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HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITORS)

Bridging the Gap for Patients with Diabetes and Cardiovascular Disease Through Cardiometabolic Collaboration

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Abstract

Purpose of Review Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with type 2 diabetes (T2D). Recent cardiovascular outcome trials (CVOTs) have established sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1 RA) as powerful medications that can lower glucose as well as reduce the risk of complications of CVD in many individuals with T2D. The combination of glycemic and cardiovascular benefits of SGLT2i and GLP1 RA has highlighted the importance of collaborative care of patients by diabetes and cardiovascular specialists. We review several models of cardiometabolic care for patients with diabetes and CVD and discuss practical ways in which diabetes and cardiovascular specialists can work together to improve cardiometabolic care.

Recent Findings CVOTs for SGLT2i and GLP1 RA have demonstrated a significant reduction in major adverse cardiovascular events in individuals with T2D and CVD, in addition to their beneficial effects on glucose lowering and weight loss. Additionally, several models of care, including population health screening models with or without a remote management intervention, multidisciplinary clinics, and combined cardiometabolic training, have been proposed to better facilitate the multifaceted care that individuals with diabetes and CVD require.

Summary Innovative models of cardiometabolic care have the potential to improve the quality of care that individuals with diabetes and CVD receive. Through collaboration and co-management, diabetes specialists, cardiovascular specialists, and primary care providers have the ability to optimize diabetes and cardiovascular care.

Keywords Type 2 diabetes · Cardiometabolic · SGLT2 inhibitors · GLP1 receptor agonists · Cardiovascular outcome trials

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Introduction: Call to Action for Cardiometabolic Collaboration Between Diabetes Specialists and Cardiovascular Specialists

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in individuals with diabetes. Atherosclerotic CVD (ASCVD) in particular, encompassing coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease, is itself the number one cause of morbidity and mortality in individuals with diabetes. Diabetes confers a two-fold excess risk for CHD and stroke [1], and about two-thirds of deaths in individuals with diabetes are attributable to CVD [2]. While there is evidence that 10-year CHD risk and event rates for acute myocardial infarction (MI) and stroke among adults with diabetes in the USA significantly improved from 2000 to 2010, more recent evidence indicates these improvements plateaued after 2010, and rates for

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MI and stroke have actually increased, primarily among young and middle-aged adults [3, 4].

Common cardiometabolic conditions such as hypertension and dyslipidemia are modifiable risk factors for ASCVD. Comprehensive CV risk factor control, including counseling on a healthy diet, regular physical activity, weight loss, and smoking cessation, as well as control of blood pressure, low density lipoprotein (LDL) cholesterol, and guideline-appropriate use of antiplatelet agents, reduces CV events and improves survival in individuals with diabetes [5, 6]. Despite the established impact and tolerability of many of these interventions, like statin therapy, underutilization of such therapies is well documented. Such data are relevant not only to improving outcomes in patients with diabetes but also to fully realizing the benefit of other advances once documented.

Elevated glucose levels are the hallmark of diabetes. Yet while intensive glucose control has been consistently associated with significant reduction in microvascular outcomes, the effects of intensive glucose control on CV outcomes have been more complex. Thus, many CV specialists caring for individuals with diabetes have focused on managing traditional CV risk factors rather than managing glucose-lowering therapies.

The advent of new glucose-lowering medications that reduce CV outcomes has placed the overlap between cardiology and diabetology front and center. Several sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1 RA) have demonstrated significant reductions in major adverse cardiovascular events (MACE) [7–12, 13••, 14] and renal outcomes [13••] in CV outcome trials (CVOTs) (Table 1).

In 2015, results of the EMPA-REG OUTCOME trial were published, which randomized 7020 participants with established CVD and type 2 diabetes (T2D) to the SGLT2i empagliflozin or placebo [7]. EMPA-REG OUTCOME demonstrated a 14% reduction in the primary outcome of 3-point MACE, a composite of death from CV causes, non-fatal MI, and non-fatal stroke. It also demonstrated a 38% reduction in death from CV causes, a 35% reduction in hospitalization for heart failure (HF), a 32% reduction in all-cause mortality, and a 39% reduction in incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease) and incident albuminuria [7, 15].

Subsequent CVOTs with two other SGLT2i, canagliflozin [9] and dapagliflozin [12], have also shown significant CV risk reduction. Benefits in reduction in MACE, hospitalization for HF, and worsening nephropathy appear to be class effects of SGLT2i [16]. More recently, the CREDENCE trial demonstrated significant renal risk reduction with canagliflozin in patients with stage 2 to 3 chronic kidney disease (CKD) and T2D with baseline albuminuria on maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers [13••]. Additionally, the DAPA-HF trial demonstrated a significant reduction in the risk of worsening heart failure or death from cardiovascular causes with dapagliflozin in patients with heart failure and a reduced ejection fraction of 40% or less, with or without diabetes [17].

In 2016, the results of the LEADER trial were published, which randomized 9340 participants with high CV risk to receive the GLP1 RA liraglutide or placebo [8]. LEADER demonstrated a 13% reduction in 3-point MACE, a 22% reduction in death from CV causes, a 15% reduction in death from any cause, and a 23% reduction in nephropathy (new onset of macroalbuminuria or a doubling of serum creatinine and an estimated glomerular filtration rate of ≤ 45 ml per minute per 1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease). While the CVOT for lixisenatide [18] did not show significant CV risk reduction, and the CVOT for once weekly exenatide [19] showed a trend toward CV risk reduction that just missed significance, the CVOTs for once weekly semaglutide [10], albiglutide [11], and dulaglutide [14] all demonstrated significant reduction in 3-point MACE. These clear, significant signals of CV risk reduction with SGLT2i and GLP1 RA have markedly transformed the landscape of pharmacotherapy recommendations in individuals with diabetes and CVD. The CVOT for an oral version of semaglutide demonstrated a non-significant 21% decrease in 3-point MACE, with significant reductions in death from CV causes (hazard ratio 0.49; 95% confidence interval, 0.27 to 0.92) and death from any cause (hazard ratio 0.51; 95% confidence interval, 0.31 to 0.84) [20].

Based on the wealth of data from these studies demonstrating CV and renal benefit in addition to glucose-lowering effects, numerous professional endocrinology and cardiology societies have updated their guidance in management to emphasize the use of SGLT2i and GLP1 RA in patients with CVD and diabetes. In 2018, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes issued a joint consensus report for the management of hyperglycemia in T2D, which emphasized that the presence of ASCVD, HF, and CKD should be a major consideration in pharmacologic management of T2D [21]. Specifically, the report emphasized the cardiorenal benefits of SGLT2i and GLP1 RA and recommended consideration of these medications (after first-line therapy of metformin and comprehensive lifestyle education) in patients with known ASCVD, HF, and/or CKD. This CV-focused paradigm was incorporated into the ADA's 2019 Standards of Care [22]. Recent professional statements and guidelines from the American Association of Clinical Endocrinologists, American College of Endocrinology, American College of Cardiology, American Heart Association, Heart Failure Society of America, and European Society for Cardiology have also prioritized the role of SGLT2i and GLP1 RA in the management of patients with CVD, HF, and/or CKD [23–28].

Despite ample evidence of the importance of CV risk factor control in reducing CV events and improving survival in patients with diabetes, nearly half of patients with diabetes fail to achieve

Table 1 Key CVOT results for SGLT2i and GLP1 RA

			Primary outcome	Secondary outcomes of interest		
Class	CVOT	Agent	3-point MACE*	Hospitalization for HF	All-cause mortality	Worsening nephropathy
SGLT2i	EMPA-REG OUTCOME ($n = 7020$)	Empagliflozin	*0.86 (0.74–0.99)*	*0.65 (0.50–0.85)*	*0.68 (0.57–0.82)*	*0.61 (0.53–0.70)*
	CANVAS program ($n = 10,142$)	Canagliflozin	*0.86 (0.75–0.97)*	*0.67 (0.52–0.87)*	0.87 (0.74–1.01)	*0.60 (0.47–0.77)*
	DECLARE-TIMI 58 ($n = 17,160$)	Dapagliflozin	*0.93 (0.84–1.03)*[#]	*0.73 (0.61–0.88)*	0.93 (0.82–1.04)	*0.76 (0.67–0.87)*
GLP1 RA	ELIXA ($n = 6068$)	Lixisenatide	1.02 (0.89–1.17)[†]	0.96 (0.75–1.23)	0.94 (0.78–1.13)	n/a
	LEADER ($n = 9340$)	Liraglutide	*0.87 (0.78–0.97)*	0.87 (0.73–1.05)	*0.85 (0.74–0.97)*	*0.78 (0.67–0.92)*
	SUSTAIN-6 ($n = 3297$)	Semaglutide (injectable)	*0.74 (0.58–0.95)*	1.11 (0.77–1.61)	1.05 (0.74–1.50)	*0.64 (0.46–0.88)*
	EXSCEL ($n = 14,752$)	Exenatide weekly	0.91 (0.83–1.00)	0.94 (0.78–1.13)	0.86 (0.77–0.97)[‡]	n/a
	HARMONY Outcomes ($n = 9463$)	Albiglutide	*0.78 (0.68–0.90)*	n/a	0.95 (0.79–1.16)	n/a
	REWIND ($n = 9901$)	Dulaglutide	*0.88 (0.79–0.99)*	0.93 (0.77–1.12)	0.90 (0.80–1.01)	*0.85 (0.77–0.93)*
	PIONEER-6 ($n = 3183$)	Semaglutide (oral)	0.79 0.57–1.11	0.86 (0.48–1.55)	*0.51 (0.31–0.84)*	n/a

CVOT, cardiovascular outcome trial; *FDA*, Food and Drug Administration; *SGLT2i*, sodium glucose co-transporter-2 inhibitor; *GLP1 RA*, glucagon-like peptide-1 receptor agonist; *MACE*, major adverse cardiovascular events; *CV*, cardiovascular; *HF*, heart failure

Hazard ratios that reached statistical significance are indicated by italicized font

*Most CVOTs for SGLT2i and GLP1 RA used 3-point MACE (death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke) as the sole primary outcome, except for DECLARE-TIMI 58 and ELIXA, as outlined below

[#] DECLARE-TIMI 58 had co-primary outcomes: (1) 3-point MACE, HR 0.93 (0.84–1.03) (did not reach significance) and (2) combined CV death or hospitalization for HF, 0.83 (0.73–0.95) (reached significance)

[†] In ELIXA, the primary outcome was 4-point MACE (3-point MACE + hospitalization for unstable angina)

[‡] In EXSCEL, a 14% reduction in all-cause mortality was seen with exenatide, but this result is considered exploratory due to the hierarchical statistical testing

blood pressure or LDL cholesterol goals [3]. Additionally, despite results of major CVOTs and updates in professional guidelines, glucose-lowering medications with evidence of CV benefit remain markedly underutilized in the treatment of diabetes in patients with CVD [29–32]. For example, in a US-based registry of 1735 patients with T2D and ASCVD, only 9.0% were on SGLT2i, and only 7.9% were on GLP1 RA [31]. Furthermore, given the huge array of medication options for these patients—as of now, 12 classes of glucose-lowering agents, about 10 classes of antihypertensive agents, and 9 therapies for HF with reduced ejection fraction have been approved by the US Food and Drug Administration (FDA)—polypharmacy and complexity in this high-risk cohort of people with diabetes and CVD will be common. Successful co-management and collaboration between healthcare professionals at the frontline of diabetes and CVD—primary care providers, diabetes specialists, and CV specialists—can optimize efforts to reduce morbidity and mortality, streamline therapies, and improve patient access, costs, and quality of life, while reducing side effects.

One potential contributor to limited utilization of these newer glucose-lowering agents with CV benefit may be the unprecedented need for interaction and shifting treatment responsibilities among various care providers involved in managing diabetes and its associated CV risk. In this review, we aim to detail proposed models of effective collaboration among primary care providers, diabetes specialists, and CV specialists in the co-management of individuals with diabetes and CVD. In the first half, we will examine models of cardiometabolic management in patients with diabetes and CVD. In the second half, we will discuss practical aspects of what is needed for successful cardiometabolic collaboration between diabetes specialists and CV specialists on behalf of patients.

First, we will discuss several models of cardiometabolic care. We will review several existing paradigms of care and their strengths and limitations specifically in regard to diabetes management, as well as discuss several less common but promising models that could provide innovative ways to deliver collaborative cardiometabolic care.

Consultative/Referral Model

In this model, individuals with diabetes and CVD see individual providers/specialists (primary care providers, diabetes specialists, and CV specialists) in providers' respective practices. Each practitioner focuses on his or her care in a specific area. This is the current model that most patients in the USA experience and the one traditionally used by primary care providers and specialists.

Advantages

This model does not require any changes to the current system and practice of individual care providers. Patients may perceive they are getting the best care available when they see the specialist.

Challenges

The consultative/referral model has several aspects that may impede optimal care of the patient. Among providers involved in the care of the patient, confusion can occur over respective roles in the management of various components of cardiometabolic disease. For example, primary care providers, diabetes specialists, and CV specialists all manage hypertension and dyslipidemia. Which provider ought to take the lead in managing these components? Lack of clarity of respective roles can result in clinical inertia, potentially incorrect assumptions about why a given medicine perceived as falling under a specific specialty's purview was not started, and/or confusion if multiple providers weigh in or institute treatment on an overlapping condition, like diabetes. Additionally, providers may be concerned about their medication plans for a patient being unduly adjusted by another provider. Difficulties in effective communication can also compound issues of management. Providers may find it both inefficient and inconvenient to communicate their management plans and medication changes to other providers. This is especially true when patients see providers located within different healthcare systems or centers and is often a real or perceived issue for primary care providers.

Patient inconvenience and dissatisfaction can also occur. Involvement of multiple providers can result in delays in care as patients await appointments to see specialists. Patients are often forced to see multiple providers at different visits and at different times, resulting in an inherently inefficient process. Moreover, patients may receive different recommendations from different specialists. The lack of attention to an issue, like the failure of a CV specialist to discuss or address diabetes, can reinforce the false notion of diabetes not being important to CV outcomes. Polypharmacy and the risk of confusion or duplication of medications are potential dangers as well.

Given variable densities of available specialists across the USA, certain geographic areas serving communities of patients may lack access to subspecialty providers [33]. As such, provision of care may be limited by available resources, and thus care models may be less flexible.

Ultimately, the consultative/referral model works best when providers have clearly delineated roles and effective lines of communication and when patients have sufficient health literacy to facilitate communication between providers. However, the data for underutilization of agents with established cardiometabolic benefits does suggest the need to consider other models of care.

Population Healthcare Delivery Models, With or Without a Remote Management Intervention

The widespread use of electronic health records (EHR) has allowed the identification of patients with suboptimal achievement of target values across a population of patients. In one model, such approaches can be coupled to notifications to primary care providers, specialists, and even the patient as a way of calling attention to the particular issue. In a more intensive model, population health screening can be coupled to actual patient management, generating a referral to a clinic or implementation of an algorithm-based protocol to initiate and titrate medications to target doses or goals. Remote monitoring of patients through the use of electronic blood pressure cuffs, glucometers, and laboratory testing enables convenient supervision for efficacy and adherence to medications. While physicians often help direct these programs, many are led by advanced practice providers or pharmacists [34]; some may even use patient navigators [35]. Such approaches have shown promising results in hypertension management [34, 35] and lipid management [36].

Advantages

Major advantages of this model include generalizability and scalability. Such programs have the potential to reach larger portions of the population. They can directly address limitations of the current healthcare system; specifically, they can identify patients with suboptimal care, overcome therapeutic inertia, mitigate delays in medication titration, facilitate remote monitoring, educate patients, and engage patients in self-care. Incremental adjustments to care may be facilitated outside of the confines of limited, short-duration, episodic ambulatory visits.

Several key advantages exist with the use of non-medical professionals (e.g., navigators) to monitor and titrate medications (based on clinical algorithms under the supervision of medical professionals) as well as teach and motivate patients: (1) reduced burden on healthcare professionals in day-to-day management of cardiometabolic issues; (2) increased time spent with and engagement with patients; (3) scalability to reach larger numbers of patients. Moreover, algorithms can be applicable and adaptable across health systems based on personnel and the needs of specific populations.

Challenges

Few such programs currently exist. Algorithmized care may be relatively easier to implement in some aspects of cardiometabolic care, such as hypertension and lipid management, but more difficult and more nuanced in other aspects, like diabetes. Start-up costs need to be factored in, including software development, and training of navigators can be time-intensive. Funding sources and reimbursement would need to be clarified, especially prior to demonstration of cost-benefit; such a model could work well within an integrated healthcare model. More active approaches of management also bring with them many complicated issues regarding communication between the program and primary care providers, as well as issues of territory and liability. Transitions of care need to be delineated and carefully monitored; for example, once a patient reaches a final goal dose of medication, a provider needs to be identified to transition to providing longitudinal, long-term prescriptions. If a patient has multiple conditions, ways to consolidate and integrate disease-specific pathways (e.g., hypertension pathway, lipid pathway, diabetes pathway) may need to be designed. Effective remote monitoring requires patient buy-in to regularly check measurements (e.g., blood pressure, blood sugars) and/or to have laboratory work drawn.

Multidisciplinary Clinic Model

Multidisciplinary clinics exist across various medical fields. These clinics include multiple specialists present in a single clinic location, where the patient can see multiple providers at a single visit.

Advantages

Multidisciplinary clinics provide key advantages of convenience and communication for both patients and providers. Patients can see multiple providers at a single visit, minimizing the need for multiple visits. Providers have the opportunity to discuss patients and teach and learn from one another. Provider consolidation in both time and space can also facilitate communication and efficient decision-making.

Multidisciplinary clinics also facilitate incorporation of other specialists into a centralized clinic, such as certified diabetes educators, dieticians, exercise physiologists, psychologists, behavioral specialists, social workers, weight loss specialists, nephrology specialists, ophthalmologists, and podiatrists.

Challenges

Possible barriers to this model include the need for the development and implementation of such multidisciplinary clinics, as well as start-up costs. Additionally, from a population perspective, availability and reach are an issue; enough multidisciplinary clinics cannot be created to effectively treat all of the patients who have diabetes and CVD, especially in areas with limited access to specialists.

Combined Cardiometabolic Training Model

Training dedicated cardiometabolic specialists through tailored residency and/or fellowship programs represents another potential model. For example, creation of a cardiometabolic subspecialty training track in internal medicine has been proposed [37]. Such training would aim to develop cardiometabolic specialists adept at managing ASCVD, diabetes, obesity, dyslipidemia, sleep-disordered breathing, non-alcoholic fatty liver disease, and metabolic syndrome. Preparation would include training in internal medicine, preventive cardiology, diabetes, and obesity medicine. Cardiometabolic specialists would be skilled at lifestyle counseling and pharmacologic management, including lipid-lowering agents, antihypertensive agents, weight loss agents, and glucose-lowering agents.

Advantages

A combined cardiometabolic training model would allow harmonious unification of cardiometabolic management under one specialist. Patient convenience would be enhanced as patients could consolidate visits to multiple specialists into a single visit with one specialist. Polypharmacy would be reduced as a single provider could prescribe and keep track of multiple cardiometabolic medications for a given patient. Miscommunication between providers would be mitigated as well. Healthcare delivery from a single cardiometabolic specialist may also help patients better understand the crucial relationships between cardiovascular disease, diabetes, obesity, lipid disorders, sleep-disordered breathing, and other cardiometabolic diseases and how lifestyle changes such as a healthy diet and regular exercise can significantly improve multiple interrelated conditions.

Challenges

To our knowledge, no such training program currently exists. Hence, such a training program would need to be developed, accredited, and implemented. The training program would also need to find a clear home to operate under (i.e., cardiology or endocrinology). Because such a training program would require mentorship from endocrinologists, cardiologists, and internists, buy-in from each specialty would be needed, and broadly speaking, support from specialty professional societies would aid in the success of such a program. Finally, this model has relatively

small reach in being able to treat the millions of individuals with diabetes and CVD in the USA.

What Is Needed for Successful Cardiometabolic Collaboration for Improved Patient Care

The models above provide a framework for paradigms of integrated and improved cardiometabolic care for patients with diabetes and CVD. Regardless of the care model, however, we believe that diabetes specialists and CV specialists can already implement several specific changes to their current practice to deliver improved cardiometabolic care and facilitate collaboration between the specialties.

At the Level of the Specialist

Broadening/Shifting of Perspective

CV specialists are well-positioned to identify patients with undiagnosed diabetes through appropriate screening. Given that T2D is common in individuals with ASCVD or HF, CV specialists should periodically consider screening these populations for T2D. One national study found that only 13% of individuals with CVD seen by cardiologists were screened for diabetes [38]. Systematic screening of patients with CVD may detect high rates of undiagnosed diabetes [39]. It is estimated that 7.2 million Americans live with undiagnosed diabetes [40]; early identification of at-risk individuals can facilitate optimal cardiometabolic care.

Even during consultative care, CV specialists can identify patients with diabetes and known ASCVD, HF, and/or CKD who might benefit from SGLT2i and/or GLP1 RA and consider recommending to patients or the provider managing their diabetes that these medications be considered if appropriate. This is particularly apt given that CV specialists may encounter patients in settings that could be linked with changes in therapy (e.g., post-procedure, in-hospital, post-event). Ultimately, each of these encounters represents a potential opportunity to optimize therapy and move toward shared therapeutic goals. To effectively implement evidence-based glucose-lowering therapies known to modify CV risk, CV specialists will need to be comfortable with certain aspects of diabetes care, including initiating prescriptions, understanding common side effects of these agents and their management, and carrying out necessary follow-up.

For diabetes specialists, expanding the view of diabetes management from a "glucocentric" view focused on glycemic control to a broader cardiometabolic view can improve care of individuals with diabetes and CVD. As a practical example, as diabetes specialists, we (LC and VA) traditionally routinely list specific elements of diabetes care in the assessment and plan in our notes, such as hemoglobin A1C goal, diet and nutrition counseling, weight management counseling, lipid and hypertension management, and microvascular complication surveillance. In light of cardiorenal benefits seen by SGLT2i and GLP1 RA, and in the spirit of the ADA Standards of Care update in 2019 to consider ASCVD, HF, and CKD in guiding diabetes pharmacotherapy after lifestyle counseling and metformin, we have included a simple series of yes/no bullet points in our assessment/plan, alongside hemoglobin A1C goal—ASCVD (yes/no), HF (yes/no), CKD (yes/no). This places cardiorenal comorbidities at the forefront of our thinking.

Practical Management of Medications

We believe that CV specialists and diabetes specialists can adopt learning from the other specialty's experience when adjusting medications in patients with diabetes and CVD.

Practical diabetes tips in medication management for CV specialists:

- Insulin and/or sulfonylurea doses may need to be decreased with the addition of a GLP1 RA or SGLT2i, to reduce the risk of hypoglycemia.
- Dipeptidyl peptidase 4 inhibitors (DPP4i) should be discontinued when GLP1 RA are added, given their overlapping mechanisms of action. Furthermore, DPP4i are less effective in lowering glucose compared with GLP1 RA and, while safe, do not have evidence for CV risk reduction.
- GLP1 RA are typically started at the lowest dose and uptitrated to increase tolerability and minimize gastrointestinal side effects.
- Some GLP1 RA require separate prescriptions for pen needles (liraglutide (Victoza®), lixisenatide (Adlyxin®)). Other GLP1 RA either come with pen needles in the box (exenatide (Byetta®), exenatide extended release (Bydureon®), semaglutide (Ozempic®)) or with the needle built into the autoinjector (dulaglutide (Trulicity®), exenatide extended release (Bydureon BCise®)).
- Measures to mitigate gastrointestinal side effects of GLP1 RA (e.g., nausea, vomiting, diarrhea, and early satiety) and enhance compliance include education on smaller, lower fat meals and anticipatory guidance to patients that these side effects are common with initiation but improve with continued use.
- Right upper quadrant pain should prompt consideration for gallbladder disease in patients on GLP1 RA, as GLP1 RA are associated with an increased risk for cholelithiasis and cholecystitis [41, 42].
- SGLT2i commonly cause increased urinary frequency and an increased risk of genital yeast infections in both women and men.

- Malaise, nausea, vomiting, and/or confusion in a patient on SGLT2i may prompt evaluation for diabetic ketoacidosis (DKA), a rare side effect of SGLT2i. SGLT2i-related DKA may be euglycemic, i.e., seen with glucose levels lower than typically seen for diabetic ketoacidosis, such as < 250 mg/dL (13.9 mmol/L).
- New perineal lesions, erythema, or edema in patients on SGLT2i should prompt urgent evaluation to rule out Fournier gangrene (necrotizing infection of the perineum), which is associated with SGLT2i use, albeit rarely [43].
- Canagliflozin was associated with an increased risk of lower limb amputations and fractures in its CVOT [9], though these associations were not seen in CREDENCE.

Practical cardiology tips for diabetes specialists:

- Diuretic doses may need to be adjusted when SGLT2i are initiated, given the mild diuretic effect of SGLT2i [44]. For patients with HF, consider discussing diuretic dose adjustment with the patient's cardiology team.
- The acute hemodynamic effects of SGLT2i are uncertain among high-risk patients with HF; ongoing clinical trials will clarify the safety and appropriate setting of SGLT2i initiation (inpatient versus outpatient).
- SGLT2i are known to minimally increase LDL cholesterol; however, this small effect does not adversely influence CV risk and is unlikely to require alteration of anti-lipid therapies.

Practical tips for both CV specialists and diabetes specialists:

- SGLT2i have a long-term renal protective effect, but early decreases in estimated glomerular filtration rate (eGFR) may be expected shortly after initiation as intraglomerular pressures are decreased. Specifically, serum creatinine may rise and eGFR may fall in the few weeks after SGLT2i are initiated [13••].

At a Systems Level

Guidelines

Professional guidelines are an important resource for the busy clinician, and conflicting guidelines can also contribute to therapeutic inertia. In the cardiometabolic arena, recent years have seen greater harmonization in the guidelines across different societies as well as greater co-authored/endorsed guidelines among societies. These will better ensure consistent goals and united approaches. Additionally, making guidelines "living"—updated periodically as key updates and trials are published—allows for timely incorporation of important new evidence. The ADA, for example, has made its annual Standards of Medical Care in Diabetes a living document. Management tools (applications, algorithms, checklists, EHR tools, and automation) based on these living guidelines will further support their implementation.

Conclusions

These are exciting times to be medical professionals caring for individuals with diabetes and CVD. Our understanding of CV risk factors has broadened and deepened considerably over the past two decades. We have a more comprehensive array of tools, from new pharmacologic agents to sophisticated EHR pathways, to manage these conditions than ever before. CVOTs for SGLT2i and GLP1 RA demonstrating significant reductions in CV and renal events have revolutionized the landscape of CVD, renal, and diabetes management and provided new pathways for CV risk reduction. These advances have created new opportunities for diabetes specialists and CV specialists to co-manage individuals with diabetes and CVD.

As effective and sustainable collaboration and co-management pathways are operationalized, several challenges will need to be overcome. First, many aspects of cardiometabolic management are shared among diabetes specialists, CV specialists, and primary care providers, including management of hypertension, lipids, sleep-disordered breathing, obesity, and diabetes. This can lead to clinical inertia (if one provider expects one aspect will be managed by another provider) and treatment inconsistencies (particularly if providers differ on their view of goals and optimal treatment). To overcome these challenges, it will be important for providers to agree on therapeutic goals (e.g., blood pressure thresholds, lipid goals, and glycemic targets) and to clarify which provider is primarily managing which problem and with what strategy. Guidelines harmonized across professional societies can facilitate shared therapeutic goals and consistent messaging to patients. With the rapid advances in this area, co-management provides the opportunity for ongoing peer education between colleagues as well, and thus ongoing two-way dialog and openness to input from colleagues will be important in implementing evidence-based guidance.

Second, effective, efficient, and fully integrated communication between medical professionals is essential but remains surprisingly difficult. Successful cardiometabolic management across providers requires timely updates on diagnoses, laboratory results, and medication adjustments. Even with electronic means of messaging and EHR advances, secure communication between providers across institutions/clinics is not always easy, and fax and mail are still often used, and thus important recommendations may not be fully incorporated, placing a greater onus on the patient for helping to coordinate his or her own care. Establishing secure and easy-to-use

messaging systems across institutions will help minimize delays in treatment and may optimize patient care.

Third, current prevailing care models remain suboptimally equipped to deal with both the cross-disciplinary nature of cardiometabolic care, as well as the sheer population-level scale of patients who would benefit from coordinated cardiometabolic care. Innovative models of care should be explored, such as co-localizing diabetes and CV specialists in multidisciplinary clinics, harnessing EHR capacity to identify patients with suboptimal care, equipping patients and providers with remote monitoring of blood pressure and glucose, developing clinical care algorithms that can allow additional providers and potentially even non-medical professionals empowered by specialists and primary care providers to facilitate timely titration of medications, and establishing training and ongoing education programs that equip providers to optimally manage all aspects of cardiometabolic care.

Excess morbidity, mortality, healthcare expenditures, and adverse quality of life related to diabetes and CVD are substantial, and the challenges in effectively treating these conditions are great. But the opportunities for improving cardiometabolic care are enormous, and collaboration between diabetes specialists and CV specialists on behalf of patients is a crucial component of overcoming these challenges—one that can be both satisfying for specialists and lifesaving for patients.

Compliance with Ethical Standards

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