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Note From the Editors

Time to Rethink Reducing Cardiovascular Risk: Are We Ready?

The ultimate goal of managing diabetes is to improve quality of life and reduce diabetes-related complications—both microvascular and macrovascular. Although people living with diabetes are most fearful of the microvascular complications of blindness, dialysis and amputations, the leading cause of death is cardiovascular (CV) (1,2). In addition, among those with cardiovascular disease (CVD), >50% have diabetes or prediabetes (3). Therefore, strategies that reduce CV outcomes must be prioritized in the management of diabetes. To achieve this, a multifactorial approach is required, as utilized in the landmark STENO-2 studies, which showed that a multifactorial approach among those living with type 2 diabetes and microalbuminuria for approximately 8 years resulted in a median of 7.9 years of life gained and marked reductions in micro- and macrovascular complications after 21 years of follow up (4), and shown again even more recently in patients with established CVD (5).

Accordingly, this issue of the *Journal* focuses on CVD in diabetes. Raggi provides an update on the evidence for screening for CVD in people with diabetes, discussing the merits of imaging modalities and coronary artery calcium score, among others (6). For those with established CVD, Godoy et al address revascularization options and their pros and cons (7). In recent years, there has been a renewed interest in heart failure and diabetes—partly related to the availability of effective therapies in the diabetes world, namely sodium glucose cotransporter 2 inhibitors (SGLT2i). Sharma et al review the data surrounding SGLT2i use in heart failure (8). In keeping with the theme of a multifactorial approach to cardiovascular risk reduction, Lazarte et al review the latest evidence around lipid-lowering therapies and CV risk reduction, including novel therapies, such as PCSK9 inhibitors and high-dose eicosapent ethyl (9). In addition, 2 antihyperglycemic therapy classes have emerged as major players in CV risk reduction: glucagon-like peptide-1 receptor agonists (GLP1RA) and SGLT2i. Varin et al summarize the CV outcome data surrounding GLP1RA (10), whereas Woo does the same for SGLT2i (11). Sharma et al then discuss the multiple proposed mechanisms through which these 2 classes are believed to cause CV benefit (12).

Putting It All Together—Time for a Change

Glycemic management is a foundation of diabetes management. The very definition of diabetes is dependent on elevated blood glucose levels. In addition to the known adverse effects of advanced glycation end products on vascular biology, numerous clinical outcome studies have shown that reducing blood glucose levels reduces microvascular complications and, when implemented early enough, also reduces macrovascular complications (13). However, glycemic management is only 1 component of the multifactorial approach that has been shown to reduce diabetes complications (14). Although listed first in the "ABCDES" of vascular protection in diabetes (Figure 1) by Diabetes Canada, this is only a function of the order of the alphabet and not a commentary on the level of priority. Guidelines and consensus statements to date have acknowledged the practice-changing evidence surrounding certain GLP1RA and SGLT2i and are actively recommending their use in appropriate patients (those with CVD, at high risk of CVD, with chronic kidney disease or heart failure) (15–18). However, those recommendations are in the context of glycated hemoglobin (A1C)—to be added if the A1C is not at target. Interestingly, however, the trials substantiating these recommendations were designed to minimize differences in A1C between treatment arms, further emphasizing that A1C lowering does not well represent putative mechanisms of benefit, which go beyond A1C lowering (12). Furthermore, almost all guidelines recommend the addition of these therapies only after metformin. These recommendations create a potential scenario whereby a patient with CVD could remain on metformin alone for several years and not have the benefit of GLP1RA or SGLT2i because her/his A1C is <7%. Is that still appropriate given that the inclusion criteria from the more recent CV outcome trials had much lower A1C or no lower A1C limit (18,19)? Further complicating this question is the emerging evidence of benefits of some of these agents on reduction of renal disease and heart failure hospitalization in patients without atherosclerotic CVD who have multiple risk factors warranting so-called "primary prevention" (18,20).

New Approach Proposed

Given the wealth of evidence supporting the CV outcome reducing properties of certain GLP1RA and SGLT2i, is it time for them to be considered in the same way that renin-angiotensin-aldosterone system inhibition, statins and acetylsalicylic acid are considered? These latter therapies are recommended in appropriate patients irrespective of baseline blood pressure or low-density lipoprotein cholesterol level in patients with atherosclerotic CVD mainly because of their vascular and/or renal protection properties and not solely because they happen to lower blood pressure or lipids (14). Is it time now that certain GLP1RA and SGLT2i be considered vascular (or renal) protecting therapies that happen to lower blood glucose? A new approach to selecting antihyperglycemic therapy in type 2 diabetes is proposed in Figure 2. The guiding principle is that of preferentially selecting therapies with proven CV and/or renal benefit for a particular patient type, as reflecting those patients studied in recent trials. After implementation, the resulting glycemic levels should be assessed and then other therapies added to achieve glycemic targets, which is a paradigm that prioritizes an outcome-based approach above a

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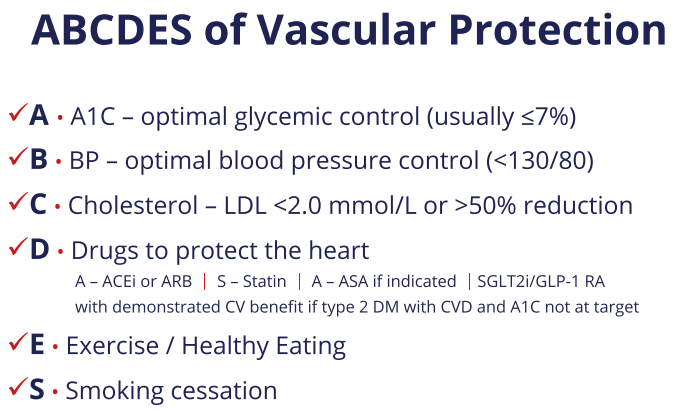

Figure 1. The ABCDES approach to vascular protection by Diabetes Canada (14). *A1C*, glycated hemoglobin; *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *ASA*, acetylsalicylic acid; *BP*, blood pressure; *CV*, cardiovascular; *CVD*, cardiovascular disease; *GLP1 RA*, glucagon-like peptide-1 receptor agonist; *DM*, diabetes mellitus; *LDL*, low-density lipoprotein; *SGLT2i*, sodium glucose cotransporter 2 inhibitor.

glycemic-based approach. In this new paradigm, metformin would no longer remain as the sole first-line therapy but rather as part of first-line therapy in appropriate patients to ensure that proven outcome-reducing therapies are included early in the long-term management of vascular risk and/or the hyperglycemia of diabetes per se. The removal of metformin as first-line therapy for some patients has already been suggested by the European Society of Cardiology (16) and by the American College of Cardiology/American Heart Association (17). However, this radical shift must consider that metformin was background therapy for >70% of the participants in the various CV outcome trials. So, although it is difficult to totally exclude metformin in the initial consideration, it is also worth noting that those with or without metformin benefited to a similar degree (21). Of course, this algorithm is not to be implemented in isolation. It is to be implemented in the context of the comprehensive ABCDES of a multifactorial approach that also includes healthy behaviour interventions and achievement of multiple goals of therapy.

Whose Role Is It?

Since the positive CV outcome trials of antihyperglycemic therapies have emerged, there has been an ongoing debate about whether these therapies belong in the endocrinology, cardiology, nephrology or primary care space. Although academically stimulating and even sometimes humourous, these artificial debates do not supersede the fact that these new therapies benefit the person living with diabetes. They belong to them. It is the responsibility of all of us, as members of the multidisciplinary health-care team supporting the person living with diabetes, to understand and get comfortable using these therapies. It is also the responsibility of all of us to communicate and educate within and outside of our respective disciplines because these therapies impact multiple components of care. In the last several decades, effective outcome-reducing therapies that have become standard of care have resulted in reductions in adverse outcomes among people living with the long-term burden of diabetes. Let us now grasp this opportunity for translation of this new evidence to its fullest to further reduce the adverse outcomes of people living with diabetes.

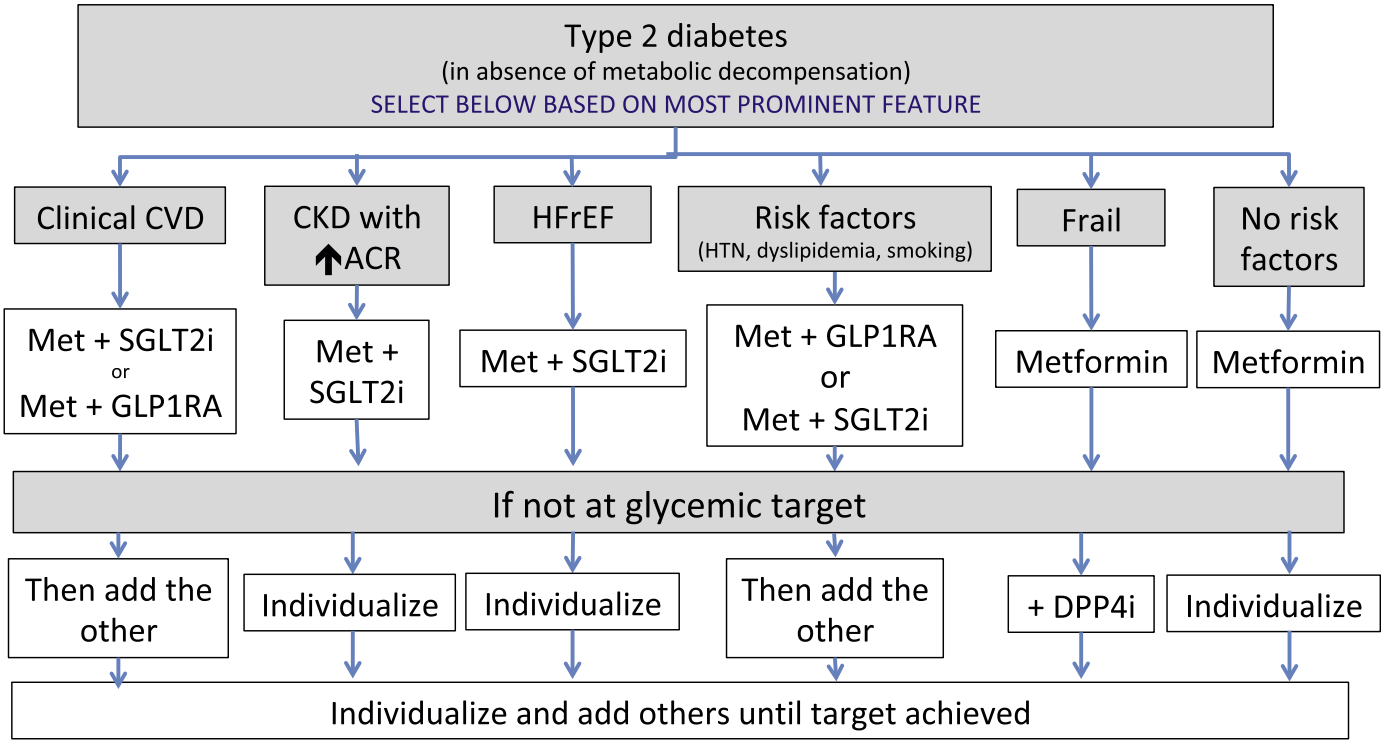

Figure 2. Proposed algorithm for the selection of antihyperglycemic therapy in type 2 diabetes. *ACR*, albumin-creatinine ratio; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *DPP4i*, dipeptidyl peptidase 4 inhibitor; *GLP1RA*, glucagon-like peptide-1 receptor agonist; HfrEF, heart failure with reduced ejection fraction; *HTN*, hypertension; *Met*, metformin; *SGLT2i*, sodium glucose cotransporter 2 inhibitor.

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