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FOR DEBATE

Setting the record straight on TIDE: a lost opportunity for patients with diabetes

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Abstract Much has been written regarding the recently discontinued Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial (ClinicalTrials.gov NCT00879970; *Diabetologia* 55: 36–45) and a variety of opinions have been advanced regarding its purpose, context and design (*N Engl J Med* 397: 959–964). As such, we deemed it appropriate to clarify TIDE's objectives, research questions and design and the clinical equipoise regarding its research questions.

Keywords Bias · Cardiovascular · Diabetes · Early termination of trials · Equipoise · Pharmacoepidemiology · Randomised controlled trials

Abbreviations

BARI-2D	Bypass Angioplasty Revascularisation Investigation 2 Diabetes
CV	Cardiovascular
FDA	Food and Drug Administration
PHRI	Population Health Research Institute
RECORD	Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes
TIDE	Thiazolidinedione Intervention with Vitamin D Evaluation

Type 2 diabetes is a serious chronic disease that is rapidly rising in prevalence and that remains a strong, independent risk factor for death from cardiovascular (CV) and other serious health outcomes. Large, ethical multi-centre randomised control trials conducted over the last 20 years have studied a variety of ways to reduce the risk of serious health outcomes in people with diabetes, and have yielded important advances that are estimated to have saved millions of lives and substantially reduced morbidity. These include the use of statin therapy, blood pressure lowering and ACE inhibitors that have been studied in populations at high risk for CV disease as well as in those who also have diabetes. Indeed, this knowledge would not have been attainable without the willing participation of thousands of patients with diabetes from around the world in large, carefully designed trials, conducted with the appropriate oversight and safety mechanisms in place. Many other interventions have also been tested in ethical, large trials that have not shown an effect, and at times even demonstrated harm. Some of these include proprietary medications studied in trials funded by pharmaceutical companies, and others include vitamins or supplements that would never have been studied in large trials unless novel, ethical and creative approaches were considered. Examples include vitamin E, vitamin B6 and *n*-3 (also referred to as omega 3) fatty acid supplements. The common threads underlying all of this research include: (1) an important scientific question that could affect the lives of millions of people if clearly answered; (2) clinical trial protocols designed by large, multi-disciplinary academic groups; (3) careful and methodical oversight by an experienced and judicious independent data monitoring committee; (4) review by multiple regulatory agencies and ethics committees; and (5) transparent, peer-reviewed reporting of results. The fact that some of these large outcomes trials showed that potentially beneficial therapies including dalcetrapib, torcetrapib, rimonabant and sibutramine were ineffective or harmful [1–4] and that other large outcomes trials showed that potentially ineffective or potentially harmful therapies such as tiotropium [5], calcium channel blockers [6, 7], beta blockers [8], digoxin [9] and metformin [10] were

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effective and safe attests to the rigor and value of this approach and the importance of conducting such research. Indeed, the history of medicine is replete with strident, vocal declarations regarding the harms of a particular drug that were refuted once appropriate ethical research had been conducted.

Such was the situation in 2008 that prompted the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial investigators to assess the CV effects of the thiazolidinedione class of drugs, and particularly rosiglitazone [11]. At that time a large body of evidence suggested that both rosiglitazone and pioglitazone might reduce CV events. This included a wealth of literature showing that both drugs consistently reduced risk factors for CV events including markers of inflammation [12], albuminuria [13], insulin resistance [14, 15], blood pressure [16] and HbA_{1c} [17], and raised putative protective factors such as adiponectin [18] and HDL [19]. By that time randomised controlled trials had also reported that both drugs reduced coronary or carotid atherosclerosis [20–22], and the need for revascularisation following percutaneous coronary intervention [23]. Several large database studies had also reported lower rates of CV events with both of these drugs [24–26] and two large trials had shown that they both reduced the incidence of diabetes by 60–80% [27, 28]. Moreover one large randomised outcomes trial strongly suggested that the addition of pioglitazone versus placebo reduced CV events in high risk patients with diabetes [29]. Conversely, it was also known that these drugs both modestly raised LDL (rosiglitazone more so than pioglitazone [19]) and caused fluid retention, pulmonary oedema, weight gain and anaemia. In addition, controversial meta-analyses of mostly small trials with very few outcomes [30–33], and other database studies, reported higher rates of CV outcomes with rosiglitazone [34–36] and with longer exposure to pioglitazone [36]. Taken together, these data supported a position of clinical equipoise regarding the effect of these drugs on CV outcomes, raised questions regarding whether rosiglitazone and pioglitazone had different or similar effects on CV outcomes, and provided the basis for the TIDE trial, which was designed to answer the following questions with respect to the thiazolidinediones:

(1) Does the addition of a thiazolidinedione (either rosiglitazone or pioglitazone) to the therapeutic regimen reduce CV events compared with placebo?
(2) Is rosiglitazone non-inferior to placebo with respect to CV events?
(3) Is rosiglitazone non-inferior to pioglitazone with respect to CV events?

Uncertainty regarding the effect of these drugs on CV outcomes was further driven by research studies published as TIDE was underway. These include: (1) the large Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) outcomes trial, which reported that the addition of rosiglitazone to either metformin or a sulfonylurea was non-inferior to the combination of metformin plus a sulfonylurea with respect to any CV hospitalisation or death (HR 0.99, 95% CI 0.85–1.16) [37]; and (2) the Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI-2D) trial in which patients with proven coronary artery disease randomly allocated to a strategy of insulin sensitisation (of whom 55% were using rosiglitazone after 3 years) had rates of mortality and CV outcomes that did not differ from those of patients allocated to a strategy of insulin provision (RR 0.91, p=0.13) [38]. There were also new pharmacoepidemiological studies suggesting a CV benefit of pioglitazone compared with rosiglitazone [39]. Indeed, following their review of the available literature, a science advisory from the American Heart Association and the American College of Cardiology Foundation that was published in 2010 [40] concluded that there was ‘clinical equipoise’ regarding the CV effects of rosiglitazone, and called on ‘academic researchers, industry and government agencies to collaborate on definitive randomized trials’ to answer the question. The committee also concluded that the available data were inadequate to determine whether the effects of pioglitazone and rosiglitazone on CV outcomes differed and wrote that ‘only direct head-to-head comparisons of outcomes data in prospective randomized trials can provide convincing conclusions about the comparability of these 2 agents’ [40].

It is clear from the above that the totality of the available data clearly supported the position of clinical equipoise and supported the thiazolidinedione research questions posed by the TIDE randomised controlled trial. Furthermore, this position was endorsed by the TIDE global network of experienced clinical trialists, by academic opinion leaders who designed and were conducting the trial, and by a highly experienced independent data and monitoring committee tasked with overseeing participant safety. Indeed, although the Food and Drug Administration (FDA) officially withdrew its approval of the TIDE trial following heated public debate regarding the uncertainty noted above, the importance of completing TIDE was endorsed by four of its six senior representatives at that time [41]. Most recently, the fact that the FDA convened another advisory panel to review rosiglitazone data from the RECORD trial [42] highlights the murky nature of the available evidence and the uncertainty that could have been resolved by the blinded, placebo-controlled TIDE trial.

In addition to answering an important question regarding the CV effects of the thiazolidinediones, the TIDE trial was designed to assess the effect of vitamin D on mortality and cancer. Many health benefits have been attributed to vitamin D, and many people take it despite the fact that its only proven benefit has been on bone health and reduced fractures. As additional benefits can only be assessed within a large clinical outcomes trial (that is very unlikely to be funded by manufacturers of vitamin D), the TIDE investigators saw a unique

opportunity to leverage the infrastructure provided by TIDE to answer a question of significant public health importance. In light of this, the investigators were able to convince the sponsor (GlaxoSmithKline) to support the testing of vitamin D as part of a factorial design. Such a strategy of using the infrastructure provided by a pharmaceutical sponsor to answer questions of critical public health importance using factorial designs was pioneered by the Population Health Research Institute (PHRI) and has been very successfully used by PHRI to test the CV and mortality effects of vitamin E [43], B vitamins [44] and *n*-3 fatty acids [45].

TIDE was therefore an ethical, rigorously designed and carefully monitored trial that would have provided clear answers to several research questions directly related to the health and well-being of people with diabetes. Its cancellation signifies a missed opportunity to determine whether either or both thiazolidinediones can prevent important health outcomes, and whether or not patients with diabetes should be taking vitamin D, and at what dose. Thus if these agents actually do more good than harm, TIDE's cancellation means that millions of patients will have been denied this benefit.

Perhaps the most important lesson from the TIDE experience is that properly designed trials evaluating important clinical outcomes should be done early in the life-course of a drug, before opinions that are entrenched by confounded epidemiological data and small trials make it difficult to conduct such a definitive outcomes trial. In 2008 the FDA mandated that manufacturers of all new diabetes medications sponsor pre- or post-marketing CV outcome trials [46], which are now occurring earlier in drug development than was the case for TIDE. For these newer drugs, at least, the medical community and regulators will be able to make timely decisions based on high quality evidence.

Duality of interest ZP, JB and HCG were the TIDE trial project officer, project manager and joint principal investigator, respectively. ZP has received honoraria for lectures and advice from GlaxoSmithKline and Eli Lilly. JB has nothing to declare. HCG has consulted for and received honoraria from the following companies that manufacture glucose-lowering drugs: Astra Zeneca, Bayer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, NovoNordisk, Roche and sanofi. His institution has also received grants from Lilly and sanofi for research he is leading. GlaxoSmithKline had no input into this article at any time.

Contribution statement All three authors conceived the article. ZP drafted it, and JB and HCG critically revised it. All three authors approved the final version. ZP, as guarantor, accepts full responsibility for the work, had access to the data, and controlled the decision to publish.

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