

CLINICAL RECOMMENDATIONS ON ASIAN POPULATIONS

2021 Consensus Pathway of the Taiwan Society of Cardiology on Novel Therapy for Type 2 Diabetes



Chern-En Chiang, MD, PhD,^{a,b,c} Kwo-Chang Ueng, MD,^d Ting-Hsing Chao, MD,^e Tsung-Hsien Lin, MD, PhD,^f Yih-Jer Wu, MD, PhD,^{g,h} Kang-Ling Wang, MD,^{a,b,c} Shih-Hsien Sung, MD, PhD,^{i,j,k} Hung-I Yeh, MD, PhD,^{g,h} Yi-Heng Li, MD, PhD,^l Ping-Yen Liu, MD, PhD,^{l,m} Kuan-Cheng Chang, MD, PhD,^{n,o} Kou-Gi Shyu, MD, PhD,^p Jin-Long Huang, MD, PhD,^q Cheng-Dao Tsai, MD,^r Huei-Fong Hung, MD,^p Ming-En Liu, MD,^s Tze-Fan Chao, MD, PhD,^{b,t} Shu-Meng Cheng, MD, PhD,^u Hao-Min Cheng, MD, PhD,^{b,c,v,w} Pao-Hsien Chu, MD,^{x,y} Wei-Hsian Yin, MD, PhD,^{c,z} Yen-Wen Wu, MD, PhD,^{c,aa,bb,cc} Wen-Jone Chen, MD, PhD,^{dd} Wen-Ter Lai, MD,^f Shing-Jong Lin, MD, PhD,^{ee,ff,gg} San-Jou Yeh, MD,^x Juey-Jen Hwang, MD, PhD,^{hh,ii} Charles Jia-Yin Hou, MD^h

ABSTRACT

Type 2 diabetes is a major threat to human health in the 21st century. More than half a billion people may suffer from this pandemic disease in 2030, leading to a huge burden of cardiovascular complications. Recently, 2 novel antidiabetic agents, glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors, reduced cardiovascular complications in a number of randomized control trials. To integrate new information and to achieve a streamlined process for better patient care, a working group was appointed by the Taiwan Society of Cardiology to formulate a stepwise consensus pathway for these therapies to reduce cardiovascular events in patients with type 2 diabetes. This consensus pathway is complementary to clinical guidelines, acting as a reference to improve patient care. (JACC: Asia 2021;1:129-146) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

From the ^aGeneral Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan; ^bDivision of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ^cSchool of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^dDepartment of Internal Medicine, School of Medicine, Chung-Shan Medical University Hospital, Taichung, Taiwan; ^eDepartment of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; ^fDepartment of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; ^gDepartment of Medicine, Mackay Medical College, New Taipei City, Taiwan; ^hCardiovascular Center, Mackay Memorial Hospital, Taipei, Taiwan; ⁱDepartment of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^jDepartment of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ^kInstitute of Public Health and Community Medicine Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^lDivision of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; ^mInstitute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan; ⁿDivision of Cardiovascular Medicine, China Medical University Hospital, Taichung, Taiwan; ^oSchool of Medicine, China Medical University, Taichung, Taiwan; ^pDivision of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; ^qCardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan; ^rDepartment of Medicine, Changhua Christian Hospital, Changhua, Taiwan; ^sDivision of Cardiology, Department of Internal Medicine, Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan; ^tInstitute of Clinical Medicine, and Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^uDivision of Cardiology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; ^vCenter for Evidence-Based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ^wInstitute of Health and Welfare Policy, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^xDepartment of Cardiology, Chang Gung Memorial Hospital, Taoyuan, Taiwan; ^ySchool of Medicine, Chang Gung University, Taoyuan, Taiwan; ^zHeart Center, Cheng Hsin General Hospital, Taipei, Taiwan; ^{aa}Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan; ^{bb}Department of Nuclear Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; ^{cc}Department of Internal Medicine and Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan; ^{dd}Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; ^{ee}Taipei Heart Institute, Taipei Medical University, Taipei, Taiwan; ^{ff}Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; ^{gg}Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; ^{hh}Cardiovascular Division, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan; and the ⁱⁱCardiovascular Center, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan.

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CKD = chronic kidney disease

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

GLP-1RA = glucagon-like peptide 1 receptor agonist

MACE = major adverse cardiovascular events

SGLT2 = sodium-glucose cotransporter 2

The Taiwan Society of Cardiology has published several clinical practice guidelines or consensuses to provide guidance on the management of cardiovascular (CV) diseases since 2010 (1-6). To integrate information in time and to achieve a streamlined process for better patient care, The Taiwan Society of Cardiology has recently appointed a working group to formulate consensus pathways to address key questions and to provide potential solutions for high-value clinical topics. The first challenge is to provide a consensus pathway for novel antidiabetic agents to reduce CV events in patients with type 2 diabetes. These novel antidiabetic

agents, namely glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, reduced CV complications in a number of randomized control trials. This consensus pathway is complementary to clinical guidelines, acting as a reference to improve patient care.

INTRODUCTION

Type 2 diabetes has become a major threat to human health in the 21st century (7). More than half a billion people may suffer from this pandemic disease in 2030 and more than 60% of patients with diabetes will experience macrovascular complications, including myocardial infarction, stroke, peripheral artery disease, and CV death (8). Despite a linear relationship between glycated hemoglobin (HbA_{1c}) and macrovascular complications has been demonstrated for years, traditional antidiabetic agents, such as sulfonylurea or insulin, were unable to decrease these complications (9-12). Before 2015, metformin was the only drug proven to be effective in reducing myocardial infarction and death in patients with type 2 diabetes (13).

Based on a single meta-analysis claiming that rosiglitazone was associated with significant increases in the risk of myocardial infarction and CV death (14), the U.S. Food and Drug Administration issued a mandate on December 17, 2008, that CV outcome trials were requested for all novel antidiabetic drugs to confirm their CV safety. Rosiglitazone is actually safe, confirmed by the late-coming RECORD

(Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial (15,16), but more than 200,000 patients have been enrolled in more than 20 CV outcome trials since 2008 (17). Surprisingly, 2 classes of these novel antidiabetic agents, namely GLP-1RAs and SGLT2 inhibitors, were effective in reducing CV end points. In the 2019 European Society of Cardiology/European Association for the Study of Diabetes guidelines on diabetes, prediabetes, and cardiovascular diseases (18), GLP-1RAs and SGLT2 inhibitors were recommended as the frontline therapy ahead of metformin in drug-naïve patients with atherosclerotic cardiovascular disease (ASCVD) or with high or very high CV risks.

The mechanisms of CV protection for these 2 classes of drugs are different. The CV outcome trials confirm that GLP-1RAs are effective in reducing major adverse cardiovascular events (MACE) and that SGLT2 inhibitors mainly decrease heart failure (HF) and end-stage renal disease, although MACE may also be reduced. But how to prioritize these 2 agents is quite difficult in some clinical settings, because patients with diabetes may have multiple concomitant diseases, including HF, chronic kidney disease (CKD), and ASCVD. In the American College of Cardiology 2020 expert consensus decision pathway on novel therapies for CV risk reduction in patients with type 2 diabetes (19), GLP-1RAs and SGLT2 inhibitors were given different decision pathways for high-risk patients. But how to decide which one should be the first-line therapy in patients with multiple concomitant diseases has not been mentioned and there has been no clear suggestion for patients with risk factors alone but devoid of documented CV disease (19). Since the initiative of the 2020 American College of Cardiology decision pathway, 5 more trials and other meta-analyses have been published (20-27), rendering an even stronger support to update an evidence-based decision pathway. A working group was recently appointed by Taiwan Society of Cardiology to formulate a consensus pathway as guidance to these novel therapies to reduce CV events in patients with type 2 diabetes. All the available randomized control trials, meta-analyses, and network meta-analyses were carefully reviewed by the working group in an attempt to finalize a timely decision pathway for these 2 novel agents.

Laurence S. Sperling, MD, served as Guest Associate Editor. Nathan Wong, PhD, as Guest Editor-in-Chief for this paper. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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TABLE 1 Effects of Novel Antidiabetic Drugs on Cardiovascular Outcomes in Clinical Trials

First Author (Ref. #)	Trial Name (n)	Drug Name	Target Patients	Outcome					
				MACE	Composite Renal Including Albuminuria	Composite Renal Excluding Albuminuria	Heart Failure	CV Death	All-Cause Death
DPP-4 inhibitors									
Scirica et al (49)	SAVOR-TIMI 53 (n = 16,492)	Saxagliptin	Diabetes	↔	↔	↔	↑	↔	↔
Green et al (94)	TECOS (n = 14,671)	Sitagliptin	Diabetes	↔	↔	↔	↔	↔	↔
White et al (95)	EXAMINE (n = 5,380)	Alogliptin	Diabetes	↔	↔	↔	↑	↔	↔
Rosenstock et al (96)	CAROLINA (n = 6,042)	Linagliptin	Diabetes	↔	NR	NR	↔	↔	↔
Rosenstock et al (97)	CARMELINA (n = 6,991)	Linagliptin	DKD	↔	↔	↔	↔	↔	↔
GLP-1 receptor agonists									
Pfeffer et al (77)	ELIXA (n = 6,068)	Lixisenatide	Diabetes	↔	↔	↔	↔	↔	↔
Holman et al (98)	EXSCEL (n = 14,752)	Exenatide-SR	Diabetes	↔	↔	↔	↔	↔	↓
Marso et al (51)	LEADER (n = 9,340)	Liraglutide	Diabetes	↓	↓	↔	↔	↓	↓
Hernandez et al (52)	HARMONY (n = 9,463)	Albiglutide	Diabetes	↓	NR	NR	↔	↔	↔
Marso et al (53)	SUSTAIN-6 (n = 3,297)	Semaglutide	Diabetes	↓	↓	↔	↔	↔	↔
Husain et al (99)	PIONEER-6 (n = 3,183)	Semaglutide (oral)	Diabetes	↔	NR	NR	↔	↓	↓
Gerstein et al (54)	REWIND (n = 9,901)	Dulaglutide	Diabetes	↓	↓	↔	↔	↔	↔
SGLT2 inhibitors									
Zinman et al (55)	EMPA-REG OUTCOME (n = 7,020)	Empagliflozin	Diabetes	↓	↓	↓	↓	↓	↓
Neal et al (56)	CANVAS Program (n = 10,142)	Canagliflozin	Diabetes	↓	↓	↓	↓	↔	↔
Wiviott et al (57)	DECLARE-TIMI 58 (n = 17,160)	Dapagliflozin	Diabetes	↔	NR	↓	↓	↔	↔
Cannon et al (20)	VERTIS CV (n = 8,246)	Ertugliflozin	Diabetes	↔	NR	↔	↓	↔	↔
Perkovic et al (58)	CREDESCENCE (n = 4,401)	Canagliflozin	DKD	↓	↓	↓	↓	↔	↔
Heerspink et al (22)	DAPA-CKD (n = 4,304)	Dapagliflozin	CKD	NR	NR	↓	↓	↔	↓
Bhatt et al (23)	SCORED (n = 10,584)	Sotagliflozin	DKD	↓	NR	↔	↓	↔	↔
McMurray et al (60)	DAPA-HF (n = 4,744)	Dapagliflozin	HF	NR	NR	↔	↓	↓	↓
Packer et al (21)	EMPEROR-Reduced (n = 3,730)	Empagliflozin	HF	NR	NR	↓	↓	↔	↔
Bhatt et al (24)	SOLOIST-WHF (n = 1,222)	Sotagliflozin	HF	NR	NR	NR	↓	↔	↔

Arrows indicate risk: decreased, neutral, or increased.
 CKD = chronic kidney disease; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; HF = heart failure; MACE = major adverse cardiovascular events; NR = not reported; SGLT2 = sodium-glucose cotransporter 2.

GLP-1RAs AND SGLT2 INHIBITORS

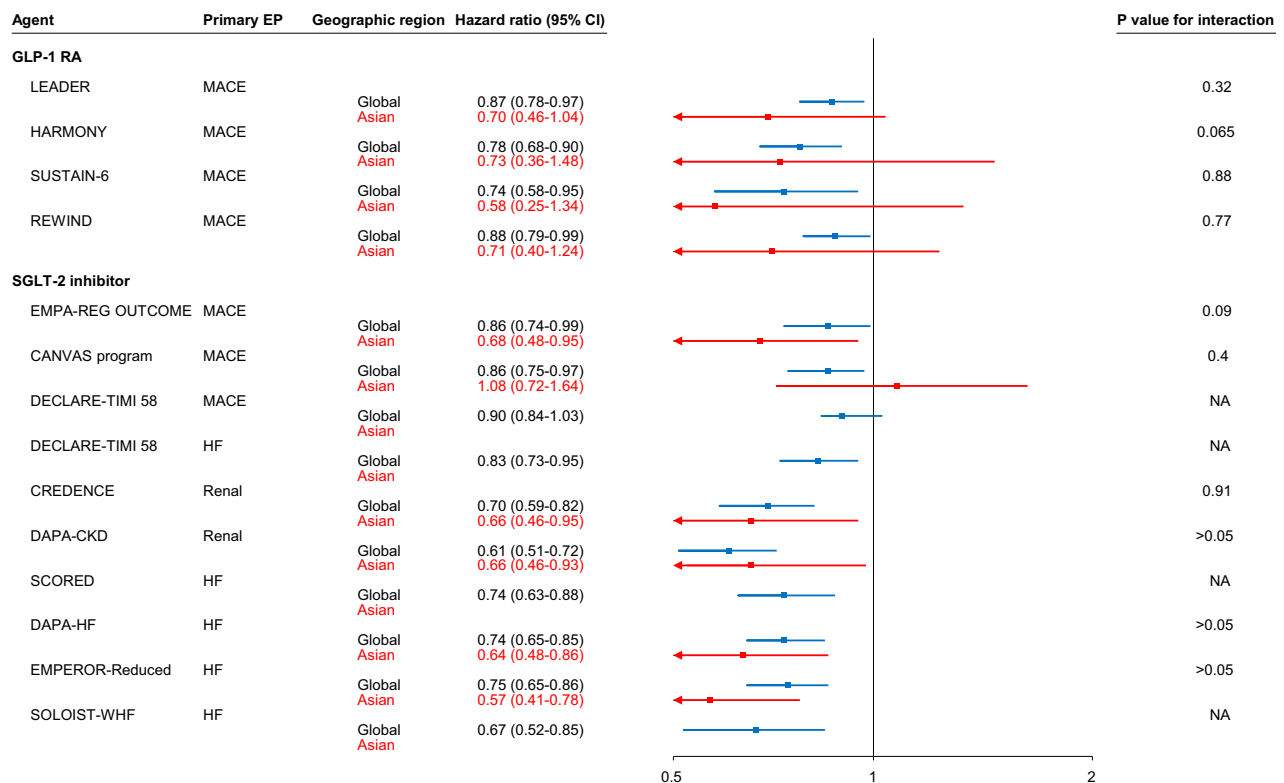
The first approved GLP-1RA for the treatment of type 2 diabetes was exenatide, a synthetic exendin-4 originated from saliva of a lizard from Arizona, *Heloderma suspectum* (28). Exenatide has a limited sequence homology of 53% to human GLP-1 and a very short half-life of approximately 2-3 hours (29). In contrast, GLP-1RAs with human backbone structure, such as liraglutide, semaglutide, albiglutide, and dulaglutide, have more than 90% homology to human GLP-1 (29). Except for liraglutide, whose half-life is around 13 hours, their half-lives are around 5-7 days (29). GLP-1RAs induced glucose-dependent insulin secretion and inhibited glucagon release (30). GLP-1 receptors are widely expressed in various CV tissues (31-33). Clinical trials of human-backbone GLP-1RAs demonstrated remarkable CV benefits (34).

French chemists isolated phlorizin in 1835, a substance from the bark of apple trees (35). Chronic administration of phlorizin in a canine model produced many symptoms similar to those observed in

human diabetes (glucosuria, polyuria, and weight loss) (35). This observation led to the discovery of SGLT2 inhibitors 150 years later (35). SGLT2 inhibitors blocked SGLT2 in the proximal tubule in the kidney (36), resulting in glucosuria, blood glucose lowering, and body weight loss (37). SGLT2 inhibitors also caused osmotic diuresis and natriuresis (38), decreased blood pressure (39), and decreased left ventricular mass and improved left ventricular diastolic function (40) in patients with diabetes. Moreover, SGLT2 inhibitors inhibited Na⁺/H⁺ exchanger 1 in the myocardium and reduced cytoplasmic concentrations of sodium and calcium (41,42), leading to a reduction in intracellular calcium overload and cardiac protection (43).

SEARCH STRATEGY AND SELECTION CRITERIA

We searched all randomized CV outcome trials of dipeptidyl peptidase 4 inhibitors, GLP-1RAs, and SGLT2 inhibitors from January 1, 2012, to February 1, 2021, with the use of PubMed. The search algorithm is

FIGURE 1 Forest Plot of End Points for Asians Versus Whole Study Population

Clinical trials with positive findings are shown. In general, the efficacy of GLP-1 receptor agonists and SGLT2 inhibitors in Asians were consistent with those in the whole study population. There were 4 trials for GLP-1RAs, including LEADER (51), HARMONY (52), SUSTAIN-6 (53), and REWIND (54); 9 trials for SGLT2 inhibitors, including EMPA-REG OUTCOME (55), CANVAS Program (56), DECLARE-TIMI 58 (57), CREDESCENCE (58), DAPA-CKD (22), the SCORED (23), DAPA-HF (60), EMPEROR-Reduced (21), and SOLOIST-WHF (24). CI = confidence interval; EP = end point; GLP-1RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; MACE = major adverse cardiovascular events; NA = not available; SGLT2 = sodium-glucose cotransporter 2.

provided in the [Supplemental Methods](#). We restricted our search to trials including more than 1,000 patients. Data search and extraction were performed by 2 independent reviewers (S.-H.S. and H.-M.C.), and any discrepancies were resolved by consensus or by consulting a third reviewer (C.-E.C). The PRISMA flow chart is shown in [Supplemental Figure 1](#). We identified a total of 22 trials ([Table 1](#)). All trials met criteria for being well conducted and had low risk of bias according to the Cochrane tool for assessing risk of bias in randomized clinical trials (44) ([Supplemental Figure 2](#)).

We also searched PubMed for meta-analyses of outcome trials of GLP-1RAs and SGLT2 inhibitors. Meta-analyses that involved other types of antidiabetic agents were not included. Network meta-analyses that compared GLP-1RA and SGLT2 inhibitor were included. We limited our search from January 1, 2019, to February 15, 2021, to take advantage of more recent trials. Meta-analyses that

included the same trials but were published in different journals were evaluated and selected, based on the consensus of the 3 reviewers (S.-H.S., H.-M.C., and C.-E.C). We identified 5 meta-analyses (26,45-48) and 2 network meta-analyses (25,27).

PARADIGM SHIFT IN ANTIDIABETIC MANAGEMENT

Since the US Food and Drug Administration issued the mandate in 2008 that novel antidiabetic agents should be tested for safety by means of randomized control trials, 22 randomized control trials have been completed ([Table 1](#)). In general, DPP-4 inhibitors had neutral effects on CV and renal outcomes, with the exception of saxagliptin and alogliptin, which increased the risk of HF (49,50). GLP-1RAs that belong to the exendine-4-backbone group (lixisenatide and exenatide) had no beneficial effect on CV and renal outcomes. The human-backbone group (liraglutide,

TABLE 2 Effects of GLP-1RAs and SGLT2 Inhibitors on MACE in Meta-analyses

First Author (Ref. #)	N (Ref. #)	HR (95% CI)	P Value	P for Interaction
MACE				
Kristensen et al (47)	56,004			
GLP-1RA vs placebo		0.88 (0.82-0.94)	<0.0001	
Previous ASCVD		0.86 (0.80-0.93)		0.24
Risk factors alone		0.94 (0.83-1.07)		
Zelniker et al (45,46)	77,242 (45), 34,322 (46)			
SGLT2i vs placebo		0.89 (0.83-0.96)	0.0014	
Previous ASCVD		0.86 (0.80-0.93)		0.05
Risk factors alone		1.00 (0.87-1.16)		
CV death				
Kristensen et al (47)	56,004			
GLP-1RA vs placebo		0.88 (0.81-0.96)	0.003	
Zelniker et al (46)	34,322			
SGLT2i vs placebo (46)		0.84 (0.75-0.94)	0.0023	
Previous ASCVD		0.80 (0.71-0.91)	0.0005	0.31
Risk factors alone		1.02 (0.80-1.30)	0.89	
Myocardial infarction				
Kristensen et al (47)	56,004			
GLP-1RA vs placebo		0.91 (0.84-1.00)	0.043	
Zelniker et al (46)	34,322			
SGLT2i vs placebo		0.89 (0.80-0.98)	0.0177	
Previous ASCVD		0.85 (0.76-0.95)	0.00045	0.17
Risk factors alone		0.99 (0.79-1.24)	0.92	
Stroke				
Kristensen et al (47)	56,004			
GLP-1RA vs placebo		0.84 (0.76-0.93)	<0.0001	
Zelniker et al (46)	34,322			
SGLT2i vs placebo		0.97 (0.86-1.10)	0.64	
Previous ASCVD		0.98 (0.84-1.14)	0.78	0.83
Risk factors alone		1.01 (0.80-1.28)	0.94	

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; GLP-1RA = glucagon-like peptide 1 receptor agonist; HR = hazard ratio; MACE = major adverse cardiovascular events; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

albiglutide, semaglutide, and dulaglutide) reduced MACE and the composite renal end point that included albuminuria (51-54). However, they did not reduce the composite renal end point when albuminuria was excluded in the analysis, nor could they prevent HF. When SGLT2 inhibitors were tested in patients with diabetes, the rates of composite renal end points and HF were reduced (55-57). Ertugliflozin was an exception in that primary MACE end points and 2 secondary end points (composite of CV death and hospitalization for HF, and composite renal end points) all failed to reach significant differences (20). Among the 3 CKD trials of SGLT2 inhibitors, CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) (58), DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) (22), and SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate

Renal Impairment Who Are at Cardiovascular Risk) (23), 2 of them (CREDENCE and DAPA-CKD) demonstrated significant reduction in renal end points and HF (22,58). The SCORED trial was prematurely terminated owing to a funding issue (23). The primary end points were modified and the CV events were un adjudicated. The results were therefore less convincing (23). In addition, sotagliflozin is a dual SGLT2 and SGLT-1 inhibitor (59). Its mechanism of action and adverse effects are different from other SGLT2 inhibitors. We did not include it in the present consensus pathway. Finally, among the 3 trials dedicated to HF patients, DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) (60), EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) (21), and SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) (24), SGLT2

TABLE 3 Effects of GLP-1RAs and SGLT2 Inhibitors on Hospitalization for Heart Failure in Meta-analyses

First Author (Ref. #)	N	HR (95% CI)	P Value	P for Interaction
Kristensen et al (47)	56,004			
GLP-1RA vs placebo		0.91 (0.83-0.99)	0.028	
Zelniker et al (46)	34,322			
SGLT2i vs placebo		0.69 (0.61-0.79)	<0.001	
History of HF		0.68 (0.55-0.83)	0.0002	0.76
No history of HF		0.71 (0.60-0.83)	<0.0001	
Salah et al (26)	59,747			
SGLT2i vs placebo (all patients)		0.69 (0.64-0.74)	<0.000001	
SGLT2i vs placebo (patients with DM and HF)		0.71 (0.61-0.83)	<0.0001	
SGLT2i vs placebo (patients with HF ± DM)		0.69 (0.62-0.76)	<0.00001	

DM = diabetes mellitus; HF = heart failure; other abbreviations as in Table 2.

inhibitors consistently reduced the HF end point. Similarly to the SCORED trial, SOLOIST-WHF was prematurely terminated because of a funding issue, and the primary end points were modified and the events were unadjudicated (24).

Based on these randomized control trials, the recent 2019 European Society of Cardiology/European Association for the Study of Diabetes guidelines (18), the 2019 update of American Diabetes Association/European Association for the Study of Diabetes consensus on the management of hyperglycemia in type 2 diabetes (61), and the 2021 American Diabetes Association guidelines (62) have changed management from “glucose-driven strategy” to “event-driven strategy” for patients with diabetes and high CV risk. For patients with established ASCVD or high ASCVD risk, either GLP-1RA or SGLT2 inhibitor should be considered, while SGLT2 inhibitor should be the first choice for CKD patients or patients with HF with reduced ejection fraction.

METHODS FOR FORMATION OF THE CONSENSUS PATHWAY

Novel antidiabetic agents with demonstrated benefit on primary end points in randomized control trials were discussed and included in this consensus pathway. We excluded agents that failed to achieve significant effects on primary end points in randomized control trials, such as lixisenatide, exenatide-SR, and ertugliflozin. Albiglutide was not discussed as it had been withdrawn from the market.

The working group of the consensus pathway systematically analyzed the following important clinical evidence to support the use of SGLT2 inhibitors and GLP-1RAs:

- Asian subgroup data versus global data (checking the *P* value for interaction) in randomized control trials.

- Placebo-controlled randomized control trials:
 - Effect size (relative risk reduction).
 - Significance level (*P* value).
- Meta-analyses of placebo-controlled randomized control trials:
 - Effect size (relative risk reduction).
 - Significance level (*P* value).
- Network meta-analyses comparing SGLT2 inhibitors to GLP-1RAs:
 - Effect size (relative risk reduction).
 - Significance level (*P* value).

The working group focused on the following end points: 3-point MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke) and their individual components, HF, and renal events. For patients with type 2 diabetes, concomitant HF increases total death by about 3-fold, the highest compared with other comorbidities (63). Therefore, HF was our first consideration when formulating the stepwise consensus pathway. Patients with diabetic kidney disease have higher mortality rate than patients with diabetes who have ASCVD (64). Second to HF, CKD was our next consideration, followed by ASCVD. Patients with risk factors alone were our last consideration, because they have lower mortality rates than those with ASCVD (54,57). The working group members convened twice (February 20, 2021, and March 13, 2021) to review all evidence extensively. Each suggestion was reached by consensus.

ASIAN SUBGROUP IN RANDOMIZED CONTROL TRIALS OF SGLT2 INHIBITOR AND GLP-1RA

Proportions of Asians in these randomized control trials are shown in Supplemental Figure 3. Twelve Asian countries/territories recruited patients for these trials (Supplemental Table 1). In general, efficacy on the primary end points for Asian subgroups

was consistent with that of the whole study population. **Figure 1** is a forest plot of primary end points for Asian patients versus the whole study population in individual trials. Except the unreported ones, the *P* values for interaction were >0.05 in all randomized control trials, suggesting that the efficacy of these agents in Asian patients was consistent with that in the whole study population. In a recent meta-analysis comparing Asians with Whites in randomized control trials of SGLT2 inhibitors and GLP-1RAs, Asian patients with HF with reduced ejection fraction derived greater benefit in CV death/hospitalization for HF from SGLT2 inhibitors, and Asian patients with type 2 diabetes derived greater MACE benefit from GLP-1RAs (65). Although there is no specific Asian outcome trial, findings from these global trials can be reasonably applied to Asian patients.

PRIMARY AND SECONDARY PREVENTION OF MACE

Liraglutide, semaglutide, and dulaglutide are GLP-1RAs with demonstrated benefits in reducing 3-point MACE in patients with diabetes (Table 1). A meta-analysis including all 7 trials of GLP-1RAs further provided solid evidence to support the role of GLP-1RA in reducing 3-point MACE (47). The efficacy was consistent in patients with ASCVD (secondary prevention) or with risk factors alone (primary prevention), with a *P* value for interaction of 0.24 (47) (Table 2). GLP-1RAs also reduced the risk of each component of the 3-point MACE, ie, CV death, myocardial infarction, and stroke (Table 2). More details regarding the differential effects on each MACE component in patients with ASCVD (secondary prevention) or with risk factors alone (primary prevention) were not provided.

Empagliflozin, canagliflozin, and dapagliflozin are SGLT2 inhibitors with demonstrated benefits in reducing primary end points in patients with diabetes (Table 1). DECLARE (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) had 2 coprimary end points, MACE and CV death/hospitalization for HF (57). Dapagliflozin decreased CV death/hospitalization for HF, but not MACE (57). Two meta-analyses demonstrated the beneficial effects of SGLT2 inhibitors on MACE and other CV end points (45,46). The differential effects on MACE, CV death, myocardial infarction, and stroke in patients with ASCVD or with risk factors alone were also provided (45,46). Table 2 presents a summary of their effects on MACE, CV death, myocardial infarction, and stroke. SGLT2 inhibitors, compared with placebo, reduced MACE only in patients with ASCVD

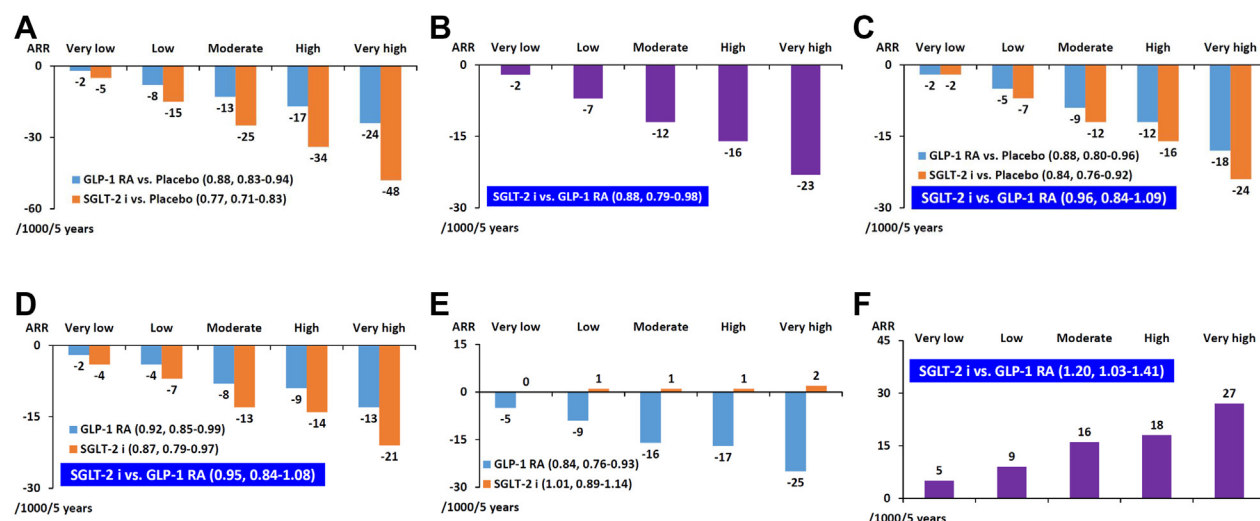
TABLE 4 Effects of GLP-1RAs and SGLT2 Inhibitors on Renal End Points in Meta-analyses

First Author (Ref. #)	N	HR (95% CI)	P Value
Composite renal end point including albuminuria			
Zelniker et al (45)	77,242		
GLP-1RA vs placebo		0.82 (0.75-0.89)	<0.001
SGLT2i vs placebo		0.62 (0.58-0.67)	<0.001
Kristensen et al (47)	56,004		
GLP-1RA vs placebo		0.83 (0.78-0.89)	<0.001
Composite renal end point excluding albuminuria			
Zelniker et al (45)	77,242		
GLP-1RA vs placebo		0.92 (0.80-1.06)	0.24
SGLT2i vs placebo		0.55 (0.48-0.64)	<0.001
Zelniker et al (46)	34,322		
SGLT2i vs placebo			
All patients		0.55 (0.48-0.64)	<0.001
Patients with kidney disease		0.67 (0.51-0.89)	<0.001
Kristensen et al (47)	56,004		
GLP-1RA vs placebo		0.87 (0.73-1.03)	0.098
Yamada et al (network meta-analysis) (25)	32,949		
GLP-1RA vs placebo		0.86 (0.72-1.03)	NR
Salah et al (26)	59,747		
SGLT2i vs placebo			
Patients with kidney disease		0.68 (0.48-0.95)	0.03

NR = not reported; other abbreviations as in Table 2.

(secondary prevention), not in patients with risk factors alone (primary prevention), with a *P* value for interaction of 0.05. A more recent meta-analysis included the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial and concluded that the effect of SGLT2 inhibitors on the reduction of MACE was consistent for primary prevention and secondary prevention (48). However, this particular meta-analysis was not included in our analysis in this section because the CREDENCE trial exclusively enrolled patients with diabetic kidney disease, not the full spectrum of patients with diabetes. The CREDENCE trial is discussed in the section dealing with renal events.

As presented in Table 2, both GLP-1RAs and SGLT2 inhibitors reduce CV death and myocardial infarction. Only GLP-1RAs reduce stroke, whereas SGLT2 inhibitors have no effect on stroke. In the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial, dulaglutide decreased fatal and nonfatal stroke by 26% (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.62-0.94; *P* = 0.0096), and the effect was consistent in patients with or without previous stroke (*P* for interaction = 0.83) (66). Therefore, it is reasonable to advocate GLP-1RA exclusively in patients with a history of stroke.

FIGURE 2 SGLT2 Inhibitors Versus GLP-1RAs on Cardiovascular Outcomes

The bars represent absolute effects of treatment per 1,000 patients treated for 5 years for patients at very low risk (no cardiovascular risk factors), low risk (3 or more cardiovascular risk factors), moderate risk (atherosclerotic cardiovascular disease), high risk (chronic kidney disease), and very high risk (atherosclerotic vascular disease plus chronic kidney disease). **(A)** All-cause death: SGLT2 inhibitor and GLP-1RA compared with placebo. **(B)** All-cause death: SGLT2 inhibitor compared with GLP-1RA. **(C)** Cardiovascular death: SGLT2 inhibitor and GLP-1RA compared with placebo. **(D)** Nonfatal myocardial infarction: SGLT2 inhibitor and GLP-1RA compared with placebo. **(E)** Nonfatal stroke: SGLT2 inhibitor and GLP-1RA compared with placebo. **(F)** Nonfatal stroke: SGLT2 inhibitor compared with GLP-1RA. Adapted from Palmer et al (27) with permission. ARR = absolute risk reduction; other abbreviations as in Figure 1.

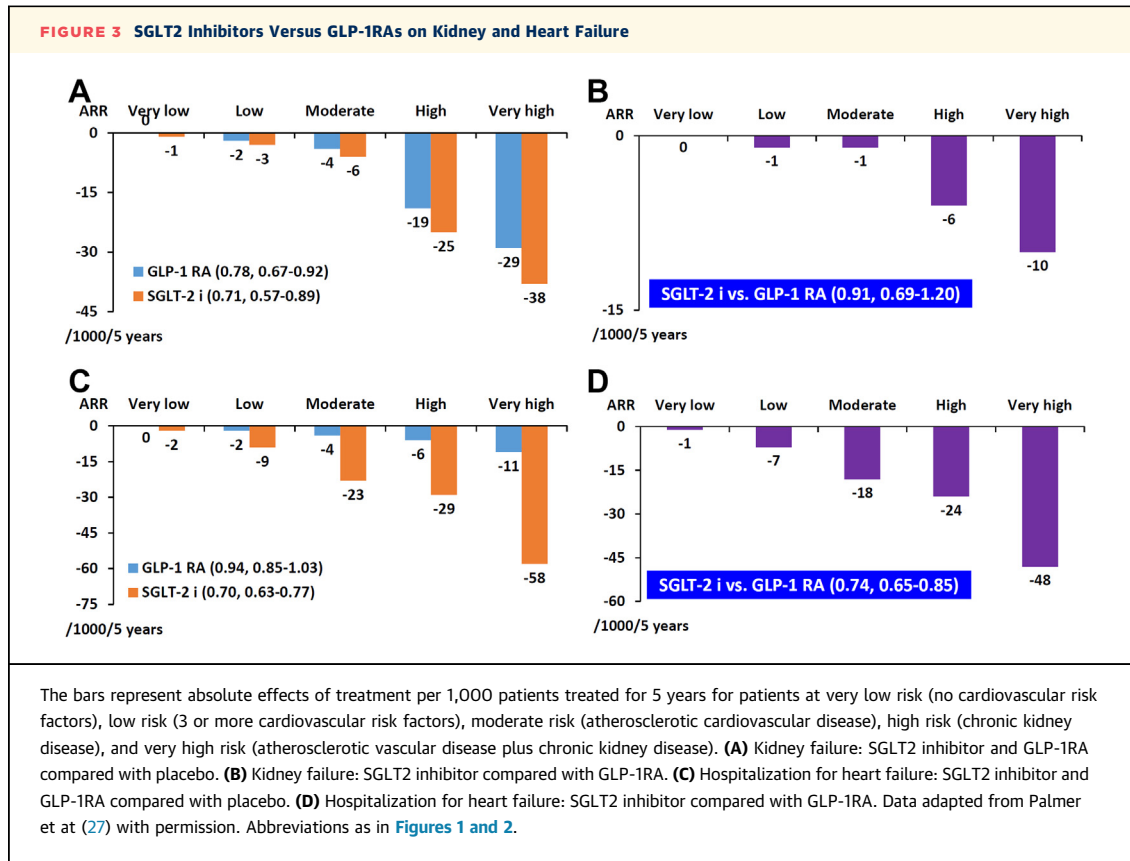
- For primary prevention of MACE: Only GLP-1RAs significantly reduced MACE compared with placebo.
- For secondary prevention of MACE: Both GLP-1RAs and SGLT2 inhibitors significantly reduced MACE compared with placebo.
- For primary and secondary prevention of stroke: Only GLP-1RAs significantly reduced stroke compared with placebo.

PRIMARY AND SECONDARY PREVENTION OF HF WITH REDUCED EJECTION FRACTION

In general, GLP-1RAs have no effect on HF prevention, as presented in Table 1. Nevertheless, a meta-analysis of the 7 GLP-1RA trials showed a marginal effect on HF (HR 0.91, 95% CI 0.83-0.99; $P = 0.028$) (26) (Table 3). The effect of HF reduction was mainly observed in patients without HF (primary prevention), given that only about 20% of patients had a history of HF in these trials. Moreover, there is no GLP-1RA trial dedicated specifically for HF patients (secondary prevention). In contrast, SGLT2 inhibitors decreased the risk of HF in all randomized control trials (Table 1), including those trials for patients with diabetes as a whole (55-57) and those dedicated for HF patients (21,60). DAPA-HF and EMPEROR-Reduced

exclusively enrolled patients with HF with reduced ejection fraction (21,60). Patients with diabetes and without diabetes were enrolled. In both trials, SGLT2 inhibitors significantly reduced CV death and hospitalization for HF (21,60). CV death and all-cause death were also reduced by dapagliflozin (60). Randomized control trials testing SGLT2 inhibitors in patients with HF with preserved ejection fraction are still ongoing and final results are worth waiting for. Two meta-analyses demonstrated the effects of SGLT2 inhibitors on HF with reduced ejection fraction (26,46). One meta-analysis included exclusively diabetic trials (55-57), and only 10%-20% patients in these trials had previous history of HF (46). The other (26) included most recent trials, such as DAPA-HF (60) and EMPEROR-Reduced (21). As presented in Table 3, SGLT2 inhibitors significantly reduce the risk of HF in both meta-analyses, regardless of history of previous HF.

- For primary prevention of HF with reduced ejection fraction: GLP-1RAs had marginal effects compared with placebo, and SGLT2 inhibitors significantly reduced HF compared with placebo.
- For secondary prevention of HF with reduced ejection fraction: Only SGLT2 inhibitors significantly reduced HF compared with placebo.



PRIMARY AND SECONDARY PREVENTION OF RENAL EVENTS

Among GLP-1RAs, liraglutide, semaglutide, and dulaglutide reduced composite renal end points that included albuminuria in the analysis, regardless of history of CKD (67,68); yet none of them achieved significant reduction in composite renal end points when albuminuria was excluded from the analysis (Table 1). More specifically, GLP-1RAs were effective in reducing albuminuria, but were unable to halt the deterioration of estimated glomerular filtration rate (eGFR) or to decrease the risk of end-stage renal disease (53,67,68). Meta-analyses demonstrated similar findings (25,26,45) (Table 4). A trial of semaglutide dedicated for diabetic kidney disease is ongoing (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease [FLOW]; NCT03819153).

Reduction in albuminuria is not a reliable surrogate for clinical kidney end point. For example, in the blood pressure study of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (69), the baseline mean eGFR was 91.6 mL/min/1.73 m² in the

intensive arm (target systolic blood pressure <120 mm Hg) versus 91.7 mL/min/1.73 m² in the standard arm (target systolic blood pressure <140 mm Hg) ($P = 0.93$), while the baseline median urinary albumin/creatinine ratio was 14.6 mg/g versus 14.0 mg/g ($P > 0.05$). At the end of study, the urinary albumin/creatinine ratio was 12.6 mg/g versus 14.9 mg/g ($P < 0.001$), and the new onset of albuminuria was 6.6% versus 8.7% ($P = 0.009$), suggesting that intensive blood pressure control was more effective in reducing albuminuria than standard blood pressure control. However, the eGFR decreased to 74.8 mL/min/1.73 m² versus 80.6 mL/min/1.73 m² ($P < 0.001$) (69). Similar findings were observed in the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial in which the combination of benazepril plus hydrochlorothiazide was compared with the combination of benazepril plus amlodipine (70). The former was more effective in reducing urinary albumin/creatinine ratio, but the event rates of the renal end point (composite of doubling of serum creatinine concentration, eGFR <15 mL/min/1.73 m², or need for dialysis) were

TABLE 5 All-Cause Death in Patients With Diabetes With Different Comorbidities in Clinical Trials

First Author (Ref. #)	Trial Name (n)	All-Cause Death, Placebo Group, per 100 Person-Years
DM + ASCVD		
Zinman et al (55)	EMPA-REG OUTCOME (n = 7,020)	2.86
Hernandez et al (52)	HARMONY (n = 9,463)	2.56
Pfeffer et al (77)	ELIXA (n = 6,068)	3.3
DM + CKD		
Perkovic et al (58)	CREDESCENCE (n = 4,401)	3.5
Heerspink et al (22)	DAPA-CKD (n = 4,304)	3.1
Bhatt et al (23)	SCORED (n = 10,584)	3.5
DM + HFREF		
McMurray et al (60)	DAPA-HF (n = 4,744)	9.5
Packer et al (21)	EMPEROR-Reduced (n = 3,730)	10.7
Bhatt et al (24)	SOLOIST-WHF (n = 1,222)	16.3

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; HFREF = heart failure with reduced ejection fraction.

double (70). Therefore, a reduction in albuminuria is not a surrogate for kidney protection in this consensus pathway.

In contrast, most SGLT2 inhibitors, except ertugliflozin, reduced all composite renal end points in diabetes trials (Table 1). More specifically, SGLT2 inhibitors not only reduced albuminuria, but also preserved eGFR and decreased the risk of end-stage renal disease (56,71,72). The CREDESCENCE trial enrolled only patients with diabetic kidney disease, and demonstrated that canagliflozin significantly reduced the components of all renal end points (58). The DAPA-CKD trial recruited CKD patients with and without diabetes (22). Dapagliflozin decreased the decline of eGFR and reduced the risk of end-stage renal disease, although the effect on albuminuria was not reported (73). The benefits were consistent in patient with and without diabetes. Meta-analyses demonstrated similar findings that SGLT2 inhibitors significantly reduce all composite renal end points in patients with and without previous CKD (Table 4).

- For both primary and secondary prevention of CKD: GLP-1RAs, compared with placebo, reduce composite renal end points that include albuminuria, but not when albuminuria is excluded from the analysis.
- For both primary and secondary prevention of CKD: SGLT2 inhibitors, compared with placebo, reduce all composite renal end points.

NETWORK META-ANALYSIS

There is no existing randomized control trial published comparing SGLT2 inhibitors with GLP-1RAs at

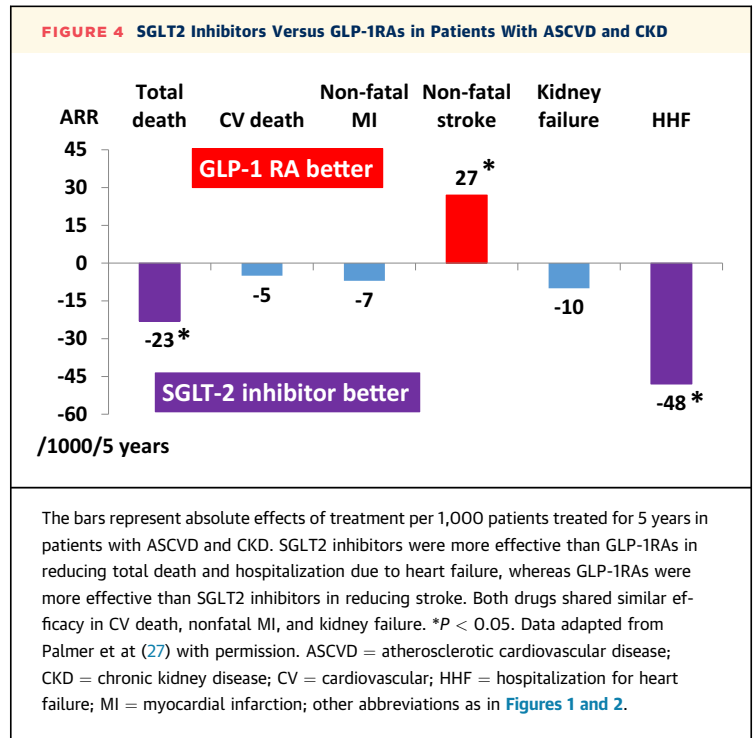
the present time. Adapting data from network meta-analysis is feasible for comparison. Two network meta-analyses focusing on comparison of SGLT2 inhibitors versus GLP-1RAs are cited here (25,27). The network meta-analysis by Yamada et al investigated the effects of these drugs on MACE and renal events (25). SGLT2 inhibitors shared similar effects with GLP-1RAs on MACE (relative risk: 0.94, 95% CI: 0.78-1.12) but were associated with a lower risk of renal events than GLP-1RAs (relative risk: 0.79, 95% CI: 0.63-0.99) (25).

A more comprehensive network meta-analysis updated to August 11, 2020, with data sourced from Medline, Embase, and Cochrane Central, was published by Parmer et al (27) and included a total of 421,346 patients from 764 trials, but 5 randomized control trials published after August 11, 2020, namely, VERTIS CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease) (20), EMPEROR-Reduced (21), DAPA-CKD (22), SCORED (23), and SOLOIST-WHF (24), were not included. The investigators estimated absolute effects of treatment per 1,000 patients treated for 5 years in patients at very low risk (no CV risk factors), low risk (3 or more CV risk factors), moderate risk (ASCVD), high risk (CKD), and very high risk (ASCVD + CKD). Six end points of interested were examined: all-cause death, CV death, nonfatal myocardial infarction, nonfatal stroke, kidney failure, and hospitalization for HF. The results are summarized in Figures 2 and 3. Both SGLT2 inhibitors and GLP-1RAs reduced all-cause death compared with placebo (HR: 0.77, 95% CI: 0.71-0.83 and HR: 0.88, 95% CI: 0.83-0.94, respectively). However, SGLT2 inhibitors were more effective than GLP-1RAs in reducing all-cause death (HR: 0.88, 95% CI: 0.79-0.98). For CV death and nonfatal myocardial infarction, both agents were effective compared with placebo (CV death: HR: 0.84, 95% CI: 0.76-0.92 and HR: 0.88, 95% CI: 0.80-0.96, respectively; nonfatal myocardial infarction: HR: 0.87, 95% CI: 0.79-0.97 and HR: 0.92, 95% CI: 0.85-0.99, respectively). SGLT2 inhibitors shared similar effects with GLP-1RAs in CV death and nonfatal myocardial infarction (CV death: HR: 0.96, 95% CI: 0.84-1.09; nonfatal myocardial infarction: HR: 0.85, 95% CI: 0.84-1.08). For nonfatal stroke, only GLP-1RAs were effective compared with placebo (SGLT2 inhibitors: HR: 1.01, 95% CI: 0.89-1.14; GLP-1RAs: HR: 0.84, 95% CI: 0.76-0.93). SGLT2 inhibitors caused more nonfatal stroke compared with GLP-1RAs (HR: 1.20, 95% CI: 1.03-1.41). For kidney failure, both agents were effective compared with placebo (HR: 0.71, 95% CI: 0.57-0.89 and HR: 0.78, 95% CI: 0.67-0.92,

respectively). SGLT2 inhibitors shared similar effects with GLP-1RAs in kidney failure (HR: 0.90, 95% CI: 0.69-1.20). SGLT2 inhibitors, but not GLP-1RAs, reduced the risk of hospitalization for HF compared with placebo (HR: 0.70, 95% CI: 0.63-0.77 and HR: 0.94, 95% CI: 0.85-1.03, respectively). SGLT2 inhibitors were more effective than GLP-1RAs in reducing hospitalization for HF (HR: 0.74, 95% CI: 0.65-0.85). Although GLP-1RAs shared similar efficacy with SGLT2 inhibitors in reducing kidney failure in this analysis, DAPA-CKD (22) and other trials (20,21,23,24) were not included in this network meta-analysis. It is generally thought that SGLT2 inhibitors are more effective than GLP-1RAs in renal protection.

PATIENTS WITH MULTIPLE COMORBID DISEASES

HF, CKD, and ASCVD are the most important comorbid diseases in patients with type 2 diabetes and are the main consideration in this consensus pathway. Patients with HF have the highest risk of all-cause death, followed by those with CKD and with ASCVD (Table 5). In the DAPA-HF trial, 56.4% had ischemic etiology, ie, they had HF with reduced ejection fraction and ASCVD (60,74). Compared with placebo, dapagliflozin reduced the primary end point to a similar extent in patients with and without ischemic etiology (HR: 0.77, 95% CI: 0.65-0.92 and HR: 0.71, 95% CI: 0.58-0.87, respectively; *P* for interaction = 0.55). Consistent benefits were observed for the components of the primary outcome and all-cause mortality (74). In the EMPEROR-Reduced trial, 51.8% had ischemic etiology (21). Compared with placebo, empagliflozin reduced the primary end point to a similar extent in both patients with and without ischemic etiology (HR: 0.82, 95% CI: 0.68-0.99 and HR: 0.67, 95% CI: 0.55-0.82, respectively; *P* for interaction > 0.05). In the DAPA-HF trial, 41% had eGFR <60 mL/min/1.73 m², ie, they had HF with reduced ejection fraction and CKD (75). The effect of dapagliflozin on the primary and secondary outcomes did not differ by eGFR category or by examining eGFR as a continuous measurement (75). The HR for the primary end point in patients with eGFR <60 mL/min/1.73 m² was 0.71 (95% CI: 0.59-0.86) versus 0.77 (95% CI: 0.64-0.93) in those with eGFR ≥60 mL/min/1.73 m² (*P* for interaction = 0.54) (75). In the EMPEROR-Reduced trial, 48.3% had eGFR <60 mL/min/1.73 m² (21). Compared with placebo, empagliflozin reduced the primary end point to a similar extent in patients with eGFR below and above 60 mL/min/1.73 m² (HR: 0.78, 95% CI: 0.65-0.93 and HR: 0.72, 95% CI: 0.58-0.90, respectively; *P* for interaction = 0.63) (76). Taken together, in patients



with HF with reduced ejection fraction plus ASCVD or CKD, SGLT2 inhibitors consistently reduced CV death and hospitalization for HF. Therefore, HF is taken as the first priority in the present stepwise consensus pathway for patients who have multiple comorbidities, and SGLT2 inhibitor is the treatment of choice.

The mortality rates in patients with CKD were generally higher than those with ASCVD (Table 5). The ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)) trial enrolled patients with acute coronary syndrome (77), and the mortality rate in this trial was higher than in other randomized control trials that enrolled patients with chronic ASCVD (52,55). SGLT2 inhibitors reduced all-cause death in CKD trials. For example, dapagliflozin decreased all-cause death by 26% versus placebo (HR: 0.74, 95% CI: 0.56-0.98) in the DAPA-CKD trial (73), in contrast to lack of evidence for GLP-1RAs. In DAPA-CKD, 37.4% had both CKD and ASCVD (78). Dapagliflozin reduced the primary composite end point (a composite of sustained decline in eGFR of ≥50%, end-stage renal disease, and death from renal or CV causes) to a similar extent in patients with (HR: 0.61, 95% CI: 0.47-0.79) and without (HR: 0.61, 95% CI: 0.48-0.78) ASCVD, with a *P* for interaction of 0.90. This was also true for the composite of hospitalization for HF and CV death

TABLE 6 Baseline Characteristics for Pooled Cohort Equation to Predict 10-Year Risk of ASCVD^a (86) and HF^b (89)

	ASCVD	HF
Sex	✓	✓
Age	✓	✓
Race	✓	✓
Total cholesterol	✓	✓
HDL cholesterol	✓	✓
Systolic blood pressure	✓	✓
Hypertension treatment	✓	✓
Smoker	✓	✓
Diabetes	✓	✓
Fasting glucose		✓
Body mass index		✓
QRS duration		✓

^a<https://clinical.com/Cardiology/ASCVD/PooledCohort.aspx>. ^b<https://hf-risk-calculator.surge.sh>.
ASCVD = atherosclerotic cardiovascular disease; HDL = high-density lipoprotein; HF = heart failure.

(HR: 0.70, 95% CI: 0.52-0.94 versus HR: 0.67, 95% CI: 0.40-1.13; *P* for interaction = 0.88) and for all-cause death (HR: 0.70, 95% CI: 0.51-0.95 versus HR: 0.63, 95% CI: 0.41-0.98; *P* for interaction = 0.71) (78). For patients with ASCVD and CKD included in the

network meta-analysis by Palmer et al, SGLT2 inhibitors were more effective than GLP-1RAs in reducing all-cause death and hospitalization for HF, whereas GLP-1RAs were more effective than SGLT2 inhibitors in reducing nonfatal stroke (27) (Figure 4). Taken together, in patients with CKD + ASCVD, SGLT2 inhibitors consistently reduced composite renal end points, CV death/hospitalization for HF, and all-cause death. Therefore, CKD sits in the second place in this stepwise consensus pathway for patients with multiple comorbidities, and SGLT2 inhibitors are preferred.

PREDICTION OF ASCVD AND HF IN PATIENTS WITH RISK FACTORS ALONE

Patients with diabetes may present with risk factors alone without ASCVD or HF. In a recent nationwide survey from Taiwan, more than 60% of patients with diabetes had risk factors alone without any history of CV disease (79). For patients with risk factors alone, equations for prediction of future risk of ASCVD and HF are required for the consensus pathway. We considered several factors in our selection of risk equations: 1) the risk equations should be based on the same derivative cohorts that can predict 10-year risk of both ASCVD and HF; 2) the total risk of ASCVD, including coronary heart disease and stroke, should be included in the calculation; 3) the risk equations have been widely adopted in major treatment guidelines; and 4) the risk equations have been developed specifically for diabetes population, including the UK Prospective Diabetes Study risk engine (80), the model from the Swedish National Diabetes Register (81), and an Australian cardiovascular risk equation (82). However, these prediction equations can predict the risk of coronary heart disease, but not the risks of stroke and HF. The Thrombolysis in Myocardial Infarction risk score can predict the risk of HF in patients with diabetes (83), but a risk score for ASCVD in patients with diabetes is lacking. Several prediction models were developed from general population, such as the Framingham Risk Score (84), the Prospective Cardiovascular Münster (PROCAM) score (85), the Pooled Cohort Equation (86), etc. The Framingham Risk Score and the PROCAM score can predict the risk of coronary heart disease, but not the risk of stroke (84,85). The Pooled Cohort Equation can predict 10-year risk of the first episode of ASCVD, including coronary heart disease and stroke, and has been widely accepted (86). It has been adopted by the recent U.S. lipid guidelines (87) and the US blood pressure guidelines

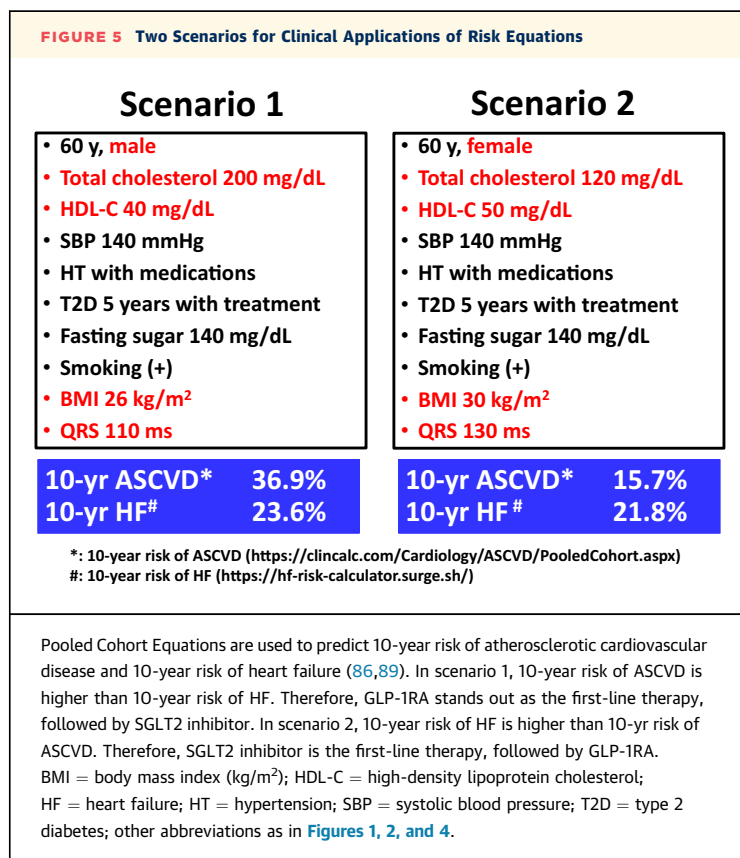


TABLE 7 Adverse Events of SGLT2 Inhibitors and GLP-1RAs

	SGLT2i vs Placebo	GLP-1RA vs Placebo	SGLT2i vs GLP-1RA	Anticipated Absolute Effects (95% CI), SGLT2i vs GLP-1RAs Over 5 Years per 1,000 Patients
Severe hypoglycemia	0.90 (0.70-1.16)	0.92 (0.79-1.08)	0.98 (0.73-1.31)	0 (-6 to +7)
Blindness	0.17 (0.01-4.07)	1.00 (0.23-4.41)	0.99 (0.57-1.73)	0 (0 to +1)
Amputation	1.14 (0.96-1.35)	0.33 (0.01-8.18)	3.43 (0.14-84.5)	72 (-27 to +1,000)
Diabetic ketoacidosis	1.04 (0.61-1.78)	0.61 (0.33-1.11)	1.71 (0.79-3.69)	1 (0 to +3)
Genital tract infection	3.50 (3.01-4.07)	0.70 (0.34-1.44)	5.00 (2.45-10.2)	158 (+64 to +299)
Fournier gangrene	0.56 (0.16-19.2)	NA	NA	NA
Severe gastrointestinal events	NA	2.46 (1.22-4.97)	NA	NA
Pancreatic cancer	1.77 (0.55-5.75)	1.19 (0.78-1.81)	1.49 (0.43-5.19)	+2 (-3 to +21)
Pancreatitis	0.64 (0.39-1.05)	1.18 (0.90-1.56)	0.54 (0.31-0.94)	-3 (-4 to 0)

Values are odds ratio (95% confidence interval). Adapted from Palmer et al (27) with permission.
 GLP-1RA = glucagon-like peptide 1 receptor agonists; NA = not available; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

(88). The Pooled Cohort Equation has been validated in patients with diabetes (86). A different formulation of Pooled Cohort Equation can also predict 10-year risk of the first incidence of HF (89), and has been validated in patients with diabetes as well (90). Web-based tools of the Pooled Cohort Equations are available for ASCVD and HF. The working group adopted the Pooled Cohort Equations in the present consensus to predict 10-year risks of ASCVD and HF in patients with risk factors alone (86,89). Table 6 presents the baseline characteristics that are required for these 2 risk equations. Figure 5 demonstrates 2 different scenarios for clinical applications of these 2 risk equations.

The websites of the online calculators for these 2 risk equations are <https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx> for 10-year risk of ASCVD and <https://hf-risk-calculator.surge.sh> for 10-year risk of HF.

ADVERSE EVENTS

Adverse events of these 2 classes of drugs should be taken into account when making the appropriate choice from the decision pathway. Table 7 presents the adverse events of these 2 classes of drugs (27). Except for 2 adverse events, the safety profiles of SGLT2 inhibitors were similar to GLP-1RAs. Genital tract infection was more common for SGLT2 inhibitors compared with placebo and GLP-1RAs. Severe gastrointestinal events were more common for GLP-1RAs compared with placebo, whereas data for SGLT2 inhibitors were limited. Pancreatitis was slightly less common for SGLT2 inhibitors compared with GLP-1RAs, albeit the absolute risk was very low. Patients with previous history of repeated

genital tract infections should be educated to improve personal hygiene before starting SGLT2 inhibitors. In patients planned for initiation of GLP-1RAs, gastrointestinal adverse events should be educated to improve gastrointestinal tolerability.

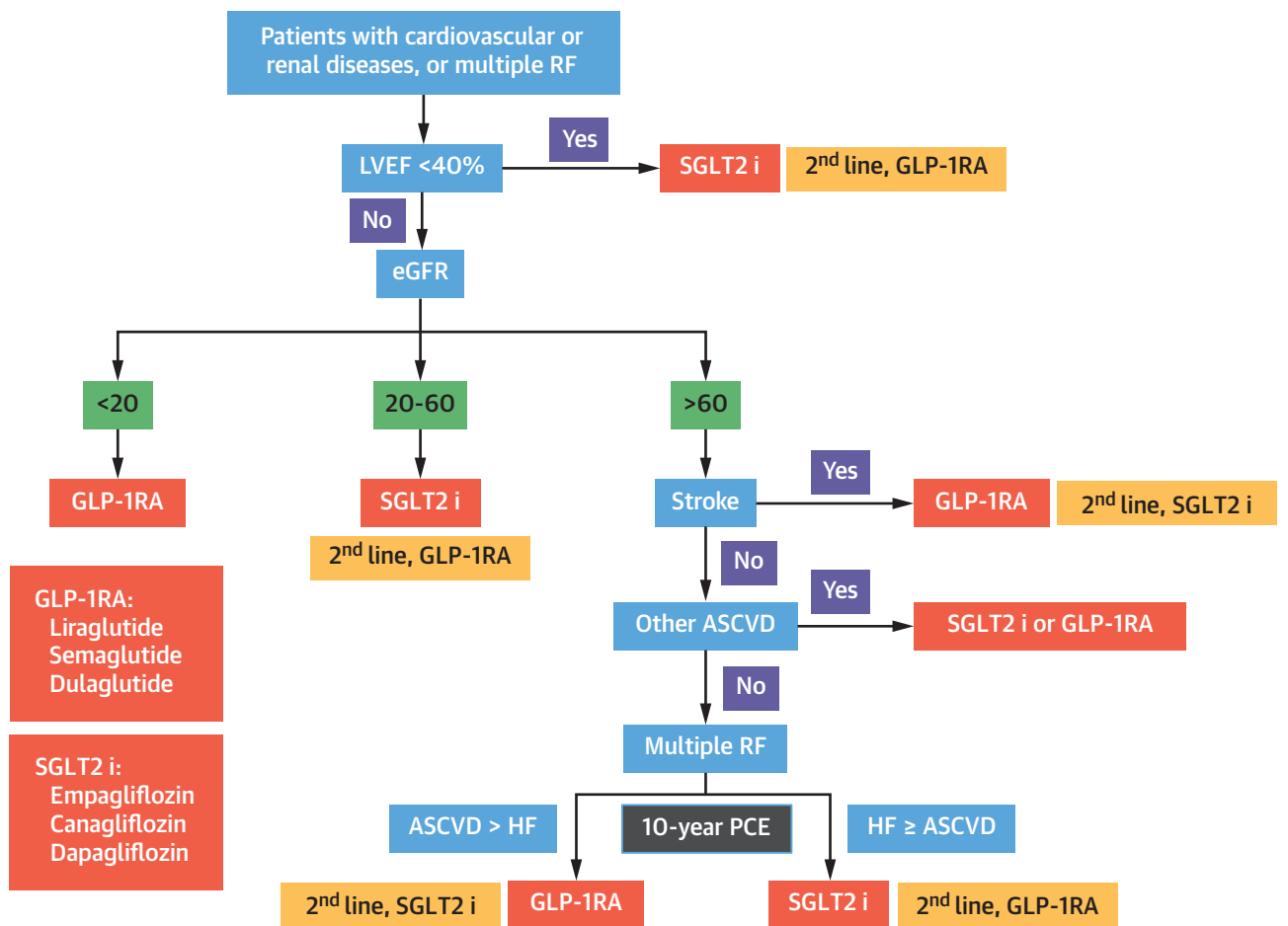
CONSENSUS PATHWAY

Patients with diabetes who have comorbid CV or renal diseases have higher risk of death and CV events compared with those who do not have these comorbidities. Therefore, the first step in the consensus pathway is to check for comorbid CV or renal diseases. As presented in Table 5, HF is associated with a higher risk of all-cause death than are CKD and ASCVD, and only SGLT2 inhibitors, not GLP-1RAs, can reduce CV death and hospitalization for HF. CKD ranks second in the consensus pathway, because it causes higher risk of death than ASCVD does. SGLT2 inhibitors, but not GLP-1RAs, reduce the composite renal end points, including eGFR deterioration and end-stage renal disease, in patients with CKD. Stroke should be the third consideration in the consensus pathway, where GLP-1RAs prevail.

Following are the 5 steps in our consensus pathway.

Step 1: Patients with HF with reduced ejection fraction (<40%) should be identified. SGLT2 inhibitors are recommended first and GLP-1RAs second.

Step 2: Patients with CKD with an eGFR ≤60 mL/min/1.73 m² should be next of interest. SGLT2 inhibitors are still the first recommendation and GLP-1RAs the second. When eGFR is <20 mL/min/1.73 m², SGLT2 inhibitors are

CENTRAL ILLUSTRATION Consensus Pathway on Novel Therapy for Type 2 DiabetesChiang, C.-E. et al. *JACC: Asia*. 2021;1(2):129-146.

SGLT2 inhibitors include those with proven efficacy, including empagliflozin, canagliflozin, and dapagliflozin. GLP-1RAs include those with proven efficacy, including liraglutide, semaglutide, and dulaglutide. ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate (mL/min/1.73 m²); GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; LVEF = left ventricular ejection fraction; PCE = Pooled Cohort Equation; RF = risk factor; SGLT2 i = sodium-glucose cotransporter 2 inhibitor.

contraindicated and GLP-1RAs remain as the choice.

Step 3: Patients with a history of stroke should be the next group of interest, because only GLP-1RAs are effective in reducing stroke.

Step 4: Patients with other types of ASCVD, excluding stroke, should be recognized. Either SGLT2 inhibitors or GLP-1RAs can be used, because both are equally effective in reducing MACE in patients with preexisting ASCVD.

Step 5: Patients with multiple risk factors are the final group of interest. Ten-year risk of HF and ASCVD should be calculated with the use of the Pooled Cohort Equations. SGLT2 inhibitors are preferred if the 10-year risk of HF is greater than or equal to that of ASCVD, and GLP-1RAs remain as the second choice. The opposite leading role of GLP-1RAs emerges when the 10-year risk of ASCVD is greater than that of HF, and SGLT2 inhibitors step down. **Central Illustration** shows the consensus pathway.

TABLE 8 Management of Other Risk Factors in Patients With High Cardiovascular Risk^a

Target	Standard-of-Care Therapies
Blood pressure <130/80 mm Hg	ACEI/ARB, CCB, thiazide, or in combination if required
LDL-C <70 mg/dL	High-intensity statins, or in combination with ezetimibe and PCSK9 inhibitors if required
Antiplatelet	Aspirin, or clopidogrel if aspirin intolerance

^aExisting ASCVD or 10-year ASCVD risk $\geq 15\%$ (86).
 ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CCB = calcium channel blocker; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

GLYCEMIC MANAGEMENT

Standard-of-care therapies for glycemic management also should be considered in patients with type 2 diabetes. We suggest a target HbA_{1c} of <7.0% for most adults (6,91). A more stringent HbA_{1c} target of <6.5% may be considered if this can be achieved without significant hypoglycemia or other adverse events (91). Metformin should be added if the HbA_{1c} target cannot be achieved with the use of SGLT2 inhibitors or GLP-1RAs (6,18). Other antidiabetic agents, such as pioglitazone, dipeptidyl peptidase 4 inhibitors, and sulfonylurea can be added after metformin when appropriate (6,18).

MANAGEMENT OF OTHER CV RISK FACTORS

For individuals with diabetes and a higher CV risk (existing ASCVD or 10-year ASCVD risk $\geq 15\%$ as defined by Pooled Cohort Equation) (86), intensive blood pressure and lipid control, together with antiplatelet therapies, also are required (4,92,93). Table 8 shows the treatment targets and standard of care therapies for patients with high CV risk. Details about these strategies are beyond the scope of the present consensus.

SUMMARY

The working group of the Taiwan Society of Cardiology has formulated a new stepwise consensus

pathway. This consensus pathway provides health care workers a complement to guidelines in choosing novel antidiabetic agents in their daily practice. The consensus pathway was based on the most updated evidence from recent randomized control trials, meta-analyses, and network meta-analyses. Nevertheless, final decisions regarding use of these therapies may still need to be individualized and based on clinicians’ discretion.

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HIGHLIGHTS

- SGLT2 inhibitors and GLP-1 RAs decreased CV endpoints in a majority of clinical trials.
- SGLT2 inhibitors reduced renal endpoints and HF, while GLP-1RAs reduced stroke.
- Using a 5-step algorithm, we can prioritize medication in different clinical settings.

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ADDRESS FOR CORRESPONDENCE: Dr Chern-En Chiang, General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan. E-mail: cechiang@vghtpe.gov.tw.

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APPENDIX For supplemental methods, figures, and a table, please see the online version of this paper.

