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Podcast_20231216: "The Unbearable Lightness of Efficacy in Clinical Trials"

The famous idiom by Benjamin Franklin, a polymath and a founding father of the US Constitution, states "*but in this world nothing can be said to be certain, except death and taxes*." Naturally, a clinical trial designed with death as the primary endpoint provides the most compelling evidence of the efficacy. In today's modern medicine, however, death is less common. Therefore, designing a clinical trial with death as the primary endpoint is more challenging, as it requires a large sample size and/or a longer duration of the intervention. The trend, especially for the less common and the so-called orphan diseases, is to design a modest sample-size clinical trial with a soft primary endpoint. Implicit in this approach is the desire that once efficacy for a soft endpoint is shown, it will be extrapolated to be broader.

The endpoints used in some of the recent clinical trials are unbearably light. There are numerous examples not only in the cardiovascular field but also in cancer and other medical conditions. I use two very recent phase III randomized placebo-controlled clinical trials, which were published in a major medical journal, to illustrate my point.

In the first example, patients with an uncommon disease were treated with intravenous infusion of the study drug or a placebo for one year. Upon completion of the study, patients in both groups walked less distance in 6 minutes than they did at the beginning of the study. Nevertheless, the study drug was considered to be effective, as the decline in the 6-minute walking distance, which was the primary endpoint of the study, was ~ 15 meters less in those treated with the study drug in one year than in those treated with a placebo.

The second study was designed to determine the effectiveness of a glucagon-like peptide 1 (GLP1) agonist in the treatment of obese patients with heart failure with preserved ejection fraction. This class of drugs is highly effective in reducing body weight in obese individuals. After one year of treatment, patients felt better, based on the Kansas City Cardiomyopathy Questionnaire clinical summary score, and walked about 20 meters further in a 6-minute walk test as compared to those who were treated with a placebo. The study drug was considered to be effective in the treatment of patients with heart failure with preserved ejection fraction. Of course, the study participants who were treated with the GLP1 agonist lost in average about 30 pounds. I wonder whether any obese patient after losing 30 lbs would not feel better or walk further, regardless of whether he or she had heart failure with preserved ejection fraction!

There are numerous examples of clinical trials that are designed to show efficacy based on soft endpoints and are advocated as effective therapies for the broader disease conditions. Physicians should be aware of the limitations of such studies, be critical in assessing efficacy, and recognize the limitations of soft endpoints. The efficacy of a clinical trial on an unbearably light endpoint may not extend to effectiveness in reducing a hard endpoint, such as death. It is the latter that is only certain.

Sincerely,
Dr. Ali J. Marian
Editor-in-Chief of the *JCA*