and Recommendations

There are no ongoing trials on Vitamin B12, methylcobalamin, cyanocobalamin, or cobalamin for persons with diabetes as of June 1, 2023. The source proposes the following research questions:

- How does one define vitamin B12 deficiency? What is the normal vitamin B12 level among persons with and without diabetes?
- Will there be any benefit in treating Vitamin B12 deficiency due to Metformin administration?
- Knowing that calcium supplementation may offset malabsorption of Vitamin B12 while on metformin, should calcium tablets be routinely given among persons with diabetes on Metformin to prevent B12 deficiency?
- What is the active form of vitamin B12 that can be detected in the laboratory assays?
- If supplementation is necessary, which Vitamin B12 form shall be given?

Guideline Question 10. Should we recommend the use of Costus igneus (Insulin Plant) among adults with T2DM?

Q10.1. Methods

A search was conducted through PubMed/MEDLINE and supplemented by handsearching. PubMed/MEDLINE was queried using the combined MeSH and keyword search on the terms diabetes, "insulin plant," Costus igneus, and Costus pictus. The plant terms were combined with the diabetes term, and filters were applied for Clinical Trial, Randomized Controlled Trial, Review, and the adolescent (13 to 18 years) age group. A separate toxicity search was performed for safety background, in which the toxicity term was combined with the plant terms (insulin plant / Costus igneus / Costus pictus). The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

Q10.2. Search strategy

#	Query / topic	Filters	Yield
1	diabetes	(none)	927,395
2	"insulin plant"	(none)	16
3	costus igneus	(none)	14
4	#1 AND #2 OR #3	(none)	22
5	costus pictus	(none)	17
6	#1 AND #2 OR #3 OR #5	(none)	33
7	#1 AND #2 OR #3 OR #5	Clinical Trial	0
8	#1 AND #2 OR #3 OR #5	Randomized Controlled Trial	0
9	#1 AND #2 OR #3 OR #5	Review	3
10	#1 AND #2 OR #3 OR #5	Adolescent: 13 to 18 years	0
11	toxicity	(none)	1,051,354
12	#2 OR #3 OR #5 AND #11	(none)	7 (final yield for toxicity arm)

Q10.3. Recommendations from other groups

There are no recommendations from other guidelines for Costus igneus (Insulin Plant).

Q10.4. Research Gaps and Recommendations

- Only 2 preclinical studies mentioning insulin-like protein were identified; the protein is still being characterized for its mode of action.
- Extraction is not standardized.
- Toxicologic studies are still needed.

- No first-in-human (FIH) study has been published.

From the earlier EAMC/UPPGH Sep 2022 draft: this plant currently is still in the drug discovery stage; active pharmaceutical ingredients should be identified prior to its preclinical research; no human studies to date.

Guideline Question 11. Should we recommend a fasting plasma glucose (FPG) target of 80 to 130 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

Q11.1. Methods

This review was conducted following PRISMA guidelines. The reviewers searched MEDLINE from inception to September 13, 2023 for eligible studies using the search terms "diabetes mellitus type 2," "microvascular complications," "macrovascular complications," "mortality," "glycosylated hemoglobin," and "fasting plasma glucose." To identify studies that may not have been published in full or were missed through the electronic search, the reviewers manually searched all references from relevant previous studies. Only published articles written in English were obtained. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials and meta-analyses.

Q11.2. Search strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	((("intensive control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("microvascular complications"[All Fields] OR ("neuropathies"[All Fields] OR "neuropathy"[All Fields]) OR ("kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields] OR "nephropathies"[All Fields] OR "nephropathy"[All Fields]) OR ("retinal diseases"[MeSH Terms] OR ("retinal"[All Fields] AND "diseases"[All Fields]) OR "retinal diseases"[All Fields] OR "retinopathies"[All Fields] OR "retinopathy"[All Fields]) OR "kidney disease"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) OR (("intensive	March 3, 2023 8PM	32	11

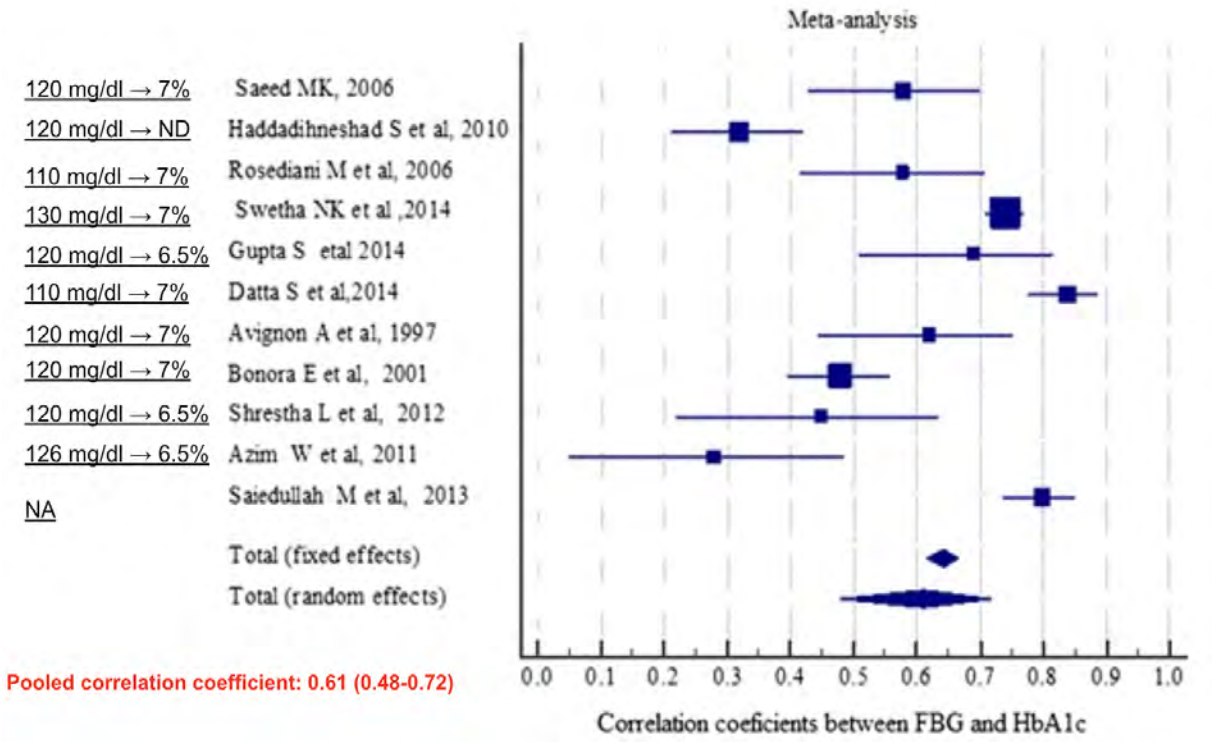
	control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("macrovascular complications"[All Fields] OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) OR "myocardial infarction"[All Fields] OR "peripheral arterial disease"[All Fields] OR "major adverse cardiovascular events"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) OR (("intensive control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR "all cause mortality"[All Fields] OR "cardiovascular mortality"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])			

Q11.3. GRADE Evidence Profile and Forest Plots

Per source GRADE table for FPG reduction on cardiovascular outcomes (more intensive FPG reduction vs less intensive FPG reduction, from Monami et al. 2013):

Outcome	No. of studies	Study design	RoB / Inconsistency / Indirectness / Imprecision / Other	Effect (OR; 95% CI)	Certainty	Importance
Major cardiovascular events	13	randomised trials	not serious / not serious / not serious / none	OR 0.950 (0.818 to 1.105); 1 fewer per 1,000 (from 1 fewer to 1 fewer)	Moderate (⊕⊕⊕○)	CRITICAL
All-cause mortality	8	randomised trials	not serious / not serious / not serious / none	OR 0.904 (0.825 to 0.991); 1 fewer per 1,000 (from 1 fewer to 1 fewer)	Moderate (⊕⊕⊕○)	CRITICAL
Cardiovascular mortality	8	randomised trials	not serious / not serious / not serious / none	OR 0.857 (0.760 to 0.967); 1 fewer per 1,000 (from 1 fewer to 1 fewer)	Moderate (⊕⊕⊕○)	CRITICAL

Forest Plot



Q11.4. Recommendations from other groups

There is no specific FPG-target recommendation from other guidelines or societies. The American Diabetes Association recommends pre-prandial capillary plasma glucose of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) to approximate the target HbA1c level (ungraded recommendation).

Q11.5. Research Gaps and Recommendations

- What is the proportion of Filipinos with diabetes mellitus type 2 who have no access to HbA1c as a standard parameter for glucose monitoring?
- What level of FPG is associated with good glycemic control (target HbA1c) among the Filipino population?
- What are the FPG and PPG targets that lead to actual reduction in diabetic complications?

Guideline Question 12.
Should we recommend an HbA1c target of <7% for glycemic control among nonpregnant adults with T2DM?

Q12.1. Methods

This review was conducted following PRISMA guidelines. The reviewers searched MEDLINE from inception to September 13, 2023 for eligible studies using the search terms "diabetes mellitus type 2," "microvascular complications," "macrovascular complications," "mortality," "intensive control," and "conventional control." To identify RCTs that may not have been published in full or were missed through the electronic search, the reviewers manually searched all references from relevant previous studies. Only published articles written in English were obtained. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials.

Q12.2 Search Strategy and Yield

Database	Search strategy / Search terms	Date and time of search	Results	
			Yield	Eligible
MEDLINE	((("intensive control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("microvascular complications"[All Fields] OR ("neuropathies"[All Fields] OR "neuropathy"[All Fields]) OR ("kidney diseases"[MeSH Terms] OR ("kidney"[All Fields] AND "diseases"[All Fields]) OR "kidney diseases"[All Fields] OR "nephropathies"[All Fields] OR "nephropathy"[All Fields]) OR ("retinal diseases"[MeSH Terms] OR ("retinal"[All Fields] AND "diseases"[All Fields]) OR "retinal diseases"[All Fields] OR "retinopathies"[All Fields] OR "retinopathy"[All Fields]) OR "kidney disease"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) OR ((("intensive control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("macrovascular complications"[All Fields] OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) OR "myocardial infarction"[All Fields] OR "peripheral arterial disease"[All Fields] OR "major adverse cardiovascular events"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic	March 3, 2023 8PM	32	11

Database	Search strategy / Search terms	Date and time of search	Results	
			Yield	Eligible
	review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) OR (("intensive control"[All Fields] OR "stringent control"[All Fields] OR "conventional control"[All Fields] OR "less intensive control"[All Fields] OR "standard therapy"[All Fields] OR "intensive therapy"[All Fields] OR "conventional therapy"[All Fields] OR "less intensive therapy"[All Fields]) AND (("diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "T2DM"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR "all cause mortality"[All Fields] OR "cardiovascular mortality"[All Fields]) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])			

Q12.3. GRADE Evidence Profile and Forest Plots

A. Summary of evidence on the effects of intensive versus standard glycemic control on composite and individual microvascular complications in the different randomized controlled trials (RCTs) involving patients with T2DM.

No of studies	Design	Quality Assessment					No of people		Effect	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional			
Composite microvascular outcomes											
3	RCTs	Not serious	Not serious	Not serious	Not serious	–	1331/ 13770	1312/ 11830	0.88 (0.81-0.95)	HIGH	Critical
New or worsening nephropathy											
9	RCTs	Not serious	Not serious	Not serious	Not serious	–	3414/ 14755	3522/ 13174	0.76 (0.70-0.9)	HIGH	Critical
Retinopathy											
9	RCTs	Not serious	Not serious	Not serious	Not serious	–	1033/ 11027	886/ 8324	0.79 (0.70-0.9)	HIGH	Critical
Neuropathy											
7	RCTs	Not serious	Not serious	Not serious	Not serious	–	4284/ 11738	4101/ 10251	0.97 (0.92-1.03)	HIGH	Critical

B. Summary of evidence on the effects of intensive versus standard glycemic control on cardiovascular and all-cause mortality in RCTs involving patients with T2DM.

No of studies	Design	Quality Assessment					No of people		Effect (OR)	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional			
Cardiovascular mortality											
7	RCTs	Not serious	Not serious (considerable heterogeneity)	Not serious	Not serious	–	956/ 18597	699/ 16383	1.16 (0.95-1.42)	MODERATE	Critical
All-cause mortality											
11	RCTs	Not serious	Not serious (moderate heterogeneity)	Not serious	Not serious	–	1760/ 18654	1376/ 16415	1.03 (0.93-1.13)	HIGH	Critical

No of studies	Design	Quality Assessment					No of people		Effect (OR)	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional			
Severe hypoglycemia											
9	RCTs	Not serious	Not serious (considerable heterogeneity)	Not serious	Not serious	–	1095/ 14887	380/ 12957	2.93 (1.71-3.34)	MODERATE	Critical

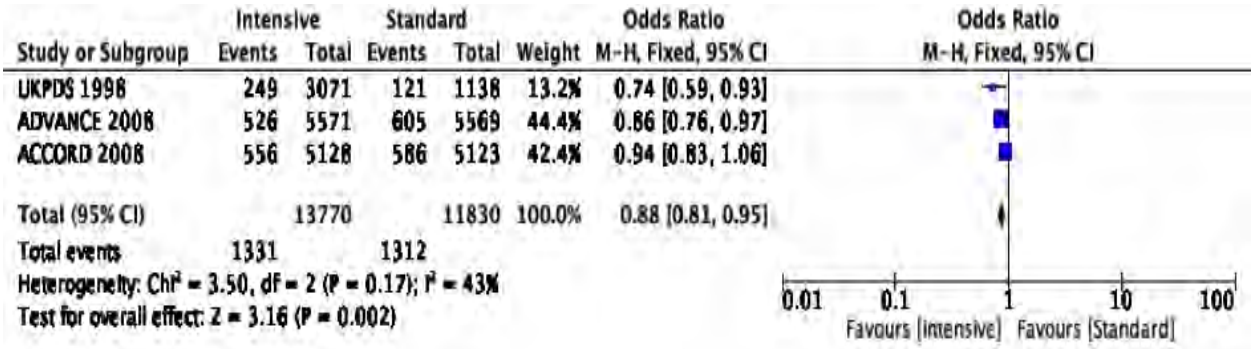


Figure 12-A. Meta-analysis: Effect of intensive versus standard glycemic control on composite microvascular outcomes in RCTs among patients with T2DM.

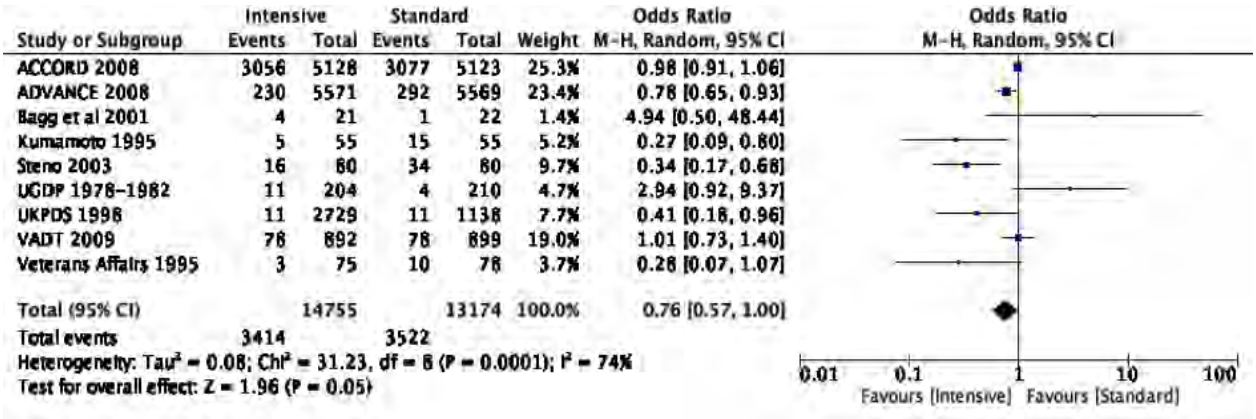


Figure 12-B. Meta-analysis: Effect of intensive versus standard glycemic control on new or worsening nephropathy in RCTs among patients with T2DM.

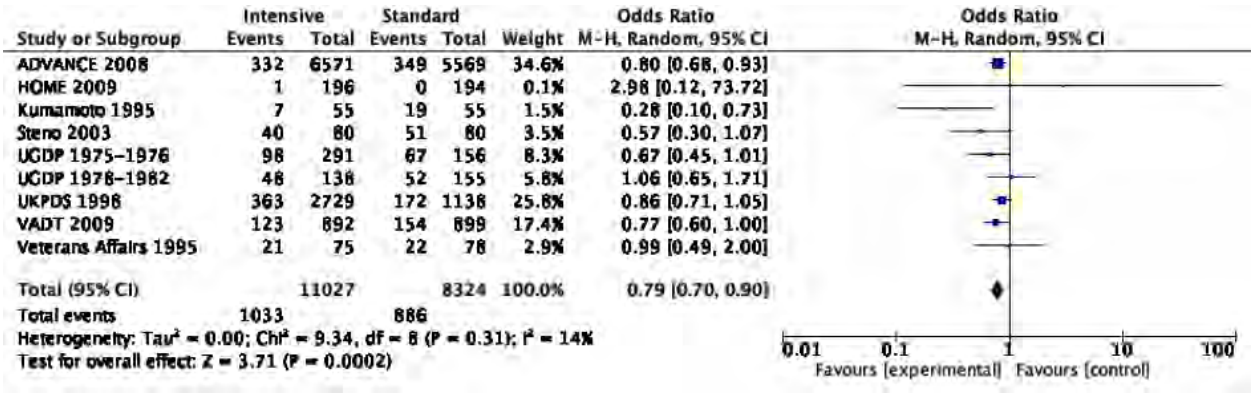


Figure 12-C. Meta-analysis: Effect of intensive versus standard glycemic control on retinopathy in RCTs among patients with T2DM.

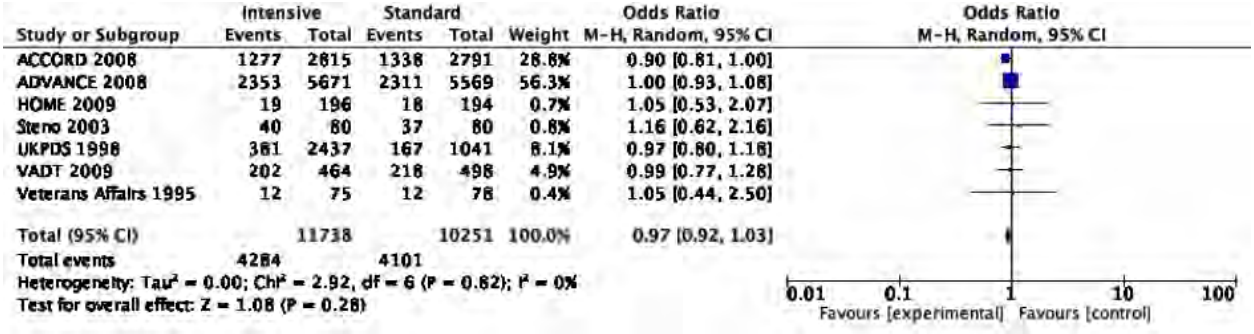


Figure 12-D. Meta-analysis: Effect of intensive versus standard glycemic control on neuropathy in RCTs among patients with T2DM.

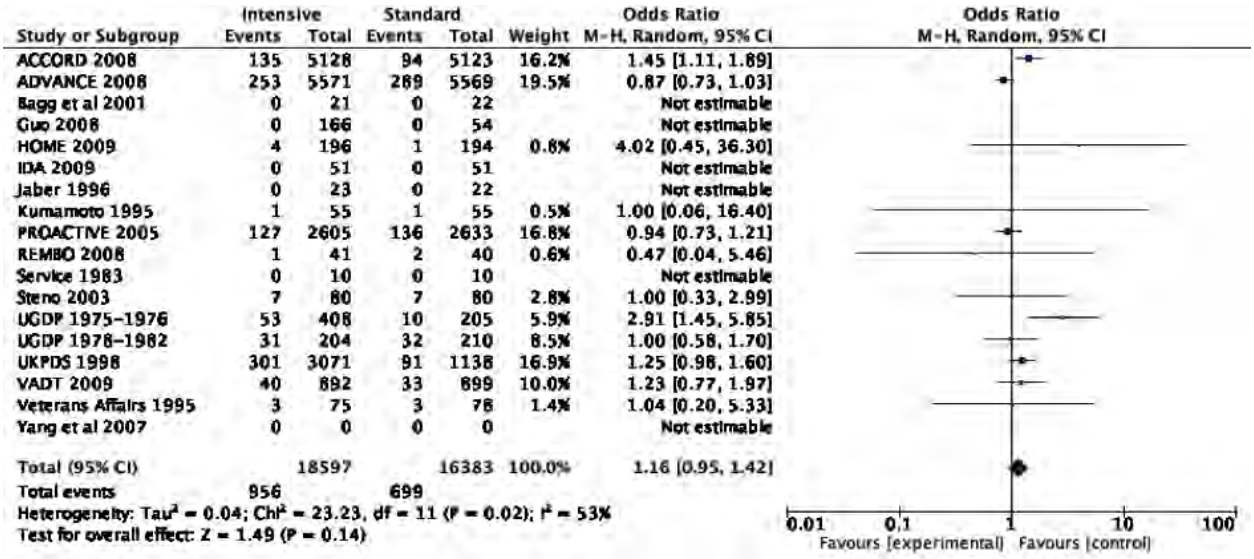


Figure 12-E. Meta-analysis: Effect of intensive versus standard glycemic control on cardiovascular mortality in RCTs among patients with DMT2.

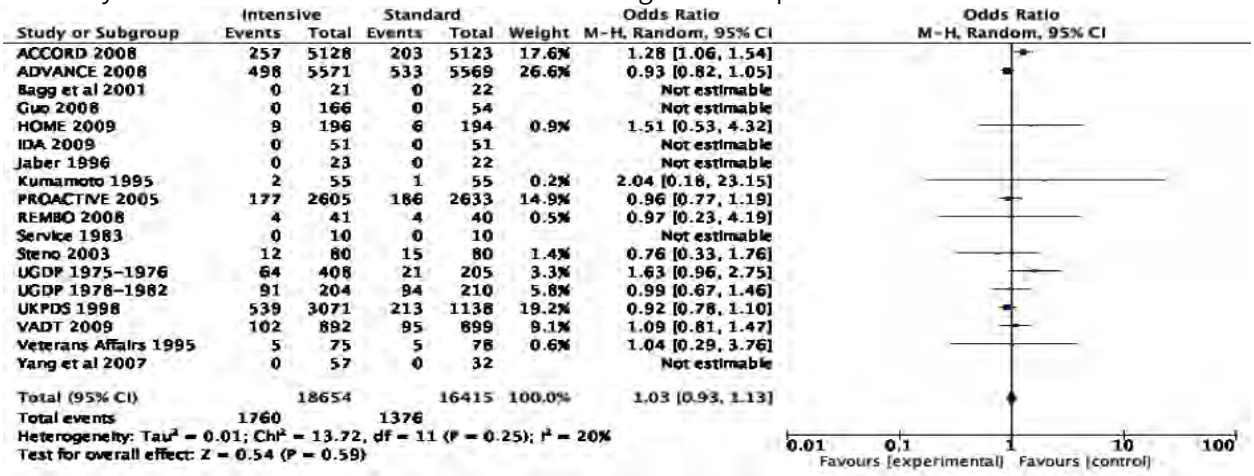


Figure 12-F. Meta-analysis: Effect of intensive versus standard glycemic control on all-cause mortality in RCTs among patients with DMT2.

C. Summary of evidence: Effects of intensive versus standard glycemic control on composite macrovascular and individual macrovascular complications in RCTs involving patients with DMT2.

No of studies	Design	Quality Assessment					No of people		Effect (OR)	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional			
Composite macrovascular outcomes											
7	RCTs	Not serious	Not serious (moderate heterogeneity)	Not serious	Not serious	–	1337/ 14471	1325/ 12884	0.92 (0.82-1.03)	HIGH	Critical
Nonfatal MI											
11	RCTs	Not serious	Not serious (low heterogeneity)	Not serious	Not serious	–	814/ 18110	787/ 16012	0.83 (0.75-0.92)	HIGH	Critical
Nonfatal stroke											
8	RCTs	Not serious	Not serious (considerable heterogeneity)	Not serious	Not serious	–	520/ 17564	486/ 15658	0.87 (0.68-1.11)	MODERATE	Critical
Peripheral arterial disease											
8	RCTs	Not serious	Not serious (low heterogeneity)	Not serious	Not serious	–	587/ 12978	555/ 10884	0.97 (0.83-1.15)	HIGH	Critical

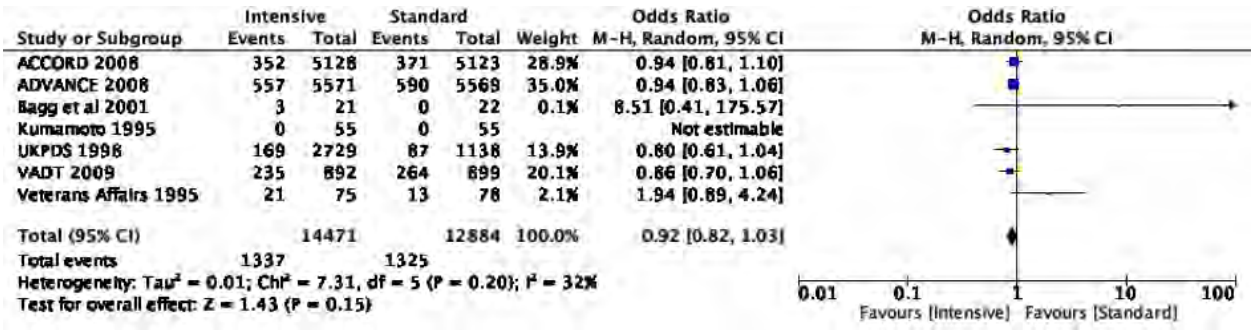


Figure 12.1-A. Meta-analysis: Effect of intensive versus standard glycemic control on composite macrovascular complications in RCTs among patients with DMT2.

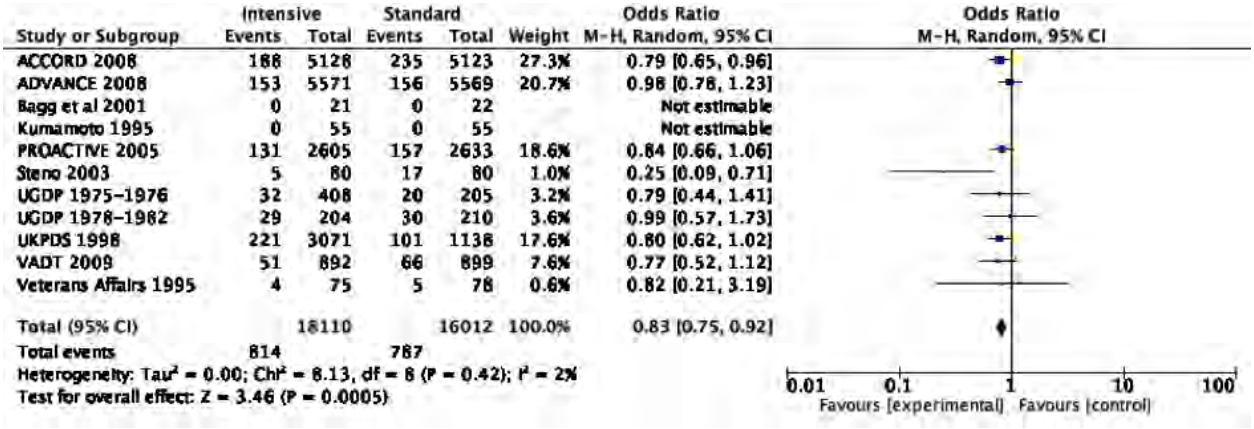


Figure 12.1-B. Meta-analysis: Effect of intensive versus standard glycemic control on nonfatal myocardial infarction in RCTs among patients with DMT2.

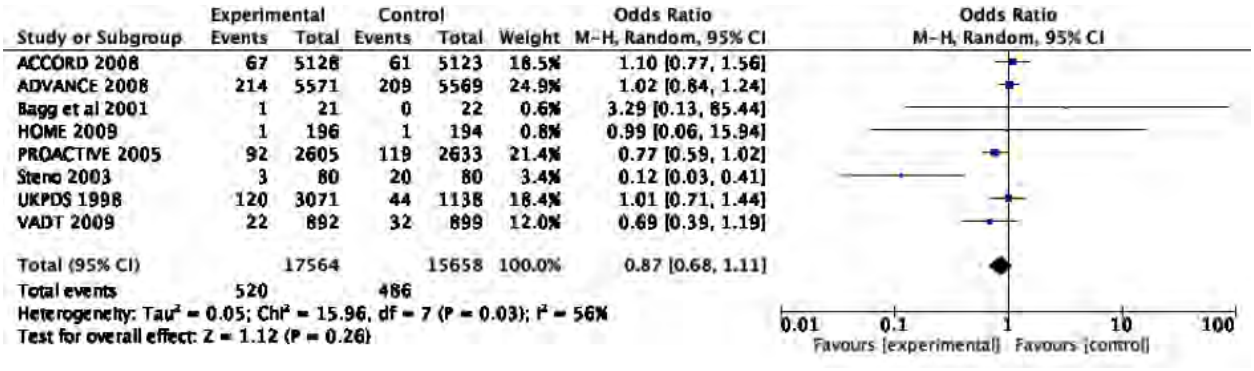


Figure 12.1-C. Meta-analysis: Effect of intensive versus standard glycemic control on nonfatal stroke in RCTs among patients with DMT2.

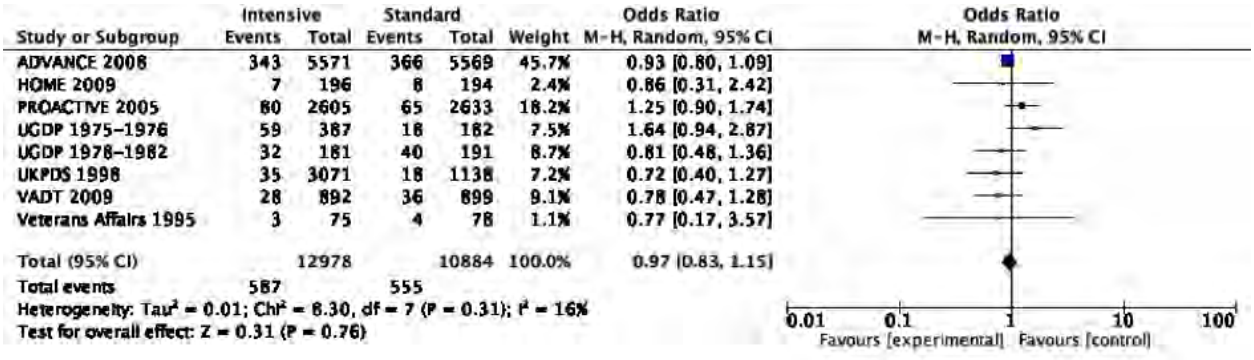


Figure 12.1-D. Meta-analysis: Effect of intensive versus standard glycemic control on peripheral arterial disease in RCTs among patients with DMT2.

D. Summary of evidence: Pooled odds ratio of severe hypoglycemia in RCTs involving intensive versus standard glycemic control on patients with DMT2.

No of studies	Design	Quality Assessment					No of people		Effect (OR)	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision		Intensive	Conventional			
Severe hypoglycemia											
11	RCT	Not serious	Not serious (considerable heterogeneity)	Not serious	Not serious		1121/ 16988	414/ 15671	1.74 (1.06-2.85)	MODERATE	Critical

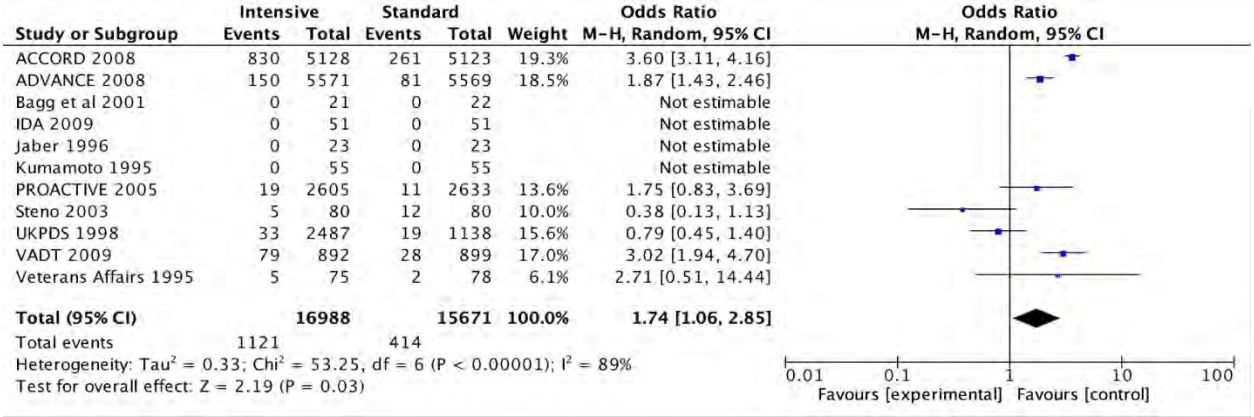


Figure 12.2-A. Meta-analysis: Pooled odds ratio of severe hypoglycemia in RCTs involving intensive versus standard glycemic control on patients with DMT2.

Q12.4. Recommendations from other groups

Recommended HbA1c targets from different guidelines:

Group	General target	Less stringent target	More stringent target
ADA	<7% (without significant hypoglycemia)	<8% (with specific risk factors)	—
AACE	<6.5% (if can be safely achieved)	7 to 8% (with specific risk factors)	—
NICE	7% (on drugs associated with hypoglycemia)	—	6.5% (newly diagnosed on single drug)
ACP	7 to 8%	—	—
SIGN	7%	—	6.5% (at diagnosis)
Malaysia	6.6 to 7%	7.1 to 8.0%	6.0 to 6.5%
Japan	<7% (normoglycemia)	<8% (difficult intensification)	<6% (prevent most complications)

All guidelines, directly or indirectly, recommend individualization or personalization of HbA1c targets on the basis of discussion of benefits and harms, patient preferences, and determinants of health.

Q12.5 Recommendations From Other Groups

The American Diabetes Association [14] recommends a general A1C target of <7% without significant hypoglycemia, while the American Association of Clinical Endocrinologists [15] recommend a general A1C target <6.5%. Both agencies emphasized the importance of individualizing glycemic goal based on

various patient characteristics. Hypoglycemia is the most important consideration in deciding whether to adopt stricter or more relaxed A1C targets, alongside considerations such as life expectancy, comorbidities, and complications [16].

Among Asian agencies, the 2019 Japanese Clinical Practice Guidelines stratified A1c target based on individual patient characteristics and predisposition to develop hypoglycemia [17]. On the other hand, the 2019 Chinese Standards of Medical Care for Type 2 recommended a general A1c target <7% [18] with flexibility for more or less stringent targets. The Malaysian Clinical Practice Guidelines stratified A1C goals as tight (6.0 to 6.5%), general (6.6-7.0%) and less tight (7.1 to 8.0%).

Group or Agency	Recommendation	Strength of Recommendation / Certainty/Quality of Evidence
American Diabetes Association (ADA 2023) [14]	An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate.	Grade A
	On the basis of health care professional judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment.	Grade B
	Less stringent A1C goals (such as <8% [64 mmol/mol]), may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Health care professionals should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets.	Grade B
American Association of Clinical Endocrinology 2023 [15]	Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of complications, CVD risk factors, comorbid conditions and risk for hypoglycemia.	Grade A, Level 1
	In general the goal of therapy should be an A1C <6.5% for most non pregnant adults, if it can be achieved safety.	Grade D, Level 4
	A less stringent goal should be considered (A1C 7 to 8%) in patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, intensive co-morbid conditions or long standing DM in which A1C goal has been difficult to attain despite intensive efforts.	Grade A, Level 1
UK NICE 2022 [16]	For adults with T2DM managed either by lifestyle and diet combined with single drug not associated with hypoglycemia, support the person to aim for an HbA1C of 6.5% (48 mmol/mol).	Not mentioned
	For adults on drug associated with hypoglycemia, support the person to aim for an HbA1C of 7%	

Group or Agency	Recommendation	Strength of Recommendation / Certainty/Quality of Evidence
	Consider relaxing the target HbA1C level on a case-to-case basis and in discussion with adults with type 2 diabetes, with particular consideration for people who are older or frailer, if: ● they are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy; ● tight blood glucose control would put them at high risk if they developed hypoglycaemia, for example, if they are at risk of falling, they have impaired awareness of hypoglycaemia, or they drive or operate machinery as part of their job; ● intensive management would not be appropriate, for example if they have significant comorbidities.	
Japanese Clinical Practice Guidelines for Diabetes 2019 [17]	The glycemic control target should be determined for each individual in light of his/her age, duration of diabetes, presence of organ damage, risk of hypoglycemia, and access to any support available ● <6.0% is intended for individuals capable of achieving glycemic control with appropriate diet therapy (MNT) or exercise therapy or those capable of achieving glycemic control while on pharmacotherapy without developing hypoglycemia. ● <7.0% is intended for prevention of diabetic complications, which is assumed to correspond to fasting glucose <130 mg/dL and postprandial 2-h glucose <180 mg/dL as measured glucose values. ● <8% is Intended for individuals deemed less amenable to treatment intensification due to associated hypoglycemia or for some other reason.	Not mentioned
Standards of medical care for type 2 diabetes in China 2019 [18]	The reasonable HbA1c goal for most nonpregnant adult is<7%. This goal of HbA1c≥7% can generally be used as the criterion for initiating clinical treatment or adjusting the treatment plan. More stringent HbA1c targets (such as <6.5%, or even close to the normal reference value) are indicated in patients with T2DM with a short duration of disease, long life expectancy, no complications, and no significant CVD, without significant hypoglycaemia or other adverse effects of treatment. Less stringent HbA1c goals (such as <8.0%) are indicated in patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, long-standing diabetes in whom the goal is	Not mentioned

Group or Agency	Recommendation	Strength of Recommendation / Certainty/Quality of Evidence
	difficult to achieve despite comprehensive treatment including diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents (including insulin)	

Q12.6. Research Gaps and Recommendations

- What is the proportion of Filipinos with diabetes mellitus type 2 who achieve good control with HbA1c <7%?
- What proportion of Filipino patients with diabetes mellitus type 2 who achieve good control has associated hypoglycemia?
- What is the average expenditure per capita per annum to achieve good glycemic control?

Guideline Question 12.

Should we recommend self-monitoring of blood glucose (SMBG) targets of fasting capillary plasma glucose of 80 to 130 mg/dL and 2-hour postprandial capillary plasma glucose of <180 mg/dL to approximate the HbA1c target of <7% among nonpregnant adults with T2DM?

Q12.1. Methods and search strategy

This review was conducted following PRISMA guidelines. The reviewers searched MEDLINE from inception to September 13, 2023. The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials and meta-analyses. This review was conducted following PRISMA guidelines. The reviewers searched MEDLINE from inception to September 13, 2023 for eligible studies using the search terms "diabetes mellitus type 2," "self-monitoring of blood glucose," "SMBG," "capillary plasma glucose," "glycosylated hemoglobin," "microvascular complications," and "macrovascular complications." To identify studies that may not have been published in full or were missed through the electronic search, the reviewers manually searched all references from relevant previous studies. Only published articles written in English were obtained. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials and meta-analyses.

Q12.2. GRADE Evidence Profile and Forest Plots

A. Summary of Evidence: Effect of fasting plasma glucose reduction on major cardiovascular events, all-cause mortality, and cardiovascular mortality.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	More intensive FPG reduction	Less intensive FPG reduction	Relative (95% CI)	Absolute (95% CI)		
Major cardiovascular events												
13	randomised trials	not serious	not serious	not serious	not serious	none			**OR 0.950** (0.818 to 1.105)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality												
8	randomised trials	not serious	not serious	not serious	not serious	none			**OR 0.904** (0.825 to 0.991)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Cardiovascular mortality												
8	randomised trials	not serious	not serious	not serious	not serious	none			**OR 0.857** (0.760 to 0.967)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **OR:** Mantel-Haenszel odds ratio

Bibliography: Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr Metab Cardiovasc Dis. 2013 Jul;23(7):591-8.
NB: Trials with a between-group difference of FPG greater than 1 mmol/l (18mg/dl)

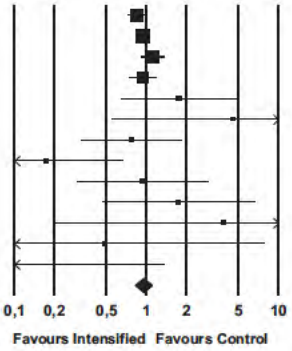
B. Summary of Evidence: Effect of postprandial glucose reduction on major cardiovascular events, all-cause mortality, and cardiovascular mortality.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**more intensive** PPG reduction	**less intensive** PPG reduction	**Relative (95% CI)**	**Absolute (95% CI)**		
major cardiovascular events												
5	randomised trials	not serious	not serious	not serious	not serious	none			**OR 0.898** (0.509 to 1.583)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
All-cause mortality												
8	randomised trials	not serious	not serious	not serious	not serious	none			**OR 1.082** (0.751 to 1.557)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Cardiovascular mortality												
4	randomised trials	not serious	not serious	not serious	not serious	none			**OR 1.608** (0.631 to 4.094)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **OR:** Mantel-Haenszel odds ratio
Bibliography: Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr Metab Cardiovasc Dis. 2013 Jul;23(7):591-8.
NB: Trials with a between-group difference of PPG greater than 1 mmol/l (18mg/dl)

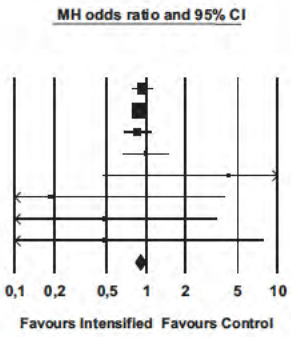
A) MAJOR CARDIOVASCULAR EVENTS

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
UKPDS 33-34 1998	0,852	0,723	1,003	-1,920	0,055
ADVANCE Group 2008	0,937	0,830	1,059	-1,035	0,301
Home 2009	1,124	0,917	1,378	1,123	0,262
Raz 2009	0,941	0,732	1,211	-0,470	0,638
Rosenstock 2010	1,769	0,635	4,930	1,092	0,275
Chan 2008 (29)	4,545	0,551	37,465	1,407	0,159
Rosenstock 2006	0,778	0,322	1,882	-0,556	0,578
Schweizer 2007 (47)	0,176	0,046	0,671	-2,546	0,011
Hodis 2006	0,941	0,296	2,993	-0,103	0,918
Madsbad 2001	1,766	0,462	6,759	0,831	0,406
Unpublished 1	3,866	0,198	75,655	0,891	0,373
Pratley 2011 (28)	0,490	0,030	7,869	-0,504	0,614
Johnston 1998 (a)	0,072	0,004	1,399	-1,738	0,082
Overall MH - OR	0,950	0,818	1,105	-0,662	0,508



B) ALL-CAUSE MORTALITY

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
UKPDS 33-34 1998	0,941	0,790	1,121	-0,678	0,498
ADVANCE Group 2008	0,890	0,784	1,011	-1,788	0,074
Home 2009	0,860	0,679	1,091	-1,241	0,215
Raz 2009	0,998	0,664	1,500	-0,010	0,992
Rosenstock 2010	4,228	0,470	38,046	1,286	0,198
Rosenstock 2006	0,188	0,009	3,960	-1,075	0,282
Schweizer 2007 (47)	0,481	0,067	3,434	-0,730	0,465
Pratley 2011 (28)	0,490	0,030	7,869	-0,504	0,614
Overall MH - OR	0,904	0,825	0,991	-2,155	0,031



C) CARDIOVASCULAR MORTALITY

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
UKPDS 33-34 1998	0,805	0,647	1,001	-1,950	0,051
ADVANCE Group 2008	0,869	0,731	1,033	-1,589	0,112
Home 2009	0,844	0,595	1,196	-0,956	0,339
Raz 2009	1,072	0,698	1,647	0,319	0,750
Rosenstock 2010	3,161	0,327	30,552	0,994	0,320
Rosenstock 2006	0,188	0,009	3,960	-1,075	0,282
Schweizer 2007 (47)	0,481	0,067	3,434	-0,730	0,465
Pratley 2011 (28)	0,163	0,007	4,021	-1,109	0,267
Overall MH - OR	0,857	0,760	0,967	-2,501	0,012

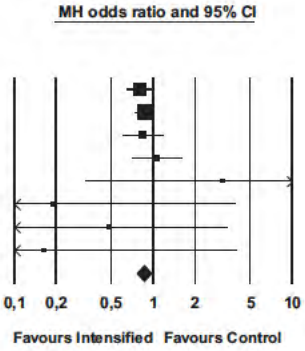
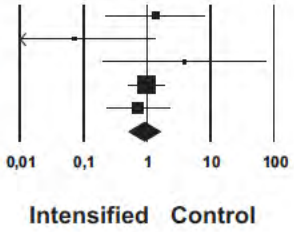


Figure MH-Odd Ratio for major cardiovascular events (Panel A), all-cause mortality (Panel B), and cardiovascular mortality (Panel C) in patients on more intensive treatments, in trials with a between-group difference of FPG greater than 1 mmol/l.

Bibliography: Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr Metab Cardiovasc Dis. 2013 Jul;23(7):591-8.

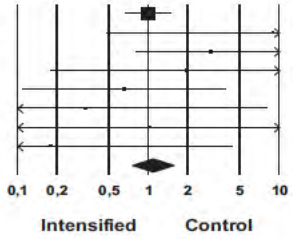
A) MAJOR CARDIOVASCULAR EVENTS

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ristic 2007	1,362	0,223	8,323	0,335	0,738
Johnston 1998 (a)	0,072	0,004	1,399	-1,738	0,082
Unpublished 1	3,866	0,198	75,655	0,891	0,373
Gram 2011	0,971	0,488	1,930	-0,085	0,932
Fritsche 2010	0,724	0,225	2,332	-0,541	0,588
Overall MH-OR	0,898	0,509	1,583	-0,372	0,710



B) ALL- CAUSE MORTALITY

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Raz 2009	0,998	0,664	1,500	-0,010	0,992
Gram 2011	8,951	0,479	167,447	1,467	0,142
Holman 2009	3,013	0,805	11,272	1,639	0,101
Nauck 2007 a	1,968	0,177	21,845	0,551	0,581
Williams-Herman 2010	0,652	0,109	3,918	-0,467	0,640
Garber 2010	0,333	0,014	8,222	-0,672	0,502
Fritsche 2010	1,026	0,064	16,556	0,018	0,985
Johnston 1998 (b)	0,181	0,007	4,469	-1,045	0,296
Overall MH-OR	1,082	0,751	1,557	0,422	0,673



C) CARDIOVASCULAR MORTALITY

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Raz 2009	1,072	0,698	1,647	0,319	0,750
Holman 2009	9,117	1,146	72,543	2,089	0,037
Nauck 2007 a	1,968	0,177	21,845	0,551	0,581
Williams-Herman 2010	0,980	0,061	15,708	-0,014	0,989
Overall MH-OR	1,608	0,631	4,094	0,996	0,319

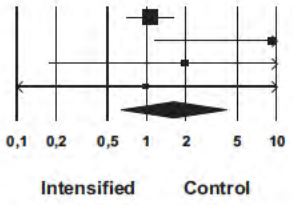


Figure MH-Odd Ratio for major cardiovascular events (Panel A), all-cause mortality (Panel B), and cardiovascular mortality (Panel C) in patients on more intensive treatments, in trials with a between-group difference of PPG greater than 1 mmol/l.

Bibliography: Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. Nutr Metab Cardiovasc Dis. 2013 Jul;23(7):591-8.

D. Summary of glycemic target recommendations for most nonpregnant adults with diabetes

HbA1c	<7.0%
Fasting or preprandial capillary blood glucose	80–130mg/dl (4.4–7.2 mmol/L)
2-hour postprandial capillary blood glucose	<180mg/dl (<10.0 mmol/L)

Q12.3. Recommendations from other groups

Recommended SMBG targets by guideline (ADA Grade E, Canadian Grade B Level 2, IDF, Japan, Malaysian Grade B).

Summary of glycemic target recommendations

- HbA1c: <7.0%.
- Fasting or preprandial capillary blood glucose: 80 to 130 mg/dL (4.4 to 7.2 mmol/L).
- 2-hour postprandial capillary blood glucose: <180 mg/dL (<10.0 mmol/L).

Q12.4. Research Gaps and Recommendations

- What are the FPG and PPG targets that lead to actual reduction in diabetic complications?
- Are there Filipino-specific data establishing optimal preprandial and postprandial SMBG targets corresponding to good glycemic outcomes?

Guideline Question 14. Should we give influenza vaccine annually among adults with T2DM?

Q14.1. Methods

Literature was searched through MEDLINE via PubMed, supplemented by handsearching, for eligible studies on the use of annual influenza vaccination for the prevention of respiratory tract infections among adults with type 2 diabetes mellitus, using the search terms "diabetes mellitus type 2," "influenza vaccine," "influenza vaccination," "respiratory tract infections," and "influenza." Records were screened, retrieved, and assessed for eligibility, with additional records identified through handsearching also retrieved and assessed for eligibility. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

Q14.2. Search strategy

PubMed search strategy (verbatim selected lines from source slides 7-8):

#	Query	Filters	Yield
1	vaccine (vaccines[MeSH] OR variants)	(none)	509,179
2	diabetes (diabetes mellitus[MeSH] OR variants)	(none)	951,230
3	#1 AND #2	(none)	5,516
4	#1 AND #2	Meta-Analysis	64
5	#1 AND #2	Meta-Analysis, last 10 years	56
8	#1 AND #2	Meta-Analysis, last 10 years, Adolescent 13 to 18 yr, Adult 19+ yr	19
9-10	#1 AND #2	Meta-Analysis OR Systematic Review, last 10 years, adolescent/adult	37
11	#1 AND #2	Meta-Analysis OR Systematic Review, 2007 to 2023, adolescent/adult	42 (final yield)

Q14.3. Assessment of Risk of Bias

Risk of bias of the studies included in Dicembrini et al. 2023 was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, with conversion to AHRQ standards (good, fair, poor). The studies tabulated by Dicembrini et al. were rated good quality overall.

Included studies and NOS scoring summary (Selection 1 to 4, Comparability 1, Outcome 1 to 3):

First Author	Year	Journal	S1	S2	S3	S4	C1	O1	O2	O3
Heymann	2004	Diabetes Care	1	1	1	1	0	1	1	1
Lau (18 to 65)	2013	Thorax	1	0	1	1	0	1	1	0
Lau (over 65)	2013	Thorax	0	1	1	1	1	1	0	1
Looijmans	2006	Diabetes Care	1	1	0	1	0	1	1	1
Martinez-Bas	2020	Clin Infect Dis	1	0	1	1	1	1	1	0
Modin	2020	Diabetes Care	1	1	1	1	2	1	0	1
Rodriguez Blanco	2012	Human Vacc Immunother	0	1	0	1	0	1	1	1
Rondy	2017	Euro Surveillance	1	0	1	1	1	1	1	0
Ruiz	2019	J Intern Med	1	1	0	1	2	1	0	1
Sanchez Munoz-Torrero	2002	Rev Clin Esp 2003	0	1	1	1	0	1	1	1
Schade	2000	Med J West Virginia	1	1	1	1	2	1	1	1
Vamos	2016	CMAJ	1	0	0	1	1	1	0	1
Wang	2007	Vaccine	1	1	1	1	2	1	1	1
Wang	2013	Vaccine	1	1	1	1	0	1	1	1

Q14.4. GRADE Evidence Profile

Overall certainty of evidence: Moderate. The review noted considerations for risk of bias (observational designs only; NOS-assessed good quality overall), inconsistency (variation in vaccine doses and preparations), imprecision (small populations and wide confidence intervals around some pooled estimates), and indirectness (vaccine formulation and uncertainty around peak-season effects).

GRADE domain	Consideration
Risk of bias	Observational designs only; NOS-assessed as good quality overall
Inconsistency	Variation in vaccine doses and preparations
Imprecision	Small populations and wide confidence intervals around some pooled estimates
Indirectness	Vaccine formulation and uncertainty around peak-season effects
Publication Bias	None detected

Q14.5. Recommendations from other groups

Group / Document	Recommendation	Strength / Grade
American Diabetes Association (ADA) Standards of Care in Diabetes - 2025, Section 4 (Comprehensive Medical Evaluation and Assessment of Comorbidities), Table 4.3 "Immunization recommendations"	ADA strongly recommends annual influenza vaccination for all people with diabetes aged ≥6 months of age. People with diabetes should AVOID the live attenuated influenza vaccine (LAIV). The 2025 Standards revised the Immunizations subsection to reflect updates for influenza (along with COVID-19, pneumococcal, and respiratory syncytial virus).	Aligned with the ACIP/CDC schedule; ADA-defined evidence grade per source Table 4.3
CDC Advisory Committee on Immunization Practices (ACIP) - Prevention and Control of Seasonal Influenza with Vaccines, United States, 2025-26 Influenza Season (MMWR Recomm Rep)	Routine annual influenza vaccination is recommended for all persons aged ≥6 months without a contraindication. Diabetes mellitus is listed among chronic medical conditions that predispose to influenza complications, making vaccination a priority. For adults <65 years with diabetes: no preferential recommendation among licensed inactivated/recombinant vaccines. For adults ≥65 years: preferential recommendation for high-dose (HDIIV3), adjuvanted (aIIV3), or recombinant (RIV3) influenza vaccine. Vaccination should be offered by the end of October.	ACIP recommendation

Group / Document	Recommendation	Strength / Grade
World Health Organization (WHO) - Vaccines against influenza: WHO position paper, May 2022 (Weekly Epidemiological Record 97;19)	WHO recommends seasonal influenza vaccination for priority risk groups including individuals with comorbidities and underlying medical conditions (a group that includes diabetes), alongside health workers, older adults, and pregnant women. Annual vaccination using the WHO-recommended seasonal vaccine composition.	WHO position paper recommendation
Philippine Guidelines on Periodic Health Examination - Adult Immunization, 2023 Updates (PHEX-Adult Immunization, Philippines)	PHEX-Adult Immunization 2023 Updates include influenza vaccination among the 16 covered adult vaccinations, with recommendations informed by efficacy, safety, and cost-effectiveness in the Filipino adult population.	Per the originating CPG - exact grade to be verified against the PHEX-Adult Immunization 2023 PDF
Philippine Department of Health (DOH) - DOH Memorandum No. 2020-0384 and the Expanded Program on Immunization (EPI)	DOH provides essential health services including influenza immunization through LGUs and barangay health centers, with continued influenza immunization prioritized for senior citizens. Reported coverage in adults aged ≥60 years was approximately 36.3% as of 2019.	Programmatic guidance (DOH)

Q14.6. Research Gaps and Recommendations

- None of the included studies reported data on ICU admission, glycemic control, or cardiovascular mortality as outcomes among vaccinated persons with diabetes - these remain research gaps.
- Variation in vaccine doses and preparations across studies; standardized comparative effectiveness studies are needed.
- Local Philippine data on influenza vaccine uptake and clinical outcomes among Filipino adults with type 2 diabetes are needed.

Guideline Question 15.Should we give pneumococcal vaccine annually among adults with T2DM?

Q15.1. Methods and Search Strategy

Literature was searched through MEDLINE via PubMed, supplemented by handsearching, for eligible studies on the use of pneumococcal vaccination for the prevention of respiratory tract infections and pneumococcal disease among adults with type 2 diabetes mellitus. The literature search and screening process were conducted jointly with the influenza vaccine question (Q13), as both drew from a single combined PubMed search covering vaccination in adults with type 2 diabetes mellitus. The search combined terms for the population (e.g., "diabetes mellitus type 2," "type 2 diabetes mellitus," "T2DM") with terms for the interventions and outcomes of interest (e.g., "pneumococcal vaccine," "pneumococcal vaccination," "influenza vaccine," "respiratory tract infections," "pneumonia"), supplemented by handsearching of reference lists. Records identified through the electronic search were screened by title and abstract, with potentially eligible records retrieved and assessed for eligibility against the predefined inclusion criteria; additional records identified through handsearching were likewise retrieved and assessed. The references of included studies were also hand-searched to identify further evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

Q15.2. Results

Pooled results from 5 studies enrolling a total of 163,756 participants showed a significant decrease in all-cause mortality with pneumococcal vaccination: HR 0.78 (95% CI 0.73 to 0.83), with no statistically significant heterogeneity (χ^2 test P = 0.21; I^2 = 32%). This corresponds to a 22% decrease in all-cause mortality in the population studied (patients with CVD or at very high CV risk, which included persons with diabetes mellitus with target organ damage).

Vaccine effectiveness ranges (Dunne et al. 2023, 9 studies, high-income countries):

- Vaccine-type pneumococcal pneumonia: PPV23 2 to 6%; PCV13 41 to 71%.
- Pneumococcal pneumonia or severe pneumococcal disease (IPD or pneumococcal pneumonia): PPV23 −10 to 11%; PCV13 40 to 79%; sequential PCV13/PPV23 39 to 83%.
- All-cause pneumonia or lower respiratory tract infection: PPV23 −8 to 3%; PCV13 9 to 12%.

Q15.3. GRADE Evidence Profile

Overall certainty of evidence: Low (per source slide 39). Considerations included serious risk of bias (3 of 7 included studies in Marques Antunes 2021), inconsistency (variation in vaccine type and dosing), imprecision (sparse events in some secondary outcomes), and indirectness (the included population was not restricted to persons with diabetes mellitus alone).

Overall certainty of evidence: **Low**

GRADE domain	Consideration
Risk of bias	Serious; 3 of 7 included studies in Marques Antunes 2021
Inconsistency	Variation in vaccine type and dosing
Imprecision	Sparse events in some secondary outcomes

Indirectness	Included population was not restricted to persons with diabetes mellitus alone

Q15.4. Recommendations from other groups

Group / Document	Recommendation	Strength / Grade
American Diabetes Association (ADA) Standards of Care in Diabetes - 2025, Section 4 (Comprehensive Medical Evaluation and Assessment of Comorbidities), Table 4.3 "Immunization recommendations"	ADA strongly recommends pneumococcal vaccination for adults with diabetes per the current ACIP/CDC schedule. The 2025 Standards specifically updated the pneumococcal vaccination guidance and included additional clarification on the pneumonia vaccines for people with diabetes.	Aligned with the ACIP/CDC schedule; ADA-defined evidence grade per source Table 4.3
CDC Advisory Committee on Immunization Practices (ACIP) - Expanded Recommendations for Use of Pneumococcal Conjugate Vaccines Among Adults Aged ≥50 Years, United States, 2024 (MMWR Recomm Rep)	A single dose of PCV (PCV15, PCV20, or PCV21) is recommended for all PCV-naïve adults aged ≥50 years. If PCV15 is used, a subsequent dose of PPSV23 is recommended (≥1 year after PCV15; ≥8 weeks for adults with immunocompromising conditions). If PCV20 or PCV21 is used, no subsequent PPSV23 is routinely required. For adults aged 19 to 49 years with risk conditions (including diabetes mellitus), prior recommendations apply: a single PCV (PCV15 followed by PPSV23; or PCV20 alone; or PCV21 alone).	ACIP recommendation
CDC ACIP - Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023 (MMWR Recomm Rep)	For adults aged 19 to 64 years with chronic medical conditions (including diabetes mellitus) and no prior PCV: a single dose of PCV15 or PCV20. If PCV15 is used, follow with PPSV23. For adults ≥65 years: pneumococcal vaccination per the age-based recommendations.	ACIP recommendation
World Health Organization (WHO) - Pneumococcal vaccines: WHO position paper (most recent adult-relevant guidance available on WHO Pneumococcus position-papers page)	WHO identifies adults with chronic medical conditions including diabetes, cardiac disease, chronic liver/kidney/pulmonary disease, CSF leak, and cochlear implant as being at increased risk of pneumococcal disease and a priority population for national vaccination programs that include adult schedules.	WHO position paper guidance

Group / Document	Recommendation	Strength / Grade
Philippine Department of Health (DOH) - National Immunization Program (NIP)	DOH provides one (1) lifetime dose of pneumococcal vaccine free of charge for senior citizens aged ≥60 years. Reported Philippine pneumococcal vaccine coverage in adults ≥60 years is approximately 52.9%.	National program guidance
Health Technology Assessment (HTA) Council Philippines - Evidence to Recommendations: Pneumococcal Vaccination for Elderly Adults ≥60 Years (2025)	HTA Philippines published an Evidence-to-Recommendations document supporting pneumococcal vaccination for elderly adults aged ≥60 years.	National HTA recommendation
Philippine Guidelines on Periodic Health Examination - Adult Immunization, 2023 Updates (PHEX-Adult Immunization, Philippines)	PHEX-Adult Immunization 2023 Updates include pneumococcal vaccination among the 16 covered adult vaccinations, with recommendations informed by efficacy, safety, and cost-effectiveness in the Filipino adult population.	

Note: the ACIP 2024 expansion to all adults aged ≥50 years means that adults with diabetes in the 50 to 64 year age band - previously covered as a risk group under the 19 to 64 chronic-condition recommendation - are now covered by the age-based recommendation regardless of risk status. For adults with diabetes aged 19 to 49 years, the risk-based recommendation (PCV15 + PPSV23, PCV20 alone, or PCV21 alone) still applies.

Q15.5. Research Gaps and Recommendations

- No included study evaluated invasive pneumococcal disease alone as an outcome (Dunne et al. 2023).
- The Marques Antunes 2021 review included a mixed-CV-risk population; no published meta-analysis isolates pneumococcal vaccine effectiveness in adults with T2DM specifically.
- Local Philippine data on pneumococcal vaccine uptake, serotype coverage, and clinical outcomes among Filipino adults with type 2 diabetes are needed.

Guideline Question 16. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and concomitant tuberculosis?

Q16.1. Methods and search strategy

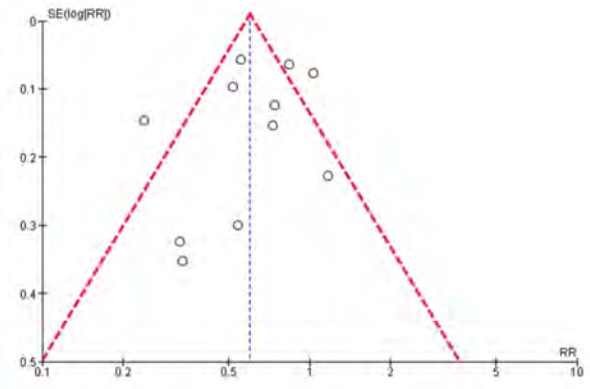
A systematic search was conducted until May 25, 2023 through MEDLINE via PubMed, the Cochrane Library, and HERDIN Plus, using a combination of medical subject headings (MeSH) and keywords ("type 2 diabetes mellitus," "tuberculosis") in the initial search. Only articles published in the English language were included. Studies were eligible if they reported the outcomes of interest, namely glycemic control, microvascular complications, macrovascular complications, hypoglycemia, weight loss/gain, organ toxicity, and quality of life. The search strategy for clinical practice guidelines (CPGs) did not yield any eligible publications; a search for indirect evidence on the management of type 2 diabetes mellitus and pulmonary tuberculosis was therefore conducted. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. Risk of bias was evaluated using the Cochrane RoB2 tool for randomized controlled trials and AMSTAR-2 for meta-analyses.

Q16.2 Assessment of Risk of Bias

Authors' assessment of risk of bias of the included studies

CCS, case-control study; NOS, Newcastle-Ottawa Scale tool; RCS, retrospective cohort study; RCT, randomized controlled trial; RoB2

Study	Design	Tool	Conclusion
Padmapriydarsini C, 2022, India[20]	Phase 3 RCT	ROB2	Low risk
Bailey CJ, 2012, USA, Canada, Mexico, Russia, India, South Africa, Puerto Rico[37]	RCT	ROB2	Low risk
FDA, 2010, USA[35]	RCT	ROB2	Low risk
Heo E, 2021, South Korea[21]	RCS	NOS	Low risk
Lee YJ, 2018, South Korea[22]	RCS	NOS	Low risk
Lin HF, 2017, Taiwan[24]	RCS	NOS	Low risk
Degner NR, 2018, Taiwan[23]	RCS	NOS	Low risk
Lee MC, 2018, Taiwan[27]	RCS	NOS	Low risk
Lin SY, 2018, Taiwan[25]	RCS	NOS	Low risk
Pan SW, 2018, Taiwan[29]	RCS	NOS	Low risk
Tseng CH, 2018, Taiwan[30]	RCS	NOS	Low risk
Al-Shaer MH, 2018, Qatar[31]	RCS	NOS	Low risk
Park S, 2019, South Korea[32]	RCS	NOS	Low risk
Lee MC, 2019, Taiwan[28]	RCS	NOS	Low risk
Fu CP, 2021, Taiwan[33]	RCS	NOS	Low risk
Chen HH, 2020, Taiwan[34]	RCS	NOS	Low risk
Su WJ, 2018, Taiwan[36]	RCS	NOS	Low risk
Lin KH, 2020, Taiwan[26]	CCS	NOS	Low risk



, Cochrane Risk of Bias tool for randomized trials version 2

Q16.3. GRADE Evidence Profile and Forest Plots

A structured clinical algorithm compared to routine follow-up for type 2 diabetes mellitus with tuberculosis

Bibliography: [1]

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With routine follow-up	With a structured clinical algorithm	Relative effect (95% CI)	Risk with routine follow-up	Risk difference with a structured clinical algorithm
Glycemic control at 3 months (follow-up: 6 months; assessed with: HbA1c <8%)											
138 (1 RCT)[1]	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	23/67 (34.3%)	37/71 (52.1%)	**OR 2.08** (1.05 to 4.14)	343 per 1,000	**178 more per 1,000** (from 11 more to 341 more)
Glycemic control at 6 months (follow-up: 6 months; assessed with: HbA1c <8%)											
134 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	25/66 (37.9%)	45/68 (66.2%)	**OR 3.21** (1.58 to 6.51)	379 per 1,000	**283 more per 1,000** (from 112 more to 420 more)
Mortality											
150 (1 RCT)	not serious	not serious	not serious	extremely serious[a]	all plausible residual confounding would suggest spurious effect, while no effect was observed	⨁⨁◯◯ Low	0/74 (0.0%)	2/76 (2.6%)	not estimable	0 per 1,000	
Hypoglycemia (assessed with: BG <65 mg/dL)											
140 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	8/68 (11.8%)	25/72 (34.7%)	**HR 2.94** (-- to --)	118 per 1,000	**190 more per 1,000** (from -- to --)
Any adverse events (follow-up: 6 months)											
146 (1 RCT)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	60/74 (81.1%)	72/72 (100.0%)	**HR 1.23** (-- to --)	811 per 1,000	**60 more per 1,000** (from -- to --)

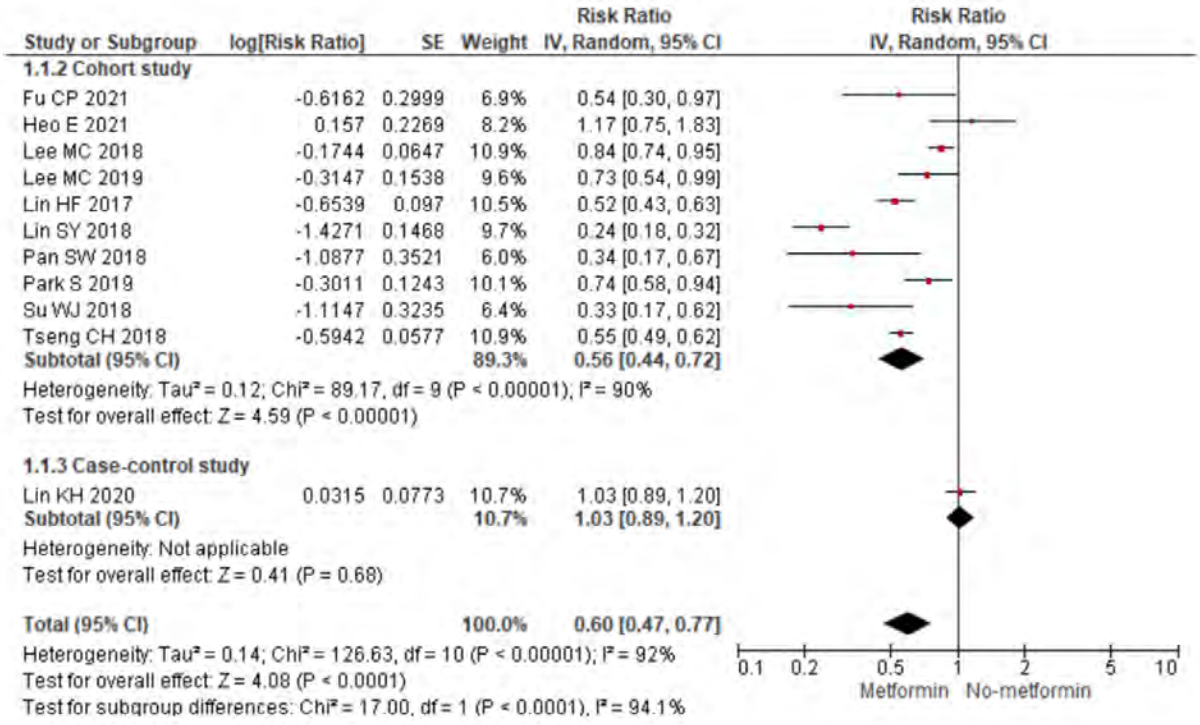
CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio

Explanations

a. Small sample size, with 0 event rate in control group
b. More frequent assessment in the intervention group

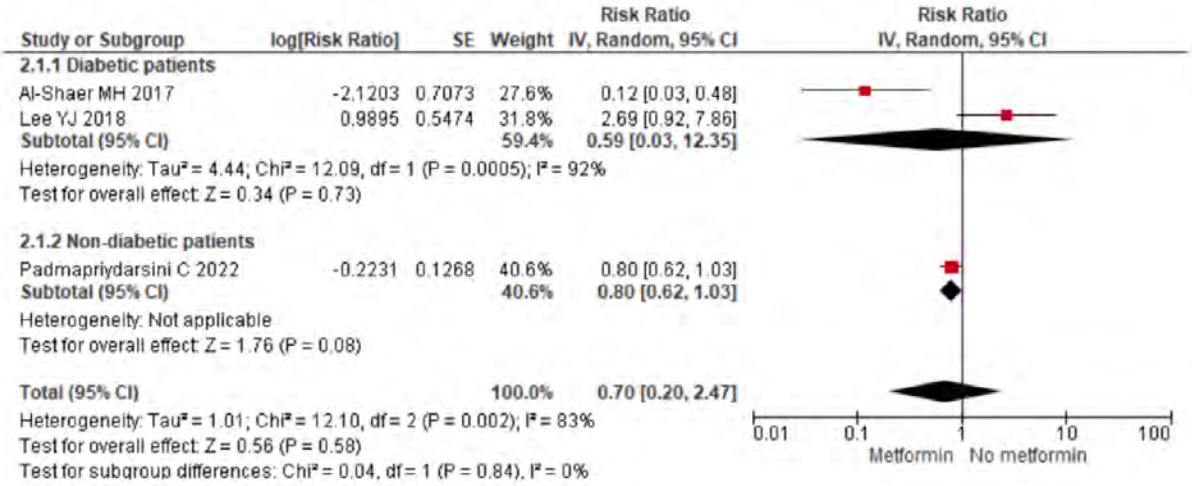
References

1.Ruslami R, Koesoemadinata RC,Soetedjo NNM,et al.. The effect of a structured clinical algorithm on glycemic control in patients with combined tuberculosis and diabetes in Indonesia: A randomized trial. Diabetes Res Clin Pract; 2021.



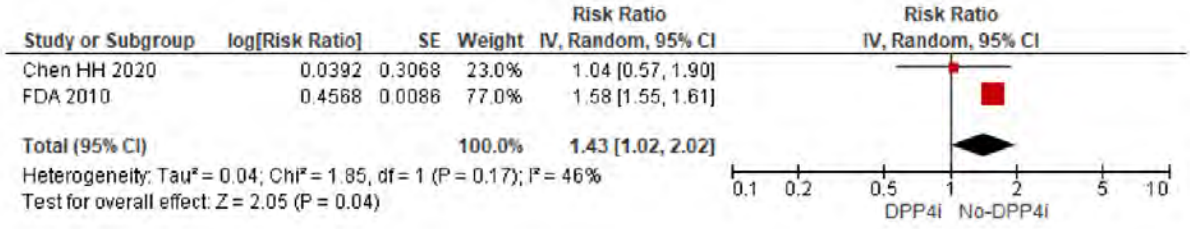
(a)

Forest plots of the effect of metformin on the risk of active TB (a) and sputum culture conversion (b) according to the presence of diabetes.[19]

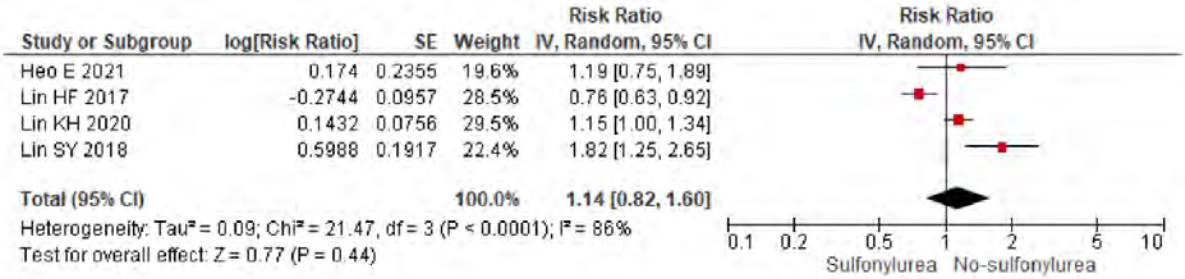


(b)

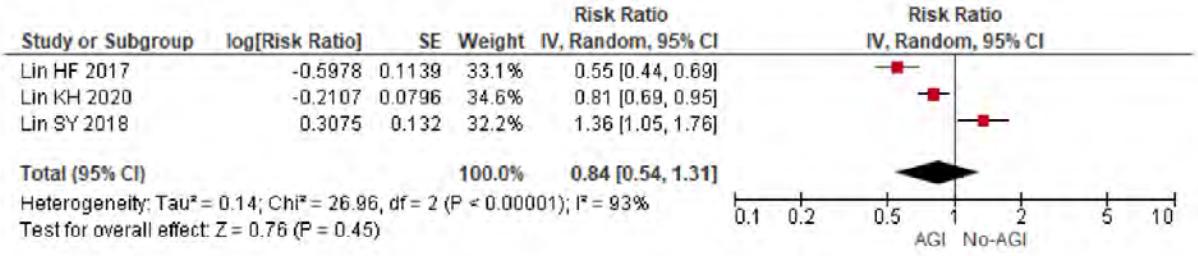
Forest plots of the effect of DPP4-i (a), SU (b), MEG (c), TZD (d) and AGI (e) on the risk of active TB in patients with diabetes.[19]



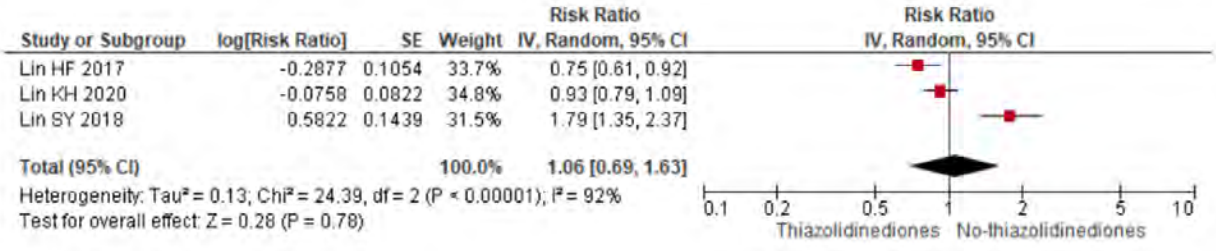
(a)



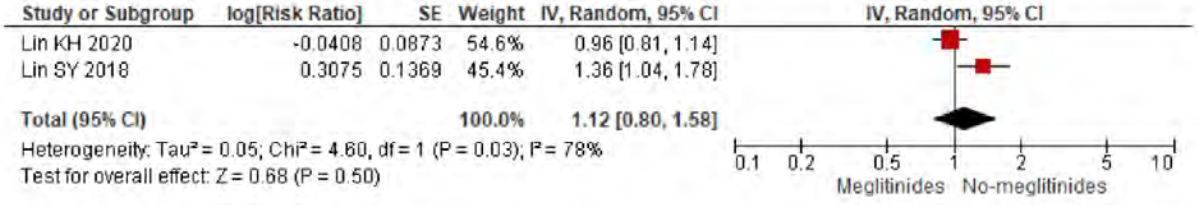
(b)



(c)



(d)



(e)

Q16.4. Recommendations from other groups

Group / Agency	Recommendation	Strength / Certainty
National Tuberculosis Control Program (Philippines, 2020)	Use of modern insulin or insulin analogs in patients with diabetes, particularly in the early phase of TB, to establish strict glycemic control.	Not specified in source
International Union Against Tuberculosis and Lung Disease (The Union)	Achieve an HbA1c target of <8% or fasting blood glucose <180 mg/dL during treatment for tuberculosis, similar to the goals for patients with diabetes and significant comorbidity. Metformin, sulfonylureas, and insulin are recommended in consideration of experience and wide availability in resource-limited areas. The use of DPP-4i, GLP-1 RA, and SGLT2i were not discussed because of limited availability of these medications in resource-limited settings.	Not specified in source

Q16.5. Research Gaps and Recommendations

Recommendations for glucose targets for patients with DM and TB are generally extrapolated from evidence on glycemic control in general DM populations. Most studies on DM treatment in TB are retrospective cohort studies with mixed populations. Studies on insulin use and associated outcomes are scarce in TB. Additional considerations in treatment recommendations include availability of medications and social determinants of health.

- Direct RCTs of specific antidiabetic agents in T2DM patients with active TB are needed.
- Studies on insulin use and associated outcomes in TB are scarce.
- Local Philippine data on prescribing patterns and glycemic outcomes in T2DM patients with concomitant TB.
- Cost-effectiveness studies of structured care programs and specific antidiabetic agents for T2DM with TB in low- and middle-income settings.

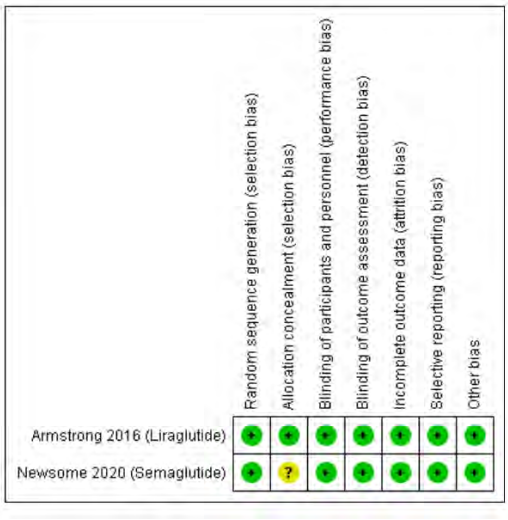
Guideline Question 17. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD)?

Q17.1. Methods and search strategy

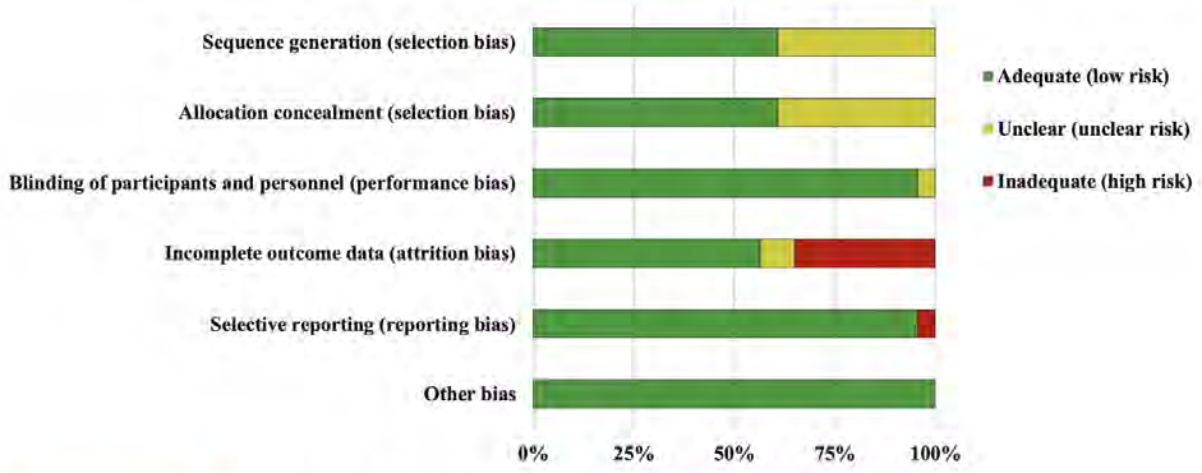
A systematic search was conducted through MEDLINE via PubMed, the Cochrane Library, and HERDIN Plus, using a combination of medical subject headings (MeSH) and keywords for "type 2 diabetes mellitus" and "metabolic dysfunction-associated steatotic liver disease" (including the prior terminology "non-alcoholic fatty liver disease"). Only articles published in the English language were included. Studies were eligible if they reported the outcomes of interest for the management of type 2 diabetes mellitus and MASLD. The search strategy for clinical practice guidelines (CPGs) did not yield any eligible publications; a search for indirect evidence on the management of type 2 diabetes mellitus and non-alcoholic fatty liver disease was therefore conducted. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The risk of bias of included randomized controlled trials was appraised using the Cochrane Risk of Bias tool.

Q16.2. Assessment of Risk of Bias

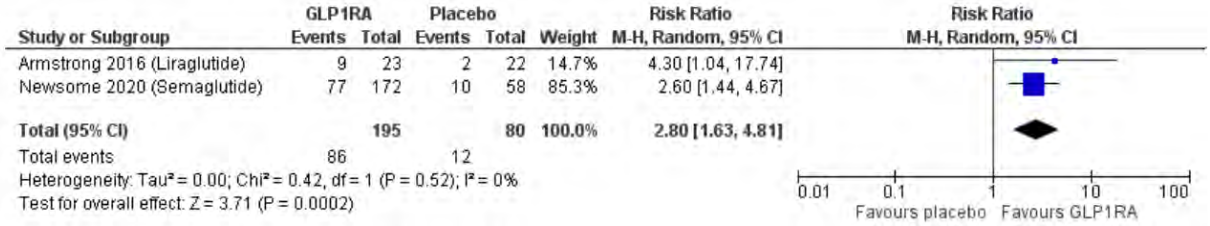
Risk of bias of the 2 included RCTs (Armstrong 2016, Newsome 2021) was appraised using the Cochrane Risk of Bias tool.



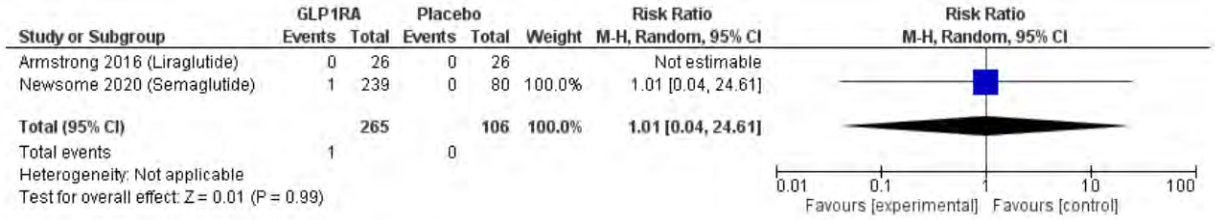
For the Musso 2017 meta-analysis, study quality and risk-of-bias assessment was extracted from the source meta-analysis.



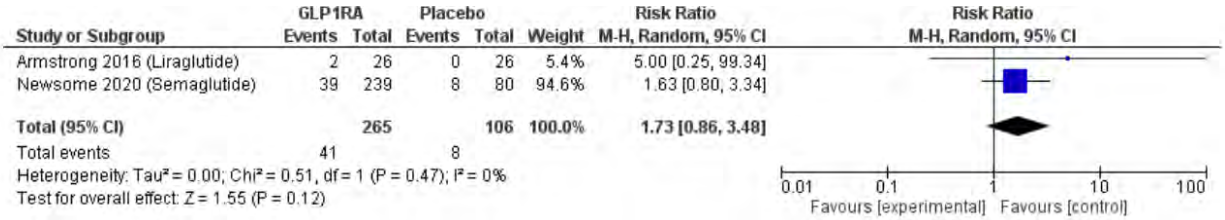
Q17.3. GRADE Evidence Profile and Forest Plots



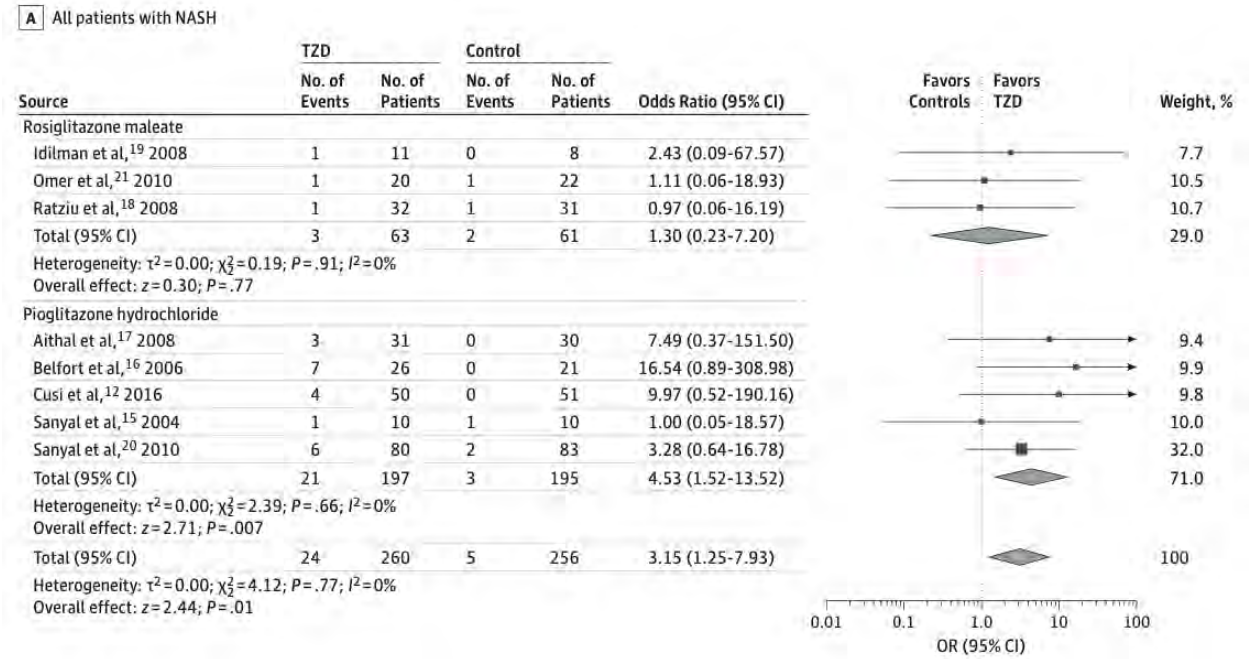
Association of GLP-1RA vs placebo with histologic NASH resolution



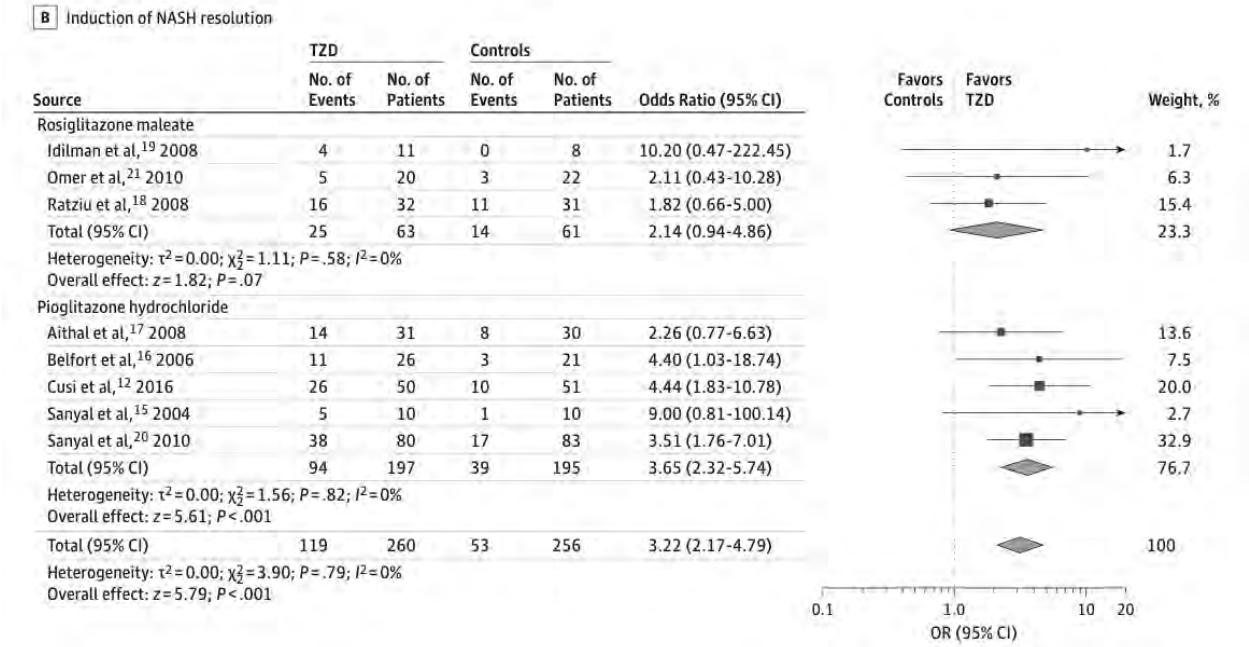
Association of GLP-1RA vs placebo with mortality



Association of GLP-1RA vs placebo with serious adverse events



Meta-analysis of Pioglitazone on improvement of advanced fibrosis (Musso et al)



Meta-analysis of Pioglitazone on improvement in NASH resolution (Musso et al)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP-1-RA	placebo	Relative (95% CI)	Absolute (95% CI)		
Resolution of NAFLD/NASH												
2	16andomized trials	not serious	not serious	serious[a]	serious[b]	none	86/195 (44.1%)	12/80 (15.0%)	**RR 2.80** (1.63 to 4.81)	**270 more per 1,000** (from 94 more to 571 more)	⊕⊕◯◯ Low	CRITICAL
Mortality												
2	16andomized trials	not serious	not serious	serious[a]	very 16andomi,c,d	none	1/265 (0.4%)	0/106 (0.0%)	**RR 1.01** (0.04 to 24.61)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very Low	CRITICAL
Serious adverse event												
2	16andomized trials	not serious	not serious	serious[a]	serious[b]	none	41/265 (15.5%)	8/106 (7.5%)	**RR 1.73** (0.86 to 3.48)	**55 more per 1,000** (from 11 fewer to 187 more)	⊕⊕◯◯ Low	IMPORTANT

Summary of the GRADE appraisal

Outcome	Basis (number/type of study, total participants)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Resolution of MASLD/NASH	2 RCTs (n=275)	RR 2.80 (1.63 to 4.81)	Benefit	Moderate
Mortality	2 RCTs (n=371)	RR 1.01 (0.04 to 24.61)	Inconclusive	Very low
Serious adverse events	2 RCTs (n=371)	RR 1.73 (0.86 to 3.48)	Inconclusive	Moderate

Source: GLP-1 RA versus placebo in NAFLD; pooled from Armstrong MJ et al. Lancet 2016;387:679-690 and Newsome PN et al. N Engl J Med 2021;384:113-124.

Q17.4. Recommendations from other groups

Group / Agency	Recommendation	Grade / Strength of Evidence
American Association of Clinical Endocrinology (AACE), co-sponsored by the American Association for the Study of Liver Diseases (AASLD) - Cusi K et al. Endocr Pract. 2022;28:528-562	Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.	Grade A, high strength of evidence, BEL 1
AACE / AASLD - Cusi K et al. Endocr Pract. 2022;28:528-562	Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests.	Grade A, high strength of evidence, BEL 1
AACE / AASLD - Cusi K et al. Endocr Pract. 2022;28:528-562	Due to the lack of evidence of efficacy, metformin, acarbose, DPP-4 inhibitors, and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH.	Grade B, high strength of evidence, BEL 1, downgraded due to the use of surrogate outcome measures in many of the studies
Croatian Guidelines for the Diagnosis and Treatment of NAFLD - Jukić LV et al. Acta Clin Croat. 2021;60(Suppl 1):36-52	Although metformin is in the first line of treatment for diabetes mellitus, owing to the beneficial effect of other drugs that affect insulin resistance (pioglitazone, liraglutide) on histological changes in the liver of NAFLD patients, they should be considered when choosing therapy for patients with NASH.	Not specified in source

Q17.5. Research Gaps and Recommendations

- Per the source speaker notes (slide 19), the recent change in terminology from NAFLD to MAFLD (metabolic-associated fatty liver disease) should be acknowledged - clarify implications for diagnostic and therapeutic populations.
- Emphasize that there are no specific treatments currently approved for fatty liver; cornerstone is achievement of target weight loss and improvement in lipid parameters.
- Direct RCTs of pioglitazone and GLP-1 RA in T2DM patients with biopsy-proven NASH using clinical (rather than surrogate / histological) endpoints are needed.
- Local Philippine data on prevalence of NAFLD/MAFLD among Filipino adults with type 2 diabetes, and on prescribing patterns of pioglitazone and GLP-1 RA in this population.
- Cost-effectiveness studies of GLP-1 RA and pioglitazone as NAFLD adjunctive therapy in low- and middle-income settings.

Guideline Question 18.
Should we recommend specific oral antidiabetic agents or injectable therapies to prevent the occurrence of stroke or its recurrence among adults with type 2 diabetes mellitus and established cardiovascular disease?

Q18.1. Methods

Literature was searched through PubMed/MEDLINE and supplemented by handsearching of major cardiovascular outcome trials (CVOTs). PubMed/MEDLINE was queried using a combination of medical subject headings (MeSH) and keywords for diabetes, cerebrovascular disease/stroke, and glucose-lowering agents. The population term for diabetes was combined with the terms for cerebrovascular disease and stroke (diabetes AND cerebrovascular disease OR stroke), progressively applying publication-type filters (Clinical Trial, Meta-Analysis, Randomized Controlled Trial, and Systematic Review) together with age-group and date restrictions (adolescent/adult; last 10 years, 2013 to 2023). The resulting set was then narrowed by combining it with the intervention term (glucose-lowering agents) to yield the final pool of eligible studies, with the full search strings preserved verbatim in the source documentation. The references of included studies, together with major cardiovascular outcome trials, were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

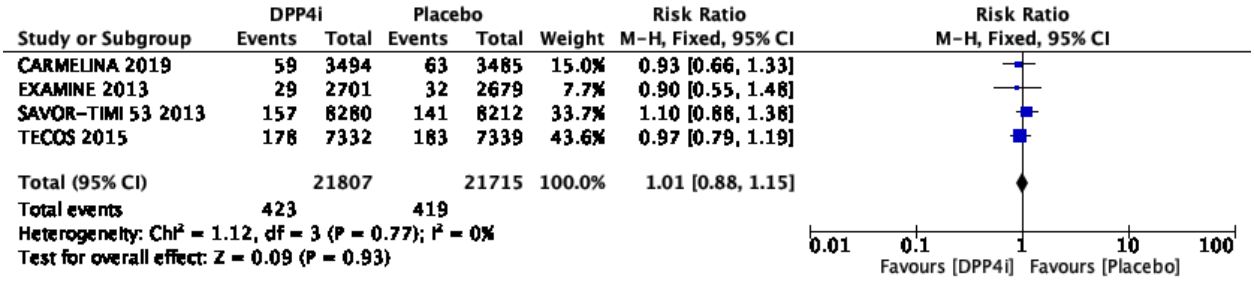
Q18.2. Search strategy

PubMed search history

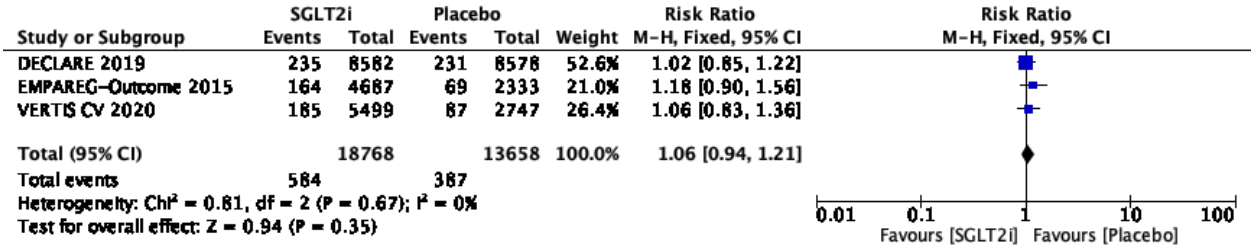
Query / topic	Filters	Yield
diabetes (term #1)	(none)	954,079
cerebrovascular disease (term #2)	(none)	464,022
stroke (term #3)	(none)	443,431
#1 AND #2 OR #3	(none)	453,462
#1 AND #2 OR #3	RCT	20,258
#1 AND #2 OR #3	Clinical Trial, RCT	29,766
#1 AND #2 OR #3	Clinical Trial, MA, RCT	40,099
#1 AND #2 OR #3	Clinical Trial, MA, RCT, Systematic Review	45,805
#1 AND #2 OR #3	MA, RCT, Systematic Review, 1966 to 2023, adolescent/adult	28,834
#1 AND #2 OR #3	MA, RCT, Systematic Review, 2000 to 2023, adolescent/adult	18,094

Query / topic	Filters	Yield
#1 AND #2 OR #3	Clinical Trial, MA, RCT, Systematic Review, 2000 to 2023, adolescent/adult	24,666
#1 AND #2 OR #3	MA, RCT, Systematic Review, last 10 years, adolescent/adult	10,749
(#15) AND (glucose lowering agent)	MA, RCT, Systematic Review, last 10 years, adolescent/adult	61 (final yield, narrowed by intervention)

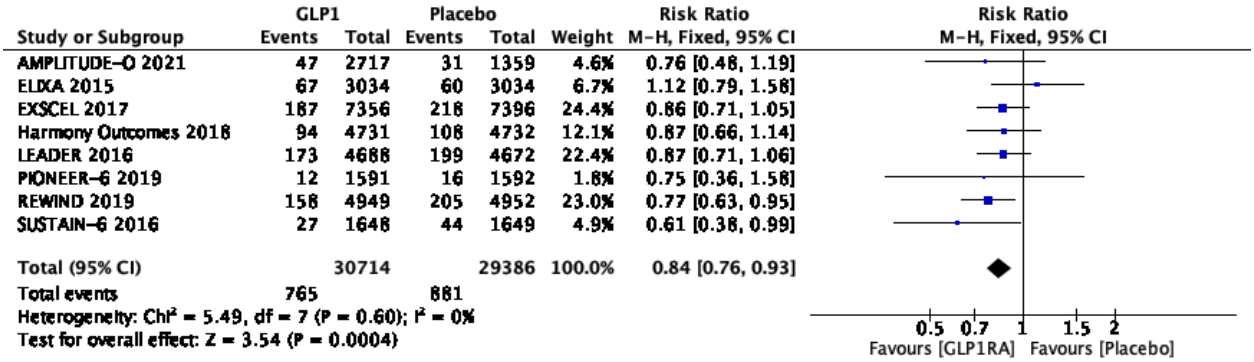
Q18.3. GRADE Evidence Profile and Forest Plots



DPP4-i versus Placebo, incidence of stroke



SGLT2i versus Placebo, incidence of stroke



GLP1-RA versus Placebo, incidence of stroke

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihyperglycemic medication	[Placebo]	Relative (95% CI)	Absolute (95% CI)	
Non-fatal or fatal stroke with GLP1 RA (follow-up: range 13 months to 5.4 years; assessed with: presence or absence)											
8	randomised trials	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	765/30714 (2.5%)	881/29386 (3.0%)	**RR 0.84** (0.76 to 0.93)	**5 fewer per 1,000** (from 7 fewer to 2 fewer)	⨁⨁◯◯ Low
Non-fatal or fatal stroke with SGLT2i (follow-up: range 3.1 years to 4.2 years; assessed with: presence or absence)											
3	randomised trials	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	584/18768 (3.1%)	387/13658 (2.8%)	**RR 1.06** (0.94 to 1.21)	**2 more per 1,000** (from 2 fewer to 6 more)	⨁⨁◯◯ Low
Non-fatal or fatal stroke with DPP4i (follow-up: range 18 months to 3 years; assessed with: presence or absence)											
4	randomised trials	not serious	not serious	serious[a]	not serious	publication bias strongly suspected[b]	423/21807 (1.9%)	419/21715 (1.9%)	**RR 1.01** (0.88 to 1.15)	**0 fewer per 1,000** (from 2 fewer to 3 more)	⨁⨁◯◯ Low

CI: confidence interval; **RR:** risk ratio

Summary of Findings: Fatal or Nonfatal Stroke

Intervention	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
DPP4i	4 RCT's N=43,522	1.01	0.88 to 1.15	Inconclusive	Low
Pioglitazone	1 RCT N= 5,238	0.81	0.65 to 1.06	Inconclusive	Low
SGLT2i	3 RCT's N=32,426	1.06	0.94 to 1.21	Inconclusive	Low
SGLT2i - Canvas	Canvas Trial 1 RCT, N=10,142	Number of participants per 1000 px years Canagliflozin 7.9 Placebo 9.6 Effect estimate: 0..67 (0.52-0.87)		Favours Canagliflozin	Low
GLP1RA	8 RCT's N=60,100	0.84	0.76 to 0.93	Favours GLP1 RA	Low

Q18.4. Recommendations from other groups

American Diabetes Association (ADA) Standards of Care 2024 (Diabetes Care, Volume 47, Supplement 1, January 2024): in people with type 2 diabetes and established ASCVD or indicators of high cardiovascular risk, an SGLT2 inhibitor or GLP-1 receptor agonist with proven cardiovascular benefit is recommended.

Q18.5. Research Gaps and Recommendations

Ongoing trials identified in clinicaltrials.gov:

- Pioglitazone and SGLT2 Inhibitors vs DPP-4 Inhibitors in Patients With Stroke (NCT04419337; recruiting; Chang Gung Memorial Hospital; last update 2023-03-30).

- Effects of Semaglutide on Intracranial Blood Flow and Brain-Barrier Permeability in Type 2 Diabetes (NCT05780905; not yet recruiting; University of Washington; last update 2023-03-23).

Research gaps:

- Direct, stroke-primary-endpoint trials (rather than MACE composite) in T2DM populations are needed.
- Local Philippine data on stroke incidence and antidiabetic-agent prescribing patterns among Filipino adults with T2DM and CVD.
- Cost-effectiveness studies of GLP-1 receptor agonists and SGLT2 inhibitors for stroke prevention in low- and middle-income settings.

Guideline Question 19. Should we use specific oral antidiabetic agents or injectable therapies among adults with T2DM and obesity?

Q19.1. Methods

A comprehensive search was conducted for this review from inception to January 6, 2024 following the PRISMA guidelines. The search was performed across PubMed/MEDLINE using the terms "type 2 diabetes mellitus," "obese," "oral anti-diabetic agents," "GLP-1 receptor agonists," "metformin," "SGLT2 inhibitors," "injectables," and variations thereof. A manual search of electronic databases and included studies from previous guidelines and studies was also performed to ensure that all eligible studies were captured. Randomized controlled trials published in English that included adult patients with type 2 diabetes mellitus and obesity were selected. The relevant outcomes identified were change in body weight and percentage weight loss with these agents. The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024.

Q19.2 GRADE Evidence Profile and Forest Plots

Q19.2A. Question: GLP1-1 receptor agonist compared to placebo for persons with type 2 diabetes and obesity

Setting: outpatient management of type 2 diabetes and obesity

Bibliography: Vosoughi, Kia & Roghani, Roham & Camilleri, Michael. (2022). Effects of GLP-1 agonists on proportion of weight loss in obesity with or without diabetes: Systematic review and meta-analysis. Obesity Medicine. 35. 100456. 10.1016/j.obmed.2022.100456.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP1-1 receptor agonist	placebo	Relative (95% CI)	Absolute (95% CI)		
>/= 5% weight loss (follow-up: mean 12 weeks; assessed with: proportion)												
22	randomised trials	not serious	not serious	not serious	serious[a]	none	6830/11957 (57.1%)	1727/5230 (33.0%)	**OR 5.03** (3.00 to 6.32)	**382 more per 1,000** (from 266 more to 427 more)	⨁⨁⨁◯ Moderate	CRITICAL
>/= 10% weight loss (follow-up: mean 12 weeks)												
22	randomised trials	not serious	not serious	not serious	serious[a,b]	none	3658/11629 (31.5%)	447/5054 (8.8%)	**OR 5.31** (3.90 to 7.22)	**252 more per 1,000** (from 186 more to 324 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. small sample size

b. heterogeneity

Q19.2B Question: GLP-1 receptor agonist compared to other anti diabetic agents for persons with type 2 diabetes and obesity

Setting: outpatient management of type 2 diabetes and obesity

Bibliography: Tsapas A, Karagiannis T, Kakotrichi P, Avgerinos I, Mantsiou C, Tousinas G, Manolopoulos A, Liakos A, Malandris K, Matthews DR, Bekiari E. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Obes Metab. 2021 Sep;23(9):2116-2124. doi: 10.1111/dom.14451. Epub 2021 Jun 15. PMID: 34047443.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLP-1 receptor agonist	other anti diabetic agents	Relative (95% CI)	Absolute (95% CI)		
Change in body weight with semaglutide (follow-up: median 26 weeks; assessed with: kg)												
407	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **3.8 kg lower** (4.46 lower to 3.14 higher)	⨁⨁⨁⨁ High	CRITICAL
Change in body weight with liraglutide (follow-up: median 26 weeks; assessed with: kg)												
407	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **2.37 kg lower** (2.75 lower to 1.98 lower)	⨁⨁⨁⨁ High	CRITICAL
Change in body weight with dulaglutide (follow-up: median 26 weeks; assessed with: kg)												
407	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **0.8 kg lower** (1.41 lower to 0.19 lower)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **MD:** mean difference

Q19.2C Question: Oral anti diabetic agents compared to placebo or lifestyle modification for persons with type 2 diabetes and obesity

Setting: outpatient management of diabetes and obesity

Bibliography: Author(s): Pu R, Shi D, Gan T, Ren X, Ba Y, Huo Y, Bai Y, Zheng T, Cheng N. Effects of metformin in obesity treatment in different populations: a meta-analysis. Ther Adv Endocrinol Metab. 2020 May 21;11:2042018820926000. doi: 10.1177/2042018820926000. PMID: 32499908; PMCID: PMC7243386.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral anti diabetic agents	placebo or lifestyle modification	Relative (95% CI)	Absolute (95% CI)		
Effect of Metformin on weight loss (follow-up: range 3 months to 32 months; assessed with: BMI)												
21	randomised trials	not serious	not serious	not serious	serious[a]	none	683	321	-	MD **0.98 kg/m2 lower** (1.25 lower to 0.72 lower)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. heterogeneous populations

Outcomes	Pooled outcomes (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	Quality of evidence (GRADE)
Weight	WMD -1.79 (-1.93 to -1.66)	98,398 (114 studies)	I^2 = 90% (P < 0.001)	⨁⨁⊖⊖[a]
Body Mass Index	WMD -0.71 (-0.94 to -0.47)	1,237 (15 studies)	I^2 = 38% (P < 0.001)	⨁⨁⨁⊖[b]

GRADE, Grading of Recommendations, Assessment, Development and Evaluation; WMD, weighted mean difference.

[a]Downgraded by two levels for severe statistical heterogeneity.

[b]Downgraded by one level for moderate statistical heterogeneity.

Adapted from: Cheong AJY, Teo YN, Teo YH, Syn NL, Ong HT, Ting AZH, Chia AZQ, Chong EY, Chan MY, Lee CH, Lim AYL, Kong WKF, Wong RCC, Chai P, Sia CH. SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials. Obesity (Silver Spring). 2022 Jan;30(1):117-128. doi: 10.1002/oby.23331. PMID: 34932882.

Q19.2C Question: Oral diabetic agents compared to other diabetic agents for type 2 diabetes and obesity

Setting: outpatient management of type 2 diabetes and obesity

Bibliography: Author(s): Tsapas 2021 Tsapas A, Karagiannis T, Kakotrichi P, Avgerinos I, Mantsiou C, Tousinas G, Manolopoulos A, Liakos A, Malandris K, Matthews DR, Bekiari E. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Obes Metab. 2021 Sep;23(9):2116-2124. doi: 10.1111/dom.14451. Epub 2021 Jun 15. PMID: 34047443.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral diabetic agents	other diabetic agents	Relative (95% CI)	Absolute (95% CI)		
Reduction in weight with empagliflozin (follow-up: median 26 weeks; assessed with: kg)												
116	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **0.92 kg lower** (2.41 lower to 1.43 lower)	⨁⨁⨁⨁ High	CRITICAL
Reduction in weight with canagliflozin (follow-up: median 26 weeks; assessed with: kg)												
116	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **1.83 kg lower** (2.42 lower to 1.23 lower)	⨁⨁⨁⨁ High	CRITICAL
Reduction in weight with dapagliflozin (follow-up: median 26 weeks; assessed with: kg)												
116	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **1.82 kg lower** (2.23 lower to 1.41 lower)	⨁⨁⨁⨁ High	CRITICAL
Reduction in weight with metformin (follow-up: median 26 weeks; assessed with: kg)												
116	randomised trials	not serious	not serious	not serious	not serious	none			-	MD **0.62 kg lower** (1 lower to 0.25 lower)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **MD:** mean difference

Annex: Forest Plots

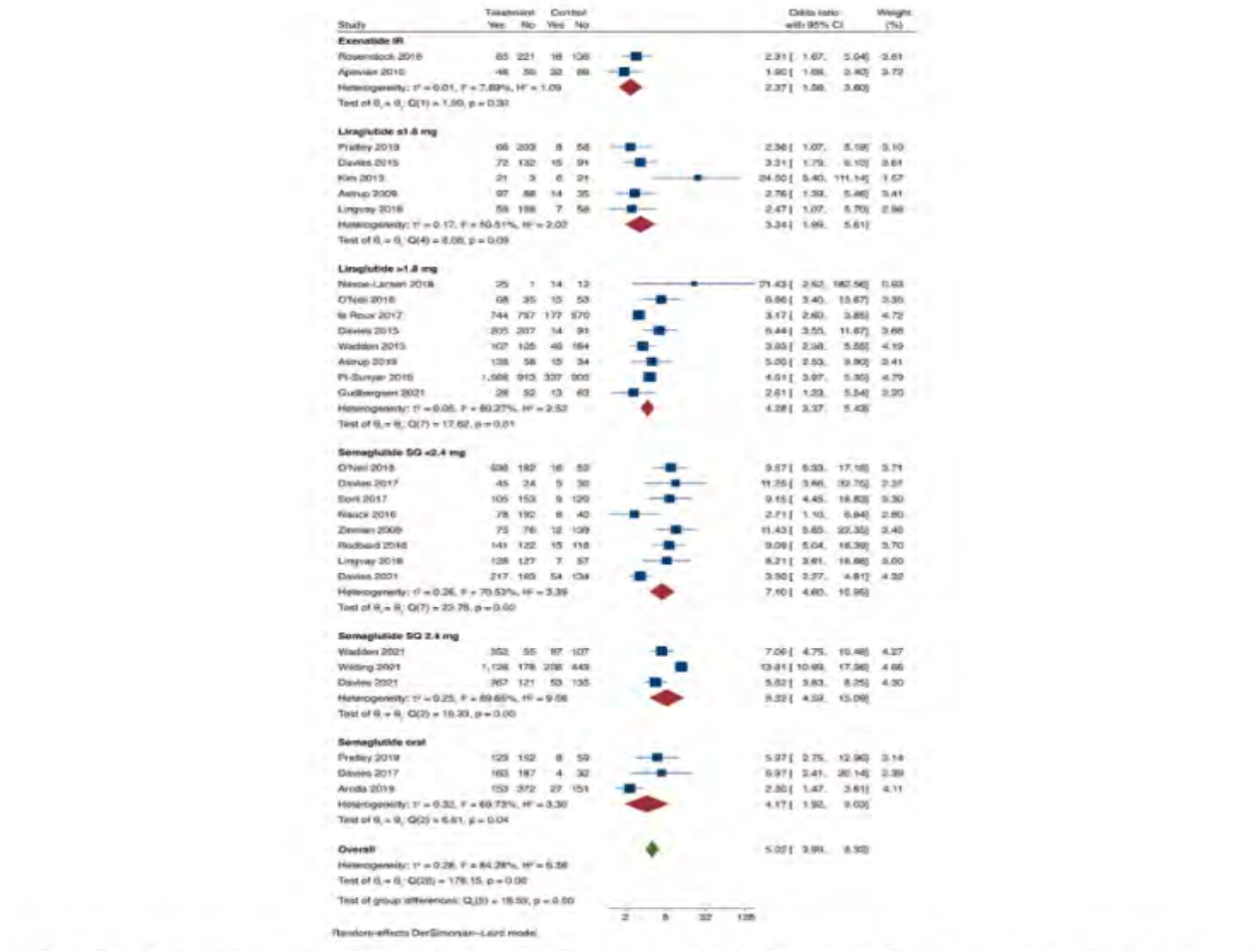


Fig 1. Forest plot of GLP-1 agonists showing proportion of participants achieving > 5% weight loss
Adapted from Vosoughi, Kia & Roghani, Roham & Camilleri, Michael. (2022). Effects of GLP-1 agonists on proportion of weight loss in obesity with or without diabetes: Systematic review and meta-analysis. Obesity Medicine. 35. 100456. 10.1016/j.obmed.2022.100456.

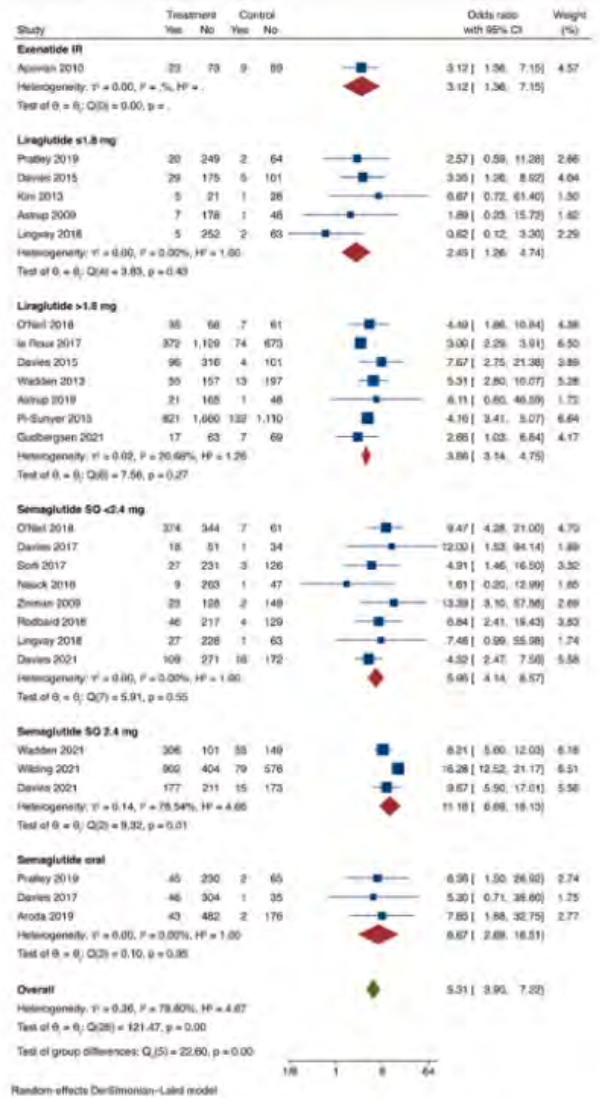


Fig 2. Forest plot of GLP-1 agonists showing proportion of participants achieving > 10% weight loss
Adapted from Vosoughi, Kia & Roghani, Roham & Camilleri, Michael. (2022). Effects of GLP-1 agonists on proportion of weight loss in obesity with or without diabetes: Systematic review and meta-analysis. Obesity Medicine. 35. 100456. 10.1016/j.obmed.2022.100456.

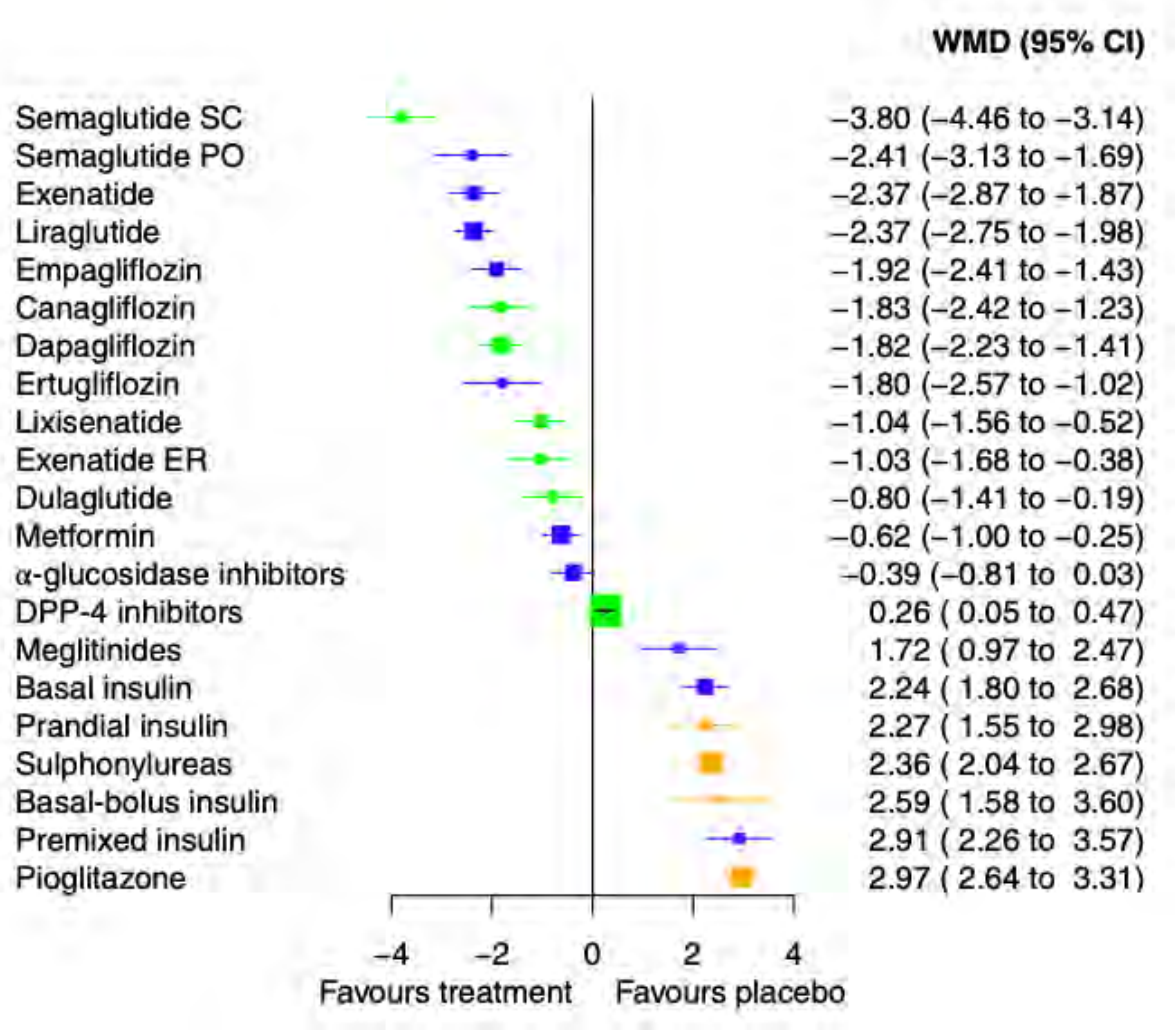


Figure 3: Network Meta-analysis of antidiabetic agents and reduction in weight (kg). Adapted from Tsapas A, Karagiannis T, Kakotrichi P, Avgerinos I, Mantsiou C, Tousinas G, Manolopoulos A, Liakos A, Malandris K, Matthews DR, Bekiari E. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Obes Metab. 2021 Sep;23(9):2116-2124. doi: 10.1111/dom.14451. Epub 2021 Jun 15. PMID: 34047443.

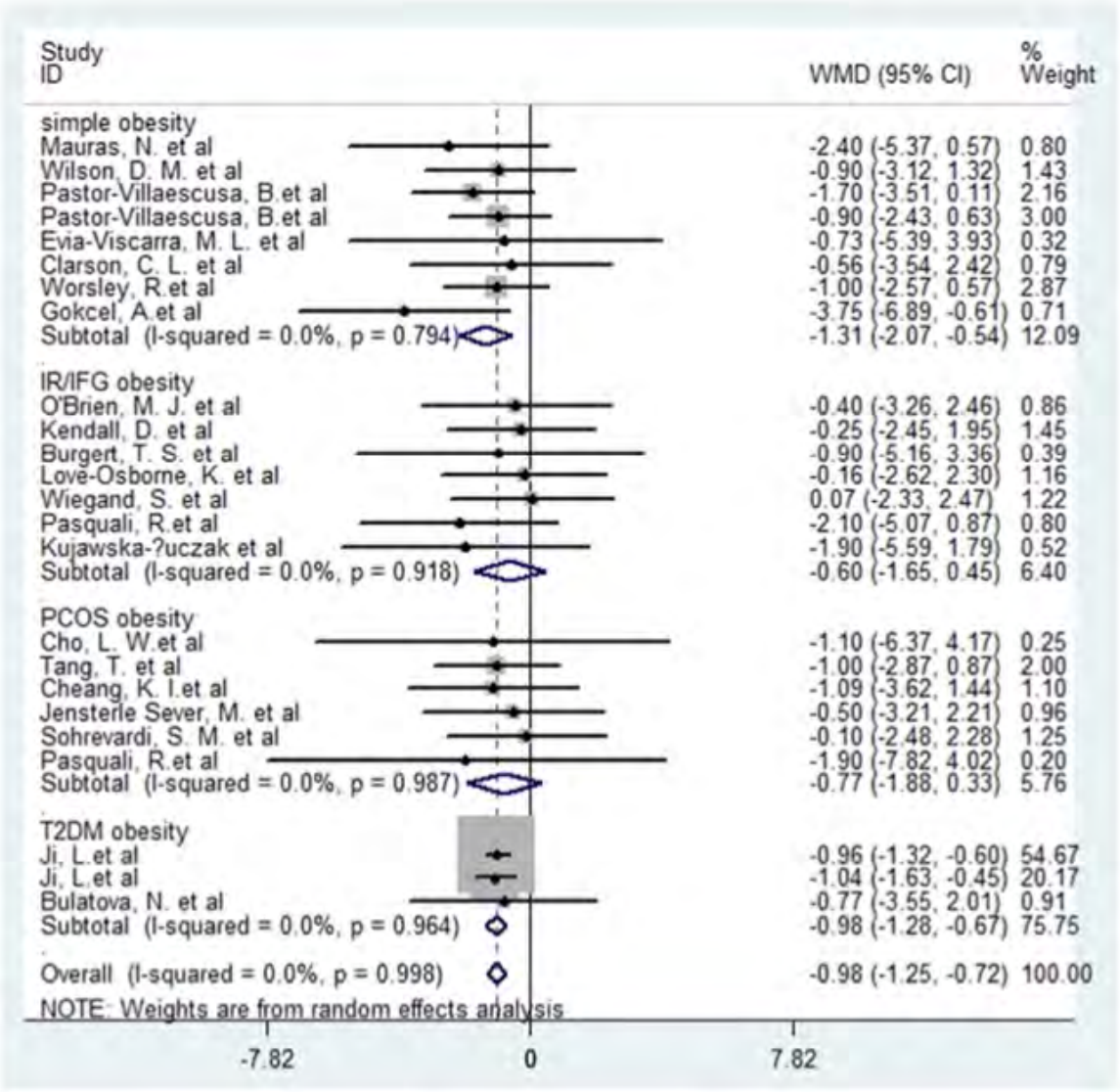


Fig 4. Meta-analysis of metformin treatment and effect on BMI reduction. Adapted from Pu et al 2020 (Metformin) Pu R, Shi D, Gan T, Ren X, Ba Y, Huo Y, Bai Y, Zheng T, Cheng N. Effects of metformin in obesity treatment in different populations: a meta-analysis. Ther Adv Endocrinol Metab. 2020 May 21;11:2042018820926000. doi: 10.1177/2042018820926000. PMID: 32499908; PMCID: PMC7243386.

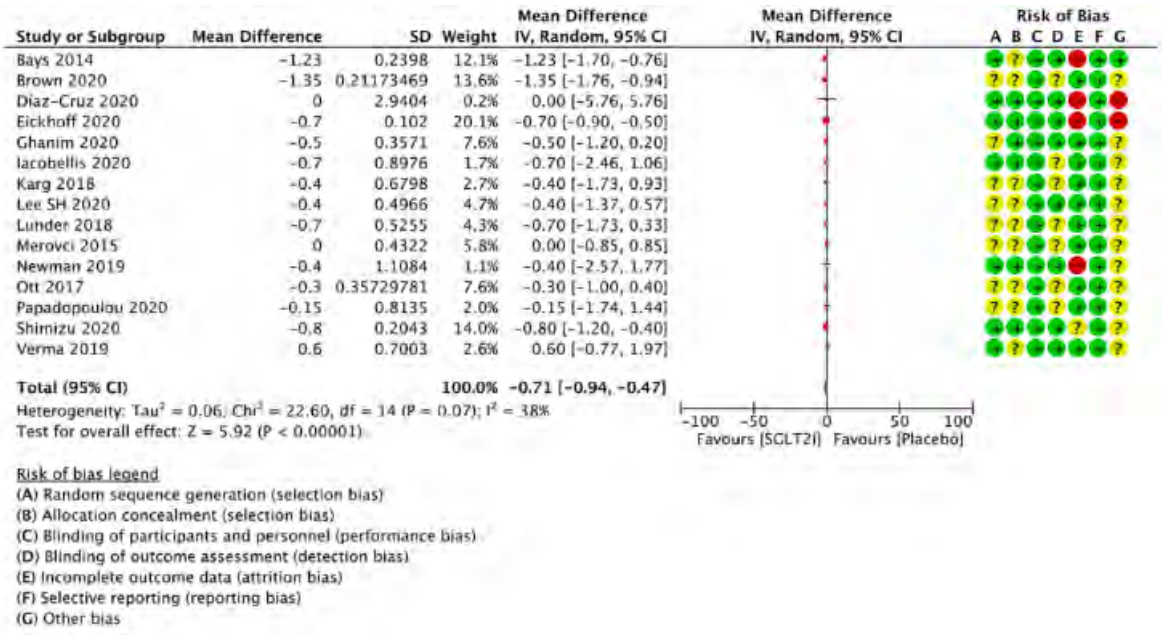


Fig 5. Pooled BMI Outcomes for SGLT2i. Adapted from Cheong, AJY, Teo, YN, Teo, YH, et al. SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials. Obesity (Silver Spring). 2022; 30: 117–128. doi:10.1002/oby.23331

Q19.3. Recommendations from other groups

Group / Agency	Recommendation	Strength / Certainty
American Diabetes Association 2023	When choosing glucose-lowering medications for people with overweight and obesity, consider the medication's effect on weight. Obesity pharmacotherapy is effective as an adjunct to nutrition, physical activity, and behavioral counseling for selected people with type 2 diabetes…	B (supported evidence from well-conducted cohort studies)
American Association of Clinical Endocrinologists 2023	Maintain optimal weight. Consider weight loss medications for BMI > 25 to 27 kg/m^2.	Strong

Q19.4. Research Gaps and Recommendations

- There is a need for more local data on the impact of GLP-1 receptor agonists and other oral agents on the degree of weight loss observed in Filipino patients.
- Cost-effectiveness studies of these agents on the Filipino population would also be ideal.

Guideline Question 20. Should we recommend specific oral antidiabetic agents or injectable therapies among adults with T2DM and chronic kidney disease (CKD) or end-stage renal disease (ESRD) on dialysis?

Q20.1. Methods and Search Strategy

A systematic search was conducted through MEDLINE via PubMed, the Cochrane Library, and HERDIN Plus, using a combination of medical subject headings (MeSH) and keywords for "type 2 diabetes mellitus," "chronic kidney disease," "end-stage renal disease," "dialysis," and the glucose-lowering agents of interest (oral antidiabetic agents and injectable therapies). Only articles published in the English language were included. Studies were eligible if they reported the outcomes of interest for the management of type 2 diabetes mellitus among adults with CKD or ESRD on dialysis. The search identified one clinical practice guideline (KDIGO 2022), which was appraised using the AGREE-II instrument; one meta-analysis (Bae 2019); two retrospective cohort studies (Hsiao 2016 and Ou 2021); and one randomized controlled trial (Singhsakul 2019). The references of included studies were also hand-searched to identify additional evidence. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The risk of bias of included studies was appraised using the appropriate tools for each study design.

Q20.2 Risk of Bias Assessment

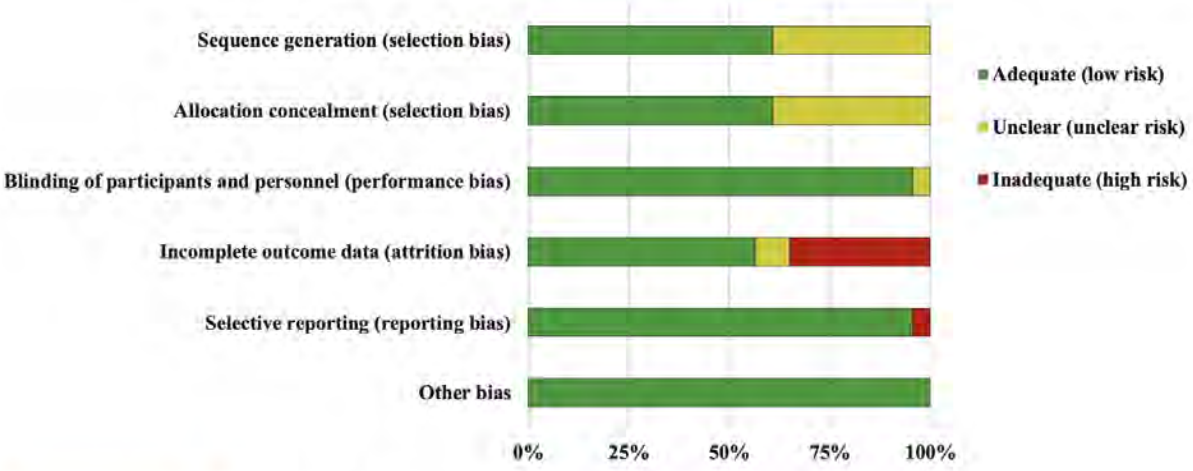
Supplemental Table S2. Risk of Bias Assessment for Individual Studies

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
Cornel et al. (2016) [12][a]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Green et al. (2015) [14][b]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Groop et al. (2013) [23]	Unclear	Unclear	Adequate	Unclear	Inadequate	Pooled analysis of four RCTs ([22-25])
Del Prato et al. (2011) [25]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Haak et al. (2012) [27]	Unclear	Unclear	Adequate	Inadequate	Adequate	None
Owens et al. (2011) [26]	Unclear	Unclear	Adequate	Inadequate	Adequate	None
Taskinen et al. (2011) [24]	Unclear	Unclear	Adequate	Inadequate	Adequate	None
Groop et al. (2017) [15]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Mosenzon et al. (2017) [11]	Adequate	Adequate	Adequate	Inadequate	Adequate	None
White et al. (2013) [39]	Unclear	Unclear	Adequate	Adequate	Adequate	None
Yoon et al. (2017) [40]	Adequate	Adequate	Adequate	Adequate	Adequate	None
DeFronzo et al. (2015) [30]	Adequate	Adequate	Adequate	Inadequate	Adequate	None
Lavalle-Gonzalez et al. (2013) [31]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Lewin et al. (2015) [32]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Nakamura et al. (2014) [38]	Unclear	Unclear	Unclear	Inadequate	Adequate	None
Mori et al. (2014) [28]	Unclear	Unclear	Adequate	Adequate	Adequate	Open-label RCT
Nomoto et al. (2016) [36]	Adequate	Unclear	Adequate	Adequate	Adequate	None
Nomoto et al. (2017) [29]	Unclear	Adequate	Adequate	Inadequate	Adequate	None
Roden et al. (2013) [41]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Schernthaner et al. (2013) [33]	Adequate	Adequate	Adequate	Inadequate	Adequate	None
Takihata et al. (2013) [35]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Tonneijck et al. (2016) [34]	Adequate	Adequate	Adequate	Adequate	Adequate	None
Zografou et al. (2015) [37]	Unclear	Unclear	Adequate	Unclear	Adequate	None

RCT, randomized controlled trial.
[a,b]These publications reported different renal outcomes from the same study.

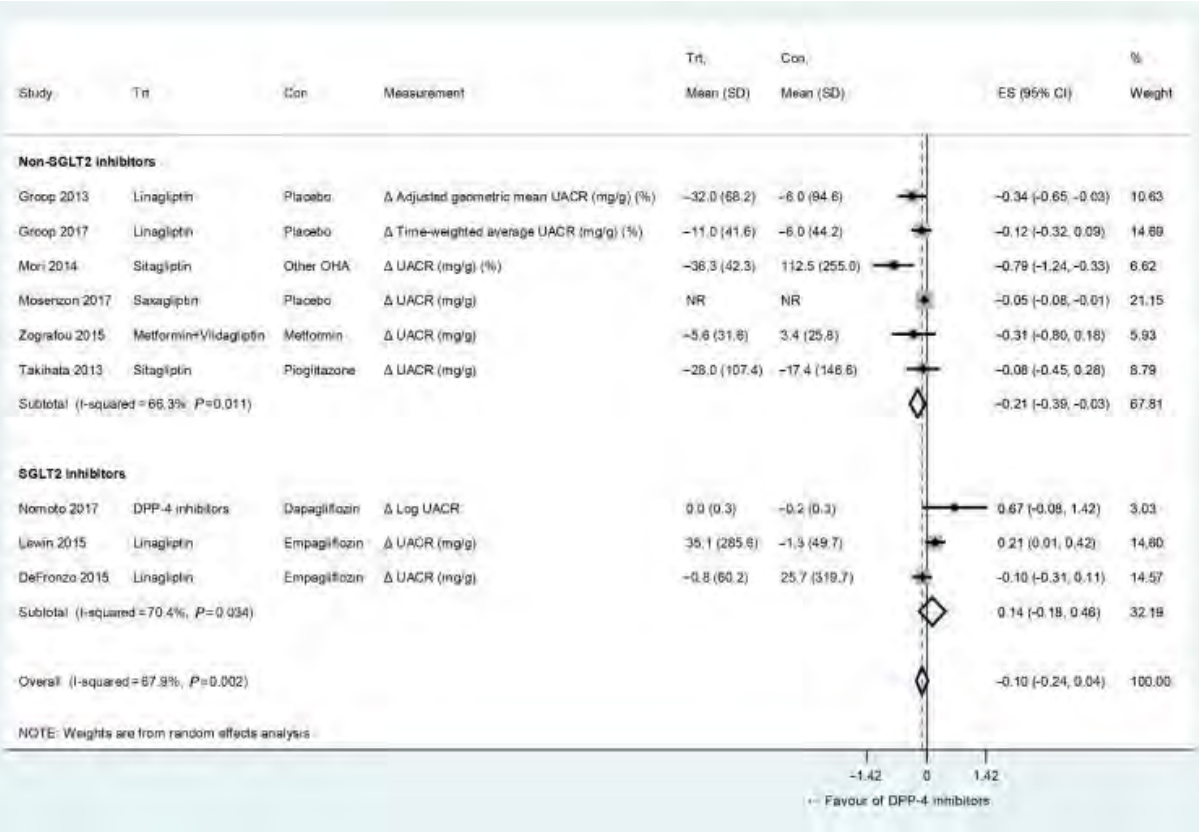
Bae JH, et al. Endocrinol Metab. 2019;34:80-92

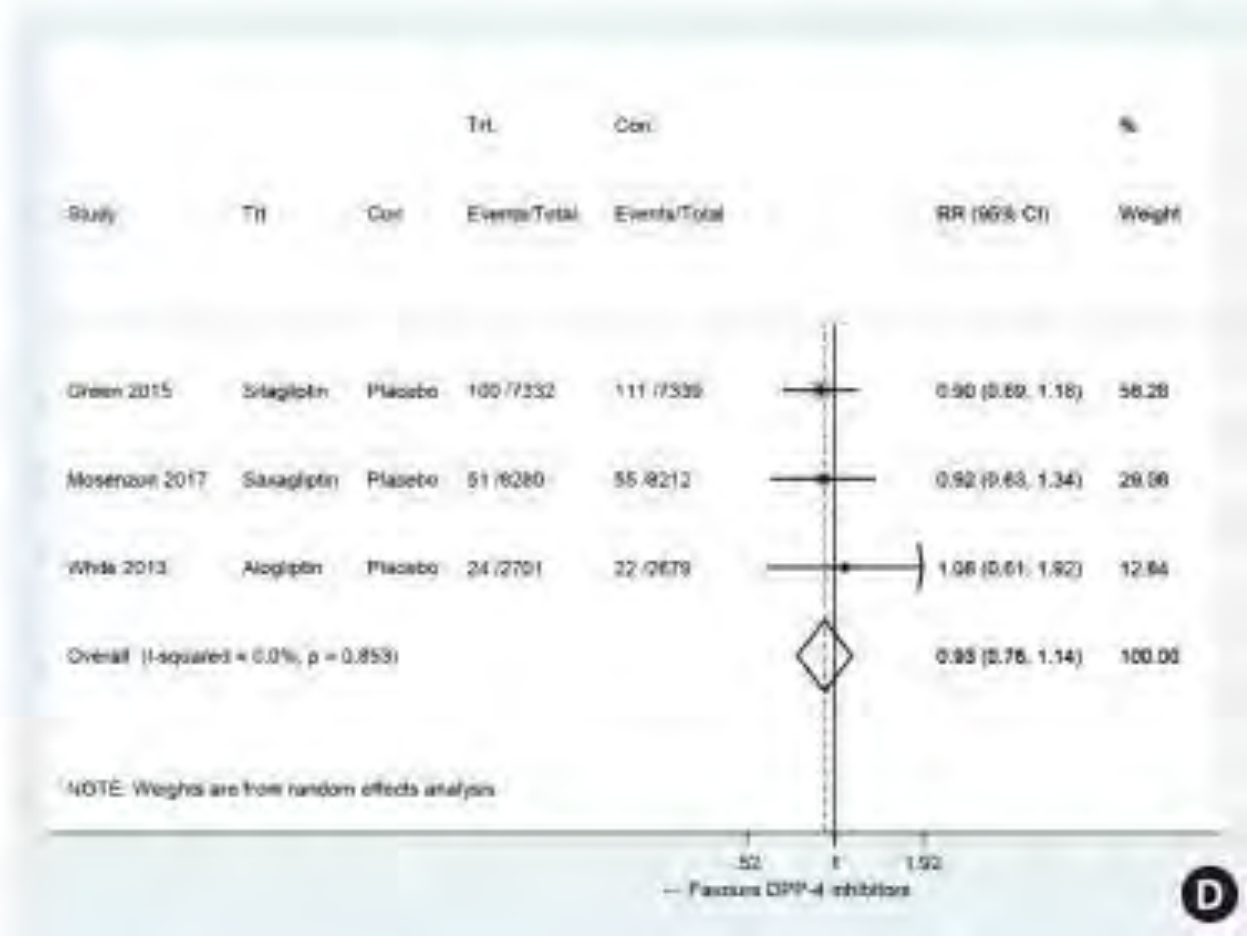
Study Quality and ROB Assessment of Meta-analysis of DPP4-i on Renal Outcomes



Supplemental Fig. S1. Study quality and risk of bias assessment.

Q20.3 GRADE Evidence Profile and Forest Plots
Meta-analysis of DPP4-i on change in UACR





Meta-analysis of DPP4-i on progression to end-stage renal disease

Antidiabetes medication compared to no antidiabetes medication for type 2 diabetes with endstage renal disease on dialysis

Bibliography:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no antidiabetes medication	With antidiabetes medication	Relative effect (95% CI)	Risk with no antidiabetes medication	Risk difference with antidiabetes medication
All-cause mortality (follow-up: mean 5 years)											
3868 (2 non-randomised studies)	serious[1,2,a]	serious[1,2,b]	serious[1,2,c]	serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient[a]	⨁◯◯◯ Very low	300/554 (54.2%)	1145/3314 (34.6%)	not estimable	Low	
										0 per 1,000	

CI: confidence interval; **HR:** hazard ratio

Explanations

a. Recruitment was through a national health insurance database including both hemodialysis and peritoneal dialysis patients, possibly causing differences in glycemic control and the need for anti-diabetes medication. Both studies defined use of anti-diabetes drugs as at least 90 days per year after initiation of dialysis, which may have been affected by confounders (e.g. the need to withhold medication due to recurrent hypoglycemia).
b. Causes of death were not specified, and these may have been markedly different in treated versus non-treated groups. Some baseline characteristics, such as the age, presence of retinopathy, use of lipid-lowering drugs and RAAS blockers) were also different between the groups.
c. There are differences in interventions (dialysis method).

References

1.Hsiao Po-Jen, Wu Kun-Lin,Chiu Szu-Han,Chan Jenq-Shyong,Lin Yu-Feng,Wu Chung-Ze,Wu Chia-Chao,Kao Sen Yeong,Fang Te-Chao,Lin Shih-Hua,Chen Jin-Shuen. Impact of the use of anti-diabetic drugs on survival of diabetic dialysis patients: a 5-year retrospective cohort study in Taiwan. Clin Exp Nephrol. 2016.
2.Ou Shih-Shiang, Chen Hsin-Yu,Fang Nai-Wen,Yin Chun-Nao,Chen Chien-Liang,Chen Jin-Shuen. Effect of anti-diabetic drugs in dialysis patients with diabetes: a nationwide retrospective cohort study. Cardiovasc Diabetol. 2021.

Q20.4. Recommendations from other groups

Recommendations from other groups

Group or Agency	Recommendation
Italian Diabetes Society and Italian Society of Nephrology, 2019 (Pugliese G et al. Nutr Metab Cardiovasc Dis. 2019)	Insulin treatment (human and analog preparations) is safe in all eGFR categories, although it may be necessary to reduce dosage in patients with advanced renal dysfunction. Use of insulin secretagogues should be limited because of increased risk of hypoglycemia. Metformin: contraindicated in patients with eGFR <30 mL/min/1.73 m^2; used at reduced dose (~50%) or should not be started in individuals with eGFR 30–45 mL/min/1.73 m^2. Cautious use of pioglitazone in advanced renal dysfunction due to increased fluid retention, anemia and bone disease. Acarbose should be avoided in individuals with eGFR <30 mL/min/1.73 m^2. DPP-4 inhibitors can be used in patients with impaired renal function (with some requiring dose adjustment). GLP-1 receptor agonists may be used up to eGFR 30 mL/min/1.73 m^2 or 15 mL/min/1.73 m^2. SGLT2 inhibitors can be used up to eGFR 45 mL/min/1.73 m^2.
Korean Diabetes Association and Korean Society of Nephrology, 2020 (Hur KY et al. Diabetes Metab J. 2020;44:3–10)	Metformin can be used safely when eGFR ≥45 mL/min/1.73 m^2. Metformin should not be started if eGFR is between 30 and 44 mL/min/1.73 m^2; if in use, daily dose of ≤1000 mg is recommended. Metformin is contraindicated when eGFR <30 mL/min/1.73 m^2.
Croatian Guidelines for the Diagnosis and Treatment of NAFLD (Jukić LV et al. Acta Clin Croat. 2021;60[Suppl 1]:36–52)	Although metformin is in the first line of treatment for diabetes mellitus, owing to the beneficial effect of other drugs that affect insulin resistance (pioglitazone, liraglutide) on histological changes in the liver of NAFLD patients, they should be considered when choosing therapy for patients with NASH.

Guideline Question 21.

Should we recommend specific oral antidiabetic agents or injectables among adults with T2DM and cirrhosis or chronic liver disease (CLD)?

Q21.1. Methods and Search Strategy

A systematic search was conducted through MEDLINE via PubMed, the Cochrane Library, and HERDIN Plus, using a combination of medical subject headings (MeSH) and keywords that paired the population terms for the condition (e.g., "type 2 diabetes mellitus," "T2DM") with terms for the comorbidity (e.g., "cirrhosis," "chronic liver disease," "hepatic impairment," "liver disease") and, where applicable, terms for the interventions of interest (oral antidiabetic agents and injectable therapies). Publication-type filters were applied for clinical trials, randomized controlled trials, systematic reviews, and meta-analyses, and only articles published in the English language were included. Studies were eligible if they reported the outcomes of interest for the management of type 2 diabetes mellitus among adults with cirrhosis or chronic liver disease (CLD), namely glycemic control, hepatic decompensation, hypoglycemia, organ toxicity, and other relevant safety outcomes. The search strategy for clinical practice guidelines (CPGs) was conducted first; where this did not yield eligible publications, a search for indirect evidence on the management of type 2 diabetes mellitus and chronic liver disease was undertaken. Handsearching of the reference lists of included studies and relevant guidelines supplemented the electronic search. The evidence review was subsequently updated to include relevant guidelines, systematic reviews, and individual studies addressing the clinical questions, covering publications from database inception through October 2024. The risk of bias of included studies was appraised using the appropriate tools for each study design (e.g., the Cochrane Risk of Bias tool for randomized controlled trials and AMSTAR-2 for systematic reviews and meta-analyses).

Q21.2. Recommendations from other groups

Group or Agency	Recommendation
French Association for the Study of the Liver (AFEF) and the Francophone Diabetes Society (SFD): Joint Statement (Boursier J et al. Diabetes Metab. 2021;47:101272)	Pioglitazone and GLP-1RAs are recommended for persons with T2D and biopsy-proven NASH (Grade A, high strength of evidence, BEL 1). Clinicians must consider treating diabetes with pioglitazone and/or GLP-1RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests (Grade A, high strength of evidence, BEL 1). Due to the lack of evidence of efficacy, metformin, acarbose, DPP-4 inhibitors and insulin are not recommended for the treatment of steatohepatitis (no benefit on hepatocyte necrosis or inflammation) but may be continued as needed for the treatment of hyperglycemia in persons with T2D and NAFLD or NASH (Grade B, high strength of evidence, BEL 1, downgraded due to the use of surrogate outcome measures in many of the studies).
Croatian Guidelines for the Diagnosis and Treatment of NAFLD (Jukić LV et al. Acta Clin Croat. 2021;60[Suppl 1]:36–52)	Although metformin is in the first line of treatment for diabetes mellitus, owing to the beneficial effect of other drugs that affect insulin resistance (pioglitazone, liraglutide) on histological changes in the liver of NAFLD patients, they should be considered when choosing therapy for patients with NASH.