Cardiovascular safety and GLP-1 receptor agonists

Abstract
Owing to the situation that exists following the rosiglitazone controversy aligned with the high cardiovascular risk profile that underlies type 2 diabetes mellitus, there is a requirement from the licensing agencies that new antidiabetic drugs must be shown not to increase cardiovascular risk during phase 3 development. This includes studying patients with high cardiovascular risk, who were previously excluded from phase 2 studies.

All of the currently available GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide) have satisfied these safety criteria, with the suggestion that there might be some cardiovascular benefit with this class. Large randomised controlled trials are ongoing to assess safety as well as potential benefit. The results of these randomised controlled trials will influence the long-term use of GLP-1 receptor agonists and their place in treatment guidelines.

Cardiovascular safety results
Prior to approval by the regulatory bodies, the CV safety of GLP-1 receptor agonists has been analysed in phase 2 and 3 trials. Although generally of short duration and subsequently with low numbers of CV events in both treated and untreated patients, these studies have been analysed together to assess CV safety, and will be discussed in the following paragraphs.

Exenatide
Exenatide was the first of the GLP-1 receptor agonists to be introduced and was approved firstly by the FDA.
in 2005 and by the EMA in 2006. The standard preparation is injected subcutaneously twice-daily, and a once-weekly preparation, exenatide LAR, has recently been introduced. The twice-daily formulation of exenatide was approved prior to the introduction of the more exacting safety demands, but data from the trial programme up to 2008 have now been published.

Ratner et al. conducted a meta-analysis of 12 studies in which patients receiving standard oral agents (thiazolidinedione, sulphonylurea, metformin alone or in combination) had been randomised to receive either exenatide twice-daily (n=2316) or a comparator agent, either placebo (n=971) or insulin (n=658). Baseline characteristics were similar between the two groups: subjects were aged between 18 and 75 years with HbA1c <11% (97mmol/mol), and received either exenatide (the majority receiving 10μg daily) or comparator for at least 12 weeks. CV events were reviewed retrospectively in accordance with normal clinical trial monitoring. The overall relative risk for primary major adverse CV events (MACE) was 0.7 (95% CI 0.38–1.31) and for secondary outcomes (MACE, arrhythmia and heart failure) was 0.69 (95% CI 0.46–1.03). There was no difference in blood pressure, heart rate or risk of development of renal impairment between the two groups.

In addition to information from the trial programme, Best et al. performed a ‘real world’ retrospective analysis of databases of medical insurance claims (Lifelink, USA) to examine the CV safety of exenatide. From an overall database of 37 million US medical insurance claims between 2005 and 2009, CV outcomes for 39,275 patients exposed to exenatide twice-daily (for at least 31 days) and 381,218 patients who had been exposed to other glucose-lowering drugs (HR 0.81; 95% CI 0.68–0.95; p=0.01), as were CV hospitalisation (HR 0.88; 95% CI 0.79–0.98; p=0.02) and all-cause hospitalisation (HR 0.94; 95% CI 0.91–0.97; p=0.001). At baseline, those exposed to exenatide had higher rates of hypertension, hyperlipidaemia, obesity and previous CV disease than those exposed to other glucose-lowering agents. Although the analysis was not able to fully analyse variables such as smoking and BMI, and assumed accuracy of reporting of CV disease, these data at least appear to confirm CV safety of exenatide in a ‘real world’ setting.

Liraglutide
Liraglutide, a once-daily injected GLP-1 receptor agonist, was first approved by the EMA in 2009 and by the FDA in 2010, and is licensed as monotherapy or in combination with other glucose-lowering drugs. To evaluate its CV safety, Marso et al. analysed all completed randomised phase 2 and 3 studies plus open-label extensions. Overall, the authors examined 15 studies, including 4257 patients exposed to liraglutide for 26–52 weeks, with or without other oral glucose lowering agents, and 2381 exposed to comparator agents, which included metformin, glimepiride, rosiglitazone, insulin or placebo. Patients with T2DM aged 18–80 years, with HbA1c 7–11% (53–97mmol/mol) and BMI of <45kg/m², but without a history of MI or uncontrolled hypertension within six months, were included. Major adverse CV events (MACE) were adjudicated post hoc by two study investigators who were blinded to treatment. The overall incidence rate for MACE was 0.73 (95% CI 0.38–1.41) for liraglutide versus comparator agents. Although this fulfils the FDA requirements for CV safety, it is difficult to draw conclusions from a meta-analysis of such a heterogeneous population.

Combined data
Monami et al. reported in 2011 on all the CV safety data available from studies of GLP-1 analogues. From 36 studies comparing GLP-1 analogues with either placebo or active comparator, the analysis was restricted to 20 studies in which there had been major CV events. Overall MACE data were analysed on 6490 patients on exenatide or liraglutide for at least 12 weeks and on 3995 patients who received either comparator agents or placebo. The total number of CV events was 65 (0.01%) in the GLP-1 group and 49 (0.01%) in the comparator group. Treatment with GLP-1 analogues was not associated with an increased risk of CV events (odds ratio for MACE for GLP-1 analogues on an intention to treat basis 0.74 [95% CI 0.5–1.08; p=0.12]). A significant reduction in CV events was observed in placebo-controlled trials, but not in drug studies comparing GLP-1 analogues with active comparators. There was no pattern indicating a difference in CV risk between exenatide and liraglutide.

Cardiovascular outcome trials
The results of CV safety analyses must be interpreted with caution, since the majority of studies analysed are of short duration, with low numbers of CV events, and additionally these were not primarily designed to examine CV safety. Moreover, the heterogeneity of the studies within the meta-analyses cannot be accurately quantified, since they have different comparator agents, are of different duration and have different methods to adjudicate CV endpoints. To address these deficiencies, and to fulfil regulatory body requirements, a number of CV outcome studies involving the GLP-1 receptor agonists are being undertaken, which will be reporting over the next few years.

Exenatide
Exenatide was approved by regulatory bodies before the 2006 FDA requirements for endpoint data, and as a result there have been no large-scale CV outcome trials conducted for standard twice-daily exenatide treatment. The EXCEL trial (Exenatide study of Cardiovascular Event Lowering) is a 5.5-year follow-up trial in which patients with T2DM...
are randomised to take exenatide 2mg once-weekly or placebo in addition to their normal diabetes medications. The study team aim to recruit 9500 patients with T2DM aged over 18 years and with HbA1c 7–10% (53–86mmol/mol). The primary outcome measure is time to first confirmed CV event in the primary composite CV endpoint (CV-related death, non-fatal MI, non-fatal stroke), while the secondary endpoints include time to first confirmed endpoint for each component of the primary composite endpoint, as well as all-cause death, and hospitalisation for acute coronary syndrome and heart failure. The study began in June 2010, and is expected to be completed in 2017.

**Liraglutide**

The LEADER study (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) is a five-year follow-up multi-centre study examining the CV effects of liraglutide. A total of 9341 subjects aged ≥50 years with HbA1c ≥7% (53mmol/mol) and concomitant vascular disease or chronic renal failure, or aged ≥60 years with vascular risk factors, are being allocated to receive liraglutide at a maximum dose of 1.8mg daily or placebo, in addition to their standard diabetes treatment. The primary outcome measure is time from randomisation to first occurrence of CV death, non-fatal MI, or non-fatal stroke. Secondary endpoints are an expanded CV composite outcome including coronary revascularisation, unstable angina, hospitalisation for chronic heart failure, as well as all-cause death. The study, which is recruiting at 147 sites worldwide, began in August 2010 and is expected to complete in 2016.

**Lixisenatide**

Lixisenatide is a new once-daily GLP-1 analogue which has recently been approved by the EMA and was submitted for review by the FDA in February 2013. The ELIXA trial (Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during treatment with Lixisenatide trial) is a CV outcomes study in which patients with T2DM and aged ≥50 years are being randomised after an acute coronary syndrome (ACS) event to take either lixisenatide once-daily or placebo, in addition to their other normal medications. The study, which aims to recruit 6000 patients, will follow up patients for a median of 91 weeks; patients will be excluded if they undergo coronary artery bypass grafting after their initial ACS event.

The primary outcome measure is time to first primary CV event – that is, CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina. Secondary outcomes also include hospitalisation for heart failure, and percentage change in the albumin:creatinine ratio. The study expects to be completed in May 2014.

**Dulaglutide**

REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) is a further study of CV outcomes with a new once-weekly incretin, dulaglutide, which is awaiting review by regulatory bodies. Patients with T2DM aged ≥50 years, with HbA1c ≤9.5% (80mmol/mol), with or without a history of vascular disease are being randomised to take either dulaglutide 1.5mg weekly or placebo. Patients will be followed up for an average of 6.5 years. The primary outcome event is time to first occurrence of CV death, non-fatal MI or stroke. Secondary outcome measures include development of microvascular disease, as well as all-cause mortality and hospitalisation for unstable angina or heart failure.

A comparison of cardiovascular outcome studies for GLP-1 receptor agonists is provided in Table 1.
Review

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Discussion
The reduction of CV morbidity and mortality is arguably the most important aim of the long-term treatment of T2DM. Despite the fact that the long-term CV safety of GLP-1 receptor agonists remains unknown, they have been widely prescribed for patients with T2DM since 2006 and are now established in national guidelines. While accepting the limitations of CV safety analyses, from the information available to date there appears to be no increase in major CV events associated with GLP-1 receptor agonists. The drugs are well tolerated in the majority of patients, and the introduction of long-acting versions allows for individualisation of therapy.

Several studies have suggested that GLP-1 analogues have beneficial effects on CV parameters, beyond their role in glucose lowering. It is known that GLP-1 receptor agonists lead to weight loss, and that improvement in glycemic control leads to improved endothelial function, but there are other less well understood mechanisms through which GLP-1 analogues may improve CV health. Activation of neural pathways leading to decreased sympathetic nervous system activation, and direct vasodilatory stimulation via GLP receptors may contribute to the lowering of blood pressure reported in preclinical studies. GLP-1 receptor agonists are also associated with improvements in lipid profile, as well as pro-inflammatory biomarkers such as highly sensitive C-reactive protein (hsCRP).

GLP-1 receptors are not just present in the pancreas, but may be present throughout the vasculature. In animal models of ischaemia-reperfusion injury, GLP-1 reduces infarct size, and prevents deterioration of left ventricular function. A few small, human studies have evaluated the cardiac effects of GLP-1 receptor agonists. One recent study reported that, in patients with acute MI, short-term infusion of exenatide improved myocardial salvage. In another recent study, Nathanson et al. reported that, in patients with T2DM and congestive heart failure, administration of intravenous exenatide was associated with improvement in cardiac index, as well as pulmonary capillary wedge pressure.

In contrast to these perceived beneficial effects on the CV system, GLP-1 analogues have been associated with a small but significant increase in heart rate, itself an independent risk factor for CV disease, as well as QTc prolongation on electrocardiography. Whether these concerns also relate to newer once-weekly GLP-1 analogues is as yet unknown.

It is clear, therefore, that the ongoing CV outcome trials which will begin reporting in 2014 will be of utmost importance in determining the place of GLP-1 analogues in prescribing algorithms, and in clarifying the risk:benefit ratio of this drug class.

Declaration of interests
DMC: none. RD has accepted speaker fees, participated in advisory boards and received educational support to attend conferences from Astra Zeneca/BMS, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, MSD, Novo Nordisk, and Takeda. MF has received payment for advisory boards and speaker fees from Astra Zeneca/BMS, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi.

References

Drug notes
Find out how non-diabetes drugs impact diabetes patients. Visit the Practical Diabetes website and click on drug notes
Bromocriptine
Bumetanide
Carbamazepine
Clofazimine
Dabigatran
Darbepoetin alfa
Diazoxide
Digoxin
Dipyridamole
Dronedarone
Duloxetine
Erythromycin
Labeletal
Lidocaine
Methyldopa
Metoclopramide
Omacor
Prasugrel
Quinidine sulphate
Ranolazine
Spironolactone
Testosterone
Torcetrapib

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