Series: Cardiovascular outcome trials for diabetes drugs. Cardiovascular outcome trials with GLP-1 receptor agonists from exenatide and EXSCEL

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Abstract

LEADER was a landmark cardiovascular outcome trial with the GLP-1 receptor agonist liraglutide, which demonstrated significant reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), driven by a reduction in cardiovascular deaths and accompanied by a significant reduction in all-cause mortality. Shortly afterwards, the SUSTAIN-6 trial with once-weekly semaglutide demonstrated non-inferiority for MACE, with a nominal reduction in MACE that was driven by a reduction in the risk of non-fatal strokes. Since then, a further six cardiovascular trials have been published with GLP-1 receptor agonists, with major differences in study design and outcomes.

Four trials have been performed with once-weekly formulations. The EXSCEL trial with once-weekly exenatide showed non-inferiority for MACE, but not superiority, with a reduction in all-cause mortality which was an exploratory outcome. The Harmony Outcomes trial with albiglutide demonstrated significant reductions in MACE, driven by reductions in fatal or non-fatal myocardial infarction. REWIND, with dulaglutide, also demonstrated significant reductions in MACE, this time driven by reductions in strokes. The AMPLITUDE-O trial with efpeglenatide showed significant reductions in MACE, but none of the individual components of MACE was significantly reduced as a secondary endpoint, and in contrast to other trials there was also a significant reduction in heart failure events. The fifth trial was the PIONEER 6 trial with the oral formulation of semaglutide, and this showed non-inferiority for MACE, but not superiority, with reductions in cardiovascular deaths and all-cause mortality which were secondary outcomes. Finally, FREEDOM-CVO with a subcutaneous minipump of exenatide showed non-inferiority for MACE and MACE plus hospitalisation for unstable angina. A reduction in albuminuria was seen in several of these trials, but there was no definite effect on eGFR or end-stage renal disease.

Meta-analysis of the cardiovascular outcome trials with GLP-1 receptor agonists has demonstrated significant reductions in MACE, cardiovascular death, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction, and all-cause mortality. It remains unclear why updated guidance from NICE on the management of T2DM in adults fails to acknowledge these evidence-based cardiovascular benefits.

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Key words: diabetes, cardiovascular outcome trial, exenatide, albiglutide, dulaglutide, oral semaglutide, efpeglenatide, ITCA 650

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Introduction

Licensing requirements for new antidiabetic drugs changed in the US and EU following the rosiglitazone controversy, with a much greater requirement to demonstrate cardiovascular safety. Between 2015 and 2021 nine dedicated cardiovascular outcome trials (CVOTs) were completed with glucagon-like peptide 1(GLP-1) receptor agonists in patients with T2DM.[1-9] ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) was the first of these and demonstrated no cardiovascular benefit with lixisenatide, with no difference in major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.[1] By contrast, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial with liraglutide demonstrated significant reductions in MACE, cardiovascular death and all-cause mortality,[2] and SUSTAIN -6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes in Subjects with Type 2 Diabetes) with once-weekly semaglutide demonstrated benefits in reducing MACE and non-fatal stroke.[3] These three trials were reviewed earlier in this series.[10-12]

This review describes results from the other six completed CVOTs with GLP-1 receptor agonists in patients with T2DM: EXSCEL (Exenatide Study of Cardiovascular Event Lowering) with once-weekly exenatide,[4] Harmony Outcomes with albiglutide,[5] REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) with dulaglutide,[6] PIONEER (Peptide Innovation for Early Diabetes Treatment)[6] with oral semaglutide,[7] AMPLITUDE-O with efpeglenatide,[8] and FREEDOM-CVO with ITCA 650.[9] This review describes the primary endpoint and

Table 1. Key features of EXSCEL, Harmony Outcomes, REWIND, PIONEER 6, AMPLITUDE-O, and FREEDOM-CVO

	EXSCEL[4,13,14]	Harmony Outcomes[5,17]	REWIND[6,21]	PIONEER 6[7,23]	AMPLITUDE-O[8,24]	FREEDOM-CVO[9]
GLP-1 receptor agonist	Exenatide extended release 2 mg	Albiglutide 30-50 mg	Dulaglutide 1.5 mg	Oral semaglutide 14 mg	Efpeglenatide 4 and 6 mg	ITCA 650
Subjects	14,752	9,463	9,901	3,183	4,076	4,156
Follow-up	Median 3.2 years	Median 1.6 years	Median 5.4 years	Median 16 months	Median 1.8 years	Median 16 months
Age	62 years	64 years	66 years	66 years	64 years	63 years
Duration of diabetes	13 years	14 years	57% over 10 years	15 years	16 years	10 years
Baseline HbA_{1c}	8.1%	8.7%	7.3%	8.2%	8.9%	8.0%
Baseline CVD	73% ASCVD 53% CAD 17% stroke/cvd 16% HF 27% CV risk	100% ASCVD 71% CAD 47% MI 18% stroke 20% HF	31% ASCVD 16% MI 5% stroke 9% HF 69% CV risk	85% ASCVD or CKD 27% CAD 35% MI 16% stroke/cvd 12% HF 15% CV risk	90% ASCVD 18% HF	76% ASCVD 49% CAD 26% MI 11% stroke/cvd 16% HF 24% CV risk
Baseline diabetes treatments	77% metformin 36% sulfonylurea 46% insulin 15% DPP-4 inhibitor 1% SGLT2 inhibitor	74% metformin 29% sulfonylurea 59% insulin 15% DPP-4 inhibitor 6% SGLT2 inhibitor	81% metformin 46% sulfonylurea 24% insulin 6% DPP-4 inhibitor <1% SGLT2 inhibitor	77% metformin 32% sulfonylurea 61% insulin <1% DPP-4 inhibitor 10% SGLT2 inhibitor	73% metformin 25% sulfonylurea 63% insulin 0% DPP-4 inhibitor 15% SGLT2 inhibitor	85% metformin 45% sulfonylurea 35% insulin 0% DPP-4 inhibitor 0% SGLT2 inhibitor

ASCVD = atherosclerotic cardiovascular disease, CAD = coronary artery disease, CV risk = subjects without established cardiovascular disease but at increased risk of developing cardiovascular disease, HF = heart failure, MI = myocardial infarction, stroke/cvd = stroke or cerebrovascular disease

important secondary outcomes from the principal publications and directs attention to any important subsequent publications of data from subgroups and / or post hoc analyses.

EXSCEL

The twice-daily formulation of exenatide was approved in the US and EU before the requirement for increased cardiovascular safety data, and no dedicated CVOT was performed with this formulation. The rationale and design of the EXSCEL trial with once-weekly exenatide (SR) was published in 2016,[13] and the baseline characteristics of patients enrolled in the trial were published in 2017.[14] A key feature of the study design was that this was conducted as a streamlined, pragmatic trial with visits every six months, which is less frequent than in a conventional CVOT, and laboratory efficacy and safety data were collected from the usual care setting rather than a central laboratory.

The principal results from EXSCEL were presented in 2017 at the meeting of the European Association for the Study of Diabetes (EASD) and published simultaneously in the *New England Journal of Medicine*.[4] The key features of the trial and baseline characteristics of subjects are described in Table 1. One of the striking features of EXSCEL was the high rate of premature study medication discontinuation, which was 43% in the exenatide group and 45% in the placebo group. This high rate of discontinuation might be explained by the infrequent contact between the subjects and the local study team (including the drug [and therefore trial] being passed from company to company; Lilly to BMS to AZ]), or by dissatisfaction with the injection device.

The results for MACE in EXSCEL demonstrated non-inferiority for exenatide versus placebo Superiority was not demonstrated but only just missed (P<0.06 for superiority) (Figure 1, Box 1). Statistical hypothesis testing was scheduled to proceed sequentially, and as there was no significant reduction in MACE any further statistical analysis of EXSCEL is deemed to be exploratory. There was a nominal reduction in all-cause mortality with exenatide SR, but there were no nominal differences in any of the components of the composite MACE outcome (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke), hospitalisation for acute coronary syndrome or hospitalisation for heart failure (Figure 2).

Results of a meta-analysis and other results from EXSCEL

The EXSCEL study group published a meta-analysis of ELIXA, LEADER, SUSTAIN-6 and EXSCEL shortly after publication of the principal paper.[15] This meta-analysis showed reductions in MACE, cardiovascular death and all-cause mortality, but not in myocardial infarctions, strokes or hospitalisation for heart failure. The study group interpreted the results as showing cardiovascular safety for

Figure 1. Major adverse cardiovascular event (MACE) rates (%) comparing GLP-1 receptor agonists and placebo from EXSCEL, Harmony Outcomes, REWIND, PIONEER 6 and AMPLITUDE-O. Statistically significant differences are marked with an asterisk.

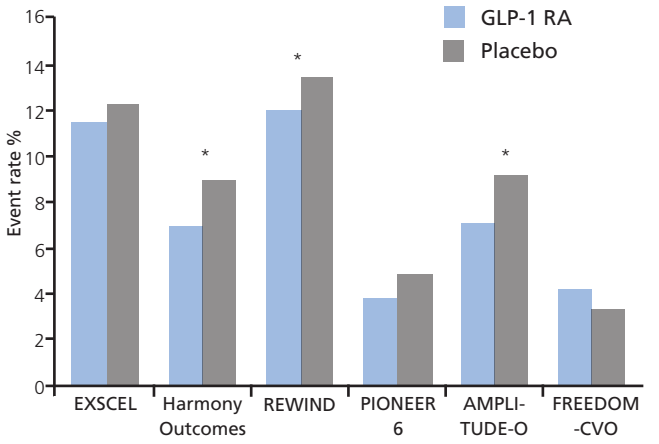
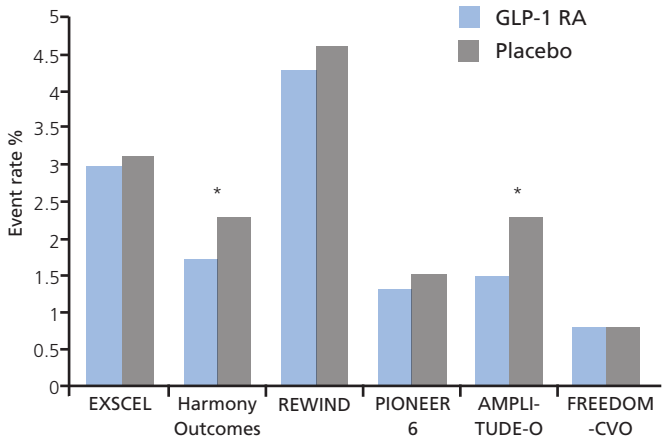


Figure 2. Hospitalisation for heart failure rates (%) comparing GLP-1 receptor agonists and placebo from EXSCEL, Harmony Outcomes, REWIND, PIONEER 6 and AMPLITUDE-O. Statistically significant differences are marked with an asterisk.



Box 1 Results of the EXSCEL trial

Principal result

- No significant difference in MACE

Other results from EXSCEL

- No reduction in all-cause mortality in subjects with baseline heart failure, reductions in all-cause mortality in subjects without baseline heart failure.[16]
- Post hoc analysis of subjects who started open-label SGLT2 inhibitors showed a numerically lower risk of MACE in subjects on SGLT2 inhibitor plus exenatide than in subjects on exenatide alone or placebo alone.[30]
- There was a greater risk of cardiovascular events after an episode of severe hypoglycaemia, and the risk of severe hypoglycaemia was greater after cardiovascular events.[31]
- Post hoc analysis showed that once-weekly exenatide reduced urinary albumin:creatinine ratio (UACR). An improvement in eGFR slope was seen in subjects with elevated baseline UACR. Unfortunately, data for baseline UACR were only available in one quarter of the study population.[32]

all four GLP-1 receptor agonists, with reductions in MACE, cardiovascular mortality and all-cause mortality to varying degrees for individual drugs.

Since the CVOTs were first mandated by the FDA there has been an increased interest in heart failure, both as an outcome and as a co-morbidity. 16% of the subjects in EXSCEL had investigator-documented heart failure at baseline.[16] There was no reduction in all-cause mortality in subjects with baseline heart failure, whereas in subjects without heart failure at baseline there were significant reductions in all-cause mortality and a composite of all-cause mortality and hospitalisation for heart failure.

There are several further publications from EXSCEL (Box 1).

Box 2 Results of the Harmony Outcomes trial

Principal result

- Significant reduction in MACE

Other results from Harmony Outcomes

- No effect of albiglutide on reducing heart failure events in patients with a prior history of heart failure.[19]
- Half of the respondents reported using electronic health records to find potential trial recruits.[20]

Harmony Outcomes

Albiglutide was a once-weekly GLP-1 receptor agonist based on the human GLP-1 molecule. It was withdrawn from the market in 2018 for commercial reasons. The Harmony Outcomes study was initiated in 2015, and a paper describing the rationale, design and baseline characteristics was published in 2018.[17]

The principal results from Harmony Outcomes were presented at the 2018 meeting of the EASD, with simultaneous publication in the *Lancet*.[5] In Harmony Outcomes there was a significant reduction in MACE with albiglutide, demonstrating superiority versus placebo (Figure 1, Box 2). Significant reductions in fatal or non-fatal myocardial infarction were observed, but not in cardiovascular death or fatal or non-fatal stroke.

Other results from Harmony Outcomes

Data on heart failure outcomes were not included in the principal publication from Harmony Outcomes, which focused on atherosclerotic outcomes. Data on heart failure events from Harmony Outcomes were included in a subsequent meta-analysis of the seven CVOTs with GLP-1 receptor agonists that had been completed at that time.[18] Significant reductions in hospital admission for heart failure were observed with GLP-1 receptor agonists in

addition to reductions in atherosclerotic outcomes and a broad composite renal outcome. Of the seven CVOTs, only Harmony Outcomes showed a significant reduction in hospital admissions for heart failure (Figure 2).

20% of the subjects in Harmony Outcomes had investigator-documented heart failure at baseline.[19] A recent publication from Harmony Outcomes showed similar results to the EXSCEL analysis, with no effect of albiglutide on reducing heart failure events in patients with a prior history of heart failure. To date there has only been one other publication from Harmony Outcomes, looking at the use of electronic health records for recruitment in clinical trials (Box 2).[20]

REWIND

A paper describing the design and baseline characteristics of REWIND was published in 2018.[21] A key difference in REWIND was that 69% of subjects had T2DM and increased cardiovascular risk and only 31% had existing cardiovascular disease, whereas other CVOTs with GLP-1 receptor agonists had a higher proportion of subjects with existing cardiovascular disease (Table 1). The principal results of REWIND were presented in 2019 at the meeting of the American Diabetes Association (ADA), with simultaneous publication in the *Lancet*.[6] There was a significant reduction in MACE with dulaglutide in REWIND (Figure 1), with significant reductions in non-fatal stroke but not non-fatal myocardial infarction or cardiovascular death as components of MACE. All-cause death was not significantly different in the two groups, and rates of hospital admission or an urgent visit for heart failure were similar (Figure 2).

Other results from REWIND

Detailed renal results from REWIND were presented and published at the same time as the cardiovascular results.[22] The exploratory secondary renal composite of new-onset macroalbuminuria, sustained decline in eGFR of >30% or the need for chronic renal replacement therapy was reduced in the dulaglutide group. This was driven primarily by reduction in new-onset macroalbuminuria, but there was a numerical reduction in the need for renal replacement therapy (16 in the dulaglutide group, 21 in the placebo group). There are many other publications of results from REWIND (Box 3).

PIONEER 6

A paper describing the rationale, design and baseline characteristics of PIONEER 6 was published in 2019.[23] This was a pre-licensing trial to demonstrate non-inferiority and was not powered to demonstrate superiority. The principal results were presented later in 2019 at the meeting of the ADA, with simultaneous publication in the *New England Journal of Medicine*.[7] The primary MACE endpoint was non-inferior comparing semaglutide and placebo, but superiority was not shown. The secondary outcome of cardiovascular death was reduced with semaglutide, as was all-cause mortality. These outcomes were not controlled for multiple comparisons and should be considered exploratory.

Box 3 Results of the REWIND trial

Principal result

- Significant reduction in MACE

Other results from REWIND

- Significant reduction in an exploratory secondary renal composite of new-onset macroalbuminuria, sustained decline in eGFR of >30% or the need for chronic renal replacement therapy.[22]
- In an exploratory analysis there was a significant reduction in strokes, including ischaemic strokes, with dulaglutide, but there was no effect on haemorrhagic strokes or stroke severity.[33]
- Cognitive function was assessed at baseline and follow-up, and after post-hoc adjustment for individual standardised baseline scores, the hazard of substantial cognitive impairment was significantly reduced in subjects allocated to dulagutide.[34]
- A standardised International Index of Erectile Function questionnaire was completed in 70% of male subjects. It showed that long-term use of dulaglutide might reduce the incidence of moderate or severe erectile dysfunction in men with T2DM.[35]
- In REWIND heart failure events were not reduced with dulaglutide, and there was no effect on all-cause mortality either in subjects with or without baseline heart failure.[36]

Other results from PIONEER 6

The small number of subjects and cardiovascular events in PIONEER 6 make further analysis of the data very difficult. To solve this problem data from PIONEER 6 and SUSTAIN-6 with subcutaneous semaglutide have been pooled for further analysis (Box 4). Few further insights on oral semaglutide have been obtained using this pooled analysis approach as there were twice as many events in the longer SUSTAIN-6 trial.

AMPLITUDE-O

Efpeglenatide was an exendin-4 based GLP-1 receptor agonist under development by Sanofi as a once-weekly injection. The development was stopped for commercial reasons and efpeglenatide is currently not available for clinical use. Sanofi indicated that it would complete ongoing studies, including the AMPLITUDE-O CVOT. A paper describing the design and baseline characteristics of AMPLITUDE-O was published in 2020.[24] Key features and baseline characteristics are described in Table 1.

The principal results from AMPLITUDE-O were presented at the virtual meeting of the ADA in 2021, with simultaneous pub-

Box 4 Results of the PIONEER 6 trial

Principal result

- Oral semaglutide non-inferior for MACE

Results from the pooled analysis of SUSTAIN-6 and PIONEER 6

- Semaglutide reduced MACE, especially non-fatal strokes, in several subgroups, except for patients with prior heart failure in whom there was no reduction in MACE.[37]
- Semaglutide reduced the first instance of stroke, driven primarily by prevention of small-vessel occlusion.[38]
- The cardiovascular outcomes with semaglutide were similar regardless of the baseline use of metformin or not.[39]

Box 5 Results of the AMPLITUDE-O trial

Principal result

- Significant reduction in MACE

Other results from AMPLITUDE-O

- The reduction in MACE and a composite renal outcome was similar in subjects regardless of whether they were receiving a SGLT2 inhibitor at baseline or not.[26]

lication in the *New England Journal of Medicine*.[8] In AMPLITUDE-O there was a significant reduction in primary outcome of MACE (Figure 1, Box 5). Significant reductions were also seen in a composite renal outcome. There were no statistically significant differences in death from any cause, death from cardiovascular disease, myocardial infarction or stroke. Hospitalisation for heart failure was reduced in the efpeglenatide group, but because of hierarchical testing this result should be considered exploratory.

Results of the meta-analysis and other results from AMPLITUDE-O

Shortly after the AMPLITUDE-O trial results were published, the AMPLITUDE-O investigators published a meta-analysis of the eight CVOTs with GLP-1 receptor agonists, including data from AMPLITUDE-O.[25] This meta-analysis showed that GLP-1 receptor agonists significantly reduced MACE, all-cause mortality and a composite renal outcome, with a significant 11% reduction in hospital admission for heart failure. The benefits were independent of the structural basis of the GLP-1 receptor agonist and showed benefits for exendin-based agonists as well as human GLP-1 based molecules.

So far there has been only one further publication from AMPLITUDE-O. An exploratory analysis compared the 15% of subjects who were using a SGLT2 inhibitor at baseline with subjects not receiving a baseline SGLT2 inhibitor and showed no difference in efficacy and safety of efpeglenatide, supporting the combined use of SGLT2 inhibitors and GLP-1 receptor agonists in people with T2DM.[26]

FREEDOM-CVO

ITCA 650 was an implantable mini-pump containing exenatide, released subcutaneously over a six-month period. It failed to receive approval from the FDA on two occasions. FREEDOM-CVO was a short pre-licensing CVOT comparing ITCA 650 and placebo, and patients were followed for a median of 16 months.[9] The study was completed in 2016 and finally published in 2021. The primary endpoint was MACE plus hospitalisation for unstable angina, sometimes termed four-point MACE, and a non-inferiority margin of 1.8 for the upper bound of the 95% confidence interval was used. The results showed a numerical increase in events in the ITCA 650 group, with a Hazard Ratio of 1.21 and 95% confidence intervals of 0.90-1.63, which was less than the non-inferiority margin of 1.8 (P<0.004). The results for MACE were similar (Figure 1), and heart failure event rates were low (Figure 2). The investigators concluded that a larger CVOT of longer duration would be needed to define more precisely the cardiovascular effects of ITCA 650 in people with T2DM. There are no other publications related to this trial.

Key messages

- In the REWIND trial dulaglutide reduced major adverse cardiovascular events in patients with T2DM and high cardiovascular risk, with a significant reduction in strokes
- In the EXSCEL and PIONEER 6 trials with extended-release exenatide and oral semaglutide, respectively, there was non-inferiority but not superiority for major adverse cardiovascular events. Oral semaglutide is being studied in a larger, longer CVOT (SOUL)
- Cardiovascular outcome trials with albiglutide (Harmony Outcomes) and efpeglenatide (AMPLITUDE-O) showed significant reductions in major adverse cardiovascular events and hospitalisation for heart failure, but these drugs are not currently available for clinical use

Discussion

The CVOTs with dulaglutide (REWIND), albiglutide (Harmony Outcomes) and efpeglenatide (AMPLITUDE-O) showed clear benefits in reducing atherosclerotic cardiovascular outcomes. Neither albiglutide nor efpeglenatide are currently available for clinical use, which is somewhat ironic as these two molecules appear to have the additional benefit of reducing hospitalisation for heat failure.

Dulaglutide joins liraglutide and once-weekly semaglutide as GLP-1 receptor agonists with proven cardiovascular benefits, which should be used for the management of T2DM in people with existing atherosclerotic cardiovascular disease or people at high cardiovascular risk. An unexpected increase in retinopathy was observed in the SUSTAIN-6 trial with subcutaneous semaglutide, and liraglutide or dulaglutide are alternatives that have not been associated with worsening retinopathy for patients with diabetic retinopathy (the increases in retinopathy risk were not significant). It is hard to see a continuing clinical role for exenatide as neither EXSCEL nor FREEDOM-CVO demonstrated clear and compelling evidence of cardiovascular benefit. The PIONEER 6 trial with oral semaglutide was a pre-licensing trial, and the cardiovascular effects of oral semaglutide will be definitively addressed in the SOUL trial of 9,642 patients with T2DM and an estimated completion date of 2024.[27]

The CVOTs and meta-analyses also demonstrated modest improvements in renal composite outcomes, particularly in reducing albuminuria. The renal results from REWIND raise the possibility that dulaglutide might preserve renal function, but no dedicated renal outcome trial with dulaglutide is planned at present, and subcutaneous semaglutide is the only GLP-1 receptor agonist that will be studied in a dedicated renal outcome trial (FLOW).[12]

The pattern of reduction in cardiovascular and renal outcomes with GLP-1 receptor agonists differs from the reductions observed with SGLT2 inhibitors. Reductions in atherosclerotic events in people with T2DM are seen with individual drugs in both classes. SGLT2 inhibitors also have proven benefits in non-diabetic people with heart failure and chronic kidney disease. It makes sense for maximum reduction in hyperglycaemia and maximum cardiovascular benefit for people with T2DM to combine the two drug classes, and that is the approach taken by many guidelines and consensus statements e.g. the 2022 consensus report on the management of hyperglycaemia in T2DM by the ADA and EASD.[28]

The updated NICE guidance on the management of T2DM in adults published in March 2022 endorses switching to or adding an SGLT2 inhibitor if the person has established atherosclerotic CVD, but similar endorsement for GLP-1 receptor agonists is lacking. The guidance did not make any new recommendations on further treatment options so repeats the recommendations from 2015, recommending switching to a GLP-1 receptor agonist if triple therapy with metformin and two other oral drugs is not effective, and the patient has a raised body mass index.[29] The lack of any recommendation for GLP-1 receptor agonists is justified by claiming that the economic model continued to show that an SGLT2 inhibitor was likely to be the most cost-effective option, ignoring the fact that DPP-4 inhibitors and sulfonylureas do not demonstrate any cardiovascular benefits, and the possible enhanced benefit from adding GLP-1 receptor agonists to SGLT2 inhibitors.

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