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Guidelines

2018 consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

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Abstract

The global incidence and prevalence of type 2 diabetes have been escalating in recent decades. Patients with type 2 diabetes have an increased risk of atherosclerotic cardiovascular disease (ASCVD). About two-thirds of death in type 2 diabetes are due to ASCVD, including 40% from coronary heart disease (CHD), 15% from heart failure (HF), and 10% from stroke. The association between hyperglycemia and elevated CV risk has been demonstrated in multiple cohort studies. However, clinical trials of intensive glucose reduction did not significantly reduce macrovascular outcomes. It remains unclear whether the absence of demonstrable benefits is attributed to the inclusion of patients with far advanced ASCVD in whom a short treatment period is barely enough for CV protective effects to be shown, or complications associated with the treatment such as hypoglycemia hamper the beneficial effects to manifest, or simply glucose-lowering per se is ineffective.

Since the US FDA issued a mandate in December 2008 that every new anti-diabetic agent requires rigorous assessments of its CV safety, there have been more than 200,000 patients enrolled in a number of randomized controlled trials (RCTs), and around half of them have been completed and published. The results of these CV outcome trials are important for clinicians in their 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.

The Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC), aiming to formulate a treatment consensus in type 2 diabetic patients with CVD, have appointed a jointed consensus group for the 2018 Consensus of TSOC/DAROC (Taiwan) on the Pharmacological Management of Patients with Type 2 Diabetes and CV Diseases. The consensus is comprised of 5 major parts: 1) Treatment of diabetes in patients with hypertension, 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 the evidence, mainly RCTs, and also included meta-analyses, cohort studies, and studies using claim data. The treatment targets of HbA1c were provided. The anti-diabetic 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: Anti-diabetic agents; Chronic kidney disease; Coronary heart disease; Heart failure; Hypertension; Stroke; Type 2 diabetes

Contents

1. Introduction

The global incidence and prevalence of type 2 diabetes has quadrupled between 1980 and 2004.[1] The prevalence is still escalating. It is expected that the diabetic population will increase from 415 million in 2015 to 642 million by 2040.[2] The increasing trend is particularly pronounced in the developing countries.[3] Atherosclerotic cardiovascular disease (ASCVD) is the major cause of death and disability in patients with type 2 diabetes.[4] About two-thirds of causes of death in type 2 diabetes are due to ASCVD, including 40% from coronary heart disease (CHD), 15% from heart failure (HF), and 10% from stroke.[5] Given that many macrovascular complications develop even 10–15 years before the clinical diagnosis of diabetes, management of diabetes and the associated ASCVD become even more difficult.[6]

A plethora of evidence supports the association between hyperglycemia and elevated cardiovascular (CV) risk. In the United Kingdom Prospective Diabetes Study (UKPDS), for each 1% reduction in mean glycated hemoglobin (HbA1c) there are reductions in diabetes-related death and in myocardial infarction (MI) by 21% and 14%, respectively.[7] In the Emerging Risk Factors Collaboration group, every 1 mmol/L (18 mg/dL) increase in fasting glucose is associated with a 12% increase in the risk of ASCVD.[8] However, clinical trials of intensive glucose reduction did not significantly reduce macrovascular outcomes in four major randomized controlled trials (RCTs): the UKPDS trial,[9] the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial,[10] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[11] and the Veterans Association Diabetes Trial (VADT).[12] The biology underlying this paradoxical finding has not been fully understood. In the intensive group, sulfonylurea and insulin were more extensively used, and hypoglycemia was more frequently encountered. A recent study using Taiwan National Health Insurance Research Database (NHIRD) showed that severe hypoglycemia was associated with increased risk of total mortality (Hazard ratio [HR] 2.48, 95% confidence interval [CI] 1.41–4.38).[13] Moreover, a longer follow-up period may be needed to address the effects of glucose-lowering on CV protection, which has been demonstrated in follow-up studies of these RCTs.[14–16] It remains unclear whether the absence of demonstrable benefits is attributed to the inclusion of patients with far advanced ASCVD in whom a short treatment period is barely enough for CV protective effects to manifest, or complications associated with the treatment such as hypoglycemia hamper the beneficial effects to manifest, or simply glucose-lowering per se is ineffective. Nevertheless, a meta-analysis comprising 5 RCTs (UKPDS, ACCORD, ADVANCE, VADT, and the PROspective pioglitazone Clinical Trial In macroVascular Events [PROactive][17]) does show a benefit of lowering glucose in reducing non-fatal MI and CHD.[18] With a much safer profile of the new generations of anti-diabetic agents, including dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4 i), glucagon-like peptide (GLP)-1 receptor agonists (GLP-1 RA), and sodium/glucose co-transporter 2 (SGLT-2) inhibitors (SGLT-2 i), a more favorable effect on CV outcomes can be anticipated.

In 2007, a provocative meta-analysis raised a tremendous concern[19] showing that rosiglitazone was associated with a significant increase in the risk of MI (odds ratio [OR] 1.43, 95% CI 1.03 to 1.98; P = 0.03) and a trend of increase in the risk of CV death (OR 1.64, 95% CI 0.98 to 2.74; P = 0.06).[19] Afterwards, the US Food and Drug Administration (FDA) issued guidance in December 2008 recommending rigorous assessments of the CV safety of new anti-diabetic agents. The primary endpoints should include a composite endpoint of CV death, non-fatal MI, and non-fatal stroke (3-point MACE). The European Medicines Agency (EMA) also issued their regulatory requirement in 2012. Thereafter, more than 200,000 patients have been enrolled in a number of CV outcome trials accordingly, and around half of them have been completed and published. Most of these RCTs enrolled patients at relatively higher CV risk. Table 1 shows recent CV outcome trials, ranked by the baseline CV risk levels, i.e., the percentages of pre-existing ASCVD. The proportions of patients with pre-existing ASCVD ranging from 58% in the Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial[20] to 100% in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial[21] (stable ASCVD) and the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)[22] trial (100% ACS patients), or in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)[23] trial (100% ACS patients). The event rates in the control group actually parallel the baseline risk levels. The risk of 3-point MACE ranged from 2.85%/year in the ORIGIN trial to 6.2%/year in the ELIXA trial (Table 1). These results of these outcome trials are important for clinicians in their 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.

The Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC), aiming to formulate a treatment consensus in type 2 diabetic patients with CVD, have appointed a jointed consensus group for the 2018 Consensus of TSOC/DAROC on the Management of Patients with Type 2 Diabetes and Cardiovascular Diseases. The consensus is comprised of 5 major parts: 1) Treatment of diabetes in patients with hypertension (HT), 2) Treatment of diabetes in patients with CHD, 3) Treatment of diabetes in patients with chronic kidney disease (CKD), 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 the evidence, mainly RCTs, not limited to those shown in Table 1, and also included meta-analyses, cohort studies, and studies using claim data. The rationale for prioritizing anti-diabetic agents for different CVD was based on the findings from RCTs first. The strongest evidence came from an RCT specifically testing one drug vs. another (or placebo) in patients with a specific disease condition such as CHD, stroke,

Table 1
Background characteristics and event rates of the control groups of recent CV outcome trials ranked by CV risk levels[a].

Trial	Background characteristics								Event rates (control groups), %/year			
	ASCVD	RF	CHD	MI	Stroke	CKD[a]	HF	HT	3-point MACE	HF	CV death	ALL death
ORIGIN[20] (2012)	58%	42%	NR	35.2%	13.6%	NR	NR	79.5%	2.85%	0.95%	1.55%	2.6%
CANVAS[30] (2017)	65.6%	33.3%	56.4%	NR	19.3%	17.5%	14.4%	90%	3.15%	0.87%	1.28%	1.95%
EXSCEL[29] (2017)	73%	27%	52.7%	NR	17.3%	22.1%	16.6%	NR	4.0%	1.0%	1.5%	2.3%
TECOS[26] (2015)	74.5%	25.5%	NR	42.6%	24.5%	9.3%[a]	18.0%	86.2%	3.62%	1.09%	1.67%	2.45%
SAVOR[25] (2013)	78.7%	21.3%	NR	37.8%	12.7%	15.6%[a]	12.8%	81.4%	3.7%	1.4%	1.45%	2.1%
LEADER[27] (2016)	80.6%	19.4%	NR	30.0%	16.6%	22.3%	14%	NR	3.9%	1.4%	1.6%	2.5%
SUSTAIN-6[28] (2016)	83%	17%	60.5%	32.5%	11.6%	28.5%	25%	92.8%	4.44%	1.61%	1.35%	1.76%
EMPA-REG OUTCOME[21] (2015)	100%	0%	75.6%	46.4%	23.7%	26.0[a]	10.5%	95%	4.39%	1.45%	2.02%	2.86%
ELIXA[22] (2015)	100% (ACS)	0%	100%	82.4%	6.2%	23.2%	22.3%	77.1%	6.2%	1.9%	2.4%	3.3%
EXAMINE[23] (2013)	100% (ACS)	0%	100%	87.5%	7.2%	29.6%	27.8%	83.6%	No normalized data			
IRIS[b] [44] (2016)	NR	NR	11.4%	NR	87.2%	NR	NR	71.8%	No normalized data			

ACS = acute coronary syndrome; ASCVD = atherosclerotic vascular disease; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; DPP-4 i = dipeptidyl peptidase 4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HT = hypertension; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; RF = risk factor alone; SGLT-2 i = sodium glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.
[a] = data from the control group.
[b] = non-diabetic trial.

or CKD. However, the number of such disease-specific trials is very limited. Most of the recent RCTs enrolled patients across the spectrum of ASCVDs including CHD, ischemic stroke, and peripheral artery disease rather than having a limited enrollment to a specific patient population. The second tier of evidence came from any subgroup analysis of the 3-point MACE in patients with or without a specific CVD. We examined if the efficacy remained significant or was even better in patients with pre-existing CVD. The third tier evidence is based on the assessments of the individual endpoint, i.e., MI or stroke, among the 3-point MACE and evaluated if any given drug reduced any specific endpoint. If the previous 3 level 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.

This consensus was developed by a panel consist of experts from the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan). They had searched the most updated recommendations, along with their clinical experiences and rationale, focusing on treatment target of HbA1c and therapeutic choices. 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, i.e., 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. Treatment of diabetes in patients with hypertension

2.1. Rationale

HT is the most common co-morbidity in patients with diabetes. The estimated prevalence is 40–50% in general diabetic populations.[24] The prevalence of HT is even higher (over 70%) in RCTs, including target-driven or placebo-controlled drug trials, because they usually enrolled high-risk patients.[10–12,17,21–23,25–30] There has been no trials specifically designed to examine the HbA1c target or the CV effect of anti-diabetic agents in diabetic patients with HT. But most of trials demonstrated consistent findings among patients with different blood pressure (BP) levels or the presence or absence of HT. It is permissible to apply the results of all these diabetes outcome trials to diabetic patients with HT.

2.2. Target of HbA1c

The benefits of glucose lowering depend on duration of therapy, the degree of the HbA1c reduction, and the choice of drugs. The Diabetes Control and Complications Trial (DCCT)/

Epidemiology of Diabetes Interventions and Complications (EDIC) Study showed that targeting an HbA1c level of 7.0%, compared to 9.0%, resulted in a 57% reduction in the 3-point MACE in type 1 diabetic patients through a mean follow-up of 17 years.[31] It is noteworthy that the vascular benefit of more aggressive glucose control was not apparent until 8 years after the start of the DCCT study.[31] For patients with type 2 diabetes, almost all RCTs demonstrated numerically lower CV events with achieved HbA1c down to the level of 7.0%,[17,21,27,28,30,31] albeit not reaching statistical significance in some trials.[22,23,25,26,29] Among all these trials, the benefits of vascular protection seemed to be proportional to the differences in the achieved HbA1c levels between groups. However, the timing of the emergence of additional vascular benefits differed among different oral hypoglycemic agents. In the UKPDS trial, the vascular benefits with metformin (with a difference in mean achieved HbA1c of 0.6% compared to diet control) became evident at approximately 5 years after the start of the study, whereas for those assigned to sulfonylurea/insulin (with a difference in mean achieved HbA1c of 0.9%), the vascular benefits occurred 15 years later.[14] In contrast, the vascular benefits of SGLT-2 inhibitors and GLP-1 RAs occurred much earlier: 12–18 months after the start of the study, with a similar between-group HbA1c difference (0.4–0.9%) as in the UKPDS trial.[21,27,28,30] All DPP-4 inhibitor trials are associated with a smaller between-group HbA1c difference (<0.4%) and the vascular benefits are not significantly different from the control group.[23,25,26]

Whether targeting an HbA1c level of 6.5% or lower would provide more vascular benefits has been examined in 3 target-driven RCTs.[10–12] All these 3 trials did not show a statistically significant reduction in the 3-point MACE with the achieved HbA1c levels of less than 7.0%. However, a meta-analysis demonstrated that reducing HbA1c down to 6.4% was associated with a statistically significant reduction in non-fatal MI.[18] The major concern regarding these trials is that there was a numerically increased death rate in 2 of these 3 trials.[10,12] Although the exact reasons for the increased mortality are not well understood, it is generally believed that hypoglycemia, particularly unnoticed hypoglycemia, may play a possible role. Assuming that diabetic patients with hypertension had higher CV risk and greater atherosclerosis burden, which may cause them to be more vulnerable to hypoglycemia, targeting an HbA1c level of 7.0%, rather than <6.5%, was considered prudent by the consensus group.

Further evidence to support targeting an HbA1c level of 7.0% rather than 6.5% or lower for diabetic hypertensive patients is from the combined analysis of the ACCORD-BP and ACCORD study.[32] In this 2 × 2 factorial analysis stratified by both intensive versus standard BP and glucose control strategies, it has been demonstrated that the increased mortality associated with targeting HbA1c of <6%, compared to 7.0–7.9%, mainly occurred in diabetic patients who were assigned to the intensive BP group (systolic BP of <120 mmHg). Among patients who were assigned to a standard BP target (systolic BP of <140 mmHg), there was a numerical decrease in all-cause mortality and a statistically significant reduction in 3-point MACE with targeting HbA1c of <6% (achieved HbA1c 6.4%). Given that Asian and Taiwanese hypertensive patients are more susceptible to high BPs and the associated complications, the 2017 TSOC/Taiwan Hypertension Society (THS) hypertension guidelines recommended a more aggressive office BP target (<130/80 mmHg) for diabetic hypertensive patients.[33] Although there is no direct evidence suggesting that aggressive BP management would make patients more susceptible to hypoglycemia or other adverse events related to targeting HbA1c of <6.5%, cautions should be taken while targeting HbA1c of <6.5%, particularly for diabetic patients with established CV disease, higher baseline HbA1c (>8.5%), or achieved systolic BP of <120 mmHg.

In this consensus, we recommended an HbA1c less than 7.0% for diabetic patients with HT.

2.3. Choice of drugs

To establish the hierarchy of glucose-lowering agents for diabetic patients with HT, the relative efficacy in CV protection should be the first priority, followed by the relative efficacy in BP lowering effect.

Regarding the relative efficacy in CV protection, a recent meta-analysis including 301 RCTs of all available glucose-lowering agents (alone or in combination) for at least 24 weeks in patients with type 2 diabetes (1,417,367 patient-months) showed that there were no significant differences in the CV mortality or all-cause mortality among different classes of drugs.[34] However, there are 2 major limitations of this meta-analysis. First, it did not consider the timing for the occurrence of vascular event reductions. In the UKPDS trial, the benefits of metformin in vascular risk reductions became evident at 5 years after the start of the study, whereas the benefits of sulfonylurea/insulin did not emerge until 15 years later.[14] Despite the advantage of metformin over sulfonylurea is obvious in this regard, the time taken for metformin is significantly longer than that observed in recently published trials of SGLT-2 inhibitors and certain GLP-1 RAs, of which the vascular benefits became evident 12–18 months after study start.[21,27,28,30] Second, this meta-analysis included trials published before March 2016. Therefore, a few large-scale CV outcome trials of SGLT-2 inhibitors and GLP-1 RAs, such as the CANagliflozin cardioVascular Assessment Study (CANVAS) and the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R) (i.e., the CANVAS Program), the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), and the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) were not included.[27–30] A failure of including these large-scale trials obviously makes this meta-analysis underpowered to assess the clinical impacts of the newer generation of glucose-lowering agents. If we take into account the length of time for the emergence of vascular benefits, the hierarchy for glucose-lowering agents should be (from top to bottom): SGLT-2 inhibitors, GLP-1 RAs

(less consistent findings in different trials), metformin, DPP-4 inhibitors, and glitazone/sulfonylurea/glinides/alpha-glucosidase inhibitor.

Before assessing the relative efficacy of different glucose-lowering agents in BP reductions, we have to realize the following limitations. First, the majority of the information is from patients without hypertension or under antihypertensive treatment. Because the BP-lowering effect of any agent is directly related to baseline BP levels, the reported BP-lowering effect of a given glucose-lowering agent may be underestimated, and one agent could not be compared to other agents unless a head-to-head comparison had been conducted. Second, few head-to-head comparison of BP lowering effect between different glucose-lowering agents had been done.

For metformin, a meta-analysis including 41 RCTs (3074 patients) for at least 6 weeks' duration showed an average BP reduction (placebo-corrected) of 1.1/1.0 mmHg (overall $p > 0.05$).[35] For sulfonylurea, a meta-analysis including 4 RCTs (453 patients) showed an average BP reduction of 0.0/0.7 mmHg (overall $p > 0.05$).[36] For alpha-glucosidase inhibitor, a meta-analysis including 7 RCTs (2180 patients) for at least 52 weeks' duration showed an average systolic BP reduction of 2.0 mmHg.[37] The definitive answer for alpha-glucosidase inhibitor on MACE and BP came from the recently published Acarbose Cardiovascular Evaluation (ACE) trial.[38] A total of 6522 Chinese patients with CHD were randomly assigned to acarbose and placebo. After a median follow-up of 5 years, there was no difference in the 5-point MACE (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and hospitalization for HF) (HR 0.98, 95% CI 0.86–1.11).[38] At 1 year after the start of the study, there were no significant differences in systolic BP (130.3 mm Hg in the acarbose group vs. 130.4 mm Hg in the placebo group, $p = 0.53$), and diastolic BP (78.2 mm Hg vs. 78.5, $p = 0.93$).[38] For thiazolidinedione (TZD), a meta-analysis including 37 RCTs (6731 patients) for at least 28 weeks' duration showed an average BP reduction of 3.5/1.8 mmHg (overall $p < 0.05$) compared with placebo.[39] For DPP-4 inhibitors, a meta-analysis including 15 RCTs (5636 patients) for at least 12 weeks' duration showed an average systolic BP reduction of 3.0 mmHg compared with placebo or no-treatment ($p < 0.00001$).[40] For GLP-1 RAs, a meta-analysis including 33 RCTs (12,469 patients) for at least 12 weeks' duration showed an average BP reduction of 2.2/0.5 mmHg (overall $p < 0.05$).[41] For SGLT-2 inhibitors, a meta-analysis including 27 RCTs (12,960 patients) for at least 28 weeks' duration showed an averaged systolic/diastolic BP reduction of 4.0/1.6 mmHg.[42] The 4 mmHg reduction in systolic BP with SGLT-2 inhibitors is consistent with the findings in the EMPA-REG OUTCOME trial and the CANVAS program.[21,30] The greater magnitude of BP reductions achieved by SGLT-2 inhibitors compared to other glucose-lowering agents has also been recognized by the Clinical Practice Guideline Update from the American College of Physicians.[43] In summary, in terms of BP-lowering efficacy, the hierarchy for glucose-lowering agents should be (from top to bottom): SGLT-2 inhibitors (tier 1), GLP-1 RAs/DPP-4 inhibitors/TZDs (tier 2), metformin/sulfonylurea/alpha-glucosidase inhibitors/glinides (tier 3).

Another evidence in supporting the choice of anti-diabetic drugs came from the sub-group analysis of these RCTs to explore whether the benefits or the harmful effects exist in the sub-group of patients with hypertension compared to those without hypertension. Unfortunately, only some of RCTs provided these data: the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial, the EMPA-REG OUTCOME trial, the Insulin Resistance Intervention after Stroke (IRIS) trial, and the CANVAS program.[21,25,26,30,44] All the interaction p values were >0.05. These data suggested that the effect of these anti-diabetic agents was comparable between hypertensive patients and non-hypertensive patients.

2.4. Treatment algorithm in diabetic patients with hypertension

Table 2 shows the treatment algorithm in diabetic patients with hypertension. The target of HbA1c is <7%. Taking into account the totality of evidence and economical consideration, the consensus group recommended metformin being the first-line glucose-lowering agent for diabetic patients with hypertension, followed by SGLT2 inhibitors as the second-line glucose-lowering agent. The third-line agents include GLP-1 RAs, TZDs, DPP-4 inhibitors, sulfonylurea, glinides, and alpha-glucosidase inhibitors.

Table 2
Treatment algorithm in diabetic patients with hypertension.

Target HbA1c	<7%			
Monotherapy	Metformin			
Dual therapy	Metformin + SGLT-2 i			
Triple therapy	Metformin + SGLT-2 i + GLP-1 RA[a]	Metformin + SGLT-2 i + TZD[b]	Metformin + SGLT-2 i + DPP-4 i	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 and semaglutide.

[b] Pioglitazone.

3. Treatment of diabetes in patients with coronary heart disease

3.1. Rationale

Diabetes is a CHD equivalent.[45] More than 70% of the diabetic patients died of CV diseases.[5] In the UKPDS 35, an observational part of the UKPDS trial, the risk of CHD correlated with the baseline HbA1c.[7] For every 1% increase in HbA1c, the risk of fatal and non-fatal MI increased by 14%.[7] However, the 4 RCTs testing intensive glucose control vs. conventional glucose control did not show positive results in reducing MACE in individual trials.[9–12] The percentages of patients with pre-existing CVD were 0% for the UKPDS trial, 35% for the ACCORD trial, 32% for the ADVANCE trial, and 41% for the VADT trial.[9–12] 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 anti-diabetic agents, or simply absence of effect of glucose lowering per se.[4] In the ACCORD trial, the 3-point MACE was non-significantly decreased by 10% (HR 0.90, 95% CI 0.78−1.04), but non-fatal MI was significantly decreased (HR 0.76, 95% CI 0.62−0.92, $p = 0.004$).[10] 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 non-significant increase in fatal and non-fatal HF (HR 1.18, 95% CI 0.93−1.49, $p = 0.17$).[10] Two meta-analyses showed a significant reduction in non-fatal MI with intensive glucose control.[18,46] With a much safer profiles of new anti-diabetic agents, lowering blood sugar might be effective in reducing MACE.

3.2. Target of HbA1c

The risk of CVD and total mortality has a linear relationship with the level of HbA1c.[47] The risk of MI starts to increase from a level of HbA1c of 6% or above.[7] However, 4 RCTs, including the UKPDS trial, the ACCORD trial, the ADVANCE trial, and the VADT trial, targeting lower HbA1c levels did not show an improvement in CV outcomes.[9–12] The final achieved HbA1c levels were 7.0%, 6.4%, 6.5%, and 6.5% respectively.[9–12] The risk of total mortality in the ACCORD trial was actually increased and resulted in a premature termination.[10] Notably, neither the ADVANCE trial or the VADT trial demonstrated an increase in mortality or in composite CV endpoints with intensive glucose control as defined by HbA1c< 7%.[11,12] 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),[46] 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).[46] When treating patients with anti-diabetic 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 (AMI, stroke, or death) gradually increased with rising levels of 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%.[48] 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%).[48]

Given that most of the new anti-diabetic agents have a low risk of hypoglycemia, the consensus recommended HbA1c less than 7.0% as the treatment target for the diabetic patients with CHD. 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 co-morbidities, and short diabetes duration.

3.3. Choice of drugs

There is only a trial testing the efficacy of anti-diabetic agent in patients with CHD (the ACE trial).[38] 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 non-fatal MI is generally a major component of the 3-point MACE, providing important information for this consensus.

3.3.1. 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).[49] The benefits persisted at 10 years of post-trial 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).[14] 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 ration [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, $p = 0.89$).[50] Meta-regression suggested that metformin monotherapy was marginally associated with an improved survival (OR 0.801, 95% CI 0.625−1.024, $p = 0.076$).[50] However, concomitant use with sulfonylureas was associated with a reduced survival (OR 1.432, 95% CI 1.068−1.918, $p = 0.016$).[50] 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 anti-diabetic agents or a placebo.[51] 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, $p = 0.002$).[52] In a sub-study 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.[53] 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 versus 66.9 Agatston units, $p = 0.04$; the percentage of presence of CAC, 75% versus 84%, $p = 0.02$), whereas metformin was not effective in women.[53] However, metformin did not decrease carotid intima-media thickness in CHD patients who did not have diabetes.[54]

Lactic acidosis is an uncommon but potentially lethal complication of metformin.[55] Though several comparative studies of metformin vs. other anti-diabetic agents did not show an increase in the risk of lactic acidosis,[56,57] metformin should not be used in patients with stage 4 and 5 CKD, i.e. eGFR <30 mL/min/1.73 m^2.[58]

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

3.3.2. Sulfonylureas

There are controversies in the CV safety of sulfonylureas. In the University Group Diabetes Program (UGDP) in early 1970, tolbutamide was associated with an increase in CV and total mortality.[59] In the UKPDS trial, intensive glucose lowering with sulfonylureas and insulin did not decrease the risk of MI (HR 0.84, 95% CI 0.71–1.00, $p = 0.052$).[9] In the ADVANCE trial, use of gliclazide did not reduce the 3-point MACE (HR 0.94, 95% CI 0.84–1.06), or non-fatal MI (HR 0.98, 95% CI 0.77–1.22).[11] 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 sulfonylureas (including glimepiride and gliclazide) increased total mortality when compared with metformin (HR 1.37, 95% CI 1.11–1.71, $p = 0.0003$ for first generation sulfonylureas; HR 1.24, 95% CI 1.14–1.35, $p < 0.001$ for second generation sulfonylureas).[60] The risk of MI was also numerically higher with sulfonylureas compared with metformin (HR 1.36, 95% CI 0.91–2.02 for first generation sulfonylureas; HR 1.09, 95% CI 0.94–1.27 for second generation sulfonylureas).[60] 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, non-diabetic controls, while those treated with sulfonylurea had a markedly reduced survival compared with both matched controls and those receiving metformin monotherapy.[61] From the same data, there was an increase in all-cause mortality for patients treated with metformin plus sulfonylurea versus metformin plus DPP-4 inhibitors (adjusted HR 1.497, 95% CI 1.092–2.052), and a similar trend for MACE (adjusted HR 1.547, 95% CI 1.076–2.225).[61] In a meta-analysis of 20 studies of 551,912 patients, patients receiving sulfonylurea 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).[62] In another meta-analysis of 82 RCTs and 26 observational studies, the risk of AMI was significantly higher in sulfonylurea users than users of other anti-diabetic 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).[63] In a recent cohort from the Taiwan NHIRD, DPP-4 inhibitors were better than sulfonylureas 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, $p = 0.112$).[64]

It seems that not all sulfonylureas shared similar CV risk. In patients with previous MI from a Danish cohort, the HR of all-cause mortality was increased by a number of sulfonylureas 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).[65] 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.[66] The ongoing Cardiovascular Outcome Trial of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA) trial (NCT01243424), comparing linagliptin with glimepiride in patients with type 2 diabetes, might help to clarify and define the CV safety of sulfonylurea.[67]

There are several drawbacks in using sulfonylureas 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, as compared with 81 patients (1.5%) undergoing standard control (HR 1.86, 95% CI 1.42 to 2.40; $p < 0.001$).[11] In the sub-analysis of the ADVANCE trial, severe hypoglycemia was associated with a significant increase in the adjusted risks of 3-point MACE (HR 2.88, 95% CI, 2.01 to 4.12), major micro-vascular events (HR 1.81, 95% CI, 1.19 to 2.74), death from a CV cause (HR 2.68, 95% CI, 1.72 to 4.19), and death from any cause (HR 2.69, 95% CI, 1.97 to 3.67) ($p < 0.001$ for all comparisons).[68] Furthermore, sulfonylurea increased body weight compared with metformin, as shown in the UKPDS trial.[49] The most intriguing effect of sulfonylureas is their interference with the protective mechanism in ischemic preconditioning, due to blockade of mitochondrial K_{ATP}.[69] This may account for the increase in MI and CV mortality observed in many meta-analyses. Whether new generation of sulfonylurea, such as glimepiride, has similar disadvantage will be answered by the CAROLINA trial comparing glimepiride with linagliptin (NCT01243424).

The consensus group gave sulfonylureas a low priority in the treatment of diabetic patients with CHD.

3.3.3. Glinides

There were no RCTs or observational studies to test the effect of repaglinide on the risk of MI. In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, 9306 participants with impaired glucose tolerance (IGT) and CVD (11.2% had a history of MI, 8.8% angina or positive stress test, 3.7% percutaneous coronary intervention, 4.0% multi-vessel coronary artery bypass graft) or its risk factors were assigned to nateglinide or placebo.[70] After a follow-up of 6.5 years, nateglinide did not reduce the 3-point MACE plus admission for HF (HR 0.94, 95% CI 0.82−1.09; $p = 0.43$) or the incidence of fatal and non-fatal MI (HR 0.95, 95% CI 0.75−1.20).[70] The consensus group gave glinides a low priority in diabetic patients with CHD.

3.3.4. Alpha-glucosidase inhibitor

The Study to Prevent Non-insulin-dependent diabetes mellitus (STOP-NIDDM) trial evaluated the effect of acarbose on the risk of CVD in 1368 patients with IGT.[71] 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.[71] In a nationwide cohort study in drug-naïve type 2 diabetes patients in Taiwan, there were 16.5% patients with pre-existing CHD.[72] After propensity score matching, acarbose has no effect on MI when compared with metformin (HR 0.93, 95% CI 0.81−1.07).[72] The definitive answer for the effect of acarbose on CVD came from the recently finished ACE trial.[38] 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 5-point MACE (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and hospitalization for HF) (HR 0.98, 95% CI 0.86−1.11).[38] The traditional 3-point MACE (CV death, non-fatal MI, and non-fatal stroke) did not differ either (HR 0.95, 95% CI 0.81−1.11). The risk of fatal- and non-fatal 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%, $p = 0.0007$).[38] 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.

3.3.5. Thiazolidinedione

In the PROactive trial, 5238 patients with type 2 diabetes and macrovascular disease were prospectively randomized to pioglitazone (15 mg−45 mg) and placebo for 34.5 months.[17] Among them, 46% had a history of MI, 31% history of previous PCI, and 19% previous stroke. The primary composite endpoint included all-cause mortality, non-fatal 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, $p = 0.095$).[17] The main secondary endpoint (all-cause mortality, non-fatal MI, and stroke) did show a positive effect (HR 0.84, 0.72−0.98, $p = 0.027$). Among the composite primary endpoints, non-fatal MI was numerically decreased by pioglitazone (HR 0.83, 95% CI 0.65−1.06).[17] Of 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 pre-specified and post-hoc analyses.[73] Pioglitazone had a significant beneficial effect on the pre-specified 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, $p = 0.035$).[73]

The finding of the beneficial effects of pioglitazone on MACE observed in the PROactive trial has been supported by a meta-analysis of controlled trials of over 16,000 subjects.[74] 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.[74] The individual end point components were reduced by a similar magnitude and there was no heterogeneity across the trials.[74] Several image studies also supported a role of pioglitazone in reducing MACE. The CHICAGO study demonstrated that the carotid intima-medial thickness in type 2 diabetic patients treated with pioglitazone did not progress whereas those treated with glimepiride showed progression.[75] In the PERISCOPE study, atheroma volume progressed with glimepiride but not with pioglitazone.[76]

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).[19] 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.[77] 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 end point was 1.68 (95% CI, 1.27−2.08) excess events per 100 person-years of treatment with rosiglitazone compared with pioglitazone. The corresponding number needed to harm was 60 (95% CI, 48−79) treated for 1 year.[77] In response, an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published.[78] This trial randomized 4447 patients with type 2 diabetes to rosiglitazone plus either metformin or sulfonylurea or an active control (metformin plus sulfonylurea). No elevated risk for MI or death in the

rosiglitazone group was noted at 3.75 years follow-up.[78] The final analysis showed that after a mean follow up of 5.5 years, rosiglitazone was non-inferior to a combination of metformin and sulfonylurea 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).[79]

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

3.3.6. 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/sulfonylurea 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, $p = 0.052$).[9] However, a significant reduction in MI was observed after an additional follow-up of about 11 years (HR 0.85, 95% CI 0.74–0.97).[14] 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.[20] There were 35.2% of patients with a history of MI. The rates of 3-point MACE and MI, in particular, were similar between the insulin group and the control group (HR 1.02, 95% CI 0.94–1.11; HR 1.02, 95% CI 0.88–1.19, respectively).[20] 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 Trial Comparing Cardiovascular Safety of Insulin Degludec versus Glargin in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) trial.[80] 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 to 1.06; $p < 0.001$ for noninferiority, $p > 0.05$ for superiority).[80] The subgroup analysis did not show significant difference in patients with established CVD vs. those without established CVD (HR 0.89, 95% CI 0.76–1.04; HR 1.03, 95% CI 0.62–1.72, respectively; p for interaction = 0.5742). Therefore, the consensus group did not give insulin a high priority in the initial therapy in diabetic patients with CHD.

3.3.7. DPP-4 inhibitors

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.[25] Among them, 37.8% of patients had a history of MI. The overall efficacy in the 3-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). The subgroup analysis of patients with or without a history of MI was not reported. Among the 3-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).[25] In the EXAMINE trial, 5380 patients with either an AMI or unstable angina requiring hospitalization within the previous 15–90 days were enrolled.[23] Among them, 87.5% had a history of AMI. The overall efficacy in the 3-point MACE showed no difference from the use of alogliptin compared with placebo (HR 0.96, $p = 0.32$). The subgroup analysis of patients with or without a history of AMI was not reported. Among the 3-point MACE, non-fatal MI was not different with the use of alogliptin compared with placebo (HR 1.08, 95% CI 0.88–1.33).[23] In the TECOS trial, 14,671 patients with type 2 diabetes and established CV disease were enrolled.[26] Among them, 42.6% of patients had a history of MI. The overall efficacy in the 3-point MACE showed no difference with the use of sitagliptin compared with placebo (HR 0.99, 95% CI 0.89–1.10). The subgroup analysis of patients with or without a history of MI was not reported. Among the 3-point MACE, fatal and non-fatal MI was not different with the use of sitagliptin compared with placebo (HR 0.95, 95% CI 0.81–1.11).[26] The consensus group gave a neutral position to DPP-4 inhibitors in diabetic patients with CHD.

3.3.8. GLP-1 receptor agonists

In the ELIXA trial, 6068 patients with ACS within 180 days were randomized to daily lixisenatide or placebo.[22] There were 82.4% patients with MI. The overall efficacy in the 4-point MACE (CV death, non-fatal MI, non-fatal 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 4-point MACE, MI was not different with the use of lixisenatide compared with placebo (HR 1.03, 95% CI 0.87–1.22).[22]

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.[27] In the LEADER trial, 30% patients had a history of MI. There was a significant reduction in the 3-point MACE with the use of liraglutide (HR 0.87, 95% CI 0.78–0.97, $p = 0.01$).[27] The total MI was also significantly reduced (HR 0.86, 95% CI 0.73–1.00, $p = 0.0460$), but not non-fatal MI (HR 0.88, 95% CI 0.75–1.03). The subgroup analysis showed a significant reduction of 3-point MACE in patients with established CVD compared with those without established CVD (HR 0.83, 95% CI 0.74–0.93 vs. HR 1.20, 95% CI 0.86–1.67, p for interaction 0.04), though specific data regarding patients with previous MI was not mentioned.[27]

In the SUSTAIN-6 trial, 3297 patients with high CV risk were enrolled. Among them, 60.5% had a history of CHD, including 32.5% had a history of MI.[28] The 3-point MACE was significantly reduced by semaglutide (HR 0.74, 95% CI 0.58–0.95, $p = 0.02$), including a non-significant reduction in the risk of non-fatal MI (HR 0.74, 95% CI 0.51–1.08).[28] In the subgroup analysis, patients with established CVD had a significant reduction in the 3-point MACE (HR 0.72, 95% CI 0.55–0.98), 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.[28] The specific data regarding patients with a history of MI was not mentioned.

In the most recent EXSCEL trial, weekly injection of extended-release exenatide was compared with placebo in 14,752 high risk patients.[29] In the EXSCEL trial, 52.7% patients had a history of CHD. The percentage of patients with a history of MI was not reported. The overall efficacy in the 3-point MACE showed no difference with the use of exenatide compared with placebo (HR 0.91, 95% CI 0.83–1.00).[29] The risk of fatal and non-fatal 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 non-significant reduction in the 3-point MACE (HR 0.90, 95% CI 0.82–1.00).[29] There were several differences between the EXSCEL trial and the LEADER trial.[27,29] The median follow-up time and the duration of exposure to the trial regimen were shorter in the EXSCEL trial than those in the LEADER trial (3.2 years vs. 3.8 years, and 2.4 years vs. 3.5 years, respectively). The consensus group gave a high priority to GLP-1 RAs in diabetic patients with CHD.

3.3.9. SGLT-2 inhibitors

In the landmark CV outcome trial of empagliflozin (the EMPA-REG OUTCOME trial), 7020 patients with previous CV events who received empagliflozin had reduced rates of 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, $p < 0.001$) when compared with placebo, with no difference seen for 10 or 25 mg doses.[21] In the EMPA-REG OUTCOME trial, 75.6% of patients had CHD, and 46.4% had a history of MI. The 3-point MACE was significantly reduced by the use of empagliflozin (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$).[21] The subgroup analysis showed that there was no difference in patients with and without a history of CHD. Among the 3-point MACE, there was a trend of a decrease in non-fatal MI (HR 0.87, 95% CI 0.70–1.09). Among 7020 patients treated in the EMPA-REG OUTCOME trial, 1517 (21.6%) were Asians.[81] The reduction in 3-point MACE in Asian patients was consistent with the overall population: 3-point MACE occurred in 79/1006 patients (7.9%) in the pooled empagliflozin group vs. 58/511 patients (11.4%) in the placebo group (HR 0.68, 95% CI 0.48–0.95; P-value for race interaction = 0.0872).[81] The adverse event of empagliflozin in Asian patients was similar to the overall trial population.[81]

The CANVAS program randomized 10,142 participants with diabetes and high CV risk into canagliflozin or placebo groups.[30] In the CANVAS program, 56.4% patients had a history of CHD.[30] The 3-point MACE was significantly reduced by the use of canagliflozin (HR 0.86, 95% CI 0.75–0.97, $p = 0.02$).[30] 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 3-point MACE, the fatal or non-fatal MI was numerically lower by the use of canagliflozin (HR 0.89, 95% CI 0.73–1.09).[30]

The CV outcome trial of dapagliflozin, i.e., the Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial, is still on-going. In a meta-analysis of 9339 patients, patients receiving dapagliflozin had a reduced risk of MI compared with the control group (HR 0.567, 95% CI 0.339–0.947).[82] In the CVD-REAL Nordic study, a multinational observational analysis, 22,830 patients receiving SGLT-2 inhibitor were compared with 68,490 patients receiving other glucose-lowering agents.[83] Among them, 94% of the total SGLT-2 inhibitor exposure time was attributed to dapagliflozin, empagliflozin 5%, and canagliflozin 1%. The use of SGLT-2 inhibitors was associated with a decreased risk of CV mortality (HR 0.53, 95% CI 0.40–0.71, $p < 0.0001$), the 3-point MACE (HR 0.78, 95% CI 0.69–0.87, $p < 0.0001$), and hospital events for HF (HR 0.70, 95% CI 0.61–0.81; $p < 0.0001$).[83] The sub-group analysis showed that patients with a history of CVD had benefits in both CV mortality (HR 0.60, 95% CI 0.42–0.85) and 3-point MACE (HR 0.70, 95% CI 0.59–0.83), but the p values for interaction were not provided. Among the 3-point MACE, non-fatal MI was numerically lower in the group of SGLT-2 inhibitors (HR 0.87, 95% CI 0.73–1.03).[83]

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

3.4. Treatment algorithm in diabetic patients with coronary heart disease

Table 3 shows the algorithm for the treatment of diabetes in patients with CHD. The target of HbA1c is <7%. Metformin should be the first-line therapy in diabetic patients with CHD, mainly based on the findings from the UKPDS trial,[14,49] 2 meta-analyses,[50,51] 1 observational study,[52] and its effect on the reduction in CAC severity.[53] For dual therapy, we

Table 3
Treatment algorithm in diabetic patients with CHD.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + SGLT-2 i	Metformin + GLP-1 RA[b]
Triple therapy	Metformin + TZD[a] + SGLT-2 i	Metformin + TZD[a] + GLP-1 RAs[b]	Metformin + SGLT-2 i + GLP-1 RAs[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] Pioglitazone.

[b] Liraglutide and semaglutide.

recommend metformin plus TZDs (pioglitazone only), followed by metformin plus SGLT-2 inhibitors, and then metformin plus GLP-1 RAs. The PROactive trial,[17] an important meta-analysis,[74] and 2 image studies (CHICAGO and PERISCOPE)[75 76] provided strong evidence to support the role of pioglitazone. 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. The EMPA-REG OUTCOME trial,[21] the CANVAS program,[30] and the CVD-REAL Nordic study[83] gave a rationale for the use of SGLT-2 inhibitors. The LEADER trial[27] and the SUSTAIN-6 trial[28] gave a rationale for the use of GLP-1 RAs. If the fourth drug is to be added, DPP-4 inhibitors are recommended due to their neutral effects and safety.[23,25,26] Sulfonylurea did not have any positive trial[9,11] to support its use, and the result of a Taiwanese cohort showed a worse outcome.[64] In addition, the risk of hypoglycemia is well-known. Glinides and acarbose have low priority due to lack of any supporting evidence.[38,70]

4. Treatment of diabetes in patients with stage 3 chronic kidney disease

4.1. Rationale

Diabetes-related CKD is a very common complication for patients with type 2 diabetes. It leads to end-stage renal disease (ESRD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease), accounting for approximately 50% of cases in the developed world.[84] According to a cross-sectional study of 6251 adult diabetic patients participating in the US National Health and Nutrition Examination Surveys in 2009–2014, the prevalence of albuminuria (albumin creatinine ration [ACR] >30 mg/gm) is 15.9%, and the prevalence of reduced eGFR (eGFR <60 mL/min/1.73 m^2) is 14.1%, while 26.2% have either.[85] Of note, diabetes with concomitant CKD leads to a marked increase in CVD risk.[86] From data sets of the Taiwan NHIRD, the prevalence of diabetic nephropathy increased from 13.32% in 2000 to 15.42% in 2009.[87] 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.[88]

An array of factors involving the development of CHD contribute to the development of CKD in diabetes, 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.[84] In a meta-analysis of 4 RCTs, intensive glucose control resulted in an absolute difference of 0.90% in mean HbA1c between more and less intensive control groups.[89] 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 to 0.88, $p < 0{\cdot}0001$) by intensive glycemic control, primarily driven by reduced risks of development of micro- and macro-albuminuria.[89] However, intensive glucose control did not significantly reduce the risk of development of a composite renal endpoints (eGFR less than 30 mL/min/$1{\cdot}73$ m^2, doubling of serum creatinine, or ESRD).[89] This finding was supported by another meta-analysis of 7 trials.[90] 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, $p < 0.01$).[91] 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.[92] It should be noted that in these 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, while patients with CKD stage 4 and 5 were excluded.[89] 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 3 CKD.

4.2. Target of HbA1c

Glycemic control in patients with CKD has special challenges, considering that the risk of severe hypoglycemia is doubled when the eGFR is less than 60 mL/min/1.73 m^2.[93] 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 non-dialyzing 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%.[94] 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).[91] 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 the risk of CV and all-cause mortality with intensive glucose control in the presence of stage 1–3 CKD has raised certain concern in the *post-hoc* analysis of the ACCORD data.[95] Since CVD and ESRD might increase the chance of hypoglycemia, 2012 KDOQI Clinical Practice Guideline for Diabetes and CKD,[96] and 2015 Taiwan Chronic Kidney Disease Clinical Guidelines (http://www.tsn.org.tw/UI/H/H00202.aspx. http://w3.nhri.org.tw/nhri_org/rl/lib/NewWeb/nhri/ebook/39000400094863), recommended a target HbA1c of near but not less than 7.0%. The consensus group recommended HbA1c less than 7.0% as the treatment target for patients with diabetes and stage 3 CKD. The risk of hypoglycemia should be carefully monitored.

4.3. Choice of drugs

There are no specific trials testing the efficacy and safety in CV events of anti-diabetic agents in patients with CKD.

However, the subgroup analysis comparing patient with or without CKD were generally provided. The renal events should be considered too though they are not the primary endpoints.

4.3.1. Conventional glucose-lowering agents

There have been no large RCTs specifically examining the renal protective effects of insulin, sulfonylureas, glinides, alpha-glucosidase inhibitors or metformin. The ORIGIN trial[20] and the ACE trial[38] are CV outcome trials, but the subgroup analysis of CKD patients vs. non-CKD patients was not provided.

4.3.2. 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).[97] Pioglitazone significantly decreased secondary end points (all-cause death, MI, and stroke) in patients with CKD (HR 0.66; 95% CI 0.45 to 0.98), but not in patients without CKD (HR 0.89; 95% CI 0.75 to 1.05).[97] There was a greater decline in eGFR with pioglitazone (between-group difference 0.8 mL/min/1.73 m^2/yr) than with placebo.[97]

In a meta-analysis of 15 studies involving 2860 patients, the effect of TZDs on urinary albumin excretion was inconsistent.[98] In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, participants who were treated with insulin sensitizing medications (the majority taking TZDs in combination with metformin), as compared to those treated with insulin-provision therapy (insulin plus sulfonylureas), had greater progression of urinary albumin excretion despite having lower HbA1c values. Rates of decline in eGFR, however, were similar in both treatment groups over 5 years.[99] The consensus group gave TZD a slightly positive position in the treatment of patients with diabetes and CKD.

4.3.3. 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.[100] Treatment with saxagliptin was associated with less deterioration in ACR ($p = 0.021$, $p < 0.001$, and $p = 0.049$ for individuals with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively). The changes in ACR did not correlate with that 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.[100] In addition, saxagliptin neither increased nor decreased the risk of the 3-point MACE compared with placebo, irrespective of renal function.[101] 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).[102] 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.[102]

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.[103] 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.[104] For linagliptin, the CAROLINA trial (NCT01243424) and the Cardiovascular and Renal Microvascular OutcomE Study With Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) trial (NCT01897532) are ongoing. In a pooled analysis of clinical trial data involving 3505 participants treated with the linagliptin and 1961 treated with placebo, linagliptin significantly reduced the hazard of kidney events by 16% compared with placebo (HR = 0.84; 95% CI: 0.72–0.97).[105] The effect was mainly driven by a reduction in the new onset of moderate and severe albuminuria (HR 0.82, 95% CI 0.69–0.98), but renal endpoints such as reduction in kidney function, halving of eGFR, or acute renal failure were similar between the linagliptin and the placebo groups.[105] A sensitivity analysis showed that adjustment for kidney function at baseline did not influence the association between reduced renal risk and linagliptin treatment (HR 0.83, 95% CI 0.72–0.97).[105]

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

4.3.4. GLP-1 receptor agonists

In the ELIXA trial, 6068 patients with ACS were randomized to daily lixisenatide or placebo.[22] Lixisenatide did not reduce the 3-point MACE (HR 1.02, 95% CI 0.89 to 1.17). There were 23.2% patients with pre-existing CKD. The data for subgroup analysis in patients with a baseline eGFR <60 mL/min/1.73 m^2 were not provided. The pre-specified analysis of the percentage change in the ACR, but not eGFR, showed a modest difference in favor of lixisenatide over placebo from baseline to 108 weeks (24% vs. 34%, $p = 0.004$).[22]

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.[27] The use of liraglutide was associated with a reduction in the 3-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).[27] There was also a significant reduction of pre-specified

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, end-stage renal diseases or death due to renal disease (HR 0.78, 95% CI 0.67–0.92, $p = 0.003$).[106] The renal benefit of liraglutide was mainly derived from a 26% significant reduction in new onset macroalbuminuria (HR 0.74, 95% CI 0.60–0.91, $p = 0.004$) without any significant changes in eGFR. A non-significant 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.[106]

In the SUSTAIN-6 trial, 3297 patients with high CV risk were enrolled.[28] It is shown that a once weekly injection of semaglutide significantly reduced 3-point MACE (HR 0.74, 95% CI 0.58 to 0.95, $p = 0.02$).[28] 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.[28] 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, $p = 0.005$)[28], 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).[28]

In the most recent EXSCEL trial, weekly injection of extended-release exenatide was compared with placebo in 14,752 high risk patients.[29] The 3-point MACE was not significantly changed (HR 0.91, 95% CI, 0.83 to 1.00, $p < 0.001$ for noninferiority, $p = 0.06$ for superiority).[29] There were 22.1% patients with pre-existing CKD. The 3-point MACE was not different in patients with eGFR levels <60 mL/min/1.73 m^2 vs. 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).[29] 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), but no statistical significance could be found.[29]

In summary, all these RCTs show a positive trend of use of GLP-1 RAs in 3-point MACE and renal events. The consensus group gave a high priority to GLP-1 RAs in patients with diabetes and CKD.

4.3.5. SGLT-2 inhibitors

In the EMPA-REG OUTCOME trial, 7020 patients with previous CV events who received empagliflozin (with no differences seen for 10 or 25 mg doses) had reduced rates of CV mortality and all-cause mortality when compared with placebo.[21] There were 26.0% patients with pre-existing CKD. The CV effects were consistent in patients with an eGFR <60 mL/min/1.73 m^2 vs. those ≥60 mL/min/1.73 m^2. Empagliflozin reduced renal outcomes in the EMPA-REG OUTCOME trial.[107] All patients in the study had an eGFR >30 mL/min/1.73 m^2, and approximately 25% had an eGFR <60 mL/min/1.73 m^2, 11% had macroalbuminuria, and 29% had microalbuminuria. The primary renal end point 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 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, $p < 0.001$).[107] Empagliflozin treatment resulted in a 44% risk reduction in doubling of serum creatinine levels accompanied by an eGFR < 45 mL/min/1.73 m^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, $p = 0.04$).[107] There was also a decrease in the progression to macroalbuminuria (HR 0.62, 95% CI 0.54–0.72, $p < 0.001$).[107]

The time course of the changes in eGFR in the empagliflozin group and the placebo group were different in the EMPA-REG OUTCOME trial.[107] 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, as 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).[107] Thereafter, during long-term administration from week 4 to the last week of treatment, the eGFR remained stable in the empagliflozin groups and 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, as 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).[107]

The CANVAS program randomized 10,142 participants with diabetes and high CV risk into canagliflozin or placebo groups.[30] There were 17.5% patients with pre-existing CKD. Diabetic patients receiving canagliflozin had lower rate of the 3-point MACE (HR 0.86, 95% CI 0.75 to 0.97, $p = 0.02$).[30] 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 3-point MACE (HR 0.70, 95% CI 0.55–0.90), but the inter-group difference compared with patients with an eGFR ≥ 60 mL/min/1.73 m^2 was non-significant (P for interaction 0.20).[30] For renal outcomes, the results showed a possible benefit of canagliflozin with respect to 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 to 0.77).[30]

The CV outcome trial of dapagliflozin (DECLARE-TIMI 58, NCT01730534) is ongoing. In a pooled analysis of 12 double-blind RCTs (N = 4545),[108] 6 of the 12 studies included long-term data for up to 102 weeks (N = 3036). Patients with type 2 diabetes with normal or mildly impaired renal function (eGFR 60 to <90 mL/min/1.73 m^2) were treated with dapagliflozin (2.5, 5, or 10 mg/day) or placebo. The use of dapagliflozin was not associated with an increased risk of acute

renal toxicity or deterioration of renal function.[108] A study that evaluates the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (Dapa-CKD, NCT03036150) is now recruiting patients. It is generally believed that the benefits on renal events with SGLT-2 inhibitors are class effects.

The mechanisms responsible for the reno-protective effect of the class of SGLT-2 inhibitor class are different from renin-angiotensin-aldosterone system (RAAS) inhibitors. RAAS inhibitors reduce intraglomerular pressure via efferent arteriolar vasodilatation, leading to reductions in intraglomerular hypertension and renal hyperfiltration.[109] In non-diabetic subjects, SGLT-2 is responsible for about 5% of total renal NaCl reabsorption.[110] In hyperglycemic state, SGLT-1 and SGLT-2 mRNA expression is increased by 20% and 36%, respectively,[111–113] and accounting for 14% of total renal NaCl reabsorption. Consequently, NaCl delivered to the distal tubule markedly decreases.[114] 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.[115] 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 reno-protection effect of SGLT-2 inhibitors.[110] 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 the RCTs.[110]

The consensus group gave a high priority to SGLT-2 inhibitors in patients with diabetes and mild-to-moderate CKD (eGFR $\geq$ 30 mL/min/1.73 m^2).

4.4. Dose consideration in chronic kidney disease

CKD can impact the pharmacokinetics or pharmacodynamics of anti-diabetic agents. A dose reduction may be needed in CKD patients.[116–118] Fig. 1 shows the dose adjustment of anti-diabetic 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).[116]

Metformin was excreted by the kidney and the dose should be reduced to avoid possible lactic acidosis. 2018 ADA guidelines suggest that metformin may be safely used in patients with eGFR as low as 30 mL/min/1.73 m^2,[119] and the US label for metformin has recently been revised to reflect its safety in patients with eGFR $\geq$30 mL/min/1.73 m^2.[119] 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.[120] 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 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 be used with caution in patients with HF as well as in those with CKD.

There are five available DPP-4 inhibitors. Sitagliptin, saxagliptin, alogliptin, and vildagliptin require dose adjustment in patients with CKD.[116–118] 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, and no dose alteration is necessary for liraglutide, albiglutide, and dulaglutide in stage 3 CKD. However, the experience of the use of GLP-1 RAs in patients with severe renal impairment is limited, and there have been post-marketing reports of acute renal failure and worsening of chronic renal failure for GLP-1 RAs. All GLP-1 RAs are contraindicated in stage 4–5 CKD.[117] SGLT-2 inhibitors have been approved for patients with an eGFR of $\geq$45 mL/min/1.73 m^2 (empagliflozin) or $\geq$60 mL/min/1.73 m^2 (dapagliflozin and canagliflozin), although SGLT-2 inhibitors have been used in CKD stage 3 patients in RCTs. There have been post-marketing reports of acute kidney injury in patients receiving SGLT-2 inhibitors, some requiring hospitalization and dialysis. It is suggested that before initiating SGLT-2 inhibitors factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs) should be examined, and renal function needs to be evaluated prior to initiation and be monitored thereafter.[117]

4.5. Treatment algorithm in diabetic patients with stage 3 chronic kidney disease

Table 4 shows the algorithm for the treatment of diabetes in patients with stage 3 CKD. Metformin should be the first-line therapy in diabetic patients with CKD stage 3 because it has long-standing evidence for efficacy and safety, and is inexpensive, though a dosage reduction is necessary. For dual therapy, we recommend metformin plus SGLT-2 inhibitors. The use of SGLT-2 inhibitors is compelling based on their effects in reducing 3-point MACE and renal endpoints in the EMPA-REG OUTCOME trial[107] and the CANVAS Program.[30] They can be used as the first line therapy if metformin cannot be tolerated. For the triple therapy on top of metformin/SGLT-2 inhibitors, we recommend GLP-1 RAs, followed by TZD, and 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

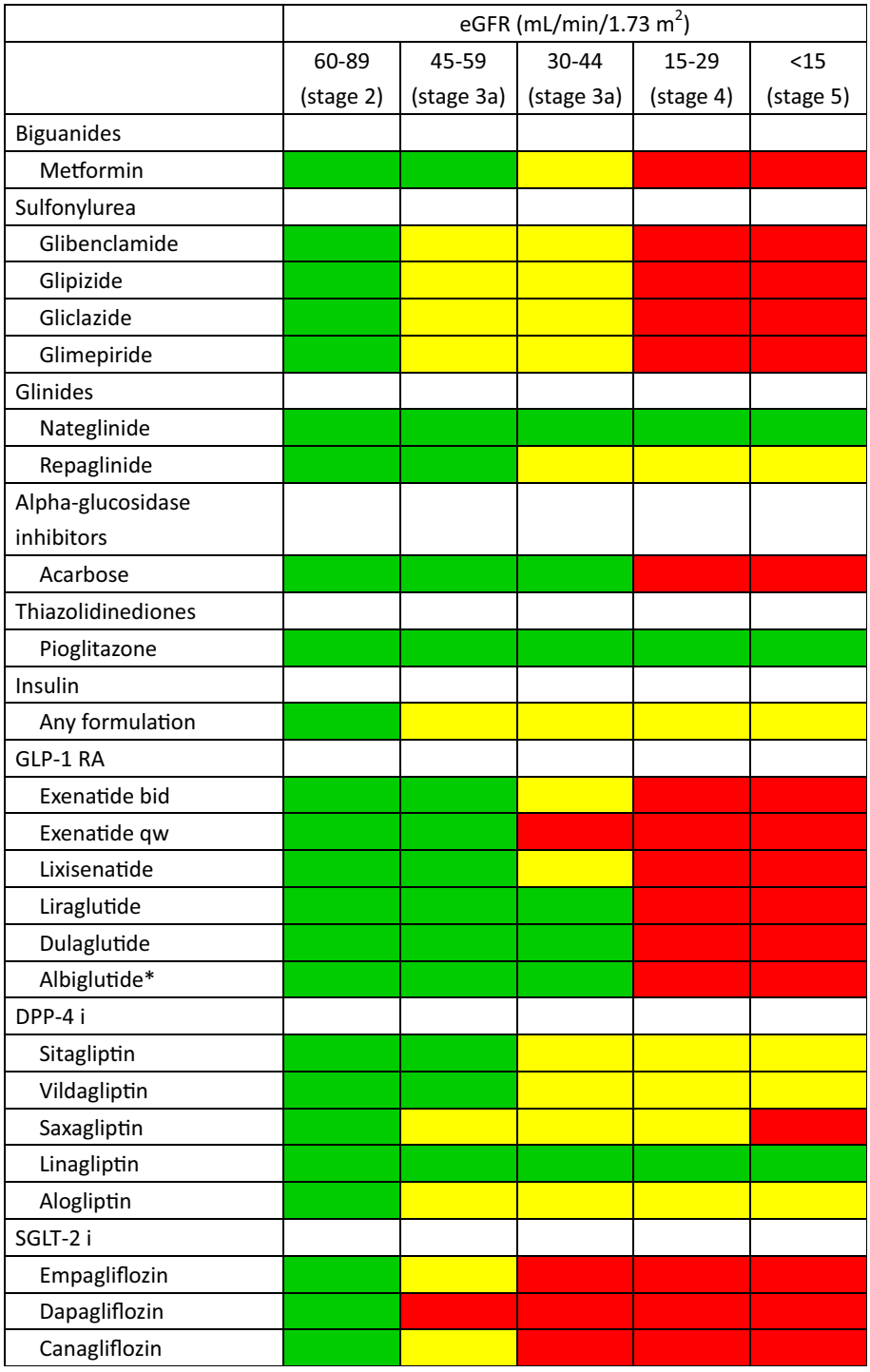

Fig. 1. Dose adjustment of anti-diabetic agents in chronic kidney disease. The green color means that dose adjustment is not required. The yellow color means that dose reduction and frequent monitoring should be considered. The red color means that these drugs are contraindicated. * = expected to be withdrawn from market at July 2018. 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. Adapted from Di Lullo et al.,[118] Davies et al.[117] and Garla et al.[116] with permission.

reduced.[27,106] The benefits in the renal events by semaglutide in the SUSTAIN-6 trial also support a higher ranking of GLP-1 RAs.[28] 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.[97] DPP-4 inhibitors have neutral effect in CV and renal endpoints. Sulfonylureas 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.

Table 4
Treatment algorithm in diabetic patients with stage 3 CKD.

Target HbA1c	<7%			
Monotherapy	Metformin			
Dual therapy	Metformin + SGLT-2 i			
Triple therapy	Metformin + SGLT-2 i + GLP-1 RA[a]	Metformin + SGLT-2 i + TZD[b]	Metformin + SGLT-2 i + DPP-4 i	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; 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 and semaglutide.
[b] Pioglitazone.

5. Treatment of diabetes in patients with a history of stroke

5.1. Rationale

Diabetes is associated with a higher risk of ischemic stroke.[5] In a meta-analysis of 102 prospective studies, patients with diabetes had increased risks of ischemic stroke (HR 2.27, 95% CI 1.95–2.65) and hemorrhagic stroke (HR 1.56, 95% CI 1.19–2.05).[121] From the data from the Taiwan NHIRD, the risk of ischemic stroke was increased in diabetic patients (OR 1.341, 95% CI 1.092–1.648).[122] The prevalence of diabetes is high both in patients with ischemic stroke/TIA (45.4%) and in patients with hemorrhagic stroke (37%).[123] In patients with stroke, the presence of diabetes confers a much worse outcome compared with patients without diabetes.[124] Furthermore, stroke increases subsequent functional disability and psychiatric disorders, such as depression, and leads to an enormous economic burden and impact on quality of life.[125] Several risk factors for stroke in patients with diabetes are potentially modifiable, including blood sugar.[124,126] Because there are only limited data for patients with a history of hemorrhagic stroke, the content of this section is mainly focused in patients with a history of ischemic stroke.

Whether glycemic control reduces stroke risk remains an open question. There has been no large-scaled RCT specifically testing anti-diabetic agents in diabetic patients with previous stroke, except one trial done in patients with insulin resistance.[44] In the UKPDS trial, intensive glucose control with an averaged achieved HbA1c of 7.0% did not decrease the risk of stroke, compared with conventional glucose control with an averaged achieved HbA1c of 7.9%.[9] In the long-term follow-up study of the UKPDS trial, the stroke incidence was not decreased (HR 0.91, 95% CI 0.73–1.13).[14] Additionally, in three major RCTs, there was no difference in the stroke risk between intensive glycemic therapy and standard therapy.[10–12] Further, in a meta-analysis of 34,533 patients with type 2 diabetes, the stroke risk was not reduced in tight glycemic control versus standard glycemic control during a mean treatment period of 5 years (HR 0.96, 95% CI 0.83–1.1).[127] Similar findings were noted in a Cochrane review of 29,986 patients with type 2 diabetes from 20 RCTs.[128] Intensive glycemic control did not reduce the risk of CV mortality (risk ratio 1.1, 95% CI 0.90–1.3) or non-fatal stroke (risk ratio 0.96, 95% CI 0.80–1.2).[128] However, one should be aware of the hypoglycemic risk of conventional anti-diabetic agents which were used in these intensive control trials. It has been shown in a study from Taiwan NHIRD that symptomatic hypoglycemia is associated with significant risk of death.[13] With newer anti-diabetic drugs with lower risk of hypoglycemia, such as TZDs, GLP-1 RA, DPP-4 inhibitors, and SGLT-2 inhibitors, the effect of glucose control on the stroke risk might be different. For instance, pioglitazone in the IRIS trial decreased stroke and MI in patients with ischemic stroke/TIA and insulin resistance (HR 0.76, 95% CI 0.62–0.93, $p = 0.007$).[44] Moreover, semaglutide decreased the risk of 3-point MACE, including non-fatal stroke (HR 0.61, 95% CI 0.38–0.99, $p = 0.04$) in high risk diabetic patients.[28]

5.2. Target of HbA1c

Although diabetes is associated with an increased risk of stroke and a worse post-stroke outcome,[124] intensive glycemic control using more traditional antidiabetic agents has a neutral effect on recurrent stroke. In this consensus, we recommended the target HbA1c to be less than 7.0% in diabetic patients with a history of stroke. However, one should balance the benefits of glycemic control with the risk of hypoglycemia, particularly when sulfonylureas, glinides and insulin are administrated.

5.3. Choice of drugs

5.3.1. Metformin

In the UKPDS trial, metformin therapy was associated with a non-significant reduction in the risk of stroke compared with conventional lifestyle therapy (HR 0.59, 95% CI 0.29–1.18) in overweight patients.[49] 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 25% reduction in the risk of stroke compared with lifestyle (HR 0.750, 95% CI 0.573–0.982, $p = 0.036$).[52] In a cohort of 14,856 patients with diabetes from the Taiwan NHIRD, the risk of ischemic stroke was substantially lower in the group with metformin use (9.2%) than in the group without metformin use (17.5%) (adjusted HR 0.468, 95% CI 0.424–0.518).[129] One observational study evaluated the effects of metformin on stroke severity and outcomes in diabetic patients with acute ischemic stroke. Patients who took metformin prior to stroke onset had a reduced neurological severity and milder neurological

symptoms, compared with those who had not taken metformin.[130] Taken together, the consensus group recommended metformin as the first line therapy for patients with diabetes and a history of stroke.

5.3.2. Sulfonylureas

In the UKPDS trial, sulfonylurea did not decrease the risk of stroke.[9] In the ADVANCE trial, use of gliclazide had no effect on the 3-point MACE and non-fatal stroke.[11] In a meta-analysis of 82 RCTs and 26 observational studies, the risk of stroke was significantly higher in sulfonylurea users than users of other anti-diabetic agents.[63] In a recent cohort study from the Taiwan NHIRD, sulfonylureas are worse than DPP-4 inhibitors as an add-on therapy of metformin in terms of CV events.[64] The risk of ischemic stroke was lower for DPP-4 inhibitors than sulfonylureas (HR 0.64, 95% CI 0.51−0.81, $p < 0.001$).[64] The ongoing CAROLINA trial (NCT01243424), comparing linagliptin with glimepiride in patients with type 2 diabetes, might help to clarify the CV effect of them.[67] The consensus group gave sulfonylurea a low priority in patients with diabetes and a history of stroke.

5.3.3. Glinides

There was no RCT or observational study testing the efficacy of repaglinide on the risk of stroke. In the NAVIGATOR trial, 9306 participants with IGT and CVD (only 3% had a history of stroke) or its risk factors were randomized to nateglinide or placebo.[70] After a follow-up of 6.5 years, nateglinide did not reduce the 3-point MACE plus admission for HF (HR 0.94, 95% CI 0.82−1.09; $p = 0.43$) or the incidence of non-fatal strokes (HR 0.89, 95% CI 0.69−1.15).[70] The consensus group gave a low priority to glinides in diabetic patients with a history of stroke.

5.3.4. Alpha-glucosidase inhibitor

The STOP-NIDDM trial evaluated the effect of acarbose on the risk of CVD in 1368 patients with IGT.[71] After a mean follow-up of 3.3 years, there was a significant reduction in CVD by acarbose (HR 0.51, 95% CI 0.28−0.95, $p = 0.03$).[71] There were only 2 patients in the acarbose group and 4 patients in the placebo group developing stroke, making a meaningful comparison inappropriate (HR 0.56, 95% CI 0.10−3.07, $p = 0.51$).[71] In a nationwide cohort study in drug-naïve patients with type 2 diabetes in Taiwan, acarbose has no effect on ischemic stroke when compared with metformin (HR 1.05, 95% CI 1.00−1.10).[72] The definitive answer for the effect of acarbose on CVD came from the recently finished ACE trial.[38] A total of 6522 Chinese patients with CHD were randomized to acarbose and placebo.[131] After a median follow-up of 5 years, there was no difference in the 5-point MACE (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and hospitalization for HF) (HR 0.98, 95% CI 0.86−1.11).[38] The risk of fatal- and non-fatal stroke was also similar in the two groups (HR 0.97, 95% CI 0.70−1.33). Gastrointestinal side effect was more common in the acarbose group (7% vs. 5%, $p = 0.0007$).[38] The ACE trial confirmed a neutral effect of acarbose in patients with CHD, though data from patients with a history of stroke were not specifically mentioned. The consensus group gave a neutral position for acarbose and did not give a priority due to its gastrointestinal side effects.

5.3.5. Thiazolidinedione

Among patients with a history of stroke who entered the PROactive trial, pioglitazone therapy was associated with a 47% relative risk (RR) reduction in recurrent stroke (HR 0.53, 95% CI 0.34−0.85, $p = 0.0085$) and a 28% RR reduction in 3-point MACE (HR, 0.72, 95% CI 0.53−1.00, $p = 0.00467$).[132] In a small study in Japanese (J-SPIRIT), 120 patients with type 2 diabetes and a history of stroke, a non-significant reduction in secondary stroke was shown (4.8% vs. 10.5%, $p = 0.49$).[133] In the IRIS trial, 3876 patients who had had a recent ischemic stroke or TIA were randomized to pioglitazone (target dose, 45 mg daily) or placebo.[44] The primary endpoint was fatal and non-fatal stroke, and MI. There was a significant reduction in the primary endpoint (HR 0.76, 95% CI 0.62 to 0.93, $p = 0.007$), and a trend towards lower stroke rates (HR 0.82, 95% CI 0.61−1.10).[44] A meta-analysis of these three RCTs, totaling 4980 participants, shows that pioglitazone is associated with lower risk of recurrence stroke (HR 0.68, 95% CI 0.50−0.92, $p = 0.01$) in patients with insulin resistance, pre-diabetes, and diabetes mellitus. There was no effect on all-cause mortality and heart failure.[134] The consensus group gave a high priority for pioglitazone in the treatment of diabetes in patients with a history of stroke.

5.3.6. Insulin

Only a few prospective interventional trials specifically tested the CV effects of insulin in type 2 diabetes. In patients receiving insulin/sulfonylurea therapy in the UKPDS, no significant difference was reported in risk of stroke compared with patients on conventional diet therapy after a follow-up of about 10 years (HR 0.91, 95% CI 0.73−1.13).[14] Similarly, in the ORIGIN trial, 12,537 patients with CV risk factors plus IFG, IGT, or type 2 diabetes were randomized to insulin glargine or standard care for a median follow-up of 6.2 years.[20] No difference was found in stroke incidence between the insulin and the control groups (HR 1.03, 95% CI 0.89−1.21).[20] Therefore, the consensus group did not give a high priority to insulin as an initial therapy in diabetic patients with a history of stroke.

5.3.7. DPP-4 inhibitors

There was no trial testing the effect of DPP-4 inhibitors in patients with a history of stroke specifically. In the SAVOR trial, 12.7% of patients had a history of stroke.[25] The overall efficacy in the 3-point MACE showed no difference with the use of saxagliptin compared with placebo. The subgroup analysis of patients with or without a history of stroke was not reported. Among the 3-point MACE, ischemic stroke was not different with the use of saxagliptin compared with placebo (HR 1.11, 95% CI 0.88−1.39).[25] In the EXAMINE trial, 7.2% of patients had a history of stroke.[23] The overall efficacy in the 3-point MACE showed no difference with the use of alogliptin

compared with placebo.[23] The subgroup analysis of patients with or without a history of stroke was not reported. Among the 3-point MACE, non-fatal stroke was not different with the use of alogliptin compared with placebo (HR 0.91, 95% CI 0.55–1.50).[23] In the TECOS trial, 24.5% of patients had a history of stroke.[26] The overall efficacy in the 3-point MACE showed no difference with the use of sitagliptin compared with placebo (HR 0.99, 95% CI 0.89–1.10).[26] The subgroup analysis of patients with or without a history of stroke was not reported. Among the 3-point MACE, fatal and non-fatal stroke was not different with the use of sitagliptin compared with placebo (HR 0.97, 95% CI 0.79–1.19).[26] In a short-term trial comparing linagliptin vs. glimepiride in diabetic patients who were poorly controlled by metformin, linagliptin was associated with significantly fewer CV events (12 vs. 26 patients; relative risk 0.46, 95% CI 0.23–0.91, $p = 0.0213$), including non-fatal stroke (3 vs. 11 patients; relative risk 0.27, 95% CI 0.08–0.97, $p = 0.03$).[135] The event number was too small to make any definite conclusion. In a meta-analysis of the three RCTs, there was no difference in the risk of stroke with the use of DPP-4 inhibitors compared with placebo (OR 0.996, 95% CI: 0.850–1.166).[136] The consensus group gave a neutral position to DPP-4 inhibitors in diabetic patients with a history of stroke.

5.3.8. GLP-1 receptor agonists

In the ELIXA trial, only 6.2% patients had a history of stroke.[22] The overall efficacy in the 3-point MACE showed no difference with the use of lixisenatide compared with placebo. The subgroup analysis of patients with or without a history of stroke was not reported. Among the 3-point MACE, the risk of stroke was not different with the use of lixisenatide compared with placebo (HR 1.12, 95% CI 0.79–1.58).[22] In the LEADER trial, 16.6% patients had a history of stroke.[27] There is a significant reduction in the 3-point MACE with the use of liraglutide (HR 0.87, 95% CI 0.78–0.97, $p = 0.01$), and a trend of reduction in the risk of stroke (HR 0.86, 95% CI 0.71–1.06, $p = 0.16$).[27] The sub-group analysis showed a significant reduction of 3-point MACE in patients with established CVD compared with those without established CVD (HR 0.83, 95% CI 0.74–0.93 vs. HR 1.20, 95% CI 0.86–1.67, p for interaction 0.04), though specific data regarding patients with previous stroke was not mentioned.[27] In the SUSTAIN-6 trial, 11.6% patients had a history of stroke.[28] The 3-point MACE was significantly reduced by semaglutide (HR 0.74, 95% CI 0.58–0.95, $p < 0.0001$), including a significant reduction in the risk of non-fatal stroke (HR 0.61, 95% CI 0.38–0.99, $p = 0.04$).[28] In the subgroup analysis, patients with established CVD had a significant reduction in the 3-point MACE (HR 0.72, 95% CI 0.55–0.98), while those without CVD have a neutral effect with the use of semaglutide (HR 1.00, 95% CI 0.41–2.46, though the p value for interaction was 0.49).[28] The specific data regarding patients with a history of stroke was not mentioned. In the EXSCEL trial, 17.3% patients had a history of stroke.[29] The overall efficacy in the 3-point MACE showed no difference with the use of exenatide compared with placebo (HR 0.91, 95% CI 0.83–1.00).[29] The risk of fatal and non-fatal stroke was numerically lower, but did not reach statistical significance (HR 0.85, 95% CI 0.70–1.03). In the subgroup analysis, patients with established CVD have a non-significant reduction in the 3-point MACE (HR 0.90, 95% CI 0.82–1.00). The consensus group gave a high priority to GLP-1 RAs in patients with diabetes and a history of stroke.

5.3.9. SGLT-2 inhibitors

In the EMPA-REG OUTCOME trial, 23.7% of patients had a history of stroke.[21] The 3-point MACE was significantly reduced by the use of empagliflozin (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$), but the subgroup analysis showed that there was no difference in patients with a history of stroke.[21] Among the 3-point MACE, there was no significant difference between empagliflozin and placebo in the risk of stroke.[21] In a modified intent-to-treat analysis, the HR for stroke was 1.18 (95% CI, 0.89–1.56; $p = 0.26$).[21] The numeric difference in stroke between empagliflozin and placebo in the modified intent-to-treat analysis was primarily because of 18 patients in the empagliflozin group with a first event >90 days after last intake of study drug (versus 3 on placebo).[137] In a sensitivity analysis based on events during treatment or ≤90 days after last dose of drug, the HR for stroke with empagliflozin versus placebo was 1.08 (95% CI, 0.81–1.45; $p = 0.60$).[137]

In the CANVAS program, 19.3% patients had a history of stroke.[30] The 3-point MACE was significantly reduced by the use of canagliflozin (HR 0.86, 95% CI 0.75–0.97, $p = 0.02$).[30] In the subgroup analysis, patients with a history of CVD had benefits and patients without a history of CVD did not have benefit (HR 0.82, 95% CI 0.72–0.95; HR 0.98, 95% CI 0.74–1.30; respectively), but the p value for interaction was insignificant ($p = 0.18$). The specific data from patients with a history of stroke was not reported. Among the 3-point MACE, the risk of fatal or non-fatal stroke was numerically lower, but did not reach statistical significance (HR 0.87, 95% CI 0.69–1.09).[30]

The CV outcome trial of dapagliflozin, i.e., the DECLARE trial, has not been finished. In a meta-analysis of 9339 patients, patients receiving dapagliflozin had a similar risk of stroke compared with the control group (HR 0.999, 95% CI 0.536–1.864).[82] The CVD-REAL Nordic study is a multinational observational analysis comparing SGLT-2 inhibitors (n = 22,830) with other glucose-lowering agents (n = 68,490).[83] Among them, 94% of the total SGLT-2 inhibitor exposure time was for the use of dapagliflozin, with 5% for empagliflozin, and 1% for canagliflozin. The use of SGLT-2 inhibitors was associated with a decreased risk of CV mortality (HR 0.53, 95% CI 0.40–0.71), the 3-point MACE (HR 0.78, 95% CI 0.69–0.87), and hospital events for HF (HR 0.70, 95% CI 0.61–0.81; $p < 0.0001$ for all).[83] But there was no significant difference in non-fatal stroke.[83]

The consensus group gave a moderate priority to SGLT-2 inhibitors in diabetic patients with a history of stroke.

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

Table 5 shows the algorithm for the treatment of diabetes in patients with a history of stroke. The target HbA1c is <7%.

Table 5
Treatment algorithm in diabetic patients with a history of stroke.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + GLP-1 RA[b]	Metformin + SGLT-2 i
Triple therapy	Metformin + TZD[a] + GLP-1 RA[b]	Metformin + TZD[a] + SGLT-2 i	Metformin + GLP-1 RA[b] + 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 and semaglutide.

Metformin should be the first-line therapy in diabetic patients with a history of stroke, mainly based on the findings from the UKPDS trial and several observational studies in Taiwan and Asia. For dual therapy, we recommend metformin plus TZDs, followed by metformin plus GLP-1 RAs, and then metformin + SGLT-2 inhibitors. The PROactive trial, the IRIS trial, and an important meta-analysis provided strong evidence to support the role of TZDs. The SUSTAIN-6 trial and the LEADER trial gave a rationale for the use of GLP-1 RAs. The CANVAS program gave some support to use SGLT-2 inhibitors. If the fourth drug is to be added, DPP-4 inhibitors are recommended due to their neutral effects and safety. Sulfonylurea did not have any positive trial to support and a Taiwanese cohort showed a worse outcome. In addition, the risk of hypoglycemia is well-known. Glinides and acarbose have low priority due to lack of any supporting evidence.

6. Treatment of diabetes in patients with heart failure

6.1. Rationale

6.1.1. Diabetes is a risk factor for developing heart failure

In the Framingham study, diabetic males and females had a 2.4–fold and a 5-fold risk of HF, respectively.[138] In the Kaiser Permanente Northwest Program, patients with diabetes were much more likely to develop HF than patients without diabetes, with a risk ratio of 2.5.[139] Poor glycemic control is associated with an increased risk of HF among diabetic patients[140]; each 1% increase in HbAIc is 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 to 1.93) greater risk of HF.[140] Several possible mechanisms account for the association between diabetes and HF: disturbance in calcium handling, endothelium dysfunction, microcirculatory dysfunction, etc.[141] Impaired LV diastolic function is a hallmark in diabetic cardiomyopathy[142]; while systolic dysfunction is the terminal stage of this progressive disease.

In a recent cohort study consisted of 1,921,260 individuals from UK, HF is the second most common manifestation of CVD in patients with type 2 diabetes, ranked after peripheral arterial occlusive disease.[143] In the VALUE trial, the cumulative risk of HF was higher than that of MI in patients with diabetes.[144] The prevalence of HF in the elderly diabetic patients was approximately 20%.[145] In recent RCTs of antidiabetic agents, the prevalence of HF in the baseline was approximately 10–30% (Table 1).

6.1.2. Heart failure patients have a higher risk of developing diabetes

HF is an established risk factor for development diabetes.[146,147] In a 7.7-year follow-up study of the Bezafibrate Infarction Prevention (BIP) study, patients with HF of NYHA class III were associated with a 1.7-fold (95% CI 1.1 to 2.6) increase in the risk of new-onset diabetes.[148] In HF registries around the world, the prevalence of diabetes in HF patients is approximately 30–50%.[149–153] In the OPTIMIZE-HF registry, 42% of hospitalized HF patients had diabetes.[149] In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, 40% of hospitalized patients with reduced ejection fraction (HFrEF) had diabetes.[150] In the GWTG-HF registry, 40% of patients with HFrEF and 45% of patients with preserved ejection fraction (HFpEF) had diabetes.[151] In the recent TSOC-HFrEF registry in Taiwan, 43.6% among 1509 patients with HFrEF had diabetes.[152] The prevalence of diabetes in a recent Asian report was from 33% to 67%.[153]

6.1.3. Higher CV risk in patients with diabetes and concomitant heart failure

HF has been called "the frequent, forgotten, and often fatal" complication of diabetes.[154] Diabetic patients with pre-existing HF had a higher CV risk compared with those without HF. Even in well-treated patients as those in clinical trials (e.g. the SAVOR trial and the EMPA-REG OUTCOME trial), patients with pre-existing HF had an approximately 4-fold increase in the future HF admission,[155,156] an approximately 3-fold increase in the future HF admission plus CV death,[156] and an approximately 2-fold increase in CV death and all-cause death.[156] The median survival for diabetic patients with concomitant HF is only 4 years.[157] 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.[145,157]

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 sub-study of the Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin-Converting-Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM) trial.[158] In the SOLVD trial, diabetes was associated with an increased risk for all-cause mortality in patients with ischemic HFrEF (RR 1.37, $p < 0.0001$).[159] In patients with HFrEF, the presence of diabetes increased the risk of 5-yr mortality (HR

1.69, 95% CI 1.20−2.38) in a French population-based study.[160] In the Digitalis Investigation Group (DIG) ancillary study in patients with HFpEF, the risk of HF death or hospitalization for worsening HF was increased in patients with diabetes (adjusted HR 1.68, 95% CI 1.26 to 2.25, $p < 0.001$).[161]

6.2. Target of HbA1c

In a meta-analysis of 4 RCTs comparing intensive vs. standard glucose lowering strategy, intensive strategy had no impact on HF admission.[46] It is uncertain whether intensive strategy will be beneficial in patients with diabetes and HF. 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 single-hospital cohort from the US of 123 patients with diabetes and advanced HFrEF, patients with HbA1c $\leq$ 7.0% had a significantly increased risk of all-cause mortality, compared with those with HbA1c > 7.0% (HR 2.6, 95% CI 1.3−5.2, $p < 0.01$), which remained significant after multivariate analysis (HR 2.3, 95% CI 1.0−5.2).[162] In a retrospective study in a national cohort of 5815 veterans with HF and diabetes treated at Veterans Affairs medical centers from the US, 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% < HbA1c $\leq$ 7.8%).[163] In a prospective cohort of 845 HF patients from the US, the risk of death or urgent heart transplantation was increased in patients with HbA1c $\leq$ 7.2% compared with those with HbA1c $\geq$ 7.3%.[164] In a population cohort from UK, 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%).[165] The consensus group reached a conclusion that the target HbA1c for patients with diabetes and HF is <8.0%.

6.3. Choice of drugs

There is no completed RCT testing the efficacy of anti-diabetic agents in reducing CV events in patients specifically with diabetes and HF, though a few are ongoing (**DAPA-HF**, Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure, NCT03036124; **EMPEROR-Reduced**, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction, NCT03057977; **EMPEROR-Preserved**, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, NCT03057951). Some anti-diabetic agents increased HF admission in RCTs, though HF admission was generally not primary endpoint. The drugs which increased HF admission should be avoided in patients with pre-existing HF.[166] On the other hand, anti-diabetic agents which decreased HF admission and/or decreased mortality in HF subgroup may be recommended before choosing others.

6.3.1. Metformin

In the UKPDS trial, patients with pre-existing HF were excluded.[49] Metformin users had numerically lower risk of developing HF compared with conventional therapy, but the number was very small and it did not reach statistical significance.[49] In a pooled analysis of 9 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 ($p = 0.01$).[167] 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 ($p = 0.009$).[168] Therefore, metformin can be used in patients with stable HF, but should be discontinued in patients with acute congestive HF (particularly when accompanied by hypoperfusion and hypoxemia), cardiovascular collapse (shock), AMI, sepsis, and other conditions associated with hypoxemia. The consensus group gave a high priority to metformin in patients with diabetes and stable HF.

6.3.2. Sulfonylureas

In the UKPDS trial, the combination of sulfonylurea and insulin did not increase the risk of HF when compared with conventional dietary-based therapy (HR 0.91, 95% CI 0.54−1.52).[9] In the ADVANCE trial, gliclazide use had a neutral effect on the HF admission, compared with other anti-diabetic agents (HR 1.05, 95% CI 0.86−1.21).[11] However, in some cohort studies, sulfonylurea generally increased the risk of HF when compared with metformin.[60,169] In a more recent cohort study of National Veterans Health Administration databases from the US, initiation of sulfonylurea in diabetic patients increased the risk of HF and CV death (adjusted HR 1.32, 95% CI 1.21−1.43) compared to patients initiating metformin.[170] The ongoing CAROLINA trial (NCT01243424) will check if sulfonylurea will have different effect on CV events including HF admission, compared with linagliptin. Until more data are available, sulfonylurea should be reserved for add-on therapy in patients whose blood glucose cannot be controlled by other effective or safer drugs. The consensus group gave a neutral position to sulfonylureas in patients with diabetes and HF.

6.3.3. Glinides

In the Left Ventricular Dysfunction in Diabetes (DYDA) 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.[171] 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, $p = 0.01$).[171] In a retrospective cohort study using the Taiwan NHIRD, the use of glinides was associated with a higher risk of HF admission compared with acarbose (adjusted HR 1.53, 95% CI 1.24−1.88).[172] 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.[70] There was no significant difference in the risk of hospitalization for HF among the nateglinide group vs. the placebo group (HR 0.85,

95% CI 0.64–1.14).[70] The consensus group gave a neutral position to glinides in patients with diabetes and HF.

6.3.4. Alpha-glucosidase inhibitor

In the STOP-NIDDM trial, the effect of acarbose on CVD, including HF, was tested in 1368 patients with IGT.[71] The number of HF event was too small to draw any conclusion (n = 0 for acarbose vs. n = 2 for placebo).[71] In the more robust ACE trial, a total of 6522 Chinese patients with CHD were randomized to acarbose and placebo. There was no significant difference in the HF admission in the acarbose group (2.0%) vs. the placebo group (2.2%) (HR 0.89, 95% CI 0.63–1.24).[38] The consensus group gave acarbose a neutral position and did not give a priority due to its gastrointestinal side effects.

6.3.5. Thiazolidinedione

TZDs activate a sodium channel in collecting tubules and enhance sodium retention and fluid overload,[173] but have no direct effect on LV function.[174] TZDs increased 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 ($p = 0.007$).[17] In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone significantly increased HF risk compared with placebo (HR 7.03, 95% CI 1.60–30.9).[175] In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) trial, rosiglitazone increased the risk of HF by about 2 fold (HR 2.1, 95% CI 1.35–3.27), compared with metformin/sulfonylurea.[176] Though there was no signal of increasing HF in the IRIS trial, which enrolled patients with insulin resistance and excluded patients with HF patients,[44] 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.[74,177–179] Therefore, TZDs should not be used in patients with symptomatic HF, and should be discontinued when HF appears.

6.3.6. Insulin

Insulin has an anti-natriuretic property and may increase sodium and fluid retention in diabetic patients.[180] But in many RCTs, the risk of HF was not increased. In the UKPDS trial, the HF risk was the same in insulin users vs. sulfonylurea users.[9] In the BARI-2D trial, insulin did not create any significant change in the HF risk compared with other anti-diabetic medications.[181] In the ORIGIN trial, the largest RCT for insulin, patients with dysglycemia, including impaired glucose tolerance, impaired fasting glucose, and diabetes, were enrolled. The percentage of patients with pre-existing HF was not provided. The basal insulin glargine resulted in a non-significant reduction in HF admission (HR 0.90, 95% CI 0.77–1.05).[20]

In patients with diabetes and HF, there are several pieces of evidence to suggest a harmful effect of insulin. In a large contemporary HF population in the Candesartan in Heart Failure-Assessment of Mortality and Morbidity (CHARM) program, including patients with HFpEF and HFrEF, insulin-treated diabetes was found to be the most strong independent predictor for CV death plus HF hospitalization, 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).[182] The total mortality showed similar trend (HR 1.80, 95% CI 1.56–2.08 vs. 1.50, 95% CI 1.34–1.68).[182] In a systemic review of controlled studies evaluating antidiabetic agents and outcomes in patients with HF, three of four studies found that insulin use was associated with increased risk for all-cause mortality (OR 1.25, 95% CI 1.03 to 1.51).[183] The consensus group gave a neutral position to insulin 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.

6.3.7. DPP-4 inhibitors

The effects of DPP-4 inhibitors in diabetic patients with high CV risk have been studied in major CV outcome trials. In the SAVOR trial, 12.8% patients had pre-existing HF. The use of saxagliptin increased HF admission (HR 1.27, 95% CI 1.07–1.51, $p = 0.007$).[25] The risk of HF admission was significantly increased in patients with a history of HF (n = 2105) (HR 1.21, $p = 0.15$; absolute risk 1.5%, NNH 67).[155] In patients without a HF history (n = 14,387), HF admission was also significantly increased (HR 1.32, $p = 0.02$; absolute risk 0.6%, number needed to harm [NNH] 167).[155] 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).[155] The risk factors for HF admission included the followings: prior HF, elevated baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP), and CKD.[155] The mechanism of increased HF admission with the use of saxagliptin was not completely understood. In the EXAMINE trial, alogliptin was compared placebo in patients with recent MI.[23] There were 27.8% patients had pre-existing HF. In the secondary publication of the EXAMINE trial, alogliptin was associated with a numerically higher risk of HF admission (HR 1.19, 95% CI 0.90–1.58).[184] The difference became significant in patients without a history of HF (HR 1.76, 95% CI 1.07–2.90).[184] In June 7 2016, US FDA added warning about HF risks to diabetic medicines containing saxagliptin and alogliptin (https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm). Therefore, for patients with diabetes and HF, saxagliptin and alogliptin should not be used.

There were several registries suggested an association of sitagliptin with HF.[185,186] In the TECOS trial, 18% patients had pre-existing HF. Sitagliptin did not increase HF admission in the overall population (HR 1.00, 95% CI 0.83–1.20),[26] or in patients with a history of HF (HR 1.05, 95% CI 0.79–1.39).[187] Post-HF death (29.8% vs. 28.8%) and CV death (22.4% vs. 23.1%) was similar in the sitagliptin and placebo groups.[187] We suggest that sitagliptin can be safely used in patients with diabetes and HF.

There was no CV outcome trial for vildagliptin. In the Vildagliptin in Ventricular Dysfunction Diabetes (VIVVID) study, patients with type 2 diabetes and HF (NYHA I-III and LVEF <0.40) were randomized to 52 weeks treatment with vildagliptin or placebo.[188] There was no change in the primary

endpoint, defined as between-treatment change from baseline in LVEF.[188] 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 $p > 0.05$). Therefore, we suggest not to use vildagliptin in patients with diabetes and HF.

For linagliptin, the CAROLINA trial (NCT01243424) and the CARMELINA trial (NCT01897532) are ongoing. In a patient-level pooled analysis of 5847 patients, linagliptin did not increase the risk of HF admission compared with other drugs (HR 1.04, 95% CI 0.43–2.47).[189]

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

6.3.8. GLP-1 receptor agonists

The effects of various GLP-1 RAs on CV events, including HF, have been tested in several RCTs. Lixisenatide was studied in the ELIXA trial in patients with ACS.[22] There were 22.3% patients with pre-existing HF. There was no difference in the 3-point MACE (non-fatal MI, non-fatal stroke, and CV death) (HR 1.02, 95% CI 0.89–1.17), nor HF admission (HR 0.96, 95% CI 0.75–1.23).[22] Subgroup analysis of patients with or without HF was not provided. In the LEADER trial, liraglutide was examined in patients with high CV risk, including about 80% with previous CVD and 14% with pre-existing HF.[27] The 3-point MACE was significantly decreased by 13% with liraglutide (HR 0.87, 95% CI 0.78–0.97, $p = 0.01$), but the risk of HF admission was not significantly changed (HR 0.87, 95% CI 0.73–1.05).[27] Subgroup analysis of patients with or without HF was not provided. In the SUSTAIN-6 trial, once-weekly semaglutide was compared with placebo in high risk patients, including 83% with previous CVD and 25% with pre-existing HF.[28] The 3-point MACE was markedly decreased by 26% by semaglutide (HR 0.74; 95% CI 0.58 to 0.95, $p = 0.02$). The risk of HF admission was not significantly different (HR 1.11, 95% CI 0.77–1.61).[28] Subgroup analysis of patients with or without HF was not provided. In the most recent EXSCEL trial, weekly injection of extended-release exenatide was compared with placebo in high risk patients, including 73% with previous CVD and 16.6% with pre-existing HF.[29] The 3-point MACE was not significantly changed (HR, 0.91; 95% CI, 0.83 to 1.00, $p < 0.001$ for noninferiority, $p = 0.06$ for superiority). There was no significant difference in the risk of HF admission (HR 0.94, 95% CI 0.78–1.13).[29] Subgroup analysis of patients with or without HF was not provided.

An important RCT with GLP-1 RA in patients with HF is the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial.[190] 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.[190] The primary endpoint was a global rank score in which all patients, regardless of treatment assignment, were ranked across 3 hierarchical tiers: time to death, time to re-hospitalization for HF, and time-averaged proportional change in NT-pro BNP level from baseline to 180 days. Compared with placebo, liraglutide had no significant effect on the primary end point (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). Pre-specified subgroup analyses in patients with diabetes did not reveal any significant between-group difference.[190] 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.

6.3.9. SGLT-2 inhibitors

There are several RCTs testing the effects of SGLT-2 inhibitors on CV outcomes, and two of them have been published.[21,30] In the EMPA-REG OUTCOME trial, a total of 7020 patients with pre-existing CVD (including 10.5% with pre-existing HF) were randomized to receive 10 mg or 25 mg of empagliflozin or placebo once daily.[21] After a median follow-up of 3.1 years, the 3-point MACE was significantly reduced by pooled empagliflozin group (HR 0.86; 95% CI 0.74 to 0.99; $p = 0.04$ for superiority). There were no significant differences in the rates of MI or stroke, but in the empagliflozin group there were significantly lower rates of CV death (HR 0.62, 95% CI 0.49–0.77, $p < 0.001$), hospitalization for HF (HR 0.65, 95% CI 0.50–0.85, $p = 0.002$), and all-cause mortality (HR 0.68, 95% CI 0.57–0.82, $p < 0.001$).[21] The effects of empagliflozin on HF admission were consistent in patients with (HR 0.75, 95% CI 0.48–1.19) vs. without HF (HR 0.59, 95% CI 0.43–0.82).[156] This is the first time that anti-diabetic agent was proven to be effective in patients with HF.

The CANVAS program randomized 10,142 participants with diabetes and high CV risk, including 65.6% with pre-existing CVD and 14.4% with pre-existing HF, into canagliflozin or placebo groups.[30] The rate of 3-point MACE was lower with canagliflozin than with placebo (HR 0.86; 95% CI 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). The HF admission was significantly reduced (HR 0.67, 95% CI 0.52–0.87). There was, however, an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; HR, 1.97; 95% CI 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.[30] The finding of a significant reduction in HF admission in the CANVAS trial is consistent with that in the EMPA-REG OUTCOME trial, suggesting a class effect of reducing HF admission with the use of SGLT-2 inhibitors.

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 for seven different SGLT-2 inhibitors were analyzed.[191] 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.[191] In the CVD-REAL study, medical claims, primary care/hospital records, and national registries were collected from 6 countries, including United States, Norway, Denmark, Sweden, Germany, and the United Kingdom.[192] Only 13% of these patients had pre-existing CVD, while 87% were free of previous CVD. Propensity score for SGLT-2 inhibitor initiation was applied to match treatment groups. There were 309,056 patients newly initiated on either SGLT-2 inhibitors or other glucose-lowering agents (154,528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2 inhibitor class, respectively. Use of SGLT-2 inhibitors was associated with lower risk of HF admission (HR 0.61; 95% CI 0.51–0.73; $p < 0.001$); death (HR 0.49; 95% CI 0.41–0.57; $p < 0.001$); and HF admission or death (HR 0.54; 95% CI 0.48–0.60; $p < 0.001$) with no significant heterogeneity by country.[192] This study suggested that the observed CV benefits are likely class-related, and the benefit may extend to low-risk patients. The data from 3 Nordic countries, Norway, Denmark, and Sweden, were analyzed in the CVD-REAL NORDIC study.[83] The total SGLT-2 inhibitor exposure time was 94% for the use of dapagliflozin, with 5% for empagliflozin, and 1% for canagliflozin, and 75% did not have previous CVD. Use of SGLT-2 inhibitors was associated with a decreased risk of CV mortality (HR 0.53, 95% CI 0.40–0.71), MACE (HR 0.78, 95% CI 0.69–0.87), and HF admission (HR 0.70, 95% CI 0.61–0.81; $p < 0{\cdot}0001$ for all).[83]

No one could have expected SGLT-2 inhibitors would decrease HF admission and mortality.[193] The mechanisms are not completely understood.[110] The first possible, and perhaps the most widely credited, mechanism that has with the positive CV and renal outcomes of SGLT-2 inhibitors relates to its effect on diuresis, both natriuresis and osmotic diuresis.[194] Short-term empagliflozin treatment was associated with a significant reduction in LV mass index [mean values: 88 vs. 75 g/m^2, P = 0.01] and improved diastolic function.[195] Compared with placebo, treatment with canagliflozin delayed the rise in serum NT-proBNP and high-sensitive troponin I (hsTnI) for over 2 years in older patients with diabetes.[196]

It has been hypothesized that patients with diabetes are overloaded with sodium, mainly because of increased sodium retention in the kidney as a consequence of hyperglycemia and hyperinsulinemia.[197] Increased intracellular sodium in the myocardium may increase the risk of arrhythmias and impair myocardial function.[197] Plasma volume contraction with the use of SGLT-2 inhibitors decreased myocardial stretch and reduced cardiac arrhythmogenesis, a possible mechanism responsible for the reduced mortality observed in RCTS of SGLT-2 inhibitors.[110] Total body sodium is very difficult to measure due to multiple reservoirs.[198] It has been shown that sodium store in the skin and skeletal muscle, measure by ^{23}NaMRI, can reflect the whole body sodium content.[198] Skin sodium content correlated with LV hypertrophy in CKD patients,[199] and use of dapagliflozin for 6 weeks decreased skin sodium content compared with placebo.[200] These findings provide important mechanistic explanation of the effect of SGLT-2 inhibitors in reducing total body sodium and HF admission.

BP-lowering effects of SGL-2 inhibitors have also been identified as a possible contributor to the beneficial effects in the outcome trials.[110,201] Systolic BP was decreased by about 4–6 mmHg with the use of SGLT-2 inhibitors.[42] In a double-blind, placebo-controlled, phase 3 study in diabetic patients with uncontrolled hypertension in whom BP was uncontrolled by 2 anti-hypertensive agents (systolic 140–165 mm Hg and diastolic 85–105 mm Hg) including ACE inhibitors or ARBs, a total of 449 patients were randomized to dapagliflozin 10 mg and placebo.[202] The seated SBP was decreased by 4.28 mmHg ($p = 0.0002$), while the systolic BP on 24-h ambulatory BP monitoring (ABPM) was decreased by 4.45 mmHg ($p < 0.01$).[202] Moreover, SGLT-2 inhibitor decreased central systolic BP by 5.14 mmHg ($p < 0.001$) and central pulse pressure by 2.77 mmHg ($p = 0.12$), compared with placebo.[203]

Other mechanisms may also play some roles in the beneficial effects of SGLT-2 inhibitors on CV outcomes. Body weight was generally decreased by about 2 kg by SGLT-2 inhibitors in CV outcome trials.[21,30] Moreover, SGLT-2 inhibitors decreased aortic stiffness[204] and augmentation index.[204] The potential role of increased lipolysis and enhanced bioavailability of free fatty acids and ketone bodies in subjects treated with SGLT2 inhibitors may also be relevant.[205,206] But it is more difficult to imagine that the increased catabolism and potential predisposition toward ketoacidosis in subjects treated with SGLT-2 inhibitors can be seen as a mechanism mediating reduced CV mortality and HF hospitalizations observed in these RCTs.[110]

SGLT-2 inhibitor is a unique class of anti-diabetic agents that decrease HF admission in both HF and non-HF diabetic patients. It has been consistently shown in RCTs and by RWE. Therefore, the consensus group recommended SGLT-2 inhibitors as the first line therapy in patients with diabetes and HF.

6.4. Treatment algorithm in diabetic patients with heart failure

Table 6 shows the algorithm for the treatment of diabetes in patients with HF. The target of HBA1c is <8%. SGLT-2 inhibitors or metformin are the first line therapy. The use of SGLT-2 inhibitors is compelling, based on their effects in reducing 3-point MACE and HF admission in the EMPA-REG OUTCOME trial,[21] the CANVAS program,[30] and the CVD-REAL study.[192] The use of metformin was based on 2 recent meta-analyses.[167,168] 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. For dual therapy, we recommended SGLT-2 inhibitors plus metformin. If a third drug is to be added, we recommended GLP-1 RAs, based on their neutral effect that have been

Table 6
Treatment algorithm in diabetic patients with heart failure.

Target HbA1c	<8%			
Monotherapy	SGLT-2 i or metformin			
Dual therapy	SGLT-2 i + metformin			
Triple therapy	SGLT-2 i + metformin + GLP-1 RA	SGLT-2 i + metformin + DPP-4 i (except saxa., alo., and vilda.)	SGLT-2 i + metformin + SU or AGI	SGLT-2 i + metformin + Glinide
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

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

confirmed in the LEADER trial,[27] the SUSTAIN-6 trial,[28] the EXSCEL trial,[29] and the FIGHT study.[190] The ranking of DPP-4 inhibitors is lower than GLP-1 RAs. Sitagliptin can be safely used, based on the finding from the TECOS trial.[26] Saxagliptin, alogliptin, and vildagliptin should be avoided, based on the findings from the SAVOR trial,[25] the EXAMINE trial,[23] and the VIVVID study.[188] Linagliptin can be used, but there is only a patient-level pooled analysis to support its use.[189] Sulfonylurea, acarbose, and glinides are ranked lower than DPP-4 inhibitors.

7. Adverse events of anti-diabetic agents

Important adverse events (AEs) of common anti-diabetic agents were shown in Fig. 2. Hypoglycemia and some emerging AEs of newer anti-diabetic agents were noted here.

7.1. Hypoglycemia

Minimizing risk of both severe and non-severe hypoglycemia is a priority in the management of diabetes.[207] Hypoglycemia is common in daily practice. In a cross-sectional survey in 5 Asian countries, symptomatic hypoglycemia was reported in 35.8% of overall patients and in 29.4% of Taiwanese patients, who were treated with oral anti-diabetic agents.[208] 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, $p < 0.001$).[209] 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, $p < 0.0001$).[13] The risk level was correlated with the severity of hypoglycemia, shown in a recent meta-analysis.[210] 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 severe hypoglycemia.[210]

Among anti-diabetic agents, sulfonylureas,[64] glinides,[211] and insulin increase the risk of hypoglycemia.[212] Metformin, alpha-glucosidase inhibitor,[213] TZD, and other newer anti-diabetic agents, such as DPP-4 inhibitors,[64,214–216] GLP-1 RAs,[217] 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.[218] Therefore, clinicians should balance the risk of hypoglycemia vs. CV benefit.

7.2. Genital tract infection

The risk of genital tract infection (GTI) is increased by SGLT-2 inhibitors. In the EMPA-REG OUTCOME trial, the annual incidence of GTI was significantly higher with

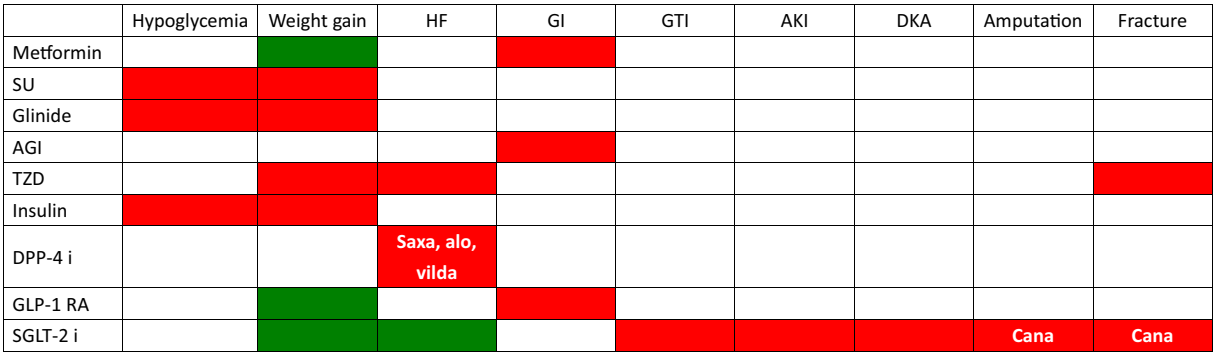

Fig. 2. Important adverse events of common anti-diabetic agents. The green color means a decreased risk. The empty box means a neutral effect. The red color means an increased risk. AGI = alpha-glucosidase inhibitor; AKI = acute kidney injury; alo = alogliptin; cana = canagliflozin; DKA = diabetic ketoacidosis; 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.

empagliflozin than with 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).[21] In the 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).[30] Therefore, personal hygiene should be emphasized in patients receiving SGLT-2 inhibitors.

7.3. Acute kidney injury

In 2016, the US FDA issued a warning of acute kidney injury (AKI) for canagliflozin and dapagliflozin (https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm) based on data from the FDA Adverse Event Reporting System (FAERS). 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 non-steroidal anti-inflammatory drugs (NSAIDs). With the same data source but a longer observation period from January 2013 to September 2016, a higher risk of AKI persisted in the users of SGLT-2 inhibitors (OR 2.88, 95% CI 2.71–3.05, $p < 0.001$).[219] These findings were also supported by a report from international pharmacovigilance database.[220] 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 (adjusted HR 0.4, 95% CI 0.2–0.7, $p = 0.004$; adjusted HR 0.6, 95% CI 0.4–1.1, $p = 0.09$, respectively).[221] In the EMPA-REG OUTCOME trial, the annual risk of AKI in pooled empagliflozin group was lower than that in the placebo group (1.0% vs. 1.6%, $p < 0.05$).[21] In the CANVAS trial, the annual risk of AKI was similar in the canagliflozin group vs. the placebo group (0.3% vs. 0.41%, $p = 0.33$).[30] Therefore, the issue of AKI with the use of SGLT-2 inhibitors is still controversial. 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 prior to initiating 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.

7.4. Diabetic ketoacidosis

From the data of FAERS from March 2013 to May 2015, 73 cases of diabetic ketoacidosis (DKA) in patients with type 1 and type 2 diabetes treated with SGLT-2 inhibitors were identified. Therefore, in May 2015, the US FDA added warnings of diabetic ketoacidosis to the labels of SGLT-2 inhibitors (https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm). A more detailed information about SGLT-2 inhibitors in the FEARS has been recently released.[222] The FAERS database contains >2500 DKA reports in which SGLT-2 inhibitors are listed as the suspect or the concomitant drugs. The proportional reporting ratio (PRR) of DKA in reports including vs. 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 US, 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.[223] After propensity-score matching to balance 46 characteristics of the patients, the HR was 2.2 (95% CI 1.4–3.6).[223]

In the EMPA-REG OUTCOME trial, the incidence of DKA was very low; only 4 out of 4687 patients (0.1%) in the pooled empagliflozin group, compared with 1 of 2333 patients (<0.1%) in the placebo group, had DKA.[21] In the CANVAS program, the rates of DKA were 0.6/1000 patient-year in the canagliflozin group and 0.3/1000 patient-year in the placebo group ($p = 0.14$).[30] Two similar reports did not find an increased risk of DKA in patients receiving SGLT-2 inhibitors.[224,225]

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 inter-current illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake.[226,227] Symptoms of DKA, including nausea, vomiting, abdominal pain, tiredness, and shortness of breath, should be monitored.[228] 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.[228] In a systemic review, the average blood glucose on presentation of DKA was 265.6 mg/dL.[229]

7.5. Amputation

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, $p < 0.001$).[30] In a sub-analysis of the EMPA-REG OUTCOME trial, the risk of lower-leg amputation was similar between the empagliflozin group and the placebo group (1.9% vs. 1.8%).[230] 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).[230] Results were similar with empagliflozin 10 mg (HR 0.96, 95% CI 0.63–1.47) and empagliflozin 25 mg (HR 1.04, 95% CI 0.69–1.58).[230] A higher risk of amputation with the use of canagliflozin was also found in FAERS.[231] The risk of amputation of canagliflozin was higher than non-SGLT-2 inhibitors (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, $p = 0.054$).[231] the US FDA has added a boxed warning solely to canagliflozin in May 2017 (https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm), based on the findings of the CANVAS program and the EMPA-REG OUTCOME trial.[21,30]

Amputation of the toe and middle of foot were the most common; however, amputations involving the leg, below and above the knee, also occurred.[30,231] Several clinical conditions may predispose patients to the risk of amputations, including a history of amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.[30,231] Physicians should remind patients of the following symptoms: new pain or tenderness, sores or ulcers, or infections in legs or feet.

7.6. Fracture

Thiazolidinediones have been shown to exert detrimental effects on the skeleton,[232] and increase the risk of fracture.[233] 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%, $p = 0.003$).[44]

Canagliflozin decreased bone mineral density,[234] and increased the risk of fracture.[235] In September 2015, US FDA has strengthened 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). The increased risk of fracture by canagliflozin has also been shown in the recent CANVAS program.[30] The incidence of fracture with canagliflozin was significantly higher than that with placebo (15.4 per 1000 patient-year vs. 11.9 per 1000 patient-year, P = 0.02).[30] There was no signal of fracture risk in the EMPA-REG OUTCOME trial.[21] The risk of bone fracture in the pooled empagliflozin group was 3.8%, similar to that in the placebo group (3.9%).[21]

8. Summary and conclusions

The prevalence of type 2 diabetes has been escalating in recent decades. The CV complications created a huge economic 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 anti-diabetic agents, proven to be effective in CV and renal protection. Just in these few years, many RCTs have demonstrated significant reductions in MI, stroke, CV death, all-cause death, HF, and ESRD, in patients with pre-existing CVD. At this very moment, TSOC and the DAROC (Taiwan) have worked together to formulate a treatment consensus for type 2 diabetic patients with 5 different categories of CVD, including HT, CHD, CKD, stroke, and HF. This consensus 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.

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Appendix

Conflicts of Interest

Chern-En Chiang has received honorarium from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi.

Tzung-Dau Wang has received honorarium from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Cordis, Daiichi-Sankyo, GSK, Medtronic, MSD, Novartis, Pfizer, Sanofi, and Takeda.

Hung-I Yeh has received honorarium from AstraZeneca, Boehringer Ingelheim, and Tanabe.

Kuan-Cheng Chang has received honorarium from AstraZeneca, Boehringer Ingelheim, Takeda, and Tanabe.

Kang-Ling Wang has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Orient EuroPharma, and Tanabe.

Ting-Hsing Chao received honorarium from AstraZeneca, MSD, and Novartis.

Wayne Huey-Herng Sheu acted as Advisor and/or Speaker for AstraZeneca, Bayer Health Care, Boehringer Ingelheim Pharmaceuticals., Daiichi-Sankyo, Eli Lilly and Company, MSD, Mitsubishi Tanabe Pharma Corporation, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Sanofi, Takeda Pharmaceutical Company.

Others reported no conflict of interest.

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