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REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS
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The Primary Outcome Is Positive — Is That Good Enough?
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There is a natural tendency to simplify the findings of a clinical trial into a binary conclusion: “Was there a positive outcome — or not?”

In order to address this question with some objectivity, attention is typically focused on whether the prespecified measure of success for the primary outcome has been met — that is, whether a P value of less than 0.05 has been achieved for the difference in treatments. In reality, a more nuanced interpretation requires a thorough examination of the totality of the evidence, including secondary end points, safety issues, and the size and quality of the trial. In this article, which focuses on the evaluation of “positive” studies — as in our previous article, which focused on the appraisal of “negative” studies — our intent is to facilitate a more sophisticated and balanced interpretation of trial evidence. Again, we make our points using examples from trials involving cardiovascular disease (our area of expertise), but the messages can be easily applied to other subject areas.

Key Questions When the Primary Outcome Is Positive

The achievement of statistical significance for the primary outcome is typically a necessary prerequisite for the adoption of a new therapy, but it is not sufficient. The totality of trial results will be scrutinized by numerous stakeholders, including regulators, payers, journal editors and reviewers, clinical experts, guidelines committees, physicians, patients, and critics. The determination of whether the findings provide evidence that is sufficient to modify medical practice requires in-depth interpretation of the trial data and the results of earlier, related trials. Answering the key questions discussed below (and listed in Table 1) may help to identify which “positive” trials provide evidence that is sufficient to advance clinical practice. In this regard, we also acknowledge that studies that unexpectedly reveal harm (e.g., the CAST trial [see box for a list of the complete names of all trials mentioned in this article], which revealed that antiarrhythmic therapy was associated with an increase in mortality) may equally inform medical practice, although here, too, close scrutiny of the validity of the results is warranted.

Is a P Value of Less Than 0.05 Good Enough?

A P value of 0.05 carries a 5% risk of a false positive result (i.e., there is no true difference between treatments). If a trial is meant to provide proof of a genuine treatment difference beyond reasonable doubt, a much smaller P value — say, P<0.001 — is required. For instance, the PARADIGM-HF trial of sacubitril–valsartan versus enalapril in patients with heart failure showed overwhelming benefit (P<0.00001) with respect to the composite primary outcome of cardiovascular
death or hospitalization for heart failure, which justified regulatory approval and the clinical adoption of sacubitril–valsartan. In contrast, in the SAINT I trial\(^5\) of NXY-059, a free-radical–trapping agent, versus placebo for the treatment of acute ischemic stroke, the P value for the primary outcome of disability at 90 days was 0.038 — not strong evidence of efficacy. A second, larger trial (SAINT II\(^6\)) was needed and revealed no significant effect (P=0.33), which prompted the authors to conclude that “NXY-059 is ineffective for the treatment of acute ischemic stroke.”

**WHAT IS THE MAGNITUDE OF TREATMENT BENEFIT?**

Beyond statistical significance, a treatment difference needs to be clinically meaningful — that is, large enough to matter. This determination requires examination of the treatment effect on both a relative scale (e.g., by calculation of the relative risk or the hazard ratio) and an absolute scale (e.g., by calculation of the differences in the rates of events during follow-up and in the number needed to treat). In addition, the extent of uncertainty in the estimated effect should be considered by examining the 95% confidence interval. For instance, if the P value is close to 0.05, the confidence interval will range from almost no effect to an upper boundary that is considerably larger than the point estimate.

An illustration of these concepts is provided in the IMPROVE-IT trial,\(^7\) in which ezetimibe was compared with placebo in patients with acute coronary syndromes who were being treated with simvastatin; the hazard ratio for the composite primary outcome of cardiovascular death, myocardial infarction, unstable angina, revascularization, or stroke was 0.94 (95% confidence interval [CI], 0.89 to 0.98; P=0.016). The 7-year primary event rates were 32.7% with ezetimibe versus 34.7% with placebo (Fig. 1), a difference of 2 percentage points, with a 95% confidence interval that ranged from close to 0 to 4 percentage points. Although the findings for this trial were described as “positive,” one might question whether the benefit of ezetimibe is large enough to warrant its cost and potential complications. An advisory panel from the Food and Drug Administration (FDA) recommended against expanding the ezetimibe label to include an indication for a reduction in cardiovascular events.\(^8\)

**IS THE PRIMARY OUTCOME CLINICALLY IMPORTANT (AND INTERNALLY CONSISTENT)?**

**Surrogate Outcomes**

Although phase 3 trials are usually powered to achieve clinically relevant outcomes, for some diseases a surrogate primary outcome measure has been accepted (e.g., a reduction in glycated hemoglobin levels as an indication of antiglyc-
mic efficacy in patients with diabetes). However, the findings of some large-scale trials have raised questions about the wisdom of such reliance on surrogate markers. For instance, in the ACCORD trial, intensive therapy resulted in markedly lower glycated hemoglobin levels than standard therapy, but the rate of cardiovascular events was not significantly lower, and mortality was higher. Similarly, in the LIDO trial, levosimendan resulted in greater hemodynamic improvement (the primary outcome) than dobutamine in patients with acute heart failure, which resulted in the regulatory approval of levosimendan in many countries. However, SURVIVE, the larger, subsequent trial of levosimendan versus dobutamine, showed no evidence of a treatment benefit for the primary outcome — 180-day mortality ($P=0.40$) — and levosimendan was not approved by the FDA.

**Composite Outcomes**

Positive composite primary outcomes must be carefully inspected to determine which components are driving the result. For instance, in the RITA-3 trial, which assessed the effects of interventional versus conservative management in patients with acute coronary syndromes, fewer patients in the intervention group had a composite primary outcome event of death, myocardial infarction, or refractory angina at 4 months (9.6% vs. 14.5%, $P=0.001$). When the trial findings were presented at a European Society of Cardiology Congress, a newsletter headline read “RITA-3: First Proof Intervention Saves Lives” — an incorrect interpretation, since this finding was driven by a halving of the rate of refractory angina, with no evidence of a difference in the rates of death or myocardial infarction in the short term. At the time, the question of whether the data justified the use of a routine invasive strategy was debatable, given its up-front risks and costs. Fortunately, a 5-year follow-up study revealed a 22% lower rate of death or myocardial infarction in the intervention group than in the conservative management group ($P=0.04$), and subsequent meta-analyses have supported the use of an early interventional approach in patients with acute coronary syndromes to improve prognosis.

More strikingly, the EXPEDITION trial of cariporide versus placebo in high-risk patients undergoing coronary-artery bypass grafting (CABG) had a very positive result ($P=0.0002$) for the primary composite outcome of death or myocardial infarction. However, this outcome was driven by a reduction in myocardial infarction ($P=0.000005$), whereas mortality was higher with cariporide ($P=0.02$), as was the rate of cerebrovascular events ($P<0.001$). These findings led to the abandonment of cariporide for this indication.

**ARE SECONDARY OUTCOMES SUPPORTIVE?**

Confidence in the overall “positivity” of a trial is enhanced if prespecified secondary outcomes also show a treatment benefit. Conversely, if secondary outcomes show no hint of benefit, doubts will materialize. For instance, in the SAINT I trial of NXY-059 in acute ischemic stroke, no evidence of benefit existed for two key secondary outcomes — scores on the National Institutes of Health Stroke Scale and the Barthel Index. This absence of evidence enhanced suspicion regarding the “positive” primary outcome, a suspicion that was reinforced by the negative result in the sequel trial, SAINT II.

In contrast, in the EMPA-REG OUTCOME trial...
of empagliflozin versus placebo in type 2 diabetes, the benefit of empagliflozin with respect to the composite primary outcome (cardiovascular death, myocardial infarction, or stroke) was of borderline significance, with a hazard ratio of 0.86 (95% CI, 0.74 to 0.99; P = 0.04). However, this finding was driven by a robustly lower rate of cardiovascular death (hazard ratio, 0.62; 95% CI, 0.49 to 0.77; P < 0.001) and was reinforced by similar findings regarding all-cause death (P < 0.001) and hospitalizations for heart failure (P = 0.002). Thus, the effect of empagliflozin was observed mainly in the secondary outcomes, although the positive finding for the primary outcome imparted initial credibility.

Are Findings Consistent Across Important Subgroups?

Relative treatment effects may vary according to patient characteristics. Alternatively, a consistent relative treatment effect across all patient types may be observed, but certain high-risk subgroups may have greater absolute benefits, as has been seen with statins in patients with multiple cardiac risk factors. Long-term statin use in primary prevention is thus commonly confined to patients with a sufficiently high baseline risk.

More challenging is the situation in which subgroup analyses in a “positive” trial identify patients who do not appear to benefit from the new treatment. Caution is warranted, since spurious findings can arise when multiple subgroups are analyzed. Nonetheless, protecting such patients from a treatment that appears to be ineffective (or harmful) may be warranted, depending on the strength of the statistical interaction and its biologic plausibility.

For instance, in the PLATO trial involving patients with an acute coronary syndrome, the risk of the composite primary outcome of cardiovascular death, myocardial infarction, or stroke was 16% lower with ticagrelor than with clopidogrel in the overall study population (P < 0.001). However, among patients receiving a high maintenance dose of aspirin, the risk was 45% higher with ticagrelor than with clopidogrel, whereas among patients receiving a low maintenance dose of aspirin, the risk was 45% higher with ticagrelor than with clopidogrel, whereas among patients receiving a low maintenance dose of aspirin, the risk was 45% higher with ticagrelor than with clopidogrel. Although the validity of this observation is still disputed (it arose from numerous exploratory subgroup analyses and lacks obvious biologic plausibility), the FDA issued a warning that a maintenance dose of more than 100 mg of aspirin reduces the effectiveness of ticagrelor and should be avoided.

Is the Trial Large Enough to Be Convincing?

When a small clinical trial achieves statistical significance for its primary outcome, cautious interpretation is warranted. Small trials lack power, so positive treatment effects are susceptible to exaggeration, and false positives may occur.

For instance, in a trial of N-acetylcysteine versus placebo to prevent nephropathy induced by radiocontrast agents, 1 of 41 patients receiving N-acetylcysteine had a primary outcome event, as compared with 9 of 42 patients who were receiving placebo, resulting in a relative risk with N-acetylcysteine of 0.10 (95% CI, 0.02 to 0.90; P = 0.01). On the basis of this small trial, the stated conclusion that N-acetylcysteine is “an effective means of preventing renal damage” is too strong; a more appropriate statement is that N-acetylcysteine “may be effective.” Such a conclusion would motivate the conduct of a larger, more definitive trial. Unfortunately, a subsequent meta-analysis of 10 randomized trials (1916 patients) reported that the evidence was too weak and heterogeneous to support use of N-acetylcysteine for this indication.

Similarly, in the PRAMI trial, 465 patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease who were un-
derning primary percutaneous coronary intervention (PCI) were randomly assigned to receive preventive angioplasty (complete revascularization during the index procedure) or initial angioplasty of the infarct artery only. The hazard ratio for the composite primary outcome (refractory angina, myocardial infarction, or cardiac death) with preventive angioplasty versus angioplasty of the infarct artery only was 0.35 (95% CI, 0.21 to 0.58; P < 0.001), with similarly lower risks for each of the three components. This controversial finding was based on relatively few primary events (21 in the intervention group vs. 53 in the group receiving standard care) and selective enrollment (recruitment took 5 years and was stopped early), giving the impression that the 65% reduction in hazard was too good to be true. Two subsequent, similarly sized trials showed mixed results. Thus, more evidence is needed to justify such a radical change in STEMI management, and the results of the ongoing, large-scale COMPLETE trial are awaited with interest.

**WAS THE TRIAL STOPPED EARLY?**

Sometimes a trial is stopped early because interim results show strong evidence of treatment superiority, which is often a newsworthy event. Unfortunately, this practice tends to exaggerate treatment efficacy. As a trial progresses, the estimated treatment effect varies randomly in relation to the true effect. If the interim estimate is based on a random high indication of efficacy, it is more likely to cross a statistical stopping boundary and to convince a data and safety monitoring board that overwhelming evidence of benefit exists. Stopping early also truncates evidence for important secondary (and safety) outcomes.

In the FAME 2 trial, for example, PCI was compared with medical therapy alone in patients with stable coronary artery disease and hemodynamically significant lesions (as assessed by means of fractional flow reserve). The trial was stopped early because the hazard ratio for the primary outcome (all-cause death, myocardial infarction, or urgent revascularization) favoring PCI was 0.39 (95% CI, 0.26 to 0.57; P < 0.001). This benefit with PCI was driven by fewer urgent revascularizations, an arguably “soft” outcome in an unblinded trial. The rate of death or myocardial infarction, although lower with PCI (hazard ratio 0.79; 95% CI, 0.49 to 1.29; P = 0.35), was inconclusive. Had the trial continued to its intended completion, a significantly lower rate of death or myocardial infarction may have emerged, which would have greatly enhanced the value of the trial.

Another recent example is the SPRINT trial of intensive versus standard blood-pressure control, which had a composite primary outcome of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death. The trial was stopped early at a median of 3.26 years rather than at the intended 5-year follow-up, and at the time the trial was stopped, the hazard ratio for the primary outcome with intensive control was 0.75 (95% CI, 0.64 to 0.89; P < 0.001). The exceptional speed to publication was surprising; only 4 weeks lapsed between the time that the trial was stopped and the time at which the manuscript was submitted for publication. The quality and completeness of any interim database are inevitably imperfect — there will be outstanding primary (and other) events yet to be ascertained and adjudicated. In addition, the moment at which a trial is stopped is the time at which an exaggerated estimate of efficacy is more likely to be present. Orderly trial closure after early stoppage takes several months and is necessary to achieve robust interpretation of all the evidence. Earlier reporting of preliminary, incomplete results is usually unwise.

**DO CONCERNS ABOUT SAFETY COUNTERBALANCE POSITIVE EFFICACY?**

When a new treatment has superior efficacy, it is important to identify concerns about safety that might offset the benefits. A balanced account of both efficacy and safety must be provided. Absolute benefits and risks should be presented in terms of differences in percentages. Consideration of the number needed to treat for benefit versus the number needed to harm may provide a guide to net clinical benefit.

In the DAPT trial, for example, an additional 18 months of dual antiplatelet therapy versus aspirin alone beginning 1 year after the implantation of a drug-eluting stent resulted in rates of major adverse cardiac and cerebrovascular events and of stent thromboses (the two primary efficacy outcomes) that were lower by 1.6% and 1.0%, respectively. However, this benefit came at the cost of higher rates of major bleeding events. According to Global Use of Strategies to Open Occluded Arteries (GUSTO)
criteria, the rate of “moderate or severe” bleeding events was 0.9% higher with continued dual antiplatelet therapy, and according to Bleeding Academic Research Consortium (BARC) criteria, the rate of bleeding that required medical attention was 2.7% higher. All-cause mortality was 0.5% higher with prolonged dual antiplatelet therapy (P = 0.05), and this change was attributed primarily to greater noncardiovascular mortality (P = 0.002), although some experts have argued that the higher rates of death may have been due to chance. Debate ensues: Is the net effect of prolonged dual antiplatelet therapy in this population beneficial or harmful?

Similarly, in the SPRINT trial, intensive lowering of blood pressure resulted in a rate of the primary composite cardiovascular outcome that was 1.6 percentage points lower and a rate of death that was 1.2 percentage points lower than the rates with standard blood-pressure control during a median follow-up period of 3.26 years. However, these benefits must be weighed against rates of hypotension, syncope, and acute kidney injury, which were higher (by 1.4 percentage points, 1.1 percentage points, and 1.8 percentage points, respectively) with intensive blood-pressure control (Fig. 3). Note that all these benefits and risks, although statistically significant, represent small absolute differences. Thus, guideline committees, treating physicians, and patients face a challenge when trying to determine which strategy to adopt.

**IS THE BALANCE OF EFFICACY AND SAFETY PATIENT-SPECIFIC?**

The net clinical benefit of a new treatment may be patient-specific — that is, worthwhile for those at an increased risk for the primary efficacy outcome but deleterious for those at an increased risk for adverse events. Calculating the individual patient trade-offs between efficacy and safety is not straightforward, and statistical modeling techniques may be useful.

For the DAPT trial, multivariable models were developed for predicting the risk of myocardial infarction or stent thrombosis and the risk of major bleeding. In addition to accounting for the duration of antiplatelet treatment (12 months vs. 30 months), these models included 9 patient and procedural characteristics and were designed to allow determination of the relative risks of ischemia versus bleeding in individual patients. Limitations included the omission of some variables that are known to predict the risk of ischemia and bleeding, the failure to directly consider the predictors of mortality, and the absence of external validation from a contemporary data set (as yet). Nonetheless, this analysis represents a useful development toward individualizing patient care.

**ARE THERE FLAWS IN TRIAL DESIGN OR CONDUCT?**

A highly significant result for the primary outcome goes a long way toward substantiating the view that findings cannot be attributed to chance.

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**Figure 3. Balancing Efficacy and Safety Outcomes in SPRINT.**

In the SPRINT trial, among 9361 selected patients with a systolic blood pressure of 130 mm Hg or more who were randomly assigned to intensive treatment (a systolic blood-pressure target of <120 mm Hg) or standard treatment (a target of <140 mm Hg), intensive treatment resulted in a substantially lower rate of the composite primary outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death than standard treatment and in lower rates of all-cause death and heart failure. However, intensive treatment was associated with significantly higher rates of serious adverse events related to hypotension, syncope, and acute kidney injury. Data are from the SPRINT Research Group.
Nonetheless, biases in the design and conduct of the trial must be ruled out before a genuine benefit can be acknowledged.

For instance, the first randomized trial of renal denervation in treatment-resistant hypertension, SYMPLICITY HTN-2, showed that at 6 months, systolic blood pressure was markedly lower in the treatment group than in the control group (mean difference, 31 mm Hg; P<0.0001). However, the absence of blinding introduced major issues (e.g., placebo and Hawthorne effects, ascertainment bias, and regression to the mean). In the subsequent, sham-controlled trial, SYMPLICITY HTN-3, renal denervation appeared to be ineffective, thereby emphasizing the potential unreliability of unblinded trials.

Limitations in the completeness and quality of the data can also corrupt the validity of a trial. Not all patients fully comply with intended treatment regimens, and some withdraw from follow-up. Judgment is required in determining whether the extent of nonadherence or withdrawals casts doubt on the legitimacy of a trial. For instance, the ATLAS ACS 2–TIMI 51 trial of rivaroxaban versus placebo in patients with acute coronary syndromes showed highly significant between-group differences in favor of the lower dose of rivaroxaban with respect to both the primary outcome (cardiovascular death, myocardial infarction, or stroke) and cardiovascular death alone. But 27.6% of the patients discontinued treatment prematurely, and data on vital status were missing for 7.2% of the patients — factors that introduced uncertainty. These problems appeared to be greater in this trial than in other large trials that address acute coronary syndromes and contributed to the FDA decision to withhold its approval of rivaroxaban for this indication.

**DO THE FINDINGS APPLY TO MY PATIENTS?**

The findings of any trial apply to the specific patients enrolled and the therapies administered (both background and experimental). The question of whether the results can be generalized to other patients must be considered. For instance, the SPRINT trial excluded patients younger than 50 years of age and those with diabetes or a history of stroke. The trial results (Fig. 3) thus apply to only approximately 20% of all patients with hypertension who are seen in practice. Investigators in the ACCORD trial previously considered the use of intensive blood-pressure control exclusively in patients with type 2 diabetes and reported no effect on cardiovascular events as compared with standard therapy. Whether the divergent results of the SPRINT and ACCORD trials are due to differences in patient characteristics, medications, trial methods, or other factors remains undetermined.

The geographic representation in a trial may also affect the generalizability of its results. Many major trials are multinational, which is an advantage in conferring global meaning. But health care practices may vary across regions (e.g., the use of primary PCI vs. fibrinolysis in patients with STEMI). If patient recruitment is dominated by one region, worldwide applicability may be limited. In addition, genetic, anatomical, environmental, and dietary differences among peoples sometimes make outcomes difficult to generalize across countries.

Similarly, the results from single-center trials must be viewed with caution. Center-specific effects, such as particular systems of care and the background therapies used, may preclude the generalizability of the findings, and single-center trials often lack quality-control measures. Results from single-center studies, even those with a reasonable sample size, should rarely serve as the basis for changing guidelines unless the results have been validated in subsequent multicenter trials. For example, the single-center TAPAS trial of thrombus aspiration during primary PCI, which involved 1071 patients with STEMI, showed dramatically lower mortality at 1 year after PCI and thrombus aspiration than after conventional PCI (hazard ratio, 0.60; 95% CI, 0.36 to 0.98; P = 0.04). In hindsight, this outcome was unrealistic given the modest benefit in reperfusion success, which was the primary outcome. However, this study led to widespread adoption of thrombus aspiration for many years. Two multicenter trials involving more than 17,000 patients have now convincingly shown that routine thrombus aspiration offers no advantages with regard to mortality or cardiovascular events.

Finally, by the time the long-term findings for the primary outcome of a randomized trial become available, advances in care may have lessened their relevance to contemporary practice. For example, in the SYNTAX and FREEDOM trials, patients with left main or multivessel disease were assigned to PCI with first-generation drug-eluting stents or to CABG. However,
If the efficacy and safety outcomes of the trial are convincingly met, the next step is to evaluate its overall quality and internal validity. It must also be determined whether the findings translate into treatment effectiveness (and net clinical benefit) in real-world patients. However, caution is required when data from nonrandomized registries are used to confirm or refute trial findings, given the potential for selection bias and residual confounding when such registries are used. At the same time, gauging the cost-effectiveness of treatments across different types of health care systems will determine the level of reimbursement (which in turn will affect the adoption of a new therapy).

For a new drug, the question of whether the results of a pivotal trial will satisfy the requirements for approval established by regulators (e.g., FDA and the European Medicines Agency) depends on the totality of the evidence from the trial and from all previous, related studies. Often, further evidence is required to clarify the safety profile of a new drug, and approval may depend on the sponsor’s willingness to undertake additional safety studies (by means of randomized trials or observational registries).

Societal guideline committees play an important role in synthesizing the knowledge base and classifying the strength of evidence for new treatments; their endorsements strongly affect practice. Ultimately, however, physicians at the point of care bear the final responsibility for accurately interpreting clinical trial results and for integrating regulatory and guideline recommendations in order to make the best treatment decisions for each patient in their care.

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