REVIEW ARTICLE

A review of glucagon-like peptide-1 receptor agonists and their effects on lowering postprandial plasma glucose and cardiovascular outcomes in the treatment of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular (CV) comorbidities, with CV disease being the most common cause of death in adults with T2DM. Although glucocentric therapies may improve glycaemic control (as determined by glycated haemoglobin levels), evidence suggests that this approach alone has limited beneficial effects on CV outcomes relative to improvements in lipid and blood pressure control. This may be explained in part by the fact that current antidiabetic treatment regimens primarily address overall glycaemia and/or fasting plasma glucose, but not the postprandial plasma glucose (PPG) excursions that have a fundamental causative role in increasing CV risk. This literature review evaluates the relationship between PPG and the risk of CV disease, discusses the treatment of T2DM with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and examines the associated CV outcomes. The literature analysis suggests that exaggerated PPG excursions are a risk factor for CV disease due to their adverse pathophysiologic effects on the vasculature, resulting in increased all-cause and CV-related mortality. Although GLP-1 RAs are well established in the current T2DM treatment paradigm, a subgroup of these compounds have a particularly pronounced, persistent and short-lived effect on gastric emptying and, hence, lower PPG substantially. However, current long-term data on CV outcomes with GLP-1 RAs, are contradictory, with both beneficial and adverse effects having been reported. This review explores the opportunity to direct treatment towards controlling PPG excursions, thereby improving not only overall glycaemic control but also CV outcomes.

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular (CV) disease, with adults with T2DM two to four times more likely to succumb to CV disease or a cerebrovascular event (stroke or a transient ischaemic episode) than individuals with normal glucose tolerance.[1,2] CV disease remains the most common cause of death among adults with T2DM,[2] and the concurrence of CV disease in patients with T2DM results in a poorer prognosis compared with individuals with CV disease alone.[2] Hence, a better understanding of the pathophysiology of vascular changes that underlie this relationship and how best to address them is likely to improve outcomes.

Several large studies have evaluated the relationship between glycaemic control with different treatment regimens and CV disease in persons with T2DM. The 10-year follow-up to the United Kingdom Prospective Diabetes Study (UKPDS) found that intensive treatment of T2DM with sulphonylurea, insulin or metformin lowered the patient's risk of myocardial infarction (MI) as well as the risks of diabetes-related death and all-cause mortality vs conventional therapy (dietary restrictions).[3,4] Individually, most other studies have shown a limited ability of current glucocentric therapies to have a discernible and favourable impact on CV disease.[5-10] However, a meta-analysis of data from the UKPDS, combined with those of three other large randomized studies,[11] found an overall 9% reduction in the risk of major CV events, mostly due to a 15% reduction in MI risk, for more- vs less-intensive glucose-control treatment regimens. Furthermore, there was a trend towards reduction in CV disease in individuals without previously reported CV events. Another systematic review of these same studies found that intensive vs conventional glucose control reduced the risk of certain CV outcomes, largely non-fatal MI, but not the risk of CV death or all-

cause mortality.[12] Similarly, a separate meta-analysis of data from these same four studies plus one other showed that intensive vs standard glycaemic control significantly reduced coronary events, but again with no significant effect on all-cause mortality. Of note, although these analyses demonstrated that intensive glucose therapy and the resulting improved glycaemic control may reduce the risk of CV disease, hyperglycaemia is a weaker risk factor for CV disease than cholesterol or blood pressure. Hence, the relative impact of reducing hyperglycaemia on CV outcomes is less than the adequate control of these other concurrent risk factors.[13] Nevertheless, many studies have implied that postprandial plasma glucose (PPG) is a powerful and independent risk factor for CV disease,[14] with the development of atherosclerosis having been described much earlier in time as a postprandial phenomenon.[15] Glycaemic control is assessed predominantly using three measurements: primarily glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG), and rarely PPG. Considering that most individuals spend the majority of the day in the postprandial and postabsorptive states (approximately 21 h per day) rather than the fasting state (3 h per day, at the end of the night),[16] the predominance of the PPG state within the daily metabolic cycle makes it an important target for the improvement of overall glycaemic control.

The current T2DM treatment paradigm comprises various drug classes and allows for individualization of therapy to control FPG and PPG based on patients' needs, disease characteristics and preferences.[17] As part of this paradigm, one class of injectable therapy is the glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Since the approval of the first of these compounds in 2006, these agents have enabled further tailoring of treatment to each patient.[18]

The potential relationship between amplified PPG and CV disease has been a focus of research in T2DM for a number of years, and interventional trials have gone one step further by trying to control PPG and, as a result, reduce the risk of CV events and slow T2DM progression. The present review aims to evaluate the relationship between PPG and CV risk, and discuss the effects of treatment with the GLP-1 RAs, which appear to reduce CV risk in persons with T2DM. The sodium-glucose cotransporter-2 (SGLT-2) inhibitors, particularly empagliflozin, also appear to lower the CV risk in patients with T2DM.[19,20] In contrast, the dipeptidyl peptidase-4 (DPP-4) inhibitors[21] and insulin therapy[22] do not affect the risk of CV disease in this population. While the CV effects of all of these drug classes warrant detailed discussion, the present review will focus on the GLP-1 RAs.

2 | CELLULAR AND VASCULAR EFFECTS OF ELEVATED PPG LEVELS

In vitro studies have shown that frequent elevations in glucose levels result in detrimental effects at the cellular level. High glucose levels for 2 h in isolated hearts, and in cultured endothelial cells, induced apoptosis and the formation of nitrotyrosine, a marker of oxidative stress that is common in a number of pathologic conditions.[23,24] Some studies have also shown that intermittent or fluctuating exaggerated PPG (defined as rising to above 7.8 mmol/L [140 mg/dL] and/or not returning to preprandial levels within 2–3 h[25]) may be worse than persistent hyperglycaemia.[26] For example, oscillating high glucose levels when compared with stable hyperglycaemia generates more nitrotyrosine and adhesion molecules and induces inflammatory cytokines *in vitro* using cultured human endothelial cells.[26] Fluctuating glucose levels also cause enhanced apoptosis in cultured endothelial cells[27] and increased mitogenicity in cultured human tubulo-interstitial cells.[28]

This impact of oscillating glucose concentrations at the cellular level translates to changes in vasculature and haemodynamic parameters. The degree of glycaemic variability has been shown to be positively related to the levels of oxidative stress markers in patients with T2DM.[29] Increased glycaemic variability also results in endothelial dysfunction with increased levels of nitrotyrosine in persons with and without T2DM,[30,31] reflecting findings from earlier *in vitro* studies.[23,24]

In response to acute hyperglycaemia, gene expression relating to free radical scavenging (detoxification) is downregulated in human skeletal muscle and adipose tissue.[32] A study of healthy male volunteers aimed to mimic the blood glycaemic parameters of poorly controlled patients with T2DM, and demonstrated that acute hyperglycaemia released free radicals, altered baroreflex activity and increased blood pressure and heart rate.[33] Considered together, these observations support the hypothesis that oxidative stress is a major pathophysiologic mechanism responsible for the development of CV disease in patients with T2DM.

In addition, acute hyperglycaemia in healthy volunteers results in activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB),[34] a protein complex involved in stress responses that is linked to cancer and inflammatory diseases. Several other studies involving persons with diabetes have shown that hyperglycaemia can activate the transcription of NF-κB-regulated inflammatory genes.[35]

In a cross-sectional study of 232 Japanese patients with T2DM, exaggerated PPG excursions were independently correlated with the presence of microangiopathy in the form of diabetic retinopathy and neuropathy.[36] Moreover, development and progression of macrovascular disease and atherosclerosis and, indeed, the 2-h PPG level, have been found to be a significant determinant of carotid

intima-media thickness (CIMT; a measure of atherosclerosis) and shown to be more closely correlated with CIMT than FPG in patients with T2DM and in subjects with normal glucose tolerance.[37] Exaggerated PPG excursions reportedly also decrease vasodilation,[38] resulting in an increase in the sheer force on the vascular endothelium due to reduced blood flow and increased blood pressure.

3 | EXAGGERATED PPG: AN INDEPENDENT RISK FACTOR FOR CV DISEASE AND ALL-CAUSE AND CV-RELATED MORTALITY

Endothelial dysfunction (including reduced vasodilation) and increased oxidative stress predict CV events in patients with documented CV disease.[39] Table 1 summarizes the findings of several observational studies that demonstrated the association between PPG and the development of CV disease in non-diabetic subjects and patients with T2DM. Moreover, these studies have indicated that a high PPG level is also an independent predictor of all-cause mortality and death due to CV disease. This finding appears to be consistent across both sexes and across multiple races.

4 | POTENTIAL FOR REDUCING CV EVENTS BY CONTROLLING PPG EXCURSIONS

Despite the evidence for an association between PPG and CV risk, reports on the possible effects of treatment that lower PPG on CV outcomes are inconclusive and conflicting. In subjects with impaired glucose tolerance, treatment with acarbose slowed the progression of CIMT reduction compared with placebo.[40] Furthermore, treatment with meglitinides, a class of short-acting oral antidiabetics that increases insulin secretion in a similar manner to sulphonylureas and addresses mainly PPG

control,[41,42] caused regression of CIMT. All together, these and other data indicate that addressing PPG excursions may have a protective effect against CV disease.[40,43,44] In support of this, postchallenge plasma glucose and spikes have been shown to be more strongly associated with CIMT than FPG and HbA1c.[45]

However, results of interventional studies that have attempted to control PPG utilizing different therapeutic strategies to improve CV outcomes have been inconsistent. On the one hand, two studies, the STOP-NIDDM trial and the MEta-analysis of Risk Improvement under Acarbose (MERIA) meta-analysis, showed that administration of acarbose to address PPG excursions in patients with T2DM and in subjects with impaired glucose tolerance significantly reduced the risk of CV events, including MI.[46] Furthermore, a study of Japanese patients with T2DM revealed that thrice-daily bolus insulin resulted in significantly ($p < 0.05$) slower progression of diabetic microvascular complications compared with a basal insulin regimen.[47]

On the other hand, the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, a 5-year randomized, placebo-controlled trial of nateglinide, a drug belonging to the aforementioned meglitinides class, in subjects with impaired glucose tolerance and evident CV disease and/or the presence of CV risk factors, reported that active treatment did not reduce CV and diabetes risk.[48] These results may be explained by the fact that in this trial nateglinide seems to have been inefficient and unable to improve glucose tolerance. The Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART2D) study investigated the use of basal or thrice-daily bolus insulin to control FPG or PPG, respectively, in patients with T2DM who had experienced an acute MI.[49] As PPG excursions were improved in patients treated with prandial insulin compared

with those receiving basal insulin only, and total glucose exposure was similarly improved in both arms,[49] one would expect the incidence of CV events to have been lower in the prandial vs basal insulin group. However, the risk of CV events was not reduced in either treatment group and, as a result, the study was halted prematurely.[49] A subsequent *post hoc* analysis of this study did show a beneficial effect of reducing PPG on CV risk in older people.[50] A feasible explanation for the lack of difference between the two treatment groups in the original HEART2D study may be the fact that both groups were treated with insulin, with insulin itself exerting a powerful inhibitory effect on activation of oxidative stress.[51,52]

5 | THE ROLE OF GLP-1 RAS IN THE CONTROL OF PPG

In recent years, incretin-based therapies have been introduced in the management of T2DM. Two distinct drug classes are currently approved: GLP-1 RAs and DPP-4 inhibitors. GLP-1 RAs mimic the actions of, and are more resistant to, degradation than native GLP-1, while DPP-4 inhibitors work by inhibiting the degradation of native GLP-1. Members of both of the incretin group of preparations have been extensively shown to improve glycaemic control.[53] Based on the pharmacodynamic and pharmacokinetic differences between the GLP-1 RAs, they can be divided into two main groups according to their predominant impact on either PPG, i.e. prandial (short acting), or FPG, i.e. non-prandial (long acting). Currently, a total of six GLP-1 RAs has been approved for the treatment of T2DM: two prandial GLP-1 RAs (exenatide twice daily and lixisenatide once daily) and four long-acting preparations (liraglutide once daily, albiglutide once weekly, dulaglutide once weekly, exenatide long-acting release [once daily]). A summary of the differences between the two

groups in terms of their mechanisms of action and their precise effects on glycaemic control is shown in Table 2.

A recent head-to-head comparison[54] assessed the effects on PPG and gastric emptying of two GLP-1 RAs, short-acting lixisenatide and long-acting liraglutide. As expected, based on previous reports that the predominant effect of lixisenatide is to delay gastric emptying, leading to reduced glucose reabsorption and subsequent reductions in PPG,[55,56] lixisenatide achieved greater reductions than liraglutide in both area under the curve $PPG_{0030–0430\ h}$ and gastric emptying ($p < 0.001$ for both, for lixisenatide vs liraglutide). Surprisingly, FPG was unchanged for both treatments. This study also evaluated 24-h heart rate, and showed differences between the two short- and long-acting agents.[54]

6 | ACCELERATED HEART RATE WITH GLP-1 RAS AND ASSOCIATED RISK

Current literature suggests that an increase in heart rate of 10 bpm leads to at least a 20% higher risk of cardiac death, and that this elevated CV risk is similar to that associated with a 10 mmHg increase in systolic blood pressure.[57] A large prospective cohort study has shown that an elevated resting heart rate (RHR) is a strong risk factor for the development of fatal MI; compared with a RHR of <60 bpm, a RHR of >90 bpm is associated with a two- and threefold higher risk of CV death in men and women, respectively.[58] Also, in a study involving patients with T2DM with a high RHR, there was a greater incidence or progression of nephropathy and retinopathy,[59] and an increased risk of all-cause mortality, CV death and major CV outcomes.[60]

As noted above, published data indicate that GLP-1 RAs can influence heart rate, although the extent of this increase varies between medications. A recent

analysis assessing the impact of lixisenatide, exenatide, liraglutide, albiglutide, exenatide long-acting release and dulaglutide on heart rate showed that, in patients with T2DM, prandial GLP-1 RAs led to a modest and transient increase in mean 24-h heart rate, whereas the long-acting GLP-1 RAs caused a more profound increase.[61] When patients with T2DM were further assessed using 24-h ambulatory heart rate monitoring, 8 weeks of treatment with liraglutide (1.2 or 1.8 mg) resulted in a clinically significant increase in 24-h mean heart rate of 9 bpm ($p < 0.0001$ vs baseline) compared with an increase of 3 bpm with lixisenatide 20 μg.[54] Moreover, the increase in heart rate with liraglutide was predominantly at night, abolishing the normal circadian rhythm in heart rate, which is reduced overnight. In a manner similar to lixisenatide, exenatide twice daily resulted in an insignificant 2 bpm increase in 24-h mean heart rate in a 12-week interventional study, and also maintained the natural circadian rhythm in heart rate.[62] Hence, some evidence suggests that any potentially adverse increases in heart rate appear to be limited to the long-acting GLP-1 RAs. The precise mechanism by which these drugs affect heart rate is unknown, although a study employing a murine model found that the GLP-1 receptor is central in the control of heart rate.[63]

7 | CV OUTCOMES WITH GLP-1 RAS

As detailed in section 4 above, some studies[40-47] demonstrate a link between high PPG levels and CV outcomes, and show that controlling PPG can have CV benefits, while other studies[48,49] are contradictory. Should such an association be confirmed, it seems plausible that GLP-1 RAs may have CV benefits, especially the short-acting preparations. It has been suggested that lixisenatide may have potential cardio-protective effects as, in isolated murine hearts subjected to acute ischaemia and

reperfusion, lixisenatide reduced infarct size and improved cardiac function.[64] Furthermore, in the Phase III GetGoal clinical trial programme for lixisenatide, improvements in hypertension were also reported for some patients in the lixisenatide treatment arms.[65] As hypertension is a strong risk factor for CV disease, lowering hypertension rates associated with hyperglycemia in general,[33] and elevated PPG in particular,[38] may contribute indirectly to the reduction of overall CV risk by GLP-1 RAs.

Similarly, exenatide may also have CV benefits. In pigs treated with either exenatide or saline, exenatide reduced MI size and prevented deterioration of systolic and diastolic cardiac function (including systolic wall thickening and myocardial stiffness).[66] Similarly, both native exendin-4[67-69] and an exenatide analogue[70] have been shown to have direct beneficial effects on cardiac function in murine models, including preservation of myocardial performance and protection against cardiac remodelling, suggesting that GLP-1 RAs have cardioprotective effects. GLP-1 RAs have demonstrated their ability to preserve or improve myocardial function during recovery following acute myocardial ischaemia. Suggested mechanisms for this benefit include attenuation of adverse cardiac remodelling (interstitial fibrosis and cardiac hypertrophy) mediated via reduced oxidative stress-induced injury,[67] improved metabolic, blood flow or neural transmission[71] and/or a reduced inflammatory and extracellular matrix response.[68,69] Moreover, in patients with ST-segment elevation MI, adjunctive exenatide to primary coronary intervention was associated with a reduction in infarct size and improvement in subclinical left ventricular function.[72] Contrarily, the FLuctuATion reduction with inSUlin and Glp-1 Added together (FLAT-SUGAR) trial, assessing glucose variability in a 26-week randomized comparison of basal insulin plus twice-

daily exenatide vs basal-bolus insulin in patients with T2DM at high CV risk, did not show any CV benefits of exenatide.[73] Although patients receiving basal insulin-exenatide treatment presented with reduced glucose variability, lower body weight, and a reduction in the levels of alanine aminotransferase and serum amyloid, while also maintaining equivalent HbA1c levels compared with those receiving basal-bolus insulin treatment, there was no statistically significant improvement in other CV risk biomarkers. Surprisingly, levels of urinary 8-iso PGF2α (a reliable biomarker of activation of oxidative stress) were improved markedly in the basal-bolus insulin treatment group. This unexpected result can be explained by the fact that patients in both treatment arms were treated with insulin, and that, as mentioned previously, exogeneous insulin exerts an inhibitory effect on oxidative stress.[52,74] Of note, positive CV effects were observed in the recent DURATION-8 trial, which assessed the efficacy and safety of co-initiation of exenatide and the SGLT-2 inhibitor dapagliflozin vs exenatide or dapagliflozin alone in patients with T2DM inadequately controlled on metformin. The combination of exenatide with dapagliflozin significantly improved CV risk factors (e.g. reduction in systolic blood pressure) compared with either drug alone.[75]

Long-acting GLP-1 RAs in animal studies have also demonstrated CV benefits. With liraglutide twice daily for 7 days and following the induction of MI, survival was significantly higher in liraglutide-treated mice vs those injected with saline.[76] Furthermore, liraglutide was also seen to reduce cardiac rupture, infarct size and improved cardiac output.[76] However, the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study showed that liraglutide vs placebo treatment was not associated with improved clinical stability following hospitalization in subjects

with advanced heart failure and reduced left ventricular ejection fraction both with and without diabetes.[77]

Since 2008, regulatory agencies require that all therapies for diabetes are assessed in a CV outcomes trial (CVOT) to ensure CV safety in order to grant and sustain approval.[78] Currently, several CVOTs are ongoing for already approved GLP-1 RAs, including Exenatide Study of Cardiovascular Event Lowering (EXSCEL) for exenatide long-acting release, Researching CV Events with a Weekly Incretin in Diabetes (REWIND) for dulaglutide, and HARMONY Outcomes for albiglutide, and are due to be completed in 2018/19 (Table 3). The recently completed SUSTAIN™-6 CVOT for semaglutide, a GLP-1 analogue currently in development for treating T2DM, showed that the primary composite endpoint (first occurrence of CV death, non-fatal MI or non-fatal stroke) occurred in 6.6% of patients receiving semaglutide vs 8.9% in the placebo group (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.58, 0.95; $p < 0.001$ for non-inferiority).[79]

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial assessed CV outcomes in patients with T2DM and acute coronary syndrome being treated with lixisenatide[80,81] and was completed in February 2015. A total of 6068 patients were randomized and followed for a median of 25 months. A primary endpoint event (first occurrence of either death from CV causes, non-fatal MI, non-fatal stroke or hospitalization for unstable angina) occurred in 13.4% of patients on lixisenatide vs 13.2% in the placebo group (HR 1.02; 95% CI 0.89, 1.17). This showed that lixisenatide was non-inferior to placebo ($p < 0.001$) but was not superior ($p = 0.81$). There were no differences in the rates of hospitalizations for heart failure or rate of death between the lixisenatide and placebo groups. Overall, the study showed that the addition of once-daily lixisenatide to the antidiabetic treatment

regimen did not significantly impact on the rate of major CV events or other related serious adverse events in patients with acute coronary syndrome. Therefore, noting the specifics of the patient population and the trial design, the results of ELIXA do not directly support the theory proposed elsewhere in this review regarding the potential to affect CV outcomes via control of PPG.

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, which was completed in December 2015, a total of 9340 people with T2DM were randomized to either liraglutide or placebo for 3.5–5 years (median follow-up of 3.8 years). The trial's primary endpoint was the composite outcome of the first occurrence of either CV death, non-fatal MI or non-fatal stroke, and occurred in 13.0% vs 14.9% of patients, respectively (HR 0.87; 95% CI 0.78, 0.97; $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority).[19] Furthermore, fewer patients died from CV causes (4.7% vs 6.0%, respectively; HR 0.78; 95% CI 0.66, 0.93; $p = 0.007$) and any cause (8.2% vs 9.6%, respectively; HR 0.85; 95% CI 0.74, 0.97; $p = 0.02$). Moreover, the rates of non-fatal MI, non-fatal stroke and hospitalization for heart failure were also non-significantly lower for liraglutide vs placebo. These results show that liraglutide can lower the risk of major adverse CV events compared with placebo. However, when analysing subgroups of patients stratified according to other antidiabetic therapies administered alongside liraglutide, the reduction in CV events was shown to be significant only in those patients receiving a single oral antidiabetic drug (OAD). This observation could potentially indicate that the significant reduction observed in the overall population may result mainly from the improvement seen in this particular subgroup, and that the beneficial effect of liraglutide on CV risk is less robust when patients are also treated with insulin and/or more than one OAD alongside liraglutide.

Although both of these CVOTs for these two currently available GLP-1 RAs were broadly similar in terms of their overall design, there are major differences between them. While in ELIXA only patients who were within 180 days post-acute coronary event and, hence, at the highest risk of a further CV event, were eligible for enrolment, in LEADER, patients with a pre-existing CV condition or with high risk for CV disease were included, corresponding to a more chronic CV risk status. Furthermore, ELIXA had a shorter median follow-up of 2.1 years compared with 3.8 years in LEADER, and also in ELIXA the primary composite endpoint comprised the first occurrence of four individual endpoints (death from CV causes, non-fatal MI, non-fatal stroke or hospitalization for unstable angina), while in LEADER only three endpoints were included (CV death, non-fatal MI or non-fatal stroke). Of note, other baseline characteristics including T2DM duration (mean [standard deviation] of 9.3 [8.3] years and 12.7 [8.0] years for ELIXA and LEADER, respectively) and HbA1c (mean [standard deviation] of 7.7 [1.3]% and 8.7 [1.5]% for ELIXA and LEADER, respectively) were also distinct between the two studies. As all of these differences between the two studies[80,82] may have impacted the overall results, comparisons between ELIXA and LEADER must be made with caution. Furthermore, the differences between the mechanisms of action of the short- and long-acting GLP-1 RAs should also be taken into account: Whereas the short-acting agent lixisenatide acts primarily by acutely lowering postprandial glucose excursions, the longer-acting agent liraglutide predominantly reduces the fasting glucose.[18] Thereby, differences in daily glycaemic variability between these two GLP-1 RAs may possibly have contributed to the different CV outcomes observed in the ELIXA and LEADER studies. Similarly, although not focused upon here, as semaglutide is an

investigational compound, any direct comparisons with SUSTAIN-6 CVOT[79] should also be made with care.

Owing to these recently published and ongoing CVOTs in diabetes, the Diabetes & Cardiovascular Disease (D&CVD) EASD Study Group has been established. In their first summit meeting in 2015, the group noted the importance of distinguishing between CVOTs with a primary focus on the CV safety of novel drugs vs those that truly aim to assess the potential reduction of CV events.[83] Notably, the former trial type is characterized by a study design that includes high-risk patients with T2DM, such as those included in ELIXA, and similar glycaemic control between active and standard treatment groups. Additionally, the group discussed whether the results observed to date are tranferable to wider patient groups. In brief, in cases of neutrality such as ELIXA, results could be extrapolated to patients with T2DM and a lower CV risk; however, in the event of CV reductions, as in LEADER, results should not be translated beyond the study group examined.[83]

While the clinical studies of CV outcomes in patients treated with GLP-1 RAs appear to demonstrate a cardioprotective function of these drugs, the precise mechanism behind this effect remains elusive. Aside from the possible link between glucose elevation and control, other factors may be involved. As the GLP-1 receptor is expressed widely throughout the body, including in the myocardium, the cardioprotective effects on GLP-1 RAs may, in part, result from direct action in the heart and through indirect actions involving GLP-1 signalling in vascular cells and other peripheral tissues.[71]

8 | CONCLUDING REMARKS

Our analysis of current literature suggests that poor glycaemic control and especially excessive glycaemic excursions predominantly after meals (PPG) may increase the risk of CV disease in patients with T2DM and individuals with normal glucose tolerance.[84-92] However, the relationship between postprandial glucose hyperglycaemia and CV outcomes is complex, with additional research needed to characterize this association further.

In order to achieve HbA1c targets in patients with T2DM, individualized treatment that controls both PPG and FPG may be the best option,[93] with antidiabetic medications that control PPG being of particular interest due to the role of PPG excursions in the pathophysiology of CV disease. In order to maintain a patient-centred, individualized approach to treatment, the respective distribution of postprandial and basal therapies should be modulated according to each patient's 24-h glycaemic profile. While this procedure is usually recommended for choosing the optimum pre-meal time at which boluses of rapid-acting insulin should be injected during the implementation of a basal-plus insulin regimen, we believe that it is useful for a similar system to be implemented for treatment regimens involving basal insulin plus a short-acting GLP-1 RA, such as lixisenatide.

As discussed, the approved GLP-1 RAs have varying effects; some specifically control PPG, others target FPG (Table 2). Hence, the use of prandial GLP-1 RAs in combination with therapies that control FPG may provide benefits owing to a greater likelihood of achieving HbA1c targets even in advanced T2DM. ELIXA, a CVOT assessing lixisenatide, has shown that lixisenatide does not pose a CV risk,[81] while data from LEADER suggest that liraglutide may have beneficial effects on the risk of CV events.[19] The lack of a detectable lowering of CV risk in ELIXA appears to

weaken the argument that CV benefits can be achieved through lowering PPG. However, in this study lixisenatide was administered only before breakfast, and while the PPG-lowering effect may have persisted to other meals (as has been demonstrated previously[94]), the predominant effect would have been after breakfast. This raises the question as to whether a CV benefit would be seen were a short-acting GLP-1 RA administered more than once daily. It is important to note that this is not a licensed regimen, but could be an interesting concept to explore in a clinical trial setting. While the completion of ongoing CVOTs will provide further insight on the risk/benefit of individualized treatment with GLP-1 analogues, a recent publication[95] has suggested that, based on results from completed CVOTs, which have not demonstrated a CV risk for the various compounds assessed, there is a need to reassess the Food and Drug Administration's requirement for a CVOT for every new antihyperglycaemic agent. The authors suggest that a more individualized approach may be justified.

In conclusion, exaggerated PPG excursions appear to have a fundamental causative role in the relationship between T2DM and increased CV risk. This finding presents an opportunity to direct treatment towards also controlling PPG excursions to improve both glycaemic control and also CV outcomes.

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Conflicts of interest

D. R. O. received honoraria from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi and Takeda for lectures and involvement in an advisory capacity. L. M. has nothing to declare. M. H. has served on advisory panels for Bristol-Myers Squibb, GlaxoSmithKline, Sanofi and Takeda; and on speaker's bureau for Bayer Health Care, Eli Lilly, GlaxoSmithKline, Roche, Sanofi and Takeda.

Author contributions

D. R. O. contributed to the design, writing and critical revision of the manuscript at all stages of development. L. M. contributed to the critical revision of the manuscript. M. H. contributed to the design and writing of the manuscript. All authors provided final approval of the manuscript and are accountable for its accuracy and intergrity.

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TABLE 1 Reported risk of CV events with PPG excursions in observational studies in either the general population or patients with T2DM

General population studies		
Study first author and citation	**Study type**	**Study findings**
de Vegt et al. (1999)[86]	Hoorn study: an 8-year follow-up of a population-based cohort of more than 2300 older (50–75 years) subjects	All-cause and CV mortality were predicted by increased 2-h PPG
Balkau et al. (1998)[84]	20-year follow-up to the Whitehall Study, the Paris Prospective Study and the Helsinki Policemen Study comprising >17,000 males	Men with higher 2-h PPG excursions had an increased risk of all-cause and CV mortality compared with individuals in lower percentiles of the 2-h PPG distribution
Lowe et al. (1997)[91]	Analysis of white (n = 11,554) and African–American (n = 666) men (35–64 years) in the Chicago Heart Association Detection Project in Industry Study	Relative risk of all-cause and CV mortality was increased in those subjects with asymptomatic post-load hyperglycaemia compared with those with normal post-load glucose levels

Donahue et al. (1987)[88]	Honolulu Heart Program: 12-year study of more than 8000 men aged 45–70 years of Japanese ancestry	Based on a subset of 6394 non-diabetic subjects, those with the most extreme PPG excursions 1 h after a 50 g glucose challenge had a significantly increased risk of fatal coronary disease compared with individuals with lower PPG excursions
Nakagami (2004)[92]	Analysis of five studies of a total of more than 6800 subjects of Japanese and Asian Indian origin	Elevated 2-h PPG increased the risk of all-cause and CV mortality

Patients with impaired glucose tolerance and T2DM		
Study first author and citation	**Study type**	**Study findings**
DECODE Study Group (1999)[87]	DECODE: a study of 13 prospective European cohort studies, including more than18,000 men and 7300 women with impaired glucose tolerance	Subjects with greater 2-h PPG excursions had an increased risk of death compared with individuals with less extreme PPG excursions

Chiasson et al. (2002)[96] Chiasson et al. (2003)[46]	STOP-NIDDM: a study of approximately 1400 subjects comparing acarbose vs placebo	Acarbose not only reduced the progression from impaired glucose tolerance to T2DM, but was also associated with a reduction in CV events
Coutinho et al. (1999)[97]	A meta-regression comprising almost 100,000 subjects	Increased 2-h PPG levels were associated with a greater risk of CV events in subjects with normal glucose tolerance and also individuals with glucose values within the diabetic range
Hanefeld et al. (1996)[89]	Diabetes Intervention Study: a prospective study of approximately 1100 patients with T2DM	Multivariate analysis revealed that PPG was an independent risk factor for death with subjects with PPG >10 mmol/L 1 h after breakfast having a 40% greater relative risk of MI than those with PPG ≤8 mmol/L
Cavalot et al. (2006)[85]	A 5-year follow-up study of 529 patients with T2DM	PPG but not FPG was found to be an independent risk factor for CV events, particularly in women

Jackson et al. (1992)[90]	The Islington Diabetes Survey: a study of 223 patients with T2DM	2-h PPG after an oral glucose tolerance test was a better predictor of CV disease (including angina, MI, or ischaemia) than HbA1c

CV, cardiovascular; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MI, myocardial infarction; PPG, postprandial plasma glucose; T2DM, type 2 diabetes mellitus.

TABLE 2 Comparison of prandial (short-) vs long-acting GLP-1 RAs[18]

Parameters	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide LAR Liraglutide
Half-life	2–5 h	12 h – several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric-emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

GLP-1 RA, glucagon-like peptide-1 receptor agonist; LAR, long-acting release.

TABLE 3 Currently ongoing CVOTs for GLP-1 RAs

Trial name (ClinicalTrials.gov Identifier)	Drug	Planned patient number	Expected completion date
EXSCEL (NCT01144338)	Exenatide	14,000	April 2018
ITCA 650 (NCT01455896)		4000	July 2018
REWIND (NCT01394952)	Dulaglutide	9622	July 2018
HARMONY Outcomes (NCT02465515)	Albiglutide	9400	May 2019

CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist.