

## REVIEW ARTICLE

# Cardiovascular safety outcomes of once-weekly GLP-1 receptor agonists in people with type 2 diabetes

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## Abstract

**What is known and objective:** People with type 2 diabetes (T2D) are at increased risk of cardiovascular disease (CVD), which in turn is associated with increased morbidity and mortality. The impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on cardiovascular (CV) outcomes has been investigated in CV outcomes trials (CVOTs). This review aims to help pharmacists and other healthcare professionals (HCPs) gain a better understanding of such CVOTs in T2D with a primary focus on the once-weekly (QW) GLP-1 RAs.

**Methods:** This narrative review mainly focuses on the evaluation of the similarities and differences in the design and results of CVOTs involving currently approved and marketed QW GLP-1 RAs—semaglutide subcutaneous, exenatide extended-release (ER) and dulaglutide. Results from CVOTs of dipeptidyl peptidase-4 inhibitors (DPP4is) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are also included.

**Results and discussion:** Three CVOTs of QW GLP-1 RAs were identified for inclusion in this review: SUSTAIN 6 (semaglutide), EXSCEL (exenatide ER) and REWIND (dulaglutide), all of which varied in terms of trial design, patient demographics and other baseline characteristics. Results from these CVOTs demonstrated the CV safety of QW GLP-1 RAs compared with standard of care. Additionally, CV and renal benefits were demonstrated for semaglutide and dulaglutide, but not for exenatide ER. The CV safety of four DPP4is and three SGLT2is was demonstrated. None of the DPP4is had a CV or renal benefit, whereas all three SGLT2is were associated with CV and renal benefits.

**What is new and conclusion:** This article provides an overview of the results from QW GLP-1 RA CVOTs, including the recently published results for dulaglutide, and places them within the broader T2D treatment landscape to help HCPs make informed decisions in daily practice. The QW GLP-1 RAs with benefits reaching beyond glycaemic control can provide a comprehensive treatment option for people with T2D at high risk of CVD, with CVD or chronic kidney disease.

## KEYWORDS

cardiovascular disease, cardiovascular outcomes trials, glucagon-like peptide-1 receptor agonist, safety, type 2 diabetes

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## 1 | WHAT IS KNOWN AND OBJECTIVE

The disease burden of type 2 diabetes (T2D) is increasing, with an estimated 30.3 million people in the United States (US) (9.4% of the population) affected by this disease as of 2015.<sup>1</sup> T2D accounts for 90%-95% of all diabetes cases in the US<sup>1</sup> and is associated with an increased risk of cardiovascular disease (CVD).<sup>2</sup> As CVD has many different prognoses,<sup>1,2</sup> it is an important aspect to consider when managing the care of people with T2D. For example, atherosclerotic CVD (ASCVD), a condition that restricts blood flow due to blocked arteries,<sup>3</sup> is the leading cause of death in people with T2D.<sup>2</sup> Also, people with T2D are at >2-fold increased risk of developing heart failure (HF) than those without T2D.<sup>4,5</sup> In addition to these CV aspects, T2D is also associated with renal failure,<sup>6</sup> and the resulting regular dialysis and/or medical complications can have a negative impact on quality of life.<sup>7</sup> Hence, glucose-lowering drugs that are beneficial to CV function, including HF risk reduction, and that maintain renal function may have positive health implications for these people.

In the 1990s, glucose-lowering treatments that provided intensive glucose control were found to reduce the risk of microvascular complications associated with T2D, compared with conventional treatment.<sup>8,9</sup> However, at that time, there were no consistent indications of macrovascular risk reduction with such treatment regimens.<sup>8-11</sup> The last decade has seen the publication of results from large clinical trials, referred to as cardiovascular outcomes trials (CVOTs), in T2D that provide evidence of the impact of several glucose-lowering drugs on macrovascular outcomes. In 2019, the American Diabetes Association (ADA) updated their treatment guidelines to include consideration of the presence of ASCVD, HF and chronic kidney disease (CKD) in people with T2D, due to results from such CVOTs (with similar inclusions in the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines).<sup>12-14</sup> Other ADA recommendations include consideration of the impact of treatment on weight, hypoglycaemia risk and treatment cost.<sup>15</sup> These standards of medical care are maintained as a 'living' document, updated as and when new and critical information is available.<sup>16</sup>

As some of the main changes to the ADA 2019 guidelines included the incretin-based glucagon-like peptide-1 receptor agonists (GLP-1 RAs), this review focuses on the CVOTs of once-weekly (QW) GLP-1 RAs: semaglutide subcutaneous (s.c) (SUSTAIN 6),<sup>17</sup> exenatide extended-release (ER) (EXSCEL)<sup>18</sup> and dulaglutide (REWIND).<sup>19</sup> The Harmony Outcomes CVOT of albiglutide is not considered in detail due to the withdrawal of this drug from the market in 2018.<sup>20</sup> CVOTs of short-acting GLP-1 RAs (once-daily [QD] or twice-daily [BID]) are not discussed here, considering that the most recent CVOTs belong to the QW formulations and such long-acting drugs could improve patient adherence to therapies based on the convenience of drug administration.<sup>21-24</sup> The review briefly mentions results from CVOTs relating to dipeptidyl peptidase-4 inhibitors (DPP4is) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) to provide a comprehensive overview of this area, and as SGLT2is have been

prominently discussed in the ADA guidelines. This review thus aims to help pharmacists and other healthcare providers understand the fundamentals of CVOT design, interpret their results, and so optimize patient treatment and education.

## 2 | METHODS

This narrative review focuses primarily on the design and results of CVOTs involving QW GLP-1 RAs, namely, semaglutide s.c. (SUSTAIN 6), exenatide ER (EXSCEL) and dulaglutide (REWIND).<sup>17-19</sup> Similarities and differences in these CVOTs were evaluated and, where possible, comparisons were made. Results from CVOTs of DPP4is and SGLT2is are also presented to place the outcomes of GLP-1 RA CVOTs in the context of the broader T2D treatment landscape.

A literature search using PubMed was conducted on 22 April 2019 to ensure that all relevant CVOTs were included. Keywords used as search terms included: 'glucagon-like peptide-1 receptor agonist', 'GLP-1 RA', AND 'cardiovascular outcomes trial', 'CVOT', AND 'type 2 diabetes', 'T2D'. Publications were analysed in depth if they were primary manuscripts that presented data from a CVOT. Other publications, which supported the review, included secondary analyses of CVOTs, reviews or meta-analyses presenting CVOT data and protocols. Papers were excluded if they were not written in English. Bibliographies of relevant CVOTs were searched to find pertinent information for pharmacists.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Understanding CVOTs in T2D

Although this review focuses on SUSTAIN 6, EXSCEL and REWIND trials,<sup>17-19</sup> first a step back is needed to understand how CVOTs have evolved within the T2D research field. Initially, approval of glucose-lowering drugs was based on their glycaemic efficacy, that is reduction of glycated haemoglobin (HbA<sub>1c</sub>) and hypoglycaemic safety profiles,<sup>25</sup> hence the effect of glucose-lowering drugs on macrovascular disease was inconclusive.<sup>8,26</sup> In 2007, however, a publication that reviewed the results from 42 clinical trials on glucose-lowering drugs found an increased risk of myocardial infarction (MI) and CV death with the use of rosiglitazone when compared with other standard of care (SOC) regimens.<sup>27</sup> Such concerns over the potential for increased macrovascular risk associated with certain glucose-lowering drugs<sup>27</sup> led to the Food and Drug Administration (FDA) requiring the demonstration of CV safety of new glucose-lowering drugs in 2008.<sup>28</sup> Based on this FDA guidance, sponsors of glucose-lowering drugs were required to demonstrate that these drugs do not cause an unacceptable increase in CV risk when compared with the control group.<sup>28</sup> The statistical confidence in such results was prespecified by the FDA, using the upper bound of the 95% confidence intervals (CIs), which had to be <1.3 for post-marketing trials and 1.3-1.8 for

TABLE 1 CVOT designs of once-weekly GLP-1 RAs

CVOT (status)	Drug	Intervention <sup>a</sup>	Primary outcome	N <sup>b</sup>	Median follow-up time (years)	Established CVD (%) <sup>c</sup>	HbA <sub>1c</sub> % <sup>d</sup> (SD/IQR)	Diabetes duration at baseline; years <sup>d</sup> (SD/IQR)	Baseline insulin usage <sup>e</sup> (% of overall patients)
SUSTAIN 6 <sup>17</sup> (completed: Mar 2016)	Semaglutide s.c. (once-weekly)	Pooled semaglutide 0.5 mg and semaglutide 1 mg vs placebo (SOC)	3-point MACE <sup>f</sup>	3297	2.1	83.0	8.7 (SD 1.5)	13.9 (SD 8.1)	58.0%
EXSCEL <sup>18</sup> (completed: May 2017)	Exenatide ER (once-weekly)	Exenatide ER 2 mg vs placebo (SOC)	3-point MACE <sup>f</sup>	14 752	3.2	73.1	8.0 (median; IQR 7.3, 8.9)	12.0 [median for both groups] (IQR, exenatide ER 7.0, 17.0; SOC 7.0, 18.0)	46.2% (exenatide ER); 46.5% (SOC)
REWIND <sup>19</sup> (completed: Aug 2018)	Dulaglutide (once-weekly)	Dulaglutide 1.5 mg vs placebo (SOC)	3-point MACE <sup>f</sup>	9901	5.4	31.5	7.3 (SD 1.1; dulaglutide); 7.4 (SD 1.1; SOC)	10.5 (SD 7.3; dulaglutide); 10.6 (SD 7.2; SOC)	24.0% (dulaglutide); 23.7% (SOC)

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; ER, extended release; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA<sub>1c</sub>, glycated haemoglobin; IQR, interquartile range; MACE, major adverse cardiovascular events; MI, myocardial infarction; s.c., subcutaneous; SD, standard deviation; SOC, standard of care.

<sup>a</sup>For all studies, patients also received background SOC therapy.

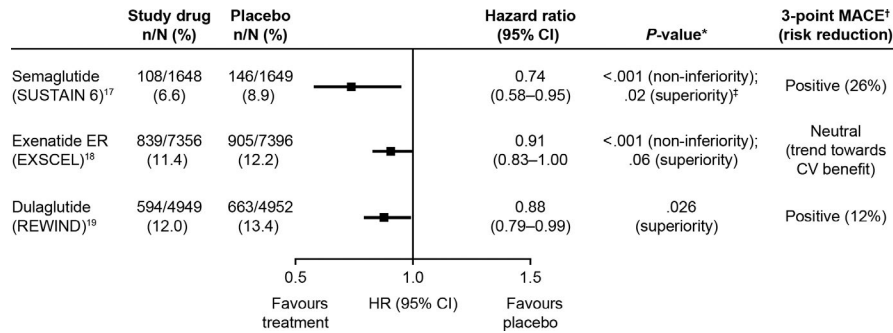
<sup>b</sup>Total number of patients randomized.

<sup>c</sup>Established CVD definition varied by trial. SUSTAIN 6: defined as age  $\geq 50$  y with previous CV, cerebrovascular, or peripheral vascular disease, chronic heart failure (New York Heart Association class II or III), or chronic kidney disease  $\geq$ stage 3; EXSCEL: age  $\geq 18$  y with history of major clinical manifestations of coronary artery disease, ischaemic cerebrovascular disease, or atherosclerotic peripheral artery disease; REWIND: age  $\geq 50$  y with MI, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularization.

<sup>d</sup>Mean values are provided unless otherwise stated.

<sup>e</sup>Note that the variations in the proportion of patients receiving insulin at baseline in these trials could be a reflection of the differences in baseline patient characteristics (eg duration of diabetes and HbA<sub>1c</sub> levels) and other demographic factors.

<sup>f</sup>3-point MACE: CV death, non-fatal MI or non-fatal stroke.



**FIGURE 1** Primary CV outcome in once-weekly GLP-1 RA CVOTs. \* $P \leq .05$  for significance; make symbol <sup>†</sup>3-point MACE: CV death, non-fatal MI or non-fatal stroke; <sup>‡</sup>post hoc analysis. CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; ER, extended release; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of patients in each treatment group

preapproval trials.<sup>28</sup> CVOTs aiming to address these FDA recommendations were originally designed to evaluate CV safety and were therefore powered to demonstrate non-inferiority vs the comparator. However, some CVOTs have since been designed to assess CV superiority of the study drug for the primary outcome to indicate if a CV benefit is present (eg REWIND<sup>19</sup>).

As the name suggests, CVOTs assess CV outcomes as the primary study endpoint, in people with T2D and at high risk of CVD, as recommended by the FDA in 2008.<sup>28</sup> They test whether new drugs have a similar (non-inferior) CV safety profile compared with placebo.<sup>29</sup> Patients generally receive background treatment with CV and glucose-lowering drugs, with the intention of minimizing CV risk, maintaining adequate glycaemic control and promoting glycaemic equipoise between the treatment groups. Minimizing between-group differences in glycaemic control reduces the likelihood that study results are due to the glucose-lowering effects of the intervention.<sup>30</sup> As the placebo groups in these trials receive SOC treatment, they are not a true reflection of placebo. Hence, for clarity, the term 'SOC' has been used throughout this review instead of placebo.

Based on the FDA guidance, CVOTs are designed to include a follow-up period of  $\geq 2$  years to collate meaningful data on long-term CV risk.<sup>28</sup> While most of the randomized efficacy clinical trials, such as SUSTAIN 1<sup>31</sup> and DURATION 1,<sup>32</sup> are time-driven and end at a prespecified time-point, most CVOTs are event-driven. This means that the design of a CVOT prespecifies the number of events that need to be accrued to assess the trial hypothesis (usually of non-inferiority compared with SOC).<sup>33</sup> The CVOT is stopped when the required number of events has been accumulated and the results are analysed.

Another aspect of CVOT design, which is different to conventional randomized efficacy clinical trials, is that they enrol an under-represented patient population in previously completed Phase 2/3 trials,<sup>33</sup> that is people with established CVD, at a high risk of CV events or with impaired renal function.<sup>28</sup> Indeed, before the FDA 2008 guidance, people with prior CV events were usually excluded from Phase 2/3 trials for glucose-lowering medication development.<sup>33</sup> The choice of a patient population with higher risk of CV

events improves external validity because these people are likely recipients of the glucose-lowering medication under evaluation, assuming its approval.<sup>28</sup> This choice also helps to ensure that sufficient CV events are captured within the trial duration to allow for meaningful estimates of risk.<sup>28</sup> Although CVOTs must follow FDA guidelines, they differ in their design, especially in terms of enrolment criteria, including demographics of the study population, definitions of pre-existing CVD, proportions of patients with pre-existing CVD vs those with CVD risk factors alone, and baseline patient characteristics (eg mean HbA<sub>1c</sub> levels), thus making cross-trial comparisons difficult.

The main study outcome (or primary endpoint) in CVOTs is a composite endpoint referred to as major adverse cardiovascular events (MACE). In accordance with the FDA guidelines, MACE must minimally include three ASCVD endpoints, namely CV mortality, non-fatal MI and non-fatal stroke—referred to as 3-point composite MACE.<sup>28</sup> To measure a broader range of CV events, other events such as hospitalization for acute coronary syndrome and urgent revascularization procedures may be included.<sup>28</sup> For example, some T2D CVOTs have included hospitalization for unstable angina as an additional event, forming a 4-point MACE endpoint.<sup>34</sup> Others have used 3-point MACE as their primary endpoint and an expanded 5-point MACE or a broader range of outcomes as secondary endpoints,<sup>17,35</sup> to understand the CV safety profile of the drugs being investigated more fully.

### 3.2 | Once-weekly GLP-1 RA CVOT designs and populations

CVOTs are large clinical trials and, combined, SUSTAIN 6, EXSCEL and REWIND enrolled 27 950 people with T2D, with the EXSCEL trial being the largest (N = 14 752; Table 1).<sup>17–19</sup> In terms of design, SUSTAIN 6 was the only preapproval CVOT among the three, had a short follow-up period of 2.1 years, and was designed to show non-inferiority of semaglutide s.c. to SOC.<sup>17</sup> Both EXSCEL and REWIND trials were post-approval trials for exenatide ER and dulaglutide, respectively,<sup>18,19</sup> with EXSCEL being a non-inferiority

**TABLE 2** Selected secondary endpoints in once-weekly GLP-1 RA CVOTs

CVOT	Secondary endpoints				
	CV death HR (95% CI); P-value*	Non-fatal MI HR (95% CI); P-value	Non-fatal stroke HR (95% CI); P-value	Hospitalization for heart failure HR (95% CI); P-value	Renal outcomes HR (95% CI); P-value
SUSTAIN 6 <sup>17</sup>	0.98 (0.65-1.48); P = .92	0.74 (0.51-1.08); P = .12	0.61 (0.38-0.99) P = .04 (39% risk reduction)	1.11 (0.77-1.61) P = .57	0.64 <sup>a</sup> (0.46-0.88) P = .005 (36% risk reduction)
EXSCEL <sup>18</sup>	0.88 (0.76-1.02); P = .628 <sup>b</sup>	0.95 (0.84-1.09); P = .628 <sup>b</sup>	0.86 (0.70-1.07); P = .628 <sup>b</sup>	0.94 (0.78-1.13) P = .485	NR
REWIND <sup>19</sup>	0.91 (0.78-1.06); P = .21	0.96 (0.79-1.16); P = .65	0.76 (0.61-0.95); P = .017 (21% risk reduction)	0.93 (0.77-1.12); P = .46	0.85 <sup>c</sup> (0.77-0.93); P = .0004

Abbreviations: CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MI, myocardial infarction; NR, not reported.

<sup>a</sup>New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level, and a creatinine clearance <45 mL per minute per 1.73 m<sup>2</sup> of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy.

<sup>b</sup>Homogeneity among components.

<sup>c</sup>New macroalbuminuria, sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal-replacement therapy.

\*P ≤ .05 for significance.

trial, and REWIND a superiority trial.<sup>18,19</sup> EXSCEL and REWIND had long follow-up periods of 3.2 and 5.4 years, respectively.<sup>18,19</sup>

While all three trials assessed 3-point MACE, they had fundamental differences in terms of eligibility criteria and SOC treatment.<sup>17-19</sup> Each of these trials had varied definitions of CV risk factors and pre-existing CVD (Table 1). In SUSTAIN 6, CV risk factors constituted hypertension (and left ventricular hypertrophy), left ventricular systolic (or diastolic) dysfunction and ankle/brachial index <0.9, whereas in REWIND, patients aged 60 years or older were at CV risk if they had at least two of the following: tobacco use, dyslipidaemia, hypertension or abdominal obesity.<sup>17,19</sup> In EXSCEL, CV risk factors did not form part of the protocol-specified eligibility criteria.<sup>18</sup> Prior CVD was defined differently in the trials (see Table 1 footnote), with the main difference being that SUSTAIN 6 included CKD in its definition, but EXSCEL and REWIND did not.<sup>17-19</sup> In addition to these different definitions, the trials also enrolled varying proportions of people with CVD, CKD and CV risk factors. Of the SUSTAIN 6 patient population, 83% had either CVD or CKD stage ≥3 (estimated glomerular filtration rate 30-59 mL/min/1.73 m<sup>2</sup>), while 17% were aged ≥60 years with CV risk factors (Table 1).<sup>17</sup> In the EXSCEL trial, approximately 70% of the patient population had a previous history of CVD and 30% had no history of any previous CV events (Table 1).<sup>18</sup> Those with any level of CV risk could be enrolled in EXSCEL if they met all other inclusion criteria.<sup>18</sup> In the REWIND trial, only 31.5% of participants had a previous history of CVD; most had no previous CVD or CV events (Table 1).<sup>19</sup> Selection criteria relating to CKD also differed between these three CVOTs: people with stage 4 CKD (estimated glomerular filtration rate 15-29 mL/min/1.73 m<sup>2</sup>) were excluded from participation in EXSCEL,<sup>18</sup> but not SUSTAIN 6 or REWIND.<sup>17,19</sup>

There were also differences between SUSTAIN 6, EXSCEL and REWIND in terms of the concomitant glucose-lowering medications permitted. All three allowed the use of concomitant anti-hyperglycaemic therapy with the exception of GLP-1 RAs, while SUSTAIN 6 and REWIND also specifically excluded pramlintide.<sup>17,19</sup> Investigator discretion was applied to the management of concomitant glucose-lowering and CV medication in all three CVOTs.<sup>17-19</sup>

To date, there have been no head-to-head T2D CVOTs within any class of glucose-lowering drugs, except insulin (insulin glargine vs insulin degludec)<sup>36</sup> and only one head-to-head T2D CVOT between two classes of drugs in this therapy area (linagliptin vs glimepiride).<sup>37</sup> To inform pharmacists, data from the three QW GLP-1 RA trials are presented here; however, any cross-trial comparisons should always be interpreted with caution, as they may be confounded by multiple uncontrolled factors due to lack of consistency in overall trial design.

### 3.3 | MACE and secondary CV outcomes in QW GLP-1 RA CVOTs

The CV safety of semaglutide s.c., exenatide ER and dulaglutide was confirmed in their respective trials.<sup>17-19</sup> SUSTAIN 6 confirmed the non-inferiority in 3-point MACE of QW treatment with semaglutide 0.5 mg or 1 mg compared with SOC.<sup>17</sup> Additionally, in a *post hoc* analysis, semaglutide 0.5 mg or 1 mg demonstrated superior CV benefits compared with SOC, as it reduced the risk of MACE by a significant 26% (hazard ratio [HR] 0.74, 95% CI: 0.58-0.95, P = .02 for superiority, Figure 1).<sup>17</sup> Results from EXSCEL confirmed the non-inferiority, but not superiority, of QW exenatide ER 2 mg, with a

TABLE 3 Key features of once-daily DPP4i and SGLT2i CVOTs

Trial	Study status	Drug	Intervention	Primary outcome	N
DPP4i					
SAVOR-TIMI 53 <sup>54</sup>	Completed (May 2013) <sup>65</sup>	Saxagliptin	Saxagliptin 5 mg (2.5 mg if eGFR ≤ 50 mL)	3-point MACE <sup>b</sup>	16 492
EXAMINE <sup>56,57</sup>	Completed (Jun 2013) <sup>66</sup>	Alogliptin	Alogliptin: 25 mg (if eGFR ≥ 60 mL/min/1.73 m <sup>2</sup> ) 12.5 mg (if eGFR ≥ 30 and <60 mL/min/1.73 m <sup>2</sup> ) 6.25 mg (if eGFR < 30 mL/min/1.73 m <sup>2</sup> ) vs SOC	3-point MACE <sup>b</sup>	5380
TECOS <sup>34</sup>	Completed (Mar 2015)	Sitagliptin	Sitagliptin 100 mg (50 mg if eGFR ≥ 30 and <50 mL/min/1.73 m <sup>2</sup> ) vs SOC	4-point MACE <sup>e</sup>	14 735
CARMELINA <sup>55</sup>	Completed (Jan 2018)	Linagliptin	Linagliptin 5 mg vs SOC	3-point MACE <sup>b</sup>	6991
CAROLINA <sup>67</sup>	Completed (Aug 2018) <sup>37</sup>	Linagliptin	Linagliptin 5 mg vs glimepiride 4 mg	3-point MACE <sup>b</sup>	6042
SGLT2i					
EMPA-REG OUTCOME <sup>60</sup>	Completed (Apr 2015) <sup>68</sup>	Empagliflozin	Empagliflozin 10 mg vs empagliflozin 25 mg vs SOC	3-point MACE <sup>b</sup>	7028
CANVAS <sup>58</sup>	Completed (Feb 2017)	Canagliflozin	Canagliflozin 100 mg vs canagliflozin 300 mg vs SOC <sup>i</sup>	3-point MACE <sup>b</sup>	10 142
CREDESCENCE <sup>61</sup>	Completed (Jul 2018) <sup>69</sup>	Canagliflozin	Canagliflozin 100 mg vs SOC	Composite of renal outcomes <sup>k</sup> and death from CVD	4401
DECLARE-TIMI 58 <sup>59</sup>	Completed (Sep 2018) <sup>70</sup>	Dapagliflozin	Dapagliflozin 10 mg vs SOC	3-point MACE <sup>n</sup>	17 160
VERTIS CV <sup>71</sup>	Ongoing, not recruiting	Ertugliflozin	Ertugliflozin 5 mg vs ertugliflozin 15 mg vs SOC	3-point MACE <sup>b</sup>	8246

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; ND, not defined; NR, not reported; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care.

<sup>a</sup>Defined differently in each trial. SAVOR-TIMI 53: age ≥40 y with previous coronary, cerebrovascular, or peripheral vascular disease; TECOS: age ≥40 y with previous coronary, ischaemic cerebrovascular, or atherosclerotic peripheral vascular disease; DECLARE-TIMI 58: age ≥40 y with clinically evident ischaemic heart disease, ischaemic cerebrovascular disease, or peripheral artery disease; EMPA-REG OUTCOME: age ≥18 y with a history of MI, coronary heart disease, unstable angina, stroke or occlusive peripheral artery disease.

<sup>b</sup>3-point MACE: CV death, non-fatal MI, or non-fatal stroke.

<sup>c</sup>Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 μmol/L).

<sup>d</sup>Both EXAMINE and CARMELINA did not define 'prior/established CVD' and did not provide the total proportion of patients with CVD; however, all randomized patients were at high CV and renal risk.

<sup>e</sup>4-point MACE: CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina.

<sup>f</sup>Analysis adjusted for history of HF at baseline.

<sup>g</sup>Sustained ESRD, death due to kidney failure or sustained decrease of ≥50% in eGFR from baseline.

<sup>h</sup>Data for acute renal failure given as number of patients (%) – data on HR not available.

<sup>i</sup>This article reports analysis of pooled data from two trials, CANVAS and CANVAS-R.

<sup>j</sup>40% reduction in eGFR, renal-replacement therapy or renal death.

<sup>k</sup>Composite renal outcomes: ESRD (dialysis for at least 30 d, kidney transplantation or sustained eGFR < 15 mL/min/1.73 m<sup>2</sup>), sustained doubling of serum creatinine level from baseline or death from renal disease.

<sup>l</sup>CREDESCENCE trial primarily assessed renal benefits of canagliflozin in people with T2D and CKD, and the CV outcomes were consistent with those in CANVAS.

<sup>m</sup>Renal-specific composite outcome: ESRD, doubling of serum creatinine level or renal death.

<sup>n</sup>3-point MACE: CV death, MI or stroke.

<sup>o</sup>≥ 40% decrease in eGFR to <60 mL/min/1.73 m<sup>2</sup>, ESRD or death from renal cause.



Established CVD <sup>a</sup> (%)	Median follow-up time (years)	CV safety of study drug confirmed? (CV benefit status)	Nephropathy HR (95% CI)	Hospitalization for HF HR (95% CI)
-78	2.1	Yes (non-inferiority confirmed)	1.08 (0.88-1.32) <sup>c</sup> P = .46	1.27 (1.07-1.51) P = .007
ND <sup>d</sup>	1.5	Yes (non-inferiority confirmed)	NR	1.07 (0.79-1.46) P = .657
74	3.0	Yes (non-inferiority confirmed)	NR	1.00 (0.83-1.20) <sup>f</sup> P = .98
ND <sup>d</sup>	2.2	Yes (non-inferiority confirmed)	0.98 (0.82-1.18) <sup>g</sup> P = .87	0.90 (0.74-1.08) P = .26
42	6.3	Yes (non-inferiority confirmed)	NR	1.21 (0.92 -1.59)
-99	3.1	Yes (superiority confirmed)	Acute renal failure: <sup>h</sup> 246 (5.2) pooled empagliflozin vs 155 (6.6) SOC P < .01	0.65 (0.50-0.85) P = .002
65.6	2.4	Yes (superiority confirmed)	0.60 (0.47-0.77) <sup>j</sup>	0.67 (0.52-0.87)
-50	2.6	Yes (lower risk of kidney failure and CV events) <sup>l</sup>	0.66 (0.53-0.81) P < .001 <sup>m</sup>	0.61 (0.47-0.80) P < .001
-41	4.2	Yes (non-inferiority confirmed)	0.53 (0.43-0.66) <sup>o</sup>	0.93 (0.82-1.04)
NR	-	-	-	-

trend towards CV benefits compared with SOC (HR 0.91, 95% CI: 0.83-1.00,  $P = .06$  for superiority, Figure 1).<sup>18</sup> The REWIND trial demonstrated superior CV benefits of dulaglutide 1.5 mg with 12% significant risk reduction of MACE compared with SOC (HR 0.88, 95% CI: 0.79-0.99,  $P = .026$  for superiority, Figure 1).<sup>19</sup> Albiglutide 30-50 mg was associated with a 22% risk reduction of MACE (HR 0.78, 95% CI: 0.68-0.90,  $P = .0006$  for superiority) in the Harmony Outcomes trial.<sup>38</sup> The results from these QW GLP-1 RA CVOTs suggest that the drugs in this class reduce CV events in people with T2D,<sup>39</sup> although the mechanisms underlying the cardioprotective effects of GLP-1 RAs are unclear.<sup>40</sup> These results have also impacted the prescribing information for two of these three QW GLP-1 RAs (semaglutide s.c. and dulaglutide), which now have an indication to reduce the risk of MACE in patients with T2D and with established CVD only (semaglutide s.c.)<sup>41</sup> or established CVD or multiple CV risk factors (dulaglutide).<sup>42</sup>

Results from SUSTAIN 6 and REWIND for the individual components of 3-point MACE indicated that the CV risk reduction observed with QW semaglutide and dulaglutide was driven by a significant risk reduction in non-fatal stroke of 39% (HR 0.61, 95% CI: 0.38-0.99,  $P = .04$ ) and 24% (HR 0.76, 95% CI: 0.61-0.95,  $P = .017$ ) with each medication vs SOC, respectively (Table 2).<sup>17,19</sup> There were, however, no significant differences in the rates of non-fatal MI and CV death between the treatment groups in either study (Table 2).<sup>17,19</sup> In EXSCEL, no differences were observed in the incidence of 3-point MACE or its individual components with exenatide ER vs SOC (Table 2).<sup>18</sup> It is important to note that the studies were not powered for the individual components of MACE, so the findings need to be interpreted with caution.

In addition to the primary MACE outcome and its components, these CVOTs also looked at prespecified secondary CV outcomes, such as hospitalization for unstable angina or HF, revascularization and death from any cause. QW GLP-1 RA CVOTs were not associated with HF reductions compared with SOC (Table 2).<sup>17-19</sup> None of the secondary CV outcomes differed significantly in participants treated with exenatide ER vs SOC,<sup>18</sup> whereas there were some with semaglutide s.c. and dulaglutide (Table 2).<sup>17,19</sup>

### 3.4 | Additional outcomes in once-weekly GLP-1 RA CVOTs

Other secondary endpoints captured in the QW GLP-1 RA CVOTs included changes in HbA<sub>1c</sub>, body weight, blood pressure, renal events and addition of concomitant medications during the trial.<sup>17-19</sup> While these CVOTs were not powered to compare these outcomes, it is useful to observe the duration of their effects as CVOTs generally have longer observation periods than glycaemic control studies.

As hyperglycaemia, obesity and high blood pressure are associated with diabetes and/or CV complications,<sup>43,44</sup> HbA<sub>1c</sub>, body weight and blood pressure are important to consider in people with T2D. Results from SUSTAIN 6, EXSCEL and REWIND demonstrated better glycaemic control and reduced body weight

in those treated with QW GLP-1 RAs compared with SOC.<sup>17-19</sup> The mean HbA<sub>1c</sub> levels were significantly lower in people receiving semaglutide 0.5 mg and 1 mg: 0.7 and 1.0 percentage points lower, respectively, vs SOC ( $P < .001$  for both comparisons).<sup>17</sup> Moreover, significant mean body weight reductions of 2.9 kg and 4.3 kg were observed with semaglutide 0.5 mg and 1 mg, respectively, vs SOC ( $P < .001$  for both comparisons).<sup>17</sup> Treatment with exenatide ER also significantly reduced HbA<sub>1c</sub> levels (overall least-squares mean difference  $-0.53\%$ ;  $P < .001$ ) and body weight (overall least-squares mean difference  $-1.27$  kg;  $P < .001$ ).<sup>18</sup> Similarly, dulaglutide was associated with a significant 0.61% lower HbA<sub>1c</sub> level and 1.46 kg lower body weight compared with SOC (both  $P < .0001$ ).<sup>19</sup> Semaglutide (1 mg), exenatide ER (2 mg) and dulaglutide (1.5 mg) lowered mean systolic blood pressure by 2.6 mm Hg ( $P < .001$ ), 1.6 mm Hg ( $P < .001$ ) and 1.7 mm Hg ( $P < .0001$ ), respectively, vs SOC.<sup>17-19</sup> These differences were present despite the recommendations to maintain equipoise in both arms and add other anti-diabetic medications to the SOC arm throughout the studies.

As renal damage due to diabetes is associated with lower quality of life and higher rates of CV events, and negatively affects survival,<sup>7</sup> renal outcomes are important to assess in people with T2D. Treatment with semaglutide s.c. (0.5 and 1 mg combined) and dulaglutide (1.5 mg) both demonstrated a significantly greater risk reduction in nephropathy compared with SOC (semaglutide: 3.8% vs 6.1%, HR 0.64,  $P = .005$ ; dulaglutide: 17.1% vs 19.6%, HR 0.85,  $P = .0004$ ; Table 2).<sup>17,19</sup> This is equivalent to 36% fewer patients with nephropathy events with semaglutide (both doses vs SOC)<sup>17</sup> and 15% with dulaglutide (1.5 mg vs SOC).<sup>19</sup> Exenatide ER appeared to have neutral effects on renal function compared with SOC (eg hospitalization due to renal failure 0.4% with exenatide ER and 0.3% with SOC; no HRs for renal events reported).<sup>18</sup>

As mentioned above, in addition to the beneficial effects described above, fewer participants in the QW GLP-1 RA group in SUSTAIN 6 or EXSCEL (semaglutide s.c. or exenatide ER) added concomitant glucose-lowering medications, including insulin, during these trials compared with SOC.<sup>17,18</sup> Furthermore, in SUSTAIN 6, fewer CV medications were introduced during the trial with semaglutide s.c. vs SOC.<sup>17</sup> Similarly, in REWIND, patients receiving dulaglutide added fewer concomitant medications (SGLT2i, metformin, sulphonylurea, insulin, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker) vs SOC at the end of the trial.<sup>19</sup> Therefore, patients may require less treatment intensification with glucose-lowering drugs, including insulin, when receiving these QW GLP-1 RAs, with the possibility of requiring fewer concomitant CV medications with semaglutide s.c. or dulaglutide vs SOC. The use of other GLP-1 RAs, in addition to the study drug, was contraindicated in all these trials.<sup>17-19</sup> Despite this, a small percentage of people received them during the course of these trials for glycaemic management (SUSTAIN 6: 1.0% semaglutide [0.5 mg] vs 0.8% SOC, 1.8% semaglutide [1 mg] vs 1.1% SOC; EXSCEL: 2.5% exenatide ER [2 mg] vs 3.6% SOC; REWIND: 0.6% [dulaglutide 1.5 mg] vs 0.9% SOC).<sup>17-19</sup>





### 3.5 | Adverse events observed in once-weekly GLP-1 RA CVOTs

There have been no statistically significant detrimental effects of the study drugs on 3-point MACE, and all T2D QW GLP-1 RA CVOTs to date have shown at least non-inferiority between the investigational treatment and the SOC group.<sup>17-19</sup> However, as with any trial, these CVOTs also noted certain side effects associated with the study drugs. GLP-1 RAs were associated with increased events of and/or discontinuations due to gastrointestinal (GI) disorders such as diarrhoea, nausea and vomiting compared with SOC.<sup>17-19</sup> Discontinuation rate due to GI tolerability issues was higher in patients receiving semaglutide 1 mg (9.4%) vs semaglutide 0.5 mg (5.7%). It is important to mention that the design of the study prohibited dose decrease, so patients randomized to semaglutide 1 mg who could not tolerate it had to discontinue the treatment.<sup>17</sup> Among those treated with exenatide ER and dulaglutide in the EXSCEL and REWIND trials, 4.5% and 2.4% of patients discontinued treatment due to severe GI tolerability issues, respectively. These side effects of GLP-1 RAs are generally more prevalent at the start of treatment and are mild-to-moderate in nature, with symptoms decreasing gradually during continued therapy.<sup>45</sup> In SUSTAIN 6, a significantly higher proportion of people treated with semaglutide 0.5 mg or 1 mg had diabetic retinopathy complications (vitreous haemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation) compared with SOC (3.0% vs 1.8%, respectively).<sup>17</sup> However, it should be noted that 83.5% and 82.8% of these patients, respectively, already had pre-existing retinopathy at baseline. It is recommended that patients with a history of diabetic retinopathy should be monitored for progression of retinopathy if they are prescribed semaglutide.<sup>41</sup> Worsening of diabetic retinopathy is associated with rapid reductions in HbA<sub>1c</sub>,<sup>46,47</sup> and this may have driven the increased risk of diabetic retinopathy in the patients within SUSTAIN 6.<sup>48</sup> In REWIND, there was no increase in retinopathy complications associated with dulaglutide compared with SOC, and no increased risk of retinopathy was noted in EXSCEL.<sup>18,19</sup> Overall, GLP-1 RAs as a class were not associated with an increased risk of retinopathy.<sup>49-51</sup>

### 3.6 | DPP4i and SGLT2i CVOTs

To understand the place of QW GLP-1 RA CVOTs in the broader treatment landscape, it is worthwhile to consider CVOT results for other contemporary T2D treatment options. The CV safety of four DPP4is (act through preventing GLP-1 degradation<sup>52</sup>) and three SGLT2is (act through increasing urinary glucose excretion<sup>53</sup>) has been assessed (Table 3). The DPP4is saxagliptin, alogliptin, sitagliptin and linagliptin had neutral CV outcomes in their respective CVOTs—SAVORTIMI 53, EXAMINE, TECOS and CARMELINA.<sup>34,54-56</sup> Although these trials established overall CV safety in terms of MACE, none of the DPP4is demonstrated either CV or renal outcome benefits

compared with SOC (Table 3).<sup>34,54-56</sup> It should be noted that the DPP4is saxagliptin and alogliptin were associated with an increased risk of hospitalization for HF compared with SOC.<sup>54,57</sup> The SGLT2i CVOTs EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 along with the cardiorenal outcomes trial CREDENCE provided evidence for CV and renal benefits or a trend towards these benefits with SGLT2i use (Table 3).<sup>58-61</sup> SGLT2is are associated with a reduction in risk of HF events and are recommended for use in patients with established kidney disease or heart failure.<sup>15</sup> If SGLT2is are contraindicated or not tolerated, a GLP-1 RA with proven CV benefits is recommended.<sup>15</sup>

These CVOTs also reported other safety outcomes. Adverse events reported more frequently with active treatment vs SOC in the DPP4i CVOTs (in  $\geq 5\%$  of patients) included renal abnormality (doubling of creatinine level, initiation of dialysis, renal transplantation or creatinine  $>6.0$  mg/dL;  $P = .04$  for saxagliptin vs SOC),<sup>54</sup> hypoglycaemia ( $P < .001$  for saxagliptin vs SOC and numerically higher in a subgroup of patients receiving sulphonylurea at baseline for linagliptin vs SOC [significance not reported])<sup>54,55</sup> and infections (difference for sitagliptin vs SOC not significant).<sup>34</sup> Additionally, the increased risk of HF associated with the DPP4is saxagliptin and alogliptin resulted in a safety warning from the FDA,<sup>62</sup> although this may not represent a class effect.<sup>34,55</sup> The SGLT2i CVOTs reported increased incidences of treatment-emergent genital infection compared with SOC.<sup>58,60</sup> An increased risk of bone fractures and risk for lower limbs amputation were reported with canagliflozin compared with SOC in the CANVAS trial; however, results from other SGLT2i CVOTs do not suggest an increased risk compared with SOC.<sup>58-61</sup> As with all treatments, the benefits of these medications should be weighed against their potential risks when making prescribing decisions.

## 4 | WHAT IS NEW AND CONCLUSION

### 4.1 | Implications for pharmacists and healthcare providers

The choice of glucose-lowering treatment strategy depends on individual patient characteristics and circumstances. Indeed, current guidelines recommend an evidence-based, personalized approach to the medication management of T2D.<sup>15</sup> The CV and renal benefits observed with GLP-1 RAs and SGLT2is in CVOTs led to changes in the ADA treatment guidelines in 2019.<sup>12</sup> These guidelines recommend assessment of patient ASCVD, HF and renal status, the need to lower body weight and minimize hypoglycaemia, and cost and patient preference.<sup>15</sup> The guideline changes reflect the fact that people with T2D have a high probability of dying from diabetes complications such as CV events, and that treatment options that have been demonstrated to reduce CV events should be used in these patients. A patient-centred approach will ensure the appropriate use of glucose-lowering medications, thus catering for the needs of patients based on individual circumstances.<sup>63</sup>

The guidelines stipulate reevaluation and adjustment of medication regimens every 3-6 months for patients not reaching their HbA<sub>1c</sub> target, with a view to incorporating new patient factors.<sup>15</sup> Such regular reevaluations should help reduce treatment inertia and prevent future complications.

GLP-1 RAs are recommended as a first injectable treatment instead of insulin for most patients requiring intensified therapy for glucose control.<sup>15</sup> This recommendation is based on at least similar efficacy of GLP-1 RAs in glycaemic management, lower risk of hypoglycaemia, and beneficial effects on body weight associated with GLP-1 RAs compared with insulin.<sup>15</sup> As SGLT2is have been shown to reduce the risk of HF events in people with T2D,<sup>58-60</sup> this class of drugs is the preferred choice of treatment in those whom HF or CKD predominates.<sup>15</sup> For people in whom HF predominates and SGLT2is are not tolerated or contraindicated,<sup>15</sup> GLP-1 RAs are the recommended add-on choice in combination therapies, as they have a neutral effect on hospitalization for HF.<sup>2,15</sup> GLP-1 RAs are also the preferred treatment choice for people with T2D and inadequate renal function.<sup>15</sup> When recommending treatment with GLP-1 RAs, however, patients should be advised of the potential GI side effects associated with this drug class,<sup>17-19</sup> although these are often mild and transient.<sup>45</sup> Starting with a lower dose and gradual uptitration can help mitigate these side effects.<sup>64</sup>

Overall, QW GLP-1 RAs have demonstrated CV and renal benefits in people with T2D, with or without CVD or at high risk of CVD, but there are differences within this class that need to be considered when prescribing them. Pharmacists are in a key position to provide recommendations and education on evidence-based preferred drug therapies, aiding other healthcare providers.

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## CONFLICTS OF INTEREST

JD Goldman reports serving on speaker's bureau for Novo Nordisk and Sanofi and as a consultant for Becton Dickinson.

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