REVIEW

THE AMERICAN JOURNAL of MEDICINE®

A Comprehensive Cardiovascular-Renal-Metabolic Risk Reduction Approach to Patients with Type 2 Diabetes Mellitus

Neha J. Pagidipati, MD, MPH,[a] Prakash Deedwania, MD[b]

[a]*Duke Clinical Research Institute, Durham NC;* [b]*School of Medicine, University of California, San Francisco, Fresno.*

ABSTRACT

Despite decades of research into risk-reduction strategies, cardiovascular disease and renal disease remain leading causes of morbidity and mortality among patients with type 2 diabetes mellitus. Given the tight clustering of cardiovascular and renal disease with the metabolic abnormalities of type 2 diabetes mellitus, we can think of these conditions together as cardiovascular-renal-metabolic disease states. A holistic view of cardiovascular-renal-metabolic disease states is critical to provide integrated patient-centered care to individuals with these disease states. Here, we explore the cardiovascular and renal risks associated with type 2 diabetes mellitus and highlight the importance of reducing cardiovascular-renal-metabolic disease risk in a comprehensive manner. We advocate a cross-disciplinary, team-based model to manage cardiovascular-renal-metabolic disease risk among patients with type 2 diabetes mellitus.

 • The American Journal of Medicine (2021) 134:1076−1084

KEYWORDS: Cardiovascular; Diabetes mellitus; Patient-centered; Prevention; Risk reduction

INTRODUCTION

Cardiovascular disease remains the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus, despite decades of research into risk-reduction strategies.[1,2] Although myocardial infarction and ischemic stroke are the most recognized drivers of mortality in this population, less well-appreciated forms of cardiovascular disease, including heart failure and peripheral arterial disease, also contribute significantly to this risk.[3-5] Further, the development of renal disease among patients with type 2 diabetes mellitus is common,[6] and it drastically increases the risk of cardiovascular disease and overall mortality.[7]

Given the tight clustering of cardiovascular and renal disease with the metabolic abnormalities of type 2 diabetes mellitus, we can think of these conditions together as cardiovascular-renal-metabolic disease states. Such terminology emphasizes the highly interconnected nature of these illnesses and emphasizes the need to take a global approach for the care of patients with type 2 diabetes mellitus.

A global view of cardiovascular-renal-metabolic diseases requires an integrated approach that focuses not only on traditional atherosclerosis prevention and management but also on heart failure and peripheral arterial disease, as well as renal disease prevention in patients with type 2 diabetes mellitus. We now have medications such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) added to our therapeutic armamentarium, which prevent several types of complications and can facilitate such an integrated approach. However, we must continue to reduce cardiovascular-renal-metabolic disease risk with traditional interventions as well, including those focused on lifestyle, weight, blood pressure, and lipid control (Figure 1).

In this review, we aim to outline various cardiovascular and renal risks associated with type 2 diabetes mellitus, highlight the therapies and strategies available to reduce cardiovascular-renal-metabolic disease risk in a

Funding: None.

Conflicts of Interest: NJP reports research grants from Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Regeneron, Sanofi, Verily Life Sciences, and Novartis; consulting fees from Boehringer Ingelheim, Eli Lilly, AstraZeneca, and Novo Nordisk; and being on a study board for Novo Nordisk. PD reports research grants from Boehringer Ingelheim, Novartis, and Sanofi.

Authorship: Both authors drafted and critically revised the manuscript.

Requests for reprints should be addressed to Prakash Deedwania, MD, UCSF, 150 N. Fresno Street, Fresno, CA, 93701.

E-mail address: deed@ucsf.edu

0002-9343/
https://doi.org/10.1016/j.amjmed.2021.04.024

comprehensive manner, and emphasize the important role of a cross-disciplinary, team-based model to manage cardiovascular-renal-metabolic disease risk among patients with type 2 diabetes mellitus.

RISKS AND PROGNOSES OF VARIOUS TYPES OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS

The risk of developing coronary heart disease or ischemic stroke among patients with type 2 diabetes mellitus is well-established in the literature. Individuals with type 2 diabetes mellitus are twice as likely to develop coronary heart disease as their counterparts without type 2 diabetes mellitus and 2-3 times as likely to develop ischemic stroke.[8] Indeed, the risk for coronary heart disease among patients with >10 years of type 2 diabetes mellitus duration approaches those with a prior history of coronary heart disease.[9,10] Further, the prognosis of coronary heart disease and ischemic stroke is significantly worse in patients with type 2 diabetes mellitus compared with those without.[11-13]

Perhaps slightly less well-appreciated are the significant risks of heart failure and peripheral arterial disease that the presence of type 2 diabetes mellitus imparts. Though the markedly increased risk of heart failure in type 2 diabetes mellitus has been known since the seminal Framingham study publication by Kannel et al[14] in 1974, lack of awareness of this complication in both the medical community and the general public has led some to call heart failure the 'ignored' complication of diabetes.[15,16] Yet individuals with type 2 diabetes mellitus have a heart failure incidence rate that it 2.5 times the rate of individuals without type 2 diabetes mellitus.[17] Similar to coronary heart disease and stroke described previously, women and younger adults with type 2 diabetes mellitus have a markedly elevated risk for heart failure.[18] Once heart failure has developed, those with type 2 diabetes mellitus have an additional 30% increased risk of mortality and an additional 35% increased risk of hospitalization for a median of 3 years.[19]

Like heart failure, peripheral arterial disease is a substantial yet perhaps less well-known consequence of type 2 diabetes mellitus. Indeed, type 2 diabetes mellitus increases the risk of peripheral arterial disease by 2- to 3-fold,[20] and approximately 20%-30% of patients with peripheral arterial disease have diabetes, though even this is likely an underestimate given the high rate of asymptomatic peripheral arterial disease.[21] In terms of prognosis, patients with peripheral arterial disease and type 2 diabetes mellitus are significantly more likely to require lower extremity amputation or to develop other ischemic events than patients with peripheral arterial disease without type 2 diabetes mellitus.[22]

CLINICAL SIGNIFICANCE

- The tight clustering of cardiovascular, renal, and metabolic abnormalities in type 2 diabetes mellitus suggests that we can think of these conditions together as cardiovascular-renal-metabolic disease states.
- Traditional approaches to cardiovascular-renal-metabolic disease should be complemented by sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, which provide benefit across the spectrum of risk.
- We advocate for a cross-disciplinary, team-based model to manage cardiovascular-renal-metabolic risk among patients with type 2 diabetes mellitus.

RISK AND PROGNOSIS OF RENAL DISEASE IN TYPE 2 DIABETES MELLITUS AND ASSOCIATED CARDIOVASCULAR DISEASE RISK

Diabetic kidney disease is characterized by albuminuria, low estimated glomerular infiltration rate (eGFR), or other manifestations of kidney damage.[23] The prevalence of this serious complication among individuals with diabetes is estimated to be between 25% and 40%.[6,24] The cardiovascular consequences of developing diabetic kidney disease are sobering. Patients with diabetic kidney disease are more likely to die from cardiovascular causes than from progression to end-stage renal disease (ESRD).[25] Diabetic kidney disease appears to be not just a marker for increased cardiovascular risk but also involved in the pathogenesis of cardiovascular disease. Augmentation of traditional risk factors such as hypertension, hyperlipidemia, and obesity cannot fully explain the worse cardiovascular and mortality outcomes in diabetic kidney disease.[26] Thus, the link between diabetic kidney disease and cardiovascular disease is strong and must be taken into account when aiming to prevent cardiovascular disease in patients with type 2 diabetes mellitus.

CARDIOVASCULAR-RENAL-METABOLIC DISEASE RISK REDUCTION STRATEGIES IN TYPE 2 DIABETES MELLITUS: TRADITIONAL APPROACHES

To prevent the many cardiovascular, renal, and metabolic complications of type 2 diabetes mellitus, providers must take a holistic approach to risk reduction in this patient population. Fortunately, traditional approaches to cardiovascular-renal-metabolic disease risk reduction are effective, especially when implemented in a comprehensive manner.

Traditional Risk Factors

Lifestyle modification, including both regular aerobic exercise and weight management, improve cardiovascular outcomes, are associated with improved renal outcomes, and lead to better glycemic control in type 2 diabetes mellitus.[27-29] Thus, all major society guidelines for type 2

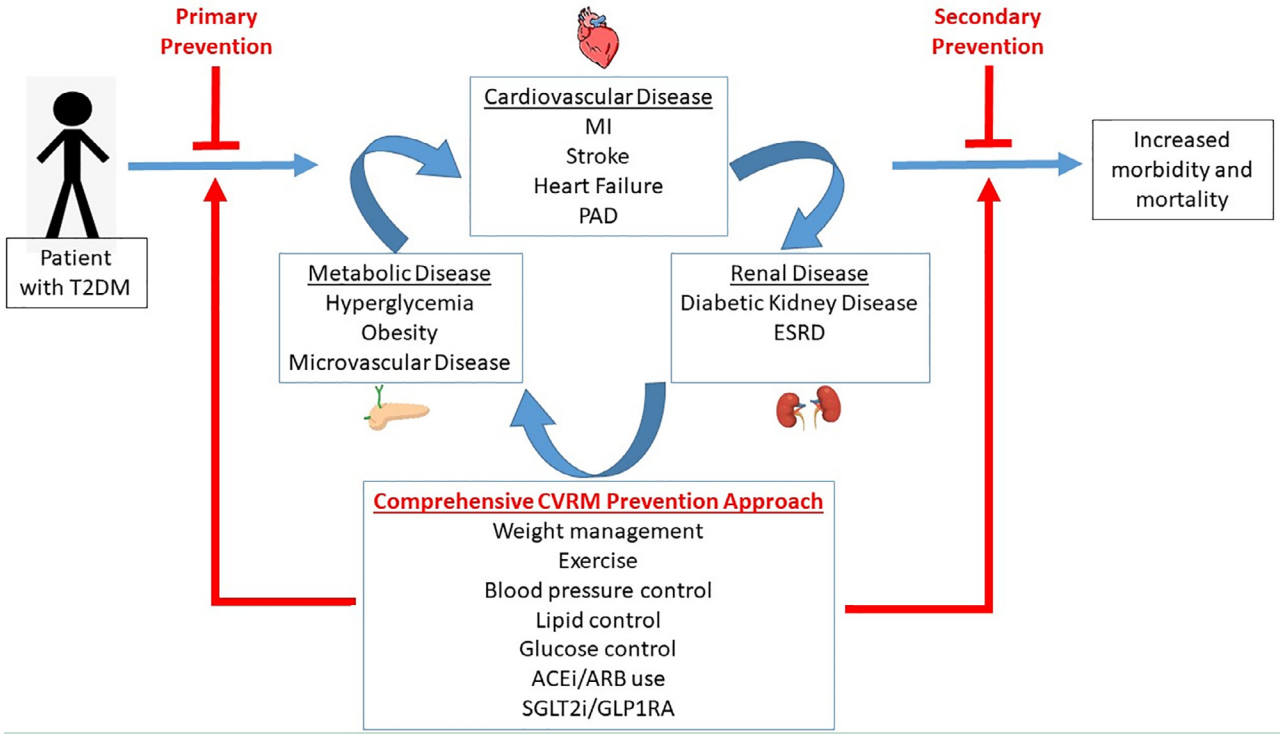

Figure 1 Comprehensive approach to cardiovascular-renal-metabolic disease risk reduction in type 2 diabetes mellitus. ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; ESRD = end-stage renal disease; GLP1RA = glucagon-like peptide-1 receptor agonist; MI = myocardial infarction; PAD = peripheral artery disease; SGLT2 = sodium-glucose cotransporter-2 inhibitors; T2DM = type 2 diabetes mellitus.

diabetes mellitus recommend at least 150 minutes of moderate-intensity aerobic exercise weekly and optimization of weight status.[27,30,31] In addition to lifestyle modification, control of blood pressure is paramount in reducing risks of coronary heart disease, stroke, heart failure, and kidney disease among individuals with type 2 diabetes mellitus.[32-34] Most society guidelines recommend a target blood pressure of <130/80 mm Hg,[31] particularly if the individual has high atherosclerotic cardiovascular disease risk[1] or is younger than 65 years of age or is at high risk for stroke.[30]

Individuals with type 2 diabetes mellitus have an increased prevalence of atherogenic dyslipidemia, which contributes to their high risk for atherosclerotic cardiovascular disease.[1] For both primary and secondary prevention patients with type 2 diabetes mellitus, statin therapy has been proven to reduce atherosclerotic cardiovascular disease events and coronary heart disease death.[35] Accordingly, society guidelines recommend treatment of all patients with type 2 diabetes mellitus with either moderate- or high-intensity statin, depending on individual atherosclerotic cardiovascular disease risk.[1,30,36] Finally, glucose control, especially if it occurs early in the course of diabetes, appears to be associated with cardiovascular benefit over the long term[30,37-39] and improvement in microvascular outcomes including diabetic kidney disease.[40,41] Thus, glucose control is an important part of overall cardiovascular-renal-metabolic disease care in patients with type 2 diabetes mellitus, particularly with respect to microvascular complications, including renal outcomes.

Comprehensive Management of Traditional Risk Factors

Control of each of the aforementioned risk factors is independently associated with improved clinical outcomes in type 2 diabetes mellitus, but many observational studies have shown that control of multiple risk factors simultaneously leads to the greatest benefit. Using data from the Swedish National Diabetes Register, Rawshani et al[42] showed that excess risk associated with type 2 diabetes mellitus for death, myocardial infarction, stroke, and heart failure hospitalization decreased step-wise for each additional risk factor that was controlled (Figure 2). Those who had all 5 risk factors controlled (hemoglobin A1c [HbA1c], low-density lipoprotein cholesterol [LDL-C], albuminuria, smoking, and blood pressure) had similar risks of death, myocardial infarction, and stroke as individuals without type 2 diabetes mellitus. This pattern also holds true in other international settings.[43]

Control of multiple risk factors simultaneously can be achieved with comprehensive strategies, as demonstrated by the landmark Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria

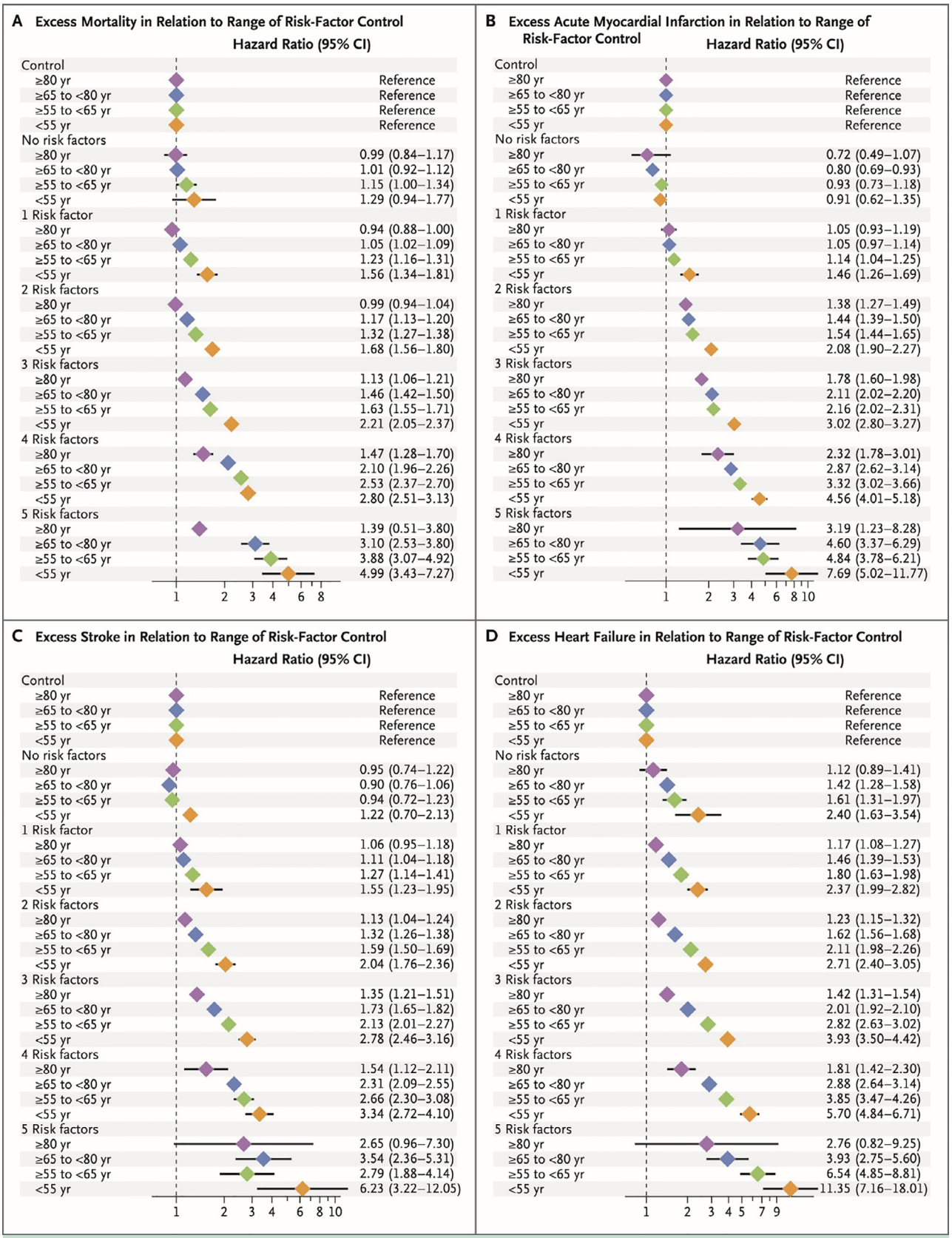

Figure 2 Risk factors and clinical outcomes in patients with type 2 diabetes mellitus. Figure borrowed (with permission) from Rawshani et al.[42] Each panel shows adjusted hazard ratios for outcomes according to age category and number of uncontrolled risk factors in patients with type 2 diabetes mellitus compared with matched controls.

(STENO-2) trial. This trial randomized patients in Denmark with type 2 diabetes mellitus and microalbuminuria to standard care compared with an intensive, multifactorial intervention to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria.[44] Over a median of 7.8 years, the intervention led to a lower risk of cardiovascular disease (hazard ratio [HR] = 0.47, 95% confidence interval [CI] = 0.24-0.73) along with continued reduction in microvascular events.[45] Perhaps most strikingly, after a median 21.2 years of follow-up postrandomization, the intervention group gained a median of 7.9 years of life compared with the standard care group.[46] Thus, the trial proved that an intensive, multifactorial intervention could control multiple risk factors simultaneously among patients with type 2 diabetes mellitus and microalbuminuria, leading to significant improvement in short- and long-term outcomes.

CARDIOVASCULAR-RENAL-METABOLIC DISEASE RISK REDUCTION STRATEGIES IN TYPE 2 DIABETES MELLITUS: NEW APPROACHES

In addition to the traditional approaches for cardiovascular-renal-metabolic disease risk reduction outlined, we now have several new tools in our armamentarium to help minimize cardiovascular-renal-metabolic disease risk in patients with type 2 diabetes mellitus. Two classes of agents, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA), have recently been proven to improve a wide array of diabetes related endpoints. Here we briefly summarize the cardiovascular, renal, and metabolic impact of these therapies in the type 2 diabetes mellitus population.

Cardiovascular-Renal-Metabolic Effects of SLGT2i in Type 2 Diabetes Mellitus

SGLT2i are agents that block glucose reabsorption through the sodium-glucose cotransporter in the proximal tubule of the nephron. Although initially developed as glucose-lowering agents, they have since been shown to have substantial cardiovascular-renal-metabolic benefits. Thus far, 7 cardiovascular outcomes trials in patients with type 2 diabetes mellitus have been published, yielding data on their impact on atherosclerotic cardiovascular disease events, hospitalization for heart failure, renal disease progression, glycemic control, and weight loss (Table 1).

Among patients with type 2 diabetes mellitus, SGLT2i appear to moderately improve 3-component myocardial infarction, stroke, or cardiovascular death (MACE) outcomes, particularly in individuals with prior atherosclerotic cardiovascular disease. A recent meta-analysis by McGuire et al[55] analyzed data from 5 cardiovascular outcomes trials with SGLT2i in patients with type 2 diabetes mellitus. They found that SGLT2i reduced risk of MACE in patient with type 2 diabetes mellitus and prior atherosclerotic cardiovascular disease (HR = 0.89, 95% CI = 0.84-0.95), but not among primary prevention patients (HR = 0.94, 95% CI = 0.83-1.07). This MACE benefit is modest and was only seen in trials for empagliflozin and canagliflozin.[47,49,51] Recently, the dual SGLT1/SGLT2 inhibitor sotagliflozin was shown to improve MACE among patients with type 2 diabetes mellitus and chronic kidney disease (HR = 0.84, 95% CI = 0.72-0.99).[54]

In contrast, the impact of SGLT2i on risk for hospitalization for heart failure among patients with type 2 diabetes mellitus is profound. The benefit across agents in the class is highly consistent, with an overall heart failure risk reduction of 32% (HR = 0.68, 95% CI = 0.61-0.76).[55] These effects are independent of baseline atherosclerotic cardiovascular disease status, prior heart failure, or baseline eGFR. Similarly, the substantial renal benefit of SGLT2i appears to be consistent across the class, with ertugliflozin being the only agent without statistically significant renal benefit.[52] Across the published trials in type 2 diabetes mellitus, SGLT2i were associated with a 38% reduction in risk of kidney-related outcomes.[55]

Beyond their atherosclerotic cardiovascular disease, heart failure, and renal benefits, SGLT2i also carry several metabolic benefits. Through increased glucosuria, SGLT2i lead to an average of 0.5%-0.7% decrease in HbA1c.[56] The glucosuria also causes an approximate 1.5-2 kg weight loss among individuals with type 2 diabetes mellitus.[57] It should be noted that the scope of benefit of SGLT2i is expanding to include populations without type 2 diabetes mellitus, both in those with heart failure with reduced ejection fraction[58,59] and in those with chronic kidney disease.[60] Ongoing trials will further elucidate the cardiovascular and renal effects of these agents in individuals without type 2 diabetes mellitus.[61-63]

Cardiovascular-Renal-Metabolic Effects of GLP1RA in Type 2 Diabetes Mellitus

GLP1RA are agents that increase the concentrations of the GLP1 peptide hormone, leading to increased glucose-dependent insulin secretion from the pancreas, decreased glucagon secretion, and delayed gastric emptying with increased satiety.[64] Similar to SGLT2i, this class was initially developed as antihyperglycemic agents, but several agents within the class have shown significant cardiovascular-renal-metabolic benefits. Table 2 outlines the 7 cardiovascular outcomes trials with GLP1RAs.

A recent meta-analysis of these trials showed that, among patients with type 2 diabetes mellitus, GLP1RA significantly decreased the risk of 3-component MACE by 12% (HR = 0.88, 95% CI = 0.82-0.94]).[76] This largely reflected the beneficial effect of GLP1RA on cardiovascular death (relative risk reduction 12%) and on fatal and nonfatal stroke (relative risk reduction 16%). There appears to be a signal that the exendin 4-based drugs (lixisenatide and exenatide) may be less effective than agents more homologous with human GLP1 (liraglutide, semaglutide, albiglutide, dulaglutide); an ongoing study with another exendin 4-

Table 1 Cardiovascular-Renal-Metabolic Benefits of SGLT2i in Type 2 Diabetes Mellitus

	EMPA-REG Outcomes[47,48]	CANVAS Program[49]	DECLARE-TIMI 58[50]	CREDENCE[51]	VERTIS CV[52]	SOLOIST-WHF[53]	SCORED[54]
Trial Characteristics							
N	7020	10,142	17,160	4401	8246	1222	10,584
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin	Sotagliflozin	Sotagliflozin
Study Population	T2DM + ASCVD	T2DM + high CV risk	T2DM + high CV risk	T2DM + CKD	T2DM + ASCVD	T2DM + WHF	T2DM + CKD
CVRM Outcomes*							
MACE	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.80 (0.67-0.95)	0.97 (0.85-1.11)		0.77 (0.65-0.91)
CV Death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)	0.92 (0.77-1.11)	0.84 (0.58 to 1.22)	0.90 (0.73−1.12)
HF Hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80)	0.70 (0.54-0.90)	0.64 (0.49 to 0.83)	0.67 (0.55−0.82)
Kidney-Related Outcomes†	0.54 (0.40-0.75)	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.66 (0.53-0.81)	0.81 (0.63-1.04)		0.71 (0.46-1.08)

ASCVD = atherosclerotic cardiovascular disease; CANVAS = Canagliflozin cardiovascular assessment study ; CI = confidence interval; CKD = chronic kidney disease; CREDENCE = Evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy; CV = cardiovascular; CVRM = cardiovascular-renal-metabolic; DECLARE-TIMI 58 = multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular outcome event trial in type 2 diabetes mellitus patients; HF = heart failure; HR = hazard ratio; MACE = composite of myocardial infarction, stroke, or CV death; SCORED = Effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SOLOIST-WHF = Effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure; T2DM = type 2 diabetes mellitus; VERTIS CV = Cardiovascular outcomes following ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease; WHF = worsening heart failure (both preserved and reduced ejection fraction).

*Outcomes displayed as HR (95% CI).

†Kidney-related outcomes vary by trial and include various permutations of worsening eGFR or creatinine, end-stage kidney disease with or without requirement for kidney replacement therapy or transplantation, or kidney death.

Table 2 Cardiovascular-Renal-Metabolic Benefits of GLP1RA in Type 2 Diabetes Mellitus

	ELIXA[65,66]	LEADER[67,68]	SUSTAIN-6[69]	EXSCEL[70,71]	Harmony Outcomes[72]	REWIND[73,74]	PIONEER 6[75]
Trial Characteristics							
N	6068	9340	2735	14,752	9463	9901	3183
GLP1RA	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Oral Semaglutide
Study Population	T2DM + recent ACS	T2DM + high CV risk	T2DM + high CV risk	T2DM + high CV risk	T2DM + ASCVD	T2DM + high CV risk	T2DM + high CV risk
CVRM Outcomes*							
MACE	1.02 (0.89-1.17)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.91 (0.83-1.00)	0.78 (0.68-0.90)	0.88 (0.79-0.99)	0.79 (0.57-1.11)
CV Death	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.93 (0.73-1.19)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
HF Hospitalization	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)		0.93 (0.77-1.12)	0.86 (0.48-1.55)
Kidney-Related Outcomes†	0.81 (0.66-0.99)	0.78 (0.67-0.92)	0.64 (0.46-0.88)	0.85 (0.74-0.98)		0.85 (0.77-0.93)	

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CV = cardiovascular; CVRM = cardiovascular-renal-metabolic; eGFR = estimated glomerular filtration rate; ELIXA = Evaluation of cardiovascular outcomes in patients with type 2 diabetes after acute coronary syndrome during treatment with AVE0010 (Lixisenatide); EXSCEL = Exenatide study of cardiovascular event lowering trial: a trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus; GLP1RA = glucagon-like peptide-1 receptor agonists; Harmony Outcomes = effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in subjects with type 2 diabetes mellitus; HF = heart failure; HR = hazard ratio; LEADER = Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results; MACE = composite of myocardial infarction, stroke, or CV death; PIONEER 6 = A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes; REWIND = Researching cardiovascular events with a weekly incretin in diabetes; SUSTAIN 6 = Trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; T2DM = type 2 diabetes mellitus.

*Outcomes displayed as HR (95% CI).

†Kidney-related outcomes vary by trial and include various permutations of now-onset macroalbuminuria, worsening eGFR or creatinine, end-stage kidney disease with or without requirement for kidney replacement therapy or transplantation, or kidney death.

based agent (efpeglenatide) will provide more clarity on this issue (NCT03496298).

In terms of renal outcomes, GLP1RA reduce urinary albumin excretion, but its impact on other renal outcomes are less clear. Indeed, in the aforementioned meta-analysis, the risk reduction of GLP1RA on worsening kidney function (defined as doubling of serum creatinine or at least 40% decline in eGFR, end-stage kidney disease, or kidney-related death) was not statistically significant.[76] The ongoing research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW) trial will shed more light on this issue (NCT03819153).

GLP1RA also have a profound impact on metabolic parameters, including weight and HbA1c. Liraglutide, exenatide, and dulaglutide leads to 2%-4% loss of total body weight, whereas semaglutide leads to 4-6 kg weight loss.[77] In general, semaglutide leads to greater weight loss than the other GLP1RA agents and is preferentially recommended by guidelines when weight loss is paramount.[78,79] GLP1RA also lead to a decrease in HbA1c of ~0.8%-1.5% by stimulating the incretin pathway, which in turn increases insulin and decreases glucagon secretion from pancreatic islet cells.[80,81] Similar to SGLT2i, the potential benefits of GLP1RA on cardiovascular outcomes outside of patients with type 2 diabetes mellitus are currently being examined.

ROLE OF A CROSS-DISCIPLINARY, TEAM-BASED MODEL FOR CARDIOVASCULAR-RENAL-METABOLIC DISEASE PREVENTION AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

Clearly, we have amassed a great deal of knowledge about how to prevent cardiovascular-renal-metabolic disease among patients with type 2 diabetes mellitus, using both traditional approaches like lifestyle modification and risk factor management, as well as emerging therapies with cardiovascular-renal-metabolic benefit. The recommendations from various professional societies have begun to reflect this comprehensive approach to cardiovascular-renal-metabolic disease prevention among patients with type 2 diabetes mellitus.[30,82] Despite these recommendations, however, there remains a large gap between what we know about preventing disease and what actually occurs in real-world settings.[43] Wong et al[83] used data from the US National Health and Nutrition Examination Survey to demonstrate that only 24% of individuals with type 2 diabetes mellitus had controlled HbA1c, blood pressure, and LDL-C in 2009-2010. Despite their overwhelming cardiovascular-renal-metabolic benefit, SGLT2i and GLP1RA were prescribed in only 10.2% of patients with type 2 diabetes mellitus and cardiovascular disease in a large, US-based commercial insurance cohort.[84] In this same cohort, ~25% of individuals were on a high-intensity statin, ~53% were on angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy, and only 2.7% were on all 3 groups of medications: high-intensity statin, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and SGLT2i/GLP1RA.

We propose that multidisciplinary teams of providers with expertise in primary care, cardiology, endocrinology, nephrology, nutrition, and exercise physiology would be ideal to provide comprehensive cardiovascular-renal-metabolic preventive care to high-risk patients with type 2 diabetes mellitus. Though each provider would play a critical role in this model, fundamentally the patient would be at the center. Such a patient-partnered approach could harness the power of a multidisciplinary team to achieve goals that are important to patients, including collaborative, coordinated care. Cardiovascular-renal-metabolic disease prevention models of care are currently being developed around the country, and we look forward to rigorous evaluations of their impact on patient care.

CONCLUSIONS

Patients with type 2 diabetes mellitus are at heightened risk of cardiovascular and renal complications and need aggressive, comprehensive, and holistic cardiovascular-renal-metabolic disease risk reduction to improve outcomes. Traditional methods of risk reduction such as weight management, regular exercise, and control of blood pressure, lipids, and glucose are effective in preventing both cardiovascular and renal events. Newer classes of medications, including SLGT2i and GLP1RA, provide significant benefit in terms of reduction in atherosclerotic cardiovascular disease, heart failure, renal complications, HbA1c lowering, and weight loss. Because of the well-demonstrated cardiorenal-protective effects, most of the national and international practice guidelines have recommended use of these newer agents in patients with diabetes and cardiovascular disease or coexisting cardiovascular risk factors. Unfortunately despite guideline recommendations, most of these proven therapies are currently underused, and risk factor targets remain largely unmet. We advocate for a comprehensive, team-based approach to cardiovascular-renal-metabolic disease risk reduction among patients with type 2 diabetes mellitus that includes multiple providers, but most importantly includes patients at the center.

References

1. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43:S111–34.
2. American Diabetes Association. Economic costs of diabetes in the U. S. in 2017. *Diabetes Care* 2018;41:917–28.
3. Seshasai SRK, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829–41.
4. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation* 2016;133:2459–502.
5. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 2015;3:105–13.

6. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011;305:2532–9.
7. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–73.
8. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–22.
9. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med* 2009;26:142–8.
10. Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. *J* Gen Intern Med 2016;31:387–93.
11. Haffner SM. Coronary heart disease in patients with diabetes. *N Engl J Med* 2000;342:1040–2.
12. Echouffo-Tcheugui JB, Xu H, Matsouaka RA, et al. Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke. *Eur Heart J* 2018;39:2376–86.
13. Jia Q, Zhao X, Wang C, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke: the China National Stroke Registry. *Stroke* 2011;42:2758–62.
14. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34.
15. Bell DS. Diabetic cardiomyopathy. *Diabetes Care* 2003;26:2949–51.
16. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol* 2014;2:843–51.
17. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–84.
18. Rosengren A, Edqvist J, Rawshani A, et al. Excess risk of hospitalisation for heart failure among people with type 2 diabetes. *Diabetologia* 2018;61:2300–9.
19. Dauriz M, Mantovani A, Bonapace S, et al. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. *Diabetes Care* 2017;40:1597–605.
20. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;116:1509–26.
21. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol* 2006;47:921–9.
22. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arterioscler Thromb Vasc Biol* 2020;40:1808–17.
23. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43:S135–51.
24. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA* 2016;316:602–10.
25. Maqbool M, Cooper ME, Jandeleit-Dahm KAM. Cardiovascular disease and diabetic kidney disease. *Semin Nephrol* 2018;38:217–32.
26. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002;13:1918–27.
27. American Diabetes Association. 5. Facilitating behavior change and well-being to improve health outcomes: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43:S48–65.
28. American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43:S89–97.
29. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2065–79.
30. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255–323.
31. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2019;74:e177–232.
32. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603–15.
33. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–67.
34. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;352:i717.
35. Cholesterol Treatment Trialists (CTT) Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117–25.
36. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;139:e1082–143.
37. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.
38. Macisaac RJ, Jerums G. Intensive glucose control and cardiovascular outcomes in type 2 diabetes. *Heart Lung Circ* 2011;20:647–54.
39. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;373:1765–72.
40. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5:431–7.
41. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–72.
42. Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633–44.
43. Pagidipati NJ, Navar AM, Pieper KS, et al. Secondary prevention of cardiovascular disease in patients with type 2 diabetes mellitus: international insights from the TECOS Trial (trial evaluating cardiovascular outcomes with sitagliptin). *Circulation* 2017;136:1193–203.
44. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999;353:617–22.
45. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93.
46. Gaede P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the STENO-2 randomised trial. *Diabetologia* 2016;59:2298–307.
47. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
48. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–34.
49. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:2099.

50. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–57.
51. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–306.
52. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;383:1425–35.
53. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;384:117–28.
54. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;384:129–39.
55. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–58.
56. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:262–74.
57. Pereira MJ, Eriksson JW. Emerging role of SGLT-2 inhibitors for the treatment of obesity. *Drugs* 2019;79:219–30.
58. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008.
59. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–24.
60. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436–46.
61. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018;11:749–61.
62. Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *Eur J Heart Fail* 2019;21:1279–87.
63. ClinicalTrials.gov, U.S. National Library of Medicine. Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure (DELIVER). Available at: https://clinicaltrials.gov/ct2/show/NCT03619213. Accessed June 9, 2021.
64. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2015;6:19–28.
65. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247–57.
66. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018;6:859–69.
67. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–22.
68. Mann JFE, Orsted DD, Buse JB. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:2197–8.
69. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–44.
70. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228–39.
71. Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL trial. *Diabetes Care* 2020;43:446–52.
72. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519–29.
73. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;394:131–8.
74. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121–30.
75. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841–51.
76. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;7:776–85.
77. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020;76:1117–45.
78. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–701.
79. Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. *Diabetes Metab* 2019;45:409–18.
80. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2012;8:728–42.
81. Donath MY, Burcelin R. GLP-1 effects on islets: hormonal, neuronal, or paracrine? *Diabetes Care* 2013;36(Suppl 2):S145–8.
82. Rangaswami J, Bhalla V, de Boer IH, et al. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: a scientific statement from the American Heart Association. *Circulation* 2020;142:e265–86.
83. Wong ND, Patao C, Wong K, Malik S, Franklin SS, Iloeje U. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes from 1999 to 2010: comparison by prevalent cardiovascular disease status. *Diab Vasc Dis Res* 2013;10:505–13.
84. Nelson AJ, Ardissino M, Haynes K, et al. Gaps in evidence-based therapy use in insured patients in the united states with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. *J Am Heart Assoc* 2021;10:e016835.