Diabetes mellitus is a well-established risk factor for virtually all cardiovascular outcomes, with clinical trials and observational studies demonstrating greater mortality, more myocardial infarctions, and more episodes of heart failure in diabetic than in nondiabetic individuals.1–6 Moreover, diabetes mellitus is often associated with other cardiovascular risk factors, including hypertension and hyperlipidemia. The increased risk for adverse cardiovascular outcomes has made diabetic patients a particularly relevant target group for therapies that reduce cardiovascular risk because diabetic patients appear to benefit as much as or more than nondiabetic patients from successful cardiovascular therapies.7–9

Clinical trials that have assessed strategies to reduce cardiovascular risk in diabetic populations have generally focused on treatment of factors that have been linked to higher risk of cardiovascular disease, such as blood pressure, lipid levels, or albuminuria. Trials of therapies for these risk factors in exclusively diabetic populations benefit from higher overall event rates, which translate to increased power in clinical trials, so that therapies can be tested in fewer patients at lower cost. Although this approach may come at the expense of a broad indication for a specific therapy, the increasing worldwide prevalence of diabetes mellitus somewhat mitigates this concern and makes trials exclusively in diabetic populations financially more palatable for sponsors.

Another reason to test therapies exclusively in a specific patient population is the finding of differential benefit in that population. Such a differential benefit in diabetic patients was observed in a subgroup analysis of the original Bypass Angioplasty Revascularization Investigation (BARI) trial, which randomized patients with multivessel coronary disease to either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).10 Although BARI showed no difference between those randomized to PCI or those randomized to CABG, CABG appeared superior in the subgroup of diabetic patients. Whether this differential benefit was a result of the diabetes mellitus per se or simply because these patients were at higher risk in general remains unclear.

Observational data linking worse glycemic control to higher rates of cardiovascular events in diabetic patients have provided impetus for assessing the impact of therapies that improve glycemic control on cardiovascular risk. Although clinical trials have shown that therapies that improve glycemic control reduce the risk of microvascular disease, including retinopathy, nephropathy, and neuropathy,11 trials attempting to reduce macrovascular events have not proven successful; in the Action to Control Cardiovascular Risk in Diabetes (ACCORD),12 Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),13 and Veterans Affairs Diabetes Trial (VADT)14 studies, improved glycemic control did not reduce the rate of cardiovascular events and in some cases was even associated with increased risk.

The BARI 2 Diabetes (BARI 2D) trial15 assessed the effect of both a cardiovascular intervention and a glycemic intervention on cardiovascular risk in a diabetic population. By utilizing a factorial design, BARI 2D was able to test efficiently and cost-effectively 2 separate hypotheses in the same population. Patients with diabetes mellitus and coronary disease were randomly assigned to either prompt revascularization with intensive medical therapy or intensive medical therapy alone and were also randomly assigned to either insulin-sensitization (including metformin or thiazolidinedione) or insulin-provision (insulin or sulfonylurea) therapy. The decision about the type of revascularization that would be performed (CABG or PCI) was made on clinical grounds before randomization to revascularization or intensive medical therapy. Importantly, this design did not allow BARI 2D to test the hypothesis that was generated by the subgroup analysis of the original BARI study because the decision to revascularize with PCI or CABG was clinically driven.

Although BARI 2D showed no difference in the primary end point of death, myocardial infarction, or stroke between patients randomized to revascularization therapy plus intensive medical therapy versus intensive medical therapy alone, or those randomized to insulin-sensitization therapy versus insulin-provision therapy, this study illustrates a number of...
the issues and challenges inherent in diabetes mellitus clinical trials. One of those challenges is understanding the a priori risk in the population being studied. Accurate estimates of event rates during the design of clinical trials are essential to determining sample sizes, deciding on the appropriate end points, and determining length of follow-up. Diabetic patients are not a homogeneous group, and event rates vary as much as 40-fold in trials of patients with diabetes mellitus, with a mortality rate ranging from 0.3% per year in the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) to >12% per year in the German Diabetes and Dialysis trial. This heterogeneity is influenced and amplified by a number of factors, most notably the presence of baseline cardiovascular disease or renal dysfunction. Additionally, background therapy tends to be better in clinical trials than in registries of seemingly similar patient populations. That was certainly the case in BARI 2D, in which event rates were lower than expected. Because clinical trials are powered on the basis of predicted event rates, understanding the factors that influence event rates in a heterogeneous population is essential before commencing a clinical trial.

The heterogeneity in baseline risk within the BARI 2D trial has affected interpretation of its results. That clinicians decided on a preferred revascularization approach (PCI or CABG) before randomization to revascularization or intensive medical therapy effectively resulted in 2 separate risk strata within the trial. Higher-risk patients were more likely to be assigned by clinicians to the arm comparing CABG with medical therapy than that comparing PCI with medical therapy. The finding that patients who were assigned to the CABG stratum, but not the PCI stratum, benefited to a greater extent from revascularization therapy than medical therapy has been misinterpreted by some as suggesting a benefit of CABG over PCI in diabetic patients. This finding illustrates the importance of baseline risk as a factor in determining whether patients will benefit from a particular therapy but provides no insight, as some have mistakenly argued, about the benefit of one form of revascularization versus the other.

Another factor influencing event rates in a trial are changes in the standard of care that occur during the course of the trial. Although it is common for background therapy to change during the course of a relatively long outcomes trial, trials that test strategies rather than specific therapies have the additional problem of therapeutic approaches changing over time. Both revascularization strategies employed in BARI 2D evolved during the course of the trial, with higher use of drug-eluting stents and greater use of minimally invasive surgical techniques as the trial progressed.

Studies that test strategies rather than individual therapies such as drugs or devices are particularly vulnerable to crossovers because they are generally unblinded, and clinicians may be more likely to intervene and offer the alternative therapy. Crossovers increase the likelihood of a null result. In BARI 2D, 42% of patients in the medical treatment group had undergone revascularization by 5 years; a similar crossover rate was observed between the 2 glycemic control arms, with a substantial number of patients in the insulin-sensitization arm receiving insulin-provision therapy by the end of the trial, a problem that is not uncommon in diabetes mellitus trials because the requirement for additional glucose-lowering medication tends to increase over time. Although crossovers can be anticipated in trials, as they were in BARI 2D, they limit the ability to distinguish between therapies. These factors have particular relevance to noninferiority trials that compare “novel” diabetic therapies with standard of care therapies. In noninferiority trials, a “positive” result is predicated on a “null” finding within a noninferiority boundary. Crossovers and noncompliance can result in a study that “proves” noninferiority simply by failing to maintain separation between therapies.

A compelling finding of the BARI 2D trial was the dissociation between the effects of therapy on the glycolated hemoglobin and insulin levels, which were lower in the insulin-sensitizing arm, and the effects on cardiovascular events, which occurred at similar rates in the 2 arms. These findings are concordant with those of other trials in which reductions in glycolated hemoglobin levels did not translate into cardiovascular risk reductions. Indeed, recent evidence that at least 1 thiazolidinedione might be associated with increased cardiovascular harm, despite effectively lowering glucose levels, argues strongly against the use of intermediate outcomes in testing diabetic and other therapies.

Taken together, the null results of the BARI 2D, ACCORD, ADVANCE, and VADT trials, coupled with recent concerns of frank harm associated with therapies that clearly improve glycemic control, reinforce that surrogate end point studies cannot substitute for large-scale clinical trials to assess cardiovascular benefit or safety. Because event rates are high in diabetic patients in general, small trials run the risk of chance imbalances in cardiovascular outcomes. Regulatory authorities are now imposing strict guidelines for studies of diabetic therapies that require that they be tested in trials large enough to assess cardiovascular safety. Although they stop short of requiring that drugs that improve glycemic control actually reduce cardiovascular risk, which is a worthy if not elusive goal, these new requirements are aimed at ensuring that drugs that improve glycemic control do not result in cardiovascular harm.

Disclosures

None.

References


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