EDITORIAL

James V. Felicetta, MD, *Editor-in-Chief*

A Good Study Gone Bad?

I've written before in these pages about the critical importance of clinical research, especially randomized controlled trials (RCT). These trials have unequivocally established themselves over the past 45 years or so as the absolute gold standard of medical studies.

Many promising therapies that seemed so logical and beneficial to patients simply haven't panned out when subjected to the rigors of a well-designed clinical trial. There are many such examples, but one that most people remember along these lines is the Women's Health Initiative. Before that study practically every health care professional believed that giving estrogens to postmenopausal women would provide significant protection from the serious cardiovascular events that plague women after menopause, but the trial showed just the opposite. Estrogens given in the postmenopausal period actually increase the number of cardiovascular events, along with a mixed bag of other advantages and disadvantages.

Well-designed clinical trials are incredibly time consuming and expensive. Only the very major players, such as the National Institutes of Health (NIH) and a very limited number of pharmaceutical companies, can afford the huge financial outlays needed to carry out these critically important clinical trials.

Trials funded by drug companies are invariably linked to the hope for future blockbuster sales. This means that the trial designs and the clinical questions asked are often not the ones of greatest interest to the scientific community but rather to those most likely to drive sales. Thus, the more "objective" trials funded by government agencies, such as the NIH, are truly the best and purest type of randomized controlled clinical trials.

That's why I find it unfortunate when major issues emerge in how an important trial is carried out. I'd like to tell you the very sad story of the Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist (TOPCAT) trial, the results of which were presented at the 2013 annual meeting of the American Heart Association and published simultaneously online. In the interest of full disclosure, I need to mention that I was originally one of the many principal investigators on the study. However, our site had to drop out midtrial because of extreme difficulties with enrollment and the financial challenges that ensued as a consequence of low enrollment. As we'll see below, however, the enrollment challenges we faced at our site were part and parcel of a much larger issue, which ultimately caused major grief for the study and its leadership.

The TOPCAT trial was designed to determine whether or not an old class of medications known as aldosterone antagonists would be of clinical benefit in patients with diastolic dysfunction. Diastolic dysfunction is a common form of heart failure (HF) wherein a patient experiences the clinical symptoms of HF, but nonetheless has a preserved systolic ejection fraction, measured either by an echocardiogram or by a cardiac catheterization. Heart failure is typically seen in patients who have had chronically untreated or undertreated hypertension. The lack of treatment leads to the ventricles becoming stiff and noncompliant, which then renders them unable to fill adequately during diastole. To date, no specific classes of medications have been shown to be of clinical benefit in diastolic dysfunction, apart from the benefits derived from lowering blood pressure to normal levels with antihypertensive medications.

The Randomized Aldactone Evaluation Study (RALES) study done in the 1990s was a landmark clinical trial that demonstrated that an old and extremely inexpensive medication, spironolactone, was very effective in reducing symptoms and prolonging survival in patients with symptomatic left heart failure. Its mechanism of action is to antagonize the effects of the mineralocorticoid aldosterone by attaching to aldosterone's receptors. Aldosterone is secreted in excessive amounts in HF as part of the body's misguided effort to retain salt and water because of a perceived deficiency in intravascular volume related to low cardiac output.

It turns out that aldosterone is directly cardiotoxic in addition to its potent effects to increase salt and water retention. So blocking its actions with spirionolactone works in more ways than one to improve outcomes in systolic HF. A newer aldosterone antagonist, epleronone, was subsequently demonstrated in the Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial to also be of real clinical value in a related setting: the systolic dysfunction

that can follow an acute myocardial infarction.

TOPCAT was to be a rigorous test of the hypothesis that aldosterone antagonism with spironolactone would also be beneficial in diastolic dysfunction. In a double-blind fashion all subjects were randomized to receive either an escalating dose of spironolactone as needed to manage HF or an increasing number of identical-looking placebo tablets. Rigorous trial entry criteria for subjects were established, and that is where the trouble started. Not that being rigorous is ever a bad thing per se, but the criteria were sufficiently limiting so that most study centers were only able to enroll a relatively small number of eligible subjects. This meant that a very large number of study sites were needed, and enrollment went beyond the typical confines of North and South America to include several sites in Russia and the Republic of Georgia. These latter 2 areas have had far less experience historically with randomized controlled trials than have the sites in the Americas.

The gold standard for calling a trial positive or negative is whether or not the primary outcome, established by the investigators before the trial starts, is met with statistical significance. The primary outcome established for TOPCAT was a very appropriate composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization specifically for the management of HF. So it was a huge disappointment when TOPCAT failed to meet its primary outcome. Although there is a definite trend toward a positive outcome, the hazard ratio (HR) of 0.89 with a confidence interval (CI) of 0.77-1.04 meant that despite 11% fewer events in the spironolactone arm, the result was a statistically significant one. One of the 3 components of the primary outcome, HF hospitalization, was actually positive if pulled out and looked at in isolation. The HR here was 0.83, with a CI of 0.69-0.99, meaning that the observed 17% reduction in hospital admissions for HF was, indeed, statistically significant.

But the statisticians noted a concerning phenomenon when they continued with their due-diligence deep dive into the data. They found that there was a big disconnect between the data collected in the study sites in the Americas and the data collected instead in Russia and the Republic of Georgia. The overall event rate in the placebo group in all the countries of North and South America was 31.8%, roughly what had been predicted a priori, but only 8.4% in Russia and the Republic of Georgia!

What does this mean? It very strongly suggested that the subjects recruited in the latter 2 nations were not nearly as ill to begin with as their counterparts in the Western world. Had they been comparable subjects, the event rates on placebo would not have varied very much, due to the magical evening-out statistical effects seen with large numbers. But if these subjects were not especially ill, their potential to benefit from aldosterone antagonism would have been considerably smaller than that of the subjects who were more ill, assuming that there is a beneficial effect to be found with aldosterone antagonism.

Indeed, when the data are reanalyzed, leaving out all the subjects from Russia and the Republic of Georgia, TOPCAT becomes a positive study with a statistically significant primary outcome favoring spironolactone over placebo. What a mess! It isn't statistically fair to just throw out a large chunk of your study subjects and then claim a positive study result. But at the same time, when something as basic as the placebo event rate varies so widely by study location, alarm bells clang with deafening intensity. This is truly an unfortunate situation, because the cost and the many other challenges of performing such large-scale clinical trials make it extremely unlikely that another such trial of aldosterone antagonism in diastolic HF will ever be attempted by anyone else.

So we're left with a very unsatisfying result. Those who suspect that the careful rules of clinical trials were not followed rigorously in Russia and Georgia will probably view TOPCAT as a positive trial and proceed aggressively to use aldosterone antagonists routinely in diastolic HF. But those who are statistical purists will continue to insist that any trial that fails to meet its primary outcome is a negative study.

For me, the choice is fairly easy: You can count me firmly in the former rather than in the latter group. I therefore recommend that you give serious consideration to prescribing spironolactone for your patients with diastolic dysfunction and check their potassium and creatinine levels periodically to avoid toxic drug effects. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the author and do not necessarily reflect those of Federal Practitioner, *Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*