Should Enrichment With Natriuretic Peptide Levels Be Mandatory in Global Clinical Trials?

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EDITORIAL COMMENT

Should Enrichment With Natriuretic Peptide Levels Be Mandatory in Global Clinical Trials?*

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The design of large, phase III randomized clinical drug trials in patients with heart failure requires a careful selection of inclusion and exclusion criteria. These criteria should: 1) reflect the target population that will most likely benefit from the investigational product; 2) be not too lenient as this allows low-risk patients and those out of the target population to be recruited; 3) be not too strict as this will limit trial recruitment and clinical applicability of the investigational product; 4) make it reasonably certain that the patients' conditions are indeed diagnosed with heart failure (diagnostic criteria); and 5) reflect a patient population at (high) risk for the primary endpoint (enrichment criteria).

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Two criteria frequently used for both diagnostic and enrichment purposes are previous heart failure hospital admission and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) thresholds. In this issue of *JACC: Heart Failure*, Cunningham et al. (1) describe what happens when NT-proBNP criteria are added to the heart failure hospitalization criteria only after one-fourth of the patients are already recruited. This happened after a protocol amendment in the COMMANDER-HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure; NCT01877915) trial.

COMMANDER-HF was a double-blind, randomized trial of the effects of the direct factor Xa inhibitor rivaroxaban in 5,022 chronic heart failure patient with a left ventricular ejection fraction of 40% or less, coronary artery disease, and a recent (<21 days) heart failure hospital admission (2). The trial did not show a reduction of the primary outcome, which was the composite of death from any cause, or myocardial infarction, or stroke.

COMMANDER-HF started with only 1 of the frequently used diagnostic/enrichment criterion (a recent heart failure hospital admission) and did not require an NT-proBNP threshold for inclusion. However, after the enrollment of 1,155 patients (23.0%), the study leadership observed an overall even rate that was lower than expected. By that time, the majority of patients (89%) were enrolled in Eastern Europe, and only 1% in North America, 4% in Latin America and Asia Pacific, and 5% in Western Europe and South Africa. Surprisingly, the paper by Cunningham et al. (1) does not list the countries which they considered to be Eastern European. Various definitions of Eastern Europe exist, as the definitions are based on historic, religious, and cultural differences and to a lesser extent on geographic boundaries. For example, Latvia and Lithuania enrolled patients in COMMANDER-HF but those are not Eastern European countries. Nonetheless, because of the very low event rate, the steering committee

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amended the enrollment criteria to require a plasma NT-proBNP concentration of >800 ng/l or a BNP concentration of >200 ng/l at any time between the index admission for decompensated HF and randomization. The purpose of the amendment "was to prevent further enrollment of low risk patients who had not truly been hospitalized for decompensated HF, and thereby increase event rates and allow for more rapid completion of this event-driven trial" (1). The addition of NT-proBNP criteria later in the trial provided a unique opportunity to compare patient characteristics and event rates before and after the protocol amendment.

First, as expected, after allowing only patients with elevated NT-proBNP levels, the event rate increased substantially. Second, after the amendment, the characteristics of the patients significantly changed as well. Although this does not come as a surprise, those designing large randomized clinical heart failure trials should be aware of those changes. For example, adding an NT-proBNP criterion will result in an older population. This may not always be desired as treatment and side effects may be different. Notably, in the paper by Cunningham et al. (1) bleeding events increased in the patients treated with rivaroxaban after the amendment as well. Higher NT-proBNP thresholds may also increase the number of patients with atrial fibrillation, but although patients with atrial fibrillation were excluded from COMMANDER-HF, this was not confirmed in the present study.

The most remarkable finding of the present study was that recruitment slowed considerably in Eastern Europe and picked up in other regions. This might have been related to the larger effect that the amendment had on Eastern Europe, but it should be noted that other regions, such as Asia Pacific, had not been initiated before the amendment. Even more surprising was the fact that the increase in the event rate after the amendment was seen only in Eastern Europe and not in any other region of the world. Thus, the increase in event rate in the trial was completely driven by the increase in Eastern Europe. These findings suggest that adding NT-proBNP enrichment criteria had a much greater impact on Eastern Europe than it did on other regions.

How can we interpret these findings? The authors suggest that when no objective NT-proBNP criteria are used, the sites in Eastern Europe that recruited patients might not have had acute decompensated heart failure after all. This may be related to cultural differences where the threshold for a heart failure hospital admission is much lower than in other parts of the world. Given these cultural differences and the substantial recruitment (>50%) from Eastern Europe in the COMMANDER-HF trial, it is remarkable that none of the executive members and/or data safety monitoring board members was from 1 of the Eastern European countries. In addition, if it is true "that sites in Eastern Europe recruited patients who might not have had acute decompensated heart failure after all (1)," why was this not picked up by the Clinical Research Organization (CRO). They should have checked eligibility criteria preferably on site from source documents, and presumably these criteria were not violated or patients should not have been allowed to be included in the final analyses. This implies that either the sites in Eastern Europe correctly recruited patients that met all eligibility criteria or the noncompliance with these criteria was not discovered and reported by the CRO. Alternatively, the definitions of "symptoms of worsening dyspnea or fatigue, objective signs of congestion, and/or adjustment of HF medications, requiring hospital admission or unscheduled parenteral diuretic" may be not be specific enough and patients in Eastern Europe might have met these criteria but did not yield the expected and required patient population.

In contrast, the present findings from COMMANDER-HF share remarkable similarities with those from TOPCAT. TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) failed to demonstrate that spironolactone reduced death from cardiovascular causes or aborted cardiac arrest or heart failure hospitalizations in 3,445 patients with heart failure with preserved ejection fraction (3). Patients could be included based on either a previous (<12 months) hospitalization due to heart failure or based on elevated NT-proBNP levels. The trial recruited patients from North America, Eastern Europe, and South America. Sites in Russia and the Republic of Georgia (officially not an Eastern European country) provided most of the early enrollment, primarily based on the hospitalization criterion because NT-proBNP levels were initially unavailable there (4). Similar to event rates in COMMANDER-HF, the clinical event rate was strikingly low in Russia and Georgia. In addition, low natriuretic peptide measurements from Russia and Georgia, available later in the trial, suggested no heart failure or only mild heart failure. The primary results showed a significant reduction of the primary endpoint in North and South America but not in Russia and Georgia (5). These data, together with the finding that no spironolactone metabolite could be demonstrated in the urine samples from a large

proportion of active-arm patients in Russia and Georgia, aroused concerns regarding study conduct at some sites in these countries. Although lessons could have been learned from TOPCAT, COMMANDER-HF was already well underway, and the amendment was applied when these results became available.

What do we learn from these important data by Cunningham et al. (1) First, as expected, adding NT-proBNP thresholds to the eligibility criteria of heart failure trials will increase event rates. Second, also expected but important to realize, adding NT-proBNP criteria will substantially change the patient characteristics and may also influence treatment responses and side effects. Third, adding NT-proBNP criteria reduces regional heterogeneity in patient characteristics and clinical events. Finally, as the Data Safety and Monitoring Board of TOPCAT recommended (4), "launch the trial in a variety of geographic jurisdictions, and do not allow 1 or 2 geographic areas to dominate early (or late) enrollment."

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REFERENCES

1. Cunningham JW, Ferreira JP, Deng H, et al. Natriuretic peptide-based inclusion criteria in a heart failure clinical trial: insights from COMMANDER HF. J Am Coll Cardiol HF 2020;8:359–68.

2. Zannad F, Anker SD, Byra WM, et al., for the COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med 2018;379:1332–42.

3. Pitt B, Pfeffer MA, Assmann SF, et al., for the TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

4. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.

5. Bristow MR, Enciso JS, Gersh BJ, et al. Detection and management of geographic disparities in the TOPCAT trial: lessons learned and derivative recommendations. J Am Coll Cardiol Basic Trans Science 2016;1:180–9.

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