

Incorporating SGLT2i and GLP-1RA for Cardiovascular and Kidney Disease Risk Reduction

Call for Action to the Cardiology Community

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ABSTRACT: Multiple sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) have been shown to impart significant cardiovascular and kidney benefits, but are underused in clinical practice. Both SGLT-2i and GLP-1RA were first studied as glucose-lowering drugs, which may have impeded uptake by cardiologists in the wake of proven cardiovascular efficacy. Their significant effect on cardiovascular and kidney outcomes, which are largely independent of glucose-lowering effects, must drive a broader use of these drugs. Cardiologists are 3 times more likely than endocrinologists to see patients with both type 2 diabetes and cardiovascular disease, thus they are ideally positioned to share responsibility for SGLT-2i and GLP-1RA treatment with primary care providers. In order to increase adoption, SGLT-2i and GLP-1RA must be reframed as primarily cardiovascular and kidney disease risk-reducing agents with a side effect of glucose-lowering. Coordinated and multifaceted interventions engaging clinicians, patients, payers, professional societies, and health systems must be implemented to incentivize the adoption of these medications as part of routine cardiovascular and kidney care. Greater use of SGLT-2i and GLP-1RA will improve outcomes for patients with type 2 diabetes at high risk for cardiovascular and kidney disease.

Key Words: cardiovascular diseases ■ diabetes mellitus, type 2 ■ glucagon-like peptide-1 receptor ■ heart failure ■ kidney diseases ■ prevention & control ■ sodium-glucose transporter 2 inhibitors

Cardiovascular disease is a common cause of premature death and disability for patients with type 2 diabetes (T2D).¹ Although a plethora of therapeutic agents targeting traditional risk factors are proven to reduce cardiovascular risk in patients with T2D,^{2–5} decades of clinical research evaluating medications and strategies designed to treat its pathognomonic hallmark, hyperglycemia, have not translated into improvements in cardiovascular outcomes associated with glycemic control per se. Whether hyperglycemia is not causally contributing to cardiovascular risk, interventions were tested

too late into the disease process or for too short periods of time, or any benefits of glucose control may have been countered by harm associated with glucose-lowering therapies remains unclear. These observations had resulted in a waning of enthusiasm for glucose-lowering therapies as agents for cardiovascular event prevention until the surprise results from positive trials evaluating sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) that have been reported since 2015. Rather than reviewing the cardiovascular efficacy and putative mechanisms,

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Nonstandard Abbreviations and Acronyms

GLP-1RA	glucagon-like peptide-1 receptor agonist
PCSK-9	proprotein convertase subtilisin/kexin type 9
SGLT-2i	sodium glucose cotransporter-2 inhibitor
T2D	type 2 diabetes

which have been covered elsewhere in detail,^{6–9} this article provides a consensus view on the key reasons for underuse of SGLT-2i and GLP-1RA by cardiologists.

The first outcomes trials evaluating the cardiovascular effects of novel glucose-lowering therapies in patients with T2D to show significant reductions in cardiovascular events were EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose), which evaluated the SGLT-2i empagliflozin,¹⁰ followed by the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), which evaluated the GLP-1RA liraglutide.¹¹ EMPA-REG OUTCOME randomized 7020 participants with established cardiovascular disease to 1 of 2 doses of empagliflozin or placebo for a median follow-up of 3.1 years. The LEADER trial randomized 9340 participants, of whom 84% had established cardiovascular disease, to liraglutide or placebo for a median follow-up of 3.8 years. Not only did each agent reduce the risk for the primary composite outcome of cardiovascular death/myocardial infarction/stroke, but each also demonstrated significant reduction for cardiovascular and for all-cause death. The caveats to interpreting composite cardiovascular end points are well-documented,¹² but the impact of these medicines (empagliflozin and liraglutide, in particular) on both cardiovascular and all-cause death is compelling. Whereas subsequent trials have revealed some heterogeneity in the estimated magnitude of effect on atherosclerotic cardiovascular events across the SGLT-2i class,⁸ the outcome trials of empagliflozin,¹⁰ canagliflozin,^{13,14} dapagliflozin,¹⁵ and ertugliflozin¹⁶ support a consistent effect of SGLT-2i on reducing hospitalization for heart failure and propensity for kidney disease progression.^{8,17,18} In contrast, the GLP-1RA trials that followed the LEADER trial showed marked heterogeneity in cardiovascular efficacy,¹⁹ potentially explained by variation in each agent's structural homology, pharmacology, adherence to protocol, and the studied population.^{19,20} Outcomes trials evaluating the GLP-1RAs albiglutide,²¹ dulaglutide,²² and semaglutide²³ demonstrated significant reductions in atherosclerotic events, with meta-analyses revealing favorable but relatively modest effects on heart failure hospitalizations and kidney disease progression.²⁴ Trials of extended-release exenatide²⁵ and lixisenatide,²⁶ how-

ever, showed cardiovascular safety without significant cardiovascular benefit.

Through the demonstration of cardiovascular risk reduction in their respective cardiovascular outcome trials, multiple compounds from each class have received cardiovascular-specific indications in their regulatory product labeling. Society consensus statements and guidelines^{27–29} have subsequently integrated SGLT-2i and GLP-1RA under the umbrella term of “glucose-lowering drugs with cardiovascular benefit” and recommended their use in patients with T2D at high cardiovascular risk. However, despite robust clinical trial observations, product labeling, multidisciplinary society endorsement, and an ever-growing body of routinely collected clinical data further supporting the safety and efficacy of these agents in patients with T2D at varying degrees of cardiovascular risk,^{30–37} <10% of eligible patients receive either class of drug in the United States.^{38,39} Whereas varying insurance coverage and out-of-pocket costs are important contributors to underuse, there remains a number of system-, patient- and clinician-level barriers to optimal adoption by the cardiovascular and renal communities.

CHALLENGES OF BEING PERCEIVED AS GLUCOSE-LOWERING DRUGS

Until recently, cardiologists had little reason to be enthusiastic about strategies for managing hyperglycemia. Not only had each of the large outcome trials failed to demonstrate incremental cardiovascular benefits of more intensive glucose control versus contemporary standard glucose management,^{40–42} there were persistent concerns about the cardiovascular safety of a number of agents, including the sulfonylurea class^{43,44} and the thiazolidinediones rosiglitazone and pioglitazone.⁴⁵ Subsequently, the US Food and Drug Administration and the European Medicines Agency in collaboration each provided guidance that companies should establish definitive evidence of the cardiovascular safety of glucose-lowering drugs developed for the treatment of T2D.^{46,47} The trials conducted in response to this guidance have primarily adopted noninferiority designs versus placebo, with all patients receiving open-label routine diabetes care otherwise, and primarily designed to establish cardiovascular safety with cardiovascular efficacy analyzed secondarily. After results from the first several trials reported cardiovascular safety but without incremental cardiovascular efficacy of dipeptidyl-peptidase-4 inhibitors and the first completed GLP-1RA trial,^{26,48–50} the unexpected landmark finding of marked cardiovascular clinical benefit observed with empagliflozin in EMPA-REG OUTCOME changed the field.¹⁰

The cardiovascular community was faced with assimilating these novel data of cardiovascular benefit observed in EMPA-REG OUTCOME and LEADER, but the SGLT-2i and GLP-1RA classes were not new

to endocrinologists. Exenatide had been commercially available in the United States since 2005 and canagliflozin since early 2013. Analogous to the cardiovascular community closely following the growth and evolution of novel agents and their effects on cardiovascular outcomes (eg, nonvitamin K antagonist oral anticoagulants, PCSK-9 [proprotein convertase subtilisin/kexin type 9] inhibitors, neprilysin inhibitors), endocrinologists were familiar with these agents and their effects on glycemic end points for several years before their cardiovascular outcome trials. Evidence of the respective disciplinary interest is reflected in the volume and timing of related content in academic medical journals (Figure 1). Review of a PubMed search for SGLT-2 inhibitor or sodium-glucose cotransporter inhibitor or GLP-1RA or glucagon-like peptide-1 receptor agonist reveals 3195 publications between 2010 and 2020. Of these articles, 39.1% were published in endocrine specialty journals, 11.0% in cardiology journals, 3.5% in nephrology journals, and 46.4% in other fields (eg, general medicine, other specialty, or pharmacology). More than half of the 351 articles in cardiology journals were published in the last 2 years, which highlights the paucity of exposure the cardiovascular community had to these agents until well after numerous outcome trials were published. In contrast, endocrine journals had covered the clinical development of both SGLT-2i and GLP-1RA before the publication of positive outcome trials, with 313 articles published between 2010 and 2015 on either agent in endocrine journals and only 36 articles in cardiology journals over the same time period. Endocrinologists thus were prepared to use (and were using) these drugs well before other providers, not only given their glucose-lowering mechanism and indication, with salutary features of no increased risk of hypoglycemia and both

classes causing weight loss, but also as a byproduct of their endocrine-focused clinical development pipeline. It comes as little surprise that in data from a large US health system in 2018, of all the prescriptions filled for SGLT-2i, endocrinologists had written 40% of them, compared with cardiologists being responsible for only 5.1%.⁵¹ In a subsequent analysis of prescribing habits for patients with cardiovascular disease and T2D from a health system in Mississippi, cardiologists were only responsible for 6% of SGLT-2i and 1.4% of GLP-1RA prescriptions in 2019 (Figure 2).⁵²

OPPORTUNITY FOR CARDIOLOGY ENGAGEMENT

The arrival of SGLT-2i and GLP-1RA provides cardiologists with an opportunity to markedly reduce cardiovascular and kidney morbidity and mortality in their patients with T2D with or at high risk for cardiovascular disease. Analogous to the arrival of statins in the 1980s, cardiology uptake was initially slow, but once cardiologists adopted the statins as a cardiovascular therapy, they drove their use in clinical practice. This, in turn, led to increased prescribing by primary care clinicians and broad prescription across the population. Similarly, with SGLT-2i and GLP-1RA, cardiologists must move past deferring initiation to other providers and become familiar with prescribing these agents themselves—not to embark on glucose control per se, but rather adding another class of medication with robust evidence for cardiovascular risk reduction. Initiation of these medications clearly remains within the purview of primary care providers and endocrinologists, however each of these provider groups faces barriers of their own. Primary care providers have a multitude of issues to consider during

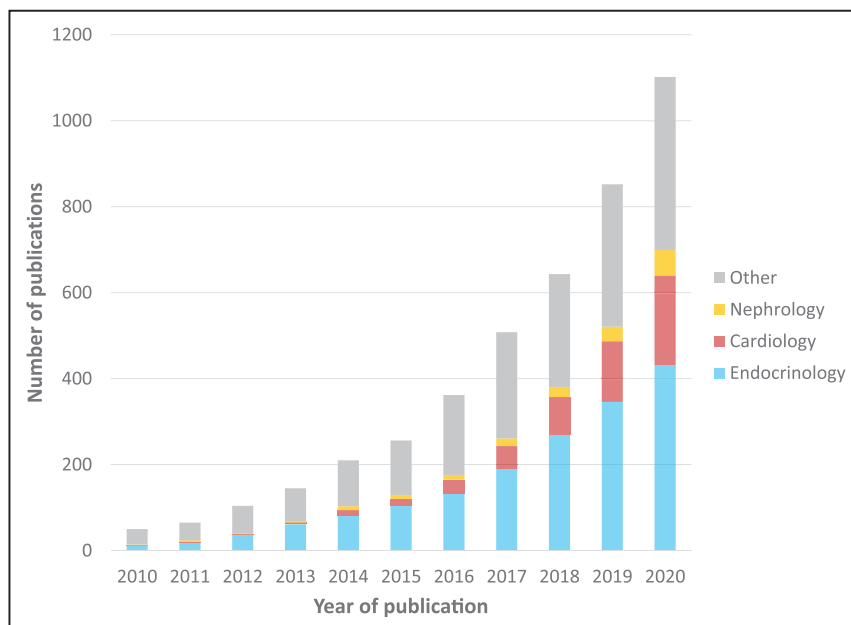


Figure 1. Articles on sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists by discipline over time. Distribution of PubMed search results for sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists by specialty journal over time.

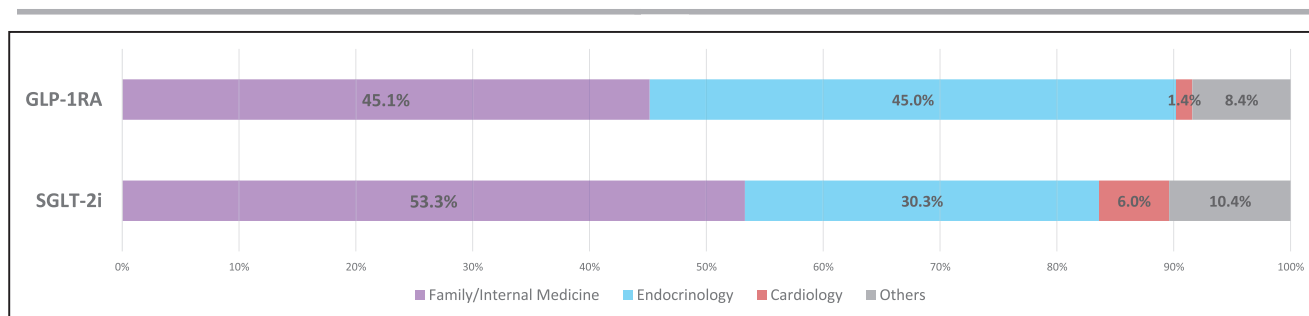


Figure 2. Prescribing habits by clinician type for patients with type 2 diabetes and cardiovascular disease.

Figure adapted from Hamid et al.⁵² using data from a single health care system in Mississippi. GLP-1RA indicates glucagon-like peptide-1 receptor agonists; and SGLT-2i, sodium glucose cotransporter-2 inhibitors.

any given visit and endocrinologists only see 1 out of 6 patients with T2D and atherosclerotic cardiovascular disease.⁵³ In contrast, 70% of patients with T2D and high cardiovascular risk are seen in cardiology outpatient clinics; thus, cardiologists are ideally positioned to lead the adoption of SGLT-2i and GLP-1RA.⁵⁴

Uptake by cardiologists has been slow. Survey data from 2019 from a large US health system showed that 80.6% of cardiologists had not prescribed an SGLT-2i in the previous 12 months and 83.9% had not prescribed a GLP-1RA.⁵⁵ Almost 2-thirds of the cardiologists surveyed reported a lack of knowledge to safely prescribe these agents and more than half believed they were not responsible for their prescription in the first place. This is not entirely unexpected when one considers the lag that often exists between evidence of efficacy and subsequent translation to clinical practice, but this is likely to have been exacerbated by the volume and rapidity of evidence generation that has occurred among patients with T2D compared with other cardiovascular disciplines (Figure 3). Education in the context of a multifaceted intervention must be implemented to drive a rightward shift in the adoption curve of these agents by cardiologists. This will involve moving from the status quo (Figure 4, dark gray), where the majority of cardiologists lack practical knowledge of either class and subsequently defer prescription responsibility to other clinicians, to a future state, in which cardiologists view these agents primarily as cardiovascular risk-reducing therapies (analogous to statins) and are comfortable, autonomous, and proactive with their prescription (Figure 4, light gray). Because the most compelling benefit of the proven SGLT-2i and GLP-1RAs is to reduce cardiovascular and kidney risk rather than to lower HbA1c (Figure 5), initiation of these medications by cardiologists and nephrologists is essential if they are committed to reducing cardiovascular risk in the large proportion of their patients with T2D. The need to reframe SGLT-2i and GLP-1RA as primarily cardiovascular drugs is illustrated by their impressive effects on cardiovascular death (Figure 5); not only are their relative effects of similar magnitude to those traditionally considered to be cardiovascular drugs, they occurred in

populations already receiving high levels of baseline preventive therapies.

NAVIGATING THERAPEUTIC BOUNDARIES: CARDIOVASCULAR DRUGS THAT LOWER BLOOD GLUCOSE

One clear barrier to uptake of SGLT-2i and GLP-1RA by cardiologists is concern about overstepping therapeutic boundaries and potentially alienating other providers in the care of the patient, some of whom may constitute a referral base.⁵⁵ However, with ever-increasing understanding of the interconnected nature of cardiovascular disease, kidney disease, and T2D, and the necessary coordinated care of patients with these common comorbidities across providers and disciplines, these therapeutic boundaries are starting to blur. Recent years have seen the development of cardiometabolic clinics with multidisciplinary providers engaged in a common space with global disease treatment focus, and some have advocated for a separate subspecialty that focuses on cardiometabolic disease.^{56–58} It is critical for patient care, as well, to provide a team-based approach for patients with T2D whenever possible. Such an approach would encourage communication and collaboration between cardiologists and diabetes care providers, whether primary care physicians or endocrinologists. For example, a cardiologist directly communicating to a patient's diabetes primary care provider or endocrinologist who is managing hyperglycemia that he or she is initiating an SGLT-2i or GLP-1RA for cardiovascular benefit and will continue to defer glucose management serves the referring providers and the patient well. Reframing these agents as a central component of cardiovascular risk reduction, separate from their effect on glucose-lowering, places them within each clinician's mandate, yet maintains space for the team of providers to collaborate and focus on each of the key specialty domains for the best health care and outcomes for the patient (Figure 6).

The results of 3 large trials of SGLT-2i that enrolled patients with or without T2D further de-emphasize the

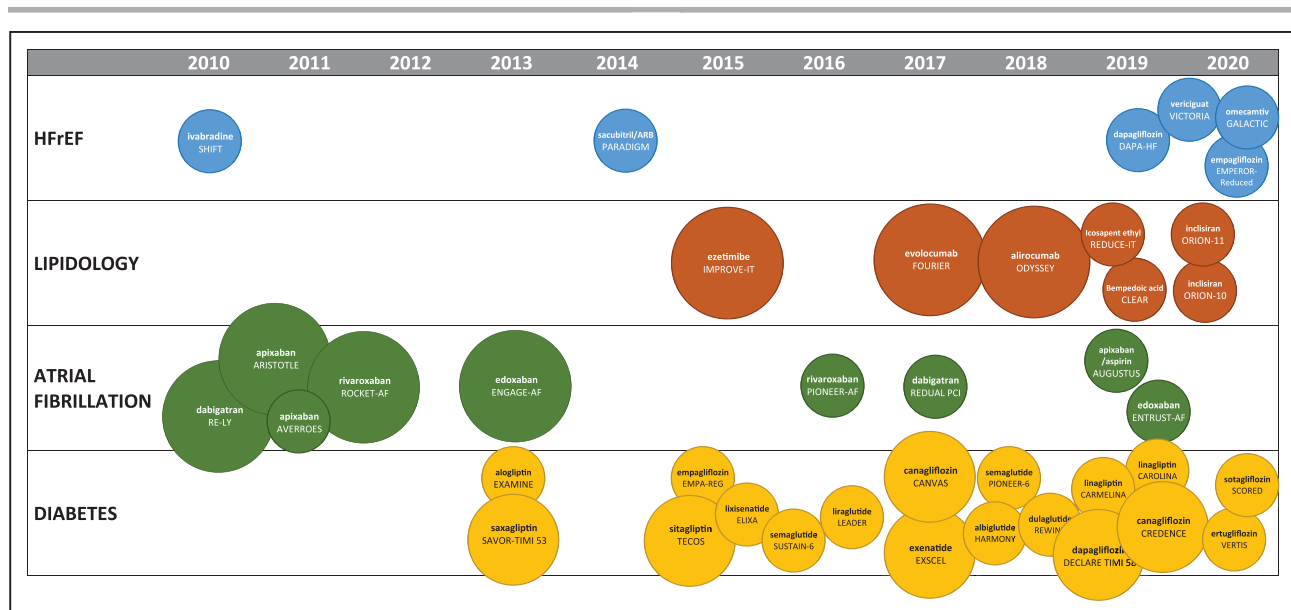


Figure 3. Rapidity and volume of evidence generation.

Timeline of evidence generation for seminal trials in key cardiovascular diseases and diabetes. Size of plot represents sample size (small <10 000; large ≥10 000). ARB indicates angiotensin receptor blocker; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AUGUSTUS, Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; AVERROES, Phase III Study of Apixaban in Patients With Atrial Fibrillation; CANVAS, Canagliflozin Cardiovascular Assessment Study; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes; CLEAR, Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; ENGAGE-AF, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation; ENTRUST-AF, Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; EXSCCEL, Exenatide Study of Cardiovascular Event Lowering; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GALACTIC, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; HARMONY, A Study to Determine the Safety and Efficacy of Albiglutide in Patients With Type 2 Diabetes; HFREF, heart failure with reduced ejection fraction; IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ODYSSEY, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome; ORION, Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol; PARADIGM, Prospective Comparison of Angiotensin-Receptor-Neprilysin Inhibitor With Angiotensin-Converting-Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; PIONEER-6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; PIONEER-AF, A Study Exploring Two Strategies of Rivaroxaban (JNJ39039039; BAY-59-7939) and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy; REDUAL PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a PCI With Stenting; REDUCE-IT, Reduction of Cardiovascular Events With EPA-Intervention Trial; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; ROCKET-AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SHIFT, Systolic Heart Failure Treatment With the I, Inhibitor Ivabradine Trial; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin; VERTIS, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease; and VICTORIA, A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction.

role of their glucose-lowering effects and amplify the importance of their overall effect on cardiorenal outcomes. Although previous cardiovascular outcome trial data had shown the salutary cardiovascular effects of SGLT-2i to be independent of baseline glycemic control, baseline glucose-lowering treatment, and glucose control achieved,^{17,59,60} DAPA-HF (Dapagliflozin and

Prevention of Adverse Outcomes in Heart Failure),⁶¹ EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction),⁶² and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)⁶³ were the first to enroll large numbers of patients without diabetes. DAPA-HF and EMPEROR-

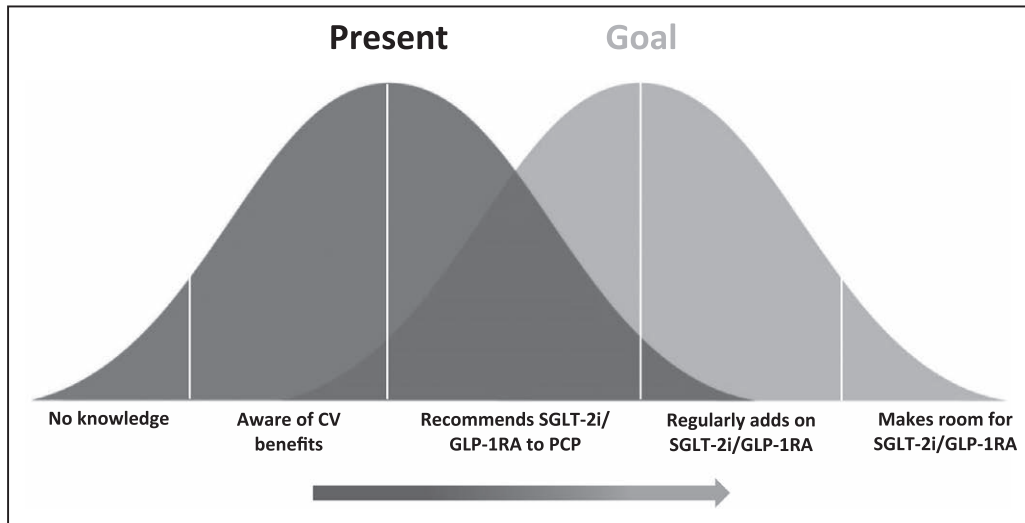


Figure 4. Conceptual representation of physician adoption and clinical competency with sodium glucose cotransporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) use. Present status (dark gray) vs future goal status (light gray) is shown. CV indicates cardiovascular; and PCP, primary care provider.

Reduced enrolled patients with heart failure with reduced ejection fraction (ejection fraction $\leq 40\%$) who were symptomatic despite guideline-directed medical therapy including renin-angiotensin system blockers, β -blockers, and mineralocorticoid receptor antagonists. In DAPA-HF, 4744 patients, 58% of whom did not have T2D, received either dapagliflozin or placebo for a median of 18.2 months; in EMPEROR-Reduced, 3730 patients, 50% of whom did not have T2D, received either empagliflozin or placebo for a median of 16 months. In both trials, a primary outcome event of heart failure hospitalization or cardiovascular death was 25% less likely to occur among patients treated with an SGLT-2i, regardless of the presence or absence of T2D. This magnitude of benefit on top of existing guideline-directed therapy⁶⁴ has firmly established the

SGLT-2i class as the 4th pillar of heart failure with reduced ejection fraction medical therapy, providing another mandate for cardiologists to become familiar with this class of drug independent of its glucose-lowering indication. In DAPA-CKD, 4304 patients with chronic kidney disease (estimated glomerular filtration rate 25 to 75 mL/min/1.73 m²) received either dapagliflozin or placebo on top of maximum tolerated renin-angiotensin-aldosterone system blocker. The trial was stopped early for benefit at a median follow-up of 2.4 years, at which time the composite primary outcome event of kidney disease progression or cardiovascular or kidney death was almost 40% less likely to occur among patients receiving dapagliflozin compared with placebo—a finding that was not statistically different between participants with and without diabetes (32%).

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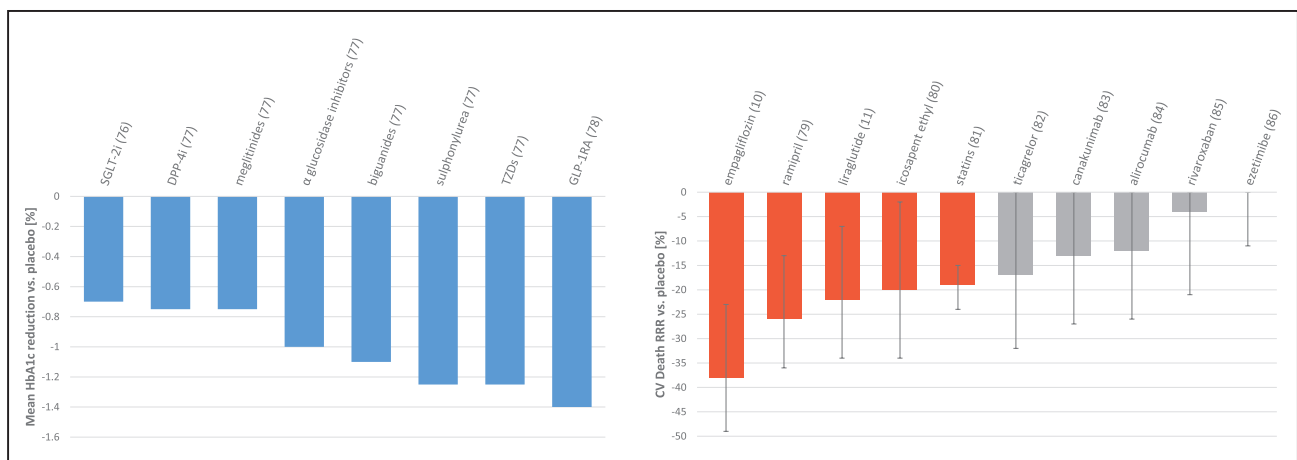


Figure 5. Comparison of effects of sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) on glycated hemoglobin (HbA1c) and cardiovascular death.

A, Mean reduction of HbA1c with commonly used glucose-lowering therapies. **B**, Mean relative risk reduction of cardiovascular death in seminal studies of traditional cardiovascular drugs in patients with atherosclerotic cardiovascular disease (red = significant; gray = nonsignificant). CV indicates cardiovascular; DPP-4i, dipeptidyl-peptidase-4 inhibitors; RRR, relative risk reduction; and TZD, thiazolidinedione.

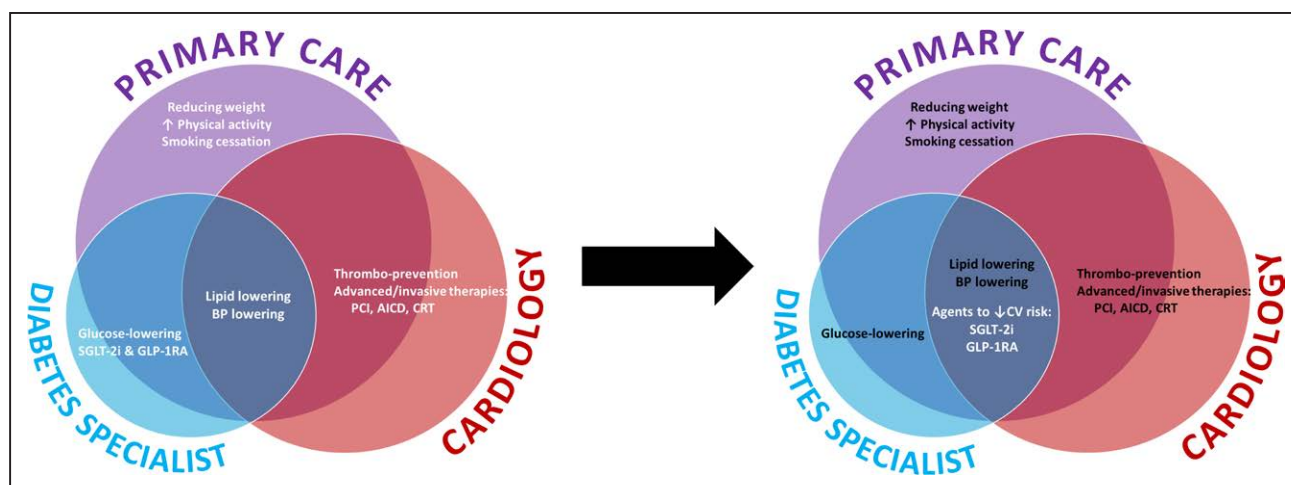


Figure 6. Reframing sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) as agents for cardiovascular risk reduction beyond their role in lowering glucose.

Optimal care of the patient with chronic diseases such as type 2 diabetes and cardiovascular disease occurs when there is interdisciplinary care. In this context, whereas there tends to be some therapeutic focus for each discipline (eg, cardiologists: advanced therapies, thromboprevention; primary care: lifestyle measures, comorbidities), glucose-lowering tends to lie outside a cardiologist's comfort zone. Reframing SGLT-2i and GLP-1RA as cardiovascular risk-reducing agents will bring them into everyone's therapeutic purview and aid in their adoption. AICD indicates automated implantable cardioverter defibrillator; BP, blood pressure; CRT, cardiac resynchronization therapy; CV, cardiovascular; and PCI, percutaneous coronary intervention.

With more than half of all patients with cardiovascular disease exhibiting some degree of chronic kidney disease,⁶⁵ these recent data identify another group of patients alongside those with T2D or heart failure with reduced ejection fraction likely to be managed by cardiologists at some stage.

SEPARATING SGLT-2i AND GLP-1RA

Conflating the SGLT-2i and GLP-1RA classes into an umbrella term of glucose-lowering drugs with proven cardiovascular benefit has been a critically important step in driving the narrative of cardiovascular risk reduction for patients with T2D, but ultimately this nomenclature may become overly simplistic. Most contemporary guidelines and society recommendations endorse considering patients with T2D as being at predominant risk for "atherosclerotic cardiovascular disease" or "heart failure" as a way of determining whether a GLP-1RA or an SGLT-2i should be added, independent of the background glucose-lowering regimen.^{28,29,66} Although it is pragmatic to determine from which agent a patient is most likely to benefit, this is often a false dichotomy because of substantial overlap in atherosclerotic cardiovascular disease and heart failure risk.¹ There is growing evidence that cardiovascular (and potentially kidney) benefits from either agent may be independent and additive.^{67–70} Thus, although combined prescription of both SGLT-2i and GLP-1RA is financially prohibitive in many payment environments and outcome data are awaited, foreseeably patients may benefit from combination of both classes of these drugs. Ultimately the ability to align a more granular understanding of the mechanistic benefits with mark-

ers for residual risk for cardiovascular and renal disease in individual patients will enable a more personalized approach to the use of these classes of medicines.

MULTIFACETED AND MULTILEVEL APPROACH IS NEEDED: RATIONALE FOR THE COORDINATE DIABETES TRIAL

A plethora of randomized clinical trial data demonstrate the favorable outcomes associated with multifactorial management of risk factors in patients with diabetes, yet in clinical practice <20% achieve guideline-recommended treatment targets.^{38,39} Barriers to optimal care for patients with diabetes exist at a system, clinician, and patient level and are ripe for interventional efforts aimed at improving the overall quality of care and designing new treatment paradigms. In particular, educational, multifaceted, and multilevel interventions to improve the implementation of guidelines has been the focus of a number of professional societies. In the United States, the American Heart Association has partnered with the American Diabetes Association and produced a number of clinician- and practice-level education resources in their Know Diabetes by Heart initiative. The American College of Cardiology has generated an educational program titled the Succeed in Managing Cardiovascular Risk in Diabetes initiative (SIM-CVRiD) that includes podcasts and quizzes. Beyond education, there has been renewed energy in considering a new preventive cardiology subspecialty, with some calling for a dedicated cardiometabolic fellowship as outlined above.^{56–58,71,72} Others have proposed the need for simplifying and harmonizing guidelines and treatment algorithms

across cardiovascular, endocrine, and kidney disciplines to improve implementation and dissemination.^{73,74}

Education remains fundamental to increasing adoption, but a large body of evidence suggests it is not enough on its own to induce sustainable clinician behavior change. Most studies suggest it is the combination of both education as well as audit and feedback that lead to meaningful improvements in health care quality.⁷⁵ To this end, the cluster-randomized COORDINATE Diabetes (Coordinating Cardiology Clinics Randomized Trial of Interventions to Improve Outcomes) is evaluating the effect of multifaceted educational outreach and practice clinician- and patient-level feedback on improving care for patients with T2D with or at high risk for cardiovascular disease (NCT03936660). The trial will cluster-randomize US cardiology clinics to either multifaceted and multilevel intervention or basic education and measure the effect on prescription of 3 key medications: high-intensity statin, renin-angiotensin system blocker (angiotensin-converting enzyme inhibitor or angiotensin receptor II blocker), and either SGLT-2i or GLP-1RA.

CONCLUSIONS

Positive outcome data from trials evaluating SGLT-2i and GLP-1RA have reshaped the management of patients with T2D at high risk for adverse cardiovascular outcomes. Yet despite proven efficacy, professional society guideline endorsement, and regulatory labels for cardiovascular benefit, these medicines remain profoundly underused in clinical practice. The initial approval of SGLT-2i and GLP-1RA as glucose-lowering drugs for T2D has likely impeded their uptake by cardiologists, who tend to consider glycemic control and HbA1c targets as outside of their therapeutic scope. Rather, SGLT-2i and GLP-1RA ought to be considered as cardiorenal risk reducing agents with an added benefit of lowering glucose, thereby firmly placing their use within a cardiologist's purview. All clinicians caring for patients with T2D must be comfortable with prescribing SGLT-2i and GLP-1RA, but cardiologists are particularly well placed to drive adoption because they are responsible for the majority of eligible cardiovascular patients. With <10% of patients with a cardiovascular indication taking either an SGLT-2i or GLP-1RA, payers, regulators, professional societies, and clinicians need to work collaboratively to develop and evaluate strategies to reframe and adopt SGLT-2i and GLP-1RA as routine cardiovascular and renal risk-mitigating therapies.

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