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REVIEW ARTICLE

Treatment of diabetes mellitus has borne much fruit in the prevention of cardiovascular disease

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ABSTRACT

Cardiovascular (CV) disease is the most alarming complication of diabetes mellitus (DM), and a strategy aiming at cardiovascular event prevention in diabetes mellitus has long been debated. Large landmark clinical trials have shown cardiovascular benefits of intensive glycemic control as a 'legacy effect' in newly diagnosed type 2 diabetes mellitus. In contrast, we have learned that excessive intervention aimed at strong glycemic control could cause unexpected cardiovascular death in patients who are resistant to treatments against hyperglycemia. It has also been shown that the comprehensive multifactorial intervention for cardiovascular risk factors that was advocated in the current guideline provided substantial cardiovascular event reduction. The impact of classical antidiabetic agents launched before 1990s on cardiovascular events is controversial. Although there are many clinical or observational studies assessing the impact of those agents on cardiovascular events, the conclusions are inconsistent owing to variable patient backgrounds and concomitant antidiabetic agents among the studies. Moreover, most of them were not large-scale, randomized, cardiovascular outcome trials. In contrast, GLP-1RA (glucagon-like peptide-1 receptor agonist) and SGLT2 (sodium-glucose cotransporter 2) inhibitors have demonstrated undeniable cardiovascular benefits in large-scale, randomized, controlled trials. Whereas GLP-1RAs decrease atherosclerotic disease, especially stroke, SGLT2 inhibitors mainly prevent heart failure. SGLT2 inhibitors are superior to GLP-1RAs with respect to hard renal outcomes. Therefore, it can be said that drugs such as GLP-1RAs and SGLT2 inhibitors that prevent cardiovascular events, in addition to their glucose-lowering effect, are incredible novel tools that we have gained for use in diabetic treatment.

INTRODUCTION

The International Diabetes Federation reported that there were 424.9 million people with diabetes mellitus (DM) aged 20–99 years worldwide in 2017, which was 281% higher than in 2000[1]. Moreover, the number of patients is estimated to increase to 629 million by 2045. Diabetes mellitus is a life-threatening disease and accounts for 11.3% and 14.1% of all-cause mortality in the world and South-East Asia including Japan, respectively, among adults aged 20–79 years[2]. The risk of cardiovascular (CV) disease such as myocardial infarction (MI) or cerebral infarction is substantially increased in patients with type 2 diabetes mellitus compared with normoglycemic subjects[3–5], which is the principal cause of death[5–8]. In contrast, diabetic care with lifestyle interventions and pharmacological approaches has decreased cardiovascular events and all-cause mortality over the past few decades[9–12].

Improvement of the prognosis is mostly attributed to lessons learned from large-scale, randomized, controlled trials (RCTs). In this review, the RCTs that assessed the effects of intensified glycemic intervention or multifactorial interventions for cardiovascular risk factors on cardiovascular outcomes in type 2 diabetes mellitus are described, and the strategy aimed at cardiovascular event prevention is discussed. Moreover, the impact of individual antidiabetic agents on cardiovascular outcomes is also summarized. Large-scale RCTs aiming at cardiovascular event prevention by classical antidiabetic agents developed before the launch of DPP-4 (dipeptidyl peptidase-4) inhibitors have been limited. In contrast, newer antidiabetic

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agents, GLP-1RAs, and SGLT2 inhibitors, have provided undeniable cardio-renal benefits in large-scale RCTs[13–17], leading to changes in diabetic treatment strategies.

PHARMACOLOGICAL INTERVENTIONS AND CV OUTCOMES

It has been a matter of debate whether intensive glycemic control could improve macrovascular diabetic complications. The UKPDS (United Kingdom Prospective Diabetes Study) compared intensive therapy involving insulin, sulfonylurea (SU), or metformin with conventional therapy of diet alone in patients with newly diagnosed type 2 diabetes mellitus. HbA1c was significantly reduced by 0.9% in the intensive therapy with insulin or sulfonylurea group than in the conventional therapy group. Insulin or sulfonylureas had numerically better, but not statistically significantly, results for myocardial infarction compared with diet alone during an average follow-up of the first 10 years (Table 1)[18]. In contrast, intensive therapy with metformin significantly reduced myocardial infarction and all-cause mortality in overweight patients compared with conventional therapy[19]. A post-trial of 10 years, however, showed that the original intensive therapy with insulin or sulfonylureas also reduced myocardial infarction and all-cause mortality significantly, despite the difference in HbA1c disappearing between the intensive and conventional therapies[20]. Thus, the UKPDS demonstrated that early and sustained glycemic control led to fewer future complications, the so-called 'legacy effect'.

In addition to the UKPDS, there were several representative RCTs assessing cardiovascular outcomes with intensive glycemic control[21–23] (Table 1). The patients enrolled in those trials had longstanding type 2 diabetes mellitus diagnosed at least 7 years earlier and were treated with combination therapies such as sulfonylureas, insulin, or thiazolidinedione (TZD), in contrast to the UKPDS in which patients were enrolled within 1 year after diagnosis and received pharmacological monotherapy. In the VADT (Primary goal of the Veterans Affairs Diabetes Trial), no significant differences in cardiovascular events were noted between intensive glycemic and conventional therapies in patients with type 2 diabetes mellitus during a median follow-up of 5.6 years (Table 1)[21]. Whereas a statistically significant reduction of cardiovascular events was seen with intensive therapy during a follow-up trial of 9.8 years, such a finding disappeared during a 15-year follow-up[24,25]. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, intensive glycemic therapy did not reduce cardiovascular events compared with conventional therapy during a median follow-up of 5 years[22]. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, near-normal glycemic control with intensive therapy rather increased cardiovascular mortality and all-cause mortality compared with standard glycemic control during a median intervention period of 3.7 years, although a significant reduction of non-fatal myocardial infarction was observed with intensive therapy (Table 1)[23,26]. *Post hoc* analysis of the ACCORD trial showed that all-cause mortality was particularly increased in patients who had high HbA1c levels at baseline and were resistant to intensive therapy[27]. Whether the inconsistency of cardiovascular benefits in the aforementioned four trials (UKPDS, VADT, ADVANCE, and ACCORD) could be attributed to variables of the demographic characteristics of patients, duration of follow-up, antidiabetic agents used, and their combinations, or the degree or speed of glucose-lowering among those trials is uncertain. In a meta-analysis including those trials, intensive glycemic treatment was associated with a significant reduction of non-fatal myocardial infarction by 17% and coronary artery disease (non-fatal and fatal myocardial infarction) by 15% compared with standard treatment during an average follow-up of 5 years, which suggested the cardiovascular benefits of intensive glucose-lowering[28].

In comparison with trials targeting the single risk factor of hyperglycemia, the Steno-2 trial was designed to provide a multifactorial intervention for cardiovascular risk factors with pharmacological approaches in patients with type 2 diabetes mellitus and microalbuminuria[29–31] (Table 2). Multifactorial intensive therapy significantly reduced HbA1c, LDL-C, triglyceride, and systolic blood pressure (BP)/diastolic BP levels from baseline compared with conventional therapy, which led to a 53% decrease in primary events and a 61% decrease in progression to macroalbuminuria with multifactorial intensive therapy during a mean follow-up of 7.8 years[29]. Moreover, those cardiovascular and renal benefits persisted during a mean follow-up of 13.3 years despite the difference in risk factors disappearing between the two therapies[30]. It was estimated that original intensive therapy resulted in a 7.9 year longer lifespan than conventional therapy over 21.2 years of follow-up[31]. Of note, the number of patients enrolled in the Steno-2 trial (n = 160) was much smaller than that of the recent studies described below (Table 2).

In recent RCTs, there were not as many cardiovascular events as before, because the quality of the treatment delivered to the patients has improved. Thus, differences in cardiovascular events between intensive and conventional therapies are not easy to discern. The ADDITION-Europe (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) trial was conducted in patients with newly diagnosed type 2 diabetes mellitus (Table 2). Although the reductions of HbA1c, BP, and LDL-C levels from baseline were greater with intensive treatment than with conventional treatment, those risk factors were well managed even with the conventional treatment that was implemented based on the current guidelines. Multifactorial intensive treatment reduced cardiovascular events by 17% compared with conventional therapy during a mean follow-up of 5.3 years, but the difference was not statistically significant[32]. A follow-up trial for 9.61 years also confirmed no significant difference in cardiovascular events between the two treatments (Table 2)[33]. When the incidence of cardiovascular events with conventional treatment was compared between the trials, the rates of myocardial infarction and

Table 1 | Intensive glycemic control trials

	UKPDS (SUs-insulin)	UKPDS (Metformin)	ACCORD	ADVANCE	VADT
Age, year	53.2 (53.4)	53 (53)	62.2 (62.2)	66	60.5 (60.3)
Number	3867	753	10251	11140	1791
Median study duration, year	10.0	10.7	3.7	5.0	5.6
DM duration, year	Newly diagnosed	Newly diagnosed	Median 10.0 (10.0)	Mean 7.9 (8.0)	Mean 11.5 (11.5)
History of CV disease, %	7.5	7.5	35.6 (34.8)	32.2 (32.3)	39.8 (40.1)
BW [baseline], kg	77.3 (78.1)	87 (87)	93.5 (93.6)	78.2 (78.0)	97.2 (97.2)
BW increase [during follow-up], kg	+3.1†	No increase	3.1 kg increase at 3 years weight gain >10 kg: 27.8% (14.1%)†	0.7 kg increase†	4.2 kg increased‡
BMI [baseline]	27.5 (27.8)	31.6 (31.8)	32.2 (32.2)	28 (28)	31.3 (31.2)
HbA1c [baseline], %	Mean 7.09 (7.05)	Mean 7.3 (7.1)	Median 8.1 (8.1)	Mean 7.48 (7.48)	Mean 9.4 (9.4)
HbA1c [during intervention], %	Median 7.0 (7.9)†	Median 7.4 (8.0)	Median 6.4 (7.5)	Mean 6.49 (7.24)†	Median 6.9 (8.4)
Hypoglycemia	Increase	Increase	Increase†	86% increase†	Increased†
Primary outcome	Aggregate endpoints First occurrence of (i) any diabetes-related endpoints (ii) diabetes-related death (iii) all-cause mortality	Aggregate endpoints First occurrence of (i) any diabetes-related endpoints, (ii) diabetes-related death, and (iii) all-cause mortality	A composite of (i) non-fatal MI (ii) non-fatal stroke (iii) CV death	A composite of (i) macrovascular events (CV death, non-fatal MI or non-fatal stroke) (ii) microvascular events (new or worsening nephropathy or retinopathy)	A composite of CV events (MI, stroke, CV death, heart failure, surgical intervention for cardiac, cerebrovascular, or peripheral disease, inoperable coronary artery disease, and amputation for ischemic gangrene)
Primary outcome	(i) 12% decrease‡ (ii) 10% decrease (iii) 6% decrease	(i) 32% decrease‡ (ii) 42% decrease‡ (iii) 36% decrease‡	10% decrease	10% decrease† Major CV events: 6%	12% decrease
CV death	–	–	35% increase‡	12% decrease	32% increase
MI	16% decrease	39% decrease‡	Non-fatal: 24% decrease‡ Fatal MI: 63% increase	Non-fatal MI: 2% decrease	18% decrease
Stroke	11% increase	41% decrease	Non-fatal: 6% increase	Non-fatal stroke: 2% increase	22% decrease
Death from any cause	6% decrease	36% decrease‡	22% increase‡	7% decrease	7% increase
Albuminuria	Significant decrease	No significant decrease	Microalbuminuria: 21% decrease† Macroalbuminuria: 31% decrease†	Microalbuminuria: 9% decrease‡ Macroalbuminuria: 30% decrease†	Any increase in albuminuria‡ Macroalbuminuria: decrease†
Follow-up trial, y after intervention start	16.8	17.7	4.8	None	9.8
CV events	MI: 15% decrease‡ Stroke: 9% decrease	MI: 33% decrease† Stroke: 20% decrease	Non-fatal MI: 19% decrease‡ Fatal MI: 68% increase		17% decrease‡
CV death	–	–	–		12% decreased
Death from any cause	13% decrease†	27% decrease†	–		5% increased

Values of the conventional group are shown in parentheses. †$P < 0.01$ vs the conventional group. ‡$P < 0.05$ vs the conventional group. BMI, body mass index; BW, body weight; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction.

Table 2 | Multifactorial intervention trials

	Steno-2	ADDITION-Europe	J-DOIT3
Age, year	54.9 (55.2)	60.3 (60.2)	58.9 (59.1)
Number	160	3057	2542
Study duration, year	Mean 7.8	Mean 5.3	Median 8.5
DM duration, year	Median 5.5 (6.0)	Newly diagnosed	Mean 8.58 (8.47)
History of CV disease, %	MI; 7.5 (2.5), stroke 2.5 (3.8)	MI: 6.8 (6.1), stoke 2.9 (1.9)	12 (11)
SBP [baseline], mmHg	146 (149)	148.5 (149.8)	133.5 (134.1)
DBP [baseline], mmHg	85 (86)	86.1 (86.5)	79.3 (80.0)
SBP [during intervention], mmHg	131 (146)§	134.8 (138.1)¶	123 (129)†
DBP [during intervention], mmHg	73 (78)§	79.5 (80.7)¶	71.5 (74.4)†
Mean HbA1c [baseline], %	8.4 (8.8)	7.0 (7.0)	8.01 (7.98)
Mean HbA1c [during intervention], %	7.9 (9.0)§	6.6 (6.7)¶	6.79 (7.20)†
LDL-C [baseline, mg/dL	133 (137)	131.5 (135.3)	125.5 (125.6)
LDL-C [during intervention], mg/dL	83 (126)§	81.2 (88.9)¶	85.5 (103.7)†
Primary outcome	A composite of CV death, non-fatal MI, CABG, percutaneous coronary intervention, non-fatal stroke, amputation for ischemia, or surgery for peripheral atherosclerotic artery disease	A composite of first CV event (CV death, non-fatal MI, noon-fatal stroke, revascularization, and nontraumatic amputation)	A composite of all-cause mortality, MI, CABG, PTCA, stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting
Primary outcome	53% decrease†	17% decrease	19% decrease
Non-fatal MI	–	30% decrease	Coronary events: 14% decrease
Non-fatal stroke	–	2% decrease	Cerebrovascular events: 58% decrease†
CV death	–	12% decrease	–
Death from any cause	–	9% decrease	1% increase
Nephropathy	61% decrease†	–	32% decrease†
Follow-up trial, year after intervention start	13.3	9.61	Ongoing
CV events	59% decrease†	13% decrease	
CV death	57% decrease‡	3% decrease	
Death from any cause, %	46% decrease‡	10% decrease	
Nephropathy	56% decrease†	UACR: 7% decrease	

The values of the conventional group are shown in parentheses. †$P < 0.01$ vs conventional group. ‡$P < 0.05$ vs conventional group. §$P < 0.01$ for comparison of the changes from baseline between intensive and conventional groups. ¶Significant for comparison of the changes from baseline between the intensive and conventional groups. CABG, coronary artery bypass graft; CV, cardiovascular, DBP, diastolic blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; UACR, urine albumin-creatinine ratio.

all-cause mortality were 3.5% and 15.9%, respectively, in the ADDITION-Europe trial, with corresponding rates of 16.5% and 18.7% in the UKPDS[18]. Thus, the current guideline-based conventional treatment was successful in preventing macrovascular events.

The J-DOIT3 (Japan Diabetes Optimal Treatment study for three major risk factors of cardiovascular diseases) trial was recently conducted to assess the effectiveness and safety of aggressive multifactorial intervention for cardiovascular events[34] (Table 2). Similar to the ADDITION-Europe trial, the management of cardiovascular risk factors in conventional therapy in the J-DOIT3 trial was better than that of conventional therapy in the Steno-2 study (Table 2). Thus, the incidence of coronary events and all-cause mortality were very small in the J-DOIT3 trial. Nevertheless, multifactorial intensive therapy was associated with a 19% decrease in the primary composite outcomes, though this was not significant, compared with conventional therapy during a median follow-up of 8.5 years (Table 2). A *post hoc* analysis of the primary outcome showed decreased cerebrovascular events by 58% ($P = 0.042$) with multifactorial intensive therapy. A follow-up study of the J-DOIT3 trial is now underway, and it will be of interest to see whether it will confirm the 'legacy effect'.

The benefits of intensive glycemic control on cardiovascular events have been debated over the past few decades, establishing its efficacy from a long-term perspective. On the other hand, comprehensive multifactorial intervention for cardiovascular risk factors is a more effective strategy for successfully preventing macrovascular complications compared with intensive glycemic control.

CLASSICAL ANTIDIABETIC AGENTS

The number of large-scale RCTs designed to assess cardiovascular outcomes with use of classical antidiabetic agents is limited, unlike with DPP-4 inhibitors, GLP-1RAs, or SGLT2 inhibitors.

Insulin

Many case-control or epidemiological studies generally demonstrated worse cardiovascular outcomes in patients with type 2 diabetes mellitus treated with insulin than with other antidiabetic agents[35–37]. In a nested case-control study, insulin use alone or in combination with oral antidiabetic agents had a >2.5-fold increase of cardiovascular events compared with no antidiabetic agent use in patients with type 2 diabetes mellitus[36]. Likewise, insulin monotherapy was associated with a 74% increase of three-point major adverse cardiac events (3P-MACE), defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, compared with metformin monotherapy[35]. The cardiovascular mortality increased gradually in proportion to the insulin exposure level[37].

In contrast to the retrospective studies, RCTs showed that insulin had a neutral effect on cardiovascular outcomes. The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial demonstrated that glargine, a long-acting insulin, did not increase 3P-MACE compared with standard care during a median follow-up of 6.2 years in individuals with early diagnosed type 2 diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance (IGT) who had either prior cardiovascular events or cardiovascular risk factors[38]. In addition, DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) showed the non-inferiority of degludec versus glargine with respect to cardiovascular events[39].

Inconsistency of the impact of insulin on cardiovascular events between retrospective studies and RCTs could be associated with differences in the patients' background variables (insulin resistance, duration of diabetes mellitus, and comorbidities), as well as the strategy of insulin administration (type of insulin and target glucose level) with its side effects such as weight gain and hypoglycemia, among the studies.

Metformin

Metformin has been generally recommended for use in type 2 diabetes mellitus as a first-line agent by the American Diabetes Association and European Association for the Study of Diabetes[40]. In the UKPDS, intensive therapy with metformin significantly reduced myocardial infarction by 39% compared with conventional therapy with diet alone in a limited number of overweight patients with newly diagnosed type 2 diabetes mellitus[19]. The benefits of metformin on cardiovascular outcomes compared with glipizide or insulin were also reported[41,42]. Numerous meta-analyses assessed the effects of metformin on cardiovascular outcomes[42–46]. Metformin is generally associated with cardiovascular reduction, but it may be affected by its combination with other antidiabetic agents. The combination of metformin with sulfonylureas may exert a detrimental effect on all-cause mortality compared with each monotherapy[45,46]. Conversely, the combination of metformin with DPP-4 inhibitors showed good effects on cardiovascular outcomes compared with DPP-4 inhibitors alone[47]. The conundrum concerning the association of cardiovascular outcomes with metformin and co-administration of other anti-diabetic agents is still unresolved.

In contrast to its possible cardioprotective effects in type 2 diabetes mellitus, such effects were not observed in non-diabetic individuals. In an RCT in which metformin was administered prior to coronary artery bypass grafting in anticipation of a direct cardioprotective effect, metformin did not reduce myocardial ischemia-reperfusion injury in non-diabetic individuals[48]. Similarly, metformin use did not improve the left ventricular ejection fraction after percutaneous coronary intervention in non-diabetic patients with myocardial infarction[49]. Given that metformin may reduce cardiovascular mortality and morbidity in type 2 diabetes mellitus, the cardioprotective effects of metformin may be mainly attributed to its glucose-lowering action rather than its pleiotropic actions on the tissues, such as vascular endothelial cells or cardiomyocytes[50,51].

Sulfonylureas

Sulfonylureas have commonly been used in clinical practice because of their powerful glycemic efficacy with low cost, although their use is decreasing with the appearance of newer agents such DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors[52]. Sulfonylureas are associated with hypoglycemia and modest weight gain[53], and therefore their safety for cardiovascular outcomes has been contentious[44,54–58]. Numerous meta-analyses have been reported, but conclusions regarding their safety with respect to cardiovascular morbidity and mortality and all-cause mortality are inconsistent.

Concerns regarding the causal link between sulfonylureas and adverse cardiovascular events were partially resolved by two recent large-scale RCTs[59,60]. The TOSCA.IT (Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial) compared long-term cardiovascular outcomes between sulfonylureas (mostly glibenclamide and glimepiride) and pioglitazone in patients with type 2 diabetes mellitus whose conditions were inadequately controlled with metformin monotherapy[59]. The incidence of the primary composite outcome (all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, and urgent coronary revascularization) was similar between sulfonylureas and pioglitazone during a median follow-up of 53.7 months. The CAROLINA (Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Patients with Type 2 Diabetes) trial also demonstrated a non-inferior risk of 3P-MACE in glimepiride compared with linagliptin, a DPP-4 inhibitor, during a mean follow-up of 6.3 years in patients with newly diagnosed type 2 diabetes mellitus who were at high risk for cardiovascular disease[60,61]. Cardiovascular safety may differ among individual compounds[57,58,62–65]; a network meta-analysis showed that gliclazide and glimepiride were preferable to glibenclamide with respect to cardiovascular mortality and all-cause mortality[63].

α-Glucosidase inhibitors

The STOP-NIDDM (Study TO Prevent Noninsulin-Dependent Diabetes Mellitus) trial (n = 1,429) demonstrated that acarbose significantly reduced cardiovascular events by 49% and new onset hypertension by 38% in patients with impaired glucose tolerance compared with placebo during a mean follow-up of 3.3 years[66,67]. Of cardiovascular events, myocardial infarction was particularly prevented. However, only 47 patients had cardiovascular events, and, thus, the study was not powered to draw any conclusion about cardiovascular events. In contrast, in the ACE (The Acarbose Cardiovascular Evaluation) trial (n = 6,552), acarbose did not reduce the risk of cardiovascular events, including cardiovascular death and fatal/non-fatal myocardial infarction, in patients with impaired glucose tolerance and coronary artery disease[68]. The impact of α-glucosidase inhibitors (αGIs) on cardiovascular events in patients with type 2 diabetes mellitus differed between meta-analyses. A meta-analysis of seven RCTs showed that acarbose significantly reduced myocardial infarction by 64% and any cardiovascular event by 35% in patients with type 2 diabetes mellitus[69], although there were concerns regarding a methodological flaw in that meta-analysis[70]. In contrast, a recent meta-analysis of RCTs showed that αGIs (acarbose or miglitol) had neutral effects on all-cause mortality with an unknown impact on MACE due to the lack of RCTs reporting MACE as a primary or as predefined secondary outcomes with event adjudication[71].

Thiazolidinediones

Thiazolidinediones (TZDs) are the ligands for peroxisome proliferator-activated receptors γ (PPARγ) and exert metabolic actions via PPARγ, which regulates gene expression as a nuclear transcription factor. Thiazolidinediones are insulin-sensitizing agents whose action is mediated by the modulation of adipocytokines such as adiponectin[72]. Rosiglitazone was reported to increase myocardial infarction by 43% compared with placebo/comparator agents in a meta-analysis of 42 trials[73]. Cardiovascular death also tended to be increased by rosiglitazone treatment. In contrast, pioglitazone significantly reduced the composite cardiovascular outcome of all-cause mortality, non-fatal myocardial infarction, or stroke by 16% compared with placebo in patients with type 2 diabetes mellitus who had a history of cardiovascular disease in the PROactive study (PROspective pioglitAzone Clinical Trial In macro Vascular Events)[74]. Pioglitazone also slowed the progression of atheroma volume in coronary artery[75] or carotid artery intima-media thickness (IMT)[76] in patients with type 2 diabetes mellitus when compared with glimepiride. Moreover, it has been recently reported that pioglitazone reduced the composite primary outcome of myocardial infarction or stroke in individuals with insulin resistance with a recent history of ischemic stroke or transient ischemic attack[77]. Although those studies indicated the benefits of pioglitazone with respect to atherosclerotic cardiovascular events, it should be noted that pioglitazone was associated with the incidence of heart failure (HF)[74,78].

Meglitinides

The number of studies assessing cardiovascular outcomes of meglitinides is limited. Repaglinide has been shown to improve postprandial hyperglycemia and regression of carotid IMT compared with glyburide in patients with type 2 diabetes mellitus[79]. In contrast, the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial (n = 9,306) demonstrated the neutral effect of nateglinide on cardiovascular events during a median follow-up of 6.3 years in patients with impaired glucose tolerance with a history of cardiovascular disease or at high risk for cardiovascular disease[80].

The positive association of postprandial hyperglycemia and cardiovascular events in impaired glucose tolerance and type 2 diabetes mellitus is evident[81–83]. However, anti-diabetic agents targeting postprandial glucose excursions, i.e., αGIs and meglitinides, have not shown cardiovascular benefits in RCTs[68,71,80].

NEWER ANTI-DIABETIC AGENTS

Incretin-based therapy

Incretin-based therapy, DPP-4 inhibitors and GLP-1RAs, has provided cardio-renal benefits. Many putative mechanisms have been proposed, including BP-lowering, alteration of plasma lipid metabolism, inhibition of renal sodium reabsorption, anti-inflammatory effect on the vascular bed, and improvement of endothelial dysfunction, among others[84–93].

DPP-4 inhibitors

In agreement with the guidance of the Food and Drug Administration in 2008, large cardiovascular outcome trials have been performed to assess the cardiovascular safety of newer antidiabetic agents, and the first trials were for DPP-4 inhibitors. Whereas cardiovascular safety with respect to 3P-MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) has been shown[94–97], discordant results for hospitalization for HF were observed across DPP-4 inhibitors.

The SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction) 53 trial showed that saxagliptin significantly increased hospitalization for HF by 27% compared with placebo in patients with established cardiovascular disease or at high risk for cardiovascular disease[94]. In contrast to saxagliptin, other molecules of the class, alogliptin, sitagliptin, and linagliptin, have been shown to have a neutral effect on HF in large RCTs[95–97]. A meta-analysis of those trials suggested the overall safety of DPP-4 inhibitors as a class for HF[98,99], but concern regarding HF related to saxagliptin may deserve further investigation[100]. Of note, those RCTs exclusively targeted patients with established cardiovascular disease or at high risk for cardiovascular disease, not necessarily reflecting the patients seen in daily clinical practice. Therefore, it is possible that DPP-4 inhibitors exert cardiovascular benefits in daily clinical practice. Indeed, sitagliptin significantly attenuated the progression of carotid IMT in insulin-treated type 2 diabetes mellitus with no apparent history of cardiovascular disease[101].

With respect to renal outcomes, saxagliptin improved the urine albumin-creatinine ratio (UACR) compared with placebo regardless of baseline ACR levels in the SAVOR-TIMI 53 trial[94,102]. Linagliptin also prevented the progression of albuminuria in the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin) trial, in which 74% of patients had eGFR <60 mL/min/1.73 m^2 and/or UACR >300 mg/g creatinine[97]. In contrast to their preventive effect on incident albuminuria, DPP-4 inhibitors did not reduce hard renal outcomes[103,104]. Because it has been confirmed that intensive glycemic control reduced albuminuria in many RCTs, i.e. UKPDS, VADT, ADVANCE, and ACCORD[105], whether DPP-4 inhibitors could exert clinical renal benefits beyond their glucose-lowering effect is controversial.

GLP-1RAs

Cardio-renal effects have been reported from eight large clinical trials of GLP-1RAs[106–113]. The ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, the first large clinical trial of GLP-1RAs, demonstrated the non-superiority of short-acting exendin-4-based lixisenatide to placebo with respect to a composite endpoint of 3P-MACE (CV death, myocardial infarction, or stroke) plus hospitalization for unstable angina during a median follow-up of 25 months[106]. In contrast, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial showed that liraglutide, a human GLP-1-based molecule, significantly reduced cardiovascular death by 22% and 3P-MACE by 13% compared with placebo during a median follow-up of 3.8 years[107]. The findings for cardiovascular outcomes were inconsistent among the trials. Significant cardiovascular benefits have been shown for liraglutide, albiglutide, injectable semaglutide, and dulaglutide, but not lixisenatide, exenatide, and oral semaglutide. Thus, factors affecting cardiovascular outcomes, including drug-specific properties, i.e. use of human GLP-1-based molecules or exendin-4 based agonists, or short- or long-acting formulations, have been debated[114,115]. However, a recent meta-analysis including the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial showed MACE benefits of GLP-1RAs independent of their structure or pharmacokinetic properties[14,113]. GLP-1RAs significantly decreased MACE by 14%, cardiovascular death by 13%, fatal and non-fatal myocardial infarction by 10%, and fatal and non-fatal stroke by 17% compared with placebo[14]. There was no statistically significant heterogeneity in MACE benefits between patients with established cardiovascular disease and those at high risk for cardiovascular disease. Interestingly, the relative risk reduction by GLP-1RAs was greatest in fatal and non-fatal stroke among individual components of 3P-MACE, in contrast to SGLT2 inhibitors that did not significantly reduce stroke. The GLP-1RAs significantly reduced hospitalization for HF by 11%, but this was much smaller than seen with SGLT2 inhibitors.

A recent meta-analysis assessing renal outcomes demonstrated that GLP-1RAs were associated with a significant 21% reduction of the composite renal outcomes, which largely contributed to the prevention of incident macroalbuminuria. In contrast, worsening kidney function defined as either doubling of serum creatinine or at least a 40% decline in eGFR did not differ between GLP-1RAs and placebo[14], which was in contrast to the findings regarding SGLT2 inhibitors for renal outcomes described below.

SGLT2 inhibitors

SGLT2 inhibitors modestly decrease weight and blood pressure and improve lipid profiles, in addition to their glucose-lowering effect[116]. Decreased intraglomerular pressure by the amelioration of activated tubuloglomerular feedback[117], alleviation of renal hypoxia[118,119], and arterial stiffness/vascular resistance[120], blunting of sympathetic nerve system activity[121], and increase

in ketone bodies and erythropoietin[122] have been proposed as mechanisms of cardio-renal protection by SGLT2 inhibitors. A direct action of SGLT2 inhibitors *per se* on cardiomyocytes or coronary artery endothelial cells has also been reported[123–126].

The EMPA-REGOUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose) trial demonstrated that empagliflozin significantly reduced 3P-MACE by 14% (mainly due to the prevention of cardiovascular death by 38%) and hospitalization for HF by 35% compared with placebo in patients with type 2 diabetes mellitus and established cardiovascular disease during a median follow-up of 3.1 years (Table 3)[127,128]. In the following CANVAS Program (Canagliflozin Cardiovascular Assessment Study)[129,130] and DECLARE-TIMI 58 (The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58)[131,132] trials, canagliflozin and dapagliflozin also decreased hospitalization for HF in patients with type 2 diabetes mellitus and established cardiovascular disease or at high risk for cardiovascular disease (Table 3). Because the patients' baseline background characteristics varied among these RCTs, whether cardiovascular benefits were confined to patients with established cardiovascular disease was a concern. Among several meta-analyses for large RCTs[15–17], a more recent meta-analysis demonstrated that SGLT2 inhibitors significantly reduced MACE, myocardial infarction, and cardiovascular death. Though the benefits of MACE and myocardial infarction had no statistically significant interaction with patients with established cardiovascular disease or at high risk for cardiovascular disease, cardiovascular death showed moderate evidence of greater protection in patients with established cardiovascular disease[17]. Inhibition of hospitalization for HF was the most pronounced in cardiovascular events, with a similar benefit in patients regardless of whether they had a history of cardiovascular disease or HF[15,17]. In contrast, there was no effect on stroke, which was in contrast to the findings for GLP-1RAs[14].

The cardiovascular benefits of SGLT2 inhibitors go beyond type 2 diabetes mellitus. Two large RCTs have recently demonstrated the prevention of HF or cardiovascular death in patients with HF owing to reduced ejection fraction (HFrEF) with and without type 2 diabetes mellitus (Table 3)[133–136]. A meta-analysis of these trials demonstrated that dapagliflozin and empagliflozin significantly reduced cardiovascular death by 14% and first hospitalization for HF by 31% in patients with HFrEF compared with placebo, and these cardiovascular benefits were independent of whether the patients had diabetes mellitus[137]. It has also been reported that empagliflozin and sotagliflozin prevented hospitalization for HF in patients with HF with preserved ejection fraction (HFpEF) independent of the presence or absence of diabetes mellitus[138,139]. Therefore, the use of SGLT2 inhibitors is expected to be a novel treatment strategy for HF, independent of whether patients have diabetes mellitus.

With respect to renal outcomes, SGLT2 inhibitors have been shown to prevent hard renal outcomes in addition to incident macroalbuminuria in the aforementioned RCTs (EMPA-REGOUTCOME trial, CANVAS Program, and DECLARE-TIMI 58 trial) (Table 3)[129,131,140]. A meta-analysis demonstrated that SGLT2 inhibitors improved a composite hard renal outcome including worsening eGFR, end-stage renal disease, or renal death, regardless of whether patients had a history of cardiovascular disease[15]. Of note, the majority of cases in those RCTs had relatively preserved renal function[127,129,131]. While patients in those trials had eGFRs that ranged from 74.2 to 85.7 mL/min/1.73 m^2, approximately 80% had no albuminuria or microalbuminuria[15]. Thus, whether the renal benefits of SGLT2 inhibitors were confined to patients with preserved renal function was uncertain. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, however, found that canagliflozin reduced hard renal outcomes in patients with type 2 diabetes mellitus who had an eGFR of 56.2 mL/min/1.73 m^2 with UACR of 927 during a median follow up of 2.62 years[141]. Similarly, the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney disease) trial showed the efficacy of dapagliflozin for hard renal outcomes in patients with CKD who had eGFR of 43.2 mL/min/1.73 m^2 with UACR of 965 during a median follow-up of 2.4 years (Table 3)[142–144]. Moreover, renal benefits did not depend on the presence of type 2 diabetes mellitus or underlying causes leading to CKD such as diabetic nephropathy, ischemia, and hypertension, or glomerulonephritis[143].

As recommended by guidelines from academic societies[40,145–147], the use of GLP-1RAs or SGLT2 inhibitors with proven cardiovascular benefits is appropriate in patients with type 2 diabetes mellitus and established cardiovascular disease or at high risk for cardiovascular disease. Some SGLT2 inhibitors have been shown to reduce HF in patients with HFrEF or HFpEF independent of the presence or absence of diabetes mellitus. Both agents are associated with renal protection, but SGLT2 inhibitors appear to be superior to GLP-1RAs with respect to hard renal outcomes. Combination therapy with both agents would provide additive cardiovascular and renal benefits. In the AMPLITUDE-O trial, efpeglenatide, an exendin-based GLP1RA, reduced MACE and a composite renal outcome in patients with type 2 diabetes mellitus and cardiovascular or renal disease in patients who had already received SGLT2 inhibitors at baseline[113,148].

CONCLUSION

In this review, the RCTs that have been conducted over the past few decades were described, and a strategy aimed at cardiovascular event prevention was discussed. Intensive glycemic treatment prevents cardiovascular disease as a legacy effect from a long-term perspective. However, excessive intervention aiming at strong glycemic control could cause unexpected cardiovascular death in patients who are resistant to treatment against hyperglycemia. Comprehensive multifactorial intervention for cardiovascular risk factors, which is advocated in the current guidelines, has borne much fruit in preventing cardiovascular

Table 3 | Effects of SGLT2 inhibitors on CV and renal outcomes

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-HF	EMPERROR-reduced	DAPA-CKD
Agents	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin	Empagliflozin	Dapagliflozin
Age, year	63.1 (63.2)	63.2 (63.4)	63.9 (64.0)	62.9 (63.2)	66.2 (66.5)	67.2 (66.5)	61.8 (61.9)
Number	7020	10142	17160	4401	4744 (type 2 DM: 1983)	3730 type 2 DM: (1856)	4304 (type 2 DM: 2906)
Median study duration, year	3.1	2.4	4.2	2.62	1.5	1.3	2.4
DM duration, year	57% >10	13.5 (13.7)	11.0 (10.0)	15.5 (16.0)	–	–	–
History of CV disease, %	99.4 (98.9)	64.8 (66.7)	40.5 (40.4)	50.5 (50.3)	–	–	37.8 (37.0)
History of heart failure, %	9.9 (10.5)	13.9 (15.1)	9.9 (10.2)	14.9 (14.7)	100	100	10.9 (10.8)
eGFR, mL/min/1.73 m^2	74.2 (73.8)	76.7 (76.2)	85.4 (85.1)	56.3 (56.0)	66.0 (65.5)	61.8 (62.2)	43.2 (43.0)
UACR, mg/g	26.0 (25.5)	12.4 (12.1)	13.1	923 (931)	–	CKD (+); 15 (16), CKD (–): 36 (36)	965 (934)
eGFR >60%, %	74.1 (74)	79.9	93.0 (92.3)	41.1 (41.1)	59.4 (59.3)	52.0 (51.4)	89.1 (89.8)
eGFR <60%, %	25.9 (26.0)	20.1	7.1 (7.7)	58.9 (58.9)	40.6 (40.7)	47.9 (48.5)	10.9 (10.2)
Normoalbuminuria, %	59.5 (59.2)	69.9 (69.8)	69.0 (69.2)	0.7 (0.7)	–	55.7	–
Microalbuminuria, %	28.5 (28.9)	23.0 (22.0)	23.9(23.9)	11.4 (11.1)	–	33.1	–
Macroalbuminuria, %	10.9 (11.1)	7.1 (8.2)	7.0 (6.8)	87.9 (88.2)	–	10.6	–
Detail of primary outcome	3P-MACE (CV death, non-fatal MI, non-fatal stroke)	3P-MACE (CV death, non-fatal MI, non-fatal stroke)	(i) 3P-MACE (CV death, MI, ischemic stroke) (ii) hospitalization for heart failure or CV death	Doubling Cr, end-stage kidney disease (dialysis, transplantation, eGFR of <15 mL/min/1.73 m^2), renal death, or CV death	Worsening heart failure	(hospitalization or urgent visit for heart failure) or CV death	Hospitalization for worsening heart failure or CV death
≥50% decrease in eGFR, end-stage kidney disease (dialysis, kidney transplantation, eGFR of <15 mL/min/1.73 m^2), renal death or CV death							
Primary outcome	14% decrease†	14% decrease†	(i) 3P-MACE: 7% decrease (ii) 17% decrease‡	30% decrease‡ [3P-MACE (CV death, MI, stroke): 20% decrease†]	26% decrease‡	25% decrease‡	49% decrease‡

Table 3. (*Continued*)

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-HF	EMPERROR-reduced	DAPA-CKD
Non-fatal MI	13% decrease	15% decrease	Fatal/non-fatal MI; 11% decrease	–	–	–	–
Non-fatal stroke	24% increase	10% decrease	Ischemic stroke; 1% increase	Fatal/non-fatal: 23%	–	–	–
CV death Hospitalization for heart failure	38% decrease‡ 35% decrease‡	13% decrease 33% decrease	2% decrease 27% decrease, significant	22% decrease 39% decrease‡	18% decrease CV death or	8% decrease hospitalization for heart failure: 25% decrease‡ Hospitalization for heart failure: 30% decrease Hospitalization for heart failure: 31% decrease‡	19% decrease Composite of CV death or hospitalization for heart failure: 29% decrease‡ Hospitalization for heart failure: 49% decrease
Death from any cause Renal events	32% decrease‡ Progression to	13% decrease	7% decrease macroalbuminuria; 38% decrease‡ A doubling serum Cr accompanied by an eGFR of ≤45 mL/min/1.73 m^2; 44% decrease‡ Renal replacement therapy; 55% decrease†	17% decrease Progression of albuminuria: 27% decrease 40% reduction in eGFR, renal replacement therapy, or renal death: 40% decrease	17% decrease ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, end-stage renal disease (dialysis, kidney	8% decrease transplantation, or eGFR of <15 mL/min/1.73 m^2), or renal death: 47% decrease‡ ≥40% decrease to eGFR <60 mL/min/1.73 m^2: 46% decrease‡ End-stage renal disease: 69% decrease† Renal death: 40% decrease	31% decrease‡ A doubling Cr: 40% decrease‡ End-stage renal disease 32% decrease‡ End-stage kidney disease (dialysis, kidney transplantation, eGFR of <15 mL/min/1.73 m^2), doubling Cr, or renal death: 34%‡

Table 3. (*Continued*)

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA-HF	EMPERROR-reduced	DAPA-CKD
≥50% reduction in eGFR, end-stage kidney disease (dialysis, kidney transplantation, or eGFR of 15 mL/min/1.73 m^2), or renal death: 29% decrease	Mean slope change in eGFR: 73% increase‡ Dialysis, kidney transplantation, ≥40% reduction in eGFR, eGFR of <15 mL/min/1.73 m^2 in patients with baseline eGFR ≥30, or eGFR <10 mL/min/1.73 m^2 in patients with baseline eGFR <30.: 50% decrease	≥50% decrease in eGFR: 47% decrease End-stage renal disease: 36% decrease ≥50% decrease in eGFR, end-stage kidney disease (dialysis, kidney transplantation, eGFR of <15 mL/min/1.73 m^2), death from renal causes: 44% decrease‡					

The values of the conventional group are shown in parentheses. †$P < 0.05$ vs the conventional group. ‡$P < 0.01$ vs the conventional group. Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; β3P-MACE, three-point major adverse cardiovascular events; UACR, urine albumin-creatinine ratio.

diseases in type 2 diabetes mellitus. The efficacy of classical antidiabetic agents for improving cardiovascular outcomes has been reported in various case-control or observational studies, but large-scale, randomized, cardiovascular outcome trials have been limited. In contrast, both GLP1RAs and SGLT2 inhibitors have provided cardiovascular benefits in large-scale RCTs, leading to a paradigm shift beyond glucose control to a broader strategy of comprehensive cardiovascular risk reduction in type 2 diabetes mellitus. Recently, imeglimin and dual glucose-dependent insulinotropic peptide (GIP)/GLP-1RA, tirzepatide, have been developed[149–151]. Imeglimin improves mitochondrial function, which may result in cardiovascular event reduction[152]. Tirzepatide has shown greater effects on weight and glycemia than placebo/active comparators such as selective GLP-1RAs or basal insulin[151]. GIP appears to exert both anti-atherogenic and pro-atherogenic effects in animal studies[153]. Whether these antidiabetic agents will provide cardiovascular benefits independent of their glucose-lowering effect will be interesting to investigate.

DISCLOSURE

The authors declare no conflicts of interest.
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