EDITOR’S PAGE

Don’t Be Negative on Negative Trials

Too often, negative trials are viewed as failures. Great effort is put into designing and executing a trial with an end point, which if reached, may prove the value of the therapy. If the end point is not reached, the value of the therapy is not proved. This does not mean that the therapy is proved to be of no value.

Recently, I tried to explain the value of some negative trials to a friend who knows a lot about winning and losing, as in, “Did your team win the Super Bowl or lose the Super Bowl?” He is a very positive guy, is a huge sports fan, and abhors a tie. My explanation to him about the value of trials that were not positive left him somewhat baffled. This conversation came after the first couple of days of the American Heart Association (AHA) meeting in Chicago. He asked me, “What is happening at the American Heart Association meeting?” I told him that most of the trials that were being reported were negative and he said, “That’s too bad.” But, was it?

Negative trials far outweighed positive trials in the late-breaking trial category reported at the AHA. Among the trials being reported were the CLOSURE I (Safety and Efficacy of the STARFlex Septal Closure System vs. Best Medical Therapy in Patients with a Stroke or TIA due to Presumed Paradoxical Embolism Through a PFO) (1) trial, which failed to show that routine percutaneous closure device placement for patent foramen ovale (PFO) reduced the chance of subsequent stroke; the SMART AV (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) (2) trial, which failed to show that routine echocardiography following resynchronization therapy for congestive heart failure improved outcomes; the GRAVITAS (Gauging Responsiveness with A VerifyNow Assay—Impact on Thrombosis and Safety) (3) trial, which failed to show a significant reduction in events with doubling of the clopidogrel dose after stent placement; and several more. My friend interpreted this news as a failure to get value for the significant expenditures involved in performing these trials. I reminded him that disproving a hypothesis is perhaps the greatest contribution of the scientific method and should not be viewed as failure.

He said, “I understand. The trials you listed were really not negative but positive in proving that no PFOs should be closed, no one should have an increased dose of clopidogrel, and echocardiography should never be done on patients who had recent resynchronization therapy.” He went on, “This is really very positive news because it shows we can save a great deal of money by eliminating PFO closures, increased clopidogrel dosing, and echocardiography for those patients.” This is unfortunately the “black and white,” “either/or” thinking that is reflected by sound bites and headlines. More importantly, it is often the only thing that patients and payers hear. The nuisances of negative trials, including the very important questions of who are the subjects, what is the design, was the result consistent across subgroups, and many others, are not asked often enough. Evidence generated from medical research is seldom absolute, but it is an evolution that moves us closer to the truth.

My friend said, “So these trials will not change anything?” Of course they will. Routine practice will not be to close all PFOs, to double the dose of clopidogrel, or to do echocardiograms. To the degree that these practices were routine there will be changes in practice. Just as the much-discussed COURAGE trial failed to show improved survival by routine stenting for stable ischemic heart disease, it did not prove that stenting should not be done in selected patients with stable ischemic heart disease. Perhaps the greatest value will be...
to help design the next trial to work toward the goal of identifying which patients should have the therapy.

As we move further into the era of cost containment in medical investigation and rely more on observational studies of populations, we must not forget the value of randomized controlled trials that point out the holes in our “conventional wisdom.” At the same time, it is important to take into account the findings of negative trials in formulating the next question to be asked. Perhaps some of those questions should be: Are there PFOs that should be closed and how can these be identified? Are there patients who require more antiplatelet therapy, and what role can doubling the clopidogrel dose play when generic formulations are available? And, which patients who haven’t shown improvement from resynchronization therapy should have echocardiographic guidance of different pacing modalities? Or, in the post-COURAGE world, which patients with documented ischemia will benefit from revascularization?

None of these questions were answered by the negative trials reported, but the questions could not have been intelligently asked without the findings of the negative trials. Are these trials failures? Far from it. They are of great value, as I told my friend.

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