Prescribing Paradigm Shift? Damned If You Do, Damned If You Don't

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Over the last decade, large cardiovascular outcome trials (CVOTs) have provided a wealth of data on the reduction of cardiovascular (CV) events by glucose-lowering agents in patients with type 2 diabetes (T2D). These trial results have started to influence management recommendations, in particular, the 2019 European Society of Cardiology (ESC) guidelines on CV disease in diabetes, which for the first time recommended that sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA) should be considered as first-line therapy in people with drug-naive T2D with CV disease (1). Colleagues in Glasgow, U.K., have responded to this recommendation by investigating the clinical implications and potential costs of implementing these guidelines (2). The background to this change in recommendations primarily relates to the results of placebo-controlled CVOTs with SGLT2i and GLP-1RA. In brief, four CVOTs examined the effect of SGLT2i on three-point major adverse cardiovascular events (3P-MACE). Empagliflozin (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME] trial) (3) and canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS]) (4) significantly reduced 3P-MACE, and in a separate trial in patients with T2D with chronic kidney disease (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [CREDENCE]), canagliflozin also significantly reduced 3P-MACE while ameliorating a decline in renal function (5). Dapagliflozin (Dapagliflozin Effect on Cardiovascular Events [DECLARE-TIMI 58] trial) had no effect on 3P-MACE (6), although all three SGLT2i showed a significant reduction in the combined end point of heart failure hospitalization or CV death. Seven placebo-controlled CVOTs examined the effect of GLP1-RA on CV events in patients with T2D at high CV risk. Two trials, ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) (7) and EXSCEL (Exenatide Study of Cardiovascular Event Lowering) (8), showed only noninferiority for the primary 3P-MACE end point. In contrast, four trials—LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) (9), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (10), Harmony Outcomes (Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease) (11), and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) (dulaglutide) (12)—reported a significant reduction of the combined 3P-MACE end point. The PIONEER-6 trial (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) reported noninferiority for 3P-MACE, but significantly reduced CV death and all-cause mortality (13). These data, derived from around 90,000 patients with T2D, provide a compelling database to support a change in management, which is reflected in the "paradigm shift" in the 2019 ESC guidelines. Until recently, risk factor control with antihypertensive therapy and lipid-lowering strategies in combination with metformin have been the cornerstone to reduce cardiovascular morbidity and mortality in patients with T2D. In previous studies, glucose lowering itself, albeit of importance for the reduction of microvascular events, had only a moderate effect on macrovascular events. Based on the recognition that the simple concept of primary and secondary prevention is unable to capture adequately the complex nature of CV risk in diabetes, the 2019 ESC guidelines have recommended that patients should be classified as being at very high, high, or moderate CV risk independent of baseline HbA_{1c} and those in the two highest risk categories should receive SGLT2i or GLP-1RA with proven CV benefit.

In this issue of *Diabetes Care*, Caparrotta et al. (2) add a significant dimension to our understanding of the consequences of implementing the ESC recommendations into clinical care, particularly in

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relation to the number of eligible patients and the potential costs involved in such an approach. This is important because ESC guidelines are based solely on best evidence and do not take into account other factors such as cost or drug availability. Caparrotta et al. used the nationwide diabetes register in Scotland and found that of the 265,774 people with T2D in Scotland, 53,194 (20.0% of people with T2D) were drug naive and 56,906 (21.4%) were on metformin monotherapy. Of these, 74.5% and 72.4%, respectively, were estimated as at least high risk given the guideline risk definitions. Thus, they conclude that 30.4% of all patients with T2D (80,830 of 265,774) are candidates for GLP-1RA or SGLT2i based on the recommendations of the ESC guidelines. The authors did not perform a detailed cost-effectiveness analysis, but the information provided may help to estimate the additional costs incurred by the implementation of the guideline. Employing additional analyses, the authors demonstrate that the introduction of a minimum target HbA_{1c} threshold of >6.5% or >7.5% would decrease the number of eligible patients by 45.1% or 80%, respectively. However, the value of introducing an HbA_{1c} threshold to guide the prescription of SGLT2i or GLP-1RA in clinical practice is questionable. To date, there is no evidence of an obvious HbA_{1c} level below which patients lose the benefit of these drugs; moreover, data from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial in heart failure patients with or without diabetes suggest that SGLT2i are beneficial even in the absence of diabetes (14). In addition, the reduction of CV events obtained by SGLT2i or GLP-1RA is most likely totally independent of their glucose-lowering properties (15,16). Thus, introducing an HbA_{1c} threshold as a "gatekeeper" for the prescription of SGLT2i or GLP-1RA may reduce the number of eligible patients but would unnecessarily deny patients an agent that reduces CV events.

The study by Caparrotta et al. (2) provides important information on current CV risk in T2D in a modern Western society. Between 65% and 70% of all patients with T2D in Scotland were at very high CV risk according to the ESC categories, including those with diabetes and established CVD, or other target organ damage, or three or more major risk factors, or early-onset T1D of long duration (>20 years). Based on data from the CVOTs with GLP-1RA, the incidence rate for mortality in this very-high-risk population lies between 1.8 and 2.6 events per 100 patients-years. Thus, the Scottish registry data clearly show that the majority of patients with T2D exhibit a markedly elevated risk for CV events and death, mirroring early data by Haffner et al. suggesting that diabetes is a CV risk equivalent (17).

We have been witness to probably the most exciting time in diabetes management since the discovery of insulin in the early part of the 20th century. Insulin kept patients alive, but often with complications, and the Diabetes Control and Complications Trial (DCCT) (18) and the UK Prospective Diabetes Study (UKPDS) (19) taught us the importance of good glycemic control for microvascular disease. The subgroup analyses of UKPDS suggested that metformin may reduce the incidence of myocardial infarction in a subgroup of overweight patients (20), but other strategies to reduce macrovascular events in diabetes were missing. It is worth considering some of the outstanding problems in the CV arena in T2D beyond macrovascular events such as myocardial infarction and stroke. Heart failure has been increasingly recognized as a serious, underdiagnosed, and undermanaged condition in our patients with T2D; in addition, chronic renal impairment is common and difficult to manage, being associated with end-stage renal disease but more commonly a marked increase in coronary artery disease (CAD), heart failure, and CV death. Finally, residual risk (worse CV outcomes in patients with T2D for the same treatment in patients without diabetes) continues to blight the CV outcomes for individuals with T2D, increasing morbidity and mortality from both CAD and heart failure in this population. The new therapies provide a genuine opportunity here: respective drugs can be chosen to manage CAD, heart failure, and renal impairment on an individualized basis. While we do not know whether they will influence residual risk, this is an area in which we will learn more as more data concerning these agents become available.

Capparotta et al. (2) have provided us with an important piece of work in this field that raises important issues regarding the management of CV risk in T2D. The outstanding question is whether even Western economies can afford the widespread use of these agents. An alternative question might be can we afford not to? Perhaps health economics and cost-effectiveness analyses will provide the answers to these difficult questions.

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