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ARTICLE

Beyond HbA1c cardiovascular protection in type 2 diabetes mellitus

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Cardiovascular disease is a significant cause of morbidity and mortality for individuals living with type 2 diabetes mellitus (T2DM). These patients have double the risk of atherosclerotic cardiovascular disease (ASCVD) compared with the general population. Furthermore, approximately a third of T2DM patients live with established ASCVD. The traditional 'glucocentric' approaches to managing T2DM have failed to mitigate the burden of ASCVD. In recent years, some cardiovascular outcome trials of the sodium glucose-2 cotransporter inhibitors (SGLT2i) and the glucagon-like peptide-1 receptor agonists (GLP-1RA) have demonstrated an ability to reduce secondary cardiovascular events significantly. These therapies have ushered in an era of 'thinking beyond HbA1c' when treating T2DM patients. There is now a renewed focus on assessing patients for ASCVD risk and adding these novel therapies early to mitigate the adverse cardiovascular events that have become familiar to this population. While the exact physiological mechanisms underlying these clinical benefits are not yet explicitly defined, both the glycaemic benefits and other pleiotropic effects improve the metabolic milieu. This review will discuss the burden of cardiovascular disease (CVD) in T2DM and present a summary of these new antidiabetic drug classes proven to reduce CVD in T2DM.

Keywords: cardiovascular disease, diabetes mellitus, HbA1c, heart failure, mortality

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterised by a decreased sensitivity to insulin in adipose tissue, skeletal muscle and the liver. It typically presents with inappropriate hyperglycaemia.[1] T2DM is a significant public health problem that poses a considerable socioeconomic burden on the individual, society and the healthcare system.[2]

Adults with T2DM have higher rates of atherosclerotic cardiovascular disease (ASCVD) when compared with those without diabetes. Diabetes mellitus increases the propensity for cardiovascular disease (CVD) by two- to threefold in men and three- to fourfold in women.[3,4] This elevated CVD risk is proportional to the high plasma glucose levels and independent of the other CVD risk factors, which are also common in T2DM patients.[4] T2DM is the third leading cause of disability-adjusted life years (DALYs) loss and the eighth leading cause of mortality globally.[5] This review will discuss the burden of cardiovascular complications in T2DM. Particular focus will be given to the relatively new antidiabetic medications, the glucagon-like receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) with proven cardiovascular and renal end-organ protection.

Global burden of type 2 diabetes mellitus

According to the 2021 International Diabetes Federation (IDF) report, the prevalence of T2DM in people aged 20–79 years is 537 million (10.5%) and is projected to reach 783 million (12%) by 2045.[2] In Africa, approximately 24 million people had T2DM in 2021. This number is predicted to increase to 55 million by 2045, an increase of 129% (Figure 1).[2]

In South Africa, approximately 4.6 million (12.9%) have diabetes. This high burden of diabetes is possibly due to the proportionate epidemic of obesity, coupled with urbanisation, westernisation, ageing and an increase in sedentary lifestyles. All these changes further independently increase the risk of complicating with ASCVD.[3]

Intensive versus standard glucose control in patients with T2DM

The traditional approach to T2DM management has primarily focused on HbA1c and has been defined as the 'glucocentric' approach. Then, less attention was given to the cardiovascular and renal complications associated with T2DM. Several landmark randomised controlled trials (RCTs) have compared intensive versus standard glucose control in patients with T2DM (Table 1).[6–9] Although these studies reported a significant reduction in microvascular events, most of their intensive arms failed to demonstrate a reduction in macrovascular events. The lack of beneficial effects on macrovascular events suggests additive atherogenic effects of the common CVD risk factors in T2DM. Therefore, there is a substantial unmet need to develop therapies to prevent and reduce cardiovascular events in these high-risk groups.

Cardiovascular complications of diabetes mellitus

Type 2 diabetes mellitus is associated with an increased risk of ASCVD with multiorgan dysfunction and is a significant cause of disability and premature death. In 2019, T2DM-related causes of death accounted for about 90 000 deaths and were the second leading cause of mortality among South African adults.[10] T2DM-related CVD may affect microcirculation and present with retinopathy, nephropathy and neuropathy. The macrovascular complications manifest as coronary artery disease (CAD) and congestive heart failure (CHF), cerebrovascular accidents (CVA) and peripheral vascular disease (PVD) (Figure 2).[11]

The pathogenesis of diabetic vascular complications is multifactorial; however, hyperglycaemia and insulin resistance

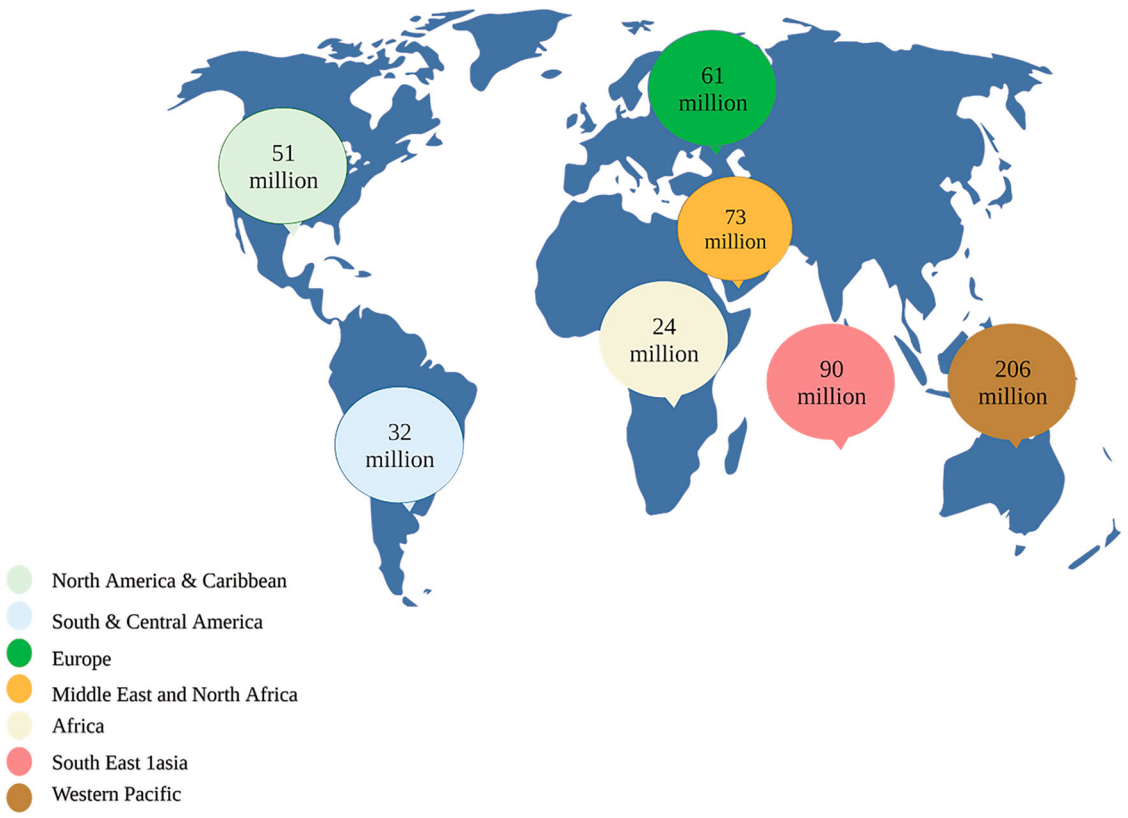

Figure 1: Global prevalence of type II diabetes mellitus in 2021. Diagram adapted from global prevalence of type II diabetes mellitus in 2021.[2]

form the basis. The chronic hyperglycaemic state leads to increased production of advanced glycation end-products, activation of protein kinase C, stimulation of the polyol pathway and enhance the generation of reactive oxygen species.[12] This will ultimately lead to vascular inflammation, altered gene expression of growth factors and cytokines, as well as platelet and macrophage activation.[12,13] Other pathological changes include endothelial and vascular smooth muscle dysfunction, accelerated atherosclerosis and the development of unstable atherosclerotic plaque. Furthermore, the concomitant CVD risk factors such as hypertension, dyslipidaemia and central obesity are also highly atherogenic and exponentially increase the risk for vascular complications.[14]

Microvascular complications

These include retinopathy, which causes visual impairment. Nephropathy is a significant cause of diabetic-mediated renal failure, and neuropathy causes dysfunction in the sensory and autonomic nervous systems.[11] There is a linear relationship between the incidence and control of microvascular complications with glycaemic control. Therefore, early intensive glucose control may result in the reduction of these complications.[6–9]

Macrovascular complications

Diabetes increases the risk for ASCVD morbidity and premature death. The atherothrombotic disease is disseminated throughout the vascular beds of the coronary, cerebrovascular and peripheral circulation.[4] The relationship between HbA1c reduction and macrovascular events is considered tenuous, yet the presence of traditional risk factors may accelerate ASCVD.[12,13] In the UK Prospective Diabetes Study (UKPDS), death due to ASCVD was 70 times higher than microvascular complications.[6] Therefore, a residual ASCVD risk remains in T2DM, even after HbA1c control.

Heart failure

Heart failure (HF) is one of the CVD downstream sequelae in T2DM, with females having a higher risk than males. A bidirectional association exists between T2DM and HF, with one disease independently increasing the risk of the other.[15] Approximately 24% of chronic heart failure patients have

Table 1: Glucose-lowering trials showing outcomes after long-term follow-up: UKPDS/ACCORD/ADVANCE/ VADT study summaries

Trial	Study population	HbA1c* (%)	Control vs. intensive HbA1c at study end (%)	Mean duration of diabetes at baseline (years)	Micro-vascular	CV disease	Mortality
UKPDS[6]	5 102	7.0 (6.2–8.2)	7.9 vs. 7.0	Newly diagnosed	Decreased	Decreased	Decreased
ACCORD[7]	10 251	8.1 (7.6–8.9)	7.5 vs. 6.4	10.0	N/A	N/A	N/A
ADVANCE[8]	11 140	7.5 ± 1.6	7.3 vs. 6.5	8.0	Unchanged	Unchanged	Unchanged
VADT[9]	1 791	9.4 ± 1.5	8.4 vs. 6.9	11.5	-	Decreased	Unchanged

*Baseline HbA1c = glycated haemoglobin; CV = cardiovascular.

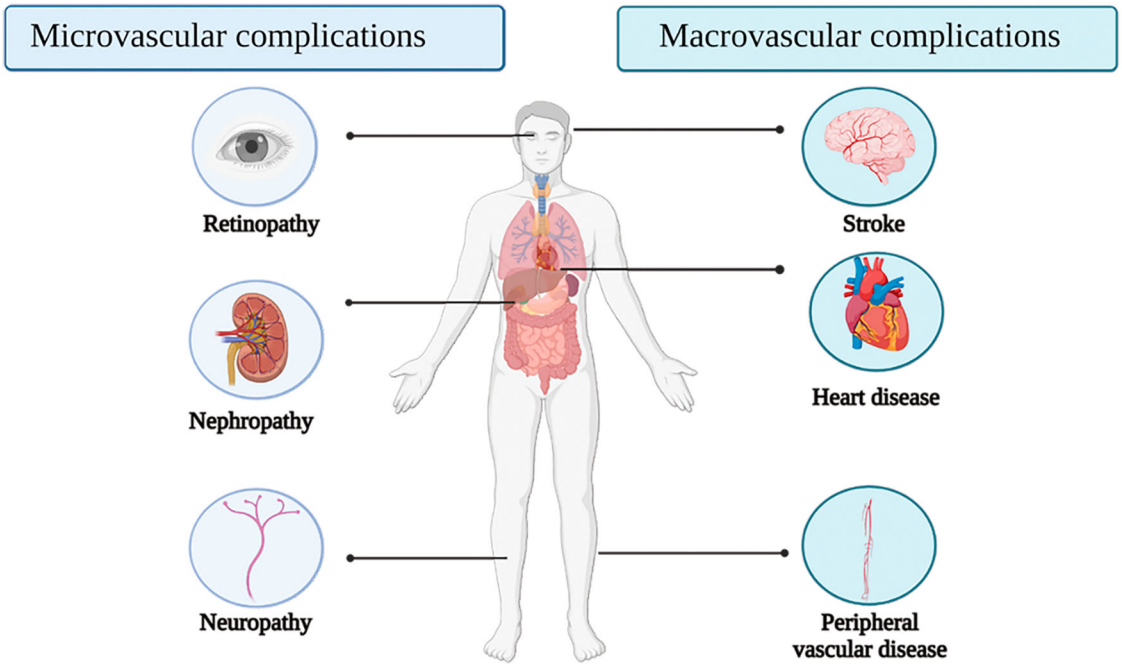

Figure 2: Clinical implications of diabetes for vascular disease complications.

T2DM. Conversely, in acutely decompensated heart failure patients, the prevalence of T2DM increases to 40%.[15] Unfavourable clinical events in T2DM patients admitted with HF include prolonged hospitalisation, an increased risk of combined CV mortality and HF-related hospitalisations, and a poorer prognosis despite receiving guideline-directed medical therapy.[16]

Antidiabetic medications and cardiovascular protection

In the past, the only requirement for registration of a new antidiabetic drug by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) was the proven glucose-lowering effect of the therapy.[17,18] However, following the demonstration of the questionable cardiovascular safety of thiazolidinedione in a meta-analysis by Singh *et al.*[19] it became mandatory for all antidiabetic medications to show cardiovascular safety.[18] These studies have become the so-called cardiovascular outcome trials (CVOTs). These current recommendations also entail that newer antidiabetic medicines should achieve a hazard ratio of < 1.3, and major adverse cardiovascular outcomes (MACE) of CV death, non-fatal MI and non-fatal stroke are to be assessed, standardised and continue to be monitored for their CVD safety post-exposure.[17,18]

Glucagon-like peptide 1 receptor agonists and CVOTs

The glucagon-like peptide 1 (GLP-1) receptor is widely distributed in the body, including the heart. The incretin-like effects of GLP-1 receptor agonists (GLP-1RA) enhance insulin secretion, inhibit glucagon release, reduce hepatic glucose synthesis, delay gastric emptying and increase satiety.[20] Apart from reducing HbA1c (~ 1%), GLP-1RA also cause weight loss by up to four kilograms.[21] The mechanism of action of GLP-1RA is highlighted in Figure 3.

In all these presented GLP-1 RA CVOTs (Table 2), more than 80% of the study participants had a history of prior CVD, except for the REWIND trial. In a meta-analysis by Giugliano *et al.*, the GLP-1RAs reduced the overall risk of MACE in those with pre-existing CVD by 16%, but only 6% in patients with CVD risk factors.[26] In addition, the use of GLP-1RA also led to risk reduction of the individual components of MACE; 13% reduction in CV death, 9% reduction in non-fatal MI, 16% reduction in non-fatal stroke and 10% reduction in HF hospitalisation. However, the risk reduction in non-fatal MI, although numerically high, was statistically non-significant.

The composite kidney outcomes of a sustained decline in estimated glomerular filtration rate (eGFR) of ≥ 50%, end-stage kidney disease (ESKD) (defined by eGFR < 15 ml/min/1.73 m^2 or a requirement for dialysis or kidney transplantation), incident macroalbuminuria and kidney-related mortality were reduced by 17% in CKD patients treated with GLP-1 RAs. The reduction in macroalbuminuria primarily drove this composite primary endpoint (HR = 0.83).[26]

Sodium-glucose cotransporter-2 inhibitors and CVOTs

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are involved in glucose reabsorption in the luminal surface of the early part of the proximal convoluted tubule. The sodium-glucose cotransporter-1 (SGLT-1) aids in reabsorbing ~10% of glucose in the gut.[27] The use of SGLT-2i results in reduced preload (diuresis and natriuresis) and reduced afterload (lowering the blood pressure), weight loss, and reduction in glucose, uric and lipid levels, among others (Figure 4).[27]

Table 3 shows the salient features of the three-point MACE of the primary composite outcome of cardiovascular death, non-fatal MI and non-fatal stroke with SGLT-2i CVOTs in T2DM. In all these trials, CV death and hospitalisation for HF formed part of the composite outcomes. In addition, the CREDENCE and DAPA-CKD trial also evaluated the composite of renal MACE: end-stage kidney disease, doubling of serum creatinine levels (eGFR ≥ 50%) and death from renal or CV causes.[28,29]

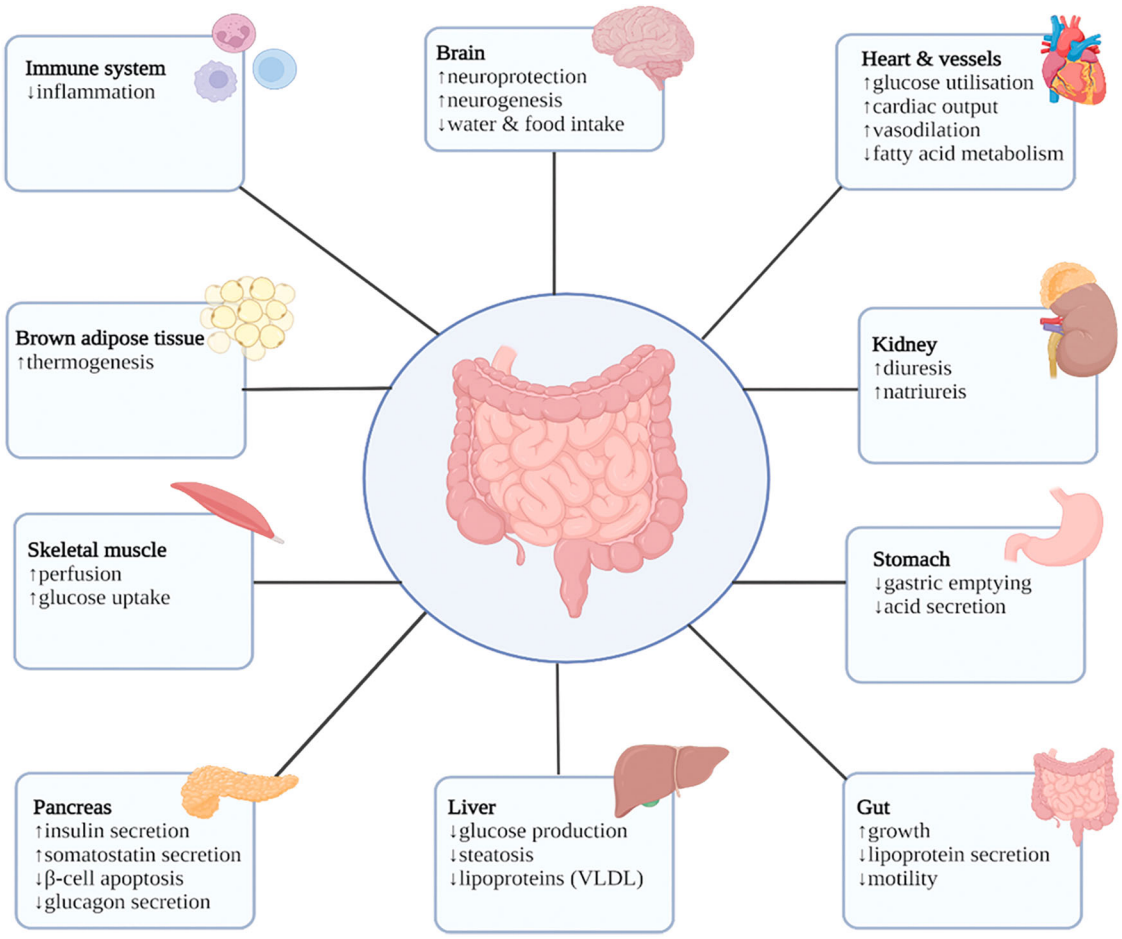

Figure 3: Mechanism of action of glucagon-like peptide-1 receptor agonists in various organs. The gut endocrine cells are the primary site of secretion of GLP-1. VLDL: very-low-density lipoprotein. Diagram adapted from Kalra, S. *et al.* Consensus Recommendations on GLP-1 RA Use in the Management of Type 2 Diabetes Mellitus: South Asian Task Force.[21]

In totality, the SGLT-2i CVOTs recruited 77 541 study participants. The SGLT-2i reduced the composite of CV death or hospitalisation for HF by 23% (HR = 0.77, 95% CI 0.73–0.82, $p < 0.001$), 26% in patients with T2DM and 23% in non-diabetes. There was an overall 16% relative risk reduction in CV death (HR = 0.84; 95% CI 0.73–0.95), and the total mortality was reduced by 13%.[30] However, VERTIS-CV did not significantly reduce CVD death.

Table 2: Summary of glucagon-like peptide-1 receptor agonists with positive cardiovascular outcome trials

Factor	LEADER[22]	SUSTAIN-6[23]	HARMONY[24]	REWIND[25]
Drug tested	Liraglutide	Semaglutide	Albiglutide	Dulaglutide
Dose	1.8 mg/day	0.5 mg and 1.0 mg weekly	30–50 mg/week	1.5 mg/week
Population size	9 340	3 297	9 463	9 901
Age, mean	64	65	64	66
Female, %	36	39.3	31	46
History of heart failure	1 667	777	1 922	853
eGFR < 60 ml/min/1.73 m^2	2 158	939	NA	2 199
HbA1c	8.7	8.7	8.7	7.3
Prior CVD, %	81	83	100	31
BMI, mean	33	33	2	32
Follow-up period (years)	3.8	2.1	1.6	5.4
Number of MACE	1 302	254	766	1 200
MACE-3P	0.87 (95% CI 0.78–0.97)	0.74 (95% CI 0.58–0.95)	0.78 (95% CI 0.68–0.90)	0·88 (95% CI 0.79–0.99)
CV death	0.78 (95% CI 0.66–0.93)	0.98 (95% CI 0.65–1.48)	0.93 (95% CI 0.73–1.19)	0.91 (95% CI 0.78–1.06)

BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiac events. Outcome data reported as hazard ratios with 95% confidence intervals.

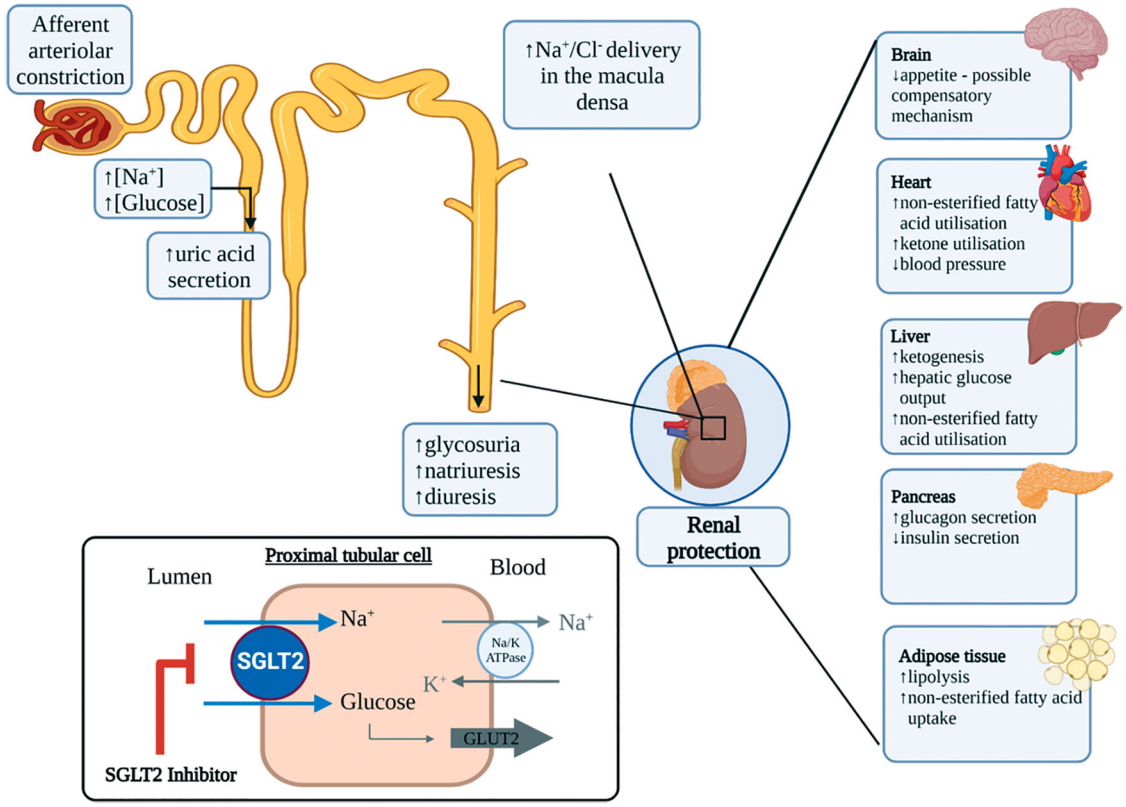

Figure 4: Mechanism of action of sodium-glucose co-transporter-2 (SGLT-2) inhibitors. SGLT-2 is expressed predominantly in the nephron's luminal membrane of proximal tubular cells. Increased sodium delivery in the macula densa leads to increased intracellular sodium concentration. Diagram adapted from Brown, E. *et al.* A review of the mechanism of action, metabolic profile, and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab. 2019;21(2): 9–18.[27]

Furthermore, in a sub-analysis of 10 SGLT-2i studies that were not heterogeneous, there was a 32% (HR = 0.68, 95% CI 0.62–0.74) reduction in the risk of worsening heart failure (hospitalisation, an urgent emergency visit requiring intravenous therapy, or heart failure) compared with placebo.[30] In another meta-analysis by Zhou *et al.*, 12 RCTs of SGLT-2i were made up of 10 883 patients with heart failure with preserved ejection fraction (HFpEF). SGLT-2i significantly reduced the composite of first heart failure hospitalisation or cardiovascular death in patients with HFpEF compared with those on placebo (HR 0.78, 95% CI 0.70–0.87). In this analysis, there was no significant difference between SGLT2i and placebo regarding cardiovascular death (HR 0.96, 95% CI 0.82–1.13). The number needed to treat to prevent one death was 31.[31] These findings expand the use of this new drug class for HFpEF patients, a group in whom few therapies have proved effective.

SGLT2i are also noted to have a reno-protective effect irrespective of the diabetes status. The risk of the composite renal outcome was reduced by 35% (HR = 0.65, 95% CI 0.56–0.75).[30] In clinical practice, the use of SGLT2i is associated with an initial dip in eGFR within the first few days of initiation. However, the renal function returns to the pre-treatment level within a few weeks of therapy.

Mechanism of cardiovascular prevention by the SGLT-2 inhibitors

As highlighted earlier, the traditional antidiabetic medication blood-glucose-lowering effect did not reduce ASCVD outcome or HF, or attenuate deterioration in kidney function.[11] This suggests that other mechanisms are at play through which these novel therapies exert this cardiovascular protective effect. Even though still speculative, some possible methods of CV protection include reduction in redox states, attenuation of endothelial dysfunction and arterial stiffness, and selective reduction in interstitial fluid with little or no activation of the renin-angiotensin-aldosterone system.[36] This occurs alongside the reduction in hyperglycaemia, uric acid and weight loss.

The induction of natriuresis by the SGLT-2 inhibitors helps improve preload conditions, while the limited effect on the sympathetic tone and reduction in blood pressure causes afterload reduction. SGLT-2 inhibitors also help maintain the heart's metabolic flexibility by switching from glucose utilisation to ketones that produce more energy. Other notable actions include the anti-fibrotic effect, and a reduction in intraglomerular pressure and albuminuria.

Almost all the SGLT-2i exhibit these cardiorenal protective effects with little heterogeneity; thus, the choice between the SGLT-2i will be guided by their salient features. For example, empagliflozin and canagliflozin are preferred if the reduction in 3P-MACE is paramount, especially in T2DM patients with or at high risk of ASCVD. In contrast, empagliflozin, canagliflozin and dapagliflozin are appropriate SGLT-2 inhibitors in individuals with kidney disease. However, for HF outcomes, empagliflozin and dapagliflozin are favoured.

Translational implications of the new antidiabetic therapies

Type 2 diabetes mellitus is a cardiovascular risk factor that warrants cardioprotection. Therefore, cardiovascular risk assessment has become an essential step when treating T2DM patients.

Table 3: Summary of sodium-glucose co-transporter-2 inhibitors with positive cardiovascular outcome trials

Factor	EMPA-REG[32]	CANVAS[33]	Declare-TIMI 58[34]	Vertis-CV[35]
Drug tested	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Population size	7 020	10 142	17 160	8 246
Age, mean	63	63	64	64
Female, %	28.8	36	37	30
HbA1c	8.1	8.2	8.3	8.2
Follow-up period (years)	3.1	3.6	4.2	3.5
Number of events	772		913	980
Primary outcome*	0.86 (95% CI 0.74–0.99)	0.86 (95% CI 0.75–0.97)	0.83 (95% CI 0.73–0.95)	0.97 (95% CI 0.85–1.11)
4P MACE	0.89 (95% CI 0.78–1.01)	–	0.93 (95% CI 0.84–1.03)	0.92 (95% CI 0.82–1.04)
CV death	0.62 (95% CI 0.49–0.77)	0.87 (95% CI 0.72–1.06)	0.98 (95% CI 0.82–1.17)	0.92 (95% CI 0.77–1.11)
Heart failure hospitalisation	0.65 (95% CI 0.50–0.85)	0.67 (95% CI 0.52–0.87)	0.73 (95% CI 0.61–0.88)	0.70 (95% CI 0.54–0.90)
All-cause mortality	0.68 (95% CI 0.57–0.82)	0.87 (95% CI 0.74–1.01)	0.76 (95% CI 0.67–0.87)	0.93 (95.8% CI 0.80–1.08)
Incident or worsening nephropathy	0.61 (95% CI 0.53–0.70)	0.73 (95% CI 0.67–0.79)	0.76 (95% CI 0.67–0.87)	–

CV = cardiovascular; MACE = major adverse cardiac events. Outcome data were reported as hazard ratios with 95% confidence intervals. The primary outcome is death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

Patients with documented ASCVD, T2DM with target organ damage or a significant CV risk factor, and severe chronic kidney disease with an eGFR of less than 30 ml/min/1.73 m^2, are all considered to have a very high ASCVD risk.[37,38] The SGLT2i and GLP-1 RA CVOTs therapies with proven ASCVD secondary prevention have now been recommended by most international guidelines to be used early in patients with very high and high ASCVD risk.[37,38] In these patients, the addition of an SGLT2i or a GLP-1RA with proven ASCVD benefit should be considered.

In managing T2DM, the multifactorial management approach emphasises that to manage the ASCVD risk optimally, all co-morbidities need to be adequately treated. The target of blood pressure control should be < 130/80 mmHg, ideally using a single-pill combination. Dyslipidaemia needs to be initially treated with a high potency statin to a targeted low-density lipoprotein (LDL-c) target of < 1.4 mmol/l. Glycated haemoglobin targets are individualised but are generally set at ~ 7%. In addition, diet, physical activity and behavioural therapy should be designed to achieve weight loss, with overweight and obese T2DM aiming for > 5% weight loss. Finally, smoking should be discouraged in all patients and smoking cessation encouraged in those who smoke.[37,38]

When deciding between an SGLT2i or the GLP-1RA, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Consensus Report recommend that only an SGLT2i or a GLP1-RA with proven cardiovascular and renal benefit should be considered. SGLT2i are preferred in patients with concomitant heart failure and chronic kidney disease. GLP-1RAs are recommended in overweight or obese patients or those with a high ASCVD burden.[37] The ADA and EASD guidelines have recommended these agents as second-line therapy to be added to foundational metformin therapy. The recently published European Society of Cardiology, in collaboration with the EASD guidelines, has further pushed the boundaries by recommending these novel therapies as first-line drugs in newly diagnosed T2DM patients presenting with ASCVD or with high or very high cardiovascular risk.[38]

Conclusion

The SGLT2i and GLP-1RA CVOTs with proven ASCVD benefits have ushered in a new era in the management of T2DM. A paradigm shift from the traditional 'glucose-centric focus' to the 'cardiovascular and renal protection focus' has now been established. Furthermore, the beneficial pleiotropic effects continue to encourage more RCTs to test the efficacy of these therapies in other disease states such as heart failure, chronic kidney disease, obesity and non-alcoholic fatty liver disease in patients with and without diabetes. The previously unmet need for ASCVD treatment in T2DM is finally being addressed. The big challenge now is for clinicians and health funders to acknowledge the compelling CVOTs data supporting these therapies and to endorse their timeous use.

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