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Review

Should metformin still be the first-line of treatment in type 2 diabetes mellitus? A comprehensive review and suggested algorithm

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ABSTRACT

For more than a century, the high occurrences of coronary and peripheral artery diseases in diabetes mellitus patients has been well recognised; despite that, the ability to improve CV event rates by optimizing glycaemic control has remained elusive. Nevertheless, the last decade has seen several cardiovascular outcome clinical trials (CVOTs) of many antihyperglycemic agents that reported promising results for cardiovascular and renal outcomes. This leads to a hot debate on the ideal drug choice for first-line treatment in T2DM. The purpose of this paper is to review the evidence supporting the use of metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors and incretin-based therapies for the management of individuals with T2DM and, discuss the rationale for selection.

1. Introduction

The high prevalence of coronary and peripheral artery disease in individuals with diabetes mellitus has been well recognised for more than a century, yet the ability to improve CV event rates by optimizing glycaemic control has remained elusive [1,2] Reducing the burden of atherosclerotic cardiovascular disease (CVD) in diabetes mellitus is of major clinical importance. Given the ever-increasing armamentarium of pharmacotherapeutics for the management of type 2 diabetes mellitus (T2DM), the last decade has seen several clinical trials of anti-hyperglycemic agents (AHAs) report promising results for cardiovascular and renal outcomes leading to a hot debate on the ideal drug choice for first-line treatment in T2DM. The purpose of this paper is to review the evidence supporting the use of metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors and incretin-based therapies for the management of individuals with T2DM and, discuss the rationale for selection first-line pharmacotherapy.

1.1. Metformin – examining the evidence

In 1998, The United Kingdom Prospective Diabetes Study (UKPDS) published data from a cohort of 5012 newly diagnosed T2DM patients with a median follow-up of 10 years. In this study, metformin was the only oral agent to reduce any diabetes-related endpoint by 32% ($p = 0.002$), diabetes-related death by 42% ($p = 0.017$) and all-cause mortality by 36% ($p = 0.011$) [3]. Comparatively, initial randomization to other intensive therapies did not produce significant reductions in these events versus diet alone. This was the first prospective dataset to provide substantive evidence in favour of metformin for reduced incidence of myocardial infarction (MI) and increased survival in overweight patients with T2DM [4]. The apparent vasoprotective effect afforded by metformin could not be explained by glycemic control alone as intensive therapy with a sulfonylurea or insulin resulted in similar glycemic control but provided less protection against myocardial infarction and other macrovascular events.

The benefits observed in the UKPDS study were sustained in the 10 year follow-up analysis, which again showed that metformin reduced any diabetes-related endpoint by 21% ($p = 0.01$), myocardial infarction by 33% ($p = 0.005$) and all-cause mortality by 27% ($p = 0.002$) [5]. Of note, a sub-study of the UKPDS, in which metformin was added to sulfonylurea therapy, showed an initially higher occurrence of diabetes-related deaths than those receiving

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sulfonylurea alone. However, the death rate was much lower in each of the sub-study groups compared to the main randomization. Long-term follow-up of this sub-study has shown that mortality equalized between the two groups. Several subsequent retrospective analyses substantiated the association of improved CV outcomes, i.e., reduced CV mortality, lower incidence of MI and heart failure (HF) with metformin [6–8].

In a Canadian health database [9], metformin use was associated with reduced all-cause mortality [odds ratio (OR) 0.60, 95% confidence interval (CI) 0.49–0.74] and deaths from CVD (OR 0.64, 95% CI 0.49–0.84) compared with sulfonylureas. The same beneficial effect was seen with metformin + sulfonylurea combination therapy compared with sulfonylurea alone (OR 0.66, 95% CI 0.58–0.75 for all-cause mortality; OR 0.64, 95% CI 0.54–0.77 for cardiovascular deaths). The overall vasculo-protective effect of metformin was then corroborated by a Cochrane analysis, which reported a metformin-induced significant risk reduction for myocardial infarction ($p = 0.02$), diabetes-related death ($p = 0.03$) and all-cause mortality ($p = 0.01$) [10]. Thereafter, data supporting the favourable effect of metformin strengthened. A US cross-sectional analysis of military health service data revealed that the lowest average annual incidence of acute myocardial infarction was seen with metformin (33.09/10,000) and the highest with insulin (51.67/10,000) and sulfonylureas (48.58/10,000), however, the p value was not provided for these observations. Similar results were observed for the annual incidence of HF (metformin 67.82/10,000, insulin 114.10/10,000, sulfonylureas 104.59/10000; p value not available) [11].

In 2009, two large, retrospective cohorts provided similar results [12,13]. One study based on a general practice database in the UK [12] reported that first-generation sulfonylureas increased the risk of myocardial infarction (HR 1.37, 95% CI 1.15–1.62, $p = 0.0003$ and HR 1.27, 95% CI 1.07–1.50, $p = 0.007$, depending on the adjustment model), compared with metformin. Second-generation sulfonylureas also increased the risk of myocardial infarction (HR 1.31, 95% CI 1.21–1.43, $p < 0.001$ and HR 1.25, 95% CI 1.15–1.36, $p < 0.001$, depending on the adjustment model) [14]. Compared to metformin, both first and second-generation sulfonylureas increased the risk of first episode of congestive HF [12]. In a US cohort [13], multivariate analysis showed that metformin administration was associated with a reduced risk of HF (HR 0.76, 95% CI 0.64–0.91) and mortality (HR 0.54, 95% CI 0.46–0.64) compared with sulfonylurea therapy.

Another large Canadian database analysis of 12272 patients who are being initiated on AHAs between 1991 and 1996, included 1833 patients with incident HF [14]. Metformin monotherapy and metformin + sulfonylurea combination therapy were shown in multivariate regression analysis to reduce all-cause mortality both at 1 year (adjusted OR 0.66, 95% CI 0.44–0.97 and adjusted OR 0.54, 95% CI 0.42–0.70, respectively) and after a mean follow-up of 2.5 years (adjusted OR 0.70, 95% CI 0.54–0.91 and adjusted OR 0.61, 95% CI 0.52–0.72, respectively). Although the investigators demonstrated the beneficial effect of metformin in HF, these findings were reported on the basis of a retrospective observational design and absence of data on severity of HF [14].

In the US, Masoudi et al. [15] carried out a retrospective cohort study of 16,417 diabetic Medicare beneficiaries discharged after hospitalisation for HF. In this cohort, crude 1-year mortality was significantly ($p = 0.0001$) lower in metformin-treated patients (24.7%) compared to those receiving other agents. The use of metformin was linked with reduced mortality (OR 0.86, 95% CI 0.78–0.97) [15]. These findings are influenced by limitations such as potential selection bias (age > 65 years), short follow-up and uncertainty regarding continuation of medication post-discharge. A systematic review published in 2007, found that metformin reduced all-cause hospital admissions at 1 year compared with other treatments (OR 0.85, 95% CI 0.76–0.95, $p = 0.004$). The authors concluded that metformin was the only hypoglycaemic agent not associated with harm in patients with HF and, indeed, led to reduced all-cause mortality in two individual studies [16].

Another study including diabetic patients with advanced systolic HF [mean ejection fraction 24%, 42% of patients classed as New York Heart Association (NYHA) III and 45% as NYHA IV], reported that metformin-treated patients exhibited significantly ($p = 0.007$) improved 1-year survival rates (91%) vs. those not receiving metformin (76%) with (HR 0.37, 95% CI 0.18–0.76).[17] At 2 years, survival rates with and without metformin were 78% and 63%, respectively ($p = 0.007$). After multivariate adjustment for potential confounders, metformin was associated with an insignificant trend for improved survival: adjusted HRs for mortality at 1 and 2 years were 0.63 (95% CI 0.21–1.89, $p = 0.40$) and 0.79 (95% CI 0.36–1.71, $p = 0.54$), respectively [17]. These results are in contrast to the previously described studies as statistical significance was not achieved. A nationwide Danish retrospective cohort study of diabetic patients with HF and median observational time 844 days demonstrated reduced all-cause mortality with metformin monotherapy (adjusted HR 0.85, 95% CI 0.75–0.98, $p = 0.02$) and metformin + sulfonylurea combination therapy (adjusted HR 0.89, 95% CI 0.82–0.96, $p = 0.003$), using sulfonylurea monotherapy as reference. [18].

Furthermore, Aguilar et al. [19] used propensity score-matched samples to explore the relationship between metformin use and the risk of death or of hospitalisation in a cohort of diabetic patients with HF treated in ambulatory clinics at Veteran Affairs medical centres. At 2 years, significantly fewer deaths ($p < 0.001$) occurred in metformin-treated patients (15.8%) than in those not receiving metformin (25.5%). Metformin was linked with significantly reduced risk of death (HR 0.76, 95% CI 0.63–0.92; $p < 0.01$) and marginally reduced risk of hospitalisation due to HF (HR 0.93, 95% CI 0.74–1.18).

Accumulation of evidence supporting improved CV outcomes with metformin prompted reconsideration of HF as a contraindication for its use. In 1994, when metformin was first approved for use, it was contraindicated in patients with kidney disease and liver disease due to concerns about lactic acidosis [20]. Later CHF was added due to reports of lactic acidosis in this setting. However, in 2006, the FDA eliminated the heart failure warning due to the accumulating evidence that metformin is safe and may be beneficial in patients with compensated heart failure. In the same year, the FDA relaxed renal contraindications for metformin use as well [21].

In 2016, Crowley et al. [22], conducted a systematic review of metformin use and its effect on several relevant clinical outcomes, including all-cause mortality and major cardiovascular events in patients with kidney disease (eGFR <60 mL min^{-1}/1.73 m2), congestive heart failure, or chronic liver disease with hepatic impairment. The authors reviewed 17 studies comparing treatment regimens that included metformin with those that did not and found that metformin use was associated with lower all-cause mortality among patients with each of the 3 chronic conditions. Additionally, metformin was associated with a lower risk for heart failure readmission in patients with heart failure and kidney disease, but it did not confer a lower risk for major cardiovascular events in those patients. Despite this well-conducted review, the benefits of metformin use in patients with kidney, heart, or liver dysfunction continued to remain uncertain as the included studies were observational and outcome assessment was not blinded. Hence, the authors concluded that the strength of evidence for the cardiovascular benefits of metformin use remains poor.

2. SGLT-2 inhibitors mechanism of action

2.1. Effects on glycemic control

SGLT2 Inhibitors are a novel class of drugs that lower plasma glucose concentration by increasing urinary glucose excretion. In clinical trials, they achieve an HbA_{1c} reduction of 0.4–1.1% (4.4–12.1 mmol/mol) versus placebo, depending upon baseline HbA_{1c}, specific drug and dose used, regardless of background therapy [23–26]. Amongst patients with HbA1c < 8% (<64 mmol/mol), SGLT2 inhibitors appear to have a dose-dependent glucose lowering effect where high-dose therapy produces a superior response in comparison to low-dose formulations. Also, a reduction of 1–2 mmol/l in fasting plasma glucose (FPG) concentration is noted with this class of drugs, which is greater than that achieved with other glucose lowering strategies [27]. These benefits are observed without a consequent increase in the incidence of hypoglycaemia.

Intriguingly, Canagliflozin (300 mg) has shown modestly greater effects on HbA_{1c} and FPG versus other SGLT2 inhibitors. This could be attributed to its inhibitory actions on SGLT1 in the intestine and activation of AMP-activated protein kinase (AMPK) [28,29]. However, at present there are no head-to-head trials directly comparing individual SGLT2 inhibitors. The glucose-lowering effect of SGLT2 inhibitors also depends upon the renal filtration of glucose, wherein, at the same ambient glucose levels, individuals with a high eGFR filter more glucose into their urine than those with a lower eGFR. Hence, a greater degree of glucosuria is seen in patients with poor glycemic control. On the other hand, the glucose-lowering effects of SGLT2 inhibitors are attenuated in patients with eGFR <60 ml min^{-1} [1.73 m]$^{-2}$ and almost absent when eGFR is < 30 ml min^{-1} [1.73 m]$^{-2}$ [30]. The insulin requirements are modestly reduced following SGLT2 inhibition while glucosuria and improved insulin sensitivity cause a modest fall in endogenous insulin secretion [31–33].

2.2. Effects on weight

Glucosuria induced energy loss by use of SGLT2 inhibitors leads to weight loss, which appears to be sustained over time. The degree of weight reduction achieved is variable depending upon the drug and dose used. A meta-analysis of randomized controlled trials involving participants treated with canagliflozin 300 mg, empagliflozin 25 mg or dapagliflozin 10 mg daily showed a weight loss of 2.66 kg, 1.81 kg and 1.80 kg, respectively, compared with placebo [34]. SGLT2 inhibitors also lower blood pressure (BP) via osmotic diuresis and intravascular volume contraction. This effect appears to be independent of reduction in plasma glucose concentration. Systolic BP is decreased by 3.4–5.4 mmHg and diastolic BP by 1.5–2.2 mmHg [23–26]. This reduction is observed in hypertensive and non-hypertensive patients irrespective of background therapy [35].

3. SGLT-2 inhibitors and CV outcome

3.1. Empagliflozin

All the SGLT2 inhibitors have demonstrated unprecedented cardiovascular benefits in large-scale clinical trials of individuals with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. In the EMPA-REG OUTCOME trial [36], individuals with diabetes and established CVD randomized to receive empagliflozin displayed a lower rate of the primary major adverse cardiac events (MACE) outcomes compared with those who received placebo (HR 0.86 [95% CI 0.74, 0.99]; p = 0.04). This was predominantly driven by a 38% reduction in the risk of cardiovascular death with no significant between-group difference in the rates of myocardial infarction or stroke. Risk of death from any cause was reduced by 32% and risk of hospitalisation for heart failure was reduced by 35%. There was a minimal difference in glycaemic control achieved between the two groups, thereby suggesting that extra-glycaemic effects were responsible for the CVD outcome. The proportion of individuals experiencing stroke in the empagliflozin vs placebo group was 3.5% (164/4687) vs 3.0% (69/2333) (HR 1.18 [95% CI 0.89, 1.56]; p = 0.26). In a subsequent analysis, Zinman et al., showed that this difference was driven by non-fatal ischaemic stroke, with no increase reported in any specific subtype [37]. This difference was due to events that occurred >90 days after the last intake of study drug, implying no direct effect of the drug. For stroke occurring during treatment or ≤90 days after the last dose of drug, the HR for empagliflozin vs placebo was 1.08 (95% CI 0.81, 1.45; p = 0.60).

3.2. Canagliflozin

In the CANVAS study, for individuals at high cardiovascular risk, the primary MACE outcome was significantly reduced in the canagliflozin arm vs placebo arm (HR 0.86 [95% CI 0.75, 0.97]; p = 0.02 for superiority) [38]. The individual components of MACE and all-cause mortality were not significantly reduced by canagliflozin, but the drug did show a similar benefit to empagliflozin (vs placebo) in reducing hospitalisations due to heart failure (HR 0.67 [95% CI 0.52, 0.87]). This study included individuals with and without CVD, thereby hinting potential benefits of canagliflozin in primary prevention [39]. However, the point estimate for the primary outcome was only 0.98 in those without established CVD, suggesting a substantial benefit for secondary prevention. In contrast, the point estimate for heart failure hospitalisation was similar in both cohorts, suggesting that this specific cardiac benefit may extend to diabetic individuals without established CVD.

3.3. Dapagliflozin

The DECLARE-TIMI 58, a phase 3, double blind, randomized, cardiovascular outcomes trial included 17160 patients with T2DM and multiple risk factors (n = 10186) or established CVD (n = 6974). This trial evaluated the effect of Dapagliflozin (10 mg) vs. placebo with a median follow-up of 4.2 years. In the primary safety outcome analysis dapagliflozin was shown to be non-inferior to placebo for MACE (CV death, MI, or ischaemic stroke), while, in the two primary efficacy analysis, dapagliflozin did not result in a lower rate of MACE (8.8% vs. 9.4% in the placebo group, HR 0.93; P = 0.17) but significantly reduced the other prespecified primary efficacy endpoint-CV death or HHF (4.9% vs. 5.8%; HR 0.83; P < 0.005). This result was consistent across multiple subgroups implying that treatment with dapagliflozin prevented CV events, specifically hospitalisation for heart failure in a broad range of patients, irrespective of a history of atherosclerotic CVD or HF. Since majority of the patients in this study did not have a history of HF, the prevention of new clinical heart failure in these patients is noteworthy [40].

4. SGLT-2 inhibitors and renal outcome

The EMPA-REG OUTCOME trial evaluated the long-term renal effects of empagliflozin and found that it was associated with slower progression of kidney disease and lower rates of clinically relevant renal events versus placebo when added to standard care. Incident or worsening nephropathy occurred in 12.7% of participants in the empagliflozin group vs 18.8% in the placebo group (HR

0.61 [95% CI 0.53, 0.70]; $p < 0.001$). There was no significant between-group difference in the rate of incident albuminuria. The renal benefit was seen irrespective of baseline eGFR, including individuals with eGFR of 30 ml min^{-1} [1.73 m]$^{-2}$. The adverse-event profile of empagliflozin in individuals with impaired kidney function at baseline was similar to that reported in the overall trial population [41]. The positive renal outcomes can be attributed to a direct renovascular action rather than improved glycaemic control due to the short duration of the study and modest HbA_{1c} reduction. Similarly, in the CANVAS-Renal study, Canagliflozin was found to have a beneficial effect on the progression of albuminuria (HR 0.73 [95% CI 0.67, 0.79]) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal-replacement therapy or death from renal causes (HR 0.60 [95% CI 0.47, 0.77]) [38].

Recently, Zelniker et al., published a systematic review and meta-analysis of cardiovascular outcome trials for the three SGLT2 inhibitors: Canagliflozin, Empagliflozin and Dapagliflozin. These SGLT2 inhibitors reduced MACE by 11% (HR 0.89, $p = 0{\cdot}0014$), reduced risk of CV death or hospitalisation for HF by 23% (0.77 $p < 0.0001$) and reduced risk of progression of renal disease by 45% (0.55, $p < 0.0001$), vs placebo. The authors concluded that SGLT2 inhibitors have moderate benefits on atherosclerotic MACE that seem confined to patients with established atherosclerotic CVD. However, they have robust benefits on reducing hospitalisation for HF and progression of renal disease regardless of existing atherosclerotic CVD or a history of HF [42].

5. SGLT-2 inhibitors possible adverse events

The most common side effect of SGLT2 inhibitors is an increased incidence of genital mycotic infections (mainly balanitis and vulvovaginitis) followed by urinary tract infections (UTIs). A meta-analysis of randomized trials comparing SGLT2 inhibitors with placebo or other medication for T2DM showed that SGLT2 inhibitors were significantly associated with a fivefold increase in the risk of genital mycotic infections (OR 5.06 [95% CI 3.44, 7.45]) and a more modest increase in UTIs (OR 1.42 [95% CI 1.06, 1.90]) [43]. Another important complication associated with the use of SGLT2 inhibitors is Diabetic Ketoacidosis (DKA). In the EMPA-REG OUTCOME study the proportion of individuals with DKA was very low in both the empagliflozin and placebo groups (4/4687 [0.09%] vs 1/2333 [0.04%], respectively) and not statistically significantly different [36]. Similarly, in the CANVAS Program, a small number of DKA events were observed in the canagliflozin and placebo groups (0.6 vs 0.3 events per 1000 patient-years, respectively; HR 2.33 [95% CI 0.76, 7.17]) [38].

It is important to note that in the CANVAS Program, participants treated with canagliflozin were at higher risk of lower-extremity amputation than those receiving placebo (6.3 vs 3.4 participants affected per 1000 person-years; HR 1.97 [95% CI 1.41, 2.75]), with 71% of the affected participants having their highest amputation at the level of the toe or metatarsal [16]. The highest absolute risk of amputation was seen in individuals with a history of amputation or peripheral vascular disease (PVD) but the relative risk of amputation with canagliflozin vs placebo was similar across these subgroups. The reason for the increased risk of amputation with this agent remains unclear. This adverse effect has not been reported with other SGLT2 inhibitors. A post hoc analysis of the EMPA-REG OUTCOME data showed that lower-limb amputation occurred in 1.9% of participants treated with empagliflozin and 1.8% of individuals treated with placebo, with an incidence rate of 6.5 per 1000 person-years in both groups [44]. When time to first event was analysed, the risk of lower-limb amputation was similar between the empagliflozin pooled group and placebo (HR 1.00 [95% CI 0.70, 1.44]). The finding was consistent across subgroups by established risk factors for amputation. Data pooled from randomized controlled trials of dapagliflozin vs placebo or vs another glucose-lowering agent showed that the risk of lower-limb amputation was similar after dapagliflozin treatment (0.1%) and control treatment (0.2%) [45].

Canagliflozin is also associated with increased risk of bone fractures. In the CANVAS Program the rate of all fractures was higher with canagliflozin vs placebo (15.4 vs 11.9 participants with fracture per 1000 person-years; HR 1.26 [95% CI 1.04, 1.52]). Similar findings were noted with respect to low-trauma fracture events (11.6 vs 9.2 participants with fracture per 1000 person-years; HR 1.23 [95% CI 0.99, 1.52]). It is important to note the heterogeneity in the findings between CANVAS and CANVAS-R, with both low-trauma fractures and all fractures occurring at greater frequency in the canagliflozin vs placebo groups in CANVAS but not in CANVAS-R [38]. This is an unusual observation as CANVAS-R participants might be considered at higher fracture risk due to greater degree of renal function impairment. The increased risk of fractures was observed within the first few weeks of initiation, with a continued rate of increase thereafter [46]. Comparatively, in the EMPA-REG OUTCOME study the proportion of participants who developed fractures was low in both the pooled empagliflozin group and the placebo group (3.8% and 3.9%, respectively) [36]. A meta-analysis of trials evaluating combined safety outcomes of canagliflozin, dapagliflozin and empagliflozin did not support a harmful effect of SGLT2 inhibitors on bone [47]. The fracture event rate was 1.59% in the SGLT2 inhibitor group and 1.56% in the control group, and the incidence of fracture events was similar among the three SGLT2 inhibitors.

6. GLP-1 analogues

6.1. Lixisenatide

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial is a double-blind randomized, placebo, controlled trial designed to assess CV outcomes. It included 6068 patients with T2DM with a history of MI or hospitalisation for unstable angina within the previous 6 months [48]. In accordance with standard of care these patients received glucose-lowering agents (metformin: 66%; sulfonylurea: 32%; insulin: 39%) and other CV drugs (ACEI/ARB: 85%; beta-blocker: 84%; statin: 93%; aspirin: 98%) for acute coronary syndrome. The mean age of patients was 60 years and the primary composite endpoint was CV death, MI, stroke, and hospitalisation for unstable angina. After a median follow-up of 25 months, the primary outcome occurred in 13.4% patients receiving lixisenatide versus 13.2% in the placebo group (HR: 1.02, 95% CI 0.89−1.17), which showed non-inferiority of lixisenatide compared to placebo ($p < 0.001$) but failed to show superiority ($p = 0.81$).

6.2. Liraglutide

Comparatively, the Liraglutide Effect and Action in Diabetes (LEADER) trial showed a CV benefit of liraglutide in patients with T2DM [49]. LEADER is a double blind, randomized, placebo, controlled trial including 9340 patients with T2DM and high CV risk to receive liraglutide 1.8 mg daily or placebo in addition to standard therapy. The primary composite endpoints were the first occurrence of CV mortality, nonfatal MI, or nonfatal stroke. In compliance with standard of care patients received glucose-lowering agents (metformin: 76%; sulfonylurea: 51%; insulin: 44%) and other CV drugs (ACEI/ARB: 51%; beta-blocker: 55%; statin: 72%; aspirin: 63%) as a majority of the patients had pre-existing CV disease (81%). Thirty percent of patients had CAD, and 16% had a previous stroke. The mean age of patients was 64 years. After a

median follow-up of 3.8 years, the primary outcome occurred in 13.0% in the liraglutide group and in 14.9% in the placebo group (HR: 0.87, 95% CI 0.78–0.97), which showed the non-inferiority of liraglutide compared to placebo ($p < 0.001$) and superiority of liraglutide compared to placebo ($p = 0.01$). CV mortality and all-cause mortality were significantly lower in the liraglutide group compared to the placebo group.

6.3. Semaglutide

The Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial was another study designed to evaluate the CV benefit of a GLP-1 agonist [50], which is not currently approved by the FDA. SUSTAIN-6 was a double blind, randomized, placebo, controlled trial, which included 3297 patients with T2DM and established CV diseases and/or chronic kidney disease. These patients were randomized to receive semaglutide (0.5 mg or 1.0 mg) or placebo in addition to standard therapy. The primary composite endpoints were the first occurrence of CV mortality, nonfatal MI, or nonfatal stroke. The mean age of patients was 64 years. After a median of 2.1 years of follow-up, the primary outcome occurred in 108 (6.6%) in the semaglutide group and in 146 (8.9) in the placebo group (HR: 0.74, 95% CI 0.58–0.95) which showed the non-inferiority of semaglutide compared to placebo ($p < 0.001$) and superiority of semaglutide compared to placebo ($p = 0.02$). Cardiovascular mortality was also significantly lower in the semaglutide group compared to the placebo group.

6.4. Extended-release exenatide

The EXSCEL study randomly assigned 14,752 patients with T2DM, with (73.1%) or without (26.9%) previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly [51]. After a median of 3.2 years, a primary composite outcome event (triple MACE) tended to occur less frequently in the exenatide group than in the placebo group (hazard ratio, 0.91; 95% CI 0.83–1.00, $P < 0.001$ for noninferiority and $P = 0.06$ for superiority). The rates of death from CV causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, HF, and hospitalisation for acute coronary syndrome did not differ significantly between the two groups. The risk of death from any cause was lower in the exenatide group than in the placebo group (HR 0.86; 95% CI 0.77–0.97). However, this difference was not considered to be statistically significant on the basis of the hierarchical testing plan as the primary outcome failed to be significant.

7. Discussion

Over time recommendations for the management of patients with T2DM have evolved in keeping with the variation in phenotype, genotype, stage of the patient in the natural history of the disease and current metabolic status. In 2002, the ADA advocated for use of treatment regimens aimed at achieving normal or near-normal glycemia with a targeted HbA_{1c} of <7% in non-pregnant adults [52]. A lower HbA_{1c} target was believed to be associated with a lower risk of MI and CV death [53]. However, following the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies where CV outcomes were evaluated and not every subject benefited from intensive glycemic control, the ADA and EASD recommended 'individualised treatment and HbA1c goals' based on age, history of severe hypoglycaemia, life expectancy, advanced microvascular and/or macrovascular complications and other comorbid conditions [54-57].

Results from the ACCORD [55], ADVANCE [56] and VADT [57] studies also prompted a change in regulatory requirements for the approval of AHAs by the FDA and European Medicines Agency (EMA) concomitantly. Hence, a wealth of data has been generated with the completion of several CV safety trials, with proven CV safety proven in each of the completed trials and with unprecedented findings of superior CV outcomes with five novel AHAs [36,38,40,49,50]. Prior to these studies, there was a dearth of data to support the use of one particular AHA over others, role of glycaemic control and appropriate HbA_{1c} targets in patients with T2DM and atherosclerotic CVD.

Due to lack of evidence Metformin remained the first choice for treatment of T2DM before and after its FDA approval in 1995; a recommendation supported by the UKPDS study mainly in addition to its global availability, affordability and overall safety. Several studies have been carried to assess the CV benefits of treatment with metformin, however, the quality of the cumulative evidence in this regard remains poor. Despite this metformin has reigned as the drug of initial choice for nearly two decades. This was highlighted in a study by Wilkinson et al., which examined UK primary care data for prescribing trends of AHAs from 2000 to 2017. Among 280241 patients started on treatment during this period, 73% (204238/280241) were initiated with metformin monotherapy. For intensification of treatment, sulfonylureas were the common second choice with a trend towards newer AHAs based on year of approval by regulatory authorities.

An increase in treatment options and robust evidence for improved CV outcomes in favour of newer agents has led to reconsideration of Metformin as first-line treatment. Based on the current evidence for newer AHAs, we propose an algorithm incorporating risk stratification to aid selection of first-line treatment (Fig. 1). Data from the LEADER [49], SUSTAIN 6 [50], EMPA-REG [36] and CANVAS [38] studies have shown improved CV outcomes for patients with T2DM and established atherosclerotic CVD. This benefit was not seen in patients without atherosclerotic CVD. Current guidance recommends the addition of SGLT2 inhibitors or GLP-1RAs with proven CV benefit as a second-line agent where Metformin monotherapy has not provided adequate glycaemic control. While this recommendation holds true for resource limited settings where cost and availability are equally important, monotherapy with SGLT2 inhibitors or GLP1-RAs or a combination of either agent with metformin can be instituted at baseline as individualised treatment based on relevant clinical parameters. AHAs with known CV benefit should be used in addition to standard of care for patients with established CVD.

It is well known that patients with T2DM and kidney disease are at an increased risk for CV events. The EMPA-REG OUTCOME [36], CANVAS [38], LEADER [49] and SUSTAIN 6 [50] studies included a substantial number of patients with stage 3 CKD where a reduction in the primary atherosclerotic CVD outcome was noted. For SGLT2 inhibitors, this contrasts with the glucose-lowering effect, which diminishes with declining eGFR. All these studies included renal endpoints as secondary outcomes. Empagliflozin was associated with a decreased incidence of new or worsening nephropathy, decreased CKD progression and ESRD or death by ESRD. Similarly, Canagliflozin was associated with regression of albuminuria and a 40% reduction in risk in the composite outcome eGFR, ESRD or renal death. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial examining canagliflozin in CKD with proteinuria has been stopped at a planned interim analysis for achieving the primary efficacy endpoint[58]. Among incretin-based therapies, Liraglutide and

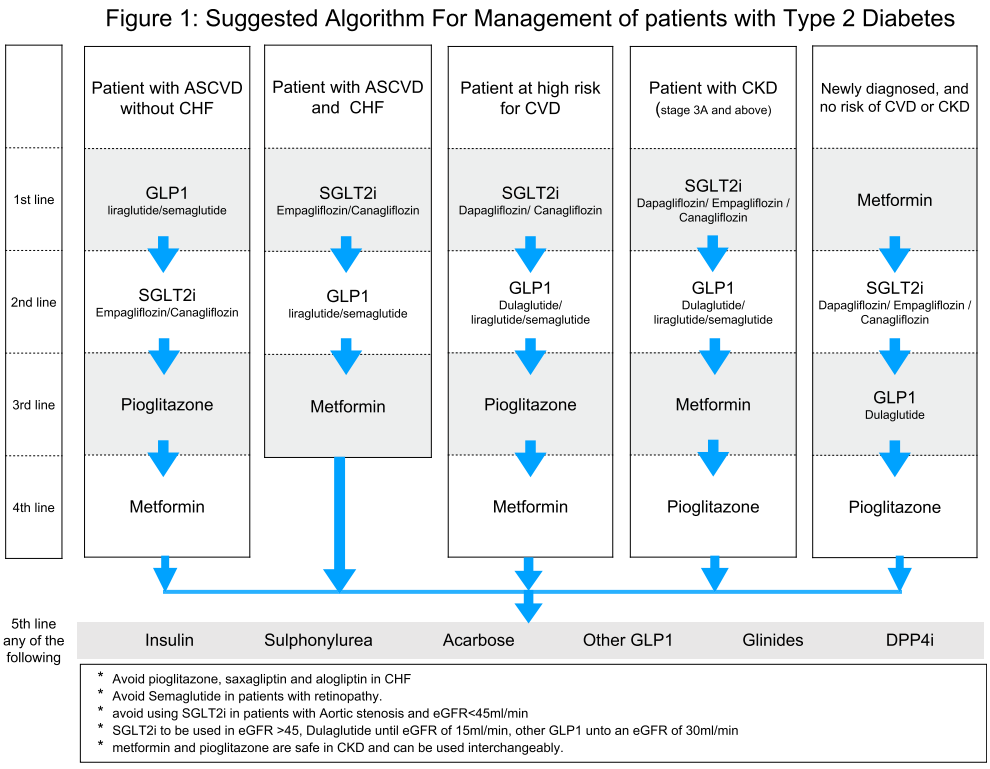

Fig. 1. A suggested algorithm for management of patients with type 2 diabetes.

Semaglutide have shown improved outcomes for new or worsening nephropathy. Therefore, in patients with T2DM and CKD, SGLT-2 inhibitors or GLP1-RAs can be considered as alternatives to metformin in accordance with eGFR recommendations.

Traditionally concerns regarding CVD have focused on atherosclerotic vasculo-occlusive events, including MI, stroke and peripheral vascular disease. However, one of the earliest and common CV disorders in patients with T2DM is HF, which is associated with an increased frequency of hospitalisation and death. Sudden death in such cases can be attributed to the underlying ventricular dysfunction rather than a new ischemic event [59]. Both Empagliflozin and Canagliflozin have demonstrated significant reduction in hospitalisation for HF as secondary prevention, while Dapagliflozin has shown significant reduction in hospitalisation for HF as primary prevention. These results support the use of SGLT2 inhibitors in this cohort of T2DM patients either in combination with Metformin as first-line treatment or as stand-alone monotherapy in whom Metformin is contraindicated or poorly tolerated (Table 1). It is important to note that HF was not well characterised at baseline in these study cohorts and evaluated as a secondary endpoint. Further studies are required to conclusively address this issue.

7.1. Suggested algorithm

Based on the previous discussion we would like to recommend the following algorithm see Fig. 1. The algorithm and the choices of medications were based on all previous studies discussed in this article.

8. Conclusion

Optimal glycaemic control is of prime importance in diabetes management, however, intensified glycaemic control has been shown to cause possibly more harm than benefit in certain patients. The validated approach towards improving outcomes across the spectrum of T2DM remains adequate lowering of blood glucose concentrations combined with multifactorial intervention for CV risk reduction. The promising cardiovascular results for newer AHAs allow for added CV risk reduction early in the course of disease thereby taking diabetes management another step closer to personalised medicine. Newer AHAs (SGLT2 inhibitors and the GLP-1 RA) have shown an unprecedented CV safety and protection in dedicated CVOTs, while Metformin lacks this structured CVOT

Table 1
Summary of CVOT trials.

Drug	EMPA-REG OUTCOME [36]	CANVAS Program [38]	DECLARE-TIMI 58 [40]	ELIXA [48]	LEADER [49]	SUSTAIN-6 [50]	EXSCEL [51]
	Empagliflozin	Canagliflozin	Dapagliflozin	Lixisenatide	Liraglutide	Semaglutide	Exenatide QW
No: of Patients	7020	10142	17160	6068	9340	3297	14752
Follow-up (yrs)	3.1	2.4	4.2	2.1	3.8	2.1	3.2
Established CVD (%)	99	65.6	40.6	100	81	58.8	73.1
Diabetes Duration (yrs)	>10	13.5	11	9.3	12.8	13.9	12
Mean Age (yrs)	63.1	63.3	63.9	60.3	64.3	64.6	62
CHF (%)	10	14.4	9.9	22.4	17.9	23.6	16.2
HR for Primary Outcome	0.86	0.86	0.93	1.02	0.87	0.74	0.91
Metformin (%)	–	–	81.8	–	–	–	–

oriented evidence. Most of the evidence from metformin remains questionable. We see the newer SGLT2 inhibitors and GLP-1 RAs with robust evidence will be soon accommodated as first line of T2DM therapy guidelines.

Conflicts of interest

Authors declare no conflicts of interest.

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Author contribution

AB, Writing manuscript, review of final version, EA Shared in the idea, review of final version, FR Writing manuscript, review of final version, PT Manuscript writing, review of final manuscript, AA Review of final manuscript, AB Idea, Manuscript writing, editing and review of final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.028.

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