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REVIEW

Obesity and metabolic syndrome

Assessment of cardiovascular risk of new drugs for the treatment of diabetes mellitus: risk assessment vs. risk aversion

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The Food and Drug Administration issued guidance for evaluating the cardiovascular risk of new diabetes mellitus drugs in 2008. Accumulating evidence from several completed trials conducted within this framework raises questions as to whether requiring safety outcome studies for all new diabetes mellitus therapies remains justified. Given the burden of cardiovascular disease in patients with diabetes, the focus should shift towards cardiovascular outcome studies designed to evaluate efficacy (i.e. to determine the efficacy of a drug over placebo or standard care) rather than demonstrating that risk is not increased by a pre-specified safety margin. All stakeholders are responsible for ensuring that new drug approvals occur under conditions of appropriate safety and effectiveness. It is also a shared responsibility to avoid unnecessary hurdles that may compromise access to useful drugs and threaten the sustainability of health systems. It is critical to renew this debate so that stakeholders can collectively determine the optimal approach for developing new drugs to treat type 2 diabetes mellitus.

Keywords Diabetes mellitus • Clinical trials • Cardiovascular disease

Introduction

The US Food and Drug Administration (FDA) issued an Industry Guidance in 2008 for evaluating the cardiovascular safety of new therapies for the treatment of patients with type 2 diabetes mellitus. The guidance was developed in response to concerns about the cardiovascular safety of these drugs, which originated with rosiglitazone.[1] This guidance shifted the focus of diabetes research towards clinical trials designed to evaluate cardiovascular safety. Briefly, for each drug, the FDA requires a pooled analysis of independently adjudicated major adverse cardiovascular events [which should include cardiovascular death, non-fatal myocardial infarction (MI),

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and non-fatal stroke and can include other endpoints] across all relevant trials to provide reassurance that there is no substantial excess cardiovascular risk. Specifically, one seeks evidence that compared with a placebo control group, the risk ratio estimate has an upper 95% confidence limit <1.8. If the upper bound of the confidence interval (CI) excludes 1.8 but includes 1.3, then a separate, prospective, post-marketing, randomized safety trial is required to rule out such a 30% increase in risk. The guidance did not specifically include heart failure hospitalization as a cardiovascular safety endpoint of interest, despite prior studies linking certain drugs for diabetes mellitus (peroxisome proliferator-activated receptor gamma agonists) with this adverse event.[2,3] At the time the guidance was released, the consequences of these requirements on diabetes drug development was uncertain.[4]

Several clinical trials designed to meet this regulatory requirement have been reported.[5–9] During the 11th and 12th Global Cardiovascular Clinical Trialists Forum held in Washington, D.C. in December 2014 and 2015, lessons learned from these clinical trials were discussed among a group of cardiovascular and endocrinology clinical trialists, biostatisticians, National Institutes of Health scientists, European and US regulators, and pharmaceutical industry scientists. This paper describes the ongoing controversies in the field and calls for stakeholders to re-evaluate the current approach to diabetes drug development such that two key objectives can be fulfilled: (i) effective and safe drugs are available to patients and (ii) patients can be informed about the magnitude and type of benefit (e.g. morbidity/mortality, surrogate, or biomarker) offered by a given therapy and potential risks that might offset these benefits.

Cardiovascular safety of therapies for diabetes mellitus

Origin of the controversy

In the University Group Diabetes Programme (UGDP) conducted in the early 1970s, albeit grossly underpowered, tolbutamide appeared to be associated with an increased risk of cardiovascular death compared with placebo.[10,11] Some meta-analyses appear to reinforce the idea that the cardiovascular profile of sulfonylureas is worse than that observed for metformin and selective dipeptidyl peptidase-4 (DPP-4) inhibitors,[12,13] although these data are not conclusive. In ADVANCE, 88% of patients in the intensive glucose arm were treated with gliclazide MR compared with 57% treated with another sulfonylurea in the standard therapy arm, and no evidence of harm was observed.[14] Historically, no regulatory measures on therapies for type 2 diabetes were adopted (except a warning in the labelling of sulfonylureas in the USA), until the rosiglitazone controversies arose in 2007 (and subsequently in 2010). At that time, emerging data with rosiglitazone introduced legitimate concerns regarding the benefit–risk equation for drugs used in the treatment of type 2 diabetes. Specifically, when a drug is being used to improve a biological marker (e.g. glycated haemoglobin), it is key to rule out off-target effects that could change the benefit–risk of using a drug for this purpose.

The regulatory reaction to the rosiglitazone case differed in the USA and Europe. While the marketing authorization of rosiglitazone was suspended in the European Union, the FDA introduced important labelling restrictions and warnings, but the drug remained available by prescription. In contrast to the immediate regulatory action, subsequent changes in regulatory approval standards were substantially more demanding in the USA than in Europe. As previously noted, the FDA required systematic demonstration that the potential increase in cardiovascular risk associated with a new drug for the treatment of type 2 diabetes should not exceed 30% compared with placebo or active control. This new standard virtually translated into the need to conduct large safety outcome studies for all new therapies for diabetes mellitus (since diabetes drugs have historically been approved on the basis of lowering glycated haemoglobin). The European Medicines Agency (EMA) requirements were less demanding, and the EMA guidance indicates that a long-term, controlled outcome study with 18–24 months of follow-up is expected for drugs when an adverse cardiovascular effect is suspected.[15] The EMA does not pre-specify non-inferiority margins that must be excluded by these analyses.[15] From the EMA perspective, a new drug that improves glycaemic control should preferably demonstrate a neutral or beneficial effect on parameters associated with cardiovascular risk.[15]

Substantial controversy remains in the field about this regulatory approach. Some worry that the policy to rule out a 95% upper bound of the hazard ratio of 1.3 for cardiovascular harm (with a presumed hazard ratio of $\sim$1.0) is overly demanding and exceeds what should be required for approval. However, others view it as not unusually demanding, since the requirement provides confidence with P in the range of 0.05 (not a very rigorous standard) that there is not a 30% excess in cardiovascular morbidity or mortality associated with a drug used to improve a biomarker (i.e. glycated haemoglobin) or slow the progression of clinically important but not immediately life-threatening conditions (e.g. retinopathy, neuropathy, nephropathy). Counter to the position that the standard is too rigorous, one could argue that such a standard is inadequate in the face of no obvious benefit on hard mortality or morbidity outcomes and that approval should be based on efficacy on hard outcomes rather than the current approach (i.e. approval based on improvements in glycated haemoglobin and demonstration of no excess cardiovascular risk).

What do the evolving data indicate?

Finalized and ongoing trials aiming to show cardiovascular safety of new therapies for type 2 diabetes have now enrolled hundreds of thousands of patients.[4,16,17] In addition, many pooled analyses of short- and medium-term trials have been conducted.[18–22]

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction-53 (SAVOR-TIMI-53) and Examination of Cardiovascular Outcomes with Alogliptin (EXAMINE) produced consistent findings of no major harm but no cardiovascular benefit for these DPP-4 inhibitors.[5,6] In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), the DPP-4 inhibitor sitagliptin was non-inferior to placebo for the primary composite endpoint (cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina, HR 0.98, 95% CI 0.88–1.09, $P < 0.001$).[7] Heart failure hospitalization rates were not different between groups (HR 1.00, 95% CI 0.83–1.20, $P = 0.98$).[7] The GLP-1 receptor agonist lixisenatide was non-inferior (but not superior) to

placebo for the primary composite outcome of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study.[9] The patient population in ELIXA was remarkably similar to EXAMINE. There was no evidence of an increased risk in heart failure events.[9] The selective sodium glucose cotransporter 2 inhibitor empagliflozin reduced the primary composite of cardiovascular death, non-fatal MI, or non-fatal stroke compared with placebo in the EMPA-REG OUTCOME trial, which included patients with type 2 diabetes mellitus and established cardiovascular disease (12.1 vs. 10.5%, HR 0.86, 95% CI 0.74–0.99, $P < 0.001$ non-inferiority, $P = 0.04$ superiority).[8] In addition, meta-analyses of exenatide,[18,22] liraglutide,[19,22] sitagliptin,[20,23–25] vildagliptin,[21,23–25] and saxagliptin[23–25] have shown no evidence of harm (but with much less exposure than the large cardiovascular outcome trials). Finally, the FDA has recently removed most of rosiglitazone's cardiovascular harm labelling and dispensing restrictions as a result of further internal and external re-evaluation of the data with independent event adjudication.[26] To date, no new sound adverse cardiovascular safety signal has arisen from these analyses, and there is now evidence of benefit from the study with empagliflozin. Altogether, these data raise the question of what quantity and quality of evidence is sufficient to provide reasonable assurance to regulatory authorities that cardiovascular safety is not compromised, and whether it remains adequate to expend resources to rule out harm instead of evaluating efficacy.

Time to rethink the policy? Issues for reflection

A legitimate question is whether a continued focus on safety in lieu of efficacy on clinical outcomes is appropriate. The relevance of this question is not limited to the treatment of diabetes. For example, cardiovascular outcome trials to rule out excess cardiovascular risk of new anti-obesity drugs[27,28] and gout[29] have also been mandated by the FDA and are under consideration by the EMA. The requirement has also led to some quandaries, such as premature disclosure of interim study results. The sponsor of the 9000-patient Light Trial (NCT01601704), designed to study the cardiovascular safety of the obesity drug buproprion–naltrexone, prematurely disclosed the study's interim results (despite strict data disclosure agreements), which led to subsequent appropriate, though unfortunate, halting of the study by the trial's executive steering committee.[30]

Hardening regulatory policies may be fully justified when based on sound knowledge, but applying indiscriminate policies may easily fall in the category of overregulation. Since all drugs have the potential for adverse outcomes, it is key to determine what level of risk (i.e. unacceptable harm) and what degree of certainty patients and providers are willing to accept to achieve the benefits associated with improved glycaemic control if no specific cardiovascular outcome benefits on efficacy endpoints are shown. Currently, with the exception of data suggesting that some sulfonylureas may perform worse in terms of cardiovascular outcome than other classes of diabetes drugs,[10–13] the accumulated evidence appears to indicate that the cardiovascular safety of agents for the treatment of type 2 diabetes is not sufficiently concerning to justify a systematic requirement of cardiovascular safety outcome studies for all drugs.

What about cardiovascular efficacy outcome studies?

Since cardiovascular disease is the leading cause of death and disability in patients with type 2 diabetes, the appropriate emphasis and resources should be shifted to proving efficacy rather than ruling out harm. The EMPA-REG OUTCOME study provides support for the position that clinical trials should aim to assess efficacy on hard outcomes.[8] One key question is whether the trials have been optimally designed to detect cardiovascular benefit if it exists. The most recent studies, SAVOR-TIMI-53, EXAMINE, ELIXA, TECOS, and EMPA-REG OUTCOME enrolled patients with known cardiovascular disease, at high risk of cardiovascular disease, or post-acute coronary syndrome.[5–9] This approach satisfied the requirements of the FDA guidance, which stipulates that Phases 2 and 3 programmes should include patients at higher risk of cardiovascular events (e.g. advanced disease, elderly, impaired renal function). Another intent was to accrue a population with a sufficiently high event rate to maintain an achievable sample size and a reasonable duration of treatment exposure and follow-up. From the standpoint of cardiovascular safety, this population would be the most likely to demonstrate adverse effects if they existed. These high-risk patients might also be the least likely to show benefit on a cardiovascular endpoint, if the advanced presence of existing disease, risk factors, or long-standing diabetes is no longer modifiable by small reductions in glycated haemoglobin (<0.5% in SAVOR-TIMI-53, EXAMINE, TECOS, and EMPA-REG OUTCOME), unless the drug exerts a positive cardiovascular effect that is independent from glycaemic control (e.g. favourable effects of empagliflozin on weight loss, blood pressure, vascular markers, visceral adiposity, albuminuria, and plasma urate[8] or potential cardioprotective effects of incretin-based hormones).[5,6,14,31,32] Whether one or a combination of properties explains the positive effect of empagliflozin in EMPA-REG OUTCOME is unknown, but it is unlikely to be related solely to improved glycaemic control since the changes in glycated haemoglobin were small. The neutral findings of other trials also suggest a unique effect of empagliflozin separate from its ability to lower serum glucose.

It is plausible that a primary prevention population of patients with type 2 diabetes with extended follow-up (>10 years)[33] could be expected to demonstrate efficacy on cardiovascular endpoints, if one exists (e.g. EXSCEL, www.clinicaltrials.gov, NCT 01144338 with planned follow-up of up to 7.5 years[34]). Unfortunately, this approach would not be generally feasible in the current climate. It would require a shift in other regulations to be successful, such as providing longer patent protection[35] to companies willing to commit to a long-term drug development programme.

When a safety outcome study may be necessary?

Clearly, every drug for the treatment of diabetes within a class or group is different and has the potential for ancillary properties that might affect risk. Regulatory requirements need to be tailored to individual drugs and individual new chemical entities. Decisions on the need for safety outcome studies should be made on an

individual basis, after careful scrutiny of a safety database sufficiently sized and prospectively designed in terms of number of patients, minimum follow-up, population at risk, and safety endpoints of interest.[36]

The focus of the study should also vary depending on the safety concern arising. For example, it is likely that the relevance of drugs for the treatment of type 2 diabetes as triggers of worsening heart failure[37–39] may have been underestimated in the past, while the weight of atherogenic and/or prothrombotic disease has been overemphasized. The FDA Guidance document states that the cardiovascular endpoints of interest are 'cardiovascular mortality, MI, and stroke, and can include hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, and possibly other endpoints'.[1] But, with the novel agents for type 2 diabetes, exclusive reliance on such endpoints may be inadequate to fully characterize cardiovascular safety. For example, modulation of incretins and their associated catabolic enzymes may impact myocardial function or regulation.[40–42] B-type natriuretic peptide (BNP) is a substrate to DPP-4, and it cleaves the physiologically active form of BNP (1–32) to BNP (3–32), which may impact plasma cGMP and the effect of BNP on diuresis, natriuresis, and vasodilation.[43,44] This field is evolving, and it remains unclear how much DPP-4 may affect the pathophysiology of natriuretic peptides in heart failure, what influence DPP-4 inhibitors may have on BNP, and how heart failure progression and clinical outcomes may be affected.[43] The existing evidence from SAVOR-TIMI-53 and EXAMINE do not show alterations in BNP or NT-pro-BNP for either of the drugs compared with placebo.[37–39]

This uncertainty underscores the need to individualize safety assessments to specific drugs. The trials community has had difficulty interpreting cardiovascular safety in the context of small, but apparently significant, increases in heart failure hospitalization risk[37,38] when there is no increase in MI, stroke, and cardiovascular death. Based on the totality of evidence, it is probable that the increased risk of heart failure hospitalizations observed in SAVOR-TIMI-53 was due to random noise, although the findings have recently led the FDA to add warnings about heart failure risk to the labels of saxagliptin and alogliptin.[45] In order to elucidate and interpret the concern about re-hospitalization for HF with DPP-4 inhibitors, further heterogeneity testing across the three trials (SAVOR-TIMI-53, EXAMINE, TECOS) needs to be conducted, and this work is ongoing.

Unfortunately, because the FDA guidance does not specifically list heart failure among the endpoints of interest, few studies have pre-specified heart failure as a primary or secondary endpoint.[4,17,46] Heart failure events occur with similar frequency as other major adverse cardiovascular events in clinical trials of patients with type 2 diabetes and elevated cardiovascular risk,[47] occurring second to MI and at a greater frequency than stroke in the placebo arms of SAVOR-TIMI-53, EXAMINE, and TECOS.[5–7] Heart failure is 'a cardiovascular outcome in diabetes that can no longer be ignored'.[46] Therefore, when a cardiovascular safety trial is deemed necessary, depending on the safety signals detected in earlier phases of development, heart failure should be assessed.[46] Whether it should be a stand-alone co-primary endpoint, a component of the primary composite endpoint, or a key secondary endpoint depends on the study population, the drug's mechanism of action, and possibly other factors. Assessment of patients' cardiac function at baseline is also useful to aid in the interpretation of results.

Conclusions

The consistency of evidence generated since the implementation of the FDA guidance on assessing cardiovascular safety of diabetes drugs raises the question of whether cardiovascular safety outcome studies remain necessary for all new diabetes drugs, and whether instead, approval should be based on a demonstration of efficacy on cardiovascular outcomes. If improvement in glycated haemoglobin continues to be accepted for approval, a more tailored approach might now be appropriate, where the need for cardiovascular outcome studies would be determined by regulators for each individual drug based on its mechanism of action, pre-clinical or Phases 1 and 2 data, and the safety database. Only requiring cardiovascular outcome safety trials when there is suspicion or a signal of an adverse effect seems reasonable given the number of recent studies that have demonstrated non-inferiority and the resources and time involved in conducting these large-scale trials.[36] A chance always exists that a drug will have an adverse effect that remains undetected until it is widely used after approval; however, the magnitude of this chance must be weighed against the burden of many thousands of subjects who participate in these trials and the resources expended to conduct the trials when effectiveness on important clinical events is not the primary objective.

The long-term impact of therapies for type 2 diabetes on certain cardiovascular morbidities that are relevant for patients is still not definitively established. Thus, if a tailored approach to conducting cardiovascular safety outcome studies were adopted, resources could be shifted away from conducting cardiovascular safety outcome trials in drugs where the suspicion for harm is low, towards conducting trials designed to find effective therapies for improving survival and reducing cardiovascular disease-related morbidity over the long term. The recent findings of EMPA-REG OUTCOME should reinvigorate interest in cardiovascular efficacy outcome studies.

It is the responsibility of investigators, sponsors, and regulators to ensure that the approval and use of new drugs for patients with increased cardiovascular risk occurs under conditions of appropriate safety and effectiveness, but it is also our responsibility to avoid instituting unnecessary hurdles that may compromise access to useful drugs and threaten the sustainability of health systems. The information currently available is considered sufficient to revisit the debate for new therapies to treat type 2 diabetes mellitus, where patients, industry, regulators, and academia can openly discuss what certainties are needed and how much uncertainty can be accepted.

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