Series: Cardiovascular outcome trials for diabetes drugs
Saxagliptin and SAVOR-TIMI 53

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Abstract

SAVOR-TIMI 53 was the first FDA-mandated cardiovascular outcome trial to be presented and published. It compared saxagliptin and placebo in 16,492 patients with type 2 diabetes. SAVOR-TIMI 53 demonstrated non-inferiority for major cardiovascular events (cardiovascular death, myocardial infarction, stroke) but not superiority. An unexpected statistically significant increase in adjudicated hospitalisation for heart failure was seen in the saxagliptin group. Post hoc analysis demonstrated that subjects at greatest risk for hospitalisation for heart failure had previous heart failure, an estimated glomerular filtration rate <60 mL/min, or elevated baseline levels of N-terminal pro-B type natriuretic peptide. As other dipeptidyl peptidase 4 (DPP-4) inhibitors are available which have not been associated with an increased risk of hospitalisation for heart failure, saxagliptin should be avoided in patients with heart failure or a reduced estimated glomerular filtration rate.

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Key words: diabetes, cardiovascular outcome trial, saxagliptin

Introduction

A controversial meta-analysis of the rosiglitazone development programme showed an increase in non-fatal myocardial infarctions in participants who had received rosiglitazone compared with placebo and active comparators.[1] Following this, the licensing requirements for new anti-diabetes drugs changed dramatically in the USA and Europe.[2,3] The phase III development programme was required to include participants who were more representative of the wider diabetes population, including older subjects, patients with existing cardiovascular disease and patients with chronic kidney disease. Any cardiovascular event occurring in the phase III development programme was to be blindly adjudicated to provide information on cardiovascular safety. A dedicated randomised controlled cardiovascular outcome trial (CVOT) was usually required either before or after licensing.

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We now have published the results of four cardiovascular outcomes trials with dipeptidyl peptidase 4 (DPP-4) inhibitors (saxagliptin, alogliptin, sitagliptin, linagliptin),[4-7] five trials with glucagon-like peptide 1 (GLP-1) receptor agonists (lixisenatide, liraglutide, semaglutide, once weekly exenatide, albiglutide),[8-12] three trials with sodium-glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin, canagliflozin, dapagliflozin)[13-15] and one trial with insulin (degludec).[16]

In this series I will describe and summarise the results of each of these CVOTs in the chronological order in which they were published, describing the primary endpoint and important secondary outcomes from the principal publication, but also direct attention to important subsequent publications of data from subgroups and post hoc analyses.

Background

The DPP-4 inhibitor saxagliptin was licensed by the FDA in the summer of 2009 for use in the USA and by the EMA in late 2009 for use in Europe. A systematic assessment of cardiovascular outcomes in the phase II and phase III trials in the development programme was published in 2010.[17] Atherosclerotic cardiovascular events (death, myocardial infarction, stroke, revascularisation procedures, cardiac ischaemia) were systematically identified. Deaths, myocardial infarction and strokes were blindly adjudicated, and no increase in MACE (major adverse cardiovascular events, a composite of cardiovascular death/myocardial infarction/stroke) was observed. Hospitalisation for heart failure was not described in that publication.

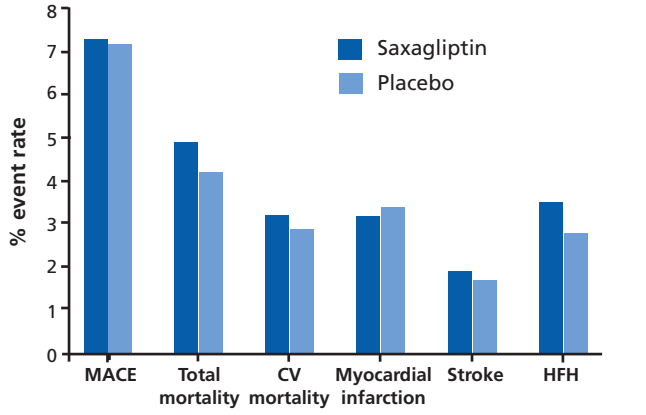
SAVOR-TIMI 53

Papers describing the design and rationale and the baseline characteristics of SAVOR-TIMI 53 were published in 2011 and early 2013, respectively.[18,19] The principal results were presented later that year at the meeting of the European Society of Cardiology and published simultaneously in the *New England Journal of Medicine*.[4] The design of the study and key baseline characteristics are described in Box 1. In SAVOR-TIMI 53 there was no significant difference in MACE, so non-inferiority was established but not superiority (Figure 1, Box 2). An unexpected significant increase in hospitalisation for heart failure was observed, which was a predefined adjudicated endpoint. The criteria to define hospitalisation for heart failure were similar to those used in heart failure studies (see Appendix at www.bjd-abcd.com). The investigators indicated that the findings merited further investigation, needed to be

Box 1 Key features of SAVOR-TIMI 53[4,18,19]

- SAVOR-TMI 53 compared saxagliptin versus placebo for a median of 2.1 years in 16,492 subjects
- The mean age of the subjects was 65 years with a median duration of diabetes of 10 years
- Mean baseline HbA_{1C} was 8.0% (64 mmol/mol). This fell to 7.6% (60 mmol/mol) at year 1 with saxagliptin and 7.9% (63 mmol/mol) with placebo
- 78% of subjects had established atherosclerotic disease, 38% prior myocardial infarction, 43% prior coronary revascularisation and 13% investigator reported heart failure
- 70% of subjects were on metformin, 40% sulfonylureas, 6% thiazolidinediones, 41% insulin

Figure 1. Two-year Kaplan–Meier estimated event rates in % comparing saxagliptin and placebo for MACE, total mortality, cardiovascular mortality, myocardial infarction, ischaemic stroke and hospitalisation for heart failure



confirmed in other ongoing studies and that a class effect should not be presumed.[4]

N-terminal pro-B type natriuretic peptide (NT-proBNP), a biomarker for heart failure, was measured in three-quarters of subjects at baseline and a randomly selected subset of subjects at 2 years. Further analysis of heart failure outcomes showed that people at the highest risk for hospitalisation for heart failure with saxagliptin had elevated baseline NT-proBNP, previous heart failure or an estimated glomerular filtration rate (eGFR) ≤60 mL/min.[20] The authors stated that there were no known mechanisms by which DPP-4 inhibition could precipitate heart failure and that the cardiovascular consequences of DPP-4 inhibition on other peptide substrates such as natriuretic peptides or bradykinins were unknown. A review of DPP-4 inhibitors and heart failure published shortly after the SAVOR-TIMI 53 heart failure analysis listed several further peptides with cardiovascular effects that are split by DPP-4, suggested that this might be the link between DPP-4 inhibitors and heart failure, and that this area requires further scientific attention.[21]

Other results from SAVOR-TIMI 53

It is expensive to run these large CVOTs, so it is understandable that the study steering committee, investigators and sponsors would wish to maximise the impact of the trial by publishing multiple further analyses in subgroups and of specific endpoints (at last count there were nearly 90 publications from UKPDS!). The key further publications from SAVOR-TIMI are detailed in Box 2. Probably the most important of these is the paper looking at the effect of saxagliptin on renal outcomes in SAVOR-TIMI 53.[22] Treatment with saxagliptin improved the albumin creatinine ratio, including in the normoalbuminuric range, but had no effect on eGFR. The beneficial effect was independent of an effect on glucose control, and the authors suggested that DPP-4 inhibitors might protect against renal oxidative stress. Improvements in endothelial function and reductions in inflammation are other possible mechanisms of benefit.[23]

Box 2 Results of the SAVOR-TIMI 53 trial

Principal results

- No reduction in MACE; increase in hospitalisation for heart failure[4,20]

Other results from SAVOR-TIMI 53

- Treatment with saxagliptin improved the albumin creatinine ratio[22]
- In subjects with moderate or severe renal impairment the cardiovascular results and renal results were similar, with no increase in MACE, increased hospitalisation for heart failure and reduced progressive albuminuria with saxagliptin[24]
- Cardiovascular results were the same in elderly and very elderly subjects with no increase in MACE and an increase in hospitalisation for heart failure with saxagliptin[25]
- A high baseline HbA_{1C} was associated with an increased risk of MACE, but not hospitalisation for heart failure[26]
- The risk for pancreatitis was low, with no increased risk with saxagliptin and no increased risk for pancreatic cancer.[27] The overall number of cancers was balanced between the two groups[28]
- Patients allocated to saxagliptin had an increased risk of any or major hypoglycaemia. Hypoglycaemia risk was increased in those taking sulfonylureas but not in those taking insulin[29]

Key messages

- SAVOR-TIMI 53 was the first modern cardiovascular outcome trial of a diabetes drug, comparing saxagliptin and placebo
- In SAVOR-TIMI 53, saxagliptin had no effect on atherosclerotic events of cardiovascular death, myocardial infarction or stroke
- An unexpected increase in hospitalisation for heart failure was observed in SAVOR-TIMI 53, and the mechanism of this increase remains uncertain

Discussion

SAVOR-TIMI 53 was the first completed FDA-mandated cardiovascular outcome trial with a new diabetes drug. It showed that saxagliptin had no effect on atherosclerotic endpoints. The increase

in hospitalisation for heart failure was unexpected and the mechanisms remain unclear. A possible increase in hospitalisation for heart failure was seen in a subgroup of the EXAMINE trial with alogliptin,[5] but not in the TECOS trial with sitagliptin[6] or the CARMELINA trial with linagliptin.[7] For patients with diagnosed heart failure or a reduced eGFR, sitagliptin or linagliptin are safer alternatives to saxagliptin.

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Appendix Definition of Heart Failure Requiring Hospitalisation in SAVOR-TIMI 53

Heart failure (HF) requiring hospitalisation is defined as an event that meets the following criteria:

1. Requires hospitalisation defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available).

   AND

2. Clinical manifestations of heart failure including at least one of the following:

   New or worsening
   - dyspnoea
   - orthopnoea
   - paroxysmal nocturnal dyspnoea
   - oedema
   - pulmonary basilar crackles
   - jugular venous distension
   - new or worsening third heart sound or gallop rhythm, or
   - radiological evidence of worsening heart failure

   AND

3. Additional/increased therapy:
   - Initiation of intravenous diuretic, inotrope or vasodilator therapy
   - Uptitration of intravenous therapy, if already on therapy
   - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, haemofiltration or dialysis that is specifically directed at treatment of heart failure.

   Biomarker results (eg, brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.