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CARDIOVASCULAR PERSPECTIVE

Confirmatory Trials for Drugs Approved on a Single Trial

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The requirement for two as opposed to one adequate and well-controlled study for drug approval has gained and lost popularity in regulatory science.[1] The rationale for two trials was that an individual trial result might be driven by bias in the specific study site, the specific study personnel, or in the design, conduct and control arm of a specific study. Thus, a second trial, which alters these preconditions, would be able to confirm whether an intervention truly works or whether the observed result was a product of a unique and irreproducible recipe. Criticism of recent trials in cardiovascular medicine force us to revisit under what circumstances two regulatory trials are preferable, and when one might suffice. Here, we consider two examples: a trial of icosapent ethyl and a trial of sacubitril-valsartan. Both have generated controversy in the professional community for specific study design choices, including choice of control arm, or use of unequal run-in periods. A confirmatory, randomized study could provide clarity in both these examples and may be demanded by regulatory agencies.

ICOSAPENT ETHYL

Consider the recent publication of icosapent ethyl, a fish oil derivative, which improved cardiovascular events from 22% to 17.2% (a between-group difference of 4.8%) over 4.9 years in a randomized trial against a mineral oil placebo.[2] The drug's large benefit runs counter to several other large randomized trials of fish oil supplementation, which were negative.[3,4] Moreover, the control arm noted a rise in LDL (low-density lipoprotein) levels over the duration of the study from 76.0 to 84.0 mg/dL, which is not typical for control arms of trials of lipid-modifying agents, and may be because of poor statin absorption caused by the mineral oil control. Moreover, diarrhea, which can be a consequence of large mineral oil intake, was higher in the control arm, 9.0% versus 11.1% (P=0.002). Thus, the specific study of icosapent ethyl results in an ambiguous conclusion as to whether the benefit seen was because of the benefit of the drug or a harm from the specific control.

SACUBITRIL-VALSARTAN

Consider also the PARADIGM-HF study (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), which randomized patients to a maximal dose of an ARB paired with sacubitril, a novel inhibitor of neprilysin, or half maximal dose of an ACE inhibitor, enalapril. Several design limitations have been identified[5] besides the unequal ARB/ACE inhibitor dosing, including a double drug run-in period of unequal times, a loss of 20% of participants during run-in, and the fact that the comparison made

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was A+B versus C. In other words, that 2 variables were altered in the intervention arm: the addition of a novel drug, and the substitution of the ACE/ARB agent. This type of trial design was observed only in 2 of 141 cardiovascular studies submitted for regulatory approval to the US Food and Drug Administration (FDA). In the only other example of A+B versus C trial design, a confirmatory trial was mandated. Moreover, just as with icosapent ethyl, a prior trial of a neprilysin inhibitor failed to lead to FDA approval.[6]

DOES A LOW *P* VALUE NEGATE THE NEED FOR CONFIRMATION?

Both sacubitril-valsartan and icosapent ethyl achieved robust *P* values for the primary end point, specifically 0.00000001[7] for icosapent and 0.0000004[8] for sacubitril-valsartan, and some have claimed that a stringent *P* value obviates the need for a confirmatory study[9], but focusing exclusively on the *P* value ignores other potential sources of error and bias in these studies. Both of these trials have features that are of concern, such as unique design elements that may partially or fully account for treatment effect. Both of these drugs remind us that the value of a confirmatory study is not to further reduce the *P* value, but to ensure that under a slightly altered set of circumstances, the benefit would persist. Would sacubitril-valsartan perform better than valsartan at comparable dose? And, would icosapent ethyl perform better than gelatin placebo, rather than mineral oil?

WHEN TWO TRIALS ARE NEEDED, AND WHEN ONE MAY SUFFICE

Two trials are desirable for blockbuster medications that will be administered to large populations. This is because the risks of false-positive results carry large population-wide exposure to agents and the drugs typically have a sizable financial burden. For promising agents, two trials can be run contemporaneously, in order not to slow drug approval. The rule for two clinical trials may not be needed for all drugs in all settings.

The need for a confirmatory trial can be waived by the FDA when the effectiveness can be extrapolated from other types of data (eg, use in a new population or different dose or regimen), or when single, well-done multicenter trial is done with a substantial improvement in a patient-centered outcome.

A confirmatory trial may also be suspended for drugs used for severely life-threatening conditions (ie, short median survival). Oncology drugs sometimes fall under this categorization, yet there are lessons to be learned from the lack of confirmatory trials before FDA approval. Bevacizumab was initially approved for the treatment of human epidermal growth factor receptor 2 negative metastatic breast cancer, in combination with paclitaxel, based on improvement in progression-free survival in one trial.[10] Later, confirmatory trials showed that there was no improvement in overall survival (in pooled analysis), which led to the FDA removing its approval for this indication. The tradeoff between providing faster treatment for an unmet need, minimizing the financial costs of excessive testing, and ensuring effectiveness and safety is an important consideration. Yet for drugs that will be used in large patient populations, approval based on a single trial with design favoring the experimental arm yields a high degree of uncertainty alongside tremendous cost.

CONCLUSIONS

Criticism of recent trials in cardiovascular medicine force us to revisit a one-trial standard for potential blockbuster drugs. The results of these trials have reminded us of the null and sometimes harmful outcomes may result from clinicians making decisions on limited information. A confirmatory study, based on well-done randomized data, could provide clarity in both these cases and can be demanded in select cases by regulatory agencies. Replication is the hallmark of good science, and nowhere is good science more needed than in drug regulation.

ARTICLE INFORMATION

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