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Cardiovascular outcome trials of the newer anti-diabetic medications

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ABSTRACT

Concerns of elevated cardiovascular disease (CVD) risk with some anti-diabetic medications warranted phase 4 clinical trials to demonstrate CVD safety of newly marketed anti-diabetic drugs. Although initially designed to evaluate safety, some of these CVD outcome trials (CVOTs) have in fact shown CVD benefits. New medication classes, like glucagon-like peptide 1 (GLP-1) analogues and sodium-glucose co-transporter 2 (SGLT2) inhibitors, have shown reductions in the risk of major adverse cardiovascular events (MACE) including, myocardial infarction, stroke, CV death, and heart failure (HF). Perhaps more importantly, SGLT2 inhibitors demonstrated reduction in the risk of HF hospitalizations, being the first class of anti-diabetic drugs to do so. Conversely, dipeptidyl peptidase 4 (DPP-4) inhibitors did not significantly affect atherosclerotic CVD end-points and some actually increased the risk of HF hospitalizations. Further, the adverse/beneficial CVD effects of these medications may not be class specific. This review focuses on the main results of these CVOTs while highlighting the heterogeneity of CVD end-points within each class and discusses important mechanistic insights and adverse effect profiles.

Contents

Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; BP, Blood Pressure; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Disease Outcome Trials; DM, Diabetes Mellitus; DPP-4, Dipeptidyl Peptidase 4; FDA, Food and Drug Administration; GLP-1, Glucagon-Like Peptide 1; HF, Heart Failure; LV, Left Ventricle; MACE, Major Adverse Cardiovascular Event; MI, Myocardial Infarction; SGLT2, Sodium-Glucose Co-Transporter 2.

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Introduction

Diabetes mellitus (DM) is a metabolic disease with multiorgan involvement. Although the primary perturbation is believed to be blood glucose elevation, diabetes involves a complex interplay of endocrine dysfunction, insulin resistance, lipid abnormalities, inflammation, atherosclerosis, myocardial and renal dysfunction.

DM increases the risk of cardiovascular disease (CVD) by 2–4-fold and its presence in those with CVD is one of the most powerful predictors of adverse clinical outcome.[1] CVD accounts for 60–75% of deaths in persons with DM and is also the leading cause of disability.[2] Much of the morbidity and mortality is from coronary artery disease, cerebrovascular disease, congestive heart failure (HF), peripheral arterial disease, and sudden cardiac death.

Blood glucose reduction has historically been the primary target in DM management and Hb A1C has been accepted as a reasonable surrogate target for DM control. However, Hb A1C reduction does not necessarily go hand in hand with CVD morbidity and mortality reduction. Indeed, hypoglycemic drugs that are efficacious in lowering HbA1C can have net neutral CVD effects and in some instances have shown to cause CV harm.

This paradigm has increasingly become clear with the new CVD outcome trials (CVOTs) where newer DM medications, like glucagon-like peptide 1 (GLP-1) analogues and sodium-glucose co-transporter 2 (SGLT2) inhibitors, even with modest HbA1C reduction, have shown significant CVD benefits.

This article aims to summarize the results and clinical implications of some of the recent CVOTs with newer anti-diabetic drugs. We will present data regarding the safety profile of these new medications and highlight some of their encouraging cardio-protective effects in diabetic patients with pre-existing CVD as well as those at high risk of future CVD events.

Brief historical context of CVOTs

Although, a number of studies in last two decades have demonstrated significant CVD protection with blood pressure (BP) control and lipid lowering, the results of glucose lowering therapies with the traditional hypoglycemic agents have been rather disappointing.[3–9] Intensive glucose control with traditional anti-diabetic drugs reduced micro-vascular events (diabetic nephropathy, retinopathy, and neuropathy), but generally failed to show significant reduction in the risk of macro-vascular events (such as myocardial infarction [MI] and stroke).[3–9] The precise reason for the failure in CVD event reduction remains to be established. It has, however, been suggested that the beneficial effects may have been counterbalanced by hypoglycemia with many of these agents.

Further, the increased risk of HF and concerns about MI with thiazolidinediones (rosiglitazone and pioglitazone) led to heightened awareness of potentially harmful CVD effects of these otherwise effective hypoglycemic agents.[10–12]

In response, the Food and Drug Administration (FDA) and other regulatory agencies mandated all new diabetes drugs to demonstrate CVD safety.[13–15] It was required for all new drugs to demonstrate in the phase-3 clinical trials that their use would not lead to unacceptably high rates of CVD events (upper bound of the 95% confidence interval for major adverse CVD event not to exceed 1.8). Post-approval, a phase-4 CVOT in patients with preexisting CVD would need to further demonstrate a CVD event rate not exceeding the upper bound of the 95% confidence interval of 1.3. In other words, the new medication would need to be non-inferior to the current standard of care over a minimum of 2-year follow-up.

As a result of this mandate, the last decade has seen a steady stream of CVOTs in patients with preexisting CVD or those at high risk of CVD. And, although, these CVOTs were designed to demonstrate safety, some of the trials have shown unprecedented CVD benefit in secondary prevention of CVD events. A summary of the major CVOTs is presented in Table 1.

DPP-4 inhibitors

The GLP-1 is an incretin secreted by the entero-endocrine cells of the intestine in response to food. It binds to pancreatic β-cell receptors and stimulates insulin release, increases glucose sensitivity, and promotes β-cell health. GLP-1 also inhibits glucagon secretion and gastric emptying.[16] Outside the pancreas, the GLP receptor is present in multiple organs including the heart, kidneys, and the nervous system and may have a more diverse role. In DM, GLP-1 is severely reduced resulting in impaired insulinotropic activity and increased insulin resistance. The enzyme DPP-4 promotes the breakdown of incretins.

Mechanism of action

DPP-4 inhibitors prolong the activity of GLP-1 and other incretins by preventing their breakdown.[17] The agents in this class have modest HbA1C reductions, but their appeal lies in that they do not cause hypoglycemia or weight gain.[17]

CVD outcome trials

Three DPP4 inhibitors namely saxagliptin, alogliptin, and sitagliptin have been tested in CVOTs (SAVOR-TIMI 53, EXAMINE, and TECOS respectively).[18–20] None were found to increase adverse CVD events, CVD mortality, or all-cause mortality. Neither was there a signal of CVD benefit.

SAVOR-TIMI 53 evaluated the safety/efficacy of saxagliptin in individuals with known CVD and those at high-risk for CVD and found no difference in the primary outcome of CVD death, MI, or stroke (7.3 vs. 7.2%; $P = 0.99$ for superiority; $P < 0.001$ for noninferiority) at a median follow-up of 2.1 years. EXAMINE looked at the effects of alogliptin in patients with a recent hospitalization for an MI or unstable angina and found no statistical difference in CVD death, MI, or stroke (11.3% vs. 11.8%; $P = 0.32$ for superiority; $P < 0.001$ for noninferiority) at 1.5 years follow-up. TECOS showed no benefit of sitagliptin in patients with preexisting CVD (11.4% vs. 11.6%; $P = 0.65$ for superiority; $P < 0.001$ for non-inferiority) either.

Adverse effects

Hospitalizations for HF were a concern with this class of drugs. SAVOR-TIMI 53 showed an unexpected 27% increased risk of HF hospitalizations (3.5% vs. 2.8%) with saxaglipitin. This adverse effect was not initially apparent with alogliptin in the main report of the EXAMINE study. But a subsequent post-hoc analysis suggested increased HF hospitalizations (2.2% vs. 1.3%) in patients without a history of HF (HR 1·76 [1·07–2·90]) but no increase in those with preexisting HF (1·00 [0·71–1·42]).[21] In 2015, the FDA issued a safety warning for the risk of HF risk with saxagliptin and alogliptin.[22] No signal of increased HF hospitalizations was seen with sitagliptin in TECOS. This group of medications should generally be avoided in ACC/AHA stage A (at risk for HF) patients.

GLP-1 analogues

Mechanism of action

GLP-1 analogues are a class of injectable hypoglycemic drugs that activate the endogenous GLP-1 receptor and exert effects similar to the GLP-1 hormone. They promote glucose dependent insulin release, inhibit glucagon secretion, and delay gastric emptying.[16]

Table 1
Summary of cardiovascular outcome trials.

CVOT	Population Characteristics: Type-2 diabetes mellitus and one of the following:	N	Mean age (y)	Median follow-up (y)	Existing ASCVD (%)	MACE	Hosp for heart failure
DPP4 inhibitors							
Saxagliptin SAVOR-TIMI53	Age ≥ 40 y with CAD, CVA, or PVD. Men ≥55 y or women ≥60 y with hypertension, dyslipidemia, or smoking.	16,492	65	2.1	78	1.00 (0.89–1.12)	1.27 (1.07–1.51)
Alogliptin EXAMINE	MI or UA hospitalization within the previous 15–90 days.	5380	61	1.5	100	0.96 (≤1.16)	1.07 (0·79–1·46)
Sitagliptin TECOS	Age ≥ 50 y with CAD, stroke, or PAD.	14,671	65	3	100	0.98 (0.89–1.08)	1.00 (0.83–1.20)
Linagliptin CARMELINA	High CV risk (CAD, stroke, PVD, and urine-albumin creatinine ratio > 200 mg/g), and/or high renal risk (↓ eGFR and micro- or macroalbuminuria).	6991	66	2.2	57	1.02 (0.89–1.17)	0.90 (0.74–1.08)
GLP1 receptor agonists							
Lixisenatide ELIXA	MI or UA hospitalization within the previous 180 days	6068	60	2.1	100	1.02 (0.89–1.17)	0.96 (0.75–1.23)
Liraglutide LEADER	Age ≥ 50 y with CAD, CVA, PAD, HF, or CKD stage ≥3 Age ≥ 60 y with microalbuminuria/proteinuria, hypertension with LVH, LV dysfunction, or ABI <0.9	9340	64	3.8	81	0.87 (0.78–0.97)	0.87 (0.73–1.05)
Semaglutide SUSTAIN-6	Age ≥ 50 y with CAD, CVA, PAD, HF, or CKD stage ≥3. Age ≥ 60 y with microalbuminuria/proteinuria, hypertension with LVH, LV dysfunction, or ABI <0.9.	3297	65	2.1	83	0.74 (0.58–0.95)	1.11 (0.77–1.61)
Exenatide EXSCEL	CAD, ischemic CVA, ≥50% carotid artery stenosis, or PAD.	14,752	62	3.2	73	0.91 (0.83–1.00)	0.94 (0.78–1.13)
Albiglutide HARMONY	Age ≥ 40 y with CAD, ischemic CVA, ≥50% carotid artery stenosis/procedure, or PAD.	9463	64	1.6	100	0.78 (0·68–0·90)	n/a
Dulaglutide REWIND	Age ≥ 50 y with CAD, ischemic CVA, carotid or PAD, or ≥ 2 of the following: hypertension, dyslipidemia, smoking, or obesity.	9901	66	5.4	31	0.88 (0.79–0.99)	0.93 (0.77–1.12)
SGLT2 inhibitors							
Empagliflozin EMPA-REG	MI, multi-vessel CAD, CAD with ischemia/UA, stroke, or PAD.	7020	63	3.1	100	0.86 (0.74–0.99)	0.65 (0.50–0.85)
Canagliflozin CANVAS	≥30 y with symptomatic CVD. ≥50 y with ≥2 of the following: diabetes for ≥10 years, smoking, hypertension, micro−/macroalbuminuria, HDL < 38.7 mg/dL.	10,142	63	3.6	66	0.86 (0.75–0.97)	0.67 (0.52–0.87)
Dapagliflozin DECLARE–TIMI 58	CAD, CVA, or PAD. Men ≥55 y or women ≥60 y with hypertension, dyslipidemia, or smoking.	17,160	64	4.2	41	0.93 (0.84–1.03)	0.73 (0.61–0.88)

Abbreviations: ABI, ankle brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVA; cerebrovascular accident; HDL, high-density lipoprotein; HF, heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; UA, unstable angina.

Drug effects

GLP-1 analogues have a lasting effect on pancreatic β-cells causing a sustained HbA1C reduction. They also have a low hypoglycemic risk, even in combination with basal insulin.[23] Compared to basal insulin, GLP-1 analogues cause weight loss rather than weight gain.[24] This is partly mediated by delayed gastric emptying leading to appetite suppression. Prolonged use of GLP-1 agonists is shown to reduce BP.[25] Small human studies in patients with HF have shown an improvement in left ventricular (LV) systolic function, exercise capacity, and quality of life indices in diabetic and non-diabetic patients receiving GLP-1 infusion.[26] A small study of patients with acute MI and severely reduced ejection fraction (10 study patients, 11 controls) showed an improvement in regional and global LV function with GLP-1 infusion.[27] In a larger study (105 patients) with ST-segment elevation MI undergoing percutaneous coronary intervention, administration of exenatide at the time of reperfusion increases myocardial salvage as measured by cardiac magnetic resonance imaging.[28] These cardio-protective effects may be mediated via GLP-1 receptors in the heart and endothelium.[29] In small preclinical and human trials, GLP-1 and GLP-1 agonists have demonstrated positive effects on markers like high-sensitivity C-reactive protein, plasminogen activator inhibitor–1, and brain natriuretic peptide.[30] They also reduce triglycerides and free fatty acids.[30,31]

CVD outcome trials

Lixisenatide, liraglutide, semaglutide, exenatide, and albiglutide have been tested in CVOTs (ELIXA,[32] LEADER,[33] SUSTAIN-6,[34] EXSCEL,[35] HARMONY[36] respectively). Initial results of the dulaglutide CVOT are also available (REWIND[37,38]). It is apparent from the results of the published trials that the benefits of GLP1 analogues may not be a class effect. While LEADER and SUSTAIN-6 were able to demonstrate CVD event reduction, the results of ELIXA were not as encouraging, and EXSCEL showed borderline beneficial effects. Subsequent trials HARMONY and REWIND have again shown CVD benefits.

ELIXA showed a neutral CVD effect of the shorter acting lixisenatide (daily injection) added to standard therapy in diabetic patients who had an MI or unstable angina episode in the preceding 6 months.[32] The positive results of the subsequent LEADER trial came as a surprise.[33] In 9340 patients with CVD, followed over 3.8 years, not only was liraglutide (daily injection) non-inferior to placebo, it was superior in reducing the primary composite outcome of CVD death, MI, and stroke (13% vs. 14.9% in placebo; $P = 0.01$). The reduction in the primary end point was driven by significantly lower CVD mortality (4.7% vs. 6%; $P = 0.007$). Moreover, liraglutide reduced all-cause mortality as well (8.2% vs. 9.6%; $P = 0.02$). While there was numerical reduction in MI and stroke rates, this did not reach statistical significance. SUSTAIN-6 ($n = 3297$, 83% with CVD, 2.1 year follow-up), which had similar inclusion criteria as LEADER, also showed composite CVD event reduction (6.6% vs. 8.9%; $P = 0.02$) with semaglutide (weekly injection), which was driven by a significant reduction in strokes (1.6% vs. 2.7%; $P = 0.04$) rather than CVD mortality or MI.[34]

Neither liraglutide nor semaglutide had a significant effect on HF admissions, suggesting a different mechanism of action than SGLT2 inhibitors. Though not completely understood, it has been postulated that these drugs may have more of an anti-atherothrombotic effect. Other

positive effects like BP lowering, weight reduction, and avoidance of hypoglycemia may contribute to improved CVD outcomes.[39]

As mentioned, the CVD benefits of GLP1 agonists are not consistent across this class of medications. EXSCEL trial comparing exenatide (weekly injection) to placebo in DM patients (73% with previous CV disease) did not show a signal of benefit in any of the CVD outcomes.

In 2018, the HARMONY trial reported that in 9463 patients followed over 1.6 years, treatment with albiglutide reduced MACE (7% vs 9%; P = 0.0006).[36] This was primarily driven by a reduction in MI with no statistical differences in the rates of CVD death or stroke. Initial news from the REWIND trial have suggested a reduction in MACE with the use of dulaglutide.[38] Full report of the trial is awaited.

Adverse effects

Gastrointestinal side effects, driven by slowed gastric emptying, are an important consideration while prescribing GLP-1 agonists and may be a reason for non-adherence or discontinuation of the medication.

SGLT2 inhibitors

SGLT2 is a low affinity, high capacity sodium-glucose co-transporter in the proximal renal tubules that is responsible for glucose reabsorption. SGLT2 inhibitors are orally administered drugs that block this receptor, thereby, preventing glucose reabsorption into the blood stream and facilitating elimination of glucose in the urine (glycosuria).

Mechanism of action

Glucose molecule, being highly polar, cannot cross lipid bilayers that form plasma membranes. Sodium-glucose co-transporters actively transport glucose across cell membranes against its concentration gradient, which in turn is facilitated by sodium transport along its electrochemical gradient.[40] In healthy kidneys, nearly all the glucose filtered by the glomeruli is actively reabsorbed in the proximal tubule by sodium-glucose co-transporters (90% by high-capacity SGLT2 and 10% by SGLT1).[41] In DM, elevated filtered glucose loads may surpass the ability of the proximal tubules to reabsorb glucose resulting in glycosuria. SGLT2 inhibitors act by blocking SGLT2 mediated reabsorption of glucose in the proximal tubules resulting in renal elimination of blood glucose.

Drug effects

Elimination of glucose via the SGLT2 inhibition depends on the glycemic load. Higher blood glucose levels cause proportionately greater elimination in the urine and significant glycosuria is avoided in fasting states. Hypoglycemic effects of SGLT2 inhibitors are dependent on renal function. Glycosuria and natriuresis from SGLT2 inhibitors facilitate diuresis, which along with blood glucose reduction causes a loss in body weight. Elimination of sodium and water also reduces BP.[42] Thus, SGLT2 inhibitors can act at multiple levels and can be especially beneficial since DM, hypertension, and obesity frequently co-exist.[43] Apart from CVD benefits modulated through osmotic diuresis, reduction in weight, arterial stiffness, and left ventricular afterload, and overall modulation of the cardio-renal axis, SGLT2 inhibitors also reduce the progression of renal disease and delay the need for dialysis.[44–48] This is a major advantage in DM patients where renal disease is an important cause of progressive morbidity and mortality.

CVD outcome trials

Three SGLT2 inhibitors – empagliflozin, canagliflozin, and dapagliflozin- have been evaluated in clinical trials. EMPA-REG OUTCOME trial evaluated the CV effects of 10 or 25 mg of empagliflozin added to standard therapy in DM patients with known CVD and demonstrated impressive results.[45] The primary composite outcome of CVD death, MI, and stroke occurred less frequently with empagliflozin (10.5% compared to 12.1% in the placebo group; P = 0.04 for superiority). This difference was largely driven by significantly lower CVD death in the treatment group (3.7% vs. 5.9%; P < 0.001) without significant differences in MI or stroke rates. All-cause death was also reduced with empagliflozin (5.7% vs. 8.3%; P < 0.001). Most interestingly, empagliflozin reduced HF admissions by 35% (2.7% vs. 4.1%; P = 0.002). This was a major paradigm shift from the previous hypoglycemic medications that either had no effect or increased HF hospitalizations (rosiglitazone, saxaglipitin). Also, the beneficial CV effects of empagliflozin appeared much earlier than GLP-1 analogues like liraglutide suggesting a prominent hemodynamic rather than anti-atherosclerotic mechanism of action. The robustness of HF outcomes in the EMPA-REG OUTCOME trial have been debated due to the lack of cardiac function and biomarker assessment (such as brain natriuretic peptide) which are otherwise a norm in most heart-failure trials. Additionally, in subgroup analysis, HF hospitalizations were statistically significantly reduced in patients without HF at baseline but not in those with HF.[46] Trials specifically evaluating HF outcomes are now underway.[47] Regardless, prior to these findings, no glucose-lowering drug had shown an improvement in HF outcomes in patients with DM.

Canagliflozin was the second SGLT2 inhibitor to undergo a CV safety trial (CANVAS) and consistent with results of EMPA-REG OUTCOME, showed reduction in HF hospitalization (5.5% vs. 8.7%).[48] Canagliflozin was shown to be superior to placebo in reducing the primary combined outcome of CVD death, MI, and stroke (26.9% vs. 31.5%; P = 0.02), but did not show improvement in any of these outcomes individually. However, the reduction in the HF related outcome was identical to that observed with empagliflozin in the EMPA-REG OUTCOME trial. The recently published CREDENCE trial further evaluated the renal outcomes of canagliflozin over 2.6 years and documented a statistically significant reduction in the composite end-point of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or CVD causes.[49] The reduction of CV death, MI, or stroke (P = 0.01) and hospitalization for heart failure (P < 0.001) was again demonstrated with no statistical difference in CVD death by itself (P = 0.05).

DECLARE–TIMI 58 trial evaluated dapagliflozin for CV safety/efficacy in a randomized, double-blind, placebo-controlled fashion.[50,51] Out of the 17,160 patients with DM, 41% had known CVD and the remaining were at a high-risk for it. Addition of 10 mg of dapagliflozin did not reduce the combined MACE outcome (8.8% vs. 9.4%; P = 0.17 for superiority; P < 0.001 for noninferiority) but did show a statistically significant reduction in the co-primary outcome of death or hospitalization for HF (4.9% vs. 5.8%; P = 0.005 for superiority). This result was primarily driven by a lower HF hospitalization rate (2.5% vs. 3.3%). There was no statistically significant reduction in CVD death, all-cause death, MI, or stroke rate.

Since the three SGLT2 inhibitor CVOTs enrolled progressively more patients for primary prevention (inclusion of patients without preexisting CVD: none in EMPA-REG OUTCOME, 34% in CANVAS, 59% in DECLARE–TIMI 58), a subsequent metanalysis evaluated the CVD effects in those with and without preexisting CVD.[52] In the pooled analysis, SGLT2 inhibitors reduced a composite end-point of MI, stroke, and CVD death in patients with preexisting CVD (0·86 [0·80–0·93]) but not those without CVD (1·00 [0·87–1·16]). Thus, this effect did not necessarily translate to primary prevention populations. Interestingly, however, the 23% reduction in HF hospitalizations and 45% reduction in progression of renal disease was seen across the primary and secondary prevention sub-cohorts. This widens the scope of SGLT2 inhibitors beyond preexisting CVD and suggests that the primary mechanism of CVD benefit with these medications is hemodynamic rather than anti-atherosclerotic (in contrast to GLP1 analogues).

Real-world data

CVD-REAL and CVD-REAL2 are large multinational registries that collected information on DM individuals started on SGLT2 inhibitors. CVD-REAL with data from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom, showed reduced risk of HF hospitalization and death with SGLT2 inhibitors compared to other hypoglycemic drugs in a propensity score matched analysis.[53] In addition to a lower risk of heart failure hospitalization and death, the CVD-REAL2 registry (with patients from South Korea, Japan, Singapore, Israel, Australia, and Canada) demonstrated a lower risk of death MI and stroke.[54] These results suggest that CVD benefits of SGLT2 inhibitors may extend beyond clinical trial population. There is, however, a need for caution in interpreting these registry data as majority of these patients (75% in CVD-REAL2) were on dapagliflozin which did not show statistically significant reductions in stroke and MI in the DECLARE TIMI-58 trial. Some have suggested that the registry data may have been overly optimistic.

Adverse effects

Prescribing physicians must be cognizant of some known adverse effects of SGLT2 inhibitors. Since SGLT2 inhibitors act by inducing glycosuria, superficial genital mycotic infections (especially in women and uncircumcised men) are more common with their use. Their use can also be associated with increased risk of urinary tract infections and diabetic ketoacidosis (rare). Increased amputation and bone fractures with canagliflozin in the CANVAS trial were also concerning. The FDA issued a warning to avoid canagliflozin in patients that may be at a higher risk for amputations.[55] This elevated risk of amputations was not seen in the CREDENCE trial.

Guideline recommendations and clinical considerations

The American Diabetes Association's (ADA) "Standards of Medical Care in Diabetes" for 2018 which includes clinical practice recommendations has recently updated the section on Cardiovascular Disease and Risk Management.[56] It has emphasized that the treatment of patients with diabetes and established atherosclerotic CVD should include an agent that has been proven to reduce major CVD events, alongside lifestyle management and metformin. While metformin remains the drug of choice for monotherapy, the treatment algorithm suggests that for dual therapy, one of the agents that reduce CVD events and mortality should be used. Currently, per guidelines, this agent should be empagliflozin or liraglutide (level of evidence - A). Canagliflozin may be used for the same indication but has received level of evidence C recommendation. In patients on injectable therapy, a GLP-1 agonist may be used as a second line agent in addition to basal insulin.

Lessons learned and future directions

Though initially designed to keep potentially harmful hypoglycemic agents off the market, the CVD safety trials have surprisingly provided clinicians with a new set of anti-diabetic drugs with proven CVD benefit in patients with DM and CVD, thus expanding the field of CVD secondary prevention. New medications like empagliflozin and liraglutide improve not only CVD mortality but also all-cause mortality in DM patients with CVD. The FDA has approved specific labels for both empagliflozin and liraglutide to reduce the risk of CVD death in adults with DM and CVD. Additionally, SGLT2 inhibitors reduce HF hospitalizations. If the results of the ongoing trials with empagliflozin in HF patients prove their utility these drugs can be considered as additional choice for the treatment of HF patients.

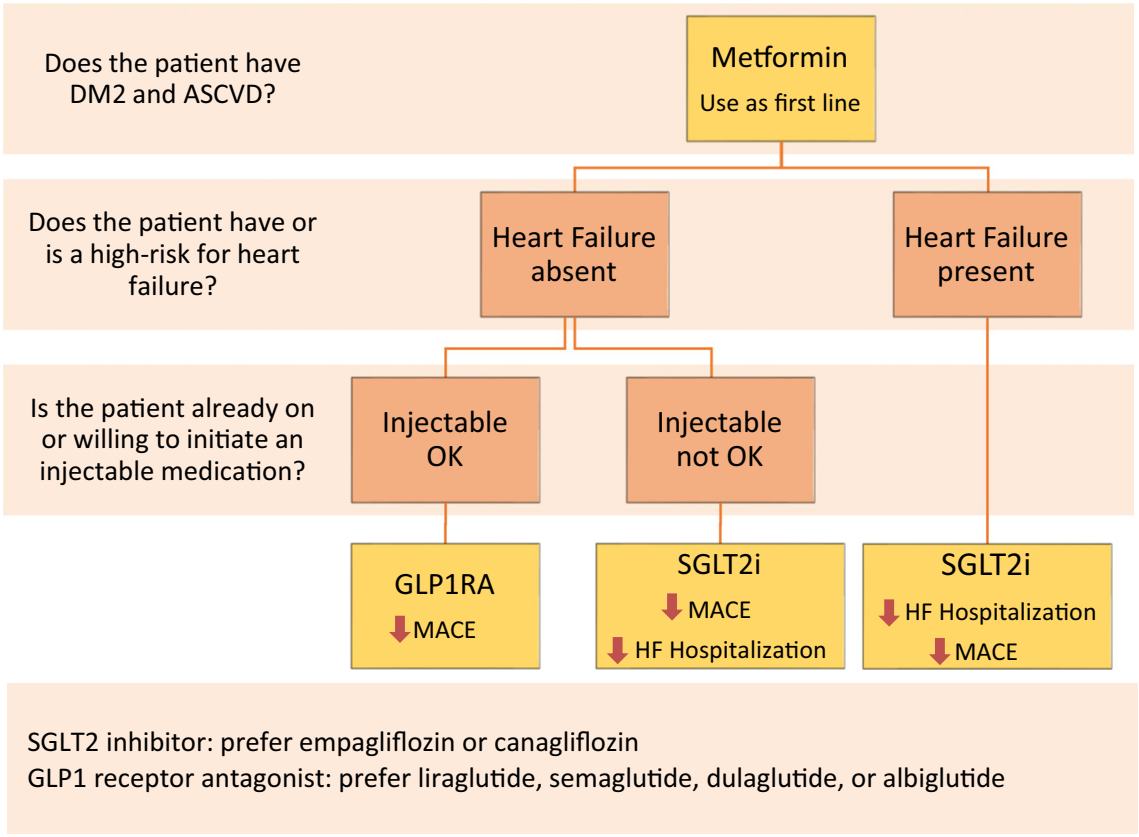

Fig. 1. Suggested algorithm for deciding on the choice of anti-diabetic medication in people with diabetes and atherosclerotic cardiovascular disease. Medication side effect profile and patient preference needs to be taken into account.

The choice of hypoglycemic medication may possibly tip in the favor of the orally administered SGLT2 inhibitors rather than injectables like GLP-1 analogues, though this may be less of a concern in patients already on injectable insulin/insulin analogues. Patients with DM and CVD that are at an increased risk of HF would probably benefit more from an SGLT2 inhibitor. Fig. 1 presents one suggested algorithm for deciding on the choice of therapy. Future trials should aim at providing a comparative assessment between DM medications rather than merely establishing efficacy against placebo.

With the increasing prevalence of obesity and subsequent DM in the United States and around the world, cardiologists are bound to encounter more DM patients in their clinical practice. And though the treatment of DM has traditionally been considered under the purview of primary care or DM specialists, the advent of medications with proven CVD efficacy makes it imperative for the cardiologist not only to be cognizant of but also actively advocate for the prescription for CVD protective DM medications. Indeed, DM care goes well beyond the reduction of glycated hemoglobin as the goal of therapy should be CVD- and all-cause mortality reduction in patients who are at the highest risk for such CVD events, namely those with preexisting CVD.

There is an immediate need for clinicians to embrace the evidence and switch from traditional diabetes medications to newer therapies with proven CVD benefits. Physician education and increasing awareness of these persuasive clinical trial results will increase their comfort level in making this transition.

Disclosures

None.

Declaration of competing interest

None.

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