

## REVIEW ARTICLE

# Cardiovascular protection with sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: Does it apply to all patients?

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## Abstract

Patients with type 2 diabetes (T2D) are at an increased risk of cardiovascular disease (CVD). Cardiovascular risk in these patients should be considered as a continuum, and comprehensive treatment strategies should aim to target multiple disease risk factors. Large-scale clinical trials of sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown an impact on cardiovascular outcomes, including heart failure hospitalization and cardiovascular death, which appears to be independent of their glucose-lowering efficacy. Reductions in major cardiovascular events appear to be greatest in patients with established CVD, particularly those with prior myocardial infarction, but are independent of heart failure or renal risk. Most large-scale trials of SGLT2 inhibitors predominantly include patients with T2D with pre-existing CVD and high cardiovascular risk at baseline, limiting their applicability to patients typically observed in clinical practice. Real-world evidence from observational studies suggests that there might also be beneficial effects of SGLT2 inhibitors on heart failure hospitalization and all-cause mortality in various cohorts of lower risk patients. The most common adverse events reported in clinical and observational studies are genital infections; however, the overall risk of these events appears to be low and easily managed. Similar safety profiles have been reported for elderly and younger patients. There is still some debate regarding the safety of canagliflozin in patients at high risk of fracture and amputation. Outstanding questions include specific patterns of cardiovascular protection according to baseline risk.

## KEYWORDS

cardiovascular disease, clinical trial, heart failure, macrovascular disease, meta-analysis, sodium-glucose co-transporter-2 inhibitor

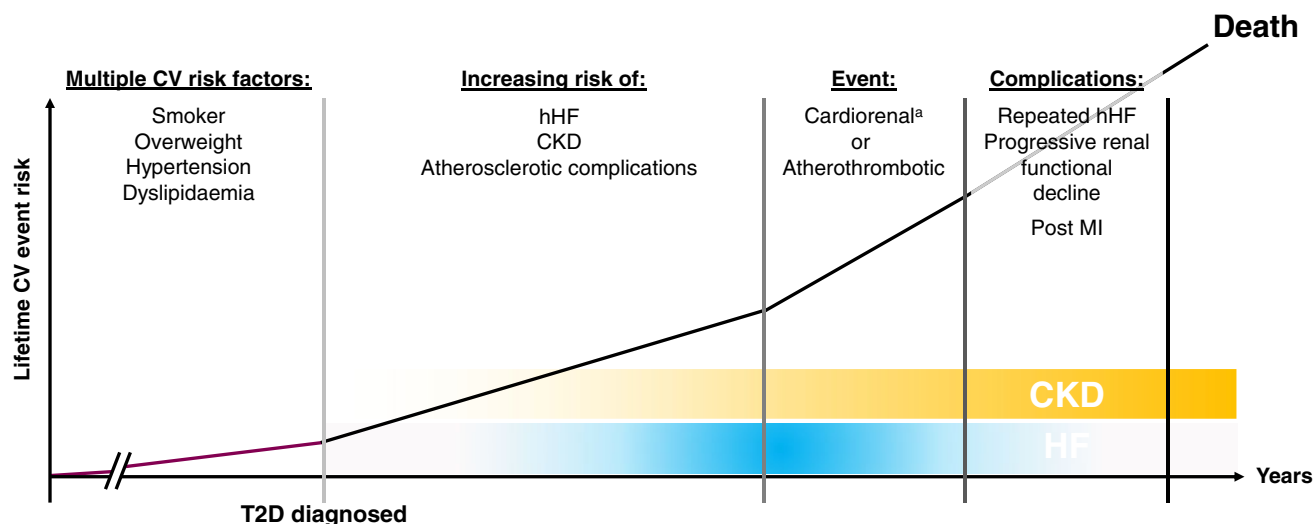
## 1 | INTRODUCTION

Type 2 diabetes (T2D) is a major risk factor for cardiovascular disease (CVD). Studies of intensive glucose-lowering therapy<sup>1–4</sup> have shown

that while hyperglycaemia correction per se reduces the incidence of microvascular complications such as nephropathy and retinopathy, the impact on CVD development and progression is less clear, and may be more attributable to specific patient- and drug-related factors.

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**FIGURE 1** The cardiovascular (CV) risk continuum in patients with type 2 diabetes (T2D).<sup>5</sup> The slope of the CV risk is illustrative. CKD, chronic kidney disease; hHF, hospitalization for heart failure; MI, myocardial infarction. <sup>a</sup>hHF and/or CKD progression

Importantly, the risk of cardiovascular (CV) events in patients with T2D should be thought of as being a continuum: already at elevated risk when first diagnosed, the risk of CV events increases both over time, reflecting the duration of exposure to hyperglycaemia, and following the incidence of a CV event such as myocardial infarction (MI; Figure 1).<sup>5,6</sup> Ideally, interventions aimed at reducing CV events should be effective across the risk continuum. The clinical and pathophysiological associations between CV, renal and metabolic (CaReMe)<sup>7</sup> disorders that contribute to CV risk should also be considered. The management of T2D therefore requires a comprehensive strategy that targets specific CaReMe elements, such as hypertension, renal dysfunction or dyslipidaemia, as appropriate, in addition to controlling hyperglycaemia.<sup>8</sup>

The PROactive study with pioglitazone<sup>9,10</sup> was the first CV outcomes trial (CVOT) to suggest that some glucose-lowering medications could produce a benefit independent of lowering hyperglycaemia or HbA1c. However, only since the publication of the EMPA-REG OUTCOME trial with the sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin, has this possibility become more widely accepted.<sup>11,12</sup> SGLT2 inhibitors act by blocking renal SGLT2, thereby facilitating glucose excretion in urine (glycosuria) and thus reducing hyperglycaemia. Simultaneously, SGLT2 inhibition also causes an increase in the excretion of sodium (natriuresis), which could aid interstitial fluid clearance without changing intravascular volume by osmotic diuresis, reducing plasma volume and decreasing systolic and diastolic blood pressures by 4–6 and 1–2 mmHg, respectively.<sup>13,14</sup> In addition, SGLT2 inhibitor treatment leads to significant weight loss of up to 5 kg,<sup>15</sup> with mean weight loss across trials of between 2.26 kg with canagliflozin and 0.79 kg with ipragliflozin compared with metformin.<sup>16</sup> Two-thirds of weight loss is accounted for by approximately equal reductions in both abdominal visceral and subcutaneous fat.<sup>17</sup> Reducing fat mass can lead to decreases in insulin resistance,<sup>18</sup> metabolic risk<sup>19</sup> and renal risk,<sup>20</sup> and to CV benefits,

including decreased risk of ischaemic heart disease,<sup>21</sup> and reduced blood pressure<sup>22</sup> and vascular injury, such as systemic arterial dysfunction.<sup>18</sup> It has also been postulated that SGLT2 inhibition shifts myocardial muscle fuel metabolism away from fat and glucose towards energy-efficient ketone bodies, which improves muscle work efficiency and function.<sup>23</sup> These factors may help to explain how SGLT2 inhibitors exhibit CV and renal benefits, denoting an overall improvement in the prevention of specific diabetes-related co-morbidities. Indeed, SGLT2 inhibitors have recently been recommended in global treatment guidelines as part of a primary prevention strategy for CVD in patients with T2D and additional CV risk factors.<sup>24,25</sup>

When considering the impact of treatment across a spectrum of risk profiles, it is important to remember that, given a consistent relative risk reduction, patients at low risk will experience a lower absolute risk reduction in events compared with those at high risk.<sup>26–28</sup> Number needed to treat (NNT) calculations provide an intuitive measure of the absolute risk reduction associated with treatment. However, to understand whether treatment impacts patients at low and high risk of events to a similar degree, irrespective of differences in baseline event rates, the relative risk rather than the absolute risk should be discussed. In addition, caution is required when discussing subgroup analyses, as trials are typically powered only to detect differences in the primary outcomes across the entire patient population. In the absence of specific trials powered to detect such differences in subpopulations, hypothesized subgroup effects can be assessed using proposed criteria to understand the strength of the existing evidence.<sup>29</sup> Definitive assessment of treatment effects in population subgroups would potentially require an individual patient meta-analysis of the relevant trials.

This paper reviews the available evidence for the CV effects (including CV death, MI, hospitalization for heart failure [hHF] and stroke) of SGLT2 inhibitors in patients with T2D, at all levels of CV risk.

## 2 | CV BENEFITS OF SGLT2 INHIBITORS IN PATIENTS WITH T2D

Established treatments for CV risk factors such as hypertension, dyslipidaemia and antiplatelet therapies can reduce the risk of CVD in patients with T2D, but some residual risk persists.<sup>30,31</sup> Three major CVOTs—EMPA-REG OUTCOME with empagliflozin,<sup>11</sup> the CANVAS programme with canagliflozin<sup>32</sup> and DECLARE-TIMI 58 with dapagliflozin<sup>33</sup>—suggest that SGLT2 inhibitors could reduce this risk; although dyslipidaemia background medication in these trials would not now be considered optimal, CV benefit was reported for SGLT2 inhibitors when used in addition to then standard-of-care therapy for CV risk factors. The risk of bias, assessed using the Cochrane framework for randomized controlled trials (RCTs),<sup>34</sup> was low across domains for all three trials.<sup>35</sup> Similar CV benefits were also reported by CREDENCE, a renal outcomes trial in patients with albuminuric diabetic kidney disease.<sup>36</sup> Nevertheless, there have been some concerns raised regarding imbalances between treatment groups in terms of HbA1c control and concomitant medication, which were not compensated for by the primary analyses and could constitute a source of bias in these trials.<sup>37</sup> In addition, the applicability of the clinical trial data to the entire CV risk spectrum of patients with T2D must be considered; with the exception of DECLARE-TIMI 58, these trials primarily enrolled patients with high CV risk. Hence, they provide little information regarding risk reductions in the majority of patients with T2D, who tend to have multiple risk factors (MRF) for CVD, but without established CV conditions. This picture is repeated across dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) CVOTs. As such, only DECLARE-TIMI 58 (N = 17 160, 59% with MRF),<sup>33</sup> REWIND (N = 9901, 69% with MRF)<sup>38</sup> and CAROLINA (N = 6041, 65% with MRF)<sup>39</sup> recruited a majority of MRF patients, of which DECLARE-TIMI

58 was the largest, both in terms of its overall and MRF populations (MRF n = 10 186) (Figure 2).<sup>33,36</sup>

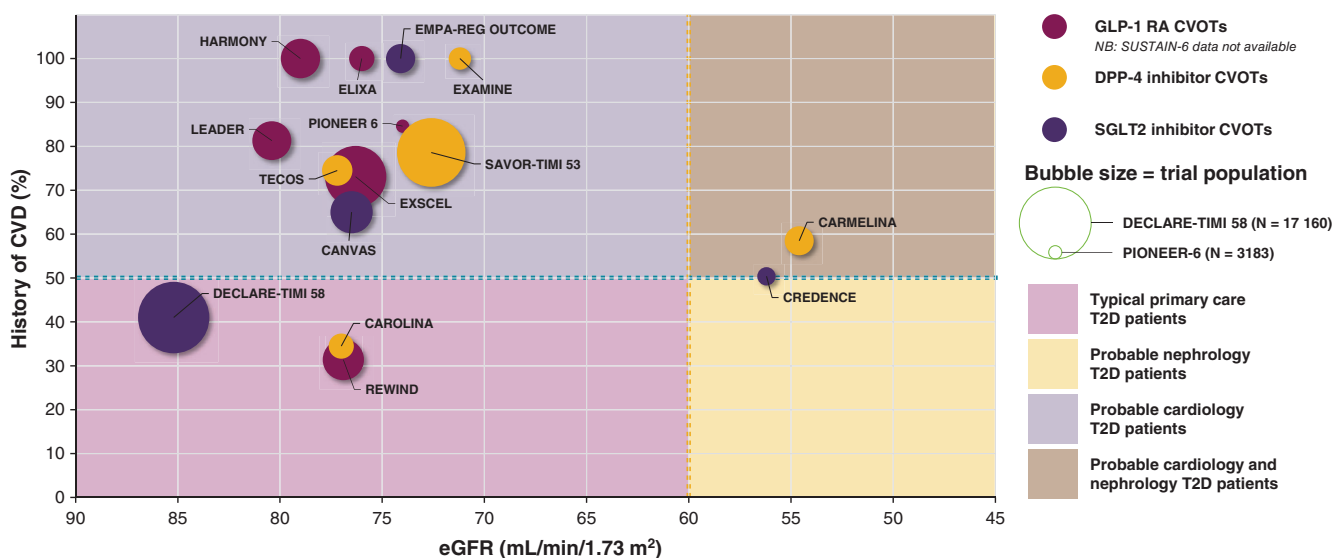
Renal health at baseline is also an important consideration when assessing the relevance of CVOT results in clinical practice. The mean estimated glomerular filtration rate (eGFR; measured as mL/min/1.73 m<sup>2</sup> of body surface area) for most CVOTs was >70, and 85.2 for DECLARE-TIMI 58. Only CREDENCE<sup>36</sup> and CARMELINA<sup>40</sup> had a mean eGFR of <60; these two trials were designed to assess the impact of canagliflozin and linagliptin, respectively, specifically in patients with reduced renal health. However, study comparisons should take into account patient distribution as well as mean values; differences include variation in eGFR categories across the SGLT2 inhibitors trials, including no patients with an eGFR of <45 in DECLARE-TIMI 58 (Table 1).

As expected, the baseline risk of CV outcomes is the key driver of absolute event rates in the different CVOTs. The placebo arm event rates for all outcomes were notably lower in the CV-renal healthy DECLARE-TIMI 58 population compared with those in EMPA-REG OUTCOME and CANVAS (Table 2). However, the baseline risk profile also seems to influence the observed relative risk, with the highest relative risk reductions reported in the SGLT2 inhibitor trials with the highest proportion of patients at high CV risk.<sup>11,33</sup>

### 2.1 | SGLT2 inhibitors in patients with T2D and high CV risk or multiple CV risk factors

#### 2.1.1 | EMPA-REG OUTCOME and CANVAS

EMPA-REG OUTCOME and CANVAS were large clinical studies focusing on CV outcomes in patients with T2D and established CVD or high



**FIGURE 2** Patient populations in major cardiovascular outcomes trials (CVOTs) with sodium-glucose co-transporter-2 (SGLT2) inhibitors,<sup>11,32,33,36</sup> glucagon-like peptide-1 receptor agonists (GLP-1 RAs)<sup>38,96–100</sup> and dipeptidyl peptidase-4 (DPP-4)<sup>39,40,101–103</sup> inhibitors according to levels of cardiovascular disease (CVD) and renal risk as measured by estimated glomerular filtration rate (eGFR). Bubble size is proportional to number of patients. T2D, type 2 diabetes

	EMPA-REG OUTCOME (N = 7020)	CANVAS (N = 10 142)	DECLARE-TIMI 58 (N = 17 160)
Multiple risk factor population, n (%)	56 (<1)	3486 (34.4)	10 186 (59.4)
eCVD population, n (%)	6964 (>99)	6656 (65.6)	6974 (40.6)
HF at baseline, n (%)	706 (10.1)	1461 (14.4)	1724 (10.0)
MI at baseline, n (%)	3273 (46.6)	2956 (29.1)	3284 (20.9)
Stroke at baseline, n (%)	1637 (23.3)	1291 (12.7)	1107 (6.5)
CAD at baseline, n (%)	5308 (75.6)	5721 (56.4)	5658 (33.0)
PAD at baseline, n (%)	1461 (20.8)	2113 (20.8)	1025 (6.0)
Mean eGFR, mL/min/1.73 m <sup>2</sup>	74	76.5	85.2
eGFR, n (%)			
≥90 mL/min/1.73 m <sup>2</sup>	1538 (21.9)	2476 (24.4)	8162 (47.6)
≥60 to <90 mL/min/1.73 m <sup>2</sup>	3661 (52.2)	5625 (55.5)	7732 (45.0)
45 to 60 mL/min/1.73 m <sup>2</sup>	1249 (17.8)	1485 (14.6)	1265 (7.4)
<45 mL/min/1.73 m <sup>2</sup>	543 (7.7)	554 (5.5)	0 (0)
Median UACR, mg/g/day	18	12	13
UACR, n (%)			
Normoalbuminuria (<30 mg/g)	4171 (60.0)	7007 (69.8)	11 652 (67.9)
Microalbuminuria (30 to ≤300 mg/g)	2013 (29.0)	2266 (22.6)	4023 (23.4)
Macroalbuminuria (>300 mg/g)	769 (11.1)	760 (7.6)	1169 (6.8)

**TABLE 1** Overview of cardiovascular and renal health in baseline populations for EMPA-REG OUTCOME,<sup>11</sup> CANVAS<sup>32,42</sup> and DECLARE-TIMI 58<sup>33,66</sup>

Abbreviations: CAD, coronary artery disease; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; UACR, urine albumin:creatinine ratio.

CV risk. EMPA-REG OUTCOME was a long-term, randomized, double-blind, placebo-controlled phase 3 trial with empagliflozin, in which the primary outcome was a three-point composite of major adverse cardiovascular events (3P-MACE, including CV death, non-fatal MI and non-fatal stroke). Secondary outcomes included four-point MACE (4P-MACE, same as for 3P-MACE but with the addition of unstable angina), silent MI, hHF, and a composite microvascular outcome.<sup>11</sup> The CANVAS programme comprised two randomized, double-blind, placebo-controlled phase 3 trials with canagliflozin, CANVAS and CANVAS-R. The primary endpoint was 3P-MACE. Secondary outcomes were death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hHF.<sup>32</sup>

The patient populations in EMPA-REG OUTCOME and CANVAS differed in terms of their CV risk profiles (Figure 3). EMPA-REG OUTCOME included 7020 patients, most of whom (n = 6964) had atherosclerotic CVD (ASCVD), defined as a history of MI >2 months prior to baseline, evidence of multi-vessel coronary artery disease, evidence of single-vessel coronary artery disease with ≥50% luminal narrowing and no successful revascularization, unstable angina >2 months prior to baseline, history of stroke >2 months prior to baseline, or occlusive peripheral artery disease; the remaining 56 patients had MRF for CVD.<sup>41</sup> Of the patients with ASCVD, 3273 (47.0%) had previously experienced a MI. By contrast, CANVAS included 10 142 patients, of

whom 7324 (72.2%) had ASCVD and 2818 (27.8%) had MRF.<sup>32</sup> Of the patients with ASCVD, 44.1% had previously experienced an MI.<sup>42</sup> Thus, overall, patients in the EMPA-REG OUTCOME trial were generally at higher CV risk than those in CANVAS; however, both trials had a majority of patients with evidence of ASCVD and/or prior CV events.

EMPA-REG OUTCOME revealed that empagliflozin significantly reduced 3P-MACE compared with placebo (hazard ratio [HR]: 0.86, 95% confidence interval [CI]: 0.74, 0.99; *P* = .04); this was primarily driven by reductions in CV death (HR: 0.62; 95% CI: 0.49, 0.77; *P* < .001). Empagliflozin also significantly reduced the incidence of hHF (HR: 0.65; 95% CI: 0.50, 0.85; *P* = .002).<sup>11</sup>

In CANVAS, canagliflozin significantly reduced 3P-MACE compared with placebo (HR: 0.86; 95% CI: 0.75, 0.97; *P* = .02).<sup>32</sup> As superiority was not achieved for the first secondary endpoint of all-cause mortality (HR: 0.87; 95% CI: 0.74, 1.01; *P* = .24), hierarchical statistical testing was stopped, and all other endpoints were considered nominal. Similar to empagliflozin, canagliflozin showed a substantial 33% reduction in the incidence of hHF (HR: 0.67; 95% CI: 0.52, 0.91).<sup>44</sup>

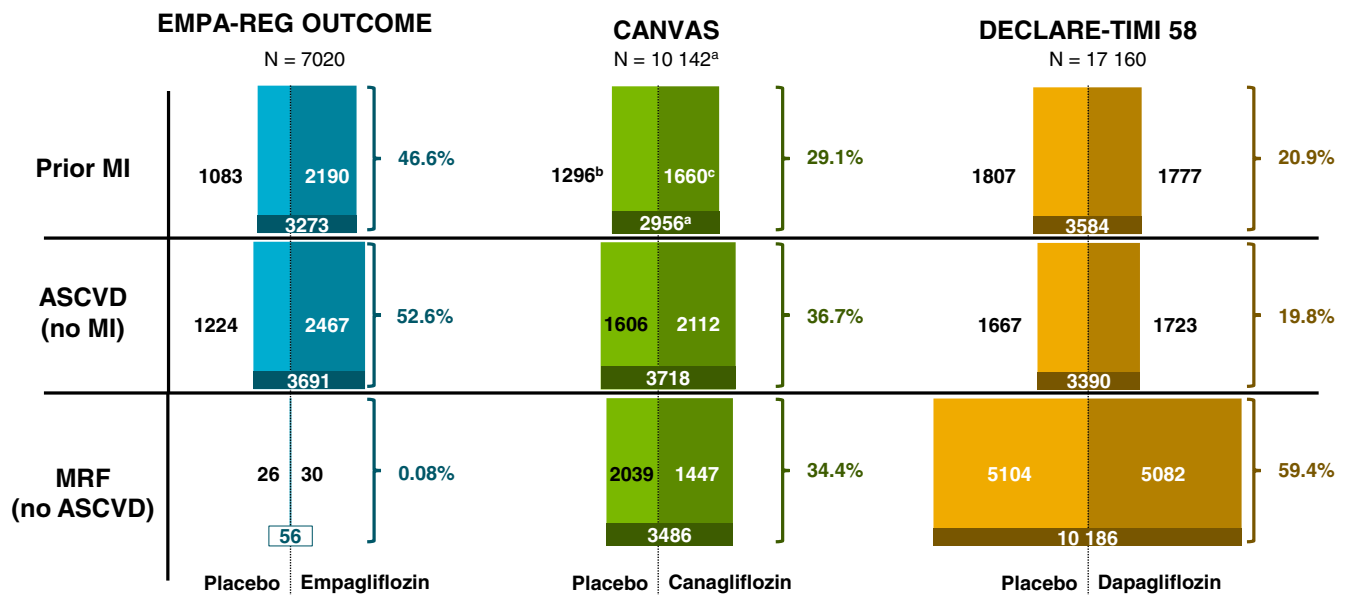
Reductions in MACE were seen earlier in EMPA-REG OUTCOME than in CANVAS; the survival curves diverged at 3 months and 1 year, respectively. This suggests that empagliflozin may have an immediate impact on MACE risk, whereas canagliflozin appears to require longer term use to achieve similar reductions. However, these differences

**TABLE 2** Event rates, hazard ratios and number needed to treat (NNT) in cardiovascular outcomes trials with sodium-glucose co-transporter-2 (SGLT2) inhibitors<sup>1,132,33,42</sup>

Event rate per 1000 patient-years Population	Treatment arm	EMPA-REG OUTCOME		CANVAS		DECLARE-TIMI 58	
		eCVD	Total	eCVD	Total	eCVD	Total
MACE	Placebo	43.9	43.9	41.3	31.5	41.0	24.2
	SGLT2 inhibitor	37.4	37.4	34.1	26.9	36.8	22.6
	HR (95% CI)	0.86 (0.74, 0.99)	0.86 (0.74, 0.99)	0.82 (0.72, 0.95)	0.86 (0.75, 0.97)	0.90 (0.79, 1.02)	0.93 (0.84, 1.03)
	NNT (3 years)	58	58	52	79	89	223
CV death	Placebo	20.2	20.2	16.8	12.8	11.6	7.1
	SGLT2 inhibitor	12.4	12.4	14.8	11.6	10.9	7.0
	HR (95% CI)	0.62 (0.49, 0.77)	0.62 (0.49, 0.77)	0.86 (0.70, 1.06)	0.87 (0.72, 1.06)	0.94 (0.76, 1.18)	0.98 (0.82, 1.17)
	NNT (3 years)	45	45	175	288	493	3405
CV death or hHF	Placebo	30.1	30.1	27.4	20.8	23.9	14.7
	SGLT2 inhibitor	19.7	19.7	21.0	16.3	19.9	12.2
	HR (95% CI)	0.66 (0.55, 0.79)	0.66 (0.55, 0.79)	0.77 (0.65, 0.92)	0.78 (0.67, 0.91)	0.83 (0.71, 0.98)	0.83 (0.73, 0.95)
	NNT (3 years)	35	35	56	78	89	139
hHF	Placebo	14.5	14.5	11.3	8.7	14.1	8.5
	SGLT2 inhibitor	9.4	9.4	7.3	5.5	11.1	6.2
	HR (95% CI)	0.65 (0.50, 0.85)	0.65 (0.50, 0.85)	0.68 (0.51, 0.90)	0.67 (0.52, 0.87)	0.78 (0.63, 0.97)	0.73 (0.61, 0.88)
	NNT (3 years)	68	68	86	106	115	148
All-cause death	Placebo	28.6	28.6	23.1	19.5	23.2	16.4
	SGLT2 inhibitor	19.4	19.4	21.1	17.3	21.3	15.1
	HR (95% CI)	0.68 (0.57, 0.82)	0.68 (0.57, 0.82)	0.89 (0.75, 1.07)	0.87 (0.74, 1.01)	0.92 (0.79, 1.08)	0.93 (0.82, 1.04)
	NNT (3 years)	39	39	178	160	188	269
MI	Placebo	19.3	19.3	16.0	12.6	24.1	13.2
	SGLT2 inhibitor	16.8	16.8	12.5	11.2	21.0	11.7
	HR (95% CI)	0.87 (0.70, 1.09)	0.87 (0.70, 1.09)	0.79 (0.63, 0.99)	0.89 (0.73, 1.09)	0.87 (0.74, 1.02)	0.89 (0.77, 1.01)
	NNT (3 years)	141	141	99	247	115	231
Stroke	Placebo	10.5	10.5	10.4	9.6	11.7	7.8
	SGLT2 inhibitor	12.2	12.2	8.8	7.9	10.9	7.5
	HR (95% CI)	1.18 (0.89, 1.56)	1.18 (0.89, 1.56)	0.88 (0.67, 1.16)	0.87 (0.69, 1.09)	0.93 (0.74, 1.17)	0.96 (0.81, 1.14)
	NNT (3 years)	—	—	214	201	431	1137

Note: NNTs are calculated by  $1/(1-EXP(-event\ rate\ with\ SGLT2\ inhibition/1000\ [number\ of\ patient-years] * 3\ [time\ for\ NNT]))$ .

Abbreviations: CI, confidence interval; CV, cardiovascular; eCVD, established cardiovascular disease; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.



**FIGURE 3** Patient populations in cardiovascular outcomes trials with sodium-glucose co-transporter-2 (SGLT2) inhibitors, according to atherosclerotic cardiovascular disease (ASCVD) and myocardial infarction (MI) status.<sup>11,32,33,42,62,66</sup> CV, cardiovascular; MRF, multiple risk factors. <sup>a</sup>CANVAS primary prevention cohort contained patients with prior CV disease, including 18 patients with MI, and therefore data in the chart do not add up to the trial N. <sup>b</sup>Includes two patients with MI from the primary prevention cohort. <sup>c</sup>Contains 16 patients with MI from the primary prevention cohort

may be because of the increased CV risk of the EMPA-REG OUTCOME population compared with that of CANVAS (Table 2).

CV death was reduced to a greater extent with empagliflozin than with canagliflozin (38% vs. 13%, respectively; no significant difference was observed between subgroups based on history of heart failure [HF]).<sup>11,32,44</sup> The all-cause mortality rates, per 1000 patient-years, were 19.4 with empagliflozin in EMPA-REG OUTCOME and 17.3 with canagliflozin in CANVAS. This may be because of the differences in the baseline characteristics of the enrolled patients, which would suggest that the benefit of SGLT2 inhibitors may be larger in patients with a previous CV event or current CVD compared with those with MRF without CVD. Alternatively, as the disparities between enrolled patient populations were limited, the possibility that specific SGLT2 inhibitors may differentially impact on CV death cannot be dismissed.

### 2.1.2 | DECLARE-TIMI 58

DECLARE-TIMI 58 was a randomized, double-blind, placebo-controlled trial in patients with T2D and MRF (n = 10 186, 59.4%) or established ASCVD (n = 6971, 40.6%). DECLARE-TIMI 58 had two primary endpoints, with the protocol amended to add a composite of CV death and hHF during the study. A statistically significant reduction in CV death and hHF was observed for dapagliflozin (HR: 0.83; 95% CI: 0.73, 0.95;  $P = .005$ ), driven by a lower rate of hHF (HR: 0.73; 95% CI: 0.61, 0.88), as well as a non-significant numerical reduction in the co-primary endpoint of 3P-MACE (HR: 0.93; 95% CI: 0.84, 1.03;  $P = .17$ ).<sup>33</sup> There was no difference detected between the dapagliflozin and placebo groups in the rate of CV death (HR: 0.98; 95% CI: 0.82, 1.17). In the primary safety analysis, dapagliflozin met

the prespecified criterion for non-inferiority with respect to MACE (upper boundary of 95% CI <1.3;  $P < .001$  for non-inferiority).<sup>33</sup>

## 2.2 | CV benefits according to CV risk

Most patients with T2D encountered in primary care are at low CV and renal risk. In these low-risk patients, the use of SGLT2 inhibitors may potentially prevent the occurrence of CV events and progression of unidentified CVD. However, clinical trial data relating to this population are limited; of the three major outcomes trials, the DECLARE-TIMI 58 population had the lowest CV and renal risk, measured by proportion of patients without ASCVD and mean eGFR, respectively (Figure 2). There are similarities in the limited availability of data for other new antihyperglycaemic agents, such as GLP-1RAs and DPP-4 inhibitors (Figure 2).

### 2.2.1 | Event rates according to baseline CV risk

Overall analysis of the results from EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials suggests that populations of patients at higher CV risk (i.e. those with established CVD) may gain greater benefits from SGLT2 inhibitor therapy than those at lower risk (Tables 1 and 2). DECLARE-TIMI 58 included a higher proportion of patients without ASCVD than EMPA-REG OUTCOME or CANVAS (Figure 3). Patients in DECLARE-TIMI 58 were less probable to show reductions in MACE or CV death, possibly because the baseline event rates (as seen in the placebo arm) were comparatively low.<sup>33,50</sup>



Data from DECLARE-TIMI 58 and the meta-analyses reviewed above<sup>33,35,46,51</sup> show that SGLT2 inhibitors provide protection against HF and chronic kidney disease (CKD) even in patients at low CV risk (i.e. those with MRF, but without established CVD). Moreover, there is evidence that the beneficial effects of SGLT2 inhibitors on HF extend beyond the initial event to include the prevention of subsequent events.<sup>52,53</sup>

## 2.2.2 | How representative of the general T2D population are the CVOTs populations?

As already mentioned, ~ 99% of patients in EMPA-REG OUTCOME had established CVD at enrolment. Therefore, these patients represented a high-risk T2D population, not representative of most patients seen in diabetes outpatient clinics. In one US observational study of detailed care records (primary care, endocrinology and multi-specialty practices in the USA), only 26% of 182 525 patients with T2D met the eligibility criteria for EMPA-REG OUTCOME; of note, up to 95% of eligible patients were not currently receiving SGLT2 inhibitor therapy.<sup>54,55</sup> In a study of 60 327 adult primary care patients with T2D in the UK, only 15.7% had the same CV risk profile as those enrolled in EMPA-REG OUTCOME, and only 1642 patients (2.7%) had been initiated on an SGLT2 inhibitor; of these, only 11.1% would have been eligible for EMPA-REG OUTCOME.<sup>56</sup>

In the CANVAS programme, 67% of patients had established CVD at enrolment.<sup>32</sup> However, among the 15 773 patients with T2D included in the Renal Insufficiency And Cardiovascular Events (RIACE) multicentre study of diabetes clinics in Italy, there was only a 23% prevalence of major acute CVD events.<sup>57,58</sup>

The DECLARE-TIMI 58 study was powered for a broader population of patients with T2D, with 40.6% of patients presenting with established CVD at enrolment.<sup>59</sup> A recent European observational study suggested that the DECLARE-TIMI 58 population most closely resembles the general T2D population, with 59% representativeness, which is ~ 2-3-fold higher than CANVAS (34% representativeness) and EMPA-REG OUTCOME (21% representativeness).<sup>60</sup>

## 2.2.3 | Subgroup analyses of major CVOTs

As trials are only powered to detect significant differences in primary outcomes within the whole population, subgroup analyses are normally underpowered and thus should be interpreted with caution, particularly where no difference is detected. Nevertheless, they have exploratory value in the absence of trials investigating specific populations of interest exclusively.

In subgroup analyses of EMPA-REG OUTCOME, the treatment effect on the primary outcome of 3P-MACE was similar across sex, race, ethnicity and CV therapies.<sup>11</sup> Analyses of subgroups with specific CV risk profiles (i.e. only cerebrovascular disease, coronary artery disease or peripheral artery disease) did not reveal differences in effects on the primary outcome or on CV death, except for a non-

significant increase in the point estimate in patients presenting with previous cerebrovascular disease alone (HR of 1.15 compared with 0.86 for the total population).<sup>11</sup> Post hoc analyses of the EMPA-REG OUTCOME trial also indicated that the benefits of empagliflozin on hHF and CV events were consistent irrespective of HF (Table 3), MI, stroke or atrial fibrillation (AF) history at baseline.<sup>61-63</sup>

A further subgroup analysis of EMPA-REG OUTCOME investigated the treatment effect on hHF when patients were stratified by 5-year risk of HF at baseline as 'low-to-average risk' (5-year HF occurrence <10%), 'high risk' (10%-20%) and 'very high risk' (>20%).<sup>43</sup> This analysis showed that empagliflozin consistently reduced hHF in patients across baseline HF risk. The HR for hHF was 0.65 in the total population, 0.59 in patients without prior HF, and 0.75 in patients with a history of HF; no heterogeneity was observed with regards to CV death or all-cause mortality.<sup>43</sup> A meta-analysis of seven trials with empagliflozin, including EMPA-REG OUTCOME, showed that the CV benefit of this SGLT2 inhibitor seen in the high-risk population may be extended to those at lower CV risk, although many of the phase 3 trials included in the analysis were not designed to study CV outcomes.<sup>64</sup> Patients in this meta-analysis were considered to be at low-to-medium risk, with MACE occurring at a rate of 4.6-28.7 per 1000 patient-years, compared with 43.9 per 1000 patient-years in EMPA-REG OUTCOME; reductions in MACE were reported in these low-risk patients (3P-MACE HR: 0.84; 95% CI: 0.73, 0.96; 4P-MACE HR: 0.86; 95% CI: 0.76, 0.98).

In CANVAS, a post hoc analysis of patients at different stages of the CV risk continuum showed that the positive effect of canagliflozin on 3P-MACE was consistent in those with and without established CVD at baseline (HR: 0.86; 95% CI: 0.75, 0.97;  $P = .02$  for superiority; no significant effect of heterogeneity;  $P = .18$  for interaction; Table 3). hHF was similarly reduced in both the primary and secondary prevention cohorts (HR: 0.68; 95% CI: 0.51, 0.90 vs. HR: 0.64; 95% CI: 0.35, 1.15;  $P = .91$  for interaction), and in patients with and without HF with reduced ejection fraction (HFREF).<sup>42,65</sup> Additionally, a separate analysis from CANVAS suggested that patients with a history of HF may have added benefit against CV death or hHF with canagliflozin (HR in patients with HF at baseline: 0.61; 95% CI: 0.46, 0.80; HR in patients without HF at baseline: 0.87; 95% CI: 0.72, 1.06;  $P = .021$  for interaction).<sup>44</sup> This indicates some uncertainty as to whether the prior occurrence of HF represents a preferential condition for observing the benefits of SGLT2 inhibitors on hHF.

No significant differences were detected between the reductions in the composite outcome of CV death or hHF for dapagliflozin-treated, DECLARE-TIMI 58-enrolled patients with or without established ASCVD ( $P = .99$  for interaction) or history of HF ( $P = .60$  for interaction) at baseline. Similarly, there was no significant difference in treatment effect on 3P-MACE in patients with and those without established ASCVD ( $P = .25$  for interaction) or history of HF ( $P = .46$  for interaction) at baseline.<sup>33</sup> Dapagliflozin significantly reduced the risk of 3P-MACE in patients who had previously experienced an MI compared with placebo (15.2% vs. 17.8%, respectively; HR: 0.84; 95% CI: 0.72, 0.99;  $P = .039$ ).<sup>66</sup> The majority of this benefit was derived by individuals who had most recently experienced the

**TABLE 3** Key subgroup analyses of primary endpoints in cardiovascular outcomes trials with sodium-glucose co-transporter-2 (SGLT2) inhibitors<sup>11,32,33,42,61</sup>

Outcome	Baseline risk factor	EMPA-REG OUTCOME (N = 7020)		CANVAS (N = 10 142)		DECLARE-TIMI 58 (N = 17 160)	
		HR (95% CI)	P interaction	HR (95% CI)	P interaction	HR (95% CI)	P interaction
MACE	Age <65 years	1.04 (0.84, 1.29)	.01	0.91 (0.76, 1.03)	.26	0.97 (0.86, 1.12)	.99
	Age ≥65 years	0.71 (0.59, 0.87)		0.80 (0.67, 0.95)		0.97 (0.85, 1.12)	
	BMI <30 kg/m <sup>2</sup>	0.74 (0.60, 0.91)	.06	0.97 (0.79, 1.20)	.29	0.94 (0.83, 1.06)	.99
	BMI ≥30 kg/m <sup>2</sup>	0.98 (0.80, 1.21)		0.79 (0.67, 0.93)		1.01 (0.86, 1.17)	
	eCVD	—	—	0.82 (0.72, 0.95)	.18	0.90 (0.79, 1.02)	.25
	MRF	—	—	0.98 (0.74, 1.30)		1.01 (0.86, 1.20)	
	Prior HF	—	—	0.80 (0.61, 1.05)	.51	1.01 (0.81, 1.27)	.46
	No prior HF	—	—	0.87 (0.76, 1.01)		0.92 (0.82, 1.02)	
	eGFR ≥90 mL/min/1.73 m <sup>2</sup>	1.10 (0.77, 1.57)	.20	0.84 (0.62, 1.12)	.20	0.94 (0.80, 1.10)	.99
	eGFR 60 to <90 mL/min/1.73 m <sup>2</sup>	0.76 (0.61, 0.94)		0.95 (0.80, 1.13)		0.95 (0.82, 1.09)	
	eGFR <60 mL/min/1.73 m <sup>2</sup>	0.88 (0.69, 1.13)		0.70 (0.55, 0.90)		0.92 (0.69, 1.23)	
	Antihypertensives	0.85 (0.73, 0.99)	.80	—	—	—	—
	No antihypertensives	0.94 (0.45, 1.95)		—		—	
	Statins/ezetimibe	0.88 (0.74, 1.04)	.54	0.84 (0.72, 1.00)	.45	—	—
	No statins/ezetimibe	0.79 (0.59, 1.07)		0.91 (0.71, 1.16)		—	
	CV death or hHF	Age <65 years	0.79 (0.60, 1.05)	—	—	—	0.84 (0.69, 1.00)
Age ≥65 years		0.58 (0.45, 0.73)		—		0.75 (0.62, 0.90)	
BMI <30 kg/m <sup>2</sup>		0.57 (0.44, 0.74)	—	—	—	0.73 (0.63, 0.85)	.06
BMI ≥30 kg/m <sup>2</sup>		0.75 (0.59, 0.94)		—		0.97 (0.77, 1.22)	
eCVD		—	—	0.77 (0.65, 0.92)	—	0.83 (0.71, 0.98)	.99
MRF		—	—	0.83 (0.58, 1.19)		0.84 (0.67, 1.04)	
Prior HF		0.72 (0.50, 1.04)	—	—	—	0.79 (0.63, 0.99)	.60
No prior HF		0.63 (0.51, 0.78)		—		0.84 (0.72, 0.99)	
eGFR ≥90 mL/min/1.73 m <sup>2</sup>		0.67 (0.41, 1.12)	—	—	—	0.96 (0.77, 1.19)	.37
eGFR 60 to <90 mL/min/1.73 m <sup>2</sup>		0.61 (0.47, 0.79)		—		0.79 (0.66, 0.95)	
eGFR <60 mL/min/1.73 m <sup>2</sup>		0.72 (0.55, 0.96)		—		0.78 (0.55, 1.09)	
Statins/ezetimibe		0.58 (0.39, 0.84)	—	—	—	—	—
No statins/ezetimibe		0.68 (0.55, 0.83)		—		—	

Abbreviations: BMI, body mass index; CI, confidence interval; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MRF, multiple risk factors.

qualifying MI event (especially those with MI ≤2 years previously), driven by the higher event rate in these patients. By contrast, there was no observed effect of dapagliflozin in patients who had not previously experienced an MI (7.1% vs. 7.1%; HR: 1.00; 95% CI: 0.88, 1.13;  $P = .97$ ), including patients with ASCVD but no history of MI (12.6% vs. 12.8%; HR: 0.98; 95% CI: 0.81, 1.19;  $P = .97$ ). The composite of CV death and hHF occurred in 8.6% of dapagliflozin-treated patients

and 10.5% of placebo-treated patients with ASCVD and previous MI, with an absolute risk reduction (ARR) of 1.9% (95% CI: 0.0, 3.8). By comparison, event rates of 3.9% and 4.5%, respectively, were seen in patients with no previous MI (ARR: 0.6%; 95% CI: 0.0, 1.3).<sup>66</sup> Additional subanalyses showed that dapagliflozin reduced hHF in patients with and without HFrEF, reduced CV death/hHF, CV death alone, and all-cause mortality in patients with HFrEF,<sup>65</sup> and reduced the risk of



AF to a similar extent irrespective of baseline ASCVD, or history of AF or HF.<sup>67</sup>

### 2.3 | Meta-analyses

A meta-analysis of EMPA-REG OUTCOME, the CANVAS programme and DECLARE-TIMI 58 investigated the effects of SGLT2 inhibitors on specific CV events in a population of 34 322 patients with T2D.<sup>35</sup> Overall, SGLT2 inhibitors were found to reduce the risk of MACE (HR: 0.89; 95% CI: 0.83, 0.96;  $P = .0014$ ); however, this benefit was restricted to the 20 620 patients with established ASCVD (HR: 0.86; 95% CI: 0.80, 0.93), and no effect was reported for the slightly smaller MRF population (HR: 1.00; 95% CI: 0.87, 1.16;  $n = 13\ 672$ ;  $P = .0501$  for interaction). SGLT2 inhibitors also significantly reduced the risk of CV death or hHF (HR: 0.77; 95% CI: 0.71, 0.84;  $P < .0001$ ) and hHF alone (HR: 0.69; 95% CI: 0.61, 0.79;  $P < .0001$ ). There was no difference in the treatment effect between patients with and without established ASCVD, both for the composite ( $P = .41$  for interaction) and hHF alone ( $P = .38$  for interaction), despite the MRF population being smaller (13 672 vs. 20 620 patients) and less at risk compared with the ASCVD population.<sup>35</sup> Of the three CVOTs included in the analysis, DECLARE-TIMI 58 contributed the largest population of patients both with and without ASCVD (Table 1). However, as about three-quarters of patients with MRF in this analysis were from the DECLARE-TIMI 58 study, and the contributions to the ASCVD group from the three programmes were more evenly balanced, the possibility of between-drug differences in efficacy on lower risk populations can again not be excluded.

This meta-analysis also investigated the CV benefit of SGLT2 inhibitors with regard to patients' prior history of HF at baseline. There were similar proportions of patients with a history of HF across studies, and, consistent with individual study analyses, a history of HF had no effect on the risk reduction seen with SGLT2 inhibitors in the composite of CV death or hHF ( $P = .51$  for interaction), CV death alone ( $P = .96$  for interaction) or hHF alone ( $P = .76$  for interaction).<sup>35</sup> However, there is a likelihood that the baseline prevalence of HF in these trials is underestimated given the high prevalence of established CVD and MI in the study populations.<sup>45</sup>

These results indicate that SGLT2 inhibitors provide hHF-prevention benefit across a broad patient population, and that this translates to a reduction in CV death. However, MACE benefits are not observed until patients have already experienced an atherosclerotic event.

Similar results were reported by multiple meta-analyses of controlled SGLT2 inhibitor trials. Analyses included between 27 studies (7363 patients)<sup>46</sup> and 71 studies (47 287 patients).<sup>47</sup> SGLT2 inhibitors were consistently found to reduce the risk of 3P-MACE compared with controls: relative risk (RR): 0.61 (95% CI: 0.48, 0.78; empagliflozin, dapagliflozin, canagliflozin or ertugliflozin; patients with no defined baseline CV risk profile)<sup>46</sup> to RR: 0.82 (95% CI: 0.67, 1.01; empagliflozin, dapagliflozin or canagliflozin; patients with no defined baseline CV risk profile),<sup>48</sup> with no apparent heterogeneity across the class.<sup>47</sup>

A particularly large meta-analysis, including 82 RCTs, four overviews and six regulatory reports, describing trials of seven SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin), reported a similar degree of protection against major CV events (RR: 0.85; 95% CI: 0.77, 0.93), HF (RR: 0.67; 95% CI: 0.55, 0.80) and all-cause death (RR: 0.79; 95% CI: 0.70-0.88) compared with control therapies. This analysis found a high likelihood of differences between individual compounds for CV death, with empagliflozin showing the greatest reduction. There was a moderate likelihood of differences among compounds for non-fatal stroke and all-cause death, and no differences for other CV outcomes.<sup>49</sup>

### 2.4 | Risk reductions in elderly versus younger patients

Theoretically, the effects of SGLT2 inhibitors on CV risk could differ in elderly and younger patients, owing to age-related CV changes, irrespective of diabetes. However, data on CV outcomes with SGLT2 inhibitors in elderly patients with T2D are scarce.

In EMPA-REG OUTCOME, reductions in effect size on the primary outcome of 3P-MACE were observed in patients aged <65 years ( $P = .01$  for subgroup heterogeneity).<sup>11</sup> By contrast, treatment effects were comparable across older and younger patients for CV death ( $P = .21$  for subgroup heterogeneity),<sup>11</sup> with consistent relative increases in mean survival regardless of age.<sup>68</sup> Effects were also comparable across older and younger patients in the CANVAS programme for CV death/hHF ( $P = .09$  for subgroup heterogeneity),<sup>44</sup> and in DECLARE-TIMI 58 for CV death/hHF and MACE ( $P = .50$  and  $P = .09$ , respectively, for subgroup heterogeneity).<sup>33</sup>

A randomized, double-blind, clinical trial including 964 patients with T2D and documented CVD (coronary heart disease, stroke or ischaemic attack, peripheral artery disease, or congestive HF) found that the frequency of cardiac disorders decreased with dapagliflozin compared with placebo in patients of all ages.<sup>69</sup>

### 2.5 | Potential benefits of SGLT2 inhibitors in the real-world setting

As already mentioned, the SGLT2 inhibitor CVOTs differ in how closely they resemble real-world clinical populations, with DECLARE-TIMI 58 representing the closest match.<sup>60</sup> It is therefore important to also consider the outcomes from real-world observational studies when assessing the effectiveness of SGLT2 inhibitors in reducing mortality and morbidity in patients with T2D across the entire risk continuum. The first cohort of CVD-REAL (conducted in Germany, Denmark, Norway, Sweden, the UK and the USA) included 309 056 patients with T2D at varying levels of CV risk, followed from treatment initiation, and showed that SGLT2 inhibitors (dapagliflozin, canagliflozin, and, to a lesser extent, empagliflozin) as a class were associated with significantly reduced rates of hHF (HR: 0.61; 95% CI:

0.51, 0.73;  $P < .001$ ) and all-cause mortality (HR: 0.49; 95% CI: 0.41, 0.57;  $P < .001$ ) compared with other glucose-lowering drugs (oGLDs).<sup>70</sup> The second cohort of CVD-REAL (CVD-REAL 2, conducted in Australia, Canada, Israel, Japan, Singapore and South Korea: regions in which a wider range of SGLT2 inhibitors are available, including ipragliflozin, luseogliflozin and tofogliflozin) included a further 235 064 patients with T2D at any level of CV risk and confirmed the association of the SGLT2 inhibitor class with significantly reduced rates of hHF (HR: 0.64; 95% CI: 0.50, 0.82;  $P < .001$ ) and all-cause mortality (HR: 0.51; 95% CI: 0.37, 0.70;  $P < .001$ ) compared with oGLDs.<sup>71</sup> Associations with significantly reduced risk of MI (HR: 0.81; 95% CI: 0.74, 0.88;  $P < .001$ ) and stroke (HR: 0.68; 95% CI: 0.55, 0.84;  $P < .001$ ) were also observed.<sup>71,72</sup> No differences in treatment effect were found between patients with and those without prior CVD for any endpoint ( $P > .2$  for interaction in all comparisons).<sup>71</sup>

CVD-REAL Nordic, a subanalysis of the CVD-REAL study in patients from Denmark, Norway and Sweden, also showed that SGLT2 inhibitors were associated with significantly reduced risks of hHF (HR: 0.70; 95% CI: 0.61, 0.81), CV death (HR: 0.53; 95% CI: 0.40, 0.71) and MACE (HR: 0.78; 95% CI: 0.69, 0.87) compared with oGLDs (all  $P < .001$ ).<sup>73</sup> An additional analysis revealed that dapagliflozin was also associated with significantly lower incidence of hHF (HR: 0.62; 95% CI: 0.50, 0.77;  $P < .001$ ), all-cause mortality (HR: 0.59; 95% CI: 0.49, 0.72;  $P < .001$ ) and MACE (HR: 0.79; 95% CI: 0.67, 0.94;  $P = .006$ ) compared with DPP-4 inhibitors.<sup>74</sup> Contrary to observations from the CVOTs, risk reduction in CV death and MACE was only associated with treatment in those aged  $\geq 65$  years in CVD-REAL Nordic (CV death:  $>65$  years HR: 0.45; 95% CI: 0.32, 0.65;  $<65$  years HR: 1.10; 95% CI: 0.65, 1.84; MACE:  $>65$  years HR: 0.66; 95% CI: 0.56, 0.78;  $<65$  years HR: 1.01; 95% CI: 0.85, 1.20), suggesting that the majority of the benefit was seen in the older population.<sup>73</sup>

Complementary to the CVD-REAL programme, EASEL, a population-based cohort study of 25 258 patients with T2D and established CVD, reported that the initiation of SGLT2 inhibitors was associated with a lower rate of all-cause mortality or hHF (HR: 0.57; 95% CI: 0.50, 0.65) and MACE (HR: 0.67; 95% CI: 0.60, 0.75) compared with oGLDs.<sup>75</sup> Additionally, in contrast to the findings of the randomized trial, dapagliflozin significantly reduced CV-specific and all-cause mortality in a large observational cohort paired to DECLARE-TIMI 58 participants using propensity score matching; the authors hypothesized that, despite propensity score matching, participants in the observational cohort were more frail than those in the randomized trial, and thus had a higher risk of death.<sup>50</sup> However, propensity score matching also cannot completely eliminate prescription bias in observational trials, which may have also contributed to the observed differences.

An initial interim analysis from the ongoing EMPRISE observational study included data from 224 528 patients with T2D with and without established CVD and reported that, compared with DPP-4 inhibitors, initiation of SGLT2 inhibitors was associated with a lower rate of hHF (HR: 0.42; 95% CI: 0.35, 0.50), which was similar in patients with and without established CVD and history of HF.<sup>76</sup>

A potential issue with large pharmacoepidemiological studies, such as CVD-REAL, EASEL and EMPRISE, is the possibility of 'immortal time bias', which could exaggerate the benefits observed regarding rates of all-cause death.<sup>77</sup> Immortal time bias can occur when two patient groups are formed within a time interval in a hierarchical manner (i.e. the first group is selected and followed from first prescription of a study drug, and the second group from the first prescription of a comparator drug). For example, in the CVD-REAL study, if those initiating an SGLT2 inhibitor had prior oGLD initiation during the study period, then the time between first use of an oGLD and first use of an SGLT2 inhibitor in the SGLT2 inhibitor-treated patients could represent 'immortal time', which was not corrected for in the original analysis.<sup>77,78</sup> While a number of methodological factors in CVD-REAL reduced the risk of biases, including propensity matching of SGLT2 inhibitor- and oGLD-treated patients,<sup>78</sup> residual confounding could still influence results even following propensity matching. A propensity score-matched analysis that used the same cohort as CVD-REAL has previously reported a 50% reduction in mortality in patients treated with DPP-4 inhibitors compared with insulin, in contrast to the findings of clinical trials,<sup>79,80</sup> supporting the use of caution when interpreting the results of even very well-conducted observational studies.

## 2.6 | Are the CV benefits for patients with T2D consistent in those with high renal risk or CKD?

In patients with T2D, both eGFR decline and increasing albuminuria add to CV risk.<sup>81</sup> Reducing the rate of decline in eGFR and albuminuria may therefore augment CV protection.<sup>82</sup> Importantly, treatment with SGLT2 inhibitors has been associated with reductions in the progression of albuminuria and the risk of renal deterioration, and may promote the regression of albuminuria.<sup>83,84</sup> Two meta-analyses of SGLT2 inhibitor CVOTs have reported a significant benefit across trials, which was reflected in the fixed effects HR of 0.55 (95% CI: 0.48, 0.64)<sup>35</sup> and an RR of 0.58 (95% CI: 0.51, 0.66)<sup>84</sup> for a composite of renal worsening, end-stage renal disease or renal-associated death. Ratios were similar in patients with (0.56 [95% CI: 0.47, 0.67]) and without (0.54 [95% CI: 0.42, 0.71]) atherosclerotic disease at baseline.<sup>35</sup>

Subanalyses of the major CVOTs with SGLT2 inhibitors suggest that there are consistent CV benefits in patients with differing levels of renal function (Table 3). In EMPA-REG OUTCOME, there was no significant difference between low, mid and high renal risk (eGFR  $\geq 90$ , 60- $<90$  and  $<60$  mL/min/1.73 m<sup>2</sup>, respectively) for the primary outcome (3P-MACE;  $P = .15$ ), CV death ( $P = .15$ ), hHF and CV death, or hHF alone.<sup>11</sup> Similarly, in DECLARE-TIMI 58, there was no significant difference between these three eGFR groups for CV death or hHF ( $P = .37$  for interaction) or MACE ( $P = .99$  for interaction).<sup>33</sup> In the CANVAS programme and CREDENCE, patients with reduced renal function experienced benefit when treated with canagliflozin; the effect on primary outcome in CANVAS (3P-MACE) was statistically comparable with those with CKD (HR: 0.70; 95% CI: 0.55-0.90) and those with preserved kidney function (HR: 0.92; 95% CI: 0.79, 1.07;

$P = .08$  for heterogeneity). Similarly, a consistent reduction in hHF risk was seen across patients with varying eGFR at baseline (HR: 0.67; 95% CI: 0.52, 0.87;  $P > .50$  for heterogeneity). CREDENCE also reported no significant differences in the primary endpoint (end-stage renal disease, doubling of serum creatinine, or renal or CV death) between patients with eGFR 30–45 mL/min/1.73 m<sup>2</sup> (HR: 0.75; 95% CI: 0.59–0.95) and those with eGFR 60–90 mL/min/1.73 m<sup>2</sup> (HR: 0.82; 95% CI: 0.60, 1.12;  $P = .11$  for interaction).<sup>36</sup>

In contrast to the findings above, a meta-analysis of these trials found that baseline renal impairment was associated with varying efficacy of SGLT2 inhibitors with regard to hHF (significantly decreasing efficacy with increasing impairment at baseline;  $P = .0073$  for interaction) and, to a directionally similar but non-significant extent, MACE ( $P = .23$  for interaction).<sup>35</sup>

### 3 | SAFETY OF SGLT2 INHIBITORS IN T2D

Data from the SGLT2 inhibitor CVOTs and meta-analyses of these trials have consistently shown that SGLT2 inhibitors have a reassuring safety profile in patients with T2D; this is supported by real-world experience. The principal adverse events reported in clinical trials include genital infections, which are anticipated adverse effects resulting from the glycosuric effect of SGLT2 inhibition.<sup>85</sup> Meta-analyses have shown increased rates of mycotic genital, but not urinary tract, infections with SGLT2 inhibitors; however, the absolute numbers of such events are comparatively low and the infections are generally easily managed.<sup>35,46</sup> Some studies, including DECLARE-TIMI 58, have reported increased rates of diabetic ketoacidosis with SGLT2 inhibitors compared with placebo or oGLDs.<sup>46,86,87</sup> Low C-peptide levels, insulin therapy and recent surgery have been proposed as risk factors for ketoacidosis; however, the overall risk appears to be low and comparable with that in the overall T2D population.<sup>88–90</sup> CANVAS found that canagliflozin was associated with significant increases in the risks of amputations or fractures compared with controls,<sup>32</sup> but no such findings have been reported in trials with other SGLT2 inhibitors.<sup>11,33</sup> CREDENCE showed no increased rate of fractures or amputations in patients treated with canagliflozin compared with placebo<sup>36</sup>; however, the overall rate of these adverse events in CREDENCE was high, and a protocol adjustment allowed investigators to remove patients who were at higher risk.<sup>91</sup> Meta-analyses have shown no overall increase in amputation or fracture risk in patients receiving SGLT2 inhibitors, and have highlighted significant heterogeneity between trials.<sup>35,46,92</sup> In addition, although Fournier's gangrene (necrotizing fasciitis of the perineum, another adverse event rarely reported following SGLT2 inhibitor treatment) was reported in six patients in the DECLARE-TIMI 58 study, five of these cases occurred in placebo-treated patients.<sup>33,93</sup>

#### 3.1 | Safety in elderly patients

In general, the safety profile of SGLT2 inhibitors is similar in elderly and younger patients. A pooled analysis of six studies with

canagliflozin reported greater reductions in HbA1c and plasma glucose in patients aged <75 years than in older patients. Bodyweight and blood pressure reductions were similar in both groups, although the 95% CIs overlapped unity for both doses of canagliflozin (100 and 300 mg) in participants aged  $\geq 75$  years. Adverse events occurred more frequently in elderly patients, with a higher incidence of adverse events related to the mechanism of action (osmotic diuresis-induced effects and urinary/genital mycotic infections).<sup>94</sup>

A Japanese postmarketing survey (STELLA-ELDER) evaluated the safety of ivermectin in elderly patients; the mean age of patients was  $72.2 \pm 5.8$  years, and 31% were aged >75 years. Almost 10% of patients in this study experienced an adverse event, with skin and subcutaneous tissue disorders, and renal and urinary disorders being the most common classes of events. Fewer than 8% of these events were reported as serious.<sup>95</sup>

In a study of patients with established CVD receiving dapagliflozin, the incidence of adverse events, serious adverse events and adverse events leading to discontinuation was balanced between groups or occurred at a numerically lower rate in the dapagliflozin group in participants aged  $\geq 75$  years. Hypoglycaemia-related adverse events and events of volume depletion were also similar between the dapagliflozin and placebo groups.<sup>70</sup>

### 4 | CONCLUSIONS

The recognition that people with T2D lie on a continuum of CV risk has led to focused attention on the importance of reducing risk across this continuum, rather than focusing only on high-risk patients. The accumulating evidence from large outcomes trials, particularly DECLARE-TIMI 58, together with real-world studies, indicates that SGLT2 inhibitors may effectively reduce some CV events (primarily hHF) irrespective of the baseline level of risk.

No significant differences in reductions in MACE were observed based on the presence of HF at baseline or specific manifestations of CVD (e.g. cerebrovascular disease, coronary artery disease or peripheral arterial disease). However, the results of DECLARE-TIMI 58 suggest that this benefit may be greater in patients with established CVD, specifically in those with a recent MI. In general, the results from CVOTs with SGLT2 inhibitors show that patients at higher CVD risk (i.e. those with established CVD or prior MI) obtain greater benefits on MACE from SGLT2 inhibitor therapy than those at lower risk. By contrast, the benefit on hHF was not observed to be significantly different in the presence or absence of a history of HF or established CVD at baseline. This was a consistent finding in all three CVOTs, although in CANVAS a greater benefit was more apparent in patients with previous HF. The beneficial effects of SGLT2 inhibitors on MACE or hHF also appear to be independent of the level of renal risk, even though meta-analyses suggest that a greater effect size in reductions of hHF and MACE may be seen in patients with greater renal impairment.

The restricted nature of the patient populations in EMPA-REG OUTCOME and CANVAS limits the applicability of the trial findings in the real-world situation, while patients in DECLARE-TIMI 58 more

closely resemble those seen in routine clinical practice. Real-world evidence from several observational studies also supports the beneficial effects of SGLT2 inhibitors on MACE, hHF, all-cause mortality and CV death in various cohorts of lower risk patients, with no differences in treatment effect reported between patients with and those without prior CVD for any endpoint. Additionally, these studies have highlighted differences in outcomes between SGLT2 inhibitors and drugs that are not associated with a risk of hypoglycaemia, such as DPP-4 inhibitors. There is limited information on CV outcomes in elderly patients, in whom there might be concerns about SGLT2 inhibitors causing osmotic diuresis-induced effects. However, observational studies suggest that CV benefits are also seen in this population, with no particular safety signals.

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## CONFLICT OF INTEREST

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All authors contributed to the conception, drafting and critical editing of the manuscript.

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