



## Evaluating the Cardiovascular Safety of Novel Treatments for Diabetes

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### Key Focus Points

- Since 2008 the FDA has required demonstration of the cardiovascular safety of new glucose-lowering agents.
- The FDA established an acceptable level for estimated increased cardiovascular risk. The upper limit of the 95% confidence interval of cardiovascular risk should be  $<1.3$  based on a combination of pre- and post-marketing studies, e.g. meta-analysis of phase 2 and 3 studies or a combination of phase 3 studies and a cardiovascular outcomes trial (CVOT). If statistical non-inferiority vs. placebo or comparator is confirmed testing for superiority is appropriate.
- Recent landmark trials - EMPA-REG OUTCOME, LEADER and SUSTAIN – have provided evidence for reduction in cardiovascular events in high risk patients with type 2 diabetes for empagliflozin, liraglutide, and semaglutide, respectively.
- Prior to embarking on large and expensive CVOTs early phase evaluations may help provide an indication of a diabetes drug's potential cardiovascular risk thereby informing development decisions.

## Introduction

Cardiovascular events are one of the leading causes of morbidity and mortality among people with type 2 diabetes. Compared to the non-diabetic population, adults with diabetes have an approximately 2-fold higher risk for a cardiovascular event and generally experience worse clinical outcomes relative to their non-diabetic counterparts. While improved glycemic control has been linked to better microvascular health, a number of glucose-lowering agents have been associated with concerns regarding their cardiovascular safety profile. Following its experience with the reported cardiovascular risks attributed to rosiglitazone, the United States Food and Drug Administration (FDA) issued non-binding recommendations (2008) that established rigorous regulatory requirements for all new glucose-lowering drugs with respect to establishing the cardiovascular safety of new drugs for diabetes. While new insulins are not specifically covered by the FDA guidance cardiovascular safety is an important consideration for all novel glucose-lowering agents.

## Regulatory Guidance for Establishing an Acceptable Cardiovascular Safety Profile

The FDA guidance requires that cardiovascular toxicity must be excluded by appropriate pre- and post-marketing clinical studies. The key points of the FDA industry guidance are summarized in Table 1.

Table 1. Summary of the key points from the FDA industry guidance

Key Points of the FDA Industry Guidance
An upper boundary of the 95% confidence interval (CI) for the risk ratio of important cardiovascular events of <1.3 should be used as a key criterion for excluding unacceptable cardiovascular risk for new treatments for type 2 diabetes.
If the pre-marketing application contains data showing that the upper boundary of the 95 % CI for the estimated increased risk, i.e. risk ratio, is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, then a post-marketing trial will generally be required to confirm that the upper boundary of the risk ratio is <1.3.
To satisfy the statistical guidelines, the analysis of cardiovascular events may include a meta-analysis of all placebo-controlled trials, add-on trials, i.e. drug vs. placebo, each added to standard glucose-lowering therapy, and active-controlled trials. Alternatively, an additional single, large, safety trial may be conducted alone, or added to other trials.
To ensure sufficient endpoints, studies should include subjects at higher risk for cardiovascular events, such as those with relatively advanced stages of the natural history of type 2 diabetes, elderly patients, and subjects with degrees of renal impairment.
A minimum of 2 years' cardiovascular safety data must be provided.
Sponsors should ensure that phase 2 and 3 studies are designed and conducted so that a meta-analysis can be performed on completion. Studies should include prospective, blinded, independent adjudication of cardiovascular events. Adjudicated events should include cardiovascular mortality, myocardial infarction, and stroke. Hospitalization for acute coronary syndromes, urgent interventional revascularization procedures, and possibly other relevant endpoints may also be included.
Sponsors should explore similarities and/or differences in subgroups, e.g. age, sex, race, if possible.

The European Medical Agency (EMA) adopted similar principles in a 2012 guideline update while not specifying the boundaries of acceptable risk. Non-clinical data should be obtained from relevant animal models together with clinical data from a meta-analysis or long-term controlled outcome study. These new regulatory requirements establish a high bar for cardiovascular safety for a new glucose-lowering agent, and necessitate a rigorous clinical development program to meet the burden of proof placed on the sponsor.

## Designing a Clinical Program to Evaluate the CV Risk of a Novel Diabetes Drug

Careful consideration is required when designing a clinical development program that will be compatible with the FDA guidance on cardiovascular safety. For example, individual outcome trials must be designed with an eventual meta-analysis in mind, meaning they must be part of an integrated program and use similar methods of data collection and analysis. An experienced program and trial design team is required to successfully integrate early and late phase studies into this type of clinical development program.

## Clinical Development Program Planning

The acceptable approaches for combining cardiovascular outcome trials into a clinical development program range from a single large outcome study to multiple traditional Phase 3 studies, and various hybrid programs that combine the two approaches. It may prove challenging to provide definitive evidence of cardiovascular safety at the <1.3 risk threshold using the multiple phase 3 studies approach if too few events occur. A single large outcome study may not allow the sponsor to test the efficacy of the novel compound in as broad a patient spectrum or against different comparators. Therefore, in many cases, a well-managed hybrid approach may offer the most efficient path.

## Determination of Non-inferiority versus Superiority

One of the key considerations in powering an individual cardiovascular outcome trial is whether the primary endpoint of the study is establishing non-inferiority or superiority of the test compound to a comparator. The primary objective of each type of trial is shown below in Table 2.

Table 2. Non-inferiority vs. superiority trials

Type of Trial	Primary Objective
<b>Non-inferiority</b>	To definitively demonstrate that the upper boundary of the estimated risk ratio does not exceed the aforementioned limit of 1.3
<b>Superiority</b>	Demonstration of clinical benefit relative to the chosen comparator

Conducting a superiority trial generally necessitates a considerably larger sample size. In addition, if a broader view is taken that includes benefits rather than the absence of harm, the claim that a drug is cardioprotective requires a pre-specified primary outcome for support.

## Study Population

The subject population best suited for assessing the clinical efficacy of a novel drug may not be the most appropriate for determining its effects on cardiovascular risk. It is important to recruit a wide range of patients (age, disease status, comorbidities, etc.) into different trials. This requires ensuring that the individual outcome trials are designed as part of an integrated program with the eventual intent of compiling data for a meta-analysis; but the patient population within a study can be relatively homogenous. The current trend towards enrolling patients with an

elevated cardiovascular risk in trials of glucose-lowering agent increases the likelihood of obtaining a sufficient number of events to form robust conclusions. However, it raises the challenge that the patients in question may have less modifiable cardiovascular disease, suggesting that cardiovascular outcomes are driven by the disease and not the drug being tested.

## Safety and Clinical Outcome Endpoint Selection

Early studies suggested a link between tight glycemic control using glucose-lowering agents and benefits; however, these associations have not invariably been supported by interventional trials. General guidance from the FDA has specified the preferred outcome in cardiovascular safety trials as major adverse cardiac events (MACE) plus hospitalization due to unstable angina. All events should be adjudicated by an independent review panel. In early phase testing, cardiovascular biomarkers are acceptable to provide preliminary evidence about the possible cardiovascular effects of a new drug.

## Completeness of Data Follow-up

Adequate follow-up and rescue procedures are vital for a successful cardiovascular outcome trial. If too many patients are lost to follow-up it can introduce bias into the study, reduce statistical power, and make it difficult to compare between trials. Carefully thought out rescue measures allow patients to remain through the follow-up period even if they have to discontinue the study treatment or require new medication to manage underlying conditions.

## Considerations for Statistical Analysis

The statistical planning for cardiovascular safety studies in patients with type 2 diabetes requires special considerations. The FDA recommends that the sponsor take a two-step approach to establishing cardiovascular safety by ruling out a cardiovascular relative risk (RR)  $>1.8$  at the time of approval and showing an RR  $<1.3$  in post-marketing trials. This strategy allows the sponsor to longer-term definitive evidence of CV safety. Attempting to meet both metrics in a single study can be complicated due to release of interim data if approval is sought after the determination that the cardiovascular RR is  $<1.8$  and before establishing it is  $<1.3$ . Participants in a trial may become aware of the findings; this may pose an ethical challenge to the physician and patients if efficacy (e.g., HbA<sub>1c</sub> levels) and early cardiovascular data suggest a benefit but patients are asked to remain on the placebo. The multiplicity of analyses and controls for primary and secondary endpoints must be carefully considered. In general, the tests for glycemic efficacy can be separated from the cardiovascular endpoints to evaluate glycemic control endpoints without multiple comparison adjustments with respect to cardiovascular endpoints. This may not be true for other endpoints, such as renal parameters, and should be evaluated in the context of the specific study.

## Historical Perspective on Glucose-lowering Drugs, and Cardiovascular Events

It should not have come as a surprise that the regulatory requirements instituted by the FDA and EMA set a high standard for establishing the cardiovascular safety for new glucose-lowering agents with strict guidelines about how such trials should be conducted. While there is an ongoing debate about whether the current regulations are a justified use of resources (see below) historically the lack of clear cardiovascular outcome data has created persistent controversies regarding the effects of diabetes treatments on cardiovascular risk.

## Sulfonylureas

Failing to establish the cardiovascular safety profile of a diabetes drug in robustly designed trials can create concerns that persist for many years. The University Group Diabetes Program (UGDP) reported an excess mortality in those treated with the sulfonylurea tolbutamide. However, this study had major methodological flaws and did not

correct for a higher pre-existing cardiovascular risk in the sulfonylurea-treated subjects. Despite this caveat, the findings of the UGDP study led to a label in the United States warning of increased cardiovascular mortality with sulfonylurea. It was not until the UK Prospective Diabetes Study (UKPDS) was conducted that SUs were exonerated as cardiotoxic agents. Decades on from the UGDP, the cardiovascular safety of sulfonylureas is being evaluated as part of the CAROLINA (CARDiovascular Outcome study of LINAgliptin versus glimepiride in early type 2 diabetes; 2010-15) study. Establishing a clear cardiovascular safety profile early during development can help alleviate the need for large post-marketing studies and avoid outcomes such as adverse FDA labeling.

## Metformin

In UKPDS 34, in overweight patients (n=342) with recently diagnosed type 2 diabetes randomized to metformin lower rates of myocardial infarction (39% reduction;  $p=0.01$ ), a 50% risk reduction in coronary deaths ( $p=0.02$ ), and decreased all-cause mortality compared to dietary treatment were all observed. The small sample size in UKPDS 34 has led to a long-running debate about the robustness of these findings. The cardioprotective effects of metformin are currently being re-examined in subjects with non-diabetic hyperglycemia and high cardiovascular risk (Glucose Lowering in Non-diabetic hyperglycemia Trial, GLINT).

## Dipeptidyl Peptidase-4 Inhibitors

The importance of conducting an appropriately powered cardiovascular outcomes trial (CVOT) as part of the clinical development program is illustrated by the experience of the dipeptidyl peptidase-4 (DPP-4) inhibitors. A 2011 meta-analysis of more than 50 trials involving drugs in this class suggested a potential cardiovascular benefit over comparators with a reduced risk for MACE compared with placebo or active drugs. However, two large, high profile, placebo-controlled cardiovascular outcome studies, SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction) and EXAMINE (EXamination of cARDiovascular outcoMes with alogliptIN versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome), showed no cardiovascular benefits of DPP-4 inhibitors. In fact, the SAVOR trial found that saxagliptin increased the risk for hospital admission for heart failure. In response, the FDA issued a drug safety communication detailing the agency's intention to request additional clinical trial data from the manufacturer. It is worth noting in this context, that the SAVOR trial generated three to four times the amount of data as the entire phase 3 development program for saxagliptin. In addition to the importance of large cardiovascular outcome trials, the experiences with the SAVOR and EXAMINE studies suggest that detailed early-phase safety assessments of new diabetes drugs might help to avert expensive studies in the later phases of development by eliminating drugs with unfavorable cardiovascular biomarker profiles. The more recently reported Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) found no evidence of an excess of heart failure with another DPP-4 inhibitor, sitagliptin.

## Recent CVOTs in Type 2 Diabetes

In brief, three recent studies have demonstrated cardiovascular protection in CVOTs.

**EMPA-REG OUTCOME** - The first sodium-glucose cotransporter (SGLT)-2 inhibitor CVOT to complete studied the effects of empagliflozin 10 or 25 mg daily vs. placebo in 7020 high-risk patients with type 2 diabetes. This landmark trial not only proved the cardiovascular safety of empagliflozin but demonstrated a 14% reduction for the primary MACE outcome (HR 0.86, 95.02% CI 0.74, 0.99,  $p=0.04$  for superiority) over a median follow up period of 3.1 years. There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35%

relative risk reduction), and all-cause death (5.7% and 8.3%, respectively; 32% relative risk reduction). Of note, heart failure and mortality benefits emerged almost immediately in with nonsignificant effects on non-fatal MI and stroke. EMPA-REG OUTCOME is the first clinical trial to report significant reductions in cardiovascular risk from a glucose-lowering drug thereby representing a paradigm shift in diabetes therapy.

**LEADER** - A total of 9340 patients underwent randomization to liraglutide or placebo. The median follow-up was 3.8 years. The once-daily GLP-1 receptor agonist liraglutide reduced both cardiovascular and all-cause death (22% and 15% relative reductions, respectively). The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) results stand in contrast to those of the ELIXA trial in which lixisenatide failed to similarly reduce cardiovascular risk. Whether this discrepancy represents differences in the medications, including the shorter half-life of lixisenatide, differences in potency between liraglutide and lixisenatide, or differences in the trial populations remains uncertain. While classic cardiovascular risk factors, e.g. glycemic control, body weight and blood pressure, were improved or mitigated, the mechanisms of benefit in EMPA-REG OUTCOME and LEADER remain uncertain. The pattern of cardiovascular benefits associated with liraglutide differed from that observed in EMPA-REG OUTCOME. The observed benefits with empagliflozin may be more closely linked to hemodynamic or myocardial metabolic effects, whereas in LEADER the observed benefits are perhaps related to the modified progression of atherosclerotic vascular disease.

**SUSTAIN-6** - SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) was a smaller study than EMPA-REG OUTCOME or LEADER. In SUSTAIN-6 the effect of the once-weekly GLP-1 receptor agonist semaglutide at doses of 0.5 and 1.0 mg was assessed in 3297 high-risk patients with type 2 diabetes the majority of whom (83%) had established cardiovascular disease, chronic kidney disease at baseline. The primary composite outcome (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) occurred in 6.6% of participants in the semaglutide group and in 8.9% in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95;  $P < 0.001$  for non-inferiority;  $p = 0.02$  for superiority although the test for superiority was not a pre-specified endpoint in SUSTAIN-6). The rate of death from cardiovascular causes was similar for the two groups. While semaglutide (like liraglutide) showed renoprotection effects retinopathy complications were significantly higher with semaglutide. As was the case in LEADER, minor increases in heart rate were observed with semaglutide. As in the case of LEADER, the timescale for the emergence of cardiovascular benefit in SUSTAIN-6 (after approximately 18 months) has led to the suggestion that atherosclerosis may be favourably impacted by semaglutide. In support of this hypothesis, coronary and peripheral arterial revascularization rates were reduced in SUSTAIN-6 ( $p = 0.003$ ). There was no effect of semaglutide on hospitalization rates for adjudicated heart failure.

## Conclusions

The regulatory landscape for the development of new agents for the treatment of type 2 diabetes has undergone major changes in recent years. Establishing the cardiovascular safety profile of a novel diabetes drug is critically important for winning regulatory approval. Careful planning of individual trials is needed to ensure that cardiovascular effects are assessed in diverse and appropriate patient populations. The trials must be designed with the intention of combining the data later in a large meta-analysis. Robust early phase testing to detect cardiovascular safety signals may help prevent the expense associated with large-scale clinical trials during later phases of drug development.

## Looking Ahead

Meeting the high standard of cardiovascular safety required for regulatory approval results in increased development costs and longer development time that can delay bringing a new diabetes drug to market. To mitigate these risks

drug development programs should take cardiovascular safety testing into account during early phase clinical trials. Designing an integrated clinical development program that can (1) identify early signals of cardiovascular risk and (2) provide meaningful data for use in later analyses are important considerations. Robust early phase testing has the potential to identify cardiovascular risk signals and may help determine whether continued development is warranted. Early cardiovascular testing may include the use of cardiovascular risk biomarkers (e.g. ambulatory blood pressure measurements, endothelial function testing) or inclusion of clinically relevant outcomes that might provide preliminary evidence of a drug's safety. The inclusion of cardiovascular risk assessments in the early phases of clinical development may help streamline drug development and contribute to a reliable evidence base for assessing the cardiovascular risk associated with a novel diabetes drug. In later phase development, enrolling patients at high risk for a cardiovascular event will become a routine practice for studies involving patients with type 2 diabetes. This requires evaluation of key aspects of trial design from the inclusion/exclusion criteria to patient management in order to ensure the safety of the participants and provide robust scientific data. The FDA requirement that cardiovascular risk be established compared to an already licensed product has the ancillary benefit of providing a rigorous assessment of the cardiovascular profile of well-established diabetes drugs that have been in use for many years.

## Further Reading

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As Senior Research Fellow at ProSciento, Prof. Krentz's research involves investigator-initiated research in diabetes and cardiometabolic therapies. In addition to original articles, reviews and book chapters he has authored or edited a number of textbooks on diabetes and cardiovascular disease including *The Metabolic Syndrome and Cardiovascular Disease (2007)*, *Drug Therapy for Type 2 Diabetes (2013)* and *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development (2015)*. He is Professor of Endocrinology & Metabolism at the University of Buckingham, UK. Prof. Krentz serves on the editorial boards of several scientific journals and is founding Editor-in-Chief of Cardiovascular Endocrinology.



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Dr. Hompesch's is a highly regarded expert in early phase clinical trial design for diabetes, obesity and related metabolic drug and device development. He is also a founder of ProSciento, the leading CRO exclusively focused on metabolic diseases and one of the few CROs actively conducting clinical research and biomarker validation studies using imaging and biopsy methods to detect progressive NASH in NAFLD and diabetes patients for therapeutic development. Dr. Hompesch is the author of more than 85 peer-reviewed publications and editorials and is a regularly invited speaker at medical conferences. He is also an editor and co-author of a new textbook *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development (2015)*.





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