**Abstract**

The relationship between cardiovascular disease (CVD), heart failure (HF), and type 2 diabetes (T2DM) is widely recognised. Cardiovascular (CV) outcome trials are required for all new glucose-lowering agents to confirm safety with respect to CV risk. CV outcome trials with sodium glucose transporter inhibitors (SGLT2i) have shown CV benefit, with reductions in major CV events and HF. This review focuses on the DECLARE-TIMI 58 trial with dapagliflozin in T2DM, which showed non-inferiority for MACE and reduction in hospitalisation for heart failure and associated CV mortality in a broad range of patients with T2DM. The DAPA-HF trial of dapagliflozin in people with heart failure with reduced ejection fraction with and without T2DM, confirms benefits for those with heart failure.

**Keywords:** T2DM, CVD, SGLT2i, DECLARE, Dapagliflozin

**Introduction: Type 2 Diabetes and Cardiovascular Disease**

In the last 20 years, the number of people diagnosed with diabetes has more than doubled[1,2]. Currently, 4.7 million people are living with diabetes in the United Kingdom (UK), of those, 90% have type 2 diabetes and around one million have not yet been diagnosed [2]. Diabetes prevalence in the UK is projected to rise to 5 million by 2025 and global figures are expected to rise to 642 million by 2040 [2-4].

Type 2 diabetes is a well-recognised risk factor for cardiovascular disease and heart failure [5-8]. Consequentially, cardiovascular disease, including heart failure, is a major cause of mortality and morbidity among people with diabetes [4,5,7,9,10]. People with diabetes are twice as likely to die from heart disease or stroke. In 1998, a Finnish population study conducted by Haffner et al. highlighted the disproportionate scale of CVD related mortality between patients with and without diabetes [11]. The study compared mortality rates in relation to myocardial infarction amongst nondiabetic and diabetic subjects within a seven-year period [11]. In those with type 2 diabetes, a mortality rate of 15.4% was observed with no previous history of myocardial infarction (MI) and 42% with a history of MI. In contrast, mortality rates were 2.1% and 15.9% respectively in those without diabetes [11]. Death from cardiovascular disease accounts for up to 50% of mortality in people with diabetes in the UK and worldwide [8,12-14]. This is notably higher than the 31% global mortality rate for CVD [15].

Compared to their counterparts without diabetes, people with diabetes are 2-3 times more likely to experience heart failure, myocardial infarction and stroke [2]. A systematic review of global publications in the last decade on the prevalence of cardiovascular disease (CVD) amongst adults with type 2 diabetes, estimated that in over 4.5 million people with type 2 diabetes, the overall prevalence of cardiovascular disease was 32.2%. Atherosclerosis was present in 29.1% of individuals, followed by coronary heart disease (21.2%), heart failure (14.9%), angina (14.6%), myocardial infarction (10.0%) and stroke (7.6%) [12]. Furthermore, in the UK, a quarter of patients requiring hospitalization secondary to heart failure, myocardial infarction or stroke have diabetes [2].

 Some studies have observed that cardiovascular event rates have fallen in patients with and without diabetes in the last decade[16,17]. Whilst the improvement in diagnostics and management of diabetes and related cardiovascular risk has contributed to this reduction, rates of cardiovascular related events have not fallen as quickly in patients with T2DM as those without the disease, and event rates remain high[16].

**The Impact and Relationship between T2DM and CVD**

The negative impact of hyperglycaemia manifests as microvascular and macrovascular complications. Currently, prevention of macrovascular complications is most effectively accomplished by reducing multiple risk factors through glycaemic control, smoking cessation, diet, exercise, blood pressure control, and treatment of dyslipidaemia[12]. Nonetheless, it is important to note that there is heterogeneity in risk stratification of cardiovascular disease in patients with T2DM[18,19]. Cardiovascular risk is less in those with short duration of T2DM and low pre-existing cardiovascular risk in comparison with older patients with longer duration of disease who have been exposed to hyperglycaemia for a lengthy period often have other pre-existing cardiovascular risk factors[18].

Although hyperglycaemia is an independent risk factor for cardiovascular disease and heart failure, glucose-lowering agents such as insulin or sulphonylureas, which solely work to lower glucose, tend to have minimal or delayed cardiovascular benefit [10]. Prolonged hyperglycaemia seen in patients with type 2 diabetes usually runs in parallel with some level of insulin resistance [10]. In fact, insulin resistance normally develops prior to the onset of symptomatic hyperglycaemia[15,20]. Insulin resistance is an important feature of metabolic syndrome, which includes insulin resistance, elevated blood pressure, dyslipidaemia, and obesity which are each independent risk factors of cardiovascular disease and / or heart failure [10,15]. Attention has thus been shifted towards glucose-lowering agents which positively impact the cluster of dysfunctions that encompass metabolic syndrome. In 2004, pioglitazone—a glucose-lowering drug targeting insulin resistance garnered interest following the PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events as it reduced the rate of cardiovascular related death, nonfatal MI/Stroke by 16% in patients at high risk[21]. However utilisation of pioglitazone has remained low due to its adverse events, particularly risk of heart failure and a possible association with bladder cancer[22]. Furthermore, —another drug in the same class, rosiglitazone, stirred further controversy in 2007 following the release of a meta-analysis by Nissan et al that suggested an increase in CV events, particularly myocardial infarction[23]. The study became a catalyst that led to scrutiny of international regulatory processes and guidelines for the development of new glucose lowering agents and their possible adverse impact on cardiovascular outcomes thus initiating new regulations and guidance[24-26].. In a systematic review on the economic burden of cardiovascular disease in type 2 diabetes the total cost of treating cardiovascular comorbidities in relation to type 2 diabetes is approximately 20-49% globally [27]. In the U.K. out of £7.7 billion spent on type 2 diabetes complications, around £3 billion is spent on cardiovascular complications including MI, IHD and heart failure; making it the highest costing complication in 2014 [28].

The clinical and economic burden attributed to T2DM and its cardiovascular complications, highlights the need for effective management - achieving glucose reduction whilst also reducing cardiovascular risk factors [15,27]. Joint management would also mean addressing the conditions in harmony rather than in isolation and taking a holistic approach of tailoring the management to the patient’s clinical needs. Likewise, the relationships between type 2 diabetes, cardiovascular disease, and heart failure-particularly as a consequence of metabolic syndrome, poses the need for treatment which can address their shared factors without requiring multiple medications.

Considering this, attention has shifted towards two novel classes of anti-hyperglycaemic agents known as glucagon-like peptide receptor antagonists (GLP RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i). Each drug class has shown promising outcomes in reducing cardiovascular risk in those with T2DM[29,30].

**Introduction to SGLT2i**

Expressed in the first segment of proximal tubules in the kidney, sodium glucose co- transporters 2 (SGLT2) are the principal transporters of glucose from the glomerular filtrate, reabsorbing 80-90% of glucose filtered by the glomeruli [6]. SGLT2 are responsible for returning almost 200g of glucose back to the circulation each day, and in patients with type 2 diabetes glucose reabsorption is increased thus exacerbating existing hyperglycaemia [31-33]. Inhibition of SGLT2 blocks reabsorption of filtered renal glucose and increases urinary glucose excretion thus reducing plasma glucose [5,10,31,33,34]. As their name suggests, SGLT2 inhibitors also promote natriuresis, and this may contribute to a reduction in sodium retention that is a feature of T2DM, and to their known effects to reduce blood pressure and circulating volume [5,10,31,33,34].

**Dapagliflozin Pharmacology**

Dapagliflozin, a potent selective and reversible inhibitor of SGLT2 [32], belongs to the drug class of oral antidiabetics known as SGLT2 inhibitors (SGLT2i). It is a C-glycosyl containing beta-D-glucose wherein the anomeric hydroxy group is substituted by a 4-chloro-3-(4-ethoxybenzyl) phenyl group—giving its molecular formula, C21H25ClO6 [35]. In the fasting state, maximum plasma concentration is achieved within two hours following oral administration [31,32]. Bioavailability is 78% and half-life is approximately 12.9h with a dose of 10mg[31,32]. Elimination is largely through urine (75%) and faeces (21%)[31,32].

**Benefits of Dapagliflozin**

Dapagliflozin has proved to be an effective therapeutic agent improving glycaemic control in a diverse range of people with T2DM [5,6,33,34]. It is effective when used as monotherapy, and in combination with metformin, glimepiride, pioglitazone, sitagliptin, and insulin [6,31,33,34]. Additionally, dapagliflozin acts independently of insulin secretion or action and is thus unlikely to cause hypoglycaemia [30].

Although not fully understood, SGLT2 inhibition caused by dapagliflozin sequentially corrects and effects multiple metabolic and haemodynamic risk factors particularly associated with diabetes and cardiovascular disease [10,15]. In addition to plasma glucose reduction, glucosuria produces a negative energy balance and in combination with fluid loss secondary to osmotic diuresis contributes to weight reduction [10,32,34]. Previous studies have shown a total body weight loss of over 2kg in 24 weeks following a combination of dapagliflozin 10mg and metformin [34]. It also promotes urinary excretion of sodium, which in turn reduces plasma volume and blood pressure [6,10,15]. Systolic blood pressure has been reduced by 3-5mmHg compared to placebo in those taking dapagliflozin 10mg [36]. Dapagliflozin is also associated with lowering of uric acid levels and albuminuria [30].

**Clinical Efficacy of SGLT2 Inhibitors**

Following the controversy surrounding rosiglitazone over a decade ago, the Centre for Drug Evaluation and Research at the Food and Drug Administration (FDA) in the United States published guidance mandating any new glucose lowering drugs intended for the treatment of type two diabetes to rule out a statistically significant unacceptable increase in cardiovascular risk [24-26]. Prespecified primary composite endpoint outcomes required for evaluation of cardiovascular risk included cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke [25,37]. This is known as the classic 3-point Major Adverse Cardiovascular Events (MACE) [38]. Often other endpoints are included under the umbrella term of MACE including hospitalisation for heart failure, unstable angina and overall mortality [37,38]. More recent trials use the 3-point MACE system, particularly as different end-points and heterogeneity amongst trials makes comparison of similar studies difficult and superiority is difficult to ascertain [38]. Since the release of FDA guidance in 2008, multiple large scale cardiovascular outcome trials have provided new insights into how the disease process can be modified by some treatment approaches, causing a dramatic shift in therapeutic approach in type 2 diabetes from a focus on reducing HbA1c to recognition of the importance of reducing cardiovascular risk [29].

Unlike many earlier glucose-lowering drugs, the associations of cardiometabolic and haemodynamic advantageous characteristics of SGLT2 inhibitor treatment, alongside supporting evidence raised the hypothesis that they would reduce the cardiovascular risk in T2DM independently of their glucose-lowering effects [10]. This meant that while fulfilling the requirements set out by the FDA, some of the cardiovascular outcomes trials with SGLT2i were powered for superiority as well as non-inferiority with placebo [10]. Prior to the results of the Dapagliflozin Effect on Cardiovascular Evens- Thrombolysis in Myocardial Infarction 58 trial (DECLARE-TIMI 58), the phase 2 and 3 trials with dapagliflozin, collected information on cardiovascular events. In a meta-analysis investigating cardiovascular outcomes from these studies there was no suggestion of increased risk for major adverse cardiovascular events; furthermore, there was evidence of potential cardiovascular benefit, particularly reduction in hospitalisation for heart failure and a decreased incidence of MI and other MACE events in patients with pre-existing cardiovascular disease [30].

Whilst the DECLARE-TIMI 58 trial was ongoing, two other SGLT2i cardiovascular outcome trials were published, with empagliflozin (the EMPA-REG OUTCOME trial) [39] and canagliflozin (the CANVAS trials) [40] respectively. EMPA-REG OUTCOME included 7020 patients with T2DM and established cardiovascular disease, randomised to 10mg or 25mg of empagliflozin or placebo and followed for a median time of approximately 3 years [39]. There was a 14% relative risk reduction (RRR) of the 3-point MACE primary outcome in patients on empagliflozin therapy versus placebo (HR 0.86; 95% confidence interval, 0.74 to 0.99; P=0.04 for superiority) [39]. Considerable benefit was seen in the empagliflozin group with respect to cardiovascular mortality (38% RRR), any-cause death (32% RRR) and hospitalisation secondary to heart failure (35% RRR) [39]. No statistically significant differences were seen with rates of myocardial infarction or stroke [39]. The CANVAS trials included 10, 142 patients with T2DM [40]. Unlike EMPA-REG OUTCOME, 65.6% of participants had established cardiovascular disease and the remainder were at high risk of cardiovascular disease with multiple risk factors [40]. Canagliflozin reduced the 3-point MACE primary outcome by 14% (hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P=0.02 for superiority)[40]. It also observed a 33% RRR in heart failure associated hospitalisation [40,41]. No statistically significant reduction in cardiovascular related mortality was seen [40]. In both trials, the efficacy of 3-point MACE outcomes was more apparent in patients with pre-existing cardiovascular disease [42]. On the other hand, further sub-analysis of the trials confirmed the reduction of heart failure hospitalisation was beneficial amongst a wide range of patients including those without established cardiovascular disease [41-43].

**Cardiovascular outcomes with dapagliflozin in the DECLARE -TIMI 58 trial**

DECLARE-TIMI 58 was a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial designed to evaluate the effect of dapagliflozin 10mg once daily on cardiovascular outcomes in patients with type 2 diabetes with either established atherosclerotic cardiovascular disease or with risk factors [5]. The trial was originally designed with the primary hypothesis that dapagliflozin does not increase incidence of MACE and will reduce the incidence of cardiovascular events [5,36]. As described previously, published data from the EMPA-REG study revealed significant benefit with regards to RRR of hospitalisation secondary to heart failure and cardiovascular related death[39]. In response, the primary outcome was amended to include hospitalisation due to heart failure and cardiovascular death and thus there were two co-primary endpoints; MACE and the composite of hospitalisation for heart failure and cardiovascular death [5]. Secondary outcome measures included time to all-cause mortality and time to first event of renal composite endpoint (confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m2 and/or ESRD and/or renal or CV death) within a time frame of up to 6 years [5]. From 2013 to 2018 (median of 4.2 years), 17,160 participants with type 2 diabetes and either established cardiovascular disease (n= 6,974) or multiple risk factors (n= 10,186) were studied [5]. Patients treated with dapagliflozin achieved better glucose control during the trial (0.42%; 95% confidence interval [CI], 0.40 to 0.45) vs placebo, but the differences tended to attenuate over time. A placebo subtracted weight reduction of 1.8kg was seen in those on dapagliflozin and placebo subtracted systolic and diastolic blood pressure reduction of 2.7mm Hg and 0.7mm Hg respectively[5].

Although dapagliflozin was non-inferior for MACE events, there was no statistically significant reduction (8.8% in the dapagliflozin group and 9.4% in the placebo
group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17)[5]. However, amongst patients with established cardiovascular disease the rate of MACE was lower in the dapagliflozin group (13.9%) compared with placebo (15.3%); which is of interest although not statistically significant [5]. The same benefit was not seen in those without established cardiovascular disease [5].

For the other co-primary endpoint, patients treated with dapagliflozin had a lower rate of the composite outcome of cardiovascular mortality and hospitalisation for heart failure (hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005). This was largely driven by the reduction in hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88), with a RRR of 17% and 27% respectively which was consistent across an extensive range of patients irrespective of a history of atherosclerotic disease or heart failure, whereas the reduction in cardiovascular death was not significant[5].

A prespecified subgroup analysis of DECLARE specifically focussed on patients within the trial with a history of MI (n=3,584)[44]. Due to their high baseline risk, it was hypothesised that this specific group would gain an even greater benefit from dapagliflozin therapy [44]. In patients with prior MI there was a 16% RRR and 2.6% absolute risk reduction of MACE, whereas no significant risk reduction was noted in those without a history of MI including those with established cardiovascular disease [44]. There was also a 19% RRR of cardiovascular death and a 15% RRR of hospitalisation for heart failure in those with a prior MI [44].

Another sub-analysis of DECLARE explored the effect of dapagliflozin on heart failure and mortality, found that heart failure was reduced in patients with T2DM with or without heart failure and reduced ejection fraction and reduced CV mortality in those with T2DM with heart failure and reduced ejection fraction[45].

**Renal and other outcomes in DECLARE -TIMI-58**

In a prespecified secondary analysis, the incidence of cardiorenal events, defined as a sustained decline of at least 40% in estimated glomerular filtration rate [eGFR] to less than 60 mL/min per 1·73m², end-stage renal disease, or death from renal or cardiovascular causes was 4.3% in those taking dapagliflozin and 5.6% in those taking placebo (hazard ratio, 0.76; 95% CI, 0.67 to 0.87). Excluding cardiovascular death the hazard ratio for the renal composite outcome was 0.53; 95% CI, 0·43–0·66; this lower rate of renal disease progression was consistent amongst those with and without established cardiovascular disease, heart failure and or chronic kidney disease [5,46].

In previous trials of SGLT2i, there have been conflicting data reports of some infrequent adverse events, notably amputations, bladder cancer, fractures and severe genital and urinary tract infections, making it difficult to ascertain genuine conclusions. The DECLARE trial specifically reported these events including incidence of amputations [40,47,48], fractures [40,47,49], stroke [50], severe genital and urinary tract infections [39,40,47], diabetic ketoacidosis (DKA) [40,47,51,52] and bladder cancer [53]. Compared to placebo, rates of major hypoglycaemia, acute kidney injury, and bladder cancer were lower with dapagliflozin and no statistical difference was found between the two groups in the incidence of amputations, fractures, stroke, volume depletion or hypersensitivity[5]. Higher rates of diabetic ketoacidosis were seen in patients on dapagliflozin (0.3% vs. 0.1%, P=0.02) of which more than 80% were using insulin at baseline [5]. Genital infections which led to discontinuation of dapagliflozin or thought to be serious adverse events in both male and female patients was seen more frequently with dapagliflozin treatment (0.9% vs. 0.1%; hazard ratio, 8.36; 95% CI, 4.19 to 16.68; P<0.001), albeit serious adverse events were rare with only two events occurring in each group[5]. Out of the six reported cases of Fournier’s gangrene, only one was within the dapagliflozin group[5].

**New evidence on dapagliflozin in heart failure – the DAPA-HF trial**

During the European Society of Cardiology (ESC) Congress in September 2019, the results of the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction Trial (DAPA-HF) was presented for the first time and results subsequently published [54,55]. DAPA-HF was a randomised, placebo-controlled phase 3 trial lasting a median of 18.2 months involving 4744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less[55]. Prior to the completion of the trial, most evidence surrounding dapagliflozin and heart failure reduction was obtained from populations who for the large part, did not have heart failure at baseline[55]. The trial, completed across 410 centres in 20 countries, was thus designed to measure the efficacy and safety of dapagliflozin in subjects with pre-existing heart failure with reduced ejection fraction irrespective of a diagnosis of T2DM [55].

Assigned treatment of dapagliflozin 10mg once daily or placebo, was given in conjunction with recognised standard drug therapy for heart failure including; (a) angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or sacubitril/valsartan, and (b) a beta‐blocker (unless contraindicated or not tolerated), as well as (c) a mineralocorticoid receptor antagonist (MRA), if indicated [56]. Patients requiring standard heart failure device therapy such as an implantable cardioverter-defibrillator (26%) and/or cardiac resynchronization therapy (8%) were also included [55].

The primary outcome included a composite of cardiovascular death or worsening heart failure defined as hospitalisation or an urgent visit resulting in intravenous therapy for heart failure[55].  Secondary outcomes included a composite of hospitalisation for heart failure or cardiovascular death, total number of hospitalisations for heart failure, cardiovascular death, a composite of worsening renal function, and death from any cause [55].

The primary composite outcome (worsening heart failure or death from cardiovascular causes) favourably with dapagliflozin, occurring in 16.3% of dapagliflozin patients compared to 21.2% of placebo patients (hazard ratio, 0.74; 95% confidence interval [CI] 0.65 to 0.85; P<0.001)[55]. It was recorded within the trial duration, that 21 patients would need to be treated with dapagliflozin to prevent one primary event[55].

A first event of worsening heart failure was seen in 10% of patients on dapagliflozin versus 13.7% of patients on placebo (hazard ratio, 0.70; 95% CI, 0.59 to 0.83)[55]. Less than 10% of dapagliflozin patients were hospitalised for heart failure compared with over 13% of placebo patients. Death from cardiovascular disease occurred in 9.6% of the dapagliflozin group compared to 11.5% of the placebo group, while death from any cause occurred in 11.6% and 13.9% respectively[55]. Incidence for secondary outcomes of hospitalisation for heart failure or cardiovascular related death was lower in those taking dapagliflozin. Between the treatment groups, no difference was seen in renal composite outcomes.

Initially 42% of all patients had T2DM, with a new diagnosis of T2DM later being made in around 3% of patients in each cohort[55]. Notably, primary outcomes were consistent amongst patients with and without diabetes [55]. NYHA classes III and IV seemed to benefit less compared to NYHA class II.

No statistically significant side effects were observed, and adverse events rarely required the discontinuation of treatment[54,55].

**Real World Evidence**

The differences in patient cohorts between the three major SGLT2i trials may partly explain the observed differences in the primary outcomes. A key factor differing DECLARE from EMPA-REG and CANVAS was its patient population where 40.6% of participants had cardiovascular disease and 59.4% were at high risk with multiple comorbidities [5,15]. A study examining the representativeness of SGLT2i cardiovascular outcome trials in a general type 2 diabetes patient population found that DECLARE had the highest relatability [9]. Representing 59% of the general type 2 diabetes patient population it was followed by CANVAS (34%) and EMPA-REG (21%) [9]. Indeed, this is key in determining external validity as it indicates the DECLARE-TIMI 58 trial included and examined patients who are most representative of the general type 2 diabetes patients [9].

**Impact of Dapagliflozin**

Although dapagliflozin did not result in 3-point MACE reduction across the general population it did suggest modest benefit in those who had pre-existing cardiovascular disease. Importantly, dapagliflozin did produce superior outcomes to placebo in prevention of heart failure hospitalisation and improved renal outcomes amongst a broad range of patients with type 2 diabetes, irrespective of prior cardiovascular disease, heart failure or renal disease.Moreover, most of the patients did not have a known history of heart failure, so the prevention of new clinical heart failure is notable [5].Additional benefits of dapagliflozin therapy as validated by DECLARE included; lowering plasma glucose, blood pressure reduction, and weight loss[5]. Notably, all of which positively contribute to the metabolic syndrome and pathophysiological processes related to complications and cardiovascular events.

More recently, the results of DAPA-HF, which shows a reduction for risk of worsening heart failure and cardiovascular disease, presents a clear benefit of dapagliflozin therapy in patients with heart failure and reduced ejection fraction irrespective of the presence or absence of diabetes [54,55]. The effectiveness of dapagliflozin in patients with and without diabetes supports the idea that it has benefits beyond those directly related to glucose lowering [5,15,30,55].

Dapagliflozin and other drugs of the class have more notable dominance in impacting heart failure and renal disease due to their action on the kidneys[5]. This is also true for many features of the metabolic syndrome by which dapagliflozin and other SGLT2i impact[15]. The chain of events grossly simplified relates to glycosuria and natriuresis[5,57]. Whereby downstream effects involving natriuresis lowers blood pressure and plasma volume which in turn reduces arterial stiffness and reduces myocardial stretch[15,57,58]. Natriuresis also increases tubuloglomerular feedback, causing afferent arteriole constriction which then triggers a reduction in intraglomerular hypertension and hyperfiltration[15,57]. The impact of glycosuria on the other hand includes weight loss through negative energy balance, which also impacts blood pressure[15,57,58]. Weight loss also contributes to a reduction in epicardial fat, helping to increase cardiac contractility and reduce inflammation and fibrosis[15,57]. The modest reduction in plasma uric acid, may also impact atherosclerosis risk. Glycosuria also reduces HbA1c, the core purpose of treatment which as already known, reduces atherosclerosis, inflammation and glucose toxicity[15,57]. The collective features together create a unique cardiac and renal protective system[15] [59].

**Current Guidance**

Dapagliflozin was formally approved by the European Medicines Agency (EMA) for use in the European Union in 2012, followed by the United States Food and Drug Administration (FDA) in 2014 [31,60]. Known by its brand names Farxiga (U.S.) and Forxiga (EU), it is licensed as 5 or 10mg doses for the use in adults with type 2 diabetes to improve glycaemic control in conjunction with diet and exercise[31,60]. Dapagliflozin 10mg is contraindicated for the use in patients with type 1 diabetes due to risk of hypoglycaemia and diabetes ketoacidosis (DKA) as per FDA and EMA guidance. However based on emerging research, EMA has approved the use of dapagliflozin 5mg for the treatment of uncontrolled type 1 diabetes despite optimal insulin therapy and a BMI≥ 27 kg/m2; to be used in conjunction with insulin and appropriate guidance and risk awareness[61]. As mentioned, most common side effects include urinary tract and genital mycotic infections with a specific warning and awareness against less likely but possible DKA[5,31].

Currently the management of type 2 diabetes UK guidance published by the National Institute of Clinical Excellence (NICE) has not incorporated the most recent evidence of the use of dapagliflozin or other SGLT-2 inhibitors in the realm of cardiovascular risk protection [62], but an update is planned for 2020[63]. However, as data has been released from SGLT2i trials and related research over the years, their benefits in reducing major cardiovascular events in patients with pre-existing cardiovascular disease has been increasingly recognised internationally [30]. In 2016, European guidelines for cardiovascular disease prevention were revised to include consideration of early SGLT2 inhibitor use in the course of diabetes management in those with established cardiovascular disease [64]. Last year the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a consensus statement on management of hyperglycaemia in type 2 diabetes [65,66]. The report recommends using an SGLT2i in patients with pre-existing cardiovascular disease irrespective of glucose control due to the benefits of MACE reduction[65,67]. Following the findings from DECLARE of a reduction in progression of chronic kidney disease, the ADA and FDA respectively updated its position statement and drug label, lowering the estimated glomerular filtration (EGFR) threshold to 45 mL/min/1.73 m² from 60 mL/min/1.73 m² in an attempt to provide safe beneficial outcome to a wider patient group[68,69]. In addition, the DECLARE sub-analysis mentioned earlier which focusses on patients with previous history of MI adds to current recommendations encouraging that patients with T2DM and previous MI be considered for SGLT2i to reduce CV risk [44].

Despite DECLARE evidently demonstrating reduction of hospitalisation for heart failure regardless of previous cardiovascular history, the present guidelines focus have largely focussed on initiating treatment in those established cardiovascular disease [5,65,67]. The data suggests that dapagliflozin could also be considered in patients with type 2 diabetes without pre-existing cardiovascular disease or heart failure. However, in August 2019 the ESC released guidelines in collaboration with the EASD recommending the use of dapagliflozin or other SGLT2i in those with T2DM and CV or in those with T2DM who are at high risk of CV or heart failure[70]. Following this and based on the results from DECLARE, in October 2019, the FDA approved dapagliflozin in reducing risk of heart failure associated hospitalisation in adults with T2DM and multiple cardiovascular risk factors or pre-existing cardiovascular disease[71].

In 2019, a systematic review by Zelniker et al compared the effects of GLP-1 RA and SGLT2i for prevention of major adverse cardiovascular events and renal outcomes in T2DM(30). The study concluded that in trials which had been reported to date, similar reduction of MACE was achieved in both groups in patients with established cardiovascular disease(30). However, SGLT2i have a higher impact in preventing hospitalisation for heart failure and progression of kidney disease(30). Renoprotection was also confirmed in the recent CREDENCE trial, which compared the renal outcomes of patients with T2DM and albuminuric chronic kidney disease taking 100mg of canagliflozin versus placebo(45).

The latest DAPA HF data suggests that dapagliflozin could be used as an adjunct to standard heart failure therapy in those with heart failure and a reduced ejection fraction (+/- T2DM) and should be considered in future heart failure guidance [55,72].

**Summary and Conclusion**

Dapagliflozin and other SGLT2i have helped mediate a new holistic chapter of diabetes drug treatment where management aims will expand to include prevention of pathophysiological factors contributing to complications and particularly cardiovascular risk factors. It is a glucose-lowering drug with further additional benefits related to the pathological features of the metabolic syndrome including glucose reduction, blood pressure reduction, and weight loss[5]. Adverse events include an increased risk of genital fungal infections, and rarely ketoacidosis; DECLARE provided reassuring data in relation to previous concerns about acute kidney injury, amputations, fractures and bladder cancer.

The DECLARE trial has emphasised the advantage of dapagliflozin therapy on heart failure and renal disease progression reduction, evident in a broad spectrum of patients regardless of related pre-existing disease[5]. It supports current international recommendations with respect to patients with pre-existing cardiovascular disease and modest MACE outcome reductions[65]. The DAPA HF trial marks a transition from HbA1c and likely extends its therapeutic role, broadening into a drug which can be used even without diabetes. In view of this, further research into dapagliflozin will likely be conducted in the future.

Dapagliflozin and other SGLT2i help to bridge the gap between management of hyperglycaemia and cardiovascular risk. However, UK guidelines still need to be updated to reflect this evidence and internationally further consideration should be made towards the benefits of heart failure risk reduction in patients with T2DM and no history of heart failure or cardiovascular disease or in heart failure patients irrespective of T2DM [55,62,65,67].

**Future Perspective**

Based on current progression it can be assumed that the use of dapagliflozin and other SGLT2i will be more widely used in the treatment of T2DM, particularly in those with pre-existing cardiovascular disease, and will likely be seen in heart failure therapy in the future. Further research may be conducted in the use of dapagliflozin in other sub-groups of patients and guidelines may begin to include the consideration of dapagliflozin therapy in those without pre-existing cardiac or renal disease. For example, currently in process is the ‘Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure’ trial (DELIVER) which is an international, randomised, double-blind study in patients with heart failure and preserved ejection fraction, differentiating it from the recently published DAPA-HF trial[73]. The trial aims to evaluate the effect of dapagliflozin 10 mg versus placebo, in reducing the composite of CV death and heart failure events. The trial aims to be completed in 2021 and will give further valuable information[73].

In general, the use of dapagliflozin will be expanded beyond diabetes and it is likely that management of T2DM will become joint with management of its risk factors to not only better management but prevent complications where possible.

**Executive Summary**

* **Introduction: Type 2 Diabetes and Cardiovascular Disease**
	+ Increasingly high incidence of type 2 diabetes (T2DM) globally and in the UK
	+ People with T2DM are at higher risk of adverse cardiovascular events and heart failure
* **The Impact and Relationship Between T2DM and CVD**
	+ Risk of CVD related to metabolic syndrome which includes insulin resistance, uncontrolled/high blood pressure, dyslipidaemia and obesity
	+ Risk of CVD is also related to hyperglycaemia, but to a lesser extent and thus therapy focussing on glucose reduction with no impact on metabolic function has minimal or late CVD benefit
	+ New focus on targeting cardiovascular risk factors such as features of metabolic syndrome in drug treatment of diabetes
	+ Pioglitazone was an anti-diabetic drug which showed CVD outcome promise, however due to concerns about adverse effects it use has become more limited
* **Introduction to SGLT2i**
	+ Expressed in the first segment of proximal tubules in the kidney, sodium glucose co- transporters 2 (SGLT2) are the principal transporters of glucose from the glomerular filtrate, reabsorbing 80-90% of glucose filtered by the glomeruli
	+ In T2DM glucose reabsorption is increased which exacerbates hyperglycaemia
	+ Inhibition of SGLT2 blocks reabsorption of filtered renal glucose and increases urinary glucose excretion thus reducing plasma glucose
* **Dapagliflozin Pharmacology**
	+ Dapagliflozin belongs to the SGLT2i drug class
	+ In the fasting state, maximum plasma concentration is achieved within two hours following oral administration
	+ Bioavailability is 78% and half-life is approximately 12.9h with a dose of 10mg
	+ Elimination is largely through urine (75%) and faeces (21%)
* **Benefits of Dapagliflozin**
	+ Lowers glucose and improves glycaemic control
	+ Used as monotherapy and in combination
	+ Contributes to weight loss, reduced albuminuria, uric acid reduction, and decreases blood pressure
* **Clinical Efficacy of SGLT2 Inhibitors**
	+ Empagliflozin: benefits seen with regards to MACE, cardiovascular mortality, Any-cause death and heart failure hospitalisation
	+ Canagliflozin: benefits seen with regards to MACE and heart failure hospitalisation and renal disease.
* **Cardiovascular outcomes with dapagliflozin in the DECLARE -TIMI 58 trial**
	+ Non-inferiority with regards to MACE however superiority with regards to MACE in those with pre-existing CVD
	+ Reduction in hospitalisation of heart failure and associated cardiovascular mortality in broad range of patients
	+ Reduction of worsening heart failure risk and CVS mortality in patients with heart failure and reduced ejection fraction irrespective of diabetes
* **Renal and other outcomes in DECLARE -TIMI-58**
	+ Lower rate of renal disease progression in those taking dapagliflozin, irrespective of diabetes diagnosis
	+ Benefits seen in lowering blood pressure, weight and glucose
	+ Most common side effect was genital infections
	+ Associated with DKA though minimal
* **New evidence on dapagliflozin in heart failure – the DAPA-HF trial**
	+ Favourable results towards dapagliflozin in reducing heart failure hospitalisation and cardiovascular related death in those with heart failure and ejection fraction of 40% or less
	+ Outcomes was consistent amongst between patients irrespective of diabetes diagnosis
* **Real World Evidence**
	+ DECLARE included and examined patients who were more representative of general T2DM population in comparison to CANVAS and EMPA-REG
* **Impact of Dapagliflozin**
	+ Variety of benefits
	+ Dominance in impacting heart failure, renal disease and features of metabolic syndrome due to mechanism of action stemming from glycosuria and natriuresis creating cardiac and renal protection
* **Current Guidance**
	+ Approved in US and EU for treatment of T2DM
	+ Consensus statement released by US and EU recommending use of SGLT2i in those with established CVD disease
	+ No updated UK guidance in relation to new data
	+ No clear guidance on use in those without pre-existing CVD despite current evidence
	+ FDA has approved the use of dapagliflozin to reduce heart failure hospitalisation in those with T2DM and high cardiovascular risk/established cardiovascular disease
	+ DAPA HF suggests that dapagliflozin could be used as an adjunct to standard heart failure therapy in those with heart failure and a reduced ejection fraction (+/- T2DM)
* **Summary and Conclusion**
	+ Emerging evidence from trials of dapagliflozin and other SGLT2i helps to bridge the gap between management of hyperglycaemia and cardiovascular risk.
	+ The use of dapagliflozin will be expanded beyond diabetes
	+ Room for extensive further research, i.e. DELIVER trial currently underway for patients with heart failure and preserved ejection fraction

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