Chapter 37
Tailoring the Treatment of Type 2 Diabetes Mellitus to the Individual

Patricia R. Peter and Silvio E. Inzucchi

The Impact of Cardiovascular Disease in Patients with Diabetes

Cardiovascular disease (CVD) is a major source of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) [1]. These patients are more likely to develop and die of atherosclerotic cardiovascular disease when compared to their non-diabetic counterparts [2]. People with diabetes also have a 2–5 times higher risk of developing heart failure in their lifetime with a 50% greater risk of mortality after hospitalization for heart failure (HHF) when compared to those without diabetes [3–5]. Fortunately, there have been promising signs of improving cardiovascular outcomes in this population and decreasing burden of disease over time due to an increased focus on aggressive risk factor reduction as well as early and more efficacious cardiovascular interventions [6]. There is also new hope that the burden of cardiovascular disease will continue to decline as some of the newer classes of diabetes medications appear to not only reduce hyperglycemia but also improve cardiovascular outcomes.

Setting a Glycemic Target

The hemoglobin A1c (HbA1c) test has been used for decades to assess the overall quality of glycemic control and has formally been part of the American Diabetes Association's (ADA) diagnostic criteria for diabetes mellitus since 2010 [7]. Given

P. R. Peter · S. E. Inzucchi (✉)
Section of Endocrinology, Yale University School of Medicine,
New Haven, CT, USA
e-mail: patricia.peter@yale.edu; Silvio.Inzucchi@yale.edu

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the clear link between improving glycemic control and a reduction in rates of microvascular complications, an A1c goal of <7% has generally been accepted as striking the appropriate balance between reducing the risk of retinopathy, nephropathy, and neuropathy while avoiding the dangers of hypoglycemia (mainly a concern in those using insulin or insulin secretagogues) [8, 9]. However, the 7% threshold should be viewed as a general goal that is then adjusted based on the circumstances of each individual patient. In particular, factors that should be taken into account when setting a glycemic target include duration of disease, life expectancy, comorbid conditions, established complications, resources and support at home, patient motivation and preference, and the risks of adverse effects related to therapy, especially with regard to hypoglycemia [10]. For example, a more stringent goal of 6–6.5% might be appropriate for a motivated young patient with newly diagnosed diabetes, while a target of <8% (or even slightly higher) would be reasonable for an older individual with advanced comorbidities in whom hypoglycemia risk and quality of life considerations are of more pressing concern than the long-term sequela of hyperglycemia.

With regard to the impact of glucose control on cardiovascular complications in this population, older landmark trials in the field were largely disappointing in that they found no consistent link between tight glycemic control and improved cardiovascular outcomes [11–13]. In fact, the ACCORD trial showed increased cardiovascular mortality in those randomized to more intensive glucose control, possibly (but certainly not conclusively) due to the increased burden of hypoglycemia in that group [11]. Subsequent follow-up studies did demonstrate modestly improved cardiovascular outcomes in the groups whose HbA1c had previously been more stringently controlled, leading to a hypothesis that there was a "legacy" effect that was conferring some protective effect even though their glucose control was at present no different from their counterparts [14, 15]. Given the absence of clear-cut data linking lower glucose levels to a reduced risk of cardiovascular disease, there has recently been a new focus on prioritizing the use of glucose-lowering pharmacological agents with demonstrated cardiovascular benefits—rather than merely lowering A1c to a particular target.

Cardiovascular Implications of Glucose-Lowering Drug Classes

Managing type 2 diabetes in patients with cardiovascular disease typically starts with metformin, an agent that has been used for decades with excellent glucose-lowering efficacy and a clearly established safety profile. Supporting the early use of this agent in patients with cardiovascular disease are the results of some older, small studies that have indicated a potential cardiovascular benefit of this agent [8].

However, if hyperglycemia is inadequately controlled after metformin, the choice of what agent to use next has become increasingly complex as the number of available glucose-lowering drugs has multiplied greatly over the years. Since 2008, the Food and Drug Administration (FDA)-mandated cardiovascular outcomes trials (CVOTs) have proved essential to making these decisions as they have provided us with a wealth of information regarding the safety and potential benefits of many of the available glucose-lowering agents (Table 37.1).

Table 37.1 Summary of major cardiovascular outcomes trial data

Study (drug)	Patient population (*n*)	Mean duration of follow-up (years)	Baseline prevalence of CVD (%)	Significant CV outcomes	Other findings
SGLT2i					
EMPA-REG OUTCOME [1] (empagliflozin)	7020	3.1	99	• 14% RRR in MACE • 34% RRR in HHF or CV death • 38% RRR in CV death • 32% RRR in all-cause mortality • 35% RRR in HHF	• 46% RRR in the renal composite endpoint
CANVAS [2] (canagliflozin)	10,142	3.6	65.6	• 14% RRR in MACE • 33% RRR in HHF	• 40% RRR in the renal composite endpoint • Significantly higher rates of fracture and amputation in the treatment group
DECLARE-TIMI 58 [3] (dapagliflozin)	17,160	4.2	40	• 17% RRR in CV death or HHF • 27% RRR in HHF	• 24% RRR in the renal composite endpoint

(continued)

Table 37.1 (continued)

Study (drug)	Patient population (*n*)	Mean duration of follow-up (years)	Baseline prevalence of CVD (%)	Significant CV outcomes	Other findings
CREDENCE [4] (canagliflozin)	4401	2.6	50.4	• 20% RRR in MACE • 39% RRR in HHF • Borderline significant 22% RRR in CV death	• 30% RRR in primary renal composite outcome • No significant increase in fracture or amputation in the treatment group
VERTIS CV [5] (ertugliflozin)	8238	3.5	>99	• 30% RRR in HHF	
SCORED [6] (sotagliflozin)	10,584	1.3	48.6	• 26% RRR in composite of CV death, HHF, and urgent visits for HF	• Trial ended early due to loss of funding
GLP-1 RA					
LEADER [7] (liraglutide)	9340	3.8	81	• 13% RRR in MACE • 22% RRR in CV death • 15% RRR in all-cause mortality • Borderline significant 14% RRR in MI	• 36% RRR in the renal composite endpoint
SUSTAIN 6 [8] (semaglutide)	3297	2.1	60	• 26% RRR in MACE • 39% RRR in stroke	• 36% RRR in the renal composite endpoint • Higher rates of retinopathy in the treatment group
REWIND [9] (dulaglutide)	9901	5.4	32	• 12% RRR in MACE • 24% RRR in stroke	• 15% RRR in the renal composite endpoint

Table 37.1 (continued)

Study (drug)	Patient population (*n*)	Mean duration of follow-up (years)	Baseline prevalence of CVD (%)	Significant CV outcomes	Other findings
TZD					
PROactive [10] (pioglitazone)	5238	2.9	98	• 16% RRR in the secondary composite outcome of all-cause mortality, non-fatal MI, or stroke • Reports of nonfatal heart failure (unadjudicated) were more common in the treatment group	
IRIS[a] [11] (pioglitazone)	3895	4.8	100	• 24% RRR in stroke or MI • No increase in serous heart failure events (adjudicated) in the treatment group	• 52% RRR in progression to diabetes • Increased bone fractures in the treatment arm
DPP4i					
SAVOR-TIMI 53 [12] (saxagliptin)	16,492	2.1	78	• 27% Relative increased risk in HHF in treatment group	
CAROLINA[b] [13] (linagliptin)	6042	6.3	34.5	• No difference between linagliptin and SU with respect to any CV endpoint	

SGLT2i sodium–glucose cotransporter 2 inhibitors, *CV* cardiovascular, *CVD* cardiovascular disease, *HF* heart failure, *HHF* hospitalization for heart failure, *MACE* major adverse cardiac events, *MI* myocardial infarction, *RRR* relative risk reduction

[a]Insulin resistant, non-diabetic population

[b]Compared to glimepiride

Sodium–Glucose Cotransporter 2 Inhibitors

The sodium–glucose cotransporter SGLT 2 inhibitors (SGLT2i) are the newest class of anti-hyperglycemic agents and some of the first to show positive cardiovascular outcomes in patients with diabetes. These agents lower blood glucose by blocking renal glucose reabsorption in the proximal nephron and by increasing glucose excretion in the urine.

Several agents in this class have demonstrated improvements in the rates of major adverse cardiovascular events (MACE), which is a composite outcome that includes death from cardiovascular causes, non-fatal myocardial infarction (MI), or non-fatal stroke. In the EMPA-REG OUTCOME trial, patients with T2DM and cardiovascular disease who received empagliflozin experienced lower rates of MACE (HR = 0.86 [95% CI 0.74–0.99]; $p = 0.04$) driven primarily by a 38% relative reduction in the risk of CV (cardiovascular) death (HR = 0.62, 95% CI 0.49–0.77; $p < 0.001$) with no significant differences in the rates of MI or stroke between the two groups [16]. In both the CANVAS and the CREDENCE trials, use of canagliflozin was also associated with a lower risk of MACE, with the CREDENCE trial demonstrating a strong trend toward a significant 22% reduction in CV death (HR = 0.78, 95% CI 0.61–1.00; $p = 0.05$) [17, 18]. Dapagliflozin and ertugliflozin were both non-inferior to placebo with respect to MACE in the DECLARE TIMI 58 trial and the VERTIS CV trial, respectively [19, 20]. Thus, the reduction in CV death associated with empagliflozin has not yet been fully reproduced by other agents in this class and it remains to be seen if this is due to a unique property of this agent or more a function of differences in the study populations and trial designs. A meta-analysis by Zelniker et al. found that SGLT2i use reduced the risk of MACE by 11% (HR 0.89 [95% CI 0.83–0.96], $p = 0.0014$), but this effect was only found in patients with preexisting atherosclerotic cardiovascular disease [21]. By contrast, an updated meta-analysis by Arnott et al. including data from the CREDENCE trial with its large number of patients without established CVD found comparable reductions in MACE for those in the primary or secondary prevention setting [22]. In both of these meta-analyses, SGLT2i use was associated with a significant reduction in CV death, but there was a moderate to high level of heterogeneity among the included studies, and this risk reduction was only noted in those with established cardiovascular disease [21, 22]. Importantly, a multinational real-world observational study found that SGLT2i use was associated with reduced risk of death, myocardial infarction, and stroke in those with and without established CVD [23, 24].

The data supporting the use of these agents in patients with regard to heart failure outcomes is even more striking and consistent across all members of this class. Empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin have all been associated with significant reductions in heart failure hospitalizations in patients with T2DM, ranging from a 27 to 39% relative risk reduction across their respective CVOTs [16, 17, 19, 20]. These findings have been consistent and robust across two subsequent meta-analyses and in a large study of SGLT2i use in a real-world clinical setting [21, 22, 25]. With regard to empagliflozin specifically, the Empagliflozin

Comparative Effectiveness and Safety (EMPRISE) study assessed the efficacy and safety of this agent in a real-world setting using several large insurance claims data sources. In their first interim analysis, the investigators identified a 50% reduced risk in hospitalizations for heart failure (HR = 0.50 [95% CI 0.28–0.91]) among patients with T2DM with or without cardiovascular disease who were treated with empagliflozin versus sitagliptin [26].

The improvements in heart failure outcomes in these CVOTs have been so sufficiently compelling as to prompt several investigations into the impact of these agents in the general heart failure population, regardless of diabetes status. For example, the DAPA-HF trial demonstrated a 26% relative risk reduction (HR = 0.74 [95% CI 0.65–0.85]) of the composite outcome of worsening heart failure and death from CV causes in patients with heart failure with reduced ejection fraction (HFrEF) who received dapagliflozin when compared to placebo [27]. The majority of patients in this study who derived benefit from dapagliflozin did not have diabetes, leading to its approval by the FDA for use in HFrEF [27]. Similarly, the EMPEROR-Reduced trial investigated the use of empagliflozin in a population with HFrEF who, on average, had lower EFs and higher levels of natriuretic peptides at baseline than those in the DAPA-HF trial [28]. Echoing the results of the DAPA-HF trial, patients treated with empagliflozin experienced a 25% relative risk reduction (HR = 0.75 [95% CI 0.65–0.86]) in the composite outcome of hospitalization for heart failure and CV death, again regardless of diabetes status [28]. In terms of improving outcomes in patients with HFpEF, 21% of patients in the SOLOIST-WHF trial with EF >50% appeared to experience improved CV outcomes similar to those with reduced EF, but the authors could not draw definitive conclusions about this population given the early termination of the trial and resultant small size of this subgroup [29]. The ongoing DELIVER and EMPEROR-Preserved trials will continue to investigate the potential therapeutic impact of these agents in patients with heart failure with preserved ejection fraction (HFpEF), perhaps further expanding the indications for the use of these agents [30].

SGLT2i have also demonstrated significant promise in reducing the progression of chronic kidney disease, an important comorbidity in patients with type 2 diabetes and cardiovascular disease. Empagliflozin, canagliflozin, and dapagliflozin have all been associated with improvements in clinically important renal outcomes in their respective CVOTs and in subsequent meta-analyses [16–19, 21, 31]. Specifically, the meta-analysis by Neuen et al. found a 33% reduction in the risk of the renal composite outcome of dialysis, transplantation, or death due to kidney disease (RR = 0.67 [95% CI 0.52–0.86]) with the use of SGLT2i when compared to placebo [31]. This effect was consistent across all studies and demonstrated regardless of baseline eGFR (with most studies allowing baseline eGFR as low as 30 mL/min/1.73 m^2) [31]. These renoprotective effects appear to be glucose-independent as the DAPA-CKD trial demonstrated that dapagliflozin conferred significant improvements in renal outcomes regardless of diabetes status [32]. Notably, DAPA-CKD allowed eGFR down to 25 mL/min/1.73 m^2. The ongoing EMPA-KIDNEY study will look at using empagliflozin in a similar population of patients with CKD with and without T2DM, allowing eGFR down to 20 mL/min/1.73 m^2.

A new addition to this class of agents that has a unique mechanism of action is sotagliflozin which acts on the sodium-glucose cotransporter (SGLT)1 in the gut to block glucose absorption there in addition to inhibiting SGLT2 in the kidney. Though it was terminated early due to loss of funding from the sponsor, the SCORED trial (sotagliflozin's CVOT) enrolled over 10,000 T2DM patients with CKD who were at risk for CVD. This trial found a 26% relative risk reduction in the rates of the composite cardiovascular outcome that included CV death, HHF, and urgent visits for HF (HR = 0.74 [95% CI 0.63–0.88]) [33]. Additionally, SOLOIST-WHF initiated sotagliflozin therapy in patients with T2DM being discharged after an episode of decompensated heart failure and found a 33% reduction in the composite outcome of death from CV causes and hospitalizations and urgent visits for heart failure when compared to placebo (HR = 0.67 [95% CI 0.52–0.85]) [29]. A total number of 6.1–8.5% of patients on sotagliflozin experienced diarrhea compared to 3.4–6% of patients in the placebo groups across these two trials, an adverse effect likely related to sotagliflozin's known actions on the gut. Sotagliflozin is not yet marketed in the USA.

Since the CV benefits of these agents occur irrespective of glucose-lowering, and these effects occur within a few weeks after treatment initiation, their modest positive impact on body weight, blood pressure, and lipids is insufficient to explain their beneficial impact on CV outcomes. Instead, there has been some focus on the diuretic properties of these agents, and how they might confer more benefits than the loop diuretics that are typically used in patients with heart failure. While use of loop diuretics leads to reflexive activation of neurohormonal pathways that attempt to preserve intravascular volume, SGLT2i-induced natriuresis does not appear to lead to this potentially deleterious response [34]. This is perhaps because unlike loop diuretics, SGLT2i acts at the proximal tubule to increase sodium delivery to the macula densa, thereby blunting activation of the sodium-retaining pathways that lead to loop diuretic resistance and may contribute to HF progression [34]. Additionally, SGLT2i may alter energy metabolism at the level of the myocardium by increasing ketone production which could perhaps serve as a more efficient fuel source for the heart, impact myocardial sodium and calcium handling to correct dysregulated whole-body sodium homeostasis, or act on cardiac fibroblasts and adipokines to reduce cardiac fibrosis and inflammation [35]. Using cardiac MRI data, the EMPA-HEART CardioLink-6 and the SUGAR-DM-HF trials found that even a short duration of empagliflozin therapy (i.e., 6–9 months) led to improvements in different parameters of LV function such as LV indexed mass and end-systolic and end-diastolic indexed volumes, suggesting SGLT2 inhibition might promote reversal of deleterious CV remodeling [36, 37].

As would be expected given their mechanism of action, the most common side effect of these agents is polyuria. There is also an increased risk of genital mycotic infections that are typically easily treatable with conventional topical or oral therapies. However, if such infections are recurrent, the drug may need to be stopped. While conceivably linked to urinary tract infections (UTIs) and their complications of pyelonephritis and urosepsis, no imbalance in such events has been observed in most of the large outcomes trials. Of course, those with prior history of severe UTIs,

those with indwelling catheters, or those who retain renal stones could potentially be at higher risk of infections, and so avoiding these agents in these patients may be advisable. Fournier's gangrene has been reported in post-marketing surveys, but these events are too rare to assess in clinical trials and a causative link to SGLT2 inhibitors remains uncertain. However, avoiding the drugs in those at greatest risk for this severe form of fasciitis is logical. Patients treated with these agents are also at increased risk of diabetic ketoacidosis (DKA) despite normal or only mildly elevated serum glucose levels (the so-called euglycemic DKA). This complication was first revealed in the off-label used of SGLT2 inhibitors in patients with type 1 diabetes, but DKA can rarely occur in those with type 2 diabetes as well, especially in sick individuals already on insulin whose insulin dose has been drastically reduced. Since the drugs, as mentioned previously, do increased ketone production, which is further enhanced in the fasted state and when insulin doses are decreased, they should be stopped at least 3 days prior to any surgical procedure. The CANVAS trial demonstrated an association between canagliflozin use and an increased risk of lower extremity amputations, but this association has not been noted with other agents in this class [17]. Subsequent clinical trial and observational data on canagliflozin has shown an inconsistent association with amputation risk, leading the FDA to remove its previous black box warning about this while recommending ongoing monitoring for this potential complication [18, 38, 39]. Although these tend to be costly agents, aside from the beneficial cardiovascular implications, other benefits include their low hypoglycemia risk, promotion of modest weight loss, minor improvements in blood pressure and lipids as well as their previously discussed robust renoprotective effects [21, 31].

GLP-1 Receptor Agonists

The glucagon-like peptide 1 receptor agonists (GLP-1 RA) activate the receptor for the endogenous incretin GLP-1 and improve glucose homeostasis in several ways. These mostly injectable medications stimulate glucose-dependent insulin secretion while indirectly improving insulin sensitivity by decreasing appetite centrally and promoting weight loss. They also inhibit glucagon secretion and thereby suppress endogenous (mainly hepatic) glucose production. Finally, and to a more variable degree, they slow gastric emptying, adding to a sensation of satiety.

Several members of this class have been shown to improve major cardiovascular outcomes. In the first of these, the LEADER trial, liraglutide use was associated with a 13% reduction in MACE (HR = 0.87 [95% CI 0.78–0.97]) and 22% lower risk of CV death (HR = 0.78 [95% CI 0.66–0.93]) in patients with T2DM who were at high risk for CVD [40]. A post hoc analysis of this data found that improvements in MACE were only noted in those with prior CV events or established atherosclerotic cardiovascular disease with essentially neutral effects in those with CV risk factors alone [41]. In the SUSTAIN 6 trial, weekly semaglutide was found to reduce the risk of MACE by 26% (HR = 0.74 [95% CI 0.58–0.95]) compared to placebo

though there was no significant reduction in CV death [42]. Instead, this improvement in MACE was driven largely by a 39% relative risk reduction in non-fatal stroke (HR = 0.61 [95% CI 0.38–0.99]) [42]. The CVOT of the only oral GLP-1 RA, a different formulation of semaglutide, showed non-inferiority to placebo with regard to the primary composite outcome of CV death, non-fatal MI, or non-fatal stroke, but there was a significant risk reduction when the secondary outcomes of CV mortality and all-cause mortality were examined individually when compared to placebo [43]. As a result, when the FDA considered this data combined with that from SUSTAIN 6, it approved injectable (though not oral) semaglutide for reduction of MACE in patients with T2DM in the secondary prevention setting. Following a similar pattern to injectable semaglutide, weekly dulaglutide in the REWIND trial was associated with a 12% relative risk reduction in MACE (HR = 0.88 [95% CI 0.78–0.99]) with no impact on CV death but again driven by a 24% risk reduction in non-fatal stroke (HR = 0.76 [95% CI 0.61–0.95]) [44]. Unlike the other GLP-1 RA CVOTs, only a minority of patients in the REWIND trial had established CVD, so the results of this study suggest the benefits of this drug class extend to a primary prevention population. Albiglutide, another weekly injectable, was also associated with improved cardiovascular outcomes in patients with type 2 diabetes and CVD, but this medication was subsequently withdrawn from the market for financial reasons [45]. Exenatide's weekly formulation and daily lixisenatide demonstrated cardiovascular safety when compared to placebo, but there were no improvements in CV outcomes with use of these members of this drug class [46, 47].

Several meta-analyses have further investigated the cardiovascular benefits of this class of agents. In their review of the data from all the available GLP-1 RA CVOTs, Kristensen et al. found that GLP-1 therapy led to a 12% reduction in MACE (HR = 0.88 [95% CI 0.82–0.94]) due to significant reductions in all the component outcomes including cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction [48]. There was also a small reduction in heart failure hospitalizations that was surprising as this had not been noted previously with these agents individually [48]. These agents were found to be cardioprotective regardless of baseline cardiovascular status, but the authors caution that the data is not robust enough to strongly recommend the use of these agents in the primary prevention setting [48]. With regard to stroke outcomes, the neuroprotective findings of the SUSTAIN 6 and REWIND trials have been supported by data from subsequent meta-analyses [42, 44]. Kristensen et al. found that treatment with a GLP-1 RA led to a 16% relative risk reduction (HR = 0.84, [95% CI 0.76–0.93]) in fatal or non-fatal stroke [48]. Similarly, another meta-analysis that focused more specifically on the impact of GLP-1 RA on stroke outcomes observed a 15% reduction in the risk of non-fatal stroke (HR = 0.85 [95% CI 0.76–0.94]), 19% reduction in fatal stroke (HR = 0.81 [95% CI 0.62–1.08]), and 16% reduction in total stroke (HR = 0.84 [95% CI 0.76–0.93]) with no heterogeneity across the GLP-1 RA CVOTs [49]. There was no association between the extent of A1c lowering or body weight reduction and these favorable outcomes [49]. Of note, however, an exploratory analysis of the REWIND study found that this stroke-reduction benefit only occurred in

those with ischemic stroke and that A1c reduction accounted statistically for about half of this beneficial effect [50].

The CV benefits that result from GLP-1 RA use are likely due to a variety of mechanisms. Use of GLP-1 receptor agonists leads to amelioration of several traditionally important cardiometabolic risk factors such as hyperglycemia, weight, blood pressure, and lipids which are known to be impactful on long-term CV outcomes. In fact, a mediation analysis of the LEADER trial identified A1c as the primary significant mediator of the improved cardiovascular outcomes associated with liraglutide use, implying that glucose control was an important driver of improved CV outcomes with this agent [51]. However, the cardiovascular benefits observed with this class of agents occur relatively rapidly (i.e., often within 1–2 years) suggesting that risk factor modification alone cannot sufficiently explain the benefits noted with this class. Several other potential mechanisms have been proposed invoking a direct effect of these agents on the cardiovascular system through improvements in endothelial cell function and reduction of vascular inflammation, slowing the progression of atherosclerotic plaque formation in subclinical atherosclerotic disease [52, 53]. With regard to the beneficial impact of these agents on stroke outcomes, pre-clinical trials have observed reductions in infarct volume after treatment with these agents, primarily mediated by decreased neuroinflammation, oxidative stress, and apoptosis, which limits the extent of neuronal damage after an ischemic insult [54, 55].

Of all the currently available glucose-lowering therapies, the GLP-1 RAs are associated with the most significant and consistent weight loss benefit. In fact, liraglutide at a dose of 3.0 mg per day (higher than the recommend anti-hyperglycemic dose) is FDA-approved for the treatment of obesity regardless of diabetes status. Meanwhile, injectable semaglutide appears to be especially promising in this regard and is currently in phase 3 trials as an anti-obesity agent after an earlier dose-finding study found 11.6–13.8% reductions in baseline body weight after 52 weeks of treatment with daily doses of 0.2 mg or higher [56]. These weight reductions are comparable to or greater than that of other currently approved weight loss agents. At these doses of semaglutide, >75% of patients lost more than 5% of their baseline weight with almost 60% losing 10% or more, and the effect of this medication appeared to persist throughout the year-long treatment period rather than plateauing early as other weight loss agents have [56]. The most common side effects with these medications are dose-dependent mild to moderate GI symptoms including nausea, vomiting, and constipation that typically improve over time. These GI effects do not appear to be the primary driver of the weight loss benefits [57, 58]. Rather, these appear to be due to direct actions on the brain to suppress appetite and promote early satiety, reducing overall caloric intake [59].

One drawback to therapy with this class of agents is that most are expensive and are only available as daily or once weekly subcutaneous injections that can be off-putting to those who are leery of self-injections. Semaglutide is also more recently available as a daily oral option but absorption is poor, so current recommendations for taking it on an empty stomach with a small amount of water prior to other oral intake may prove cumbersome to some patients. Although the risk of pancreatitis,

initially a concern with these agents appears to be similar to placebo, there is some data suggesting an increased risk of cholelithiasis with their use [60, 61]. In SUSTAIN 6, treatment with semaglutide was associated with a higher risk of retinopathy complications, but this association has not been redemonstrated in subsequent analyses [62–65]. The worsening noted in this study has therefore been attributed to the rapid tempo of glucose-lowering in these patients, which can result in a transient worsening of disease but which does not translate to long-term progression of retinopathy [63]. These agents appear to have some renoprotective effects as well, but largely through reductions in albuminuria and not on "harder" renal outcomes such as doubling of serum creatinine [40, 42, 44, 48].

Thiazolidinediones

Thiazolidinediones (TZDs) act on the peroxisome proliferator-activated receptors γ (PPAR-γ) nuclear receptor to promote adipocyte differentiation, promote beta cell function, and improve insulin sensitivity in skeletal muscle and adipose tissue (and to a lesser degree in liver).

Pioglitazone has been shown to reduce the risk of cardiovascular events in patients with and without diabetes. The secondary prevention study called the PROactive trial showed that pioglitazone treatment led to a 16% risk reduction in the secondary outcome of MACE (HR = 0.84 [95% CI 0.72–0.98]; $p = 0.027$) in people with T2DM and established CVD [66]. However, because the drug proved neutral for the primary outcome (which included peripheral vascular events), the MACE effect could only be considered hypothesis generating and not conclusive. In further subgroup analyses, PROactive participants with a prior MI experienced a 28% reduction in rates of recurrent MI (HR = 0.72 [95% CI 0.52–0.99]) and those with a history of stroke had a 47% reduction in recurrent stroke (HR = 0.53 [95% CI 0.34–0.85]) [67, 68]. Similarly, in non-diabetic but insulin-resistant patients who recently had a TIA or stroke, the IRIS trial found a 24% reduction in fatal/non-fatal stroke or MI (HR = 0.76 [95% CI 0.62–0.93]) [69]. Planned secondary analyses of this study investigated these component outcomes in more detail and found that treatment with pioglitazone in this insulin-resistant secondary prevention cohort led to a 25% reduction in stroke at 5 years (HR = 0.75 [95% CI 0.60–0.94]), a 29% reduced risk of acute coronary syndrome (ACS) (HR = 0.71 [95% CI 0.54–0.94]), and a 38% reduction in type 1 spontaneous MI (HR = 0.62 [95% CI 0.40–0.96]), effect sizes that are comparable to the benefits seen with more widely used stroke preventative agents such as statins, aspirin, and anti-platelet therapy [70–72]. Supporting the data from these randomized control trials, several meta-analyses have found reductions in MACE associated with pioglitazone use in a broad population of patients, including those with insulin resistance but without overt diabetes [73–75]. Additionally, large-scale studies of pioglitazone use in the real-world setting have demonstrated decreased mortality when compared to alternative treatments such as insulin [76, 77]. Of course, comparing any drug to insulin is

confounded by indication, as those treated with insulin tend to have a more complex medical history and often a longer duration of disease. Adjustments for these factors, including propensity scores, can render the comparisons more balanced but may not fully account for all differences.

By contrast, the cardiovascular safety data has been decidedly less promising with rosiglitazone. In fact, a 2008 meta-analysis by Nissen et al. found that the odds ratio for MI was 1.43 (95% CI 1.03–1.98; $p = 0.03$) and the odds ratio for death from CV causes was 1.64 (95% CI 0.98–2.74; $p = 0.06$) for rosiglitazone when compared to placebo, providing some of the impetus for the FDA's subsequent directive mandating cardiovascular outcome trials prior to approval of future glucose-lowering agents [78]. However, RECORD, an unblinded trial looking at both primary and secondary CV prevention, compared the addition of rosiglitazone or placebo to a background of sulfonylurea/metformin combination therapy and did not demonstrate any increased risk of cardiovascular mortality—but also no benefit [79].

Although pioglitazone has clearly shown some promising potential benefits in secondary prevention of atherosclerotic cardiovascular disease (ASCVD) and stroke, concerns about an increased risk of heart failure with use of these agents have tempered the enthusiasm for this class and somewhat limited their widespread use. Pioglitazone promotes VEGF production by the smooth muscle cells to increase vascular permeability and vasodilation, which when coupled with a reduction in urinary sodium excretion by the kidneys leads to fluid retention [80]. Despite the fact that this edema is unlikely to be the result of a direct deleterious effect of pioglitazone on ventricular function, randomized control trials such as the PROactive and RECORD trials both noted increased risk of heart failure in the TZD arm of their respective studies with the RECORD trial (unlike PROactive) finding excess deaths related to heart failure as well [66, 79]. Although the IRIS study (in which dose reduction was allowed for edema and weight gain) found no increase in heart failure in the pioglitazone group as compared to placebo, several meta-analyses have echoed the findings of PROactive and RECORD by demonstrating a significantly increased risk of heart failure with use of this medication class [73, 74, 81, 82]. Although there very well could be some misattribution of medication-associated edema to true heart failure, patients should be carefully evaluated for heart failure risk prior to starting therapy with these agents.

One potential mechanistic reason why pioglitazone use could be associated with decreased risk of ASCVD and stroke involves its impact on various components of the so-called metabolic syndrome. Improving insulin resistance and preserving beta-cell function ameliorates hyperglycemia, and shifting fat from visceral depots to subcutaneous areas reduces lipotoxicity [72]. Pioglitazone has also been associated with reduced rates of progression of carotid intimal media thickness (a surrogate marker of CV risk) and coronary atherosclerosis likely through direct effects on the vasculature itself [83–85]. These direct effects could be mediated through the PPARγ receptors found in endothelial, smooth muscle and immune cells where pioglitazone can lead to downstream anti-inflammatory and antioxidant effects that can reduce atherosclerotic plaque formation [72].

Pioglitazone is a very low-cost anti-hyperglycemic agent with a durable glucose-lowering effect. The two most common adverse effects are weight gain (typically around 2–3 kg) and peripheral edema which are both dose-dependent and can be difficult for patients to tolerate [72]. As discussed previously, the latter side effect is driven by sodium retention at the level of the distal tubule in the kidney, so medications such as spironolactone, triamterene, and amiloride might ameliorate this effect. However, all TZDs should be avoided in patients with decompensated heart failure [72]. This class of agents has also been associated with an increased risk of fracture, especially in women, and so should be avoided in those at high risk for fracture [69, 79, 86, 87]. An interim analysis of the PROactive trial prompted some concerns after it found a non-significant increase in the number of cases of bladder cancer in the pioglitazone arm of the study, but this association was not redemonstrated in the full 10-year follow-up of the PROactive trial [66, 88]. The data since then has remained mixed with two randomized control trials and at least two other large cohort studies not demonstrating an increased risk of bladder tumors with use of thiazolidinediones, while a number of other studies (particularly several meta-analyses) continue to demonstrate a small increased absolute risk of bladder cancer with these agents [69, 79, 89–94]. Given this ongoing controversy, the potential risk of bladder tumors should be discussed with patients and taken into consideration when using these agents.

Dipeptidyl Peptidase-4 Inhibitors

Drugs in this class inhibit dipeptidyl peptidase-4 (DPP-4) from breaking down endogenous incretins such as GLP-1 thereby augmenting GLP-1's previously noted beneficial downstream effects on insulin secretion. All the CVOTs for this class of agents (i.e., SAVOR-TIMI 53, EXAMINE, TECOS, and CARMELINA) demonstrated CV safety with no improvement in cardiovascular outcomes when compared to placebo [95–98]. SAVOR-TIMI 53 trial found a 27% increased rate of hospitalization for heart failure with saxagliptin when compared to placebo (HR = 1.27 [95% CI 1.07–1.51]) in their mixed primary/secondary prevention population of patients with T2DM, but this association has not been demonstrated in other members of this class [95]. Several meta-analyses have supported the neutral impact on cardiovascular outcomes of these agents [99–101].

These are generally well-tolerated agents associated with minimal hypoglycemia risk but also only have modest glucose-lowering potential. Unlike the related GLP-1 agonist class, these less potent agents are not associated with GI symptoms and are weight-neutral. Given the overlap in mechanism, DPP4i should not be used in conjunction with GLP-1 agonists. Although the potential mechanism is unknown, as mentioned previously, saxagliptin use was associated with an increased rate of heart failure hospitalization and so should be avoided in those with heart failure. Although the association between these medications and the risk of acute pancreatitis is somewhat inconsistent across various studies, there is enough of a safety signal to

recommend avoiding this medication in patients at risk for pancreatitis [102–107]. Lastly, these agents are also quite costly.

Older Agents: Metformin, Sulfonylureas, and Insulin

Cardiovascular safety data are more limited in some of our oldest glucose-lowering therapies as CVOTs were not mandated by the FDA for these agents. However, the data available largely supports the cardiovascular safety of these therapies.

Metformin decreases hepatic gluconeogenesis and improves insulin sensitivity. It is highly efficacious, low cost, has a low hypoglycemia risk, and promotes modest weight loss, making it an attractive first-line therapeutic agent for many practitioners. In a cohort of overweight patients from the UK Prospective Diabetes Study (UKPDS), metformin use was associated with a 32% lower risk of the composite diabetes outcome (which included major macrovascular complications such as MI) (HR = 0.68 [95% CI 0.53–0.87]) and a 36% reduction in all-cause mortality (HR = 0.64 [95% CI 0.45–0.91]) when compared to the "conventional therapy" arm which largely consisted of dietary counseling with the addition of sulfonylurea or insulin therapy if hyperglycemia developed [8]. In the 10-year follow-up study, though glycemic differences between the two groups were lost after 1 year, a significant risk reduction in the composite diabetes outcome, myocardial infarction, and all-cause mortality was retained in the overweight patients who had previously been intensively treated with metformin [14]. Additionally, the results of the meta-analysis by Lamanna et al. also support the cardiovascular safety of metformin, finding potential benefit of metformin when compared to placebo or no treatment and no impact on CV outcomes in active comparator trials [108]. A more recent large-scale retrospective cohort study of US veterans with diabetes and impaired kidney function found a decreased risk of MACE with metformin use when compared to sulfonylurea therapy [109].

Metformin can lead to bothersome diarrhea that does improve over time and can be alleviated by taking the medication with food or as an extended-release formulation. However, in a small minority of patients, this adverse effect, along with associated abdominal pains and gas, is poorly tolerated and a reason for patient non-adherence or discontinuation. There is also a risk of lactic acidosis in decompensated heart failure and advanced CKD, so this agent should be avoided in those populations. B12 Deficiency can also develop after long-term use of this medication and should be monitored periodically.

Sulfonylureas are low-cost agents that are potent in their glucose-lowering ability. They work by increasing insulin secretion from the pancreatic beta cell so as a result they have similar side effects as insulin therapy including weight gain and hypoglycemia risk. There has historically been some concern about the cardiovascular safety of sulfonylureas due to their inhibition of the ATP-sensitive potassium channels that are present on the myocardium as well as in the pancreatic beta cell. These channels play an important role in ischemic preconditioning, a means by

which the myocardium can adapt to an ischemic insult and limit the extent of the resulting damage [110]. Some early data indicating a possible increased cardiovascular risk with an older sulfonylurea was echoed in some subsequent meta-analyses which found an increased risk of cardiovascular mortality with sulfonylurea use when compared to other glucose-lowering agents such as metformin [111, 112]. However, these concerns have largely been assuaged by the results of the CAROLINA trial which included over 6000 adults with T2DM with CV risk factors or a history of CVD and analyzed the outcomes of treatment with linagliptin versus the sulfonylurea glimepiride [113]. There was no difference in rates of MACE, all-cause death, CV death, or HHF between the two groups despite an expected and significant increase in the risk of hypoglycemia with sulfonylurea therapy [113]. Given that the CARMELINA trial found that linagliptin was non-inferior to placebo with regard to CV outcomes, it can reasonably be extrapolated that sulfonylureas (or at least glimepiride) have neutral effects on cardiac outcomes as well [98].

With regard to insulin, information about CV risk is hard to extract from the available data as insulin is often added on to other agents and typically reserved for more advanced stages of diabetes. Mechanistically, there are some data to suggest insulin might have some anti-inflammatory properties that could promote and improve endothelial function [114, 115]. In terms of data from large-scale clinical trials, the UKPDS found that the group treated with sulfonylurea or insulin had similar macrovascular outcomes as those in the diet-control group, and treatment with these agents did not lead to the benefits noted with metformin use in this study [8, 116]. Some more recent data from two large trials has lent credence to the hypothesis that insulin therapy is likely safe from a cardiovascular perspective. The ORIGIN trial, for example, found that the basal insulin glargine had no impact on cardiovascular outcomes when compared to standard care despite increases in weight gain and hypoglycemia [117]. The newer basal insulin degludec was shown to be non-inferior to glargine with respect to CV outcomes and associated with a lower hypoglycemia risk [118]. Insulin is of course essentially limitless in its glucose-lowering ability. In addition to issues with weight gain and hypoglycemia, insulin is an injectable agent that may also contribute to some reluctance from patients when initiating this therapy.

Despite being much less commonly used, meglitinides are similar to sulfonylureas, both in their mechanism of glucose-lowering (albeit with a shorter duration of action) and in their apparent cardiovascular neutrality [119]. Pramlintide is an amylin mimetic that is an injectable agent that can be used as an adjunctive therapy in patients requiring prandial insulin. From a cardiovascular perspective, this is likely to be a safe therapy, but as it cannot be mixed with insulin, the extra injections per day can be difficult to tolerate for most patients [120]. Several other older classes of glucose-lowering agents including alpha-glucosidase inhibitors, bile acid sequestrants, and dopamine agonists are rarely used for glycemic management due to their limited efficacy and/or their side effect profile.

Implementing a Personalized Treatment Strategy in Patients with CVD

The wealth of good-quality cardiovascular safety data for the newest classes of diabetes agents has led to a paradigm shift in the focus of diabetes care. Although glucose control is still important in mitigating the risk of microvascular disease, these trials have diminished the relevance of tight glucose control in addressing the profound impact of macrovascular disease in this population. Given the clear and important cardiovascular advantages afforded by certain classes of glucose-lowering drugs, some of the most recent guidance on pharmacologic therapy in diabetes management has emphasized the importance of early adoption of these agents in the care of patients with T2DM. For example, the 2021 ADA's Standards of Medical Care in Diabetes and the 2019 Update to the ADA-EASD Consensus Report recommend that GLP-1 receptor agonists and/or SGLT2 inhibitors should be used in patients at high risk of CVD events, irrespective of hemoglobin A1c values or targets [121, 122]. High-risk patients include those with established CVD (i.e., those with a history of myocardial infarction, ischemic stroke, unstable angina, abnormal stress test, or any revascularization procedure), CKD, or heart failure and those 55 years or older with >50% stenosis of any artery, left ventricular hypertrophy, eGFR <60 mL/min or albuminuria. Another similar approach put forth by the European Society of Cardiology and the European Association for the Study of Diabetes recommends risk stratifying patients based on the presence of preexisting ASCVD or microvascular complications, diabetes duration, and the burden of traditional metabolic risk factors such as hypertension and hyperlipidemia [123]. In these guidelines, for patients deemed to be highest risk for cardiovascular events, SGLT2i, or GLP-1 RA are recommended as first-line therapy even before metformin. The American College of Cardiology Guidelines Expert Consensus Decision Pathway also recommends early use of these agents in patients with T2DM at high risk for CVD [124].

It is essential to then tailor the treatment approach based on the particular cardiovascular disease process that is of most concern in each individual patient (Fig. 37.1). For example, SGLT2i should be prioritized in patients with heart failure or nephropathy given the robust improvement in these particular outcomes afforded by medications in this class. TZDs and saxagliptin would be best avoided in those with heart failure. By contrast, for those with a history of ASCVD including stroke, GLP-1 RA (particularly liraglutide, dulaglutide, and semaglutide) would be preferred with strong consideration of pioglitazone as well given its clear benefits in the stroke population in particular. This is especially true as the weight gain and fluid retention caused by TZDs might even be ameliorated by dual therapy with GLP-1 RA (weight) or SGLT2i (weight, edema).

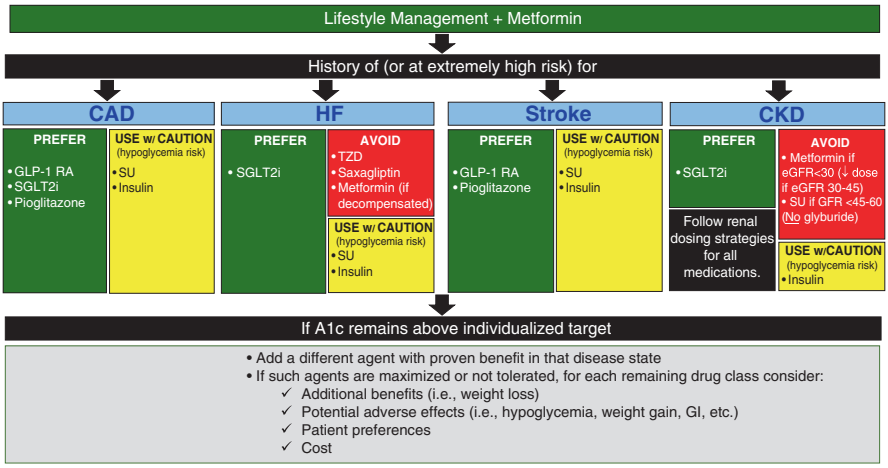

Fig. 37.1 Proposed approach to glucose-lowering in T2DM patients with CVD and/or CKD

Although the emphasis has shifted away from stringent glycemic targets in this population, a glycemic target around 7% if achievable without hypoglycemia remains a reasonable goal, mainly to prevent microvascular disease. Of course, the life expectancy and prevalent comorbidities of the individual patient need to be considered as well. Prevention of hypoglycemia is important in this population to avoid exacerbating the risk of arrhythmias or ischemia. When additional glucose-lowering is needed, the choice of subsequent agents should continue to prioritize the use of agents that have demonstrated cardiovascular benefits while weighing the practicalities surrounding use of the medication as well as the non-cardiovascular risks and benefits (Table 37.2).

Table 37.2 Risks and benefits of most commonly used glucose-lowering drug classes

Class of agent	CV advantages	CV risks	Non-CV benefits and risks
SGLT2i *Canagliflozin* *Dapagliflozin* *Empagliflozin* *Ertugliflozin* *Sotagliflozin* (*SGLT1/SGLT2i*)	Decreased CV mortality (empagliflozin) Decreased MACE (empagliflozin, canagliflozin, sotagliflozin) Decreased HF hospitalizations (all) Low hypoglycemia risk Modest decrease in BP and increase in HDL		*Benefits* Weight loss Decreased nephropathy *Risks* High cost Dehydration Increased risk of GU infections Increased risk of DKA Diarrhea (sotagliflozin) Amputation risk? (canagliflozin)
GLP-1 RA *Dulaglutide* *Exenatide* *Liraglutide* *Lixisenatide* *Semaglutide*	Decreased CV mortality (liraglutide) Decreased MACE (liraglutide, semaglutide, dulaglutide) Decrease in non-fatal strokes (semaglutide, dulaglutide) Low hypoglycemia risk	Increase HR by 2–3 beats/min	*Benefits* Weight loss Decreased nephropathy *Risks* Pancreatitis risk? Cholelithiasis risk? Retinopathy? (semaglutide) High cost Injectable
TZDs *Pioglitazone* *Rosiglitazone*	Decreased MACE (pioglitazone) Decreased stroke (pioglitazone) Low hypoglycemia risk	Increased HF risk? (pioglitazone, rosiglitazone)	*Benefits* Low-cost Improvement in NASH *Risks* Weight gain Edema Bladder cancer?
DPP-4i *Alogliptin* *Linagliptin* *Saxagliptin* *Sitagliptin*	Low hypoglycemia risk	Increased HF risk? (saxagliptin)	*Benefits* Weight neutral *Risks* High cost Pancreatitis risk?
Sulfonylureas *Glimepiride* *Glipizide* *Glyburide*		Increased risk of hypoglycemia	*Benefits* Low cost *Risks* Weight gain

(continued)

Table 37.2 (continued)

Class of agent	CV advantages	CV risks	Non-CV benefits and risks
Metformin	Potential ASCVD benefit Low hypoglycemia risk	Lactic acidosis risk in decompensated HF	*Benefits* Low cost Weight neutral (or loss) *Risks* GI upset B12 deficiency
Insulin		Increased risk of hypoglycemia	*Benefits* Unlimited glucose-lowering effect *Risks* Weight gain Injectable

ASCVD atherosclerotic cardiovascular disease, *BP* blood pressure, *CV* cardiovascular, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *DKA* diabetic ketoacidosis, *GI* gastrointestinal, *GLP-1 RA* GLP-1 receptor agonists, *GU* genitourinary, *HDL* high-density lipoprotein, *HF* heart failure, *HR* heart rate, *MACE* major adverse cardiac events, *NASH* non-alcoholic steatohepatitis, *SGLT1* sodium–glucose cotransporter 1, *SGLT2i*, sodium–glucose cotransporter 2 inhibitors, *TZDs* thiazolidinediones

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