2020 Consensus of Taiwan Society of Cardiology on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

Chern-En Chiang[a,b,c,*], Kwo-Chang Ueng[d], Ting-Hsing Chao[e], Tsung-Hsien Lin[f], Yih-Jer Wu[g,h], Kang-Ling Wang[a,b,c], Shih-Hsien Sung[i,j,k], Hung-I Yeh[g,h], Yi-Heng Li[l], Ping-Yen Liu[l,m], Kuan-Cheng Chang[n,o], Kou-Gi Shyu[p], Jin-Long Huang[q], Cheng-Dao Tsai[r], Huei-Fong Hung[p], Ming-En Liu[s], Tze-Fan Chao[b,t], Shu-Meng Cheng[u], Hao-Min Cheng[b,c,u,v,w], Pao-Hsien Chu[x,y], Wei-Hsian Yin[c,z], Yen-Wen Wu[c,aa,ab], Wen-Jone Chen[ac], Wen-Ter Lai[f,] Shing-Jong Lin[ad,ae,af], San-Jou Yeh[x], Juey-Jen Hwang[ag,ah,*]

[a]General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [d]Chung-Shan Medical University Hospital, Taichung, Taiwan, ROC; [e]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC; [f]Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC; [g]Department of Medicine, Mackay Medical College, New Taipei City, Taiwan, ROC; [h]Cardiovascular Center, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan, ROC; [i]Department of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [j]Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [k]Institute of Public Health and Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan, ROC; [l]Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC; [m]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, ROC; [n]Division of Cardiovascular Medicine, China Medical University Hospital, Taichung, Taiwan, ROC; [o]School of Medicine, China Medical University, Taichung, Taiwan, ROC; [p]Division of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ROC; [q]Cardiovascular center, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [r]Department of Medicine, Changhua Christian Hospital, Changhua, Taiwan, ROC; [s]Division of Cardiology, Department of Internal Medicine, Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan, ROC; [t]Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, ROC; [u]Division of Cardiology, Department of Medicine, Tri-Service General Hospital, Taipei, Taiwan, ROC; [u]Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [v]Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, ROC; [w]Institute of Health and Welfare Policy, National Yang-Ming University, Taipei, Taiwan, ROC; [x]Department of Cardiology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, ROC; [y]School of Medicine, Chang Gung University, Taoyuan, Taiwan, ROC; [z]Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [aa]Division of Cardiology, Cardiovascular Medical Center, and Department of Nuclear, ROC Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan, ROC; [ab]Department of Internal Medicine and Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC; [ac]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC; [ad]Taipei Heart Institute, Taipei Medical University, Taipei, Taiwan, ROC; [ae]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [af]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [ag]Cardiovascular Division, Department of Internal Medicine, National Taiwan, ROC, University College of Medicine and Hospital, Taipei, Taiwan, ROC; [ah]Cardiovascular Center, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan, ROC

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Address Correspondence. Dr. Chern-En Chiang, General Clinical Research Center, Department of Medical Research, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail: cechiang@vghtpe.gov.tw (C-E. Chiang); Dr. Juey-Jen Hwang, Cardiovascular Division, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, 7, Chung Shan S. Road. Zhongzheng Dist., Taipei 100, Taiwan, ROC. E-mail: jueyhwang@ntu.edu.tw (J.-J. Hwang).

Journal of Chinese Medical Association. (2020) 83: 587-621.

Received May 14, 2020; accepted May 15, 2020.

doi: 10.1097/JCMA.0000000000000359.

<zdoi: 10.1097/JCMA.0000000000000359>

Abstract: The global incidence and prevalence of type 2 diabetes have been escalating in recent decades. The total diabetic population is expected to increase from 415 million in 2015 to 642 million by 2040. Patients with type 2 diabetes have an increased risk of atherosclerotic cardiovascular disease (ASCVD). About two-thirds of patients with type 2 diabetes died of ASCVD. The association between hyperglycemia and elevated cardiovascular (CV) risk has been demonstrated in multiple cohort studies. However, clinical trials of intensive glucose reduction by conventional antidiabetic agents did not significantly reduce macrovascular outcomes.

In December 2008, U.S. Food and Drug Administration issued a mandate that every new antidiabetic agent requires rigorous assessments of its CV safety. Thereafter, more than 200,000 patients have been enrolled in a number of randomized controlled trials (RCTs). These trials were initially designed to prove noninferiority. It turned out that some of these trials demonstrated superiority of some new antidiabetic agents versus placebo in reducing CV endpoints, including macrovascular events, renal events, and heart failure. These results are important in clinical practice and also provide an opportunity for academic society to formulate treatment guidelines or consensus to provide specific recommendations for glucose control in various CV diseases.

In 2018, the Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC) published the first joint consensus on the "Pharmacological Management of Patients with Type 2 Diabetes and Cardiovascular Diseases." In 2020, TSOC appointed a new consensus group to revise the previous version. The updated 2020 consensus was comprised of 5 major parts: (1) treatment of diabetes in patients with multiple risk factors, (2) treatment of diabetes in patients with coronary heart disease, (3) treatment of diabetes in patients with stage 3 chronic kidney disease, (4) treatment of diabetes in patients with a history of stroke, and (5) treatment of diabetes in patients with heart failure. The members of the consensus group thoroughly reviewed all the evidence, mainly RCTs, and also included meta-analyses and real-world evidence. The treatment targets of HbA1c were finalized. The antidiabetic agents were ranked according to their clinical evidence. The consensus is not mandatory. The final decision may need to be individualized and based on clinicians' discretion.

Keywords: Antidiabetic agents; Coronary heart disease; Chronic kidney disease; Heart failure; Major atherosclerotic cardiovascular event; Risk factor; Stroke; Type 2 diabetes

1. INTRODUCTION

Type 2 diabetes is becoming a pandemic disease in the twenty-first century.[1] The global incidence and prevalence of diabetes quadrupled between 1980 and 2004.[1] The global prevalence of diabetes among adults aged 18 years or older has risen from 4.7% in 1980 to 8.5% in 2014.[2] The total diabetic population will increase from 415 million in 2015 to 642 million by 2040,[3] much higher than those of hypertension and hyperlipidemia. During the last decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries.[4] According to recent International Diabetes Federation report, more than 230 million Asian individuals are living with diabetes, accounting for approximately 55% of the world's diabetic population, and this number is expected to exceed 355 million by 2040.[5]

Atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD), is the major cause of death and disability in patients with type 2 diabetes.[6] About two-thirds of causes of death in type 2 diabetes are due to ASCVD.[7] In a recent pooled analysis of more than 1 million participants from Asia, patients with diabetes had a 1.89-fold risk of all-cause death, 3.08-fold risk of renal disease, 2.57-fold in CHD, and 2.15-fold in ischemic stroke, compared with patients without diabetes.[5] Many macrovascular complications develop 10–15 years before the clinical diagnosis of diabetes, making management of these associated ASCVD even more difficult.[8]

Though a wealth of evidence supports the association between hyperglycemia and elevated cardiovascular (CV) risk,[9,10] randomized control trials (RCTs) of intensive glucose reduction did not significantly reduce macrovascular outcomes.[11–14] We did not know why decrease in blood sugar could not be translated to a reduction in ASCVD, though some possible explanations prevailed. The durations of these RCTs were too short to show positive findings, whereas longer follow-up studies did demonstrate the efficacy of lowering levels of glucose.[11–16] Or, more hypoglycemic episodes might neutralize their beneficial effects, given that a more recently meta-analysis showed a benefit of using safer antidiabetic agents (dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 receptor agonist [GLP-1 RA], and sodium/glucose co-transporter 2 [SGLT-2] inhibitors in reducing macrovascular diseases.[17]

Previously, the improvement in glycemic control was accepted as a surrogate for a reduction in microvascular complications. Until 2008, regulatory requirements for approval of antidiabetic agents were restricted to proving effectiveness on lowering glycated hemoglobin (HbA1c) and short-term safety; there were no trials adequately powered to evaluate CV safety or efficacy.[18,19] The duration of trials is around 6–12 months or shorter, generally requiring only 300–600 patients exposed for 6 months, and only 100 patients exposed for a year.[19] These listing trials were generally too small and too short and included patients with CV risk too low to assess effects on CV safety. An important turning point in the history of drug development of antidiabetic agents happened in 2007.[20] An important meta-analysis of 27,847 patients from 42 trials disclosed serious adverse effects of rosiglitazone that the use of rosiglitazone was associated with significant increases in the risk of myocardial infarction (MI) (Odds ratio [OR] 1.43, 95% CI 1.03–1.98, p = 0.03) and CV death (OR 1.64, 95% CI 0.98–2.74, p = 0.06).[20] This unexpected finding and the increasing concerns over the CV safety of other antidiabetic drugs such as pioglitazone[21] and muraglitazar,[22] spurred the regulatory reassessment of guidance to industry sponsors with the development of new antidiabetic drugs.

The U.S. Food and Drug Administration (FDA) convened an Endocrinologic and Metabolic Drugs Advisory Committee in July 2008. The committee voted 14:2 in favor of requirement for long-term CV outcome trials to rule out increased risk of major adverse cardiovascular events (MACE) for all new antidiabetic therapies.[19] The requirement was that there was no substantial increase in CV risk both before and after marketing approval. This is a safety requirement that only noninferiority to placebo was required. The European Medicines Agency also followed the same regulatory requirement since 2012. As of September 18, 2019, 18 CV outcome trials have been completed since the issuance of the guidance, and more than 200,000 patients have been studied.[19] Most of these trials had the 3-point MACE outcome (CV death, nonfatal MI, and nonfatal stroke) that was required by U.S. FDA. Two trials added hospitalization for unstable angina to create 4-point MACE as primary endpoints (the ELIXA trial and the TECOS trial).[23,24] Table 1 shows recent CV outcomes of antidiabetic drugs: DPP-4 inhibitors, GLP-1 RAs, and SGLT-2 inhibitors. The MACE rates generally correlated with baseline CV risk ranked by prior ASCVD, except 3 trials (the CREDENCE trial,[25] the CARMELINA trial,[26] and the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF] trial[27]). The CREDENCE trial[25] and the CARMELINA trial[26] enrolled patients with chronic kidney disease (CKD), while the DAPA-HF trial only enrolled patients with heart failure (HF) with reduced ejection fraction (HFrEF).[27] Though initially designed for proving noninferiority, several trials surprisingly demonstrated superiority versus placebo. Table 2 shows the effects of new antidiabetic drugs on CV outcomes in these trials. Without these large-scale outcome trials, we never would be able to know their broad and substantial benefits. For the first time in the history, antidiabetic agents got nondiabetic indications, such as renal protection and HF reduction. We are now moving to a new era of antidiabetic treatment.

In 2018, the Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC) have published the "2018 Consensus of TSOC/DAROC on the Pharmacological Management of Patients with Type 2 Diabetes and Cardiovascular Diseases."[28] Given that many new trials and data were emerging, TSOC recently organized a new consensus group to update the previous one and formulated the new "2020 Consensus of Taiwan Society of Cardiology on the Pharmacological Management of Patients with Type 2 Diabetes and Cardiovascular Diseases." The consensus started with a reconsideration of the role of metformin as the first-line therapy, followed by 5 major parts: (1) treatment of diabetes in patients with multiple risk factors, (2) treatment of diabetes in patients with CHD, (3) treatment of diabetes in patients with stage 3 chronic kidney disease, (4) treatment of diabetes in patients with a history of stroke, and 5) treatment of diabetes in patients with HF.

The members of the consensus group comprehensively reviewed all evidences, including RCTs, meta-analyses, cohort studies, and studies using claim data. The rationale for prioritizing antidiabetic drugs for different cardiovascular disease (CVD) was based on the findings from RCTs first. The strongest evidence came from an RCT specifically testing one drug versus another (or placebo) in patients with a specific disease condition such as CHD, stroke, CKD, or HF. However, the number of such disease-specific trials is very limited. Most of the recent RCTs enrolled patients across the spectrum of ASCVD including CHD, ischemic stroke, and PAD, rather than having a limited enrollment to a specific patient population. The second tier of evidence came from any subgroup analysis of the three-point MACE in patients with or without a specific CVD. We examined if the efficacy remained significant or was even better in patients with preexisting CVD. The third tier evidence is based on the assessments of the individual endpoint, that is, MI or stroke, among the three-point MACE and evaluated if any given drug reduced any specific endpoint. If

Table 1

Background characteristics and event rates of the control groups in recent CV outcome trials of new antidiabetic drugs, ranked by prior ASCVD event

	Background characteristics				Event rates (control group)/year			
Trials	ASCVD	RF	CKD[a]	HF	MACE[b]	HF	CV death	ALL death
REWIND[61]	31.5%	68.5%	22.6%	8.7%	2.66%	0.89%	1.34%	2.29%
DECLARE[36]	40.8%	59.2%	9.1%	10.2%	2.42%	0.85%	0.71%	1.64%
CAROLINA[55]	41.7%	36.9%	17.9%	5%	2.1%	0.5%	0.9%	1.8%
CREDENCE[25]	50.4%	49.6%	60.2%	14.8%	4.87%	2.53%	2.44%	3.5%
CARMELINA[26]	57%	43%	51.1%	26.4%	5.63%	3.04%	3.40%	4.8%
DAPA-HF[27]	57.3%	42.7%	40.7%	100%	NR	9.8%	7.9%	9.5%
CANVAS[35]	65.6%	33.3%	17.9%	14.4%	3.15%	0.87%	1.28%	1.95%
EXSCEL[56]	73%	27%	22.1%	16.6%	4.0%	1.0%	1.5%	2.3%
TECOS[24]	74.5%	25.5%	9.3%	18.0%	4.17%[c]	1.09%	1.67%	2.45%
SAVOR[53]	78.7%	21.3%	15.6%	12.8%	3.7%	1.4%	1.45%	2.1%
LEADER[57]	80.6%	19.4%	22.3%	14%	3.9%	1.4%	1.6%	2.5%
SUSTAIN-6[58]	83%	17%	28.5%	25%	4.44%	1.61%	1.35%	1.76%
PIONEER-6[59]	85%	15%	28.2%	12.2%	3.7%	1.2%	1.4%	2.2%
EMPA-REG[34]	100%	0%	26.0%	10.5%	4.39%	1.45%	2.02%	2.86%
HARMONY[60]	100%	0%	19%	20%	5.87%	1.2%	1.72%	2.56%
ELIXA[23]	100% (ACS)	0%	23.2%	22.3%	6.2%[c]	1.9%	2.4%	3.3%
EXAMINE[54]	100% (ACS)	0%	29.6%	27.8%	No normalized data			

[a]eGFR < 60 mL/min/1.73m2.

[b]Data from the control group.

[c]Four-point MACE (CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina).

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPA-REG = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; MACE = major adverse cardiovascular events, including CV death, nonfatal myocardial infarction, nonfatal stroke; NR = not reported; RF = risk factor.

Table 2

Effects of new antidiabetic drugs on CV outcomes

	Drug name	MACE (HR)	MI (HR)	Stroke (HR)	Renal events (HR)	HHF (HR)	CV death (HR)	All-cause death (HR)
DPP-4 inhibitors								
SAVOR[53]	Saxagliptin	1.00 (0.89–1.12)	0.95 (0.80–1.12)	1.11 (0.88–1.39)	1.08 (0.88–1.32)	1.27 (1.07–1.51)	1.03 (0.87–1.22)	1.11 (0.96–1.27)
EXAMINE[54]	Alogliptin	0.96 (NR)	1.08 (0.88–1.33)	0.91 (0.55–1.50)	NR	1.07 (0.79–1.46)	0.85 (0.66–1.10)	0.88 (0.71–1.09)
TECOS[24]	Sitagliptin	0.98[a] (0.88–1.09)	0.95 (0.81–1.11)	0.97 (0.79–1.19)	NR	1.00 (0.83–1.20)	1.03 (0.89–1.19)	1.01 (0.90–1.14)
CARMELINA[26]	Linagliptin	1.02 (0.89–1.17)	1.12 (0.90–1.40)	0.91 (0.67–1.23)	1.04 (0.89–1.22)	0.90 (0.74–1.08)	0.96 (0.81–1.14)	0.98 (0.84–1.13)
GLP-1 receptor agonists								
ELIXA[23]	Lixisenatide	1.02[a] (0.89–1.17)	1.03 (0.87–1.22)	1.12 (0.79–1.58)	NR	0.96 (0.75–1.23)	0.98 (0.78–1.22)	0.94 (0.78–1.13)
EXSCEL[56]	Exenatide-ER	0.91 (0.83–1.00)	0.97 (0.85–1.10)	0.85 (0.70–1.03)	NR	0.94 (0.78–1.13)	0.88 (0.76–1.02)	0.86 (0.77–0.97)
LEADER[57]	Liraglutide	0.87 (0.78–0.97)	0.86 (0.73–1.00)	0.86 (0.71–1.06)	0.78 (0.67–0.92)	0.87 (0.73–1.05)	0.78 (0.66–0.93)	0.85 (0.74–0.97)
SUSTAIN-6[58]	Semaglutide	0.74 (0.58–0.95)	0.74 (0.51–1.08)	0.61 (0.38–0.99)	0.64 (0.46–0.88)	1.11 (0.77–1.61)	0.98 (0.65–1.48)	1.05 (0.74–1.50)
PIONEER-6[59]	Oral semaglutide	0.79 (0.57–1.11)	1.18 (0.73–1.90)	0.74 (0.35–1.57)	NR	0.86 (0.48–1.55)	0.49 (0.27–0.92)	0.51 (0.31–0.84)
HARMONY[60]	Albiglutide	0.78 (0.68–0.90)	0.75 (0.61–0.90)	0.86 (0.66–1.14)	NR	0.85 (0.70–1.04)	0.93 (0.73–1.19)	0.95 (0.79–1.16)
REWIND[61]	Dulaglutide	0.88 (0.79–0.99)	0.96 (0.79–1.15)	0.76 (0.62–0.94)	0.85 (0.77–0.93)	0.93 (0.77–1.12)	0.91 (0.78–1.06)	0.90 (0.80–1.01)
SGLT-2 inhibitors								
EMPA-REG[34]	Empagliflozin	0.86 (0.74–0.99)	0.87 (0.70–1.09)	1.18 (0.89–1.56)	0.54[b] (0.40–0.75)	0.65 (0.50–0.85)	0.62 (0.49–0.77)	0.68 (0.57–0.82)
CANVAS[35]	Canagliflozin	0.86 (0.75–0.97)	0.89 (0.73–1.09)	0.87 (0.69–1.09)	0.60 (0.47–0.77)	0.67 (0.52–0.87)	0.87 (0.72–1.06)	0.87 (0.74–1.01)
DECLARE[36]	Dapagliflozin	0.93 (0.84–1.03)	0.89 (0.77–1.01)	1.01 (0.84–1.21)	0.53 (0.43–0.66)	0.73 (0.61–0.88)	0.98 (0.82–1.17)	0.93 (0.82–1.04)
CREDENCE[25]	Canagliflozin	0.80 (0.67–0.95)	0.86[c] (0.64–1.16)	0.77[c] (0.55–1.08)	0.70 (0.59–0.82)	0.61 (0.47–0.80)	0.78 (0.61–1.00)	0.83 (0.68–1.02)

CV = cardiovascular; EMPA-REG = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events, including CV death, nonfatal myocardial infarction, and nonfatal stroke; MI = myocardial infarction; NR = not reported.

[a]Four-point MACE (CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina).

[b]Data from Wanner et al.[137]

[c]Data from Mahaffey et al.[293]

the previous three levels of evidence was not available or did not provide any significant information, meta-analysis was then taken into account, followed by cohort studies and claim data studies. All the available evidences were fully discussed and final decision was made by consensus. If there was disagreement in the discussion, the final decision was determined by votes.

The consensus group also tried to look for a specific HbA1c target for each individual disease. Less stringent goal for HbA1c may be needed for patients with a history of severe hypoglycemia or poor cooperation. If a patient has more than one disease entity, and the optimal HbA1c and the choice of drug is different for these disease entities, safety should be the first priority, that

is, those drugs which are contraindicated for one disease entity, though indicated in another disease entity, should not be chosen. The consensus is not mandatory. The final decision may need to be individualized and based on clinicians' discretion.

2. RECONSIDERATION OF THE POSITION OF METFORMIN

Metformin has been put in the first choice in major guidelines for decades. In fact, the supporting evidence is scarce. The only RCT testing metformin's CV effects was the United Kingdom Prospective Diabetes Study (UKPDS) 34 trial.[29] This trial enrolled patients with freshly diagnosed type 2 diabetes or prediabetes. Among 753 mildly obese patients, 342 patients were randomized to metformin and 411 patients were randomized to conventional glucose therapy. Metformin reduced MI by 39% (p = 0.01), and all-cause death by 36% (p = 0.011).[29] The total event numbers were actually very small: total 52 CV deaths for analysis of conventional care versus metformin (36 vs. 16), and a total of 251 cases with MI partitioned for analyses across 3 groups that included patients randomized to a policy of intensive control with insulins/sulfonylureas (SUs), leaving only 39 MI events in the metformin arm.[18] Furthermore, patients with recent MI, HF, or angina were excluded, limiting the generalizability of the results to patients with higher CV risk. In addition, the trial was not blinded and there was no placebo group. The findings were further challenged by other statistical issues.[30] More importantly, the results of UKPDS 34 could not be replicated or supported by meta-analysis.[31,32]

In the UKPDS trial, only 1.5% patients received aspirin, and less than 1% received statins. The percentage of patients taking renin–angiotensin–aldosterone system blockade was not reported, but presumably low. Therefore, with contemporary management of diabetes, the effects of metformin are questionable.

Among the recent RCTs of new antidiabetic agents, 18%–40% of trial participants were not treated with metformin.[18] Given that such a large number of trial participants in each of these outcome trials were no treated with metformin at baseline, the results should not be interpreted exclusively as adding the novel therapy to metformin, but instead as effects on CV outcomes independent of metformin use.[18] Therefore, unilaterally endorsing metformin as first-line medication for diabetic patients with ASCVD and stepping down to second-line drugs, especially for those with proven ASCVD efficacy, only when HbA1c is not at target are no longer evidence-based strategies and must be reconsidered.[18]

Large-scale RCTs are needed. There are 2 ongoing RCTs testing the efficacy of metformin. The VA-IMPACT trial compared metformin versus placebo in about 8,000 patients with prediabetes and established ASCVD (NCT02915198). The SMARTEST trial compared metformin versus dapagliflozin in about 4300 patients with type 2 diabetes and risk factors (NCT03982381). However, we need to wait until 2024 to have results.

In a recent subanalysis from the SAVOR trial, metformin reduced all-cause death by about 25%.[33] In an additional meta-analysis of 815,639 patients in the same article, metformin reduced 26% in all-cause death.[33] However, in patients with prior HF or moderate-to-severe CKD, metformin could not reduce all-cause death.[33] This is a strong evidence to suggest that in patients with prior HF or moderate-to-severe CKD metformin should be moved to second-line therapy, and SGLT-2 inhibitors, with established evidence in reducing renal events, CV endpoints, and hospitalization for HF, should step up as the first choice.[25,27,34–36] Indeed, in the recent European guidelines, SGLT-2 inhibitors or GLP-1 RAs, but not metformin, were recommended in drug naive patients who have ASCVD or high/very high CV risk.[37] On the other hand, metformin have several benefits, including global availability, affordability, overall safety, and tolerability, that make it the default first-line therapy in most diabetes guidelines.

3. TREATMENT OF DIABETES IN PATIENTS WITH MULTIPLE RISK FACTORS

3.1. Rationale

Type 2 diabetes is a major risk factor for ASCVD, doubling the risks of CHD, stroke, and CV death.[38] Many CV risk factors, such as hypertension,[39] dyslipidemia,[40] obesity,[41] and CKD,[42] commonly coexist with diabetes and further aggravate the overall risk for developing CVD in diabetic patients. To date, there is a dearth of study specifically looking into the target of HbA1c and antidiabetic strategy for patients with risk factor alone (primary prevention).

3.2. Target of HbA1c

Whether lowering HbA1c leads to a better CV outcome in primary prevention is complex and still an issue of debate. Several factors, such as antidiabetic drug, comorbid disease, established ASCVD, age, and duration of diabetes, may intricately determine the final impact of HbA1c on CV outcomes.

The UKPDS trial enrolled patients with an average baseline HbA1c of 7.1%–7.2%.[11,29] Those with more than one vascular events were excluded. Intensive therapy with SU or insulin-reduced HbA1c from 7.9% to 7.0% but failed to reduce macrovascular events at the end of study.[11] Instead, a reduction in macrovascular events was observed 15 years later.[43] The metformin arm of UKPDS (UKPDS 34) enrolled exclusively overweight (>120% ideal body weight) patients. Median HbA1c levels were reduced from 8.0% to 7.4%, leading to a 36% reduction in all-cause mortality (p = 0.011) and a 30% reduction in all macrovascular diseases (p = 0.020) compared with conventional (diet control) therapy.[29]

The landmark trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[12] the Action in Diabetes and Vascular Disease: Preterax and Diamicron–MR Controlled Evaluation (ADVANCE) trial,[13] and the Veterans Affairs Diabetes Trial (VADT),[14] targeting more stringent HbA1c levels to <6.5%–7.0% or even lower, generally failed to demonstrate macrovascular benefit. Unexpectedly, the ACCORD trial shows a higher all-cause mortality and CV death in the intensive treatment group.[12] When compared with patients in the UKPDS 34,[29] there were many differences among these trials. The participants in the three trials were older (60–66 vs. 53 years) and had longer diabetes durations (8–12 years vs. newly diagnosed), more established ASCVD (32%–41% vs. 7.5%), more major hypoglycemic events (2.7%–16.2% vs. <1%), as well as significant weight gain in the intensive treatment groups of the three trials, which was not observed in the UKPDS 34 trial. All these differences intricately interacted with HbA1c lowering and affected the final CV outcomes. For example, severe hypoglycemic event has been shown to be a major risk factor for the subsequent all-cause mortality and CV events[44] and undermines the CV benefit from HbA1c reduction. In contrast, a population cohort study enrolling 24 752 metformin initiators shows that an early achievement of HbA1c < 6.5% is associated with significantly 18% lower CV events (death, MI, or stroke) than HbA1c 6.5%–7.0% stratum (HR 1.18, 95% CI: 1.07–1.30).[45] The consensus group recommended HbA1c < 7.0% as the appropriate target for diabetic patients with risk factor alone. For those who are younger and have a shorter diabetes duration, a more stringent HbA1c target < 6.5% could be helpful. A less stringent

HbA1c target (for example, <8.0%) may be optimal for elderly patients with long diabetes history, established CVD, multiple comorbidities, and limited life expectancy.[37]

3.3. Choice of Drugs

RCTs provide strongest evidence in the hierarchy of antidiabetic agents for diabetic patients with risk factor alone. Nevertheless, RCT specifically for diabetic patients with risk factor alone is scarce. The subgroup analysis in RCTs could be helpful. The effect of antidiabetic drugs on reducing CV risk factors, such as blood pressure, may also be taken into account when making choices.

3.3.1. Traditional antidiabetic drugs

The UKPDS trial enrolled merely 7.5% of participants with established ASCVD,[29] that is, most patients had risk factor alone. Metformin, compared with diet control, significantly reduced macrovascular events at the end of the study without obvious increase in hypoglycemic episodes and weight gain.[29] In contrast, SU and insulin did not reduce CV events during the study period.[11] Instead, their effects on reducing CV events appeared very late, about 10 years later (Legacy Effect).[43] Considering safety, efficacy, and onset of benefit, most of guidelines recommended metformin as the first-line antidiabetic drug for primary prevention,[46] despite of different opinions.[18,30] A meta-analysis of 35 RCTs supported this recommendation that participants treated with metformin versus comparator showing that metformin treatment was associated with lower CV events, compared with placebo or no treatment (HR 0.79, 95% CI 0.64–0.98, p = 0.031), but not with active comparators (HR 1.03, 95% CI 0.72–1.77, p = 0.89).[47] However, a more recent meta-analysis enrolling 301 RCTs had different finding that there was no significant difference in terms of CV or all-cause mortality among nine different classes of antidiabetic drugs.[48] This analysis did not consider the timing for the occurrence of the vascular benefit. Concomitant use of metformin and SU increased mortality,[29,47] which might result from more hypoglycemic episodes.[44]

The ORIGIN trial enrolled 12 537 people with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes to receive basal insulin or placebo.[49] About 60% of participants had prior ASCVD. Basal insulin had a neutral effect on three-point MACE compared with standard care (including metformin) (HR 1.02, 95% CI 0.94–1.11), though new-onset diabetes was reduced.[49] The effects on three-point MACE were similar in patients with or without prior ASCVD (HRs 0.97, 95% CI 0.87–1.07 vs. 1.17, 95% CI 1.00–1.37, p value for interaction 0.05), though it indeed led to more hypoglycemic episodes and significant weight gain.[49]

The NAVIGATOR trial is the only outcome trial for glinides. It enrolled exclusively prediabetes participants and 24% had established ASCVD and 76% had risk factor alone.[50] Nateglinide had a neutral effect on the CV events (HR 0.93, 95% CI 0.83–1.03, p = 0.16), but significantly increased hypoglycemic episodes and body weight, compared with the placebo group.[50] The CV effect was similar in patients with risk factor alone compared with patients with established ASCVD (HRs 1.00, 95% CI 0.86–1.17 vs. 0.86, 95% CI 0.74–1.00, p value for interaction 0.16).[50] Taking into account all these evidence, metformin has a high priority in diabetic patients with risk factors alone. Low priority was given to SU, glinides, and insulin, due to increased risks of hypoglycemia and weight gain.

3.3.2. Alpha-glucosidase inhibitors

The STOP-NIDDM trial enrolled participants with impaired glucose tolerance, and only 4.8% of participants had established ASCVD, very close to a CV primary prevention trial of prediabetes patients.[51] Acarbose significantly reduced CV events, particularly MI, versus placebo (1 vs. 12 events, p = 0.02).[51] The trial had relatively small sample size and few CV events (1368 participants with 47 CV events in total).[51] The recent Acarbose Cardiovascular Evaluation (ACE) trial was more robust and enrolled 6522 Chinese participants with established CHD and impaired glucose tolerance (IGT) (secondary prevention), acarbose failed to demonstrate any CV benefit versus placebo (5-point MACE, HR 0.98, 95% CI 0.86-1.11, p=0.73).[52] Although there is a weak evidence for acarbose in the primary prevention, it doesn't get high priority of recommendation in diabetic patients with risk factors alone.

3.3.3. Thiazolidinedione

There has been no CV primary prevention trial of peroxisome proliferator-activated receptor gamma agonists. The PROactive trial is a secondary prevention trial enrolling 5238 high-risk patients with established ASCVD. Pioglitazone significantly reduced three-point MACE (HR 0.84, 95% CI 0.72–0.98) at the cost of a significant increase in HF hospitalization.[15]

3.3.4. DPP-4 inhibitors

Among the four RCTs of DPP-4 inhibitors, the majority of patients had established ASCVD (Table 1).[24,26,53,54] In general, all the DPP-4 inhibitors had neutral effects on MACE (Table 2). In the subgroup analyses available, all these DPP-4 inhibitors had neutral effects on MACE in patients with risk factor alone. The CAROLINA trial compared linagliptin versus glimepiride instead of placebo.[55] In the CAROLINA trial, 37% patients had risk factor alone. Linagliptin did not reduce MACE compared with glimepiride, though the latter induced more hypoglycemic episodes (10.6% vs. 37.7%, HR 0.23, 95% CI 0.21–0.26) and more weight gain (HR 1.54, 95% CI 1.28–1.80 kg).[55] In the subgroup analysis, participants with or without established ASCVD did not have significant interaction (p = 0.54).[55] Taken together, the consensus group gave DPP-4 inhibitors a neutral position in patients with risk factor alone.

3.3.5. GLP-1 receptor agonists

Among the seven RCTs of GLP-1 RAs, the majority of the enrolled patients had established ASCVD, except the REWIND trial (Table 1).[23,56–61] The REWIND trial enrolled 9901 patients including 68.5% had risk factor alone and 31.5% have prior ASCVD.[61] Dulaglutide reduced MACE (HR 0.88, 95% CI 0.079–0.99, p = 0.026) and had a trend in decreasing all-cause mortality (HR 0.9, 95% CI 0.80–1.01, p = 0.067).[61] In the subgroup analysis, participants with or without established ASCVD had exactly the same trend in the three-point MACE in response to dulaglutide treatment (both HRs 0.87, 95% CI 0.74–1.02, p for interaction = 0.97). In addition, dulaglutide significantly improved renal outcome (HR 0.85, 95% CI 0.77–0.93).[62] In the subgroup analyses of all other trials of GLP-1 RAs, MACE was not reduced in patients with risk factor alone. In a meta-analysis of 8 trials (5 GLP-1 RAs, 3 SLGT-2 inhibitors), GLP-1 RAs reduced MACE in patients with established ASCVD (HR 0.87, 95% CI 0.82–0.92), but not in patients with risk factor alone (HR 1.03, 95% CI 0.87–1.23).[63] In a more recent meta-analysis including 56 004 participants from all seven trials of GLP-1 RAs, MACE was significantly reduced by 12% (HR 0.88, 95% CI 0.82–0.94, p < 0.001). This effect seems to be consistent in patients with established ASCVD or risk factor alone (HRs 0.86, 95% CI 0.79–0.94 vs. 0.95, 95% CI 0.83–1.08, p for interaction 0.22).[64] Interestingly, two exentin-4 backbone GLP-1 RAs (lixisenatide and exenatide) failed to decrease MACE.[23,56] On the other hand, human GLP-1 backbone GLP-1 RAs, except oral

semaglutide, successfully decreased MACE and decreased all-cause mortality in some trials.[57–61] Taken together, the consensus group gave GLP-1 RAs a moderate position in patients with risk factor alone, and only those GLP-1 RAs proven to be effective were recommended (liraglutide, semaglutide, and dulaglutide).

3.3.6. SGLT-2 inhibitors

There were three large-scale RCTs primarily evaluating the CV effects of SGLT-2 inhibitors in patients with type 2 diabetes; however, no trial was performed exclusively for patients with risk factor alone (Table 1). In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) trial, only patients with prior ASCVD were enrolled.[34] In the CANVAS program, 65.6% patients had prior ASCVD, and only 33.3% had risk factor alone.[35] Canagliflozin reduced MACE (HR 0.86, 95% CI 0.75–0.97, $p < 0.001$ for noninferiority, $p = 0.02$ for superiority).[35] Though there was no statistical evidence of heterogeneity (interaction p value = 0.18) in its effects on MACE between the primary (HR 0.98, 95% CI 0.74–1.30) and secondary prevention (HR 0.82, 95% CI, 0.72–0.95) cohorts,[65] the upper boundary of the confidence interval for the primary prevention was 1.30, just on the verge of the upper boundary of noninferiority defined by U.S. FDA.[19] On the other hand, the composite renal endpoints (sustained doubling of serum creatinine, end-stage renal disease (ESRD), and death from renal causes) occurred less frequently in the canagliflozin group compared with the placebo group (HR 0·53, 95% CI 0·33–0·84). Subgroup analysis disclosed similar renal effects in patients with primary prevention versus secondary prevention (HRs 0.45, 95% CI 0.21–0.96 vs. 0.59, 95% CI 0.32–1.06, p for interaction 0.63).[66] Furthermore, CV death/hospitalization for HF was reduced in those treated with canagliflozin compared with placebo (HR 0.78, 95% CI 0.67–0.91) without heterogeneity between those risk factor alone versus those with prior ASCVD (HRs 0.83, 95% CI 0.58–1.19 vs. 0.77 95% CI 0.65–0.92, p for interaction 0.42).[67]

The Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE) trial enrolled 17 160 patients, including 59.2% with risk factor alone (men > 55 and women > 60 years, dyslipidemia, hypertension, or use of tobacco) and 40.8% with prior ASCVD.[36] The trial was quite unique that two primary endpoints were tested: MACE and CV death/hospitalization for HF.[36] Dapagliflozin did not reduce MACE (HR 0.93, 95% CI 0.84–1.03), but significantly reduced CV death/hospitalization for HF (HR 0.83, 95% CI 0.73–0.95, $p = 0.005$) both in patients with risk factor alone and patients with prior ASCVD (HRs 0.84, 95% CI 0.67–1.04 vs. 0.83, 95% CI 0.71–0.98, p for interaction 0.99).[36] Dapagliflozin also reduced prespecified secondary cardiorenal composite outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes) by 24% (HR 0.76, 95% CI 0.67–0.87, $p < 0·0001$) and the prespecified renal-specific composite outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new ESRD, or death from renal cause) by 47 % (HR 0·53, 95% CI 0·43–0·66, $p < 0·0001$).[68] The effects on the renal-specific composite outcome were consistent in patients with risk factor alone versus patients with prior ASCVD (HRs 0.51, 95% CI 0.37–0.69 vs. 0.55, 95% CI 0.41–0.75, p for interaction 0.72).[68]

In a recent meta-analysis combining three trials of SGLT-2 inhibitors (EMPA-REG, CANVAS, and DECLARE),[69] SGLT-2 inhibitors reduced MACE by 11% (HR 0.89, 95% CI 0.83–0.96, $p = 0.0014$), with benefit only seen in patients with prior ASCVD (HR 0.86, 95% CI 0.80–0.93) and not in those without (HR 1.00, 95% CI 0.87–1.16, p for interaction 0.0501). SGLT-2 inhibitors reduced the risk of CV death/hospitalization for HF by 23% (HR 0.77, 95% CI 0.71–0.84, $p < 0·0001$), with a similar benefit in patients with and without ASCVD (HR 0.76, 95% CI 0.69–0.84 vs. 0.84, 95% CI 0.69–1.01, p for interaction 0.41). SGLT-2 inhibitors reduced the risk of progression of renal disease by 45% (HR 0.55, 95% CI 0.48–0.64, $p < 0.0001$), with a similar benefit in those with and without ASCVD (HRs 0.56, 95% CI 0.47–0.67 vs. 0.54, 95% CI 0.42–0.71, p for interaction 0.71).[69] Another meta-analysis shared similar findings.[63] Taken together, the consensus group gave a high priority to SGLT-2 inhibitors for patients with risk factor alone, based on their effects on renal and HF events.

3.4. Treatment algorithm in diabetic patients with multiple risk factors

The treatment algorithm for diabetic patients with risk factor alone is shown in Table 3. The target of HbA1c is <7%. Metformin is the first-line therapy based on the findings from the UKPDS study,[29] and its global availability, affordability, overall safety, and tolerability. For dual therapy, we recommended metformin plus SGLT-2 inhibitors. SGLT-2 inhibitors reduced composite renal endpoints[66,68] and CV death/hospitalization for HF in patients with risk factor alone.[36,67] GLP-1 RAs were recommended as the first third-line therapy based on the REWIND trial[61] and a meta-analysis,[64] but only those GLP-1 RAs proven to be effective should be selected. The next recommendation would be thiazolidinedione (TZD; pioglitazone) based on the findings from the PROactive trial.[15] DPP-4 inhibitors have neutral effects on MACE and a low risk of hypoglycemia, making them the third-line therapy. SU, glinides, or alpha-glucosidase inhibitor (AGI) are the last choices.

4. TREATMENT OF DIABETES IN PATIENTS WITH CORONARY HEART DISEASE

4.1. Rationale

For many years, patients with diabetes but devoid of CHD have presumably the same risk for future MI as those with known CHD but devoid of diabetes.[70] CHD is a major determinant of long-term prognosis in patients with type 2 diabetes. Furthermore, in patients with type 2 diabetes, there is an increased mortality after MI.[70] In the UKPDS 35, an observational part of the UKPDS trial, the risk of CHD correlated with the baseline HbA1c.[9] For every 1% increase in HbA1c, the risk of fatal and nonfatal MI increased by 14%.[9] However, the four RCTs testing intensive glucose control versus conventional glucose control did not show positive results in reducing MACE in

Table 3

Treatment algorithm in diabetic patients with multiple risk factors

Target HbA1c	<7%
Monotherapy	Metformin
Dual therapy	Metformin + SGLT-2 i
Triple therapy	
First choice	Metformin + SGLT-2 i + GLP-1 RA[a]
Second choice	Metformin + SGLT-2 i + TZD[b]
Third choice	Metformin + SGLT-2 i + DPP-4 i
Fourth choice	Metformin + SGLT-2 i + SU or glinide or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

AGI = alpha-glucosidase inhibitor; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

[a]Liraglutide, semaglutide, and dulaglutide.

[b]Pioglitazone.

individual trials.[11–14] The percentages of patients with preexisting CVD were 0% in the UKPDS trial, 35% in the ACCORD trial, 32% in the ADVANCE trial, and 41% in the VADT trial.[11–14] It remains uncertain whether absence of benefits is due to inclusion of patients with advanced stage heart disease beyond a period of reversibility, short trial duration for effect to manifest, safety issue of antidiabetic agents, or simply absence of effect of glucose lowering *per se*.[6] In the ACCORD trial, the three-point MACE was nonsignificantly decreased by 10% (HR 0.90, 95% CI 0.78–1.04), but nonfatal MI was significantly decreased (HR 0.76, 95% CI 0.62–0.92, p = 0.004).[12] The trial was prematurely terminated due to an increase in total mortality (HR 1.22, 95% CI 1.01–1.46, p = 0.04) and CV mortality (HR 1.35, 95% CI 1.04–1.76, p = 0.02), driven in part by a nonsignificant increase in fatal and nonfatal HF (HR 1.18, 95% CI 0.93–1.49, p = 0.17).[12] Before 2008, most of RCTs testing aggressive management in diabetes were largely neutral or even had some harmful effects. However, two meta-analyses showed a significant reduction in nonfatal MI with intensive glucose control.[16,71]

4.2. Target of HbA1c

The risk of CVD and total mortality has a linear relationship with the level of HbA1c.[72] The risk of MI starts to increase from a level of HbA1c of 6% or above.[9] However, four RCTs, including the UKPDS trial,[11] the ACCORD trial,[12] the ADVANCE trial,[13] and the VADT trial,[14] targeting lower HbA1c levels did not show an improvement in CV outcomes. The final achieved HbA1c levels were 7.0%, 6.4%, 6.5%, and 6.5% respectively.[11–14] The risk of total mortality in the ACCORD trial was actually increased and resulted in a premature termination.[12] Notably, neither the ADVANCE trial nor the VADT trial demonstrated an increase in mortality or in composite CV endpoints with intensive glucose control defined by HbA1c < 7%.[13,14] A meta-analysis showed that allocation to more-intensive, compared with less-intensive, glucose control reduced the risk of MACEs by 9% (HR 0.91, 95% CI 0.84–0.99),[71] primarily driven by a 15% reduction in MI (HR 0.85, 95% CI 0.76–0.94), without an increase in mortality. However, intensively treated patients had significantly higher major hypoglycemic events (HR 2.48, 95% CI 1.91–3.21).[71] Iatrogenic hypoglycemia is the limiting factor in the intensive glycemic management and is an independent factor for excess morbidity and mortality. When treating patients with antidiabetic agents with low hypoglycemic potential, a lower level of HbA1c might be preferable. For instance, in a population-based cohort study including all metformin initiators in 24 752 patients with type 2 diabetes with a median age of 62.5 years, the risk of a combined outcome events (acute MI, stroke, or death) gradually increased in parallel with HbA1c achieved at 6 months, compared with a target HbA1c of <6.5%: adjusted HR 1.18 (95% CI 1.07–1.30) for 6.5%–6.99%, HR 1.23 (95% CI 1.09–1.40) for 7.0%–7.49%, HR 1.34 (95% CI 1.14–1.57) for 7.5%–7.99%, and HR 1.59 (95% CI 1.37–1.84) for ≥8%.[45] A large absolute HbA1c reduction from baseline also predicted outcome: adjusted HR 0.80 (95% CI 0.65–0.97) for a difference of 4%, HR 0.98 (95% CI 0.80–1.20) for a difference of 3%, HR 0.92 (95% CI 0.78–1.08) for a difference of 2%, and HR 0.99 (95% CI 0.89–1.10) for a difference of 1%, compared with no HbA1c change (difference = 0%).[45]

Given that most of the new antidiabetic agents have superior safety profiles, the consensus recommended HbA1c less than 7.0% as the treatment target for the diabetic patients with CHD. Modern treatment strategies, that is, drug strategy designed to maximize HbA1c reduction while minimizing hypoglycemia and weight gain were recommended. However, an HbA1c less than 6.5% may be considered in selected patients who are younger, highly educated and highly motivated, and have a low hypoglycemic risk, fewer comorbidities, and short diabetes duration.

4.3. Choice of drugs

There is only a trial testing the efficacy of antidiabetic agent specifically in patients with CHD (the ACE trial).[52] Nevertheless, most of the CV outcome trials enrolled patients with a history of CVD, including a large proportion of patients with CHD. Moreover, fatal and nonfatal MI is generally a major component of the three-point MACE, providing important information for this consensus.

4.3.1. Metformin

In the UKPDS trial, metformin therapy in overweight patients was associated with a significantly lower risk of MI and total mortality compared with conventional lifestyle therapy (HR 0.61, 95% CI 0.41–0.89; HR 0.64, 95% CI 0.45–0.81, respectively).[29] The benefits persisted at 10 years in posttrial follow-up (HR 0.67, 95% CI 0.51–0.89, p = 0.005; HR 0.73, 95% CI 0.59–0.89, p = 0.002; respectively).[43] Hong et al. reported that metformi- reduced MACE compared with glipizide (adjusted HR [aHR] 0.54, 95% CI 0.30–0.90, p = 0.026) in patients with stable CHD during a 5-year follow-up in a small RCT of 304 patients.[73] In a meta-analysis of 35 clinical trials, including 7171 metformin-treated patients and 11 301 patients treated with comparator, a significant benefit was observed in the metformin group versus placebo/no therapy group (odds ratio [OR] 0.79, 95% CI 0.64–0.98, p = 0.031), but not in active-comparator trials (OR 1.03, 95% CI 0.72–1.77, p = 0.89).[47] Meta-regression suggested that metformin monotherapy was marginally associated with an improved survival (OR 0.801, 95% CI 0.625–1.024, p = 0.076).[47] However, concomitant use with SUs was associated with a reduced survival (OR 1.432, 95% CI 1.068–1.918, p = 0.016).[47] A previously published Cochrane analysis also reported that treatment with metformin in overweight diabetic patients was associated with a decreased risk of CV mortality compared with any other antidiabetic agents or a placebo.[74] Moreover, an updated meta-analysis of 40 studies comprising 1 066 408 CHD patients showed that metformin reduced the CV mortality, all-cause mortality and incidence of CV events (aHRs 0.81, 0.67, and 0. 83, respectively).[75] Subgroup analysis showed that metformin reduced all-cause mortality in patients with a history of MI (aHR = 0.79).[75]

In a retrospective 5-year follow-up observational cohort study of 11 293 Chinese patients with type 2 diabetes, metformin monotherapy together with lifestyle recommendations was associated with a 33% reduction in CHD compared with lifestyle (HR 0.670, 95% CI 0.521–0.862, p = 0.002).[76] In a prospective nationwide ACS-DM TSOC registry from Taiwan, among 1157 type 2 diabetes patients with history of acute coronary syndrome (ACS) receiving antidiabetic agents, metformin users had a lower all-cause mortality rate (aHR 0.50, 95% 0.26–0.95) over the 2-year follow-up in the primary analysis.[77] The survival benefit of metformin therapy was consistent in the secondary analyses (aHR 0.30, 95% CI 0.17–0.54 while adjusting for all predetermined covariates, and aHR 0.34, 95% CI 0.19–0.59 while adjusting for quintiles of the propensity score).[77] In a substudy of the DPP (Diabetes Prevention Program) and the DPPOS (Diabetes Prevention Program Outcome Study), there was no difference in coronary artery calcification (CAC) between lifestyle and placebo intervention groups in either sex.[78] But CAC severity and the percentage of presence of CAC were significantly lower among men in the metformin versus the placebo group (age-adjusted mean CAC severity, 39.5 vs. 66.9 Agatston units, p = 0.04; the percentage of presence of CAC, 75% vs. 84%, p = 0.02), whereas metformin was not effective in

women.[78] However, metformin did not decrease carotid intima-media thickness in CHD patients who did not have diabetes.[79]

Lactic acidosis is an uncommon but potentially lethal complication of metformin.[80] Though several comparative studies of metformin versus other antidiabetic agents did not show an increase in the risk of lactic acidosis,[81,82] metformin should not be used in patients with stage 4 and 5 CKD, that is, eGFR <30 mL/min/1.73m^2.[83]

The consensus group recommended metformin as the first-line therapy for patients with diabetes and CHD.

4.3.2. Sulfonylureas

There are controversies in the CV safety of SUs. In the University Group Diabetes Program (UGDP) in early 1970, tolbutamide was associated with an increase in CV and total mortality.[84] In the UKPDS trial, intensive glucose lowering with SUs and insulin did not decrease the risk of MI (HR 0.84, 95% CI 0.71–1.00, p = 0.052).[11] In the ADVANCE trial, use of gliclazide did not reduce the three-point MACE (HR 0.94, 95% CI 0.84–1.06), or nonfatal MI (HR 0.98, 95% CI 0.77–1.22).[13] In a retrospective cohort study using the UK General Practice Research Database of 91 521 patients with diabetes, both the first-generation and the second-generation SUs (including glimepiride and gliclazide) increased total mortality compared with metformin (HR 1.37, 95% CI 1.11–1.71, p = 0.0003 for first-generation SUs; HR 1.24, 95% CI 1.14–1.35, p < 0.001 for second-generation SUs.[85] The risk of MI was also numerically higher with SUs compared with metformin (HR 1.36, 95% CI 0.91–2.02 for first-generation SUs; HR 1.09, 95% CI 0.94–1.27 for second-generation SUs).[85] Based on a retrospective observational data from the UK Clinical Practice Research Datalink, patients with type 2 diabetes initiating metformin monotherapy had longer survival than matched, nondiabetic controls, while those treated with SU had a markedly reduced survival compared with both matched controls and those receiving metformin monotherapy.[86] From the same data, there was an increase in all-cause mortality for patients treated with metformin plus SU versus metformin plus DPP-4 inhibitors (aHR 1.497, 95% CI 1.092–2.052), and a similar trend for MACE (aHR 1.547, 95% CI 1.076–2.225).[86] In a meta-analysis of 20 studies of 551 912 patients, patients receiving SU monotherapy or combination treatment had significantly higher all-cause mortality (OR 1.92, 95% CI 1.48–2.49) and CV mortality (OR 2.72, 95% CI 1.95–3.79).[87] In another meta-analysis of 82 RCTs and 26 observational studies, the risk of acute MI was significantly higher in SU users than users of other antidiabetic agents (HR 1.21, 95% CI 0.78–1.99 vs. biguanide; HR 2.54, 95% CI 1.14–6.57 vs. DPP-4 inhibitors; HR 41.8, 95% CI 1.64–360.4 vs. SGLT-2 inhibitors).[88] In a recent cohort from the Taiwan National Health Insurance Research Database (NHIRD), DPP-4 inhibitors were better than SUs as an add-on therapy of metformin with regard to all-cause mortality (HR 0.64, 95% CI 0.57–0.71, p < 0.001), MACE (HR 0.69, 95% CI 0.58–0.81, p < 0.001), and ischemic stroke (HR 0.62, 95% CI 0.51–0.75, p < 0.001) but not MI (HR 0.87, 95% CI 0.65–1.16, p = 0.338) and hospitalization for HF (HR 0.81, 95% CI 0.63–1.05, p = 0.112).[89]

There are several drawbacks in using SUs for diabetic care. Hypoglycemia episodes are more common than other newer agents. In the ADVANCE trial, severe hypoglycemia occurred more frequently in the intensive-control group using gliclazide than in the standard control group: 150 patients (2.7%) undergoing intensive control had at least one severe hypoglycemic episode, compared with 81 patients (1.5%) undergoing standard control (HR 1.86, 95% CI 1.42–2.40, p < 0.001).[13] In the subanalysis of the ADVANCE trial, severe hypoglycemia was associated with a significant increase in the adjusted risks of three-point MACE (aHR 2.88, 95% CI, 2.01–4.12), major microvascular events (HR 1.81, 95% CI, 1.19–2.74), death from a CV cause (HR 2.68, 95% CI, 1.72–4.19), and death from any cause (HR 2.69, 95% CI, 1.97–3.67) (p < 0.001 for all comparisons).[44] Furthermore, SU increased body weight compared with metformin, as shown in the UKPDS trial.[29] The most intriguing effect of SUs is their interference with the protective mechanism in ischemic preconditioning, due to blockade of mitochondrial K_{ATP}.[90] This may account for the increase in MI and CV mortality observed in many meta-analyses.

It seems that not all SUs share similar CV risk. In patients with previous MI from a Danish cohort, the HR of all-cause mortality was increased by a number of SUs compared with metformin (glimepiride 1.30, 95% CI 1.11–1.44; glibenclamide 1.47, 95% CI 1.22–1.76; glipizide 1.53, 95% CI 1.23–1.89; tolbutamide 1.47, 95% CI 1.17–1.84), but not for gliclazide (HR 0.90, 95% CI 0.68–1.20).[91] In another meta-analysis of 18 trials of 167 327 patients, gliclazide and glimepiride were associated with a lower risk of all-cause and CV mortality compared with glibenclamide.[92] In the CAROLINA trial, the use of glimepiride shared similar MACE rate versus linagliptin (12.0% vs. 11.8%) with the HRs consistent across all subgroups including participants with established CVD, over a median of 6.3 years in 6033 patients.[55] The CAROLINA trial provided assurance CV safety for the glimepiride when compared directly with the DPP-4 inhibitor linagliptin, suggesting either one would be relatively safe after metformin in the majority of patients.[55] These results are consistent with the largest meta-analyses of 47 RCTs comparing modern SUs (gliclazide, glimepiride) with an active comparator showing that newer SUs were not associated with an increased risk of overall mortality, CV mortality, MI, or stroke.[93] Whether this result may be generalized to the entire class of SUs is unknown, but modern SUs (glimepiride and gliclazide MR) may be preferred over other classes of antidiabetic agents as add-on therapy for the management of uncontrolled diabetes. The ongoing phase 3 Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) trial (NCT01794143) aiming to examine the comparative effectiveness of glimepiride versus alternative agents (DPP-4 inhibitor, GLP-1 RA, and basal insulin) on top of metformin in patients with type 2 diabetes, and might clarify and define the effectiveness and safety of SU.

In general, the consensus group gave SUs a low priority in the treatment of diabetic patients with CHD.

4.3.3. Glinides

There were no RCTs or observational studies to show the effect of repaglinide on the risk of MI. In the NAVIGATOR trial, 9306 participants with IGT and CVD (11.2 % had a history of MI, 8.8% angina or positive stress test, 3.7% percutaneous coronary intervention, 4.0% multivessel coronary artery bypass graft) or its risk factors were assigned to nateglinide or placebo.[50] After a follow-up of 6.5 years, nateglinide did not reduce the three-point MACE plus admission for HF (HR 0.94, 95% CI 0.82–1.09, p = 0.43) or the incidence of fatal and nonfatal MI (HR 0.95, 95% CI 0.75–1.20).[50] Nateglinide also significantly increased hypoglycemic episodes and body weight.[50] The consensus group gave glinides a low priority in diabetic patients with CHD.

4.3.4. Alpha-glucosidase inhibitor

The STOP-NIDDM trial evaluated the effect of acarbose on the risk of CVD in 1368 patients with IGT.[51] Only 4.8% patients had a previous history of CVD. After a mean follow-up of 3.3 years, there was a significant reduction in CVD (HR 0.51, 95% CI 0.28–0.95, p = 0.03) and MI (HR 0.09, 95% CI 0.01–0.72, p = 0.02) with the use of acarbose. One should be aware that

there were only 13 patients with MI events in the whole trial (1 in the acarbose group, 12 in the placebo group), making a solid conclusion inappropriate.[51] In a nationwide cohort study in drug-naive type 2 diabetes patients in Taiwan, there were 16.5% patients with preexisting CHD.[94] After propensity score matching, acarbose has no effect on MI compared with metformin (HR 0.93, 95% CI 0.81–1.07).[94] The definitive answer for the effect of acarbose on CVD came from the ACE trial.[52] A total of 6522 Chinese patients with CHD were randomized to acarbose and placebo. There were 42% with previous MI, 42% with a history of previous unstable angina, and 22% with current unstable angina. After a median follow-up of 5 years, there was no difference in the five-point MACE (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and hospitalization for HF) (HR 0.98, 95% CI 0.86–1.11).[52] The traditional three-point MACE (CV death, nonfatal MI, and nonfatal stroke) did not differ either (HR 0.95, 95% CI 0.81–1.11). The risk of fatal and nonfatal MI was also similar in the two groups (HR 1.12, 95% CI 0.87–1.46). Gastrointestinal side effect was more common in the acarbose group (7% vs. 5%, $p = 0.0007$).[52] The ACE trial confirmed a neutral effect of acarbose in patients with CHD. The consensus group gave acarbose a neutral position and did not give a priority due to its gastrointestinal side effects.

4.3.5. Thiazolidinedione

In the PROactive trial, 5238 patients with type 2 diabetes and macrovascular disease were prospectively randomized to pioglitazone (15–45 mg) and placebo for 34.5 months.[15] Among them, 46% had a history of MI, 31% history of previous percutaneous coronary intervention, and 19% previous stroke. The primary composite endpoint included all-cause mortality, nonfatal MI (including silent MI), stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. There was a trend of beneficial effect with the use of pioglitazone in the primary composite endpoints (HR 0.90, 95% CI 0.80–1.02, $p = 0.095$).[15] The main secondary endpoint (all-cause mortality, nonfatal MI, and stroke) did show a positive effect (HR 0.84, 0.72–0.98, $p = 0.027$). Among the composite primary endpoints, nonfatal MI was numerically decreased by pioglitazone (HR 0.83, 95% CI 0.65–1.06).[15] In the total cohort, the subgroup of patients who had a previous MI (n = 1230 in the pioglitazone group and n = 1215 in the placebo group) was evaluated using prespecified and posthoc analyses.[95] Pioglitazone had a significant beneficial effect on the prespecified end point of fatal and nonfatal MI (HR 0.72, 95% CI 0.52–0.99, $p = 0.045$) and ACS (HR 0.63, 95% CI 0.41–0.97, $p = 0.035$).[95]

The finding of the beneficial effects of pioglitazone on MACE observed in the PROactive trial was supported by two meta-analyses of controlled trials of over 16 000 subjects.[96,97] The risk of death, MI, or stroke was reduced in those treated with pioglitazone (HR 0.82, 95% CI 0.72–0.94, $p = 0.005$). There was an increase in HF (HR 1.41, 95% CI 1.14–1.76, $p = 0.002$), but HF mortality was not increased.[96] The individual endpoint components were reduced by a similar magnitude and there was no heterogeneity across the trials.[96] Another meta-analysis of 10 RCTs of pioglitazone in patients with CVD reported that pioglitazone reduced recurrent MACE (relative risk [RR] 0.74, 95% 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).[97] Pioglitazone did not reduce all-cause mortality (RR 0.94, 95% CI 0.81–1.08), but increased risk of HF (RR 1.33, 95% CI 1.14–1.54).[97]

The results of PROactive were further supported by two subsequent studies examining the impact of pioglitazone on important surrogates of atherosclerosis, namely carotid intima/medial thickness (IMT) and coronary atheroma volume as delineated with intravascular ultrasound.[98,99] The CHICAGO study demonstrated that the carotid IMT in type 2 diabetic patients treated with pioglitazone did not progress whereas those treated with glimepiride showed progression.[98] In the PERISCOPE study, atheroma volume progressed with glimepiride but not with pioglitazone.[99]

There is a concern with rosiglitazone in CV safety. In a meta-analysis of 42 trials, rosiglitazone was associated with an increased risk of MI and a trend of increased CV death (HR 1.43, 95% CI 1.03–1.98, $p = 0.03$; HR 1.64, 95% CI 0.98–2.74, $p = 0.06$, respectively).[20] In a nationwide, observational, retrospective cohort of 227 571 Medicare beneficiaries aged 65 years or older (mean age, 74.4 years) who initiated treatment with rosiglitazone or pioglitazone for up to 3 years.[100] The adjusted HRs for rosiglitazone compared with pioglitazone were 1.06 (95% CI 0.96–1.18) for MI; 1.27 (95% CI 1.12–1.45) for stroke; 1.25 (95% CI 1.16–1.34) for HF; 1.14 (95% CI 1.05–1.24) for death; and 1.18 (95% CI 1.12–1.23) for the composite of MI, stroke, HF, or death. The attributable risk for this composite endpoint was 1.68 (95% CI 1.27–2.08) excess events per 100 person-years of treatment with rosiglitazone compared with pioglitazone.[100] The corresponding number needed to harm was 60 (95% CI 48–79) treated for 1 year.[100] In response, an interim analysis of the RECORD trial was published.[101] This trial randomized 4447 patients with type 2 diabetes to rosiglitazone plus either metformin or SU or an active control (metformin plus SU). No elevated risk for MI or death in the rosiglitazone group was noted at 3.75 years follow-up.[101] The final analysis showed that after a mean follow-up of 5.5 years, rosiglitazone was noninferior to a combination of metformin and SU with regards to the primary endpoint of CV hospitalization or CV death (HR 0.99, 95% CI 0.85–1.16), but its effect on MI was inconclusive due to small number of events (HR 1.14, 95% CI 0.80–1.63).[102]

The consensus group gave a high priority to pioglitazone in the treatment of diabetes patients with CHD.

4.3.6. Insulin

Only a few prospective interventional trials have specifically tested the CV effects of insulin treatment in type 2 diabetes. In the UKPDS trial, patients received insulin/SU therapy had similar risk of MI compared with patients on conventional diet therapy for a follow-up of 10 years (HR 0.84, 95% CI 0.71–1.00, $p = 0.052$).[11] However, a significant reduction in MI was observed after an additional follow-up of about 10 years (HR 0.85, 95% CI 0.74–0.97).[43] In the ORIGIN trial, 12 537 patients with CV risk factors plus impaired fasting glucose (IFG), IGT, or type 2 diabetes were randomized to receive insulin glargine or standard care for a median follow-up of 6.2 years.[49] There were 35.2% of patients with a history of MI. The rates of three-point MACE and MI, in particular, were similar between the insulin group and the control group (HRs 1.02, 95% CI 0.94–1.11; 1.02, 95% CI 0.88–1.19, respectively).[49] Recently, 7637 patients with type 2 diabetes were randomized to receive either insulin degludec (3818 patients) once daily or insulin glargine U100 (3819 patients) once daily in the DEVOTE trial.[103] A total of 6509 (85.2%) had established CV disease, CKD, or both. The percentage of patients with a history of MI was not reported. Although severe hypoglycemia occurred less in the degludec group (OR 0.60, 95% CI 0.48–0.76, $p < 0.001$ for superiority), the primary outcome did not show significant difference (HR 0.91, 95% CI 0.78–1.06, $p < 0.001$ for noninferiority, $p > 0.05$ for superiority).[103] The subgroup analysis did not show significant difference in patients with established CVD versus those without established CVD (HRs 0.89, 95% CI 0.76–1.04; 1.03, 95% CI 0.62–1.72, respectively, p for interaction = 0.5742).

In the BARI 2D trial, 295 active smokers were randomized to receive insulin therapy or placebo (insulin sensitization therapy) and followed for a median of 5.3 years.[104] Among them, 60% patients had a history of MI. Insulin therapy was independently associated with a significantly increased hazard of MI (HR 3.23, 95% CI 1.43–7.28, p = 0.005).[104] A meta-analysis of 3 RCTs including 7649 patients on insulin therapy and 8322 taking OADs reported that insulin did not differ from OADs in all-cause mortality (RR 1.00, 95% CI 0.93–1.07), CV death (RR 1.00, 95% CI 0.91–1.09), MI (RR 1.04, 95% CI 0.93–1.16), angina (RR 0.97, 95% CI 0.88–1.06), sudden death (RR 1.02, 95% CI 0.66–1.56), or stroke (RR 1.01, 95% CI 0.88–1.15).[105]

Therefore, the consensus group did not give insulin a high priority in the initial therapy in diabetic patients with CHD.

4.3.7. DPP-4 inhibitors

Four DPP-4 inhibitors, namely saxagliptin, alogliptin, sitagliptin, linagliptin, have been tested in 4 large-scale RCTs (SAVOR, EXAMINE, TECOS, and CAMELINA, respectively).[24,26,53,54] In general, the effects on MACE and all-cause mortality were neutral. In the SAVOR trial, 16,492 patients with type 2 diabetes who had a history of, or were at risk for, CV events were randomized to receive saxagliptin or placebo and followed for a median of 2.1 years.[53] Among them, 37.8% of patients had a history of MI. The overall efficacy in the three-point MACE showed no difference with the use of saxagliptin compared with placebo (HR 1.00, 95% CI 0.89–1.12, p = 0.99 for superiority: p < 0.001 for noninferiority). Among the three-point MACE, the risk of MI was not different with the use of saxagliptin compared with placebo (HR 0.95, 95% CI 0.80–1.12).[53] In the EXAMINE trial, 5380 patients with either an acute MI or unstable angina requiring hospitalization within the previous 15–90 days were enrolled.[54] Among them, 87.5% had a history of acute MI. The overall efficacy in the three-point MACE showed no difference from the use of alogliptin compared with placebo (HR 0.96, p = 0.32). Among the three-point MACE, nonfatal MI was not different with the use of alogliptin compared with placebo (HR 1.08, 95% CI 0.88–1.33).[54] Recently a landmark analysis of the EXAMINE trial reported that early (up to 6 months) DPP-4 inhibition with alogliptin did not increase the risk of early CV death/MI/stroke (HR 0.96, 95% CI, 0.76–1.21) or hospitalization for HF (1.23, 95% CI 0.84–1.82).[106] The TECOS trial randomized 14 671 patients with type 2 diabetes and established CV disease to sitagliptin or placebo, in addition to usual care.[24] Among them, 42.6% of patients had a history of MI. The four-point MACE (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) occurred in 839 patients in the sitagliptin group (11.4%, 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%, 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the four-point MACE (HR 0.98, 95% CI 0.88–1.09, p < 0.001). Among the four-point MACE, fatal and nonfatal MI was not different with the use of sitagliptin compared with placebo (HR 0.95, 95% CI 0.81–1.11).[24] The subgroup analysis of patients experiencing an MI during a median follow-up of 3.0 years was reported recently.[107] The composite outcome occurred in 58 (20.1%, 13.9 per 100 person-years) sitagliptin group participants and 50 (16.6%, 11.7 per 100 person-years) placebo group participants (HR 1.21, 95% CI 0.83–1.77, p = 0.32, adjusted HR 1.23, 95% CI 0.83–1.82, p = 0.31). On-treatment sensitivity analyses also showed no significant between-group differences in post-MI outcomes.[107] In the CARMELINA trial, 6979 patients were followed up for a median 2.2 years.[26] Among participants, 58% of patients had a history of CHD. Use of linagliptin versus placebo resulted in a similar effect on the three-point MACE (12.4% vs. 12.1%).[26] A pooled analysis of safety data from 19 trials evaluating high-risk diabetic patients with pre-existing CHD showed that the addition of linagliptin to existing treatment was not associated with an increase in cardiac adverse events (AEs).[108]

In summary, DPP-4 inhibitors have demonstrated their effect on CV safety but not on MACE among more than 50 000 patients in large-scale RCTs. These data suggest that DPP4 inhibitors are a safe choice within the glucose-lowering stepped algorithm. The consensus group gave a neutral position to DPP-4 inhibitors in diabetic patients with CHD.

4.3.8. GLP-1 receptor agonists

Seven RCTs of GLP-1 RAs (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, and PIONEER 6) have been reported in the past 4 years using lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide, and oral semaglutide, respectively.[23,56–61] Most RCTs used a three-point MACE as a primary outcome, except for the ELIXA trial which used a four-point MACE, including time to first occurrence of hospitalization for unstable angina. Asides from noninferiority for CV outcomes, many of them demonstrated superiority of these drugs versus placebo.

In the ELIXA trial, 6,068 patients with ACS within 180 days were randomized to daily lixisenatide or placebo.[23] There were 82.4% patients with MI. The overall efficacy in the four-point MACE (CV death, nonfatal MI, nonfatal stroke, and unstable angina) showed no difference with the use of lixisenatide compared with placebo (HR 1.02, 95% CI 0.89–1.17). Among the four-point MACE, MI was not different with the use of lixisenatide compared with placebo (HR 1.03, 95% CI 0.87–1.22).[23]

The LEADER trial examined the effects of a daily injection of liraglutide versus placebo in 9340 high-risk patients over a median follow-up of 3.8 years.[57] In the LEADER trial, 30% patients had a history of MI. There was a significant reduction in the three-point MACE with the use of liraglutide versus placebo (HR 0.87, 95% CI 0.78–0.97, p = 0.01).[57] The reduction in the primary endpoint was driven by significantly lower CV mortality (4.7% vs. 6%, p = 0.007). Moreover, liraglutide reduced all-cause mortality (8.2% vs. 9.6%, p = 0.02). Total MI was also significantly reduced (HR 0.86, 95% CI 0.73–1.00, p = 0.0460), but not nonfatal MI (HR 0.88, 95% CI 0.75–1.03). Liraglutide reduced three-point MACE in patients with a history of MI/stroke compared with placebo (17.3% vs. 20.4%; HR, 0.85; 95% CI, 0.73–0.99). In patients with risk factors alone, the HR for liraglutide versus placebo was 1.08 (95% CI, 0.84–1.38, p for interaction = 0.11).[57]

In the SUSTAIN-6 trial, which had similar inclusion criteria as the LEADER trial, 3297 patients with high CV risk were enrolled.[58] Among them, 60.5% had a history of CHD, including 32.5% had a history of MI. The three-point MACE was significantly reduced by semaglutide for subcutaneous injection once weekly (HR 0.74, 95% CI 0.58–0.95, p = 0.02), including a nonsignificant reduction in the risk of nonfatal MI (HR 0.74, 95% CI 0.51c1.08).[58] In the subgroup analysis, patients with established CVD had a significant reduction in the three-point MACE (HR 0.72, 95% CI 0.55–0.93), while those without CVD had a neutral effect with the use of semaglutide (HR 1.00, 95% CI 0.41–2.46), though p value for interaction was 0.49.[58] In a post-hoc analysis from the SUSTAIN 6 trial, semaglutide reduced the risk of MACE in all subjects versus placebo, regardless of baseline CV risk profile (prior MI/stroke vs no prior MI/stroke).[109]

In the EXSCEL trial, a total of 14 752 patients were randomized to exenatide or placebo with a median duration of follow-up of 3.2 years.[56] Of these participants, 52.7% patients had a history of CHD. The overall efficacy in the three-point MACE

showed no difference with the use of exenatide compared with placebo (HR 0.91, 95% CI 0.83–1.00).[56] The risk of fatal and nonfatal MI was not reduced (HR 0.97, 95% CI 0.85–1.10), but total mortality was significantly reduced (HR 0.86, 95% CI 0.77–0.97). In the subgroup analysis, patients with established CVD had a nonsignificant reduction in the three-point MACE (HR 0.90, 95% CI 0.82–1.00). This trial had no run-in period and therefore had one of the highest discontinuation rates of medication compared with the other RCTs.[56] It otherwise was the largest study. In the subgroup analysis, patients with established CVD had a nonsignificant reduction in the three-point MACE (HR 0.90, 95% CI 0.82–1.00).[56]

In the Harmony trial, CV effects of once-weekly albiglutide in patients with diabetes were evaluated.[60] A total of 6493 participants with approximately 100% prior CVD was followed for a median of 1.6 years. With respect to the primary endpoints, albiglutide showed superiority compared with placebo (HR 0.78, 95% CI 0.68–0.90, $p = 0.0006$, $p < 0.0001$ for noninferiority). Other secondary endpoints, such as expanded composite outcome (death from CVD, nonfatal MI, nonfatal stroke or urgent revascularization for unstable angina)(HR 0.78, 95% CI 0.69–0.90, $p = 0.0005$) and fatal or nonfatal MI (HR 0.75, 95% CI 0.61–0.90, $p = 0.003$) were all significant reduced by albiglutide.[60] However, albiglutide was withdrawn from the market by the company in July 2018.

The REWIND trial recruited a majority of people who did not have established CVD, but had other risk factors.[61] Among them, just 31.5% out of a total 9901 people had prior CVD. During a median follow-up of 5.4 years, MACE occurred in 12.0% of people taking weekly subcutaneous injection of dulaglutide versus 13.4% of those taking placebo (HR 0.88, 95% CI 0.79–0.99, $p = 0.026$).[61] In subgroup analyses, the effect of dulaglutide was the same regardless of whether patients had established CVD. Consistent effects were observed for all three components of the composite primary outcome: CV death (HR 0.91, 95% CI 0.78–1.06, $p = 0.21$), nonfatal MI (HR 0.96, 0.79–1.16, $p = 0.65$), and nonfatal stroke (HR 0.76, 0.61–0.95, $p = 0.017$, p for heterogeneity = 0.89).

In the PIONEER 6 trial, a total of 3183 patients were randomly assigned to receive once-daily oral semaglutide or placebo with a median duration of follow-up of 15.9 months.[59] Of these participants, 84.7% were at least 50 years old and had established CVD or CKD.[59] The overall efficacy in the three-point MACE showed no difference with the use of once-daily oral semaglutide compared with usual diabetic care (HR 0.79, 95% CI 0.57–1.11).[59] The risk nonfatal MI (HR 1.18, 95% CI 0.73–1.90) or unstable angina resulting in hospitalization (HR 1.56, 95% CI 0.60–4.01) were not reduced, but CV death (HR 0.49, 95% CI 0.27–0.92) and all-cause mortality (HR 0.51, 95% CI 0.31–0.84) were significantly reduced.[59] This trial had the shortest duration and the lowest event rates among all RCTs of GLP-1 RAs. Although the HR of this trial did not reach significance, it was very similar to that for injectable semaglutide in the SUSTAIN-6 trial (HR 0.79 vs. 0.74).[58]

Protective effects of GLP-1 RA were supported by two meta-analyses.[63,64] In a meta-analysis of 8 trials of 77,242 patients comparing GLP-1 RAs with SGLT-2 inhibitors,[63] both classes of drugs were effective in reducing MACE versus placebo in patients with established CVD (GLP-1 RAs HR 0.88, 95% CI, 0.84–0.94, $p < 0.001$; SGLT-2 inhibitor HR, 0.89, 95% CI 0.83–0.96, $p = 0.001$), whereas no effect was seen in patients without established CVD.[63] In a more recent meta-analyses of all seven RCTs of GLP-1 RAs, GLP-1 RAs reduced MACE by 12% (HR 0·88, 95% CI 0·82–0·94, $p < 0·001$), which was significant in patients with established CVD (HR 0.86 95% CI 0.80–0.93), but not in patients who had no established CVD (HR 0.94, 95% CI 0.83–1.07), though p value for interaction was insignificant.[64]

Given that not all GLP-1 RAs showed CV benefit, it is unclear whether clinicians should prefer one drug over the others (drug specific) or consider that the efficacy as a class effect. Recent analyses reported that either the time of exposure to the GLP-1 RA[110] or their normalized efficacy of lowering HbA1c[111] appears to be the causes of these heterogeneity. The consensus group gave a high priority to GLP-1 RAs in diabetic patients with CHD, but only recommended those GLP-1 RAs proven to be effective in RCTs.

4.3.9. SGLT-2 inhibitors

To date, three SGLT2 inhibitors, namely empagliflozin, canagliflozin, and dapagliflozin, have been tested in three large-scale RCTs (EMPA-REG, CANVAS, and DECLARE).[34–36] In the landmark CV outcome trial of empagliflozin (the EMPA-REG trial), 7020 patients with previous CV events who received empagliflozin had reduced risk of MACE versus placebo (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$).[34] In this trial, 75.6% of patients had CHD, and 46.4% had a history of MI. The subgroup analysis showed that there was no difference in patients with or without a history of CHD. Among the three-point MACE, there was a trend of a decrease in nonfatal MI (HR 0.87, 95% CI 0.70–1.09). Empagliflozin also reduced CV mortality (HR 0.62, 95% CI 0.49–0.77, $p < 0.001$) and all-cause mortality (HR 0.68, 95% CI 0.57–0.82, $p < 0.001$) compared with placebo, with no difference between 10 or 25 mg doses.[34] Out of 7020 participants, 25% in the empagliflozin group and 24% in the placebo group had a history of coronary artery bypass surgery.[112] In this subgroup, empagliflozin was associated with a 20% reduction in the risk of MACE (10.6% vs. 13.3%; HR 0.80, 95% CI 0.60–1.06), a 48% reduction for CV death (3.0% vs. 5.7%; HR 0.52, 95% CI 0.32–0.84), a 43% reduction for all-cause mortality (5.1% vs. 8.9%; HR 0.57, 95% CI 0.39–0.83), and a 50% reduction for hospitalization for HF (3.3% vs. 6.7%; HR 0.50, 95% CI 0.32–0.77).[112] The risk of MI or stroke was similar between the empagliflozin and placebo group. These results supported the use of empagliflozin as secondary prevention after coronary artery bypass graft surgery in diabetic patients to reduce the risk of MACE and mortality.[112] Among 1517 (21.6%) Asians, empagliflozin reduced MACE by 32% (HR 0.68, 95% CI 0.48–0.95).[113] The effects of empagliflozin on the components of MACE, all-cause mortality, and HF outcomes in Asian patients were consistent with the overall population.[113] The AEs of empagliflozin in Asian patients were similar to the overall trial population.[113]

The CANVAS program randomized 10 142 participants with diabetes and high CV risk into canagliflozin or placebo groups.[35] In the CANVAS program, 56.4% patients had a history of CHD.[35] The three-point MACE was significantly reduced by the use of canagliflozin versus placebo (HR 0.86, 95% CI 0.75–0.97, $p = 0.02$).[35] In the subgroup analysis, patients with a history of CVD had benefits (HR 0.82, 95% CI 0.72–0.95), but p value for interaction was 0.18. The specific data from patients with a history of CHD was not reported. Among the three-point MACE, the fatal or nonfatal MI was numerically lower by the use of canagliflozin (HR 0.89, 95% CI 0.73–1.09).[35]

In the DECLARE trial, 17 160 patients, including 6974 with preexisting CVD (40.8%), were randomized to receive dapagliflozin or placebo and followed for a median of 4.2 years.[36] Among them, 32% patients had a history of CHD. Dapagliflozin did not reduce MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93, 95% CI 0.84–1.03, $p = 0.17$) but did reduce CV death or hospitalization for HF versus placebo (4.9% vs. 5.8%; HR 0.83, 95% CI 0.73–0.95, $p = 0.005$) in the overall trial population.[36] Patients with established CV disease had a nonsignificant reduction in MACE (13.9% vs. 15.3%, HR 0.90,

95% CI 0.79–1.02), which was in line with the effect size seen in the EMPA-REG and the CANVAS trials. In the prespecified subanalysis from DECLARE trial, 3584 patients with a history of MI were compared with those without prior MI (n = 13 576).[114] In patients with previous MI, 15.2% of patients in the dapagliflozin arm versus 17.8% in the placebo arm experienced MACE, yielding a relative risk reduction of 16% (HR 0.84, 95% CI 0.72–0.99, p = 0.039). The absolute risk reduction translates into a number needed to treat of 39 over 4 years. In contrast, there was no effect in patients without previous MI (7.1% vs. 7.1%; HR 1.00, 95% CI 0.88–1.13, p = 0.97). Recurrent MI was also reduced in patients with previous MI with dapagliflozin versus placebo (HR 0.78, 95% CI 0.63–0.95). Patients with type 1 MI (HR 0.80, 95% CI 0.63–1.02) and type 2 MI (HR 0.64, 95% CI 0.42–0.97) all got benefits.[114] The reduction in type 2 MI by dapagliflozin may be due to a mismatch between myocardial oxygen supply and demand, rather than effects on plaque rupture and atherothrombosis.[114]

Overall, these findings are comparable with previous findings that SGLT-2 inhibitors are more effective against HF and renal outcomes than against ASCVD. The reduction in ASCVD was only observed in patients with established CVD. Of note, in a meta-analysis of SGLT-2 inhibitors from three RCTs, the reduction in MI were limited to patients with established CVD.[69]

The consensus group gave a high priority to SGLT-2 inhibitors in patients with diabetes and a history of CHD.

4.4. Treatment algorithm in diabetic patients with CHD

Table 4 shows the algorithm for the pharmacological treatment of diabetes in patients with CHD. The target of HbA1c is <7%. Metformin remains the first-line therapy in diabetic patients with CHD, mainly based on the findings from the UKPDS trial,[29,43] three meta-analyses,[47,74,75] two observational study,[76,77] and its effect on the reduction in CAC severity.[78] For dual therapy, we recommend metformin plus SGLT-2 inhibitors, followed by metformin plus GLP-1 RAs, and then metformin plus TZD (pioglitazone only). The PROactive trial,[15] two important meta-analyses,[96,97] and two image studies (CHICAGO and PERISCOPE)[96,99] provided evidences to support pioglitazone in the management of type 2 diabetes and CHD.

The role of GLP-1 RAs was supported by five RCTs,[57–61] and two meta-analyses.[63,64] Three RCTs provided evidence for use of SGLT-2 inhibitors.[34–36] The ranking of SGLT-2 inhibitors is a little bit higher than GLP-1 RAs mainly because of a more convenient oral administration of the former. Given that patients with diabetes and CHD are at an increased risk of HF, SGLT-2 inhibitors are more favored than GLP-1 RAs. The consensus group only recommended those GLP-1 RAs proven to be effective in RCTs (Liraglutide, semaglutide, and dulaglutide). Whether oral semaglutide, which has to be administered daily 30 minutes prior to meal ingestion, will be preferred over the weekly injectable therapies, is yet to be determined. If the fourth drug is to be added, DPP-4 inhibitors are recommended due to their neutral effects and safety.[24,26,53,54] SU did not have any positive trial to support its use,[11,13] and the result of a Taiwanese cohort showed a worse outcome.[89] In addition, the risk of hypoglycemia is well-known. Glinides and acarbose have low priority due to lack of any supporting evidence.[50,52]

Table 4

Treatment algorithm in diabetic patients with CHD

Target HbA1c	<7%
Monotherapy	Metformin
Dual therapy	
First choice	Metformin + SGLT-2 i
Second choice	Metformin + GLP-1 RA[a]
Third choice	Metformin +TZD[b]
Triple therapy	
First choice	Metformin + SGLT-2 i + GLP-1 RA[a]
Second choice	Metformin + SGLT-2 i + TZD[b]
Third choice	Metformin + GLP-1 RA[a] + TZD[b]
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

CHD = coronary heart disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.

[a]Liraglutide, semaglutide, and dulaglutide.

[b]Pioglitazone.

5. TREATMENT OF DIABETES IN PATIENTS WITH STAGE 3 CHRONIC KIDNEY DISEASE

5.1. Rationale

Diabetes-related CKD is a very common complication for patients with type 2 diabetes. It leads to ESRD, accounting for approximately 50% of cases in the developed world.[115] According to a cross-sectional study of 6251 adult diabetic patients participating in the U.S. National Health and Nutrition Examination Surveys (NHANES) in 2009–2014, the prevalence of albuminuria (albumin creatinine ration [ACR] >30 mg/g) was 15.9%, and the prevalence of reduced eGFR (eGFR <60 mL/min/1.73 m^2) was 14.1%, while 26.2% had either.[116] Of note, diabetes with concomitant CKD leads to a marked increase in CVD risk.[117] From the Taiwan NHIRD, the prevalence of diabetic nephropathy increased from 13.32% in 2000 to 15.42% in 2009.[118] In another Taiwan cohort study of 462 293 individuals aged older than 20 years, the prevalence of stage 3–5 CKD (defined by an eGFR < 60 mL/min/1.73 m^2) was 7.1% (stage 3 = 6.8%, stage 4 = 0.2%, and stage 5 = 0.1%), and the DM prevalence was 14.5%, 25.6%, and 23.6%, respectively.[119]

An array of similar risk factors contributed to CHD and diabetic CKD, including hyperglycemia, hypertension, dyslipidemia, smoking, ethnicity, sex, age, and a long diabetes duration. Good glycemic control is the mainstay for preventing microvascular complications, including CKD, in patients with diabetes.[115] In a meta-analysis of four RCTs, intensive glucose control resulted in an absolute difference of 0.90% in mean HbA1c between more and less-intensive control groups.[120] The relative risk of kidney events (defined as a composite of ESRD, renal death, development of an eGFR <30 mL/min/1.73 m^2, or development of overt diabetic nephropathy) was reduced by 20% (HR 0.80, 95% CI 0.72–0.88, p < 0.0001) by intensive glycemic control, primarily driven by reduced risks of development of micro- and macroalbuminuria.[120] However, intensive glucose control did not significantly reduce the risk of composite renal endpoints (eGFR < 30 mL/min/1.73 m^2, doubling of serum creatinine, or ESRD).[120] This finding was supported by another meta-analysis of seven trials.[121] On the other hand, long-term data from the ADVANCE trial (ADVANCE-ON) demonstrated a significant reduction in ESRD in the intensive glycemic group for a follow-up of 10 years (HR 0.54, 95% CI 0.34–0.85, p < 0.01).[122] Because albuminuria and likely ESRD were reduced by intensive glucose control, the American Diabetes Association (ADA) guideline suggests a general HbA1c goal of <7% to prevent or delay the progression of albuminuria and other microvascular complications in diabetes.[123] It should be noted that in those studies most subjects had an eGFR>60 mL/min/1.73 m^2 (or CKD stage 1 and 2) and only about 10%–25% had CKD stage 3, whereas patients with CKD stage 4 and 5 were excluded.[120] The impact of glycemic control in patients with stage 4 and 5 CKD remains unclear. The goal of this consensus was mainly focused on diabetic patients with stage 2–3 CKD.

5.2. Target of HbA1c

Glycemic control in patients with CKD face special challenges, considering that the risk of severe hypoglycemia is doubled when the eGFR is less than 60 mL/min/1.73 m^2.[124] In other words, glucose management in diabetic patients with CKD should be a balance between glycemic control to reduce the progression of kidney disease and the avoidance of hypoglycemia. An observational study of nondialyzing CKD patients with diabetes has demonstrated a U-shaped relationship between HbA1c level and mortality, with increased mortality in patients with HbA1c levels above 8.0% or below 6.5%.[125] In the ADVANCE-ON study, the benefit of intensive glycemic control to prevent ESRD was decreased in patients with moderately reduced kidney function (CKD stage 3 or greater).[122] Moreover, the effects of glucose lowering on the risks of death, CV death, or MACEs did not differ by levels of kidney function. An increase in CV and all-cause mortality with intensive glucose control in the presence of stage 1–3 CKD has raised concern in the post-hoc analysis of the ACCORD data.[126] Furthermore, hypoglycemia risk increased by 66% in patients with baseline serum creatinine >1.3 mg/dL compared with those with normal kidney function in the ACCORD study.[127] The consensus group recommended HbA1c <7.0% as the treatment target for patients with diabetes and stage 2–3 CKD. The risk of hypoglycemia should be carefully monitored.

5.3. Choice of drugs

The CREDENCE trial is the only RCT testing the efficacy and safety of antidiabetic agents specifically in patients with CKD.[25] However, the subgroup analysis comparing patient with or without CKD were generally provided in major RCTs. In general, renal events are not the primary endpoints but can provide some information.

5.3.1. Conventional glucose-lowering agents

There have been no large RCTs specifically examining the renal protective effects of insulin, SUs, glinides, alpha-glucosidase inhibitors, or metformin. The ORIGIN trial[49] and the ACE trial[52] are CV outcome trials, but the subgroup analyses of CKD patients versus non-CKD patients were not provided.

5.3.2. Thiazolidinedione

Among the 5238 patients in the PROactive trial, GFR data were available for 5154 (98.4%) patients. In the post-hoc analysis of the PROactive trial, 597 (11.6%) of the 5154 study patients had CKD (GFR <60 mL/min/1.73 m^2).[128] Pioglitazone significantly decreased secondary end points (all-cause death, MI, and stroke) in patients with CKD (HR 0.66, 95% CI 0.45–0.98), but not in patients without CKD (HR 0.89, 95% CI 0.75–1.05).[128] There was a greater decline in eGFR with pioglitazone (between-group difference 0.8 mL/min/1.73 m^2/y) than with placebo.[128] In a meta-analysis of 15 studies involving 2860 patients, the effect of TZDs on urinary albumin excretion was inconsistent.[129] In the BARI 2D trial, participants who were treated with insulin sensitizing medications (the majority taking TZDs in combination with metformin), compared with those treated with insulin-provision therapy (insulin plus SUs), had greater progression of urinary albumin excretion despite having lower HbA1c values.[130] Rates of decline in eGFR, however, were similar in both treatment groups over 5 years.[130] The consensus group gave TZD a slightly positive position in the treatment of patients with diabetes and CKD.

5.3.3. DPP-4 inhibitors

In the SAVOR trial, 9696 (58.8%) subjects had normoalbuminuria (ACR <30 mg/g), 4426 (26.8%) had microalbuminuria (ACR 30–300 mg/g), and 1638 (9.9%) had macroalbuminuria (ACR >300 mg/g), whereas 2% had eGFR less than 30 mL/min/1.73 m^2, 13.5% eGFR between 30 and 50 mL/min/1.73 m^2, and 84.5% eGFR>50 mL/min/1.73 m^2.[131] Treatment with saxagliptin was associated with less deterioration in ACR (p values 0.021, < 0.001, and 0.049 for individuals with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively).[131] The changes in ACR did not correlate with those in HbA1c. The change in eGFR was similar in the saxagliptin and placebo groups. Renal safety outcomes, including doubling of serum creatinine, initiation of chronic dialysis, renal transplantation, or serum creatinine >6.0 mg/dL, were similar as well.[131] In addition, saxagliptin neither increased nor decreased the risk of the three-point MACE compared with placebo, irrespective of renal function.[132] Therefore, use of saxagliptin could decrease albuminuria safely in patients with CKD, though improvement in eGFR was not observed. In the TECOS trial, 14 671 participants were categorized at baseline into eGFR stages 1, 2, 3a, and 3b (>90, 60–89, 45–59, or 30–44 mL/min/1.73 m^2, respectively).[133] Sitagliptin therapy was not associated with a reduction in CV outcomes for any eGFR stage. In addition, kidney function declined at the same rate for each eGFR stage, with no significant interactions of treatment effect according to eGFR levels. Therefore, sitagliptin has no clinically significant impact on CV or renal outcomes, irrespective of baseline eGFR.[133] There was no secondary publication of the renal effect of alogliptin in the EXAMINE trial. A small study of 36 CKD patients with type 2 diabetes treated with alogliptin for 6 months did not show any significant change in eGFR in patients with an eGFR less than 60 mL/min/1.73 m^2.[134] There was no CV outcome trial for vildagliptin. According to a comprehensive review, vildagliptin can be safely used in patients with type 2 diabetes and varying degrees of renal impairment, but dose adjustments for renal impairment are required.[135] In the CARMELINA trial, 74% had prior CKD (defined as eGFR <60 mL/min/1.73 m^2 and/or urine albumin-creatinine ratio (UACR) >300 mg/g creatinine), 33% had both CVD and CKD, and 15.2% had an eGFR less than 30 mL/min/1.73 m^2.[26] Linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.[26] The risk of the secondary kidney composite outcome (sustained ESRD, death due to kidney failure, or sustained decrease of ≥40% in eGFR from baseline) was not significantly different between the groups randomized to linagliptin (9.4%; 4.89 per 100 person-years) and placebo (8.8%; 4.66 per 100 person-years) (absolute incidence rate difference, 0.22 [95% CI, −0.52 to 0.97] per 100 person years). Progression of albuminuria category (i.e., change from normoalbuminuria to microalbuminuria/macroalbuminuria or change from microalbuminuria to macroalbuminuria) occurred less frequently in the linagliptin group (763/2162 [35.3%]) than in the placebo group (819/2129 [38.5%]; HR 0.86, 95% CI 0.78–0.95, p = 0.003).[26] In the CAROLINA trial, 4462 (74.0%) subjects had normoalbuminuria (ACR <30 mg/g), 1275 (21.1%) had microalbuminuria (ACR 30–300 mg/g), and 1,638 (9.9%) had macroalbuminuria (ACR >300 mg/g); whereas 0.4% had eGFR <30 mL/min/1.73 m^2, 18.2% eGFR between 30 and 60 mL/min/1.73 m^2, and 80.9% eGFR>60 mL/min/1.73 m^2.[55] Among adults with relatively early type 2 diabetes and elevated CV risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite CV outcome. At least one episode of hypoglycemic AEs occurred in 320 (10.6%) participants in the linagliptin group and 1132 (37.7%) in the glimepiride group (HR 0.23, 95% CI 0.21–0.26, p < 0.001).[55] There was no secondary publication of the renal effect in the CAROLINA trial.

The consensus group gave a neutral position to DPP-4 inhibitors in patients with stage 2–3 CKD.

5.3.4. GLP-1 receptor agonists

In the ELIXA trial, 6068 patients with ACS were randomized to daily lixisenatide or placebo.[23] Lixisenatide did not reduce the three-point MACE (HR 1.02, 95% CI 0.89–1.17). There were 23.2% patients with preexisting CKD. The data for subgroup analysis in patients with a baseline eGFR <60 mL/min/1.73 m^2 were not provided. The prespecified analysis of the percentage changes in the ACR, but not eGFR, showed a modest difference in favor of lixisenatide over placebo from baseline to 108 weeks (24% vs. 34%, $p = 0.004$).[23] In the EXSCEL trial, weekly injection of extended-release exenatide was compared with placebo in 14 752 high-risk patients.[56] The three-point MACE was not significantly changed (HR 0.91, 95% CI 0.83–1.00, $p < 0.001$ for noninferiority, $p = 0.06$ for superiority).[56] There were 22.1% patients with preexisting CKD. The three-point MACE was not different in patients with eGFR levels <60 mL/min/1.73 m^2 versus those with eGFR levels ≥ 60 mL/min/1.73 m^2 (HR 1.01, 95% CI 0.86–1.19 vs. HR 0.86, 95% CI 0.77–0.97, p for interaction 0.12).[56] The incidence of microalbuminuria, macroalbuminuria, and ESRD was provided (exenatide vs. placebo, 7.2% vs. 7.5%, 2.2% vs. 2.8%, and 0.7% vs. 0.9%, respectively) without statistical significance.[56]

The LEADER trial examined the effects of a daily injection of liraglutide vs. placebo in 9340 high-risk patients over a median follow-up of 3.8 years.[57] The use of liraglutide was associated with a reduction in the three-point MACE (HR 0.87, 95% CI 0.78–0.97, $p = 0.01$). A total of 22.3% of the trial participants had an eGFR <60 mL/min/1.73 m^2. Patients with eGFR levels <60 mL/min/1.73 m^2 benefited more than those with eGFR levels ≥ 60 mL/min/1.73 m^2 (HR 0.69, 95% CI 0.57–0.85 vs. HR 0.94, 95% CI 0.85–1.07, p for interaction 0.01).[57] There was also a significant reduction of prespecified secondary renal outcomes, defined as a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and eGFR<45 mL/min/1.73 m^2, ESRD or death due to renal disease (HR 0.78, 95% CI 0.67–0.92, $p = 0.003$).[136] The renal benefit of liraglutide was mainly derived from a 26% reduction in new-onset macroalbuminuria (HR 0.74, 95% CI 0.60–0.91, $p = 0.004$) without any significant changes in eGFR. A nonsignificant reduction in doubling of serum creatinine (HR 0.89, 95% CI 0.67–1.19) and the need for the initiation of renal replacement therapy (HR 0.87, 95% CI 0.61–1.24) were also observed in liraglutide-treated patients.[136] In the SUSTAIN-6 trial, 3297 patients with high CV risk were enrolled.[58] A once weekly injection of semaglutide significantly reduced three-point MACE (HR 0.74, 95% CI 0.58–0.95, $p = 0.02$).[58] A total of 28.5% patients had an eGFR < 60 mL/min/1.73 m^2. There is no significant treatment interactions regarding eGFR status.[58] The new or worsening nephropathy (persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 mL/min/1.73 m^2, or the need for continuous renal replacement therapy) was significantly reduced (HR 0.64, 95% CI 0.46–0.88, $p = 0.005$), mainly driven by a reduction in the progression to macroalbuminuria (HR 0.54, 95% CI 0.37–0.77, $p = 0.001$). There was no significant reduction in progression of eGFR (HR 1.28, 95% CI 0.64–2.58) and need of renal replacement therapy (HR 0.91, 95% CI 0.40–2.07).[58]

In the REWIND trial, 9901 participants were enrolled.[61] At baseline, 791 (7·9%) had macroalbuminuria and mean eGFR was 76·9 mL/min per 1·73 m^2. During a median follow-up of 5.4 years, the primary composite outcome occurred in 594 (12·0%) participants in the dulaglutide group and in 663 (13·4%) participants in the placebo group (HR 0·88, 95% CI 0·79–0·99, $p = 0·026$). The renal outcome (new macroalbuminuria, 30% fall in eGFR, or renal replacement therapy) developed in 848 (17·1%) participants in the dulaglutide group and in 970 (19·6%) participants in the placebo group (HR 0·85, 95% CI 0·77–0·93, $p = 0·0004$). The striking effect was the reduction in new macroalbuminuria (HR 0·77, 95% CI 0·68–0·87, $p < 0·0001$). Sustained decline in eGFR of 30% or more (HR of 0·89, 95% CI 0·78–1·01, $p = 0·066$) and chronic renal replacement therapy (HR 0·75, 95% CI 0·39–1·44, $p = 0·39$) were not significantly changed.[61,62] In the PIONEER-6 trial, 3183 patients were enrolled.[59] Twenty-nine (0.9%) subjects had eGFR less than 30 mL/min/1.73 m^2, 827 (26.0%) eGFR between 30 and 60 mL/min/1.73 m^2, 1389 (43.6%) eGFR between 60 and 90 mL/min/1.73 m^2, and 919 (28.9%) eGFR>90 mL/min/1.73 m^2. A total of 1,051 participants (~33%) had microalbuminuria or proteinuria. MACE occurred in 61 of 1591 patients (3.8%) in the oral semaglutide group and 76 of 1592 (4.8%) in the placebo group (HR 0.79, 95% CI 0.57–1.11, $p < 0.001$ for noninferiority).[59] The assessment of renal or microvascular composite endpoint was not predefined in the PIONEER-6 trial.

In summary, all these RCTs show a positive effect of GLP-1 RAs in three-point MACE and renal events, though the main renal effect was the reduction in albuminuria, not in hard renal endpoints. The consensus group gave a high priority to GLP-1 RAs in patients with diabetes and CKD.

5.3.5. SGLT-2 inhibitors

In the EMPA-REG trial, 7020 patients with previous CV events were enrolled.[34] Patients who received empagliflozin had reduced rates of MACE, CV mortality, and all-cause mortality compared with placebo.[34] There were 26.0% patients with preexisting CKD. The CV effects were consistent in patients with an eGFR <60 mL/min/1.73 m^2 versus those ≥60 mL/min/1.73 m^2. Empagliflozin reduced renal outcomes in the EMPA-REG OUTCOME trial.[137] All patients in the study had an eGFR >30 mL/min/1.73m^2, and approximately 25% had an eGFR <60 mL/min/1.73 m^2, 11% had macroalbuminuria, and 29% had microalbuminuria. The primary renal endpoint of the trial was the composite of new-onset or worsening of nephropathy (progression to macroalbuminuria, doubling of serum creatinine level associated with an eGFR < 45 mL/min/1.73 m^2, initiation of renal replacement therapy and death from renal disease). This renal endpoint occurred in 18.8% in the placebo group and 12.7% in the empaglifozin group (HR 0.61, 95% CI 0.53–0.70, $p < 0.001$).[137] Empaglifozin treatment resulted in a 44% risk reduction in doubling of serum creatinine levels accompanied by an eGFR < 45 mL/min/1.73m^2(HR 0.56, 95% CI 0.39–0.79, $p < 0.001$), and a 55% risk reduction in initiation of renal replacement therapy (HR 0.45, 95% CI 0.21–0.97, $p = 0.04$).[137] There was also a decrease in the progression to macroalbuminuria (HR 0.62, 95% CI 0.54–0.72, $p < 0.001$).[137] The time course of the changes in eGFR in the empagliflozin group and the placebo group were different in the EMPA-REG trial.[37] From baseline to week 4, there was a short-term decrease in the eGFR in the empagliflozin group, with mean (±SE) adjusted estimates of weekly decreases of 0.62 ± 0.04 mL/min/1.73 m^2 in the 10-mg group and 0.82 ± 0.04 mL/min/1.73 m^2 in the 25-mg group, compared with a small increase of 0.01 ± 0.04 mL/min/1.73 m^2 in the placebo group ($p <$ 0.001 for both comparisons with placebo).[137] Thereafter, during long-term administration from week 4 to the last week of treatment, the eGFR remained stable in the empagliflozin groups but declined steadily in the placebo group, with adjusted estimates of annual decreases of 0.19 ± 0.11 mL/min/1.73 m^2 in the 10-mg and 25-mg empagliflozin groups, compared with a decrease of 1.67 ± 0.13 mL/min/1.73 m^2 in the placebo group ($p < 0.001$ for both comparisons with placebo).[137]

The CANVAS program randomized 10 142 participants with diabetes and high CV risk into canagliflozin or placebo groups.[35] There were 17.5% patients with preexisting CKD. Diabetic patients receiving canagliflozin had lower rate of the three-point MACE (HR 0.86, 95% CI 0.75–0.97, p = 0.02).[35] Among the participants, 22.6% had microalbuminuria and 7.6% had macroalbuminuria. Patients with an eGFR <60 mL/min/1.73 m^2 had a significant reduction in the three-point MACE (HR 0.70, 95% CI 0.55–0.90), but the intergroup difference compared with patients with an eGFR ≥ 60 mL/min/1.73 m^2 was nonsignificant (p for interaction 0.20).[35] For renal outcomes, the results showed significant benefits of canagliflozin in the progression of albuminuria (HR 0.73, 95% CI 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal replacement therapy, or death from renal causes (HR 0.60, 95% CI 0.47–0.77).[35]

The DECLARE trial randomized 17 160 participants including 6974 (40·6%) with established ASCVD and 10 186 (59·4%) with multiple risk factors.[36] About 8162 (47·6%) had an eGFR of at least 90 mL/min per 1.73 m^2, 7732 (45·1%) had an eGFR of 60 to <90 mL/min per 1.73 m^2, and 1265 (7·4%) had an eGFR of <60 mL/min per 1.73 m^2 at baseline. Dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (p < 0.001 for noninferiority) but did result in a lower rate of CV death/hospitalization for HF (4.9% vs. 5.8%; HR 0.83, 95% CI 0.73–0.95, p = 0.005). The hospitalization for HF was reduced by 27% (HR 0.73, 95% CI, 0.61–0.88).[36] The cardiorenal secondary composite outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal or CV cause) was significantly reduced with dapagliflozin versus placebo (HR 0.76, 95% CI 0.67–0.87, p < 0.0001); the renal-specific outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal cause) was also reduced (HR 0.53, 95% CI 0.43–0.66, p < 0.0001). The risk of ESRD or renal death was lower in the dapagliflozin group than in the placebo group (11 [0·1%] vs. 27 [0·3%]; HR 0.41, 95% CI 0.20–0.82, p = 0.012). Both the cardiorenal and renal-specific composite outcomes were improved by dapagliflozin versus placebo across various prespecified subgroups, including those defined by baseline eGFR (cardiorenal outcome: p for interaction = 0·97; renal-specific outcome: p for interaction = 0·87) and the presence or absence of established ASCVD (cardiorenal outcome: p interaction = 0·67; renal-specific outcome: p for interaction = 0·72).

The CREDENCE trial was designed specifically to test the renal effect of SGLT-2 inhibitor canagliflozin.[25] Patients with type 2 diabetes and albuminuric CKD were assigned to receive canagliflozin at a dose of 100 mg daily or placebo. All patients had an eGFR of 30–90 mL/min/1.73 m^2 and albuminuria (UACR 300–5000) and were treated with renin–angiotensin–aldosterone system (RAAS) blockade. Of the 4401 patients enrolled, baseline mean eGFR was 56.2 mL/min/1.73 m^2 and median UACR was 927 mg/g. The relative risk of the primary outcome of composite of ESRD (dialysis, transplantation, or a sustained estimated GFR of <15 mL/min/1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes was 30% lower in the canagliflozin group than in the placebo group (HR 0.70, 95% CI 0.59–0.82, p = 0.00001). The relative risk of the renal-specific composite of ESRD, a doubling of the creatinine level, or death from renal causes was lower by 34% (HR 0.66, 95% CI 0.53–0.81, p < 0.001), and the relative risk of ESRD was lowered by 32% (HR 0.68, 95% CI 0.54–0.86, p = 0.002).[25] The canagliflozin group also had a lower risk of CV death, MI, or stroke (HR 0.80, 95% CI 0.67-0.95, p = 0.01) and hospitalization for HF (HR 0.61, 95% CI 0.47–0.80, p < 0.001).[25]

In a recent meta-analysis of 8 trials of 77 242 patients, both GLP-1 RAs and SGLT-2 inhibitors were effective in reducing MACE, hospitalization for HF, and renal endpoints.[63] Both drugs decreased broad kidney endpoints which included the reduction in proteinuria. But only SGLT-2 inhibitors decreased hard kidney endpoints. Overall, SGLT-2 inhibitors were the treatment of choice for CKD.[63] Three ongoing SGLT2i trials including Dapagliflozin and Renal Outcomes and Cardiovascular Mortality in Patients with CKD (DAPA-CKD) (NCT03036150), Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) (NCT03315143), and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) (NCT03594110) will provide ample data of the effect of dapagliflozin, sotagliflozin, and empagliflozin on renal and CV outcomes in patients with CKD. It is generally believed that the benefits on renal events with SGLT-2 inhibitors are class effects. The mechanisms responsible for the renoprotective effect of SGLT-2 inhibitor are different from RAAS inhibitors. RAAS inhibitors reduce intraglomerular pressure via efferent arteriolar vasodilatation, leading to reductions in intraglomerular hypertension and renal hyperfiltration.[138] In nondiabetic subjects, SGLT-2 is responsible for about 5% of total renal NaCl reabsorption.[139] In hyperglycemic state, SGLT-1 and SGLT-2 mRNA expression is increased by 20% and 36%, respectively,[140–142] and accounting for 14% of total renal NaCl reabsorption. Consequently, NaCl delivered to the distal tubule markedly decreases.[143] The decline in macula densa NaCl delivery is sensed erroneously as a signal of a reduction in effective circulatory volume by the juxtaglomerular apparatus. Due to the tubuloglomerular feedback, this leads to maladaptive afferent arterial vasodilatation and increase intraglomerular pressure.[144] SGLT-2 inhibitors increase distal renal NaCl delivery, and reverse the process, leading to vasoconstriction of afferent arteriole and suppression of hyperfiltration. This is the fundamental mechanism of the renoprotection effect of SGLT-2 inhibitors.[139] BP reduction has been suggested as a possible mechanism. However, it is unlikely that BP-lowering effect improves kidney function over the relatively short period of drug exposure in these RCTs.[139]

The consensus group gave a very high priority to SGLT-2 inhibitors in patients with diabetes and stage 3 CKD (eGFR ≥ 30 mL/min/1.73 m^2).

5.4. Treatment algorithm in diabetic patients with stage 3 CKD

Table 5 shows the algorithm for the treatment of diabetes in patients with stage 2–3 CKD. The target of HbA1c is <7%. SGLT-2 inhibitors or metformin is the first-line therapy, but

Table 5

Treatment algorithm in diabetic patients with stage 3 CKD

Target HbA1c	<7%
Monotherapy	
First choice	SGLT-2 i
Second choice	Metformin
Dual therapy	SGLT-2 i + metformin
Triple therapy	
First choice	SGLT-2 i + metformin + GLP-1 RA[a]
Second choice	SGLT-2 i + metformin + TZD[b]
Third choice	SGLT-2 i + metformin + DPP-4 i
Fourth choice	SGLT-2 i + metformin + SU or glinide or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

AGI = alpha-glucosidase inhibitor; CKD = chronic kidney disease; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

[a]Liraglutide, semaglutide, and dulaglutide.

[b]Pioglitazone.

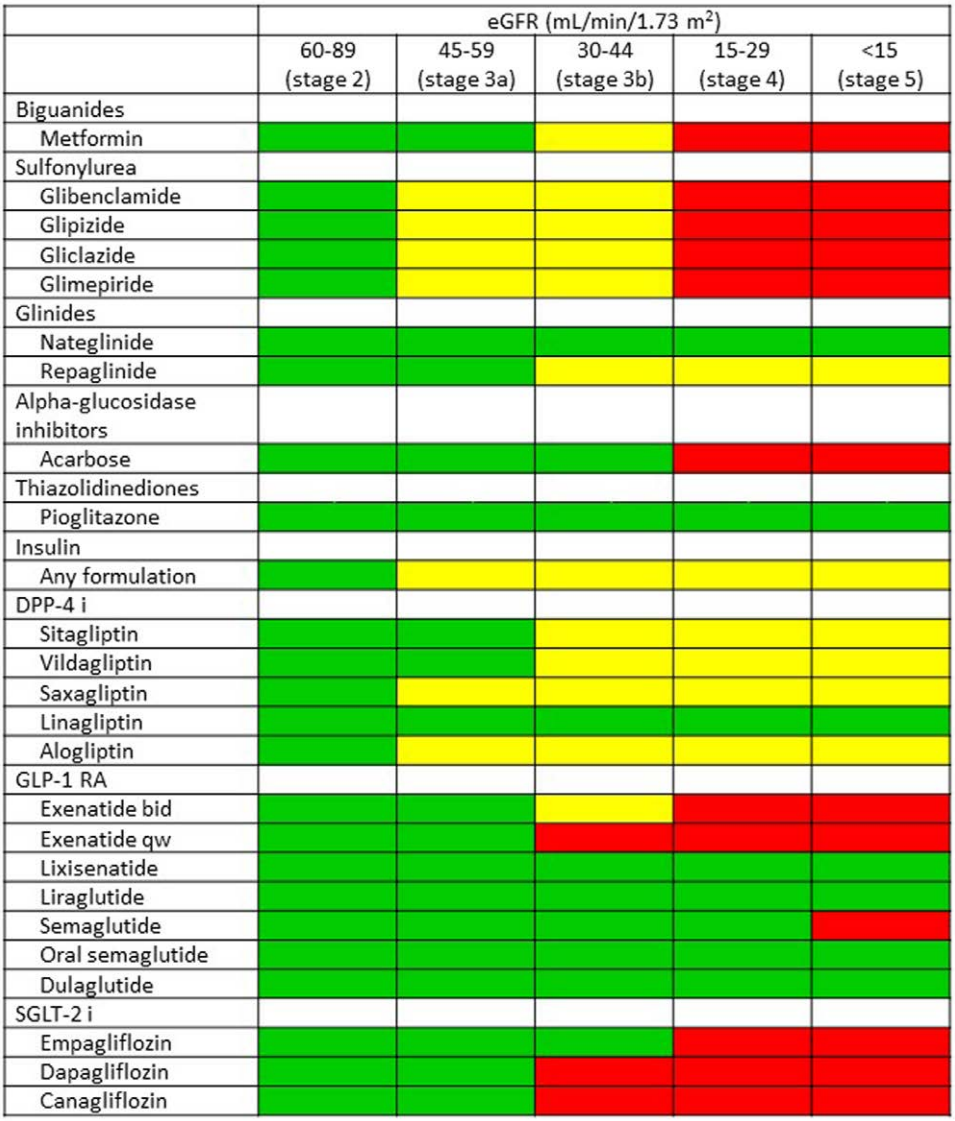

Fig. 1. Dose adjustment algorithm of antidiabetic agents in chronic kidney disease. Green color means that dose adjustment is not required. Yellow color means that dose reduction and frequent monitoring should be considered. Red color means that these drugs should not be used.Bid = twice daily; DPP-4 i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; qw = once weekly; SGLT-2 i = sodium glucose co-transporter 2 inhibitor.

SGLT-2 inhibitors are preferred ahead of metformin. For dual therapy, we recommend SGLT-2 inhibitors plus metformin. The use of SGLT-2 inhibitors is compelling based on their effects in reducing three-point MACE and renal endpoints in the CREDENCE trial,[25] the EMPA-REG trial,[34] the CANVAS Program,[35] and the DECLARE trial.[36] For triple therapy on top of metformin/SGLT-2 inhibitors, we recommended GLP-1 RAs, followed by TZD, and then DPP-4 inhibitors. The role of GLP-1 RAs was supported by the LEADER trial in which the patients with CKD stage 3 had better CV outcomes and the renal endpoints were significantly reduced.[57,136] The benefits in the renal events by semaglutide in the SUSTAIN-6 trial and dulaglutide in the REWIND trial also support a higher ranking of GLP-1 RAs than TZD and DPP-4 inhibitors.[58,61] The role of TZD was supported by the post-hoc analysis of the PROactive trial in which patients with stage 3 CKD had benefits in the secondary CV endpoints.[128] DPP-4 inhibitors have neutral effect in CV and renal endpoints. SUs and glinides have hypoglycemic risk in diabetics with stage 3 CKD. Acarbose has gastrointestinal side effects (bloating, diarrhea). For these reasons, they were ranked in a lower tier and should be reserved for patients who cannot tolerate or have contraindication for GLP-1 RAs, TZD, or DPP-4 inhibitors.

5.5. Dose consideration in CKD

CKD can impact the pharmacokinetics or pharmacodynamics of antidiabetic agents. A dose reduction is needed for certain antidiabetic agents in CKD patients.[145–147] **Figure 1** shows the dose adjustment of antidiabetic agents in CKD. Traditionally, insulin was suggested for the treatment of diabetes in patients with more advanced CKD. However, insulin dose should be reduced in patients with CKD regardless of the type of insulin (rapid, intermediate, or long-acting).[145] Metformin was excreted by the kidney and the dose should be reduced to avoid possible lactic acidosis. 2020 ADA guidelines suggest that metformin may be safely used in patients with eGFR as low as 30 mL/min/1.73 m^2,[46] and the

U.S. label for metformin has recently been revised to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m^2.[148] Nateglinide is metabolized by the liver, and a dose reduction is not needed. In contrast, the dose of repaglinide needs to be adjusted when eGFR falls to <30 mL/min/1.73 m^2.[149] Alpha-glucosidase inhibitors (e.g., acarbose) are metabolized nearly completely within the gastrointestinal tract, and less than 2% of an oral dose is recovered as the active drug or its metabolites in the urine. Given the modest efficacy in glycemic control and the lack of long-term trials in patients with kidney disease, it is suggested to avoid acarbose in CKD stage 4 and 5. Pioglitazone is nearly completely metabolized by the liver, and thus can be used in patients with CKD stage 3–5 without dose adjustment. However, this medication may cause fluid retention and should not be used in patients with HF. There are five available DPP-4 inhibitors. Sitagliptin, saxagliptin, alogliptin, and vildagliptin require dose adjustment in patients with CKD.[145–147] Linagliptin is primarily eliminated via the enterohepatic system, and therefore, no dose adjustment is necessary. Thus, linagliptin might be an option in patients with advanced CKD. Other DPP-4 inhibitors may be used in the setting of CKD with proper dose adjustment. For GLP-1 RAs, dose adjustment is required in exenatide and lixisenatide in patients with CKD stage 3, but they cannot be used in CKD stage 4–5. Other GLP-1 RAs, such as liraglutide, semaglutide, oral semaglutide, and dulaglutide can be used in CKD stage 4–5 without dose adjustment, with an exception of semaglutide. Semaglutide cannot be used in ESRD. SGLT-2 inhibitors have been approved for patients with an eGFR of ≥45 mL/min/1.73 m^2, although SGLT-2 inhibitors have been used in CKD stage 3 patients in RCTs. There have been post-marketing reports of acute kidney injury (AKI) in patients receiving SGLT-2 inhibitors and some patients required hospitalization and dialysis. It is suggested that before initiating SGLT-2 inhibitors factors that may predispose patients to AKI including hypovolemia, chronic renal insufficiency, and concomitant medications (diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs [NSAIDs]) should be examined, and renal function needs to be evaluated before initiation and be monitored thereafter.[146]

6. TREATMENT OF DIABETES IN PATIENTS WITH A HISTORY OF STROKE

6.1. Rationale

A meta-analysis of individual patient data of 980 793 adults from 68 prospective studies showed that diabetes approximately doubled the risk of occlusive vascular death in men and tripled the risk in women.[150] Ischemic stroke is one of the major vascular complications of diabetes mellitus.[7] Diabetes is a common risk factor of ischemic stroke and hemorrhagic stroke in Taiwan; the prevalence of diabetes was 45.4% in patients with ischemic stroke/transient ischemic accident (TIA) and 37% in patients with hemorrhagic stroke, respectively.[151] A meta-analysis including 102 prospective studies revealed that diabetes was associated with an increased risk of ischemic stroke (HR 2.27, 95% CI 1.95–2.65) and hemorrhagic stroke (HR 1.56, 95% CI 1.19–2.05).[38] According to the results of a cohort study in China, history of diabetes was found to be associated with an increased risk of stroke (OR 1.57, 95% CI 1.33–2.14).[152] In patients with stroke, the presence of diabetes was associated with increased risks of mortality, recurrent stroke, and long-term functional deficit after stroke compared with patients without diabetes.[153] Furthermore, in patients with type 2 diabetes, CV event rates were higher in patients with prior stroke compared with those without prior stroke.[154] Blood glucose is one of the modifiable risk factors for stroke in patients with diabetes;[153] however, whether glycemic control would reduce stroke risk for primary or secondary prevention remains a subject of debate. Herein, the content of this section will focus on ischemic stroke only, owing to limited data for hemorrhagic stroke. Actually, there was only one large-scale RCT to test the CV outcomes of antidiabetic drug specifically in patients with a history of ischemic stroke and insulin resistance.[155]

6.2. Target of HbA1c

The results from the UKPDS study revealed that intensive glucose control to achieve an averaged HbA1c level of 7.0% did not reduce stroke risk, compared with conventional glucose control to achieve an averaged HbA1c level of 7.9% (HR 1.11, 95% CI 0.81–1.51);[11] this was observed in its long-term follow-up study as well (HR 0.91, 95% CI 0.73–1.13).[43] Furthermore, three subsequent RCTs with a total of 23 183 patients did not show significant benefit for stroke with intensive glucose control (targeting HbA1c < 6.5% or 6.0%) versus standard therapy in patients with type 2 diabetes.[12–14] In a meta-analysis of five RCTs of 33 040 participants, intensive glycemic control with a mean difference of 0.9% in achieved HbA1c levels versus standard treatment did not reduce stroke risk (HR 0.93, 95% CI 0.81–1.06).[16] The results were in line with another meta-analysis of 34 533 patients.[156] Nevertheless, it should be kept in mind that conventional antidiabetic drugs used in these RCTs led to higher hypoglycemic events in the intensive group,[28] and symptomatic hypoglycemia is associated with increased CV events and death.[44,157] Optimal HbA1c level for stroke patients might be different if newer antidiabetic drugs were used.[28,158] For example, in a retrospective cohort study of 67 544 patients with type 2 diabetes, the U-shaped association of baseline HbA1c level and stroke risk was present in patients receiving insulin or SUs but not in patients receiving other drugs.[158]

Although diabetes is definitely associated with a higher risk of stroke and has a negative impact on clinical outcome after stroke,[6] there is no clear evidence to support intensive glycemic control using traditional antidiabetic agents. Therefore, in this updated consensus, we still recommended HbA1c <7.0% in diabetic patients with a history of stroke.

6.3. Choice of drugs

6.3.1. Metformin

In the long-term follow-up study of the UKPDS trial, metformin therapy was associated with a lower risk of MI and total death but a nonsignificant reduction in the risk of stroke compared with conventional lifestyle therapy (HR 0.80, 95% CI 0.5–1.27).[43] A post-hoc analysis of 12 156 participants in the SAVOR trial, patients receiving metformin (74%) had a lower risk of total mortality but a similar risk of ischemic stroke versus those not receiving metformin (26%).[33] A meta-analysis of RCTs including 2079 diabetic participants treated with metformin or placebo revealed that metformin therapy was not associated with a lower risk of stroke (HR 1.04, 95% CI 0.73–1.48).[32] In a retrospective observational cohort study of 11 293 Chinese patients with type 2 diabetes, metformin treatment plus lifestyle modification was associated with a lower risk of stroke compared with lifestyle modification only (HR 0.750, 95% CI 0.573–0.982).[76] A cohort study of 14 856 diabetic patients from Taiwan NHIRD showed a lower risk of ischemic stroke in patients receiving metformin versus those without (aHR 0.468, 95% CI 0.424–0.518).[159] However, in a cohort study from Taiwan NHIRD consisted of 17 760 diabetic patients with a new diagnosis of ESRD undergoing hemodialysis, metformin use was associated with a higher risk of ischemic stroke (aHR 1.64, 95% CI 1.32–2.04) and hemorrhagic stroke (aHR 2.15, 95% CI 1.51–3.07).[160] Only one observational study was performed to evaluate the secondary prevention role of metformin on stroke severity and functional

outcome in 355 diabetic patients with acute ischemic stroke.[161] In this study, 38.6% patients had a history of stroke.[161] Patients treated with metformin before stroke had a reduced neurological severity and milder neurological symptoms compared with those without metformin treatment.[161] Although there is no strong evidence supporting primary or secondary prevention role of metformin for risk of stroke in diabetic patients, the consensus group still recommended metformin as the first-line therapy for patients with diabetes and a history of stroke given its low price, affordability, and the role as a standard first-line therapy in the majority of RCTs.

6.3.2. Sulfonylureas

In the long-term follow-up study of the UKPDS trial, SU treatment did not reduce the risk of total mortality, MI or stroke (HR for glibenclamide 1.88, 95% CI 0.52–2.08).[11] In the ADVANCE trial, 9.2% of 11 140 diabetic patients had a history of stroke.[13] This study demonstrated that gliclazide-based intensive sugar control had no beneficial effect on the three-point MACE, death, or nonfatal stroke.[13] The subgroup analysis of patients with or without stroke was not reported.[13] In the CAROLINA trial, 12.1% of 6042 diabetic patients with elevated CV risk had a history of stroke.[55] This study compared linagliptin with glimepiride in patients with type 2 diabetes showing a similar risk of nonfatal stroke between both groups (HR 0.87, 95% CI 0.66–1.15).[55] The subgroup analysis of patients with or without stroke was not reported.[55] A meta-analysis of 82 RCTs and 26 observational studies showed a higher risk of death or stroke in patients treated with SU than in those with other antidiabetic agents.[88] A cohort study of 10 089 diabetic patients (21% with a history of stroke) by analyzing Taiwan NHIRD revealed worse CV outcome in patients treated with SUs than those with DPP-4 inhibitors as an add-on therapy of metformin.[89] The risk of ischemic stroke was lower for DPP-4 inhibitors than SUs (HR 0.64, 95% CI 0.51–0.81).[89] One recently published cohort study of 94 750 diabetic patients (10.3% with a history of stroke) consistently demonstrated that SU treatment was associated with a higher risk of ischemic stroke than metformin use (HR 1.25, 95% CI 1.002–1.56).[162] The subgroup analysis of patients with or without history of stroke showed consistent results.[162] In a retrospective cohort study of 174 882 patients with type 2 diabetes, SU treatment was associated with a higher risk of MACEs or acute MI/stroke/CV death than metformin use.[163] Taken together, the consensus group gave SU a low priority in patients with diabetes and a history of stroke. However, newer SUs with a preserved protective effect of ischemic preconditioning, such as glimepiride, might have a different CV effect than conventional SUs.

6.3.3. Glinides

Nateglinide was the only glinide being evaluated for CV outcome. In the NAVIGATOR trial, 9306 participants with IGT and either CVD (only 3% had a history of stroke) or its risk factors were treated with nateglinide or placebo. This trial did not show a better outcome in the risk of nonfatal stroke (HR 0.89, 95% CI 0.69–1.15) with nateglinide treatment.[50] Glinides also have hypoglycemic risk.[164] Therefore, the consensus group gave a low priority to glinides in diabetic patients with a history of stroke.

6.3.4. Alpha-glucosidase inhibitor

There was no clinical trial evaluating the effect of alpha-glucosidase inhibitor on CV outcome, including risk of stroke, in patients with diabetes. In the STOP-NIDDM trial, 1368 patients with IGT were randomized to acarbose or placebo,[51] showing a significant reduction in CV events, but not stroke risk (HR 0.56, 95% CI 0.10–3.07) with acarbose.[51] However, the major limitation of this study was small sample size and low event rate.[51] In the ACE trial, a total of 6522 Chinese patients with IGT and CHD were randomized to acarbose or placebo.[52] Percentage of patients with prior stroke was not reported.[52] This study did not show any beneficial effect of acarbose treatment on the risk of MACE (HR 0.98, 95% CI 0.86–1.11) or stroke (HR 0.97, 95% CI 0.70–1.33).[52] However, participants assigned to acarbose treatment experienced more gastrointestinal side effect than placebo (7% vs. 5%, p = 0.0007).[52] By analyzing a nationwide cohort data from the Taiwan NHIRD in patients with type 2 diabetes (10.1% with a history of stroke), acarbose treatment was associated with an increased risk of CV events and HF but not ischemic stroke (HR 1.05, 95% CI 1.00–1.10) compared with metformin.[94] The subgroup analysis of patients with or without stroke was not reported.[94] However, another cohort study of diabetic patients in Taiwan (6.4% with a history of stroke) comparing acarbose versus SU on top of metformin treatment showed a reduced risk of MACE (OR 0.69, 95% CI 0.52–0.91) and nonfatal stroke (OR 0.68, 95% CI 0.49–0.94) with acarbose treatment.[165] Taken together, the consensus group gave a neutral position for acarbose but did not give a priority due to its gastrointestinal side effects.

6.3.5. Thiazolidinedione

In the subgroup analysis of 984 patients with a history of stroke in the PROactive trial, pioglitazone therapy was associated with a 47% relative risk reduction in the recurrent stroke (HR 0.53, 95% CI 0.34–0.85) and a 28% relative risk reduction in three-point MACE (HR 0.72, 95% CI 0.53–1.00) in patients with type 2 diabetes and CVD.[154] A small Japanese study, the J-SPIRIT trial, showed a nonsignificant reduction in the risk of recurrent ischemic stroke among 120 patients with IGT or newly diagnosed diabetes and a history of stroke (HR 0.62, 95% CI 0.13–2.35).[166] The Insulin Resistance Intervention After Stroke (IRIS) trial was the only large-scale RCT to test the effect of pioglitazone versus placebo on the recurrent stroke in 3876 patients who had IGT and a recent ischemic stroke or TIA.[155] This study showed a 24% relative risk reduction in the primary composite endpoint (fatal and nonfatal stroke and MI) (HR 0.76, 95% CI 0.62–0.93), and a marginally significant risk reduction in the recurrent stroke (HR 0.82, 95% CI 0.61–1.10) in favor of pioglitazone treatment.[155] In a meta-analysis of these three RCTs with a total of 4980 participants, pioglitazone significantly reduced the risk of recurrence stroke (HR 0.68, 95% CI 0.50–0.92) and three-point MACE (HR 0.75, 95% CI 0.64–0.87, p = 0.0001) in patients with IGT and diabetes, but not total mortality, heart failure, or MI.[167] Furthermore, a prespecified secondary analysis of the IRIS trial showed pioglitazone treatment was associated with a significant reduction in the risk of total stroke (HR 0.75, 95% CI 0.60–0.94) and ischemic stroke (HR 0.72, 95% CI 0.57–0.91)[168] by using 2013 updated consensus criteria for ischemic stroke.[169] In addition, a post-hoc analysis of the IRIS trial showed pioglitazone was effective for secondary prevention of stroke in patients with good adherence (HR 0.64, 95% 0.42–0.99).[170] A nested case–control study of diabetic patients with acute ischemic stroke revealed a similar trend toward a reduction in the risk of recurrent stroke.[171] Taken together, the consensus group gave a high priority for pioglitazone in diabetic patients with a history of stroke.

6.3.6. Insulin

The effect of insulin on CV outcome in patients with type 2 diabetes was evaluated in only a few RCTs. In the long-term follow-up study of the UKPDS trial, intensive sugar control with insulin therapy did not show significant beneficial effect on the risk of stroke (HR 0.86, 95% CI 0.57–1.31) or death compared with

conventional diet therapy.[43] In the ORIGIN trial, 13.3% participants had a history of stroke. Insulin glargine treatment did not show significant reduction in risk of stroke (HR 1.03, 95% CI 0.89–1.21) or death compared with standard care in 12,537 patients with IFG, IGT, or type 2 diabetes.[49] In the SHINE study, intensive glucose-lowering with insulin-based treatment versus standard treatment did not show better improvement in neurological function in 1,151 patients admitted with acute ischemic stroke and presented with hyperglycemia.[171] Therefore, the consensus group did not give a high priority to insulin as an initial therapy in diabetic patients with a history of stroke.

6.3.7. DPP-4 inhibitors

There were four large-scale RCTs evaluating the CV effects of DPP-4 inhibitors in patients with type 2 diabetes;[24,26,53,54] however, none of the them was performed specifically for patients with a history of stroke. Among 16 492 patients in the SAVOR trial, 12.7% of had a history of stroke.[53] This study showed no significant effect of saxagliptin on the risk of ischemic stroke (HR 1.11, 95% CI 0.88–1.39), three-point MACE or death compared with placebo.[53] The subgroup analysis of patients with or without a history of stroke was not reported. Among 5380 patients in the EXAMINE trial, 7.2% of had a history of stroke.[54] This study showed no significant effect of alogliptin on the risk of nonfatal stroke (HR 0.91, 95% CI 0.55–1.50), three-point MACE or death compared with placebo.[54] The subgroup analysis of patients with or without a history of stroke was not reported. Among 14 671 patients in the TECOS trial, 24.5% had a history of stroke.[24] This study showed no significant effect of sitagliptin on the risk of stroke (HR 0.97, 95% CI 0.79–1.19), four-point MACE or death compared with placebo.[24] The subgroup analysis of patients with or without a history of stroke was not reported. Among 6979 patients in the CARMELINA trial, the percentage of patients with prior stroke was not provided.[26] Linagliptin did no reduce three-point MACE (HR 1.02, 95% CI 0.89–1.17), nor fatal or nonfatal stroke (HR 0.91, 95% CI 0.67–1.23).[26] A small short-term study of 777 diabetic patients previously treated with metformin showed a lower risk of nonfatal stroke (HR 0.27, 95% CI 0.08–0.97) and primary three-point MACE with linagliptin versus glimepiride.[172] The subgroup analysis of patients with or without a history of stroke was not reported.[172] Although this is the only RCT of DPP-4 inhibitors with positive results, it is difficult to make a definite conclusion owing to its small sample size and event number. Actually, according to a meta-analysis of the three large-scale RCTs including 36 543 participants, treatment with DPP-4 inhibitors was not associated with a reduced risk of stroke compared with placebo (OR 0.996, 95% CI 0.850–1.166).[173] There were five cohort studies analyzing the Taiwan NHIRD or national diabetes cohort in Taiwan to evaluate the effects of DPP-4 inhibitors on the risk of stroke in diabetic patients[174,175] and specifically with stroke.[176–178] However, these studies came out with controversial results. Two studies showed that treatment with DPP-4 inhibitors was associated with a lower risk of ischemic stroke (HR 0.757, 95% CI 0.596–0.961)[174] or stroke (HR 0.817, 95% CI 0.687–0.971)[175] in patients with type 2 diabetes, whereas three studies did not show any significant effect of DPP-4 inhibitors on the risk of recurrent stroke in diabetic patients with ischemic stroke.[176–178] Therefore, the consensus group gave a neutral position to DPP-4 inhibitors in diabetic patients with a history of stroke.

6.3.8. GLP-1 receptor agonists

There were seven large-scale RCTs evaluating the CV effects of GLP-1 RAs in patients with type 2 diabetes;[23,56–61] however, no trial was performed specifically for patients with a history of stroke. In the ELIXA trial, only 6.2% out of the total 6068 patients had a history of stroke.[23] This study showed no significant effect of lixisenatide on the risk of stroke (HR 1.12, 95% CI 0.79–1.58), three-point MACE or death compared with placebo.[23] The subgroup analysis of patients with or without a history of stroke was not reported.[23] There were 16.6% out of the total 9340 patients having a history of stroke in the LEADER trial.[57] This study showed a lower risk of three-point MACE (HR 0.87, 95% CI 0.78–0.97) or death, and a trend toward a lower risk of stroke (HR 0.86, 95% CI 0.71–1.06) with liraglutide treatment compared with placebo.[23] The subgroup analysis of the LEADER trial showed a significant reduction in the risk of three-point MACE (HR 0.85, 95% CI 0.73–0.99) and a trend of reduction in the risk of stroke (HR 0.93, 95% CI 0.70–1.23) in patients with baseline MI or stroke.[179] In the SUSTAIN-6 trial, 11.6% out of the total 3297 patients had a history of stroke.[58] This trial showed a lower risk of three-point MACE (HR 0.74, 95% CI 0.58–0.95) and nonfatal stroke (HR 0.61, 95% CI 0.38–0.99) with semaglutide compared with placebo.[58] The specific data regarding patients with a history of stroke was not reported.[58] In the EXSCEL trial, 17.3% out of the total 14 752 patients had a history of stroke.[56] This trial showed no significant effect of exenatide on the risk of stroke (HR 0.85, 95% CI 0.70–1.03) or three-point MACE (HR 0.91, 95% CI 0.83–1.00), but a significant reduction in the risk of total death was observed (HR 0.86, 95% CI 0.77–0.97).[56] The subgroup analysis of patients with or without a history of stroke was not reported.[56] In the HARMONY trial, 18% out of the total 9463 patients had a history of stroke.[60] This trial showed a lower risk of three-point MACE (HR 0.78, 95% CI 0.68–0.90) or MI (HR 0.75, 95% CI 0.61–0.90), and a trend toward a lower risk of stroke (HR 0.86, 95% CI 0.66–1.14) with albiglutide compared with placebo.[60] The subgroup analysis of patients with or without a history of stroke showed consistent results regarding the risk of three-point MACE (HR 0.80, 95% CI 0.61–1.04 vs. HR 0.77, 95% CI 0.65–0.91, p for interaction 0.835).[60] The REWIND trial included 9901 diabetic patients,[61] but the percentage of participants with a history of stroke was not reported.[61] This study showed a lower risk of three-point MACE (HR 0.88, 95% CI 0.79–0.99) and stroke (HR 0.76, 95% CI 0.62–0.94) with dulaglutide compared with placebo.[61] The subgroup analysis of patients with or without a history of stroke was not reported.[61] PIONEER 6 trial included 3183 diabetic patients,[59] the percentage of participants with a history of stroke was not reported.[59] This study showed a lower risk of total death (HR 0.51, 95% CI 0.31–0.84) and a trend of reduction in the risk of MACE (HR 0.79, 95% CI 0.57–1.11) but a similar risk of nonfatal stroke (HR 0.74, 95% CI 0.35–1.57) with oral semaglutide compared with placebo.[59] The subgroup analysis of patients with or without a history of stroke was not reported.[59] An updated meta-analysis of large-scale RCTs including 56 004 participants showed that treatment with GLP-1 RAs was associated with a lower risk of stroke (HR 0.84, 95% CI 0.76–0.93), MACE (HR 0.88, 95% CI 0.82–0.94), and death (HR 0.88, 95% CI 0.83–0.95).[64] A register-based cohort study of 70 206 diabetic patients showed a lower risk of MACE (HR 0.90, 95% CI 0.83–0.98) or death (HR 0.83, 95% CI 0.77–0.90), and a numerically lower risk of stroke (HR 0.88, 95% CI 0.77–1.01) with liraglutide compared with the use of DPP-4 inhibitors.[180] A meta-analysis of the ELIXA, LEADER, and SUSTAIN-6 trials showed GLP-1 RAs were associated with a lower risk of MACE and stroke especially in Asian subpopulations.[181] Taken together, the consensus group gave a high priority to GLP-1 RAs in patients with diabetes and a history of stroke.

6.3.9. SGLT-2 inhibitors

There were three large-scale RCTs primarily evaluating the CV effects of SGLT-2 inhibitors in patients with type 2 diabetes;

however, no trial was performed specifically for patients with a history of stroke. In the EMPA-REG trial, 23.7% out of a total 7020 patients had a history of stroke.[34] This study showed a lower risk of three-point MACE (HR 0.86, 95% CI 0.74–0.99) and death but no significant effect on the risk of stroke (HR 1.18, 95% CI 0.89–1.56) with empagliflozin compared with placebo.[34] The subgroup analysis of patients with or without a history of stroke consistently showed no beneficial effect on the risk of stroke.[182] In the CANVAS program, 19.3% out of a total 10 142 patients had a history of stroke.[35] This study showed a lower risk of three-point MACE (HR 0.86, 95% CI 0.75–0.97) and a trend toward a lower risk of stroke (HR 0.87, 95% CI 0.69–1.09) with canagliflozin compared with placebo.[35] A subgroup analysis of 1958 patients with a history of stroke showed that canagliflozin treatment was not associated with a lower risk of recurrent stroke (HR 0.87, 95% CI 0.69–1.09) but the risk of hemorrhagic stroke (HR 0.68, 95% CI 0.55–0.84) was reduced with canagliflozin compared with placebo.[183] The observed effect for hemorrhagic stroke was presumably due to small event numbers.[183] In the DECLARE trial, 7.6% out of the total 17 160 patients had a history of stroke.[36] This trial showed a trend of reduction in the risk of three-point MACE (HR 0.93, 95% CI 0.84–1.03) but a similar risk of ischemic stroke (HR 1.01, 95% CI 0.84–1.21) with dapagliflozin compared with placebo.[36] The subgroup analysis of patients with or without a history of stroke was not reported.[36] Four meta-analyses showed consistent results that the use of SGLT-2 inhibitors was associated with a lower risk of MACE but a similar risk of stroke.[184–187] However, three multinational observational analyses showed a beneficial effect of SGLT-2 inhibitors on the risks of stroke compared with other antidiabetic agents.[188–190] The CVD-REAL Nordic study comprised 91 320 patients with diabetes in North Europe, among whom 94% of the total SGLT-2 inhibitor exposure time was for the use of dapagliflozin.[188] In this study, 6.6% of patients had a history of stroke. 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).[188] Although there was no significant difference in the risk of nonfatal stroke (HR 0.86, 95% CI 0.72–1.04) between both groups,[188] the use of SGLT-2 inhibitors was associated with a lower risk of total stroke (HR 0.83, 95% CI 0.71–0.97) compared with other antidiabetic agents.[188] There was no subgroup analysis of the patients with or without a history of stroke. The CVD-REAL study enrolled 205 160 patients from United Ststes, Sweden, Norway, and Denmark.[189] Initiation of SGLT-2 inhibitors versus other antidiabetic agents was associated with a modestly lower risk of MI and stroke (MI: HR 0.85, 95% CI 0.72–1.00, p = 0.05; Stroke: HR 0.83, 95% CI 0.71–0.97, p = 0.02).[189] The CVD-REAL 2 study comprised 470 128 patients with diabetes in the Asia Pacific, the Middle East, and North American regions.[190] Among them, 75% of the total SGLT-2 inhibitor exposure time was for the use of dapagliflozin and 9% for the use of empagliflozin.[190] In this study, 8.7% of patients had a history of stroke.[190] 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), stroke (HR 0.68, 95% CI 0.55–0.84), and death.[190] There was no subgroup analysis of the patients with or without a history of stroke.[190] Although a favorable effect on stroke with SGLT-2 inhibitor treatment was not observed in all large-scale RCTs, a moderate priority to SGLT-2 inhibitors was given in diabetic patients with a history of stroke by the consensus group, owing to its significant effects on MACE, death, and hospitalization for HF.

6.4. Treatment algorithm in diabetic patients with a history of stroke

Table 6 shows the algorithm for the treatment of diabetes in patients with a history of stroke. The target HbA1c is <7%. Metformin or pioglitazone should be the first-line therapy in diabetic patients with a history of stroke. The recommendation for metformin is mainly based on the findings from the UKPDS trial[43] and several observational studies in Taiwan[159] and Asia.[76] The recommendation for pioglitazone is based on the results of the IRIS study,[155] which is the only mega trial specifically focus on the secondary prevention of stroke, the PROactive trial,[154] and an important meta-analysis.[167] For dual therapy, we recommend metformin plus pioglitazone. For triple therapy, we recommend the dual therapy (metformin + pioglitazone) plus a GLP-1 RA, followed by an SGLT-2 inhibitor. The SUSTAIN-6 trial,[58] the LEADER trial,[57] the HARMONY trial,[60] the REWIND trial,[61] and a meta-analysis give a strong support for the use of GLP-1 receptor agonists.[64] The observation from the CVD-REAL Nordic,[188] the CVD-REAL study,[189] and the CVD-REAL 2[190] studies gave some support to use SGLT-2 inhibitors. If a fourth drug is to be added, DPP-4 inhibitors are recommended owing to their neutral effects and favorable safety. Because there is no positive RCT with SU treatment and many observational studies reveal worse outcomes compared with other antidiabetic agents, this drug has a low priority for antiglycemic treatment in this clinical setting. Besides, this drug has a well-known risk of hypoglycemia. Glinides and acarbose also have a low priority owing to lack of strong evidence.

Table 6

Treatment algorithm in diabetic patients with a history of stroke

Target HbA1c	<7%
Monotherapy	
First choice	Metformin
Second choice	TZD[a]
Dual therapy	Metformin + TZD[a]
Triple therapy	
First choice	Metformin + TZD[a] + GLP-1 RA[b]
Second choice	Metformin + TZD[a] + SGLT-2 i
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.
[a]Pioglitazone.
[b]Liraglutide, semaglutide, and dulaglutide.

7. TREATMENT OF DIABETES IN PATIENTS WITH HEART FAILURE

7.1. Rationale

7.1.1. Diabetes is a risk factor for developing HF

A variety of pathophysiological mechanisms contribute to the development of HF in type 2 diabetes. The hyperglycemia results in advanced glycation endproducts, oxidative stress, inflammation, and apoptosis.[191–193] These pathophysiological derangements, combined with microvascular coronary artery disease, are responsible for the development of diabetic cardiomyopathy.[194] Diabetic cardiomyopathy was independent of CHD and arterial HT. The combination of multiple MI and diabetic cardiomyopathy cause HF.[194]

In the Framingham study, diabetic patients had a 2.4- to 5-fold risk of HF.[195] In the Kaiser Permanente Northwest Program, patients with diabetes had a 2.5-fold risk of HF.[196] Poor glycemic control is associated with an increased risk of HF among diabetic patients;[197] each 1% increase in HbAIc was associated with an 8% increase in the risk of HF (95% CI 5–12%). An HbAIc ≥10%, relative to an HbAIc <7%, was associated with 1.56-fold (95% CI 1.26–1.93) greater risk of HF.[197] In a recent cohort study from United Kingdom, HF is the second most common manifestation of CVD in patients with type 2 diabetes, ranked after

peripheral arterial occlusive disease.[198] In the VALUE trial, the cumulative risk of HF was higher than that of MI in patients with diabetes.[199] The prevalence of HF in the elderly diabetic patients was approximately 20%.[200] In recent RCTs of antidiabetic agents, the prevalence of prior HF was approximately 5%–30% (Table 1).

7.1.2. HF patients have a higher risk of developing diabetes

HF is an established risk factor for development diabetes.[201,202] In HF registries from the white people, the prevalence of diabetes in HF patients is approximately 20%.[203] The prevalence rate in Asia is higher. In the recent ASIAN-HF registry enrolling 5276 patients with HFrEF from 11 Asian countries, approximately 40% had diabetes.[204] In hospitalized patients with HF, the prevalence was higher. In the OPTIMIZE-HF registry, 42% of hospitalized HF patients had diabetes.[205] In the EVEREST trial, 40% of hospitalized patients with HFrEF had diabetes.[206] In the Get With The Guidelines-Heart Failure registry, 40% of patients with HFrEF and 45% of patients with preserved ejection fraction (HFpEF) had diabetes.[207] In the recent TSOC-HFrEF registry in Taiwan, 43.6% among 1509 patients with HFrEF had diabetes.[208]

7.1.3. Higher CV risk in patients with diabetes and concomitant HF

HF has been called "the frequent, forgotten, and often fatal" complication of diabetes.[209] Diabetic patients with preexisting HF had a higher CV risk compared with those without HF. In diabetic patients in the REACH registry, baseline HF increased CV death by 2.45-folds, and hospitalization for HF by 4.72-folds.[210] In clinical trials, such as the SAVOR trial[53] and the EMPA-REG trial,[34] patients with prior HF had an approximately 4-fold increase in the future HF admission,[211,212] an approximately 3-fold increase in the future HF admission plus CV death, and an approximately 2-fold increase in CV death and all-cause death.[212] The median survival for a diabetic patient with concomitant HF is only 4 years.[213] Incident HF resulting in emergent admission is probably the most deadly condition for diabetic patients, resulting in a 10-fold risk of all-cause death in the follow-up.[200,213]

Among patients with HFrEF, those with diabetes had a higher risk of HF hospitalization and CV mortality (adjusted HR 1.64, $p < 0.001$) compared with those without a history of diabetes in the substudy of the PARADIGM trial.[27,214]

The data for HF with preserved ejection fraction (HFpEF) are scarce at the moment. Therefore, the consensus focused on HFrEF.

7.2. Target of HbA1c

It is uncertain whether intensive strategy will be beneficial in patients with diabetes and HF, though poor glycemic control is associated with an increased risk of HF among diabetic patients.[197] There has been no study to determine the optimal HbA1c target in patients with HF. Several retrospective studies show a possible U-shape phenomenon in the relationship of HbA1c and mortality. In a retrospective study in a national cohort of 5815 veterans with HF and diabetes treated at Veterans Affairs medical centers from the United States, the association between mortality and HbA1c in diabetic patients with HF appears U-shaped, with the lowest risk of death in those patients with modest glucose control ($7.1\% < \text{HbA1c} \leq 7.8\%$).[215] In a prospective cohort of 845 HF patients from the United States, the risk of death or urgent heart transplantation was increased in patients with HbA1c ≤ 7.2% compared with those with HbA1c ≥ 7.3%.[216] In a population cohort from United Kingdom, patients with diabetes and HF had a U-shaped relationship between HbA1c and mortality, with the lowest risk in patients with modest glycemic control (HbA1c 7.1%–8.0%).[217]

The DAPA-HF trial is the first RCT to test antidiabetic drug in HFrEF in patients with or without diabetes.[27] There were 2139 (45%) patients with prior type 2 diabetes. The HBA1c was decreased from 7.4% to 7.2% by dapagliflozin.[218] The consensus group reached a conclusion that the target HbA1c for patients with diabetes and HFrEF is <7.5%.

7.3. Choice of drugs

There are five large-scale RCTs dedicated to study the effect of antidiabetic on long-term HF outcomes in patients with HF. All of them were SGLT-2 inhibitor trials. Three of them were performed in patients with HFrEF: (EMPEROR-REDUCED [NCT03057977], DAPA-HF [NCT03036124],[27] and SOLOIST-WHF [NCT03521934]). Two of them were performed in patients with HF with preserved EF (HFpEF)(EMPEROR-PRESERVED [NCT03057951], and DELIVER [NCT03619213]). SOLOIST-WHF enrolled only diabetic patients, while other four trials enrolled both diabetic and nondiabetic patients. DAPA-HF is the first completed one.[27] The other four trials will be finished before the end of 2021.

7.3.1. Metformin

In the UKPDS trial, patients with prior HF were excluded.[29] Metformin group had numerically lower risk of HF compared with conventional therapy, but the number was very small, not reaching statistically significance.[29] In a pooled analysis of nine cohort studies, the use of metformin in HF patients was associated with a 20% reduction in total mortality ($p < 0.00001$) and a 7% reduction in HF admission ($p = 0.01$).[219] In a more recent systemic review of 17 observation studies, metformin use was associated with a 22% reduction in all-cause mortality ($p = 0.003$) and a 13% reduction in HF admission ($p = 0.009$).[220] As mentioned previously, in a recent subanalysis from the SAVOR trial, metformin reduced all-cause death by about 25%.[33] However, in patients with prior HF or moderate-to-severe CKD, metformin could not reduce all-cause death.[33] This is a strong evidence to suggest that in patients with prior HF metformin should be moved to second-line therapy, given that we have strong evidence for SGLT-2 inhibitors. Metformin can be used in patients with stable HF, but should be discontinued in patients with acute congestive HF, CV collapse (shock), acute MI, sepsis, and other conditions associated with hypoxemia. The consensus group gave a moderate priority to metformin in patients with diabetes and stable HF.

7.3.2. Sulfonylureas

In the UKPDS trial, the combination of SU and insulin did not decrease the risk of HF compared with conventional dietary-based therapy (HR 0.91, 95% CI 0.54–1.52).[11] In the ADVANCE trial, gliclazide had a neutral effect on the HF admission, compared with other antidiabetic agents (HR 1.05, 95% CI 0.86–1.21).[13] In the CAROLINA trial, the HR of hospitalization for HF of linagliptin versus glimepiride was 1.21 (95% CI 0.92–1.59).[55] Given that linagliptin had neutral effect on HF in the CARMELINA trial,[26] the consensus group gave a neutral position to SUs in patients with diabetes and HF. But the hypoglycemic risk of SUs renders them a lower priority than DPP-4 inhibitors.[55]

7.3.3. Glinides

In the DYsfunction in DiAbetes study, 960 patients with type 2 diabetes but without overt heart disease were followed up for

2 years to examine the LV dysfunction and CV outcomes.[221] The use of repaglinide was associated with a 2-fold risk of all-cause death or hospitalization (OR 2.00, 95% CI 1.17–3.44, p = 0.01).[221] In a retrospective cohort study using the Taiwan NHIRD, the use of glinides was associated with a higher risk of hospitalization for HF compared with acarbose (aHR 1.53, 95% CI 1.24–1.88).[222] In the NAVIGATOR trial, 9306 patients with IGT and CVD or its risk factors were included, but patients with HF of NYHA III and IV were excluded.[50] There was no significant difference in the risk of hospitalization for HF between the nateglinide group versus the placebo group (HR 0.85, 95% CI 0.64–1.14).[50] The consensus group gave a neutral position to glinides in patients with diabetes and HF, but the priority was lower than DPP-4 inhibitors because of the higher hypoglycemic risk from glinides.

7.3.4. Alpha-glucosidase inhibitor

In the STOP-NIDDM trial, the effect of acarbose on CVD, including HF, was tested in 1368 patients with IGT.[51] The number of HF event was too small to draw any conclusion (n = 0 for acarbose vs. n = 2 for placebo).[51] In the more robust ACE trial, a total of 6522 Chinese patients with CHD and IFT were randomized to acarbose and placebo.[52] There was no significant difference in the HF admission in the acarbose group (2.0%) versus the placebo group (2.2%) (HR 0.89, 95% CI 0.63–1.24).[52] The consensus group gave acarbose a neutral position and did not give a priority due to its gastrointestinal side effects.

7.3.5. Thiazolidinedione

TZDs increase the risk of fluid overload by activating an epithelial sodium channel in collecting tubules and enhance sodium retention,[223] but they have no direct effect on LV function.[224] TZDs increase risk of HF and have been repetitively shown in multiple RCTs. In the PROactive trial, use of pioglitazone increased 50% of HF compared with placebo (p = 0.007).[15] In the DREAM trial, rosiglitazone significantly increased HF risk compared with placebo (HR 7.03, 95% CI 1.60–30.9).[225] In the RECORD trial, rosiglitazone increased the risk of HF by about 2-fold (HR 2.1, 95% CI 1.35–3.27), compared with metformin/SU.[226] Despite that there was no signal of increasing HF in the IRIS trial, which enrolled patients with insulin resistance and excluded patients with HF,[155] most of the meta-analyses have consistently shown an increased risk of HF by the use of TZDs with a HR ranged from 1.41 to 2.09.[96,227,228] Therefore, TZDs are contraindicated in patients with symptomatic HF and should be discontinued when HF occurs.

7.3.6. Insulin

Insulin has an antinatriuretic property and may increase sodium and fluid retention in diabetic patients,[229] though the risk of HF was not increased in many RCTs. In the UKPDS trial, the HF risk was the same in insulin users versus SU users.[11] In the BARI-2D trial, insulin did not increase HF risk compared with other antidiabetic medications.[230] In the ORIGIN trial, the basal insulin glargine resulted in a nonsignificant reduction in HF admission (HR 0.90, 95% CI 0.77–1.05).[49]

In patients with diabetes and HF, there are evidences suggesting a harmful effect of insulin. In the CHARM program, insulin-treated diabetes was found to be the strongest independent predictor for CV death plus hospitalization for HF, and the HR (2.03, 95% CI 1.80–2.29) was higher than those who had not been treated with insulin (HR 1.58 95% CI 1.43–1.74).[231] The total mortality showed a similar trend (HR 1.80, 95% CI 1.56–2.08 vs. 1.50, 95% CI 1.34–1.68).[231] In a systemic review of controlled studies evaluating antidiabetic agents and outcomes in patients with HF, three of four studies disclosed insulin increased risk of all-cause mortality (OR 1.25, 95% CI 1.03–1.51).[232] The consensus group gave insulin a low priority in patients with diabetes and HF. The use of insulin should be reserved for patients whose blood glucose cannot be controlled by other safer drugs, or in conditions when oral antidiabetic drugs cannot be used.

7.3.7. DPP-4 inhibitors

In the SAVOR trial, the use of saxagliptin increased hospitalization for HF (HR 1.27, 95% CI 1.07–1.51, p = 0.007).[53] The risk of hospitalization for HF was significantly increased in patients with or without a history of HF (HR 1.21, p = 0.15, absolute risk 1.5%, number needed to harm (NNH) 67; HR 1.32, p = 0.02; absolute risk 0.6%, NNH 167, respectively; p for interaction 0.67).[211] The increase in HF admission was predominantly in the first 2 years of treatment (HR 1.80, 95% CI 1.29–2.55, p = 0.001 at 180 days; HR 1.46, 95% CI 1.15–1.88, p = 0.002 at 360 days; HR 1.27, 95% CI 1.07–1.51, p = 0.007 at 720 days).[211] The risk factors for HF admission included the followings: prior HF, elevated baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP), and CKD.[211] The mechanism of increased HF admission with the use of saxagliptin was not completely understood, but an increase in stromal cell-derived factor-1 after the use of DPP-4 inhibitor may be a possible mechanism.[233] In the EXAMINE trial, alogliptin was associated with a numerically higher risk of hospitalization for HF (HR 1.07, 95% CI 0.79–1.46).[234] The difference became significant in patients without a history of HF (HR 1.76, 95% CI 1.07–2.90).[234] There was no CV outcome trial for vildagliptin. In the VIVVID study, patients with type 2 diabetes and HF (NYHA I-III and LVEF <0.40) were randomized to 52-week treatment with vildagliptin or placebo.[235] There was no change in the primary endpoint, defined as between-treatment change in LVEF from baseline.[235] However, the LV end-systolic volume and end-diastolic volume were increased compared with placebo (+9.44 mL, 95% CI –0.49 to 19.38, p = 0.062; +17.06 ml, 95% CI 4.62–29.51, p = 0.007; respectively). The CV death and total death were numerically higher in those receiving vildagliptin compared with placebo (5.5% vs. 3.2%; 8.6% vs. 3.2%, respectively, all p > 0.05). Overall, saxagliptin, alogliptin, and vildagliptin should not be used in patients with diabetes and HF.

The remaining 2 DPP-4 inhibitors, sitagliptin and linagliptin, are presumably safe in diabetic patients with HF. In the TECOS trial, sitagliptin did not increase HF admission in the overall population (HR 1.00, 95% CI 0.83–1.20),[24] or in patients with a history of HF (HR 1.05, 95% CI 0.79–1.39).[236] Post-HF death (29.8% vs. 28.8%) and CV death (22.4% vs. 23.1%) was similar in the sitagliptin and placebo groups.[236] We suggest that sitagliptin can be safely used in patients with diabetes and HF. In the CARMELINA trial, linagliptin did not increase risk hospitalization for HF (HR 0.90, 95% CI 0.74–1.08, p = 0.26),[26] the composite of CV death/hospitalization for HF (HR 0.94, 95% CI 0.82–1.08), nor risk for recurrent hospitalization for HF events (HR 0.94, 95% CI 0.75–1.20).[237] Among the subset of participants with or without a history of HF at baseline, there were no significant differences observed between the treatment groups in HHF (HR 0.88, 95% CI 0.68–1.14, p = 0.33; HR 0.92; 95% CI 0.70–1.22, p = 0.56; respectively).[237]

Overall, the consensus group gave a neutral position to 2 DPP-4 inhibitors, sitagliptin and linagliptin, in patients with diabetes and HF, but did not recommend saxagliptin, alogliptin, and vildagliptin in patients with HF.

7.3.8. GLP-1 receptor agonists

The effects of seven GLP-1 RAs on CV events, including HF, have been tested in seven RCTs.[23,56–61] In addition to MACE

events, hospitalization for HF was also prospectively adjudicated. In general, the effects of GLP-1 RAs were neutral in terms of hospitalization for HF (Table 2).

An important RCT with GLP-1 RA in patients with HF is the FIGHT trial.[238] The FIGHT trial is a phase 2, double-blind, placebo-controlled RCT testing the effect of daily injection of liraglutide in recently hospitalized patients with HFrEF, including 59% with type 2 diabetes.[238] The primary endpoint was a global rank score in which all patients, regardless of treatment assignment, were ranked across three hierarchical tiers: time to death, time to re-hospitalization for HF, and time-averaged proportional change in NT-proBNP level from baseline to 180 days. Compared with placebo, liraglutide had no significant effect on the primary endpoint (mean rank of 146 for the liraglutide group vs. 156 for the placebo group, $p = 0.31$). There were no significant between-group differences in the number of deaths (19 [12%] in the liraglutide group vs. 16 [11%] in the placebo group; HR 1.10, 95% CI 0.57–2.14, $p = 0.78$) or re-hospitalizations for HF (63 [41%] vs. 50 [34%], respectively; HR 1.30, 95% CI 0.89–1.88, $p = 0.17$). Prespecified subgroup analyses in patients with diabetes did not reveal any significant between-group difference.[238] Therefore, GLP-1 RAs have a neutral effect on HF and can be used safely in patients with diabetes and HF. The consensus group gave a neutral position to GLP-1 RAs in patients with diabetes and HF.

7.3.9. SGLT-2 inhibitors

There are several RCTs testing the effects of SGLT-2 inhibitors on CV outcomes, and four of them have been published (EMPA-REG, CANVAS, DECLARE, and CREDENCE).[25,34–36] hospitalization for HF was one of the secondary endpoints. The percentages of prior HF were 10.5%, 14.4%, 10.2%, and 14.8%, respectively.(Table 1) All these trials demonstrated a remarkably effect in reducing hospitalization for HF (–35%, –33%, –27%, and –39%, respectively). These data suggested a positive role of SGLT-2 inhibitors in reducing HF in diabetic patients. As mentioned before, there are five large-scale RCTs dedicated to study the effect of antidiabetic on long-term HF outcomes in patients with HF. The DAPA-HF trial has been completed and published.[27] Actually it was prematurely stopped at 18 months due to an early demonstration of its efficacy.

The DAPA-HF trial randomized 4744 symptomatic patients with HFrEF into dapagliflozin 10 mg or placebo.[27] Patients with LVEF >40%, or eGFR < 30 mL/min/1.73 m2 or SBP < 95 mmHg, or type 1 diabetes were excluded. There were 20 countries participated in this trial and Taiwan randomized 141 patients. The primary outcome was a composite of worsening HF (WHF, hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death. Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (HR 0.74, 95% CI 0.65–0.85, $p < 0.001$). A first WHF event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (HR 0.70, 95% CI 0.59–0.83). Death from CV causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (HR 0.82, 95% CI 0.69–0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (HR 0.83, 95% CI, 0.71–0.97). The frequency of AEs related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.[27]

Two most important subgroup analyses in the DAPA-HF trial showed dapagliflozin reduced WHF/CV death in both diabetic and nondiabetic patients (HR 0.75, 95% CI 0.63–0.90, and HR 0.73, 95% CI 0.60–0.88, respectively, p for interaction 0.80),[218] and in both angiotensin receptor–neprilysin inhibitor (ARNI) users and ARNI nonusers (HR 0.75, 95% CI 0.50–1.13, and HR 0.74, 95% CI 0.65–0.86, respectively, p for interaction = nonsignificant).[27] The effect of dapagliflozin on the primary outcome was generally consistent across other prespecified subgroups, including elderly patients.[239] Furthermore, dapagliflozin reduced composite renal endpoints (HR 0.71, 95% CI 0.44–1.16, $p = 0.17$).[27] Symptoms and life quality were both significantly improved by dapagliflozin.[27] The increase in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (indicating fewer symptoms) was greater in the dapagliflozin group than in the placebo group from baseline to month 8 (+6.1 vs +3.3, $p < 0.001$).[240] AEs rarely led to a discontinuation of the drug. There was no notable excess of any serious AE in the dapagliflozin group.[27]

Other meta-analyses and real-world evidence (RWE) were also in favor of a class effect of SGLT-2 inhibitors in reducing HF admission in patients with diabetes. In a systematic review and meta-analysis of 6 regulatory submissions (37 525 participants) and 57 published trials (33 385 participants), the data from seven different SGLT-2 inhibitors were analyzed.[241] SGLT-2 inhibitors protected against the risk of MACE (RR 0.84, 95% CI 0.75–0.95, $p = 0.006$), CV death (RR 0.63, 95% CI 0.51–0.77, $p < 0.0001$), HF (RR 0.65, 95% CI 0.50–0.85, $p = 0.002$), and all-cause mortality (RR 0.71, 95% CI 0.61–0.83, $p < 0.0001$). There was no clear evidence that the individual drugs had different effects on CV outcomes or death.[241] Other RWE including the CVD-REAL study,[242] the CVD-REAL NORDIC study,[188] and the CVD-REAL 2 study,[190] demonstrated similar results.

No one could have expected SGLT-2 inhibitors would decrease HF admission and mortality.[243] The mechanisms are becoming clearer.[139] Patients with diabetes are overloaded with sodium, mainly because of increased sodium retention in the kidney as a consequence of hyperglycemia and hyperinsulinemia.[244] Increased intracellular sodium in the myocardium may increase the risk of arrhythmias and impair myocardial function.[244] SGLT-2 inhibitors inhibit sodium glucose transporter in the proximal tubule in the kidney,[245] resulting in glucosuria and body weight loss about 3–4 Kg.[246] SGLT-2 inhibitors also cause osmotic diuresis and natriuresis.[247,248] This will result in a decrease in blood pressure,[139,249,250] and tissue sodium[251,252] and tissue water.[253,254] It has been shown that SGLT-2 inhibitors decreased LV mass and improved LV diastolic function in diabetic patients.[255] Another important effect of SGLT-2 inhibitors is inhibition on the Na^+/H^+ exchanger.[256,257] SGLT-2 inhibitors directly inhibited Na^+/H^+ exchanger 1 in the myocardium, and reduced cytoplasmic NA^+ and Ca^{++},[253,258] resulting in a reduction

Table 7

Treatment algorithm in diabetic patients with heart failure

Target HbA1c	<7.5%
Monotherapy	SGLT-2 i
Dual therapy	SGLT-2 i + metformin
Triple therapy	
First choice	SGLT-2 i + metformin + GLP-1 RA[a]
Second choice	SGLT-2 i + metformin + DPP-4 i[b]
Third choice	SGLT-2 i + metformin + SU or AGI
Fourth choice	SGLT-2 i + metformin + glinide
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

AGI = alpha-glucosidase inhibitor; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea.

[a]Liraglutide, semaglutide, and dulaglutide.

[b]Sitagliptin and linagliptin.

in intracellular calcium overload and cardiac protection.[259] Moreover, SGLT-2 inhibitors decreased aortic stiffness[260] and augmentation index.[260] SGLT-2 inhibitors increased lipolysis and enhanced bioavailability of free fatty acids and ketone bodies and improved cellular energy use.[261,262]

SGLT-2 inhibitor is a unique class of antidiabetic agent for diabetic patients with HF. In the DAPA-HF trial, dapagliflozin showed a robust effect in decreasing hospitalization for HF admission/CV death and all-cause death. It has been recommended in many international guidelines.[46,263] Therefore, the consensus group recommended SGLT-2 inhibitors as the first-line therapy in patients with diabetes and HFrEF.

7.4. Treatment algorithm in diabetic patients with HF

Table 7 shows the algorithm for the treatment of diabetes in patients with HF. The target of HbA1c is < 7.5%. SGLT-2 inhibitor is the first-line therapy, based on the DAPA-HF trial,[27] complemented by data from four RCTs (EMPA-REG, CANVAS, DECLARE, and CREDENCE).[25,34–36] For dual therapy, SGLT-2 inhibitor can be combined with metformin, based on two recent meta-analyses.[219,220] Metformin should not be used or should be discontinued in patients with clinical conditions associated with hypoxemia, such as acute HF, shock, or sepsis, to avoid lactic acidosis. If a third drug is to be added, we recommended GLP-1 RAs, based on their neutral effect in all trials of GLP-1 RA.[23,56–61] The ranking of DPP-4 inhibitors is lower than GLP-1 RAs. Sitagliptin and linagliptin can be safely used, based on the finding from the TECOS trial and the CARMELINA trial.[24,26] Saxagliptin, alogliptin, and vildagliptin should be avoided, based on the findings from the SAVOR trial,[53] the EXAMINE trial,[54] and the VIVVID study.[235] SU, acarbose, and glinides are ranked lower than DPP-4 inhibitors.

8. ADVERSE EVENTS OF ANTIDIABETIC AGENTS

Important AEs of common antidiabetic agents were shown in **Fig. 2**. Hypoglycemia and some emerging AEs of newer antidiabetic agents were noted here.

8.1. Hypoglycemia

Hypoglycemia is common in daily practice. In a cross-sectional survey in five Asian countries, symptomatic hypoglycemia was reported in 35.8% of overall patients and in 29.4% of Taiwanese patients, who were treated with oral antidiabetic agents.[264] There is an increasing trend in emergency department visits for hypoglycemia in patients with type 2 diabetes in Taiwan from 2000 to 2010 (adjusted incidence rate ratio 4.88, 95% CI 3.94–6.05, $p < 0.001$).[265] From the data of the Taiwan NHIRD between 1998 and 2009, patients with symptomatic hypoglycemia were associated with higher risks for CVD (HR 2.09, 95% CI 1.63–2.67, $p < 0.0001$), all-cause hospitalization (HR 2.51, 95% CI 2.00–3.16, $p < 0.0001$), and total mortality (HR 2.48, 95% CI 1.41–4.38, $p < 0.0001$).[157] The risk level was correlated with the severity of hypoglycemia, shown in a recent meta-analysis.[266] The HRs of adverse vascular events and mortality were 1.68 (95% CI 1.25–2.26, $p < 0.001$) for mild hypoglycemia and 2.33 (95% CI 2.07-2.61, $p < 0.001$, p for trend 0.02) for sever hypoglycemia.[266] Therefore, minimizing risk of both severe and nonsevere hypoglycemia is a priority in the management of diabetes.[267]

Among antidiabetic agents, SUs,[89] glinides,[268] and insulin increase the risk of hypoglycemia (**Fig. 2**).[269] Metformin, alpha-glucosidase inhibitor,[270] TZD, and other newer antidiabetic agents, such as DPP-4 inhibitors,[89,175,271,272] GLP-1 RAs,[273] and SGLT-2 inhibitors, have lower risk of hypoglycemia. Although a modest benefit of intensive glucose control on CV events is likely to be present, it should be noted that overly aggressive glycemic control, especially in older patients with more advanced disease, may not have significant benefits but instead may produce some risks. Therefore, clinicians should balance the risk of hypoglycemia versus CV benefit.

8.2. Genital tract infection

The risk of genital tract infection (GTI) is increased by SGLT-2 inhibitors. In the EMPA-REG trial, the annual incidence of GTI was significantly higher in the empagliflozin group than in the placebo group in both men and women (5.0% vs. 1.5%, $p<0.001$ for men; 10.0% vs. 2.6%, $p<0.001$ for women).[34] In the

Fig. 2. Important adverse events of common antidiabetic agents. Green color means a decreased risk. Empty box means a neutral effect. Red color means an increased risk. AGI = alpha-glucosidase inhibitor; AKI = acute kidney injury; alo = alogliptin; cana = canagliflozin; DKA = diabetic ketoacidosis; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GI = gastrointestinal side effects; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GTI = genital tract infection; HF = heart failure; saxa = saxagliptin; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione; vilda = vildagliptin.

CANVAS program, the annual incidence of GTI was also higher in the canagliflozin group than in the placebo group (3.49% vs. 1.08%, $p < 0.001$ for men; 6.88% vs. 1.75%, $p < 0.001$ for women).[35] In the DECLARE trial, GTI was significantly higher in the dapagliflozin group than in the placebo group (0.9% vs. 0.1%, HR 8.36, 95% CI 4.19–16.68, $p < 0.001$),[36] although GTI reported as SAE were rare (two events in each of the male and the female group). In the CREDENCE trial, the annual incidence of GTI was also higher in the canagliflozin group than in the placebo group (8.4% vs. 0.9%, HR 9.30, 95 % CI 2.83–30.60, $p < 0.001$ for men; 12.6% vs. 6.1%, HR 2.10, 95% CI 1.00–4.45, $p < 0.001$ for women).[25] Therefore, personal hygiene should be emphasized in patients receiving SGLT-2 inhibitors. One should be reminded that SGLT-2 inhibitors did not increase the risk of urinary tract infection.[274]

8.3. Fournier gangrene

Fournier gangrene was known as a necrotizing fasciitis of the perineum, characterized by a rapidly progressive necrotizing infection of the external genitalia, perineum, and perianal region requiring broad-spectrum antibiotics and immediate surgical intervention.[275] In a review of spontaneous postmarketing cases from the U.S. FDA Adverse Event Reporting System (FAERS) and published case reports, 55 unique cases of Fournier gangrene were identified in patients receiving SGLT-2 inhibitors between 1 March 2013 and 31 January 2019. For comparison, the U.S. FDA identified 19 Fournier gangrene cases associated with other antidiabetic agents between 1984 and 31 January 2019: metformin (n = 8), insulin glargine (n = 6), short-acting insulin (n = 2), sitagliptin plus metformin (n = 2), and dulaglutide (n = 1).[276] However, more recent studies based on RWE did not find an association of SGLT-2 inhibitors and Fournier gangrene.[277,278]

In the EMPA-REG,[34] CANVAS,[35] and the CREDENCE trials,[25] Fournier gangrene was not prospectively evaluated. The DECLARE trial is the only trial in which Fournier gangrene was prospectively collected and adjudicated,[36] and six cases of Fournier gangrene were reported, one in the dapagliflozin group, and five in the placebo group. Though the association of SGLT-2 inhibitors and Fournier gangrene is not clear, physicians prescribing these agents should be aware of this possible complication and have a high index of suspicion to recognize it in its early stages.[276]

8.4. Acute kidney injury

Based on data from the FAERS the U.S. FDA issued a warning of AKI for canagliflozin and dapagliflozin (https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm) in 2016. From March 29, 2013 to October 19, 2015, 101 cases of AKI were reported in 73 and 28 patients treated with canagliflozin and dapagliflozin, respectively. Among those 101 cases, 51 concomitantly used ACE inhibitors, 26 used diuretic, and 6 used NSAIDs. Real-world data showed inconsistent findings. SGLT-2 inhibitors were associated with an increased risk of AKI from international pharmacovigilance database.[279] However, in another study using longitudinal data from Mount Sinai CKD registry and Geisinger Health System cohort, the risk of AKI was reduced in users of SGLT-2 inhibitors.[280]

In the EMPA-REG trial, the annual risk of AKI in pooled empagliflozin group was lower than that in the placebo group (1.0% vs. 1.6%, $p < 0.05$).[34] In the CANVAS trial, the annual risk of AKI was similar in the canagliflozin group versus the placebo group (0.3% vs. 0.41%, $p = 0.33$).[35] In the DECLARE trial, AKI was prospectively adjudicated and the risk was significantly lower in the dapagliflozin group versus placebo group (HR 0.69, 95% CI 0.55–0.87, $p = 0.002$).[36] In the CREDENCE trial, the risk of AKI was numerically lower in the canagliflozin group versus placebo group (HR 0.85, 95% CI 0.64–1.13).[25] We recommended examining several factors that may predispose patients to AKI. These factors include hypovolemia, CKD, HF, and concomitant medications such as diuretics, ACE inhibitors, ARBs, and NSAIDs. Renal function should be evaluated before the initiation of SGLT-2 inhibitors and monitored periodically thereafter. Temporary discontinuation of SGLT-2 inhibitors should be considered in any setting of reduced oral intake such as acute illness or fasting, or with fluid losses such as gastrointestinal illness or excessive heat exposure.

8.5. Diabetic ketoacidosis

The U.S. FDA added warnings of diabetic ketoacidosis to the labels of SGLT-2 inhibitors in May 2015, based on data of FAERS from March 2013 to May 2015 that 73 cases of diabetic ketoacidosis (DKA) in patients with type 1 and type 2 diabetes treated with SGLT-2 inhibitors were identified (https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm). The FAERS database contains >2500 DKA reports in which SGLT-2 inhibitors are listed as the suspect or the concomitant drugs.[281] The proportional reporting ratio (PRR) of DKA in reports including versus those not including an SGLT-2 inhibitor was 7.9 (95% CI 7.5–8.4), and was higher for type 1 diabetes. This finding was supported by a recent report from a claim database from the United States, which included 50 220 patients who had received a new prescription of an SGLT-2 inhibitor and 90 132 who had received a new prescription of a DPP-4 inhibitor.[282] After propensity-score matching to balance 46 characteristics of the patients, the HR was 2.2 (95% CI 1.4–3.6).[282]

In four major RCTs (EMPA-REG, CANVAS, DECLARE, and the CREDENCE trial),[25,34–36] the risk of DKA in patients receiving SGLT-2 inhibitors was generally increased. The HR of DKA in the EMPA-REG, CANVAS, and DECLARE trials were 1.99 (95% CI 0.22–17.80), 2.33 (95% CI 0.76–7.17) and 2.18 (95% CI 1.10–4.30), respectively. Collectively, a significant increase in the risk of DKA was observed (HR 2.20, 95% CI 1.25–3.87, $p = 0.006$, P for interaction 0.99).[69] In the more recent CREDENCE trial, the HR for canagliflozin was 10.80 (95% CI 1.39–83.65).[25]

One should be aware that patients with SGLT-2 inhibitors-related DKA may not have very high blood glucose level, sometimes being called "euglycemic DKA", and their plasma glucose level is usually <300 mg/dL.[283] In a systemic review, the average blood glucose on presentation of DKA was 265.6 mg/dL.[284] Because DKA is a potentially lethal complication, the consensus group recommend that potential triggering factors should be identified during the exposure period to SGLT-2 inhibitors, which include intercurrent illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake.[285,286] Symptoms of DKA, including nausea, vomiting, abdominal pain, tiredness, and shortness of breath, should be monitored.[283]

8.6. Amputation

A higher risk of amputation with the use of canagliflozin was also found in FAERS.[287] The risk of amputation of canagliflozin was higher than non-SGLT-2 inhibitors (proportional reporting ratio [PRR] 5.33, 95% CI 4.04–7.04, $p < 0.0001$). In contrast, the PRR for dapagliflozin was 0.25 (95% CI 0.03–1.76, $p = 0.163$) and for empagliflozin was 2.37 (95% CI 0.99–5.70, $p = 0.054$).[287] In the CANVAS program, there was a higher risk of amputation of toes, feet, or legs with canagliflozin than with placebo (6.3 vs. 3.4 participants with amputation per 1000 patient-years, HR 1.97, 95% CI 1.41–2.75, $p < 0.001$).[35] In a subanalysis of the EMPA-REG trial, the risk of lower-leg amputation was similar between the empagliflozin group and

the placebo group (1.9% vs. 1.8%).[288] By the analysis of time to first event, the risk was also similar in the two groups (HR 1.00, 95% CI 0.70–1.44).[288] In the DECLARE trial, there was no increase in the risk of amputation by dapagliflozin versus placebo (HR 1.09, 95% CI 0.84–1.40, $p = 0.53$).[36] Likewise, no signal of increased amputation with the use of dapagliflozin versus placebo was observed in the DAPA-HF trial (0.5% vs. 0.5%, $p = 1.00$).[27] Interestingly, there was no increase in amputation with canagliflozin in the CREDENCE trial (HR 1.11, 95% CI 0.79–1.56).[25] One should be reminded that, based on the findings from the CANVAS trial, there was a protocol amendment for the CREDENCE trial in May 2016 to ask investigators to examine patients' feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation.[25] The U.S. FDA added a boxed warning solely to canagliflozin in May 2017 (https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm).

Why canagliflozin increased amputation risk in the CANVAS trial was not exactly known. One possible reason was that there was an increase in the percentages of volume depletion with the use of canagliflozin versus placebo in the CANVAS trial (26.0% vs. 18.5%, $p = 0.009$).[35] This might increase blood viscosity and the risk of thrombosis in the lower limbs. There was no increase in the percentages of volume depletion in other trials of SGLT-2 inhibitors (EMPA-REG: 5.1% for empagliflozin vs. 4.9% for placebo [$p > 0.05$][34]; DECLARE: 2.5% for dapagliflozin vs. 2.4% for placebo [$p > 0.05$][36]; DAPA-HF trial: 7.5% for dapagliflozin vs. 6.8% for placebo [$p > 0.05$][27]; CREDENCE trial: 28.4% for canagliflozin vs. 23.5% for placebo [HR 1.25, 95% CI 0.97–1.59]).[25]

Amputation of the toe and middle of foot were the most common; however, amputations involving the leg, below and above the knee, also occurred.[35,287] Several clinical conditions may predispose patients to the risk of amputations, including volume depletion, a history of amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.[35,287] Physicians should remind patients of the following symptoms: new pain or tenderness, sores or ulcers, or infections in legs or feet.

8.7. Fracture

TZDs have detrimental effects on the skeleton,[289] and increase the risk of fracture.[290] In the recent IRIS trial, the incidence of fracture in the pioglitazone group was higher than that in the placebo group (5.1% vs. 3.2%, $p = 0.003$).[155]

Canagliflozin decreased bone mineral density[291] and increased the risk of fracture.[292] In September 2015, U.S. FDA has strengthen the warning for canagliflozin related to the increased risk of bone fractures and added new information about decreased bone mineral density (https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm). In five trials of SGLT-2 inhibitors, canagliflozin in the CANVAS trial was the only one showing an increased risk of fracture (1.54% for canagliflozin vs. 1.19% for placebo, $p = 0.02$). There were no increases in other four trials (EMPA-REG: 3.8% for empagliflozin vs. 3.9% for placebo, $p > 0.05$[34]; DECLARE: 5.3% for dapagliflozin vs. 5.1% for placebo, $p = 0.59$[36]; DAPA-HF: 2.1% for dapagliflozin vs. 2.1% for placebo, $p = 1.00$[27]; CREDENCE: 1.18% for canagliflozin vs. 1.21% for placebo, $p = 0.98$).[25] The ongoing SOTA-BONE trial (NCT03386344) is examining the effect of sotagliflozin on bone density and will provide some clues in this perspective.

9. SUMMARY AND CONCLUSIONS

The prevalence of type 2 diabetes has been escalating in recent decades, resulting in a huge economic and health burden to our society. Treatment of diabetes should now be expanded from a glucose-centric concept to an event-driven strategy. Fortunately, we have many new antidiabetic agents, proven to be effective in CV and renal protection. Just in recent few years, many RCTs have demonstrated significant reductions in MI, stroke, CV death, all-cause death, HF, and ESRD, in patients with preexisting CVD. The consensus group of TSOC have formulated a treatment consensus for type 2 diabetic patients with five different type of patients, including patients with multiple risk factor, CHD, CKD, stroke, and HF. This consensus is an update version of the 2018 one[28] and provides physicians most updated information and recommendations regarding targets of HbA1c and choice of drugs. The consensus is not mandatory, and the physician's decision remains most important in diabetes management.

ACKNOWLEDGMENTS

This work was supported, in part, by grants from the Ministry of Health and Welfare (MOHW109-TDU-B-211-114001) and intramural grants from the Taipei Veterans General Hospital (109DHA0100196).

Conflicts of interest: Dr. Chiang has received honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Sanofi. Kwo-Chang Ueng declared no conflicts of interest. Ting-Hsing Chao has received honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi, and Orient EuroPharma. Tsung-Hsien Lin has received honoraria from AstraZeneca, Boehringer Ingelheim, Tanabe, MSD, Novartis, Pfizer, Takeda, Sanofi, Novo Nordisk, and Lilly. Yih-Jer Wu has received honoraria from Johnson & Johnson, Pfizer, GSK, AstraZeneca, and Boehringer Ingelheim. Kang-Ling Wang has received honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, and Pfizer. Shih-Hsien Sung declared no conflicts of interest. Hung-I Yeh has received honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Mitsubishi Tanabe, Novartis, MSD, Orient EuroPharma, Pfizer, and Sanofi. Yi-Heng Li has received honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Sanofi, Bayer, and OEP. Ping-Yen Liu declared no conflicts of interest. Kuan-Cheng Chang has received honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Tanabe, Novartis, Pfizer, and Sanofi. Kou-Gi Shyu has received honoraria from Pfizer, Daiichi-Sankyo, Bayer, AstraZeneca, Boehringer Ingelheim, Orient EuroPharma, and Eli Lilly. Jin-Long Huang has received honoraria from Abbott, Bayer, Biotronik, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, and Pfizer. Cheng-Dao Tsai has received honoraria from Pfizer, Daiichi-Sankyo, and Novartis. Huei-Fong Hung declared no conflicts of interest. Ming-En Liu has received honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, and Pfizer. Tze-Fan Chao has received honoraria from Abbott, Bayer, Biotronik, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, and Pfizer. Shu-Meng Cheng declared no conflicts of interest. Hao-Min Cheng has received honoraria from AstraZeneca, Pfizer, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, SERVIER, Eli Lilly, Sanofi, and TAKEDA. He also received grants for clinical research from Microlife Co., Ltd., Intelligent Vision Technology Co., Ltd. Pao-Hsien Chu has received honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, and Pfizer. Wei-Hsian Yin declared no conflicts of interest. Yen-Wen Wu has received honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Menarini, Mitsubishi Tanabe, Novartis, MSD, Pfizer, and Sanofi. Wen-Jone Chen declared no conflicts of interest. Wen-Ter Lai has received honoraria from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, Pfizer, and Sanofi. Shing-Jong Lin declared no conflicts of interest. San-Jou Yeh has received honoraria from AstraZeneca, Boehringer

Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi, and Tanabe. Juey-Jen Hwang declared no conflicts of interest.

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