Cardiovascular safety and DPP-4 inhibitors

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Abstract
Following the rosiglitazone controversy 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 3 studies. All of the currently available dipeptidyl peptidase (DPP)-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin) 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 DPP-4 inhibitors and their place in treatment guidelines. Copyright © 2013 John Wiley & Sons.

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Key words
DPP-4 inhibitors; cardiovascular safety; cardiovascular outcomes

Introduction
DPP-4 inhibitors were first approved for use in 2006. As oral agents associated with an approximate 1% reduction in HbA1c, weight neutrality and a low risk of hypoglycaemia, they have proved to be a popular drug class for patients with type 2 diabetes mellitus (T2DM). They are typically prescribed as second- or third-line agents after metformin and sulphonylureas; they are available as combination products and are licensed for use as monotherapy in patients who have contraindications to other antidiabetic drugs.

In patients with T2DM, cardiovascular disease (CVD) remains the principal cause of morbidity and mortality; the 2011 Scottish Diabetes Survey reported that 10.2% of T2DM patients had a history of myocardial infarction.1 Despite this, the cardiovascular (CV) benefits of correcting hyperglycaemia in these patients are uncertain; results from the ACCORD, ADVANCE and VADT trials as well as experience with drugs such as tolbutamide and rosiglitazone have all contributed to this uncertainty.2–5 In view of this, regulatory bodies have issued guidance for the development of new drugs for T2DM. The European Medicines Agency (EMA) guidance, which came into place in November 2012, states that companies must provide more information on CV safety of new glucose-lowering drugs, and that they should ‘show at least neutral or beneficial effects on associated cardiovascular risk factors’.6 The US Food and Drug Administration (FDA) also introduced guidance for industry in December 2008. Overall, they recommended that any new drug must be shown not to result in an unacceptable increase in CV risk, that phase 2 and 3 studies should include high-risk subjects and be extended beyond six months, and that sponsors should rigorously collect pre-specified CV endpoint data adjudicated by independent endpoint committees.7 CV safety assessment must be performed both before and after approval of new diabetes therapies; before submission of a new drug application meta-analyses must exclude an 80% increase in the relative risk of adverse events, while post approval CV outcome studies, if required, should exclude a 50% increased risk associated with the new agent.

In this review we will focus on the cardiovascular safety of DPP-4 inhibitors; we will summarise the cardiovascular safety data that have been reported for these drugs, and will discuss ongoing cardiovascular outcome trials.

Cardiovascular safety results
Five DPP-4 inhibitors have to date been approved for the treatment of type 2 diabetes; sitagliptin was first released in 2006, vildagliptin in 2007, saxagliptin in 2009 and linagliptin in 2011. Alogliptin, produced by Takeda, is currently under review by regulatory authorities and is approved for use in Japan. All are
associated with a reduction of HbA1c of around 1%, have a weight neutral profile, can be used in combination with other glucose-lowering drugs, and are of roughly equivalent cost.

Prior to their release, each of the DPP-4 inhibitors underwent a series of CV safety analyses. In general, these included short-term (six-month) trials. Pooled analysis data have been presented in published meta-analyses, and are summarised in the following paragraphs.

**Sitagliptin**

Sitagliptin was the first of the DPP-4 inhibitors to gain regulatory body approval, firstly by the US FDA in 2006 and then by the EMA in 2007. In order to assess CV safety, Williams-Herman et al. performed a meta-analysis reviewing 19 studies in which patients with T2DM received either sitagliptin or a comparator agent. Patients were receiving sitagliptin 100mg/day either as monotherapy or in combination with other antidiabetic drugs. In all, 5,429 patients received sitagliptin, with 4,817 in the comparator group. At baseline, 11% of patients were known to have CVD, and 82% had additional CV risk factors other than T2DM. There were no significant differences in baseline characteristics between the two groups. Study duration ranged from 12–206 weeks. There was less hypoglycaemia in the sitagliptin group (with a between group difference of -6.7 incident events per 100 patient years), although in three of the studies patients in the comparator group received sulphonylureas, likely to be responsible for the majority of this effect. Incidence rates of pre-specified major adverse cardiovascular events (MACE) were not increased with sitagliptin, with 0.6 per 100 patient-years in the sitagliptin group and 0.9 in the non-exposed group, giving a between group difference of -0.3 (95% CI 0.7–0.1). There was no formal adjudication of CV events, while incidence rates of other adverse events were comparable between the two groups.

**Vildagliptin**

Vildagliptin was first approved in 2008 by the EMA, and although widely used in Europe it has not been FDA approved due to initial concerns about non-cardiovascular endpoints.

To assess the cardiovascular and cerebrovascular (CCV) safety of vildagliptin, Schweizer et al. summarised the results of 25 phase 3 studies, which were presented as a meta-analysis in 2010. Included in the analyses were 6,116 patients receiving the standard dose of vildagliptin 50mg twice daily, 1,993 patients receiving vildagliptin 50mg four times daily, and 6,061 receiving a comparator (placebo, sulphonylurea, metformin or thiazolidinedione). An independent CCV adjudication committee consisting of cardiologists and neurologists reviewed all events in a blinded fashion. Relative risk for CV events (a composite endpoint consisting of acute coronary syndrome [ACS], transient ischaemic attack, stroke and CCV death, but not heart failure) was 0.88 for vildagliptin 50mg four times daily vs comparator and 0.84 for vildagliptin 50mg twice daily vs comparator. A subsequent larger meta-analysis by the same company consisting of 38 phase 2 and 3 studies similarly found no significant difference in adverse events between those taking vildagliptin and comparator.

**Saxagliptin**

Saxagliptin was approved by both the FDA and EMA in 2009 and its CV safety data were summarised in a meta-analysis by Frederich and colleagues. Eight phase 2 and 3 randomised double-blinded controlled trials were included in the meta-analysis, in which 3,356 patients received saxagliptin (at doses ranging from 2.5–10mg/day) and 1,251 were receiving a comparator agent.

CV events (consisting of myocardial infarction [MI], stroke, revascularisation procedures and CV death) occurred in 61 patients; 1.1% of those on saxagliptin and 1.8% of those assigned to a comparator. The Cox estimated relative risk for CV events was 0.44 for saxagliptin vs comparators when using investigator reported information, and 0.43 when using blinded retrospective event adjudication by physicians serving as consultants to the sponsors.

**Linagliptin**

Linagliptin was approved by the FDA and EMA in 2011. In contrast to the other DPP-4 inhibitors, linagliptin is largely excreted via the biliary system and gut rather than the renal tract. To assess its safety, Johansen et al. examined eight phase 3 studies in which patients received either linagliptin or comparator (either placebo, glimepiride or the α-glucosidase inhibitor voglibose) for at least 12 weeks’ duration. A total of 3,319 patients had been prescribed the standard dose of 5mg once daily and 1,920 received a comparator. An endpoint committee consisting of cardiologists and neurologists adjudicated on all CV events. The primary endpoint was a composite of fatal and non-fatal stroke and MI, and admission to hospital for unstable angina. The overall hazard ratio (HR) for linagliptin for the primary endpoint was 0.34 vs placebo or comparator (95% CI 0.16–0.7), while the HRs for secondary endpoints ranged from 0.34–0.55 (95% CI 0.17–0.94). As with the other CV safety meta-analyses, these were short-term studies; none of the patients included had been on linagliptin for more than 1.7 years.

**Alogliptin**

Cardiovascular safety data for alogliptin were summarised by White et al. and presented in poster form at the 2010 American Diabetes Association meeting. Eight studies of up to 26 weeks’ duration comparing alogliptin (12.5 or 25mg daily) with placebo were analysed. All CV events were evaluated by an independent CV adjudication committee blinded to study and treatment. Major adverse CV events occurred in 0.28% of patients receiving alogliptin and 0.50% of patients receiving placebo. An overall HR for all CV events was 0.63 (95% CI 0.21–1.91); for patients with an elevated CV risk at baseline (two or more CV risk factors in addition to T2DM), the HR was 0.52 (95% CI 0.16–1.67).

Overall, these meta-analyses show that, at least in the short term, tolerability and safety data are similar between DPP-4 inhibitors.
and comparators. The results must be viewed with caution in that they include different comparator drugs and doses, different lengths of follow up, have different primary and secondary endpoints, and different methods of CV endpoint adjudication. CV event rates in both active and comparator groups were low, and as such the meta-analyses may not be sufficiently powered to accurately detect an imbalance between the two groups. (See Figure 1.)

**Cardiovascular outcome trials**

Given the limitations of the safety data described above, it is important that the long-term CV safety profiles of DPP-4 inhibitors are clarified. To fulfil regulatory body requirements and to address this uncertainty, manufacturers of each of the DPP-4 inhibitors apart from vildagliptin have therefore designed CV outcome trials. The outline of these studies, which will be reporting over the next few years, are summarised in the following paragraphs.

**Sitagliptin**

The TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial is a six-year double-blinded trial assessing the impact on CV outcomes of addition of sitagliptin or placebo to standard care.14 Over 14 000 patients with T2DM aged ≥50 years with established CVD are being randomised to take either sitagliptin 100mg/day or placebo, and will be followed up for a minimum of three years. Primary endpoints for the trial are CV death, non-fatal MI, non-fatal stroke, and hospitalisation for unstable angina. Secondary endpoints are a composite of CV death, non-fatal MI, or non-fatal stroke, all-cause mortality, HbA1c, time to initiation of the next oral agent or insulin, and medical resource utilisation. The study began recruitment in 2008, and the investigators expect to report results in 2014.

**Saxagliptin**

The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 study was designed to examine the long-term CV safety and efficacy of saxagliptin.15 Investigators are recruiting patients with T2DM and an HbA1c of between 6.5 and 12%, who have either a history of established CVD, or who have multiple risk factors for CVD. Approximately 16 500 patients are being randomised to receive either saxagliptin 5mg daily (2.5mg daily in those with an estimated glomerular filtration rate <50ml/min) or placebo. The primary endpoint of the study is the composite of CV death, non-fatal MI, or non-fatal ischaemic stroke. Secondary endpoints include the primary composite endpoint as well as hospitalisation for heart failure, coronary revascularisation, or unstable angina. The trial began recruiting in 2010, and results are expected to be reported in 2014.

**Linagliptin**

The CAROLINA (CARRdiOvascular Outcome Study of LINagliptin in Patients With Type 2 Diabetes) study is a head-to-head active comparator study in which patients with T2DM and suboptimal glycaemic control who are at high risk of CVD are being randomised to receive either linagliptin 5mg/day or the sulphonylurea gliclifiride up to 4mg/day.16 The primary endpoint is a composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for unstable angina. The secondary outcomes examine the proportion of patients on either medication who at the study end maintain glycaemic control without need for additional medications, and without unacceptable hypoglycaemia or weight gain. The study, which began recruitment in October 2010, aims to recruit over 6000 patients and expects to report its results in 2018.

**Alogliptin**

The EXAMINE (EXamination of CArdiovascular OutcoMes with AlogliptIN versus standard of care) study is recruiting over 5400 patients who are allocated either to alogliptin (6.25–25mg/day) or to placebo in addition to their standard treatment.17 In contrast to other outcome studies, the EXAMINE study is focusing exclusively on patients with T2DM who have had a recent ACS event, defined as either an acute MI or hospitalisation with unstable angina. The primary endpoint is a composite of CV death, non-fatal MI and non-fatal stroke, while secondary endpoints include urgent revascularisation for unstable angina, hospitalisation for heart failure, and stent thrombosis. The study began recruitment in 2009, and patients will be followed up for up to 4.5 years. Over 2300 ACS patients had been randomised as of June 2011.

A comparison of cardiovascular outcome studies for DPP-4 inhibitors is provided in Table 1.

**Conclusions**

The analyses of CV safety trials that have been reported to date are reassuring, and indicate that DPP-4
inhibitors are not associated with any excess CV risk over placebo or other comparators. Indeed, the meta-analyses appear to indicate a potential beneficial effect on CV health. Why may the DPP-4 inhibitors be associated with an improvement in CV health? While the main clinical effect of the DPP-4 inhibitors appears to be in lowering glucose, preclinical studies suggest that DPP-4 inhibitors have effects beyond their incretin action on glucose metabolism. Interaction with ACE inhibitors18 and degradation of B-type natriuretic peptide (BNP)19 are two mechanisms that could potentially contribute to their CV effects.

The longer-term CV outcomes of DPP-4 inhibitors, however, arguably the most important aspect of T2DM management, remain unknown. The CV outcome trials mentioned in this review have been designed to address this, and their results, which will be reported over the coming months and years, will be of enormous importance to all those involved in the management of patients with T2DM. If CV safety is confirmed, then we can expect to see a steady increase in the use of these drugs. If CV benefit is demonstrated, however, they are likely to become the second-line choice after metformin in national and international treatment algorithms.

### Table 1. Comparison of cardiovascular outcome studies for DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>No. of patients</th>
<th>Expected reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>TECOS</td>
<td>Sitagliptin Placebo</td>
<td>T2DM ≥50 yrs HbA1c: 6.5–8.0% Established CVD</td>
<td>CV death, MI, unstable angina or stroke</td>
<td>14 000</td>
<td>2014</td>
</tr>
<tr>
<td>SAVOR (TIMI-53)</td>
<td>Saxagliptin Placebo</td>
<td>T2DM ≥40 yrs HbA1c: ≥6.5% CVD/CV risk factors</td>
<td>CV death, MI or stroke</td>
<td>16 500</td>
<td>2014</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin Glimepiride</td>
<td>T2DM ≥40 yrs and ≤85 yrs HbA1c: ≥6.5% CVD/CV risk factors</td>
<td>CV death, MI, stroke, hospitalisation for unstable angina</td>
<td>6000</td>
<td>2018</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin Placebo</td>
<td>T2DM ≥18 yrs HbA1c: 6.5–11.0% ACS</td>
<td>CV death, MI or stroke</td>
<td>5400</td>
<td>2015</td>
</tr>
</tbody>
</table>

T2DM = type 2 diabetes; CV = cardiovascular; CVD = cardiovascular disease; MI = myocardial infarction; ACS = acute coronary syndrome

### Key points

- DPP-4 inhibitors have been prescribed extensively in the UK and worldwide, but whether they have an overall benefit in terms of cardiovascular disease remains unknown.
- US and European regulatory bodies now insist upon rigorous assessment of cardiovascular endpoints for all new drugs for type 2 diabetes.
- Cardiovascular outcome studies for DPP-4 inhibitors will begin reporting in 2014, and will help to influence when and in whom these drugs should be prescribed.

### References

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