

Approach to Lower the Cardiovascular Risk of Individuals with Type 2 Diabetes Mellitus: Evidence-based Consensus Statements of the Philippine Heart Association and Philippine Society of Endocrinology Diabetes and Metabolism

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Abstract

Diabetes remains as the 6th leading cause of death in the Philippines, with more than 33,000 deaths in 2016. Given this alarming prevalence, it is imperative that this public health concern be prioritized in the country and to answer such concern, a group of cardiologists and endocrinologists who are in active clinical practice and research, formed a technical working group composed of five members. Their primary objective was to develop an evidence-based consensus document for Filipino healthcare practitioners and people in the academe that would serve as a guideline on the approach to lower the CV risk of individuals with T2DM. The TWG agreed on focusing with the pharmacological approach to treatment of lowering CV risk for T2DM patients using the ADAPTE model which is a more systematic approach to guideline adaptation. The recommendations were developed using the ADAPTE framework appraising all international practice guidelines and recommendations through to 2013. The technical working group's overall objective of guideline adaptation is to take advantage of the existing guidelines to enhance the efficient production and use of high-quality adapted guidelines specially in the local Philippine setting. Each of these articles was then assessed using the AGREE instrument. Based on the key questions that the technical working group had identified regarding the approach to lower the risk of individuals with type 2 diabetes, 9 recommendations concerning the antidiabetic drug of choice for persons with type 2 diabetes with or without established ASCVD and management of type 2 diabetes mellitus patients with hypertension and dyslipidemia were drafted and are presented in this report.

Keywords: Type 2 diabetes mellitus, cardiovascular risk, treatment recommendations

Introduction

Type 2 diabetes mellitus (T2DM) is a serious metabolic disease defined by uncontrolled elevation of blood glucose levels (hyperglycemia) stemming from certain conditions such as insulin resistance and relative insulin deficiency.¹ It is associated with a wide range of macrovascular complications such as cardiovascular diseases (CVD) (e.g., coronary artery disease (CAD) and stroke) and peripheral vascular diseases (PVD), both of which would result in dreadful outcomes if proper glycemic control is not achieved.² According to the International Diabetes Foundation (IDF), 463 million

people are living with diabetes in 2019.³ Recent data from the same group revealed that approximately 5 million people worldwide died from diabetes, and majority were because of cardiovascular complications.⁴

Cardiovascular events, such as those aforementioned CVD above, commonly occur at a younger age in patients with diabetes.⁴ According to systematic reviews, there is a higher relative risk for developing CVD in patients with diabetes; an even higher risk is noted among women and those of younger age.⁵ The prevalence and severity of diabetes and the CVD complications entailed have transformed this situation into a huge clinical burden that needs to be addressed quickly.⁶

Although diabetes management focuses mainly on blood glucose control, a greater decrease in morbidity and mortality is possible through proper cardiovascular (CV) risk management.⁷ However, ways of protecting diabetic patients from an increase in CVD risk still

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remains unestablished. This led to CV safety concerns of various glucose-lowering medications and effects on major CV events and outcomes such as non-fatal myocardial infarction, heart failure, and CV-related mortality.⁶ A number of cardiovascular outcome trials (CVOTs) were done comparing CV safety profiles of various anti-hyperglycemic agents (AHAs) and found out that some of these medications can lower CVD risk.⁶ Moreover, the IDF has stated that CVD risk of diabetic individuals can decrease through proper control of blood pressure and blood glucose.⁴ Through these efforts, a paradigm shift emphasizing a holistic approach involving proper CV risk and blood glucose management began.^{6,7}

Burden of diabetes in the Philippines

Recent IDF data ranked Philippines at 5th highest among Western Pacific countries in terms of number of diabetic cases, with more than 3 million individuals afflicted with the disease.⁴ Diabetes remains as the 6th leading cause of death in the Philippines, with more than 33,000 deaths in 2016.⁸ Given this alarming prevalence, it is imperative that this public health concern be prioritized in the country.

Methodology

In July 2018, a group of cardiologists and endocrinologists who are in active clinical practice and research, formed a technical working group (TWG) composed of five members (Sison J, Jimeno C, Matawaran B, Caole-Ang I, Gonzales E). The primary objective was to develop an evidence-based consensus document for Filipino healthcare practitioners and people in the academe that would serve as a guideline on the approach to lower the CV risk of individuals with T2DM. This assembly of experts mutually identified how the last updated guidelines were created before the advent of new therapeutic options with clinical evidence showing benefit on lowering CV risk and mortality beyond improvement of glycemic control. Because of this evident issue, the TWG proposed to develop consensus recommendations to provide guidance on diabetes management to improve patient outcomes in the Philippine setting.

The TWG agreed on focusing with the pharmacological approach to treatment of lowering CV risk for T2DM patients using the ADAPTE model which is a more systematic approach to guideline adaptation. Furthermore, the proposed advocacies of this paper are the following: 1) early glycemic control, 2) agreement with early combination therapy and 3) to introduce the concept of individualization with insertion of concept of CV risk of an individual. The intended target audience are all healthcare practitioners managing patients with Type 2 Diabetes Mellitus (T2DM) that includes general physicians, general internists, medical students, and trainees.

The first TWG meeting was convened in January 2019 to discuss the timelines and finalize the working title of the paper, the objectives, and the methodology to be

utilized in the development of this consensus paper. At this time, a general outline in the development of the consensus statements was successfully discussed which includes the following: to define the scope of the consensus statements, to assign each member of the TWG and to develop key questions based on the scope, to identify the search criteria, and search strategy, appraise the guideline quality, grade the evidence, and synthesize the evidence. The TWG decided to use the AGREE 2 instrument (Appraisal of Guidelines for Research and Evaluation II) in appraising the guidelines. The agreed methodology to be used is a combination of ADAPTE process and the adaptation of the existing Philippine practice guidelines. The ADAPTE process will be used for the recommendations about antidiabetic medications while adaptation of existing Philippine guidelines will be applied for the recommendations for hypertension and dyslipidemia. In developing the consensus statements, the TWG members will summarize the recommendations and supporting evidence from the guidelines appraised to address each key question. In achieving a consensus recommendation, the TWG decided on using the Delphi method. In this part, all members of the TWG will vote anonymously using a 5-point Likert scale (Strongly agree, Agree, Neither agree nor disagree, Disagree, Strongly disagree). Afterwards, they will define or set the acceptance value for each recommendation statements created. During the second meeting in February 2019, discussions were made to agree and finalize the inclusion and exclusion criteria as basis for the literature search strategy and the process to follow on literature search. At this time, the TWG initiated the creation of clinical questions, which is an important step in the ADAPTE process. The third meeting on August 2019, was organized to present the studies gathered by the TWG and discuss the next steps on the development of consensus paper which includes the appraisal of guidelines using the AGREE 2 instrument. The TWG also decided to assign a clinical question for each member. These clinical questions will be answered using the accepted guidelines as reference/evidence.

Methods used for consensus recommendations development

In this paper, the ADAPTE process for the adaptation of the guidelines was utilized in preparation for the development of consensus recommendations. The ADAPTE process offers a systematic approach of guideline adaptation specially when considering an endorsement or modification of existing guidelines produced in one setting for implementation into a different context or setting while keeping the evidence-based principles intact.^{9,10}

The TWG's overall objective of guideline adaptation is to take advantage of the existing guidelines to enhance the efficient production and use of high-quality adapted guidelines specially in the local Philippine setting. The agreed methodology for consensus recommendation development is a combination of ADAPTE process for the development of antidiabetic medications consensus

recommendations and adaptation of existing Philippine practice guidelines for HPN and dyslipidemia consensus recommendations. The three main phases of the ADAPTE process consists of the set-up phase, adaptation phase and the finalization phase.^{9,10}

ADAPTE process: Set-up phase

The set-up phase is the preparatory stage for the ADAPTE process which consisted of the following steps: (1) check whether the adaptation is feasible, (2) establish an organized committee, (3) select a guideline topic, (4) identify necessary resource and skills, (5) complete tasks for the set-up phase, and (6) write an adaptation plan.^{9,10} In this stage, the TWG set-up preparations for the ADAPTE process by organizing assembly meetings to discuss the general outline of the development of the consensus statements. This also includes discussions on the main focus of the consensus paper and the development of clinical questions and educating the members about the literature search strategies, workplan, next steps and tools to be used.

ADAPTE process: Adaptation phase

The adaptation phase is the stage where specific clinical questions are determined and searching of the guidelines are initiated. In addition, this process also includes assessing the guideline quality and applicability that fits the decision making and adaptation of the guidelines.⁹

Identifying the clinical questions

The development of structured clinical questions is a significant part of adaptation process which will help ensure that the final adapted guidelines corresponds to the main scope of the consensus paper.⁹ In this phase, the TWG were able to finalize the clinical questions through the PIPHOH approach (**P**opulation concerned and characteristics of the disease or condition, **I**ntervention(s) (or diagnostic test, etc.) of interest, **P**rofessionals to whom the guideline will be targeted, **E**xpected **O**utcomes including patient outcomes (e.g., improved disease-free survival, improved quality of life); system outcomes (e.g., decrease in practice variation); and/or public health outcomes (e.g., a decrease in cervical cancer incidence) and **H**ealthcare setting and context in which the guideline is to be implemented) in order to cover all relevant aspects. In this phase, the TWG identified the following relevant contexts using the PIPHOH approach:

- P** - Adult patients with T2DM
- I** - ADAPTE and adaptation of existing guidelines
- P** - All healthcare professionals
- O** - Decrease CV risk outcomes, and
- H** - Outpatient setting.

With this PIPHOH approach, the TWG defined the clinical questions stated below:

Antidiabetic medications:

1. What is the first-line antidiabetic drug for individuals with T2DM?
2. For patients with established atherosclerotic cardiovascular disease (ASCVD), what are the antidiabetic drugs of choice?
3. For patients without established ASCVD, what are the antidiabetic drugs of choice?
4. What antidiabetic drugs are not recommended because of the increase in CV risk?

Hypertension:

1. What is the definition of hypertension?
2. What is the threshold for pharmacological treatment?
3. What is the target blood pressure to lower the CV risk?
4. What antihypertensive medications are recommended to lower the CV risk?

Dyslipidemia:

1. Should statins be given for primary prevention of cardiovascular outcomes among persons with diabetes mellitus? What are the target levels for prevention of cardiovascular diseases?
2. Should fibrates be added to statins for prevention of cardiovascular diseases among persons with diabetes mellitus?

Literature sources and search strategy

This consensus paper comprised of three major aspects of CV risk reduction: (1) antidiabetic therapy, (2) hypertension (HPN) and, (3) dyslipidemia. A literature search for recent existing evidence was performed using the MEDLINE (by PubMed). The literature search was done in PubMed using the following search terms: "Diabetes Mellitus, Type 2" and "hypoglycemic agents", paired with "guideline", "consensus" or "recommendations". The search criteria for publication date were limited to year 2013 onwards.

Inclusion and exclusion criteria

The TWG utilized the following inclusion criteria as search strategy: (a) guideline must be about diabetes in the outpatient setting, (b) must be published (in text or online), (c) written in English or with English translation, (d) published in the last five years (2013 onwards) to ensure that evidence base is current, in the case that the guideline has been updated, then both the original guideline and the updated one will be retrieved and reviewed, (e) 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), and (f) only national and/or international guidelines will be included.

The exclusion criteria for the literature search are the following: (a) for duplicate guidelines (e.g., update or

revision of previous guidelines) the reviewers will only consider the most current, (b) guidelines commissioned by or published by Health Maintenance Organizations (HMOs) will not be included since the intent and use of these guidelines is different from the intended users of this guideline, (c) in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input, (d) 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 guidelines

After the literature search was completed, the TWG was able to search for 333 articles; of which, 274 were excluded based on the above-mentioned exclusion criteria. A total of 59 articles were considered for review. The TWG later decided to include thirteen additional Asian guidelines, the most recent 2019 European Society of Cardiology (ESC) guidelines about diabetes, and the Heart Failure Council of Thailand (HFCT): 2019 Heart Failure Guideline. After a comprehensive review of these articles, the TWG has decided to include only 19 articles (see Appendix 1). They were individually tasked to appraise these guidelines using the AGREE II tool. The AGREE II scores were compared taking into considerations the scope, purpose and other study characteristics (see Appendix 2).

The following articles were removed due to poor methodologic quality especially with regards to the rigor of development, as well as other issues that are unique to that guideline:

1. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017
2. Treatment of Type 2 Diabetes: From "Guidelines" to "Position Statements" and Back: Recommendations of the Israel National Diabetes Council
3. A Proposed India-Specific Algorithm for Management of Type 2 Diabetes
4. Consensus on "Basal insulin in the management of Type 2 Diabetes: Which, When and How?" - dealt only on insulin therapy
5. A Consensus Statement for the clinical use of the renal sodium-glucose co-transporter-2 inhibitor Dapagliflozin in patients with type 2 Diabetes Mellitus- poor over-all quality, no editorial independence.

An overall total of fourteen (14) articles were left and were used as the basis for these current recommendations. These are the 14 guidelines that were included and adapted for the creation of local guidelines for antidiabetic medications among patients with T2DM.

1. Garber AJ, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management

Algorithm - 2019 Executive Summary. *Endocr Pract* 2019; 25:69-100. Erratum in: *Endocr Pract* 2019; 25:204. [AACE, ACE]

2. Malaysian Endocrine & Metabolic Society, Ministry of Health Malaysia, Academy of Medicine Malaysia, Persatuan Diabetes Malaysia. Clinical practice guidelines: management of type 2 diabetes mellitus. 5th ed. <https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/3a.pdf>. December 2015. [Malaysia]
3. Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings (Revised Edition October 2018). https://www.fhb.gov.hk/pho/english/health_professionals/professionals_diabetes_pdf.html. [Hong Kong Department of Health; Hong Kong Food and Health Bureau]
4. Haneda M, et al. Japanese Clinical Practice Guideline for Diabetes 2016. *J Diabetes Investig* 2018; 9:657-697. [Japan]
5. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019 Jan; 42(Supplement 1): S90-S102. [ADA]
6. Cosentino F, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; 41:25-323. [ESC]
7. Lipscombe L, et al. 2018 Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018; 42 Suppl 1: S88-S103. [Canadian Diabetes Association]
8. UK National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management [NG28] Published date: 02 December 2015 Last updated: 28 August 2019. <https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#drug-treatment-2>. [UK NICE]
9. Qaseem A, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians - ACP. *Ann Intern Med* 2017; 166:279-290. [ACP]
10. Aschner PM, et al. Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults. *Colomb Med (Cali)* 2016; 47:109-130. [Colombia]
11. Lee BW, et al. Insulin therapy for adult patients with type 2 diabetes mellitus: a position statement of the Korean Diabetes Association, 2017. *Diabetes Metab J* 2017; 41:367-373. [Korean Diabetes Association]
12. Chiang CE, et al. 2018 Consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the

pharmacological management of patients with Type 2 diabetes and cardiovascular diseases. J Chin Med Assoc 2018; 81:189-222. [Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan)]

13. Conlin PR, et al. Synopsis of the 2017 U.S. Department of Veterans Affairs/U.S. Department of Defense Clinical Practice Guideline: Management of Type 2 Diabetes Mellitus. Ann Intern Med 2017; 167:655-663. [US VA/US Dept of Defense]
14. Ko SH, et al. Antihyperglycemic Agent Therapy for Adult Patients with Type 2 Diabetes Mellitus 2017: A Position Statement of the Korean Diabetes Association. Diabetes Metab J 2017; 41:337-348. [Korean Diabetes Association]

Part of the adaptation phase is the drafting of the guidelines⁹ for which in this paper the consensus recommendations were made through extracting the statements from the above stated 14 guidelines. This formed the basis that would answer the clinical questions for the local guideline creation. The composed recommendations were then written and then transformed into a statement that is supported by a summary of evidence.

ADAPTE process: Finalization phase

A draft of the adapted guidelines was created, recommendations were produced and was disseminated among the TWG members for comments and was revised when deemed necessary.

Ranking of recommendations

Delphi technique was used to achieve a structured process to gather consensus opinion, judgement, or choice among the TWG. All members of the TWG voted anonymously via MS Forms using a 5-point Likert scale: 5-point Likert scale (Strongly agree, Agree, Neither agree nor disagree, Disagree, Strongly Disagree). The TWG members set the acceptance value at 100%.

CONSENSUS STATEMENTS

Consensus recommendations for the antidiabetic drug of choice for individuals with T2DM with or without established ASCVD.

Recommendation 1:

The preferred drug for monotherapy and as the base drug for combination therapy for the treatment of hyperglycemia among individuals with Type 2 diabetes mellitus is METFORMIN.

Summary of evidence linked to recommendation statement

This recommendation is consistent across the different guidelines that metformin is the preferred first line drug for Type 2 diabetes mellitus. Even the UNITE for Diabetes Philippine Practice Guideline states that for persons with Type 2 diabetes, we should initiate

treatment with metformin unless with contraindications or if there is intolerance, such as the development of diarrhea, severe nausea and abdominal pain.

The decision to initiate monotherapy or combination therapy from the onset is typically dictated by the baseline HbA1c, e.g., if the value is 9.0 % or above (8.5% according to the Canadian Diabetes Association), then combination therapy may be initiated even at first diagnosis of Type 2 diabetes. Whether as optimization from initial monotherapy or deciding to start with combination therapy right away, metformin should be continued as background therapy and used in combination with other agents, including insulin, to be able to reach their glycemic target. If metformin is initiated as monotherapy, the dose should gradually be increased to an optimal dose of 2,000-2,500 mg per day. Within 3 months, if the target HbA1c of less than 7% (or less than 6.5% in young persons with Type 2 DM) is not achieved, then metformin can be combined with other agents.

The decision of what to combine with metformin will depend on the baseline HbA1c and symptoms, patient profile (risk of hypoglycemia, age, weight, renal function and presence of co-morbidities such as heart failure), social support and patient preferences e.g. dosing complexity, or avoidance of injections, and of course, cost and access. No matter what the considerations, the hierarchy of preferred drugs in the various guidelines always begins with metformin for several reasons.

Metformin is highly efficacious and is comparable to sulfonylureas in terms of glycemic lowering of as much as 1-2% HbA1c from baseline, at doses of 2,000 to 2,500 mg/day. Metformin also has low risk of hypoglycemia, can promote modest weight loss, and has durable effects compared to sulfonylureas.^{11,12} It also has robust cardiovascular safety, and in the UKPDS has even shown cardiovascular benefit in the long term. Aside from these, it is also cheap and readily accessible in most parts of the country.

The US FDA recently changed the package label for metformin use in chronic kidney disease (CKD), revising the previous contraindications of serum creatinine > 1.5 mg/dL for males and > 1.4 mg/dL for females.¹³ The recommendation is now to use the estimated glomerular filtration rate (eGFR) as the guide to prescribing. Metformin can be used in patients with stable eGFR >30 mL/min/1.73 m²; however, it should not be started in patients with an eGFR below 45 mL/min/1.73 m². Reduction in total daily dose is recommended in patients with eGFR between 30 to 45 mL/min/1.73 m², and due to risk of lactic acidosis, it should not be used in patients with eGFR <30 mL/min/1.73 m².^{14,15}

Finally, in up to 16% of users, metformin is responsible for vitamin B12 malabsorption and/or deficiency,^{16,17} which may lead to anemia and peripheral neuropathy.¹⁸ Thus, among patients taking metformin who develop

neuropathy, B12 should be monitored and supplements given.¹⁹

Recommendation 2:

For patients with established ASCVD, either SGLT2 inhibitors or GLP-1 receptor agonists, added on top of metformin, is recommended to reduce the risk of major cardiovascular events.

If either SGLT2-Inhibitors or GLP-1 agonists have been given and target blood sugar has not been reached, a combination of these two agents or other regimen may be considered.

Summary of evidence linked to recommendation statement

The TWG reviewed the following applicable treatment guidelines for this clinical question:

1. American Diabetes Association's Standard of Medical care 2020 for Cardiovascular Disease and Risk Management
2. Consensus report by the American Diabetes Association and European Association for the Study of Diabetes (EASD) for Management of Hyperglycemia in Type 2 Diabetes Mellitus 2018
3. American College of Cardiology Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease 2018
4. American College of Physicians' Clinical Practice Guideline Update on Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus 2017
5. Consensus of Taiwan Society of Cardiology on the Pharmacological Management of Patients with Type 2 Diabetes Mellitus and Cardiovascular Diseases
6. Clinical Practice Guidelines for Type 2 Diabetes Mellitus in Korea 2019

Established atherosclerotic cardiovascular disease (ASCVD) refers to the presence of ischemic heart disease (IHD) or documented coronary artery disease (CAD), cerebrovascular disease/stroke and peripheral arterial disease (PAD). Most of the guidelines reviewed discussed only outcomes related to CAD, IHD and stroke. Limited data are available for PAD.

Metformin

Almost all the guidelines reviewed still recommends metformin as the first-line therapy for patients with type 2 diabetes mellitus and established ASCVD. Low-to-moderate quality evidences on cardiovascular event reduction of metformin vs placebo or other antidiabetic drugs, its role as part of standard therapy in most of the RCT, and combined with its affordability and wide-availability, put metformin an important drug in the management of individuals with T2DM.

The UKPDS trial with 7.5% of its population with established ASCVD showed that metformin was able to significantly reduce the risk of MI and total mortality

when compared to conventional therapy. A follow up study with additional 10-year follow-up period consistently proved this observation.²⁰ A 2019 meta-analysis of 40 studies involving almost one million patients with CAD showed that metformin reduced the CV mortality, all-cause mortality and incidence of CV events. The effect was significant even when subgroup analysis was done in patients with history of MI.²¹ Two studies used coronary calcium calcification (CAC) scoring as outcome. In the subgroup analysis of this study, it was found out that CAC severity and the percentage of presence of CAC were significantly lower among male individuals in the metformin versus the placebo group.²²

Similarly, with stroke, there is also limited evidence in terms of primary and secondary prevention of stroke among T2DM patients after using metformin. The UKPDS, SAVOR trials and metaanalyses failed to show significant reduction in terms of stroke prevention with the use of metformin versus conventional therapy.²³ However, there is an observational study involving T2DM patients with acute ischemic stroke. This study found out that there is reduced neurological severity and milder neurological symptoms among patients on metformin compared with those without metformin treatment.²³

GLP-1 RA

The guidelines reviewed were consistent in recommending GLP-1 RA for T2DM patients with established ASCVD. This is because of the robustness of evidence behind the use of this agents for cardiovascular disease prevention. Table 1 shows the seven RCTs done on GLP1-RA with non-inferiority and superiority results using three-point MACE as outcomes.

A recent metaanalysis have been conducted including all these 7 RCTs. GLP1-RA was able to reduce MACE among T2DM patients by as much as 12% (HR 0.88, 95% CI 0.82-0.94, $p < 0.001$). This treatment effect was significant in patients with established ASCVD but not for patients without prior ASCVD.²⁵

On the other hand, dulaglutide is the only anti-diabetic agent indicated for primary prevention of cardiovascular events in patients who only have two or more risk factors for cardiovascular disease.²⁶

SGLT2 Inhibitors

Similarly, all the guidelines put high priority for SGLT2 inhibitors as a drug of choice for T2DM patients with established ASCVD. These guidelines have cited the results of recent CVOTs and metaanalyses of SGLT2 inhibitors. Three SGLT2 inhibitors have large-scale RCTs – Empagliflozin (EMPA-REG), Canagliflozin (CANVAS) and Dapagliflozin (DECLARE-TIMI).²³

In the EMPA-REG Trial, empagliflozin was compared with placebo in reducing three-point MACE. The study had 99% of the population with established ASCVD. Seventy-five percent of the population has CAD, 46% also with history of MI, and 23% had a history of stroke.

Table I. RCTs on GLP1-RA using three-point MACE as outcome.²⁵

Trial & Drug Name	% of eASCVD	MACE	MI	Stroke	HHF	CV Death	All-Cause Death
ELIXA Lixisenatide	100%	1.02 (0.89-1.17)	1.03 (0.87-1.22)	1.12 (0.79-1.58)	0.96 (0.75-1.23)	0.98 (0.78-1.22)	0.94 (0.78-1.13)
EXSCEL Exenatide	73%	0.91 (0.83-1.00)	0.97 (0.85-1.10)	0.85 (0.70-1.03)	0.94 (0.78-1.13)	0.88 (0.76-1.02)	0.86 (0.77-0.97)
LEADER Liraglutide	81%	0.87 (0.78-0.97)	0.86 (0.73-1.00)	0.86 (0.71-1.06)	0.87 (0.73-1.05)	0.78 (0.66-0.93)	0.85 (0.74-0.97)
SUSTAIN-6 Semaglutide	83%	0.74 (0.58-0.95)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	1.11 (0.77-1.61)	0.98 (0.65-1.48)	1.05 (0.74-1.50)
PIONEER-6 Semaglutide	85%	0.79 (0.57-1.11)	1.18 (0.73-1.90)	0.74 (0.35-1.57)	0.86 (0.48-1.55)	0.49 (0.27-0.92)	0.51 (0.31-0.84)
HARMONY Albiglutide	100%	0.78 (0.68-0.90)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	0.85 (0.70-1.04)	0.93 (0.73-1.19)	0.95 (0.79-1.16)
REWIND Dulaglutide	32%	0.88 (0.79-0.99)	0.96 (0.79-1.15)	0.76 (0.62-0.94)	0.93 (0.77-1.12)	0.91 (0.78-1.06)	0.90 (0.80-1.01)

Table II. Summary of the results of recent CVOTs and metaanalyses of SGLT2 inhibitors.²³

Trial & Drug Name	% of eASCVD	MACE	MI	Stroke	HHF	CV Death	All-Cause Death
EMPA-REG Empagliflozin	100%	0.86 (0.74-0.99)	0.87 (0.70-1.09)	1.18 (0.89-1.56)	0.65 (0.50-0.85)	0.62 (0.49-0.77)	0.68 (0.57-0.82)
CANVAS Canagliflozin	66%	0.86 (0.75-0.97)	0.89 (0.73-1.09)	0.87 (0.69-1.09)	0.67 (0.52-0.87)	0.87 (0.72-1.06)	0.87 (0.74-1.01)
DECLARE Dapagliflozin	41%	0.93 (0.84-1.03)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)	0.98 (0.82-1.17)	0.93 (0.82-1.04)

The study result showed that Empagliflozin was able to reduce the risk of MACE versus placebo by 14% (HR 0.86, 95% CI 0.74-0.99, $p = 0.04$). Among the three-point MACE, a trend towards a decrease in nonfatal MI was observed. However, there was no significant effect on the risk of stroke. The subgroup analysis of patients with or without a history of stroke consistently showed no beneficial effect on the risk of stroke.²⁷

In the CANVAS trial, 66% of the population has established ASCVD. Almost 56% of them had coronary artery disease and 19.3% had a history of stroke. Similarly, with EMPAREG, a significant 14% reduction in three-point MACE was observed (HR 0.86, 95% CI 0.75-0.97, $p = 0.02$). The risk of fatal or non-fatal MI was also observed to be lower with the use of Canagliflozin versus placebo. There is a trend toward a lower risk of stroke. For secondary prevention of stroke, a subgroup analysis of CANVAS failed to show significant reduction in recurrent ischemic stroke but shows significant reduction in risk of recurrent hemorrhagic stroke with the use of canagliflozin versus placebo.²⁸

The DECLARE trial involved 41% of patients with established ASCVD. Thirty-two percent of them had previous MI and only 8% had a history of stroke. Dapagliflozin was found to be non-inferior to placebo in reducing three-point MACE in the population, including patients with established ASCVD. Patients with established ASCVD had a nonsignificant reduction in MACE (HR 0.90, 95% CI 0.79-1.02). However, subgroup

analysis of the study found out that among patients with prior MI, use of dapagliflozin versus placebo was able to reduce risk of recurrent MI. Small number of patients had history of stroke in DECLARE. In this study, Dapagliflozin was found to be equal or non-inferior to placebo in reducing stroke (HR 1.01, 95% CI 0.84, 1.21).²⁹

The CVD-REAL 2 study is an observational study which involved almost 480,000 patients with diabetes in the Asia Pacific, the Middle East, and North American regions. A quarter of the population had established ASCVD, where 6% had coronary artery disease and 9% had stroke. The study showed that the use of SGLT-2 inhibitors was associated with a lower risk of the three-point MACE (HR 0.78, 95% CI 0.69-0.87); with significant reduction both in MI and stroke.³⁰

Thiazolidinedione

A good evidence supporting the use of TZD among T2DM patients with ASCVD came from the PROactive Trial. This trial involved patients with type 2 diabetes and macrovascular disease randomized to either pioglitazone or placebo. The study population was composed of patients with prior MI (46%) and stroke (19%). The result showed that there was a trend towards beneficial effect of pioglitazone on primary composite outcome of all-cause mortality, nonfatal MI, stroke, ACS, endovascular or surgical intervention for CAD or PAD, above-knee amputation (HR 0.90, 95% CI 0.80-1.02, $p = 0.095$).³¹

Table III. Summary of the large-scale trials of DPP4 inhibitors.²³

Trial & Drug Name	% of eASCVD	MACE	MI	Stroke	HHF	CV Death	All-Cause Death
SAVOR Saxagliptin	79%	1.00 (0.89–1.12)	0.95 (0.80–1.12)	1.11 (0.88–1.39)	1.27 (1.07–1.51)	1.03 (0.87–1.22)	1.11 (0.96–1.27)
EXAMINE Alogliptin	100%	0.96 (NR)	1.08 (0.88–1.33)	0.91 (0.55–1.50)	1.07 (0.79–1.46)	0.85 (0.66–1.10)	0.88 (0.71–1.09)
TECOS Sitagliptin	75%	0.98 (0.88–1.09)	0.95 (0.81–1.11)	0.97 (0.79–1.19)	1.00 (0.83–1.20)	1.03 (0.89–1.19)	1.01 (0.90–1.14)
CARMELINA Linagliptin	57%	1.02 (0.89–1.17)	1.12 (0.90–1.40)	0.91 (0.67–1.23)	0.90 (0.74–1.08)	0.96 (0.81–1.14)	0.98 (0.84–1.13)

Metanalyses of pioglitazone among patients with ASCVD showed that it was able to reduce recurrent MACE (RR 0.74, 95% CI 0.60–0.92), MI (RR 0.77, 95% CI 0.64–0.93), and stroke (RR 0.81, 95% CI 0.68–0.96). However, an increased risk of HF was also observed (RR 1.33, 95% CI 1.14–1.54).³²

DPP4 Inhibitors

The large-scale trials of DPP4 inhibitors proved that these agents are safe but neutral with regards to prevention of cardiovascular diseases when compared to placebo as the effects of this agent is non-inferior when it comes to MACE and all-cause mortality (*Table III*).²³

Similarly, metanalyses of the RCTs for DPP4 inhibitors showed comparable result. Cardiovascular death, stroke, MI, all-cause mortality, hospitalization for cardiovascular complications and hospitalization specifically for heart failure were not significantly reduced using DPP4 inhibitors when compared to placebo.

However, the SAVOR-TIMI trial showed that saxagliptin was associated with an increase in risk of hospitalization for heart failure.

Sulfonylureas

Recent guidelines are also consistent in putting low level of recommendations for the use of sulfonylureas (SU) for CV disease prevention among patients with T2DM. This is primarily because of the inconsistencies in the evidence with regard to CV safety and efficacy of SU.

ADVANCE trial involving patients with one risk factor for CV event did not show significant reduction in the MACE with the use of SU. Unfortunately, especially in older SU, there are metanalyses of both RCT and observational studies showed the use of SU showed increased risk of CV event when compared to other anti-diabetic medications. However, newer SU such as glimepiride demonstrated similar CV safety when compared to DPP4 inhibitor in the CAROLINA trial.^{23,33} This is consistent with the recent metaanalysis of SU using glimepiride and gliclazide showing that newer SUs were not associated with increased overall CV event such as CV death, MI or stroke.^{23,34}

There is also insufficient evidence of SU safety and efficacy with regards to stroke prevention.²³

The use of SU is limited also by the risk of hypoglycemia as evidenced in the ADVANCE trial where it resulted to 2-fold increase in the development of symptomatic hypoglycemia. Moreover, weight gain is also an important disadvantage of using SU, especially among patients with cardiometabolic conditions. SU increased body weight compared with metformin, as shown in the UKPDS trial.^{20,23}

Glinides

One RCT used nateglinide among IFG patients who are high risk for CVD and followed up for 6 years. Eleven percent of the study population had history of MI, 9% had angina or positive stress test, 8% had coronary revascularization and only 3% had stroke. Unfortunately, this trial did not show significant reduction in MACE including HF hospitalization and stroke.³⁵

Insulin

Limited trials are available with regards to the use of insulin therapy for prevention of cardiovascular diseases among T2DM.

In UKPDS, insulin or SU therapy showed similar risk of MI and stroke when compared to conventional dietary intervention for T2DM during the trial's 10-year follow-up. However, observation of the effect for an additional 10 years in this study showed significant MI reduction in the group treated with Insulin or SU.³⁶

In the ORIGIN Trial, insulin glargine was found to be non-inferior to standard medical care in diabetes in terms of primary outcome of three-point MACE. One third of the population in this trial had history of MI and almost 15% had history of stroke.³⁷

In the DEVOTE trial where 85% of patients had high CVD risk factors and established CVD, insulin degludec and insulin glargine were found, 37% to be similar in terms of primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.³⁸

Moreover, there was a metaanalysis of RCTs which involved T2DM patients which showed insulin therapy was similar to conventional OAD in reduction of all-cause mortality, CV death, MI, angina, sudden death or stroke.³⁹

It is by this reason why insulin therapy was given low recommendation as initial therapy for T2DM patients for the prevention of MACE.

Recommendation 3:

For patients without established ASCVD, the initial drug of choice is still metformin. The choice of other antidiabetic drugs when metformin is contraindicated or not tolerated depends on patient circumstances.

Summary of evidence linked to recommendation statement

The five groups of anti-diabetic drugs used clinically are the following: insulin sensitizers (metformin and pioglitazone); insulin providers (insulin, sulfonylureas, and meglitinides); incretin-based therapies [glucagon-like peptide-1 receptor agonist (GLP-1 RA) and dipeptidyl peptidase 4 (DPP4) inhibitors]; gastrointestinal glucose absorption inhibitor (acarbose); and renal glucose reuptake inhibitors (sodium-glucose co-transporter 2 inhibitors or SGLT2 inhibitors).

Metformin is the initial drug of choice among DM patients without established ASCVD. If metformin is contraindicated or not tolerable, other anti-diabetic agents listed above can be given as alternative depending on the patient profile. In deciding what anti-diabetic drugs will serve as an alternative to metformin or added to metformin to control the disease, several factors are considered.^{40,41} These include efficacy, complementary mechanism of action, risk of hypoglycemia, effect on weight gain, side effects, patient preference, and comorbidities.⁴² If there is a need to minimize hypoglycemia, the DPP4 inhibitors, GLP-1 RA, SGLT2 inhibitors and thiazolidinediones are recommended. If there is a need to minimize weight gain or promote weight loss, the GLP-1 RA and SGLT2 inhibitors are given. If cost is a major issue for the patient, sulfonylurea and thiazolidinediones are added. Insulin, meglitinides and alpha glucosidase inhibitors are also added depending on the HbA1c.^{43,44}

Other recommendations mentioned include: (1) For patients with known cardiovascular disease or at high risk for developing ASCVD, GLP-1 RA (liraglutide, semaglutide, dulaglutide) or SGLT2 inhibitors (empagliflozin, canagliflozin) are recommended because of the studies demonstrating cardiovascular benefit; (2) For patients without ASCVD and high HbA1c (9% and above), insulin or a GLP-1 RA are recommended for initial therapy; (3) For patients without ASCVD and with A1C levels <9 percent, options include sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, repaglinide, pioglitazone, GLP-1 RA or insulin.⁴⁴

Recommendation 4:

Thiazolidinediones and saxagliptin are not recommended for persons with diabetes and heart failure, or at high risk for heart failure.

Hypoglycemia can potentially increase the risk for cardiovascular events, thus, medications with higher risk of hypoglycemia such as older generation sulfonylureas and (human) insulin should be used with caution.

Summary of evidence linked to recommendation statement

Although studies suggest an association between hypoglycemia and CV events, there is no clear evidence for causality. Prevention of hypoglycemia remains critical, particularly with advanced disease or CVD, including heart failure. Several large RCTs found that T2D patients with a history of one or more severe hypoglycemic events have an approximately 2- to 4-fold higher death rate.⁴⁵ Severe hypoglycemia may precipitate fatal ventricular arrhythmia through an effect on baroreflex sensitivity⁴⁶ or hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death.⁴⁷

The insulin-secretagogue sulfonylureas (SUs) have the highest risk of serious hypoglycemia of any noninsulin therapy, and analyses of large datasets have raised concerns regarding the cardiovascular safety of this class when the comparator is metformin, which may itself have cardioprotective properties.^{48,49} However, the CAROLINA (CARDiovascular Outcome Study of LINagliptin Versus Glimepiride in Type 2 Diabetes) study, comparing the DPP4 inhibitor linagliptin vs. the sulfonylurea glimepiride, showed comparable CV safety of both drugs in patients with T2DM over 6.2 years.³³ Among the second-generation SUs, gliclazide and glimepiride are preferred over other SUs as they cause less risk of hypoglycemia.⁵⁰ The secretagogue glinides have a shorter half-life and thus carry a lower risk of prolonged hypoglycemia relative to SUs.

The thiazolidinediones (TZDs), which include Pioglitazone may confer ASCVD benefits⁵¹ however side effects that have limited TZD use include weight gain and elevated risk for chronic edema or heart failure.^{52,53} The occurrence of HF was significantly higher with pioglitazone than with placebo in the PROactive trial, but without increased mortality.⁵⁴

Five large prospective trials in T2DM populations with different CV risk that assessed the CV effects of DPP4 inhibitors have been reported to date and only in SAVOR-TIMI trial showed that saxagliptin was associated with an increase in risk of hospitalization for heart failure.⁵⁵

Although basal insulin analogs and NPH have been shown to be equally effective in reducing A1C in clinical trials, insulin analogs caused significantly less hypoglycemia thus, glargine U100 and detemir would be preferred to NPH.

The newest basal insulin formulations-glargine U300 and degludec U100, have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia,⁵⁶ particularly nocturnal hypoglycemia in

several RCTs compared to glargine U100 and detemir insulin.^{57,58} The cardiovascular outcome trial DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) comparing insulin degludec to insulin glargine U100 showed no significant difference in MACE (composites of CV death, non-fatal MI or non-fatal stroke) but showed a significant reduction in the frequency of hypoglycemia in favor of the degludec arm.⁵⁹ In addition, premixed insulins provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens.⁶⁰

Consensus recommendations for the management of T2DM patients with hypertension and dyslipidemia.

The Philippine Society of Hypertension (PSH) and the Philippine Lipid and Atherosclerosis Society (PLAS) has created an actual management recommendation in 2020 for hypertension and dyslipidemia in T2DM. The TWG decided to adopt these recommendations.

CONSENSUS RECOMMENDATIONS FOR T2DM PATIENTS WITH HYPERTENSION

Recommendation 1:

The definition of hypertension is 140/90 mmHg.

Summary of evidence linked to recommendation statement

All studies in hypertension have generally used 140/90 mm Hg as entry BP. More than 90% of the patients in SPRINT, which is believed by many as the main driver of the guideline, have BP of 140/90 and above.⁶¹

Recommendation 2:

Among persons with diabetes and hypertension, it is recommended that drug therapy (along with lifestyle advice) be initiated at a blood pressure of 140/90 mm Hg or higher.

Summary of evidence linked to recommendation statement

Most persons with type 2 diabetes and hypertension can be considered to belong to a high-risk CV category,⁶² and this appears true among the general population of persons with established Type 2 diabetes in the Philippines. The justification for this recommendation is the fact that both macrovascular and microvascular complications, as well as various cardiovascular risk factors (obesity, dyslipidemia) are prevalent among persons with diabetes. In the Diabcare Philippines 2008 data, 95% of all the participants had dyslipidemia and nearly 70% had hypertension. In this cohort of patients with established Type 2 diabetes, around 20% already had some form of nephropathy, 35% retinopathy (8% severe) and 15% already had a stroke, myocardial infarction or had undergone CABG

or angioplasty or with overt CAD, and 75% had a BMI more than 23 kg/m².⁶³

Such an observation is also seen among newly adults with T2DM (mean age of 50 years) in the CANDI Manila study which showed a high prevalence of diabetes complications. Electrocardiographic findings showed that 2% have evidence of myocardial infarctions, 3% had ischemic changes, and 6% had left ventricular hypertrophy. Hypertension was found in 42% of individuals with a mean BP of 144/88 mm Hg, and 80% of all subjects had LDL > 100 mg/dL, with another 38% with elevated triglyceride >150 mg/dL.⁶⁴

Consistent then with the section on general guidelines for treatment, plus the recommendations of majority of the guidelines, the threshold for treatment continues to be 140/90 mm Hg.

Recommendation 3:

A blood pressure target of <130/80 mm Hg is recommended for most persons with diabetes mellitus and hypertension; however, do not lower down the blood pressure below 120/70 due to an increased risk for cardiovascular events.

Summary of evidence linked to recommendation statement

While cardiovascular risk reduction (myocardial infarction, CV death) is already significant for BP <140/90 mm Hg (with no additional benefit for <120 mm Hg), a lower blood pressure target has additional benefit for stroke reduction and decreased risk for nephropathy. However, there is also a recommendation not to lower the BP to less than 120/70 mm Hg due to increased risk for adverse cardiovascular outcomes.

Although proportional associations of BP lowering treatment for most CV outcomes studied were attenuated below a systolic BP level of 140 mmHg, data indicate that further reduction below 130 mmHg is associated with a lower risk of stroke, retinopathy, and albuminuria, potentially leading to net benefits for many individuals at high risk for those outcomes.⁶⁵ In the past, the recommendation to lower systolic BP to <130 mmHg had been partly based on prospective cohort data; specifically, the Pittsburgh Epidemiology of Diabetes Complications Study (in people with type 1 diabetes mellitus) and the UKPDS-36 (in people with type 2 diabetes). These studies demonstrated a linear relationship between systolic BP levels and mortality, CAD, overt diabetic nephropathy and proliferative retinopathy.^{66,67} These associations were maintained even after adjustment for other confounding factors (such as lipid levels, age, sex and glycemic control). In these studies, direct relationships were seen between the magnitude of incremental BP reduction and reductions in risk of hypertension-related complications, over time.

This target was challenged in the ACCORD BP study arm which showed that a blood pressure of < 140 mm Hg did not differ to a BP <120 in terms of CV risk

reduction; however, the same study showed that there is still substantial stroke reduction with lower systolic BP. The meta-analyses of Bangalore et al also showed that while the other components of major adverse cardiac events were not improved, lowering BP <130 mmHg conferred additional protection against stroke.^{64,68,69,70} Lowering diastolic BP to equal to or less than 80 mm Hg is also supported by the HOT trial where 1,500 persons with diabetes among 18,790 participants were included. In the over-all trial, there was no cardiovascular benefit with more intensive targets but in the subpopulation with diabetes, an intensive diastolic BP target of less than or equal to 80 mm Hg showed significantly reduced risk (51%) of CVD events.⁷¹

However, there is also a recommendation not to lower the BP to less than 120/70 mm Hg due to increased risk of adverse cardiovascular outcomes.⁷²

Recommendation 4:

It is recommended to initiate treatment with a low-dose combination of a RAS blocker (angiotensin-converting enzyme inhibitor or angiotensin-2 receptor blocker) with a calcium channel blocker or thiazide/thiazide-like diuretic, preferably using a single-pill combination (SPC). Free tablet combinations may also be given if SPCs are not available.

Summary of evidence linked to recommendation statement

Consistent with the concept that majority of persons with established diabetes are already of high CV risk, and as well are at high risk to develop microangiopathy especially nephropathy, RAS based therapies (ACE-inhibitor and Angiotensin-2 receptor blockers) are the drugs of choice as base drugs for persons with diabetes who have hypertension. The Guidelines of the Canadian Diabetes Association specifically identify those people with diabetes, and those people with evidence of increased urinary albumin excretion, as persons at high risk for CV events. Their recommendations also recognize those people with known CVD, renal disease or elevated urinary albumin excretion, as well as those people with additional CV risk factors to be high-risk people who should receive an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy.

The use of combination therapy of a RAS blocker with a CCB or thiazide/thiazide-like diuretics is advocated by at least 4 of the reviewed guidelines (CDA, ESC, ISH, Malaysia)^{64,73,74} and that treatment can be further escalated according to their recommended treatment algorithms. However, multiple drug therapy is generally required to achieve blood pressure targets among persons with diabetes (PWD). These drugs may be used as add-on therapy if BP targets are not reached: diuretics, calcium channel blockers (CCBs), beta blockers and peripheral alpha blockers. However, an ARB plus an ACEI doubles the risk of renal failure and

hyperkalemia, and is therefore not recommended.^{75,76} While initial combination therapy is advocated by these 4 guidelines, the AACE is slightly different in that it recommends combination therapy only among those with an initial BP >150/100 mm Hg since monotherapy is unlikely to be sufficient to reach BP targets. The ADA likewise recommends combination therapy among those with BP >160/100 mm Hg.

As already stated in the general guidelines, the choice for starting on initial combination therapy results in greater achievement of BP lowering at the shortest amount of time. Low-dose combination therapy has been shown to be more effective than maximal dose monotherapy in the general population of persons with hypertension.⁷⁷ In a 2015 network meta-analysis of 27 studies with nearly 50,000 participants, it was seen that there was no benefit of any single antihypertensive class in the reduction of mortality in hypertensive persons with type 2 diabetes. Reduction of cardiovascular mortality was only observed among patients treated with ACE-inhibitors and CCB combination, which may be related to lower blood pressure levels.⁷⁸ Combination therapy between an ARB and another drug class was not included in this network meta-analysis. Similarly, the combination of ARB and ACE-inhibitor is not recommended.

The other clinical trial that supports the use of combination therapy, but which was not included in the previous meta-analysis is the ADVANCE trial. The BP-lowering arm of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial used the ACE-inhibitor perindopril combined with indapamide as a single pill combination, resulting not only to decreased CV outcomes (death from CVD was reduced by 18%) but also with significant impact on microvascular outcomes including nephropathy and retinopathy. The six-year observational study called ADVANCE-ON still found significant reduction in risk of death although already attenuated. The achieved blood pressure in the intervention group was 136/73 mm Hg.^{79,80}

Although the clinical trial called ACCOMPLISH is included in the meta-analysis, it is likewise worthy to mention because like ADVANCE, it supports the use of two single-pill combination therapy. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial enrolled participants at high risk of cardiovascular events (60% with diabetes) and demonstrated a decrease in morbidity and mortality with the ACE inhibitor benazepril plus the dihydropyridine CCB amlodipine versus benazepril and the thiazide-like diuretic hydrochlorothiazide.^{81,82}

While more trials are needed to support the use of single pill combinations for the initial therapy of hypertension among persons with diabetes, there is already enough data to support the use of initial combination therapy of ACE-inh or ARB with CCB

compared to monotherapy, or alternatively ACE-inh/ARB with thiazide or thiazide-like diuretic as supported by the ADVANCE trial.

CONSENSUS STATEMENTS FOR T2DM PATIENTS WITH DYSLIPIDEMIA

Recommendation 1:

For diabetic individuals without evidence of ASCVD, statins are recommended for primary prevention of cardiovascular events.

Summary of evidence linked to recommendation statement

The recommendation in the local guideline is to give statin therapy for all adult diabetic individuals for primary prevention especially among those with Type 2 diabetes mellitus, without regard for age nor duration of diabetes. The justification for this recommendation is the frequent observation that both macrovascular and microvascular complications, as well as various CV risk factors are prevalent even among newly diagnosed diabetics.⁸³

Other guidelines have similar recommendations but add on a layer of risk on top of diabetes mellitus. The Canadian Diabetes Association guidelines recommend statin therapy for diabetic individuals with an indication for lipid-lowering therapy.⁸⁴ The American Diabetes Association on the other hand recommends high-intensity statin for patients of all ages with diabetes and overt CVD, or for those who are at least 40 years old and with additional CV risk factors (total of 3 risk factors: > 40 years old, diabetes and another CV risk factor).⁸⁵ Those who have diabetes and are aged 40-75 years old should consider using moderate-intensity statins. It is silent though for diabetic individuals who are less than age 40.

For primary prevention in individuals with diabetes, the statin dose should be optimized to reach the LDL goal of <100 mg/dL. For individuals with diabetes with >1 risk factor or target organ damage, LDL-C goal of <70 mg/dL is recommended. An LDL-C of <55 mg/dL should be attained for those who have diabetes and are at extremely high risk of having recurrent CV events due to the previous occurrence of major cardiovascular events such as myocardial infarction, unstable angina or CVD (stroke).

Recommendation 2:

Among individuals with diabetes, routine addition of fibrates to statins is not recommended for primary or secondary prevention of cardiovascular disease. However, the addition of fibrates to statins may be considered among men with controlled diabetes and low HDL (<35 mg/dL) and persistently high triglycerides (>200 mg/dL) for additional prevention of CV disease.

Summary of evidence linked to recommendation statement

This question is answered directly by the ACCORD lipid trial, and the post-trial follow-up of this trial, the ACCORDION. This study randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. This was a clinical trial on persons with high CV risk enrolling both those with subclinical CV disease or 2 or more risk factors, as well as persons with diabetes and previous cardiovascular events. The latter comprised 36.5% of the included subjects and the mean follow-up was 4.7 years.⁸³

Overall, the ACCORD Lipid trial was negative with the conclusion that there is no evidence to indicate that fenofibrate should be routinely added to a statin for the treatment of dyslipidemia in patients with type 2 diabetes mellitus. For the primary outcome of major fatal or nonfatal cardiovascular event, the hazard ratio is 0.92 (95% CI 0.79-1.08), p-value 0.32 (NS). The results for the secondary outcomes which included major coronary disease event, nonfatal myocardial infarction, stroke, total mortality and death CV diseases, or fatal or nonfatal congestive heart failure, were likewise not statistically significant.⁸⁶

The pre-specified subgroup analysis showed heterogeneity in the treatment effect according to sex, with a benefit for men and possible harm for women (men had an ~16% lower primary event rate on fenofibrate, whereas women had an ~38% greater primary event rate on fenofibrate). There is also a possible benefit for persons with both a high baseline triglyceride level and a low baseline level of HDL cholesterol.⁸⁶

The ACCORDION study is a passive follow up of the original ACCORD Lipid Trial participants, enrolling 4644 surviving participants. Similar to the original cohort, 35% had pre-existing cardiovascular events. Total post randomization follow-up duration was a median of 9.7 years. Only 4.3% of study participants continued treatment with fenofibrate following completion of ACCORD, and thus, the results of ACCORDION reflect the long-term effects of the previously randomized treatment.⁸⁷

The results of this follow up study confirm the original neutral effect of fenofibrate in the overall study cohort. Similar too, to the original study, there is still an observation of heterogeneity of treatment response in that fenofibrate appeared to reduce CV events among those with baseline hypertriglyceridemia (TG > 200 mg/dL) and low HDL cholesterol < 35 mg/dL. The investigators concluded that a definitive trial of fibrate therapy in this patient population is needed to confirm these findings.⁸³

Thus, until more data are available, there appears to be no evidence to recommend routinely adding fibrates to statins once LDL-cholesterol goals have been reached. However, it may be considered among persons with

diabetes (especially men) with high baseline TG and low HDL-cholesterol, once LDL-cholesterol goals have been reached. This statement is based on the experts' panel consensus during the presentation of the clinical practice guidelines.⁸³

Discussion

This evidence-based consensus statements on the approach to lower the cardiovascular risk of individuals with Type 2 Diabetes Mellitus was developed to provide Filipino healthcare practitioners and people in the academe consensus recommendations to provide guidance on diabetes management to improve patient outcomes in the Philippine setting.

The TWG agreed on focusing with the pharmacological approach to treatment of lowering CV risk for T2DM patients using the ADAPTE model which is a more systematic approach to guideline adaptation. The TWG did not perform a systematic review of original articles to inform recommendations. Instead, the recommendations were developed using the ADAPTE framework appraising all international practice guidelines and recommendations through to 2013. The TWG's overall objective of guideline adaptation is to take advantage of the existing guidelines to enhance the efficient production and use of high-quality adapted guidelines specially in the local Philippine setting. Having first establish the scope and purpose of the existing guidelines in the local setting, the TWG conducted a thorough search for guidelines and relevant recommendations that have been previously published. Each of these articles was then assessed using the AGREE instrument.

Based on the key questions that the TWG had identified regarding the approach to lower the risk of individuals with type 2 diabetes, 9 recommendations concerning the antidiabetic drug of choice for persons with type 2 diabetes with or without established ASCVD and management of type 2 diabetes mellitus patients with hypertension and dyslipidemia were drafted and presented.

Realizing that this has become a public health issue that needs to be dealt with in controlling the repercussions of CVD among patients with diabetes in the Philippines, the TWG added comments based on expert opinions and consensus following each recommendation in the hope that minimum care requirement is achieved for all diabetic patients in the Philippines.

Conclusion

The TWG group of expert endocrinologists and cardiologists has developed management recommendations focusing on the approach to lower the CV risk of patients with T2DM. This will serve as a guide for healthcare professionals on the diabetes management in order to improve patient outcomes in the Philippine setting.

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Appendix A

List of Guidelines initially included after the Literature Search (N=19)

No.	Article	SOURCE OF GUIDELINE
1	RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. <i>Int J Diabetes Dev Ctries</i> 2018; 38:1–115.	Research Society for the Study of Diabetes in India (RSSDI)
2	Clinical Practice Guidelines Management of Type 2 Diabetes Mellitus 5th Edition Malaysian Endocrine & Metabolic Society, Ministry of Health Malaysia, Academy of Medicine Malaysia, Persatuan Diabetes Malaysia. Clinical practice guidelines: management of type 2 diabetes mellitus. 5th ed. Ministry of Health Malaysia resource page. Available at: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/3a.pdf . Accessed August 2019	Ministry of Health Malaysia, Malaysia Endocrine & Metabolic Society (MEMS), Family Medicine Specialists Association of Malaysia, Academy of Medicine Malaysia, Diabetes Malaysia
3	Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings (Revised Edition October 2018) Task Force on Conceptual Model and Preventive Protocols, Working group on Primary Care, Food and Health Bureau. Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care settings (Revised Edition October 2018). Food and Health Bureau Hong Kong resource page. Available at: https://www.fhb.gov.hk/pho/english/health_professionals/professionals_diabetes_pdf.html . Accessed August 2019	Hong Kong Department of Health; Hong Kong Food and Health Bureau
4	Japanese Clinical Practice Guideline for Diabetes 2016 Haneda M, et al. Japanese Clinical Practice Guideline for Diabetes 2016. <i>J Diabetes Investig</i> 2018; 9:657–697.	Japan
5	2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD Cosentino F, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. <i>Eur Heart J</i> 2020; 41:255–323.	The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)
6	2018 Consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on The Pharmacological Management of Patients with Type 2 Diabetes & Cardiovascular Diseases Chiang CE, et al. 2018 Consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with Type 2 diabetes and cardiovascular diseases. <i>J Chin Med Assoc</i> 2018; 81:189–222.	Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan)
7	Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm 2019 Garber AJ, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2019 EXECUTIVE SUMMARY. <i>Endocr Pract</i> 2019; 25:69–100. Erratum in: <i>Endocr Pract</i> . 2019; 25:204.	American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)
8	9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019 American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. <i>Diabetes Care</i> 2019 Jan; 42(Supplement 1): S90-S102.	American Diabetes Association (ADA)
9	Synopsis of the 2017 U.S. Department of Veterans Affairs/ U.S. Department of Defense Clinical Practice Guideline: Management of Type 2 Diabetes Mellitus Conlin PR, et al. Synopsis of the 2017 U.S. Department of Veterans Affairs/U.S. Department of Defense Clinical Practice Guideline: Management of Type 2 Diabetes Mellitus. <i>Ann Intern Med</i> 2017; 167:655–663.	US VA/US Dept of Defense
10	Insulin therapy for adult patients with type 2 diabetes mellitus: a position statement of the Korean Diabetes Association, 2017 Lee BW, et al. Insulin therapy for adult patients with type 2 diabetes mellitus: a position statement of the Korean Diabetes Association, 2017. <i>Diabetes Metab J</i> 2017; 41:367–373.	Korean Diabetes Association
11	Antihyperglycemic Agent Therapy for Adult Patients with Type 2 Diabetes Mellitus 2017: A Position Statement of the Korean Diabetes Association. Ko SH, et al. Antihyperglycemic Agent Therapy for Adult Patients with Type 2 Diabetes Mellitus 2017: A Position Statement of the Korean Diabetes Association. <i>Diabetes Metab J</i> 2017; 41:337–348.	Korean Diabetes Association
12	Consensus on “Basal insulin in the management of Type 2 Diabetes: Which, When and How?” Ghosal S, et al. Consensus on “Basal insulin in the management of Type 2 Diabetes: Which, When and How?”. <i>J Assoc Physicians India</i> 2017; 65:51–62.	India (IDEA-2016 Expert Group)

No.	Article	SOURCE OF GUIDELINE
13	A consensus statement for the clinical use of the renal sodium-glucose co-transporter-2 inhibitor dapagliflozin in patients with type 2 diabetes mellitus Avogaro A, et al. A consensus statement for the clinical use of the renal sodium-glucose co-transporter-2 inhibitor dapagliflozin in patients with type 2 diabetes mellitus. <i>Expert Rev Clin Pharmacol</i> 2017; 10:763–772.	Italy
14	Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians – ACP Qaseem A, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians – ACP. <i>Ann Intern Med</i> 2017; 166:279–290.	American College of Physicians (ACP)
15	Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults (2016) Aschner PM, et al. Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults. <i>Colomb Med (Cali)</i> 2016; 47:109–130.	Colombia
16	Treatment of Type 2 Diabetes: From "Guidelines" to "Position Statements" and Back: Recommendations of the Israel National Diabetes Council Mosenzon O, Pollack R, Raz I. Treatment of Type 2 Diabetes: From "Guidelines" to "Position Statements" and Back: Recommendations of the Israel National Diabetes Council. <i>Diabetes Care</i> 2016;39 Suppl 2: S146–153.	Israel National Diabetes Council
17	2018 Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults Diabetes Canada Clinical Practice Guidelines Expert Committee Lipscombe L, et al. 2018 Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults Diabetes Canada Clinical Practice Guidelines Expert Committee. <i>Can J Diabetes</i> 2018;42 Suppl 1:S88–S103.	Canadian Diabetes Association
18	A Proposed India-Specific Algorithm for Management of Type 2 Diabetes India Diabetes Management Algorithm Proposal Group. A Proposed India-Specific Algorithm for Management of Type 2 Diabetes. <i>Diabetes Technol Ther</i> 2016; 18:346–350.	India Diabetes Management Algorithm Proposal Group
19	Type 2 diabetes in adults: management NICE guideline [NG28] Published date: 02 December 2015 Last updated: 28 August 2019 UK National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management NICE guideline. NICE organization resource page. Available at: https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#drug-treatment-2 . Accessed August 2019	National Institute for Health and Care Excellence (NICE)

Appendix B

AGREE II tabulated score sheet

(File may be provided by authors upon request)