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The cardiodiabetologist: not just a question of blood glucose levels

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Following the publication of numerous cardiovascular outcome studies conducted with new glucose-lowering agents, there has been a substantial change in the treatment paradigm of patients with type 2 diabetes, shifting the focus from simple glycaemic control to cardiovascular risk management. National and international guidelines of cardiology and diabetes societies have now acknowledged the important cardioprotective effects of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide receptor agonists, to the point that they are now considered first-line drugs in the management of cardiovascular risk in high-risk patients or with established cardiovascular disease, and also outside the context of established diabetes. In this brief review, we will analyse the clinical and pathophysiological evidence underlying this important paradigm shift, hypothesizing their early use in many cardiovascular patients, particularly in the pre-diabetes phase. Overall, these drugs are now a cornerstone in the therapeutic armamentarium, which the cardiologist must fully master, even independently of diabetologists.

Introduction

Subjects with type 2 diabetes (T2D) are at higher risk of cardiovascular disease (CVD) compared to non-diabetics. This increased risk, especially with regard to atherosclerotic (macrovascular) complications, begins with the glyco-metabolic changes that precede the onset of full-blown diabetes, in the so-called 'pre-diabetes', even 7–10 years before a diagnosis of T2D is made.[1]

The clinical management of patients with T2D has evolved significantly in the last decade. Intensive glucose-lowering strategies had until then largely failed to prove a reduction in cardiovascular morbidity and mortality convincingly. A meta-analysis of all studies had only suggested a modest benefit in terms of reduced risk of non-fatal myocardial infarction.[2] This substantial failure led for years to the perception among cardiologists that control of other cardiovascular risk factors, such as blood pressure and low density lipoprotein cholesterol (LDL-C), was the only important measures effective in reducing cardiovascular risk in T2D. Recently, however, several large-scale clinical outcome trials with novel glucose-lowering drugs such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) have demonstrated robust and significant reductions in major adverse cardiovascular events (MACE). The favourable effects on measures of cardiovascular outcome were, in both cases, largely independent of the glucose-lowering properties of these drugs. Thus, the results of these randomized clinical trials have substantially changed the treatment paradigm for patients with T2D, shifting the focus from simple blood glucose control to 'cardio-metabolic' interventions, with indications now given for cardiovascular risk reduction for three of the SGLT2i (empagliflozin, canagliflozin, and dapagliflozin) and three GLP-1 RAs (liraglutide, dulaglutide, and semaglutide) in the USA, Europe, and several other countries.[3] The 2023 European Society of Cardiology guidelines for the management of CVD in patients with diabetes now provide updated

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recommendations for the management of people with T2D, with a focus on cardiovascular risk reduction under the concept that T2D, atherosclerotic cardiovascular disease (ASCVD), and heart failure are often overlapping disease phenotypes, and therefore worthy, from a cardiometabolic standpoint, of further investigation and of common treatment goals.[4]

Evidence from clinical trials: the cardioprotective effects of SGLT2 inhibitors and GLP-1 receptor agonists

A 2021 meta-analysis of six randomized clinical trials evaluated the safety and efficacy of SGLT2i in subjects with high-risk T2D and established ASCVD. This meta-analysis demonstrated that, overall, SGLT2i were associated with a reduced risk of MACE, such as cardiovascular death, myocardial infarction, and stroke (hazard ratio, HR: 0.90; 95% confidence interval, 95% CI: 0.85, 0.95). In this meta-analysis, the presence or absence of ASCVD did not modify the association of treatment efficacy on MACE (HR: 0.89; 95% CI: 0.84, 0.95; HR: 0.94; 95% CI: 0.83, 1.07, respectively; *P* for interaction = 0.63). Furthermore, for each component of MACE, SGLT2i significantly reduces the risk of cardiovascular death (HR: 0.85; 95% CI: 0.78, 0.93; *P* = 0.02) and all-cause mortality, but not the risk of stroke (HR: 0.96; 95% CI: 0.87, 1.07; *P* = 0.29).[5] In parallel, a network meta-analysis published in 2021 reviewed the available evidence on the safety and efficacy of SGLT2i in subjects with known cardiovascular disease. The authors selected seven randomized, placebo-controlled clinical trials, and highlighted how SGLT2i reduce cardiovascular death [odds ratio (OR): 0.82; 95% CI: 0.70–0.95; moderate-certainty evidence], all-cause death (OR: 0.84; 95% CI: 0.74–0.96; moderate-certainty evidence), and the risk of hospitalization for heart failure (OR: 0.65, 95% CI: 0.59–0.71; high-certainty evidence). This meta-analysis did not show a reduction in the risk of myocardial infarction (OR: 0.97, 95% CI: 0.84–1.12; high-certainty evidence), and stroke (OR: 1.12, 95% CI: 0.92–1.36; moderate-certainty evidence).[6]

About GLP-1 RAs, a meta-analysis that included eight randomized placebo-controlled clinical trials involving over 60 000 patients and published in 2021 evaluated the efficacy of these drugs on cardiovascular outcome measures in subjects with both high-risk T2D and with established ASCVD. This meta-analysis demonstrated a 14% reduction in the composite outcome measure of cardiovascular death, myocardial infarction, and stroke (HR: 0.86, 95% CI: 0.80–0.93) with evidence of efficacy on each component of MACE. GLP-1 RAs were also shown to reduce all-cause mortality by 12% (HR: 0.88; 95% CI: 0.82–0.94; *P* = 0.0001) and hospital admission for heart failure by 11% (HR: 0.89; 95% CI: 0.82–0.98, *P* = 0.013).[3] In the previously cited network meta-analysis by Kanie *et al.*, the authors selected seven randomized placebo-controlled clinical trials in subjects with known cardiovascular disease; and found that GLP-1 RAs reduced the risk of cardiovascular death (OR: 0.87; 95% CI: 0.79–0.95; high-certainty evidence), death from all causes (OR: 0.88; 95% CI: 0.82–0.95; high-certainty evidence), and stroke (OR: 0.87; 95% CI: 0.77–0.98; high-certainty evidence). However, GLP-1 RAs did not significantly reduce the risk of myocardial infarction (OR: 0.89; 95% CI: 0.78–1.01; moderate-certainty evidence), and the risk of hospitalization for heart failure (OR: 0.95; 95% CI: 0.85–1.06; high-certainty evidence).[6]

Overall, these studies suggest a favourable effect of SGLT2i predominantly on the risk of heart failure, and of GLP-1 RA predominantly on atherosclerotic vascular disease.

The pathophysiology of the 'new cardioprotection' and pleiotropic effects of SGLT2 inhibitors and GLP-1 receptor agonists

SGLT2i and GLP-1RA have been shown to reduce cardiovascular events in subjects with T2D both with established cardiovascular disease and in high-risk subjects. The cardioprotective effects depend on mechanisms that certainly go beyond the simple glycaemic control and range from a reduction of other traditional cardiovascular risk factors to the reduction of systemic inflammation.

SGLT2 inhibitors

SGLT2i reduce blood glucose levels by inhibiting renal glucose reabsorption and causing glycosuria. Improved glycaemic control can help reduce microvascular complications, which in turn impact cardiovascular outcome measures in diabetic subjects. However, these effects are modest or absent in non-diabetic subjects, and these drugs have also demonstrated important haemodynamic effects, determined in part by the natriuretic effect and osmotic diuresis, thus reducing preload and systolic and diastolic blood pressure, as well as improving arterial stiffness, an independent predictor of cardiovascular events. Furthermore, the demonstrated effects on improved endothelial function are associated with anti-atherogenic properties, with some evidence (not perfectly conclusive) also of a reduction in the progression of atherosclerosis. Improved endothelial function in turn contributes to vasodilation, with a reduction in vascular resistance and blood pressure.[7] SGLT2i have been shown to improve the lipid profile, through a reduction of triglycerides and an increase in high density lipoprotein cholesterol,[8] which, together with the effects of a (modest) reduction in body weight, contribute to reducing insulin resistance and inflammation, and to determining a cardioprotective metabolic profile,[9] Animal studies also suggest that SGLT2i may protect the heart from ischaemia-reperfusion injury by modulating mitochondrial function, reducing oxidative stress, and improving myocardial metabolism.[7] Emerging evidence further suggests that SGLT2i may have anti-inflammatory and anti-fibrotic effects, exerted directly on the myocardium, which is associated with a reduction in adverse cardiac remodelling.[7]

GLP-1 receptor agonists

GLP-1 RAs have also shown a modest reduction in glycated haemoglobin levels, in a range between 0.8% and 1.5%, which, however, only partially explains the observed cardiovascular benefit. GLP-1 RAs have been shown to

favourably modify many traditional cardiovascular risk factors. Specifically, they determine a modest reduction in systolic blood pressure (from 2 to 6 mmHg), and improve the overall lipid profile by reducing total cholesterol, LDL-C, and triglycerides.[10,11] The use of GLP-1 RAs has also been shown to reduce body weight (from 2.5 to 4 kg in early studies), an effect that therefore contributes to a reduction in cardiovascular events. These anorectic effects are now widely exploited as obesity-reduction strategies. However, the combination of these modest effects on traditional cardiovascular risk factors does not seem sufficient to explain the observed impact on cardiovascular outcome measures. *In vitro* and *in vivo* studies have highlighted the pleiotropic effects of these agents with important anti-inflammatory, antithrombotic, vascular, and metabolic properties. Studies in murine models have highlighted the ability of GLP-1 RAs to improve endothelial function and reduce the progression of atherosclerosis, vascular inflammation, and vasoconstriction. Several experimental data in preclinical models of atherosclerosis have shown that GLP-1 and GLP-1 RAs reduce the development and progression of atherosclerotic lesions through plaque stabilization and reduction of platelet activation. These anti-atherogenic and anti-inflammatory effects would be mediated by the GLP-1 receptor expressed on endothelial cells, monocytes, macrophages, and smooth muscle cells. The hypothesis of anti-inflammatory properties of GLP-1 RAs was later supported by the results of small clinical trials with liraglutide, which showed reduced production of tumour necrosis factor-alpha and interleukin-1 by peripheral blood mononuclear cells. In addition, several GLP-1 RAs have been shown to reduce systemic inflammation, as evidenced by reduced circulating levels of C-reactive protein.[12]

Pre-diabetes as a treatment target for cardiovascular risk reduction

With the increasing prevalence of diabetes as a cause of micro- and macrovascular disease, increased attention has been paid to dysglycaemic states that precede and predict the development of T2D. These conditions, collectively called pre-diabetes, are characterized by impaired fasting or oral glucose levels, or by glycated haemoglobin values that are intermediate between normal values and those typical of full-blown diabetes. Pre-diabetes and the components of the metabolic syndrome to which it is associated, such as visceral obesity, arterial hypertension, hypertriglyceridaemia, and high levels of LDL-C, are intertwined conditions of increased cardiovascular risk.[1] There is currently little dispute that pre-diabetes has important prognostic implications, especially about the occurrence of myocardial infarction, ischaemic stroke, and peripheral arterial disease. There is still, however, debate on whether pre-diabetes itself can be considered a treatment target for cardiovascular risk reduction in addition to targeted treatment of the risk factors that characterize it. Specifically, the Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) trial demonstrated that, in overweight or obese individuals with known cardiovascular disease but without a diagnosis of overt diabetes, semaglutide reduces the risk of MACE by 20%. The mean glycated haemoglobin was 5.8%; two-thirds of the population had pre-diabetes at baseline with a glycated haemoglobin between 5.7% and 6.4%, while the remaining third was normoglycaemic. Enrolled patients were adequately treated for their underlying CVD; 90% were taking lipid-lowering drugs and 86% were taking antiplatelet drugs. In the SELECT study, glycated haemoglobin was reduced by only 0.32% in the semaglutide group compared with the placebo group, and the reduction in MACE was achieved already very early, before the drug could induce significant weight loss. In this context, the mechanisms underlying the drug benefits are likely the result of a combination of direct and indirect cardiometabolic effects. In a prespecified analysis of the SELECT study, it was assessed whether the effects on cardiovascular outcome measures of semaglutide vs. placebo differed based on the different glycated haemoglobin ranges of the individuals enrolled and, specifically, whether the benefits extended to the normoglycaemic population or only to those with pre-diabetes. The results showed that the reduction in the risk of cardiovascular events with semaglutide in subjects with overweight and obesity and pre-existing cardiovascular disease but without a history of diabetes was substantially independent of baseline glycated haemoglobin values.[13]

Conclusions

Although SGLT2i and GLP-1 RAs currently have several class 1 indications for cardiovascular disease risk reduction in several guidelines and recommendations of international societies, their use in cardiology is still, and unjustifiably, below their potential. Several barriers to prescribing reticence by cardiologists have been identified, and therefore interventions have been proposed to optimize the adoption of cardiovascular preventive therapies. The Coordinating Cardiology Clinics Randomized Trial of Interventions to Improve Outcomes (COORDINATE)-Diabetes study evaluated the effects of physician education and co-ordination of care between cardiologists, endocrinologists/diabetologists, and primary care physicians. In this randomized-block study comparing cardiology clinics undergoing an educational intervention with clinics without intervention, the intervention arm saw the development of interdisciplinary care pathways to address barriers to prescribing evidence-based preventive therapies. In a 12-month follow-up period, intervention arm clinics were 23% more likely to prescribe all evidence-based therapies, including SGLT2i or GLP-1 RA.[14] The use of these so-called cardiometabolic drugs is the basis of the recent conceptual evolution that considers them no longer just glucose-lowering agents, but drugs with pleiotropic action with important effects on cardiovascular risk reduction. This occurs not only in the context of diabetic subjects in primary and secondary cardiovascular prevention but also in the context of dysglycaemic states that precede the development of

full-blown diabetes. In the case of SGLT2i, the effects on heart failure also appear independent of the pre-diabetes situation. This is essential to convey the message that they now represent a cornerstone of the contemporary therapeutic armamentarium that the cardiologist must know and fully use in a manner completely complementary to, but also independent of diabetologists. Even the prescription independence of cardiologists by diabetologists is now a fact in most contexts, and fully justified by clinical data. Cardiologists deserve credit for having insisted in using in diabetes mainly (or exclusively) drugs with recognized cardiovascular benefit, not settling for pathophysiological assumptions or *a priori* hypotheses of benefit. While interaction with diabetologists is always a moment of growth, and should therefore be encouraged as much as possible, it is good in our opinion that it should not be a conditioning factor for the use of these drugs, with their wide therapeutic margin, rare and weak side effects, and benefits now fully demonstrated.

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Disclaimer

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