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Review Article

Cardiovascular outcome trials for anti-diabetes medication: A holy grail of drug development?

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ABSTRACT

Since the time questions arose on cardiovascular safety of Rosiglitazone, FDA has suggested guidelines on conduct of studies on anti-diabetic drugs so as to prove that the cardiovascular risk is acceptable. Based on the cardiovascular risks of pre-approval clinical trials, guidelines have been made to conduct cardiovascular safety outcome trials (CVSOTs) prior to the drug approval or after the drug has been approved. Unlike the trials comparing the efficacy of antidiabetic agents, the CVSOTs examine the cardiovascular safety of a drug in comparison to standard of care. These trials are expensive aspects of drug development and are associated with various technical and operational challenges. More cost effective models of assessing cardiovascular safety like use of biomarkers, electronic medical records, pragmatic and factorial designs can be adopted. This article critically looks at the antidiabetic drug approval from a cardiovascular perspective by asking a few questions and arriving at answers.

Cardiovascular diseases (CVDs) are the leading cause of death in subjects with type 2 diabetes.[1,2] The primary aim of diabetes management is to prevent death and morbidity due to CVD and microvascular diseases. Multifactorial interventions targeting lifestyle changes, weight loss, lipids, blood pressure, hyperglycemia and use of antiplatelet agents have been shown to reduce the risk of CVD.[1,4] However, there has been a growing concern on the adverse cardiovascular outcomes in trials of certain anti-hyperglycemic agents (AHA) and drug combinations used to control hyperglycemia.[4–6] It would be counterproductive if a drug used to treat diabetes itself increases the CVD risk. Following a meta-analysis of randomized controlled trials of Rosiglitazone, Nissen and Wolski[5] concluded that there an increased risk of myocardial infarction and death in subjects on Rosiglitazone. This triggered a series of discussion on the need to more closely evaluate anti-diabetic therapies from a cardiovascular perspective. In 2008, FDA issued a guidance to pharmaceutical industry on the conduct of clinical studies to

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prove that anti-diabetic drugs confer to acceptable levels of CV safety.[7] In this article, we try to answer the anti-diabetic drug approval process from a cardiovascular perspective. The authors selected few significant questions, which needed to be answered. A PubMed search was done with terms diabetes and cardiovascular outcome and cardiovascular trials. All article abstracts were screened, and articles answering our questions were selected.

1. What was the traditional FDA specifications for anti-diabetic drug approval?

Prior to the guidance, the process of drug approval required the sponsors to submit the phase 2 and phase 3 trial data on at least 2500 subjects exposed to the investigational product. At least 1300–1500 of these subjects should be exposed to the investigational product for >1 year and at least 300–500 subjects exposed to the investigational product for >18 months.[8] The end point of efficacy was glycosylated hemoglobin (HbA1c).[7] As per guidelines, these trials used the investigational agent as monotherapy or as an add on therapy. The cardiovascular adverse effects of these therapies were made out from the cardiovascular events that would occur during the course of the trial. These cardiovascular events were not pre-specified and not centrally independently adjudicated. Since the subjects included in these trials were younger, of low CV risk (patients with CV events usually excluded), shorter duration of disease and in shorter trial duration, the number of CV events accrued during the course of the trial would be low. The low event rates and lack of independent adjudication lead to poor estimates of CV safety of these agents.

2. What were the salient points in the FDA guidance issued in 2008?

The guidance issued by FDA in 2008 recommended that a new anti-diabetic drug should not increase cardiovascular risk to an unacceptable extent.[7] The key recommendations are summarized in Table 1.

The FDA also defined the point estimates and upper limit of 95% confidential intervals of risk ratios (1.3 and 1.8) for cardiovascular events in comparison to control group, which should prompt industry to design a post marketing or pre-marketing cardiovascular outcome trials (CVOTs).[7,8] CVOT since then have become an integral part of the drug approval process of anti-diabetic therapies. CVOT, despite its simplicity in design is often misunderstood as trials of glycemic efficacy by both practitioners and experts.[9] With CVOT like Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53), Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS), Examination of cardiovascular outcomes with alogliptin (EXAMINE), Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and EMPA-REG OUTCOME already completed and with more trials to follow, it is important that all stake holders including clinicians in diabetes and cardiovascular practice know the key features of these trials.[10–13]

Table 1 – Salient points of the FDA guidance: Diabetes mellitus – developing drugs and therapeutic biologicals for treatment and prevention (from references 7,35).

1. An upper bound of the 95% CI for the risk ratio of important CV events of 1.3 should be used as a key criterion for excluding unacceptable CV risk for new treatments of type 2 diabetes.
2. Study patients must include individuals with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.
3. A minimum of 2 years' CV safety data must be provided.
4. All phase 2 and phase 3 studies should include a prospective independent adjudication of CV events. Adjudicated events should include CV mortality, myocardial infarction (MI), and stroke and can include hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, and possibly other end points.
5. To satisfy the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials, and/or an additional single, large safety trial may be conducted that alone, or added to other trials, would be able to satisfy this upper bound before a new drug application/biologics license application (NDA/BLA) is approved.

3. How are regulatory CVOT different from trials like UKPDS, PROactive, ACCORD, ADVANCE and VADT?

Any trial reporting a single or composite of cardiovascular end points is labeled as a CVOT. Holman et al. analyzed trials with >1000 subjects and >1 year duration for his analysis of CVOT.[14] These can be of various types

(A) Trials reporting cardiovascular outcomes according to treatment goals (e.g. Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART2D)).[15,16]

(B) Trials reporting CV outcomes as a part of other total outcomes (e.g. UKPDS, DCCT). They may test 2 treatment goals with different regimes.[17,18]

(C) Trials looking at HbA1c goals and specific drugs and/or strategies e.g. Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial.[19]

(D) Trials comparing CV outcomes of 2 different agents e.g. Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) and Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT).[20,21]

(E) Trials looking at cardiovascular safety/benefits of specific drugs (e.g. SAVOR-TIMI 53, TECOS, EXAMINE, ELIXA, Liraglutide Effect and Action in Diabetes: (LEADER), EMPA REG OUTCOME, Canagliflozin cardiovascular assessment Study (CANVAS), Trial to Evaluate Cardiovascular and