Implications of Contemporary Clinical Trials

ACCORD(ing) to a Trialist
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“Medicine is a science of uncertainty and an art of probability.”
—William Osler (1849 to 1919)

The practice of medicine will always remain an art in which important individual patient decisions are at best guided by incomplete evidence. Randomized controlled clinical trials (RCTs), although imperfect, are the premier tools to generate reliable data to assist in decision making. In cardiovascular medicine, we have been fortunate to have a rich legacy of definitive RCTs demonstrating survival benefits of therapies that have deservedly become cornerstone components of clinical practice. However, RCTs with mortality as the primary objective are practical only for evaluating populations with exceedingly high anticipated mortality rates or would require prohibitively long follow-up to obtain a reliable answer. Construction of composite outcomes combining nonfatal clinically important events with deaths into a single end point offers an effective statistical compromise whereby the potential benefits and risks of an intervention can be assessed with relatively smaller sample sizes than in mortality RCTs. Using composite outcomes that have clinically indispensible and important components extends the application of clinical outcome trials to more prevalent populations with less severely impaired prognosis. However, the compromise is that use of composite end points introduces uncertainty into the interpretation from possible inconsistencies among the components on effect size and at times even direction.

An even greater end-point compromise is more frequently made in RCTs by targeting a primary objective of determining whether a readily quantifiable laboratory measure considered a surrogate marker of disease progression can be favorably altered by the proposed intervention. Because all patients can generally provide a measure of the surrogate or biomarker, these mechanistically targeted trials require considerably fewer patients and shorter durations. A strong link between the surrogates with observational associations of impaired outcomes offers circumstantial evidence for relating a directionally favorable change in the biomarker to a presumed improvement in clinical course. The intent of these biomarker end-point RCTs is to provide a reliable barometer of what the tested intervention would achieve on clinical outcomes if much larger, more labor- and resource-intensive clinical event RCTs were conducted. In the RCTs targeting surrogate or biomarker change as a primary objective, clinical events are generally carefully tracked and reported as a secondary outcome measure. However, the relatively limited number of events and statistical nonprimacy relegate the clinical outcomes to supportive and not definitive. As a consequence, we have more data on therapeutic alterations of surrogate end points than clinical outcomes.

There is a considerable sense of comfort that both physicians and patients derive when a therapeutic intervention is initiated and a laboratory value moves in the direction considered favorable. In the course of clinical practice, such a comfort zone can become reinforced and established, creating a therapeutic sense of righteousness and dogma, at times even creating a formidable obstacle to conducting outcomes research. In cardiovascular medicine, however, there have been multiple discordant examples that underscored the difference between an epidemiological association of a marker of risk and use of a pharmacological agent to produce the presumed favorable effect on the surrogate without achieving the desired alteration of prognosis. The extent and severity of ventricular arrhythmias in populations with impaired cardiac function were and remain strong independent markers for higher likelihood of death.8 With the availability of antiarrhythmic agents that were (and are) effective in suppressing these ventricular arrhythmias, there was an understandable logical extension that in the appropriate patients, their use would reduce the risk of death. This presumption was pervasive, and a major aspect of the care of these patients was to serially monitor rhythm so that patients with these frequently asymptomatic ventricular arrhythmias could be identified for the initiation of pharmacological therapy. Rhythm monitoring was generally performed after treatment to confirm the suppression of arrhythmias. This positive feedback of a favorable directional change in this biomarker of risk offered reassurance to both the physician and patient. The early termination of the Cardiac Arrhythmia Suppression Trial (CAST) by its Data Safety Monitoring Committee when it had sufficient evidence that this use of certain type 1 antiarrhythmic agents was increasing, not decreasing, deaths was shocking. This logical practice of monitoring and treating asymptomatic ventricular arrhythmias to improve survival was shattered by these

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unexpected data, showing that this strategy was in fact exposing patients to harm.9,10

The use of positive inotropic agents to improve ventricular contractility in patients with heart failure and reduced ejection fraction was another vivid example of a well-entrenched surrogate providing misleading information on clinical outcomes.11 Few practicing physicians would have anticipated that a therapy that improved cardiac output and ventricular ejection fraction and reduced wedge pressure in patients with congestive heart failure would be associated with shortened survival. Other more recent examples of an epidemiological marker of risk being favorably altered by pharmacological therapy that did not result in the desired improvements, such as raising high-density lipoprotein with the cholesterol-ester transfer protein inhibitor torcetrapib12 and raising hemoglobin in anemic patients with diabetes mellitus and chronic kidney disease with an erythropoietic stimulating agent,13 further underscore the need for outcomes trials rather than presumptions of clinical benefit based on the changes in biomarkers.

In this context, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial addressed 3 separate and practical questions: whether additional pharmacological therapy to more intensively lower blood pressure, to achieve better glycemic control, or to more favorably alter lipid profiles (predominantly lower triglycerides with slight high-density lipoprotein increase) would reduce the incidence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.14–16 Although advocated and often assumed, the risk-to-benefit ratio of these more intensive approaches to the management of patients with type 2 diabetes mellitus was not established. ACCORD was an ambitious, indeed enormous, program of research. The extent of resources mustered to conduct ACCORD, $≈300 million in federal funds plus major contributions in pharmaceutical supplies, serves to illustrate the huge economic commitment for a clinical event RCT.

To test the hypothesis that the strategy to control a risk factor more intensively would improve prognosis, the challenge was to achieve substantial between-group differences in the biomarkers. With the impressive control of risk factors in the patients assigned to standard therapy in ACCORD (1 year after randomization in the respective standard arm; hemoglobin A1C, 7.5%; systolic blood pressure, 133.5 mm Hg; plasma total cholesterol, 166 mg/dL; triglycerides, 184 mg/dL), this was a formidable task. The annual mortality of only 1.5% for these patients selected for type 2 diabetes mellitus plus prior cardiovascular events or multiple risks illustrates the synergistic effects of the multifactorial risk reduction regimen.17

Thanks to the diligent efforts of the physicians, coordinators, and patients, the respective intense arms achieved a >1% absolute difference in hemoglobin A1C, a 14.2-mm Hg lower systolic pressure, and plasma triglycerides of ≈145 mg/dL. To validate the test of whether more intensive reductions in these factors would reduce the risk of the clinical composite, the marked increase in adverse events attributed to the more intensive strategies indicates that operationally lower limits of therapy were reached.

For each of the 3 separate questions, despite the more intense use of therapies producing relatively large and apparently favorable alterations in the respective risk factor, the primary clinical composite was not significantly reduced. Although it is disappointing that the anticipated improvement in clinical events was not observed, we should consider the ACCORD trials to be successful in generating vital information that should affect patient care. Predictably, the ACCORD data will be dissected and debated and will be the subject of journal clubs and rounds in which the importance of subgroups and secondary and tertiary end points will undoubtedly be inflated. This issue of Circulation features an expert commentary on each of the 3 component questions that ACCORD was designed to address.18–20 In my view, kudos are due the National Heart, Lung, and Blood Institute, the Investigators, the caregivers, and the participating patients for addressing clinically relevant but difficult questions for which any reliable answer (benefit, neutral or hazard) would affect the care of large numbers of patients. Thanks for the 3 reminders that pharmacologically produced changes in surrogates cannot adequately inform us of the benefits or risks of an intervention. Although John Fitzgerald Kennedy was not referring to medicine, his famous quote, “The greater our knowledge increases the more our ignorance unfolds,”21 suitably applies.

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