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An overview of GLP-1 agonists and recent cardiovascular outcomes trials

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ABSTRACT

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are emerging as an important therapy to consider for patients with type 2 diabetes (T2D) given this class of treatment's ability to reduce glycated haemoglobin and their associated weight loss and low risk for hypoglycaemia. Additionally, seven cardiovascular outcomes trials (CVOTs) have been performed in the past 4 years using lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide and oral semaglutide. All have found non-inferiority for cardiovascular outcomes, with many finding superiority of these drugs. These findings have transformed our guidelines on pharmacological treatment of T2D. This review article will discuss GLP-1 RA therapy, review the seven CVOTs reported to date and discuss the implications on current guidelines and therapies going forward.

INTRODUCTION

It was first reported in 1964 that there was greater and more sustained insulin release in response to an oral glucose load when compared with the same glucose load given intravenously.¹ With the discovery of an incretin hormone known as glucose-dependent insulinotropic polypeptide (GIP), this enhanced release of insulin in response to ingestion of glucose became known as the 'incretin effect'.² In 1986, Nauck *et al* showed that despite similar levels of GIP in response to an oral glucose load, patients with type 2 diabetes (T2D) had an impaired incretin effect.³ Shortly after this, glucagon-like peptide 1 (GLP-1) was discovered in 1987 and was found to be more effective than GIP in stimulating insulin and reducing peak plasma glucose concentrations.⁴

GLP-1 was initially thought to primarily affect insulin release; however, it has been found to exert many other effects in glucose metabolism. GLP-1 is released from the distal ileum and colon within minutes of a meal and, while it does enhance glucose-dependent insulin production and secretion, it has also been shown to decrease glucagon secretion, increase glucose uptake and glycogen synthesis in peripheral tissues, delay gastric emptying and increase satiety,⁵ making it an ideal target for diabetes therapy. The first GLP-1 receptor agonist (GLP-1 RA) was exenatide, which was approved by the US Food and Drug Administration (FDA) in April 2005 for the treatment of T2DM,⁶ and since that time, several GLP-1 RAs have been added to the drug class given their preferable profile in terms of improved weight loss, low risk for hypoglycaemia and reduction in glycated haemoglobin (HgA1c).

Although it has been shown that improved glycaemic control can reduce the microvascular complications of diabetes,⁷ its effect on macrovascular complications is less clear,⁸ and cardiovascular disease remains the number one cause of death in patients with T2D.⁹ The main long-term data we have looking at glycaemic control in patients with T2D on macrovascular outcomes are from the UKPDS (UK Prospective Diabetes Study) and VADT (Veterans Affairs Diabetes Trial)—although neither study showed clear cardiovascular mortality benefit initially, the 10-year follow-up to UKPDS did suggest a potential 'legacy effect' of early tight glycaemic control leading to later reductions in myocardial infarction and death,¹⁰ but no similar reduction in cardiovascular mortality was seen in the follow-up VADT.¹¹ Further complicating this is the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, published in 2008, which found that more intensive glycaemic control resulted in no reduction in cardiovascular events and in fact increased overall mortality.¹² A 9-year follow-up to this study showed the intensive group had no difference in overall mortality but did have increased cardiovascular-related deaths.¹³

As more diabetes drugs came to the market, there was concern regarding the effect of these drugs on cardiovascular risk, particularly with the drug rosiglitazone, which was associated with a significant increase in the risk of myocardial infarction.¹⁴ Given these concerns, in 2008 the FDA came out with a recommendation that new glucose-lowering medications for diabetes are shown to not increase cardiovascular risk.¹⁵ This recommendation led to long-term prospective cardiovascular outcomes trials (CVOTs) for new diabetes drugs. In this process, several medications within the GLP-1 RA class have not only shown non-inferiority but have also shown superiority in terms of their cardiovascular outcomes, which we will present here. As studies begin to show important cardiovascular benefits among certain drug classes, the American Diabetes Association (ADA) has now incorporated this consideration into its 2019 guidelines on diabetes treatment.¹⁶

All of the following CVOTs presented here have been industry funded trials, and all are multicentre, double-blinded, randomised, placebo-controlled trials. The study drug administration, half-life and dosing guidelines are listed in [table 1](#). Patients were randomised to the GLP-1 RA or volume-matched control, and all participants were treated with standard of care in that providers were allowed to add diabetes medications other than incretin-based therapies. The primary endpoint in these trials was



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Table 1 GLP-1 receptor agonists with completed cardiovascular outcomes trials to date

GLP-1 RA	Administration	Half-life	Starting dose	Maximum dose	Renal function*
Lixisenatide (Adlyxin)	Daily	3 hours	10 mcg	20 mcg	Not recommended eGFR <15
Liraglutide (Victoza)	Daily	13 hours	0.6 mg	1.8 mg	No dosage adjustment
Semaglutide (Ozempic)	Weekly	1 week	0.25 mg	1.0 mg	No dosage adjustment
Exenatide QW (Bydureon)	Weekly	2 weeks	2.0 mg	2.0 mg	Not recommended eGFR <45
Albiglutide† (Eperzan)	Weekly	5 days	30 mg	50 mg	Not recommended eGFR <15
Dulaglutide (Trulicity)	Weekly	5 days	0.75 mg	1.5 mg	No dosage adjustment
Oral semaglutide (Rybelsus)	Daily	1 week	3 mg	14 mg	No dosage adjustment

*Drug manufacturer dosage adjustments for renal impairment.

†Not currently being marketed.

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; QW, every week; GLP-1 RA, glucagon-like peptide 1 receptor agonist.

the first occurrence of a three-point or four-point cardiovascular composite outcome that slightly differs based on the trial. All were evaluated with the intention-to-treat model.

CARDIOVASCULAR OUTCOMES TRIALS

Lixisenatide: ELIXA

The first CVOT among the GLP-1 RAs was the evaluation of lixisenatide in acute coronary syndrome (ELIXA) trial, published in 2016.¹⁷ Participants included were those with T2D who also had an acute coronary event within 180 days before screening. They used an initial run-in period of self-administered placebo injections to improve compliance, and following this, the subjects were randomised to lixisenatide (titrated to a maximum dose of 20 µg daily) or a volume-matched placebo. The primary endpoint was the first occurrence of one of the following: death from cardiovascular causes, non-fatal stroke, non-fatal myocardial infarction or hospitalisation for unstable angina.

A total of 6068 patients were enrolled with an average baseline HgA1c of 7.7% and a median follow-up of 25 months in each group. Of these participants in the lixisenatide group, 27.5% permanently discontinued the study drug during the trial. The primary endpoint (table 2) occurred in 13.4% of patients in the treatment group compared with 13.2% of patients in the placebo group, which was not significant. The percentage change in the urinary albumin-to-creatinine ratio was higher in the placebo group, although when adjusted for baseline HgA1c, this was not statistically significant. Adverse events leading to permanent discontinuation of the medication were higher in the lixisenatide group compared with placebo (11.4% vs 7.2%), with the most common being a gastrointestinal event including nausea or vomiting. There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis or pancreatic neoplasms.

This study was designed to show non-inferiority rather than superiority. Compared with other studies, this study had a short follow-up period of 2 years and also the highest percentage of participants on statin therapy which provides further cardiovascular benefit (table 2). Additionally, compliance with the medication was lower than most other trials for unknown reasons.

Liraglutide: LEADER

Also published in 2016 was liraglutide and cardiovascular outcomes in T2D (LEADER).¹⁸ Participants had T2D and were either 50 years of age and older with at least one cardiovascular condition or 60 years of age and older with at least one cardiovascular risk factor. This trial also used a run-in period of injecting a placebo to increase compliance, and once this run-in period of 2 weeks was completed, patients were randomly assigned to 1.8 mg liraglutide (or maximum tolerated dose) or volume-matched placebo injection. The primary outcome was the first occurrence of a composite cardiovascular outcome consisting of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

A total of 9340 participants were enrolled with a median follow-up of 3.5 years, with 96.8% having a primary outcome, dying or completing the final visit. Of all participants, 81.3% had established cardiovascular disease, 24.7% had chronic kidney disease stage 3 or greater, and the average baseline HgA1c was 8.7%. The average time patients received the intended liraglutide during the trial was 84%. The primary composite outcome (table 2) occurred in 13% of participants in the liraglutide group, significantly less than 14.9% in the placebo group. Significant secondary outcomes also included death from cardiovascular causes (4.7% in the liraglutide group compared with 6.0% in the placebo group, $p=0.007$) and death from any cause (8.2% in liraglutide group compared with 9.6% in placebo group,

Table 2 Summary of baseline characteristics and primary composite cardiovascular outcomes of the completed CVOTs for GLP-1 RA

GLP-1 RA: Study name	No. of patients	Median follow-up (years)	% with CV disease*	% of statin use	Baseline age	Baseline HgA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	60.3	7.7%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	64.3	8.7%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	64.6	8.7%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.1%	74%	62.0	8.0%	31.8	0.91 (0.83 to 1.00)	0.06
Albiglutide: Harmony	9463	1.6	100%	84%	64.1	8.7%	32.3	0.78 (0.68 to 0.90)	0.0006
Dulaglutide: REWIND	9901	5.4	31.5%	66%	66.2	7.2%	32.3	0.88 (0.79 to 0.99)	0.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7%	85%	66.0	8.2%	32.3	0.79 (0.57 to 1.11)	0.17

*Remaining participants with cardiovascular risk factors.

BMI, body mass index; CV, cardiovascular; HgA1c, glycated haemoglobin.

$p=0.02$). There were significantly lower nephropathy events in the liraglutide group compared with placebo (1.5 vs 1.9 events per 100 patient-years, $p=0.003$). There were non-significantly higher retinopathy events in the liraglutide group compared with placebo (0.6 vs 0.5 events per 100 patient-years, $p=0.33$). Adverse events leading to discontinuation were significantly higher in the liraglutide group compared with placebo (9.5% vs 7.3%), which was largely driven by gastrointestinal complaints. There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This trial had a high percentage of patients with underlying cardiovascular disease and it also had one of the highest baseline HgA1c values (table 2), suggesting a very high-risk population. This was the first study to show cardiovascular benefit, although this benefit may not apply for lower risk patients or those without established cardiovascular disease.

Semaglutide: SUSTAIN-6

The 'Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes' (SUSTAIN-6) was the next CVOT published in 2016.¹⁹ Participants were those with T2D who were 50 years of age and older with pre-existing cardiovascular disease, chronic heart failure or chronic kidney disease (stage 3 or higher), or 60 years of age and older with at least one cardiovascular risk factor. They were randomised 1:1:1:1 to 0.5 or 1.0 mg of semaglutide once weekly or a volume-matched placebo. The primary composite outcome was death from cardiovascular events, non-fatal myocardial infarction or non-fatal stroke.

A total of 3297 patients were randomised, with 3232 patients completing the trial over a median time of 2.1 years with similar discontinuation rates in all groups (20%). Eighty-three per cent of patients had established cardiovascular disease (including chronic kidney disease stage 3), 59% of patients had established cardiovascular disease not including chronic kidney disease and participants had a mean HgA1c of 8.7%. The average time patient received the intended semaglutide during the trial was 86.5%. The primary composite cardiovascular outcome (table 2) occurred in 6.6% of patients in the semaglutide group compared with 8.9% in the placebo group, which was statistically significant. There was no statistically significant difference in the risk of cardiovascular death or non-fatal myocardial infarction, although there were significantly fewer non-fatal strokes in the semaglutide group (1.6%) compared with the placebo group (2.7%). Diabetic retinopathy occurred in 3% of patients in the semaglutide group compared with 1.8% in the placebo group ($p=0.02$), although new or worsening nephropathy occurred in 3.8% of patients in the semaglutide group compared with 6.1% in the placebo group ($p=0.005$). Adverse events leading to discontinuation of treatment (majority being gastrointestinal side effects) occurred in 11.5% of those receiving 0.5 mg semaglutide and 14.5% receiving 1.0 mg semaglutide, compared with 5.7% of those receiving 0.5 mg placebo and 7.6% of those receiving 1.0 mg placebo. There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This trial also had one of the highest baseline HgA1c (table 2) compared with other trials. The trial had the largest improvement of HgA1c with semaglutide compared with control (-0.7% and -1.0% , semaglutide 0.5 mg and 1.0 mg compared with control), questioning whether the cardiovascular benefit was seen from the medication itself or the improved glycaemic control.

Once-weekly exenatide: EXSCEL

The next CVOT to be completed was 'Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes' (EXSCEL), published in 2017.²⁰ Participants with T2D were eligible if they had a HgA1c between 6.5% and 10.0%, and the trial was designed to have 70% of participants with previous cardiovascular events. Patients were assigned 1:1 to either 2 mg of extended release exenatide or volume-matched placebo once weekly, and in this trial there was no run-in period to improve adherence. The primary outcome was the first occurrence of any of the following: death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

A total of 14752 patients underwent randomisation with a median duration of follow-up of 3.2 years. Of these participants, 73.1% had previous cardiovascular disease; the median baseline HgA1c was 8%. The mean time participants received the intended exenatide treatment was 76%. The primary composite outcome (table 2) occurred in 11.4% of patients in the exenatide group compared with 12.2% in the placebo group which did not reach significance for superiority. There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This trial had no run-in period and therefore had one of the highest discontinuation rates of the medication compared with the other CVOTs. It otherwise was the largest study, but although the HR favoured exenatide: HR of 0.90, p value of 0.06 (table 2), this did not achieve significance.

Albiglutide: Harmony outcomes

Published in 2018 was 'Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes)'.²¹ Participants were 40 years and older with T2D with one of the following criteria: established cardiovascular disease, cerebrovascular disease or peripheral arterial disease. They were matched at a 1:1 ratio receiving subcutaneous injections of albiglutide or placebo once a week, titrated up to a maximum dose of 50 mg. This trial also did not have a run-in phase to improve compliance. The primary outcome was the first occurrence of one of the following: death from cardiovascular causes, myocardial infarction and stroke.

A total of 9463 participants were included, with a median baseline HgA1c of 8.7% and a median duration of study of 1.6 years. Of all participants, 71% had a history of coronary artery disease, 25% had peripheral arterial disease, 25% had cerebrovascular disease and 20% had a history of heart failure. Twenty-four per cent of participants in the albiglutide group prematurely discontinued the medication. The primary composite cardiovascular endpoint (table 2) occurred in 7% of patients in the albiglutide group compared with 9% of patients in the placebo group, which was significant. The albiglutide group also had statistically significant reductions in fatal or non-fatal myocardial infarctions with an HR of 0.75 (95% CI 0.61 to 0.90, $p=0.003$). This trial did not look at microvascular outcomes such as retinopathy or renal dysfunction. There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This trial was the shortest duration trial given its high-risk population and relatively high baseline HgA1c compared with other CVOTs (table 2). The difference in HgA1c between albiglutide and control at the end of the trial was 0.52%, which also could have contributed to the primary outcome. In SUSTAIN-6, the increased retinopathy events was hypothesised to be related

to relatively rapid reductions in HgA1c values, but this study did not look at retinopathy outcomes.

Dulaglutide: REWIND

The next CVOT was dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND), published in 2019.²² While previous trials were designed to show non-inferiority, this study tested for superiority. Participants were at least 50 years of age with T2D and either previous cardiovascular events or cardiovascular risk factors. The study included a run-in period for 3 weeks to improve compliance. Participants were then randomly assigned to dulaglutide 1.5 mg or volume-matched placebo. The primary outcome was the first occurrence of any of the following: non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes or unknown causes.

A total of 9901 patients were enrolled; average baseline HgA1c was 7.2% and median follow-up was 5.4 years. Of all participants, 31.5% had previous cardiovascular disease. Participants in the dulaglutide group took the study drug 82.2% of the time from randomisation to either the primary outcome event or final follow-up. The primary cardiovascular composite outcome occurred in 12% of participants in the dulaglutide group compared with 13.4% in the placebo group, which was significant ($p=0.026$) (table 2). Of the secondary analysis, non-fatal stroke was also significantly lower in the dulaglutide group compared with placebo (2.7% vs 3.5%, $p=0.017$). Significantly fewer renal outcomes were found with dulaglutide compared with control (17.1% vs 19.6%, $p=0.0004$). There were no difference in eye outcomes, with an incidence of 1.9% in the dulaglutide group compared with 1.5% in the placebo group ($p=0.16$). There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This study was markedly different from the previous CVOTs. It was the longest trial with the lowest risk population, with only 32% of participants with underlying cardiovascular disease and the lowest baseline HgA1c. Although 25% of participants were not taking the study medication at the final visit, as mentioned above, participants did take the study medication for 82% of the follow-up time.

Oral semaglutide: PIONEER 6

The most recent CVOT is 'Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes', published in 2019.²³ Participants were 50 years of age or older with established cardiovascular disease or chronic kidney disease, or 60 years of age or older with cardiovascular risk factors. Patients were randomly assigned to either 14 mg once daily oral semaglutide or placebo. The primary outcome was the time from randomisation to the first occurrence of one of the following: death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

A total of 3183 patients were enrolled with median time of 15.9 months in the trial. Of these patients, 84.7% had established cardiovascular disease or chronic kidney disease, and average baseline HgA1c was 8.2%. Also, 84.7% of patients completed the trial with semaglutide. The primary composite outcome occurred in 3.8% of patients receiving oral semaglutide compared with 4.8% receiving placebo, which was not significant ($p=0.17$) (table 2). There was no difference in the rate of serious adverse events, severe hypoglycaemia, pancreatitis, pancreatic neoplasms or medullary thyroid carcinoma.

This trial was the shortest duration compared with all others (table 2) and therefore had the lowest event rates compared with other trials as it was a non-inferiority trial. Although this trial did not show significant cardiovascular benefit, the HR was very similar to injectable semaglutide (HR 0.79 vs 0.74). Given the finding of increased retinopathy events in SUSTAIN-6 with injectable semaglutide, participants with proliferative retinopathy or maculopathy were excluded, which may affect the generalisability of this study.

DISCUSSION

Composite cardiovascular outcomes

To date, there have been seven GLP-1 RA CVOTs as previously outlined. Of these, all have shown non-inferiority, and liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide have shown significant reductions in composite cardiovascular outcomes. Lixisenatide had the highest risk population, with 100% of participants having had an acute coronary event in the past 180 days, and had similar incidence of the primary composite outcome around 13%, similar to the other higher risk CVOTs, but interestingly did not find a significant difference in the primary outcome.¹⁷ There is some thought that the short half-life of lixisenatide compared with the other medications (table 1) may contribute to its lack of cardiovascular benefits. The EXSCEL study also found no significant difference in cardiovascular outcomes with once-weekly exenatide²⁰; however, it should be noted that the EXSCEL study had no run-in period to improve adherence to the medication regimen, and therefore the discontinuation rate was higher, which could have attenuated the significance. Overall, the EXSCEL study also had slightly shorter duration and lower HgA1c, although given the incidence of cardiovascular events was similar to other studies, this should not have affected the outcome.

Microvascular outcomes

Many of the CVOTs found favourable renal outcomes. In the LEADER trial, there were significantly fewer nephropathy events in the liraglutide group compared with placebo,¹⁸ and similarly, in the SUSTAIN-6 trial there were significantly fewer new or worsening nephropathy events using semaglutide compared with placebo.¹⁹ The REWIND trial also showed significantly fewer adverse renal outcomes in the dulaglutide group compared with placebo.²² The ELIXA trial had a non-significant reduction in percentage change in urinary albumin-to-creatinine ratio with lixisenatide compared with placebo.¹⁷ Harmony (albiglutide),²¹ EXSCEL (once-weekly exenatide)²⁰ and PIONEER 6 (oral semaglutide)²³ did not assess renal outcomes. SUSTAIN-6 showed significantly more diabetic retinopathy with semaglutide compared with control, a finding that was most evident early on, causing the examiners to hypothesise perhaps this was related to a rapid reduction in HgA1c in patients with pre-existing retinopathy.¹⁹ The LEADER study also had a slightly higher rate of retinopathy in the liraglutide group, although this was not significant in their study,¹⁸ which was a similar finding to that of the REWIND trial where there was slightly high incidence of eye outcomes in the dulaglutide group that was not significant.²² ELIXA, EXSCEL, Harmony and PIONEER 6 trials did not evaluate for retinopathy.

Impact on current guidelines

As these CVOTs have emerged, we have seen a shift in the guidelines for treatment of T2D. In the 2017 Standards of Medical Care in Diabetes published by the ADA, there continued to be

Main messages

- ▶ Certain glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have shown benefit compared with placebo in decreasing the risk of composite cardiovascular outcomes in patients with type 2 diabetes (T2D).
- ▶ Current guidelines have changed to recommend GLP-1 RA as the preferred therapy after metformin in patients with T2D with established cardiovascular disease.
- ▶ There are ongoing trials of GLP-1 RAs to further understand the cardiovascular benefit of these medications and the efficacy of an oral preparation.

Self-assessment questions

1. Which of the following statements are true regarding current GLP-1 RAs?
 - A. Liraglutide is a once weekly injection
 - B. Lixisenatide has the shortest half-life out of all GLP-1 RA
 - C. Oral semaglutide is not yet available
 - D. Dulaglutide dosing must be adjusted for renal dysfunction
2. True or false: the following medications have shown cardiovascular benefit compared with placebo:
 - A. Lixisenatide
 - B. Liraglutide
 - C. Subcutaneous semaglutide
 - D. Once-weekly exenatide
 - E. Albiglutide
 - F. Dulaglutide
 - G. Oral semaglutide
3. Which of the following statements are true regarding the hormone GLP-1?
 - A. It is a hormone released from the GI tract that enhances insulin secretion, so can lead to hypoglycaemia, but also delays gastric emptying and increases satiety, which can help with weight loss
 - B. It is a hormone released from the GI tract that enhances insulin secretion in a glucose dependent manner, so has a low risk for hypoglycaemia, and also delays gastric emptying and increases satiety, which can help with weight loss
 - C. It is a hormone released from the GI tract that delays gastric emptying and increases satiety, which in turn lowers blood sugar values, but has no effect on insulin secretion
4. Which of the following statements is true for a patient with a GFR of 48?
 - A. She is not a candidate for treatment with a GLP-1 RA because of her GFR
 - B. She can be safely started on a GLP-1 RA although her renal function needs to be monitored as it may slightly worsen
 - C. She can be safely started on a GLP-1 RA without concern for worsening renal dysfunction
5. If a patient is on metformin alone and has an HgA1c is 9.1% along with a history of a myocardial infarction, which of the following is the best treatment option for this patient?
 - A. Once daily glargine
 - B. Dulaglutide
 - C. Glipizide
 - D. Sitagliptin

broad recommendations to start with metformin monotherapy and advance to dual therapy with metformin plus one of any of the available non-insulin medications, leaving this decision up to the provider and patient.²⁴ This recommendation changed rather drastically in the next 2 years, with the 2019 ADA guidelines suggesting that the choice of add-on therapy be based on whether the patient has established cardiovascular disease or chronic kidney disease.¹⁶ According to these new guidelines, should cardiovascular disease predominate, the first add-on therapy to metformin should be either a GLP-1 RA or SGLT2 inhibitor with established cardiovascular benefit. This is important, as not all GLP-1 RAs have shown cardiovascular benefit as outlined in this paper. While oral semaglutide is an enticing option for patients who are needle-averse, this agent is not a preferred GLP-1 RA for patients with established cardiovascular disease given it has not shown cardiovascular benefit. Additionally, the most recent guidelines also suggest that a GLP-1 RA should be the first injectable medication for most before the addition of insulin. The European Society of Cardiology has even updated their 2019 guidelines to suggest GLP-1 RA or SGLT-2 inhibitors be considered as first-line therapy for T2D patients with known cardiovascular disease or those at high risk, even before the use of metformin.²⁵

Future considerations

While these CVOTs have provided excitement regarding cardiovascular protection in high-risk patients with T2D, there is still much more to be learnt about these medications. The patients in these studies were high-risk patients, most with established cardiovascular disease. The REWIND trial was unique in that most participants did not have previous cardiovascular disease, yet it still showed a significant reduction in composite cardiovascular outcomes,²² which questions whether GLP-1 RAs may have benefit not only for secondary cardiovascular prevention but also primary prevention. Additionally, we have seen the first CVOT for an oral GLP-1 RA, semaglutide, in the PIONEER 6 trial.²³ While it did confirm non-inferiority, it did not show cardiovascular benefit; however, this study was a shorter duration and a smaller study compared with other trials so fewer overall events were observed. Given the HR was similar to the SUSTAIN-6 (subcutaneous semaglutide), which did find significant cardiovascular benefit, Novo Nordisk is doing a larger CVOT with oral semaglutide called 'A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes' (SOUL), which is currently in trial phase III (ClinicalTrials.gov Identifier NCT03914326).²⁶ This drug has previously been unavailable although was recently FDA approved in September 2019.²⁷

CONCLUSION

GLP-1 RAs have emerged as an important class of medications to consider in the treatment of patients with T2D. Liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide have all shown significant reductions in composite cardiovascular

Current research questions

- ▶ Do GLP-1 RAs have a role in primary prevention of cardiovascular disease for patients with T2D?
- ▶ Will oral semaglutide show cardiovascular benefit similar to subcutaneous semaglutide?
- ▶ Do GLP-1 RAs have a role in cardiovascular protection in patients without T2D?

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outcomes, whereas lixisenatide, weekly exenatide and oral semaglutide have shown non-inferiority but have failed to show superiority. These findings have since transformed current guidelines, which now suggest considering a GLP-1 RA as the first additional medication after metformin in patients with established cardiovascular disease.

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Answers

1. A (False), B (True), C (False), D (False)
2. A (False), B (True), C (True), D (False), E (True), F (True), G (False)
3. A (False), B (True), C (False)
4. A (False), B (False), C (True)
5. A (False), B (True), C (False), D (False)