

EDITORIAL

# Recruitment Practices in Multicenter Randomized Clinical Trials: Time for a Relook

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**M**ulticenter randomized clinical trials are considered to provide the highest quality evidence for clinical decision making. In cardiology, this is particularly true as the field boasts a massive repository of clinical trials on subjects spanning from acute coronary syndromes to atrial fibrillation to structural heart disease.<sup>1</sup> However, clinical trials are not without their own drawbacks.<sup>2</sup> Curbed efficiency, the time-consuming nature, and potential biases from heterogeneity in recruitment have raised concerns about their true “gold standard” nature.<sup>3–5</sup>

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**See Article by Ndrepepa et al.**

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In this issue of the *Journal of the American Heart Association (JAHA)*, Ndrepepa et al evaluate one potential aspect of trial biases and adeptly compare clinical outcomes between patients recruited at high recruitment centers (HRCs) and low recruitment centers (LRCs) from the ISAR-REACT 5 (Ticagrelor or Prasugrel in Patients With Acute Coronary Syndromes) trial.<sup>6,7</sup> Among the 4018 patients with acute coronary syndrome recruited in ISAR-REACT 5 trial, 3011 (75%) were recruited at HRCs and 1007 (25%) were recruited at LRCs. There was a lower cumulative incidence of the primary end point (death, myocardial infarction, or stroke) in patients recruited at LRCs as opposed to HRCs (7.3% versus

8.4%; hazard ratio [HR], 0.86). Although this value did not reach statistical significance ( $P=0.27$ ), the numerical trend was driven by significantly lower all-cause mortality among patients recruited at LRCs compared with HRCs (2.9% versus 4.5%; HR, 0.64;  $P=0.031$ ).

More notably, when evaluated for effect modification, there was a significant interaction between the treatment effect of ticagrelor versus prasugrel and patient recruitment category for all-cause death. Although all-cause death was higher among patients treated with ticagrelor than those treated with prasugrel and recruited at LRCs (4.2% versus 1.6%; HR, 2.67;  $P=0.018$ ), there was no significant difference among HRC recruited patients treated with either antiplatelet agent (4.6% versus 4.4%; HR, 1.05;  $P=0.76$ ), resulting in an interaction  $P$  value of 0.032. On careful analysis of baseline risk profiles of patients recruited at HRCs and LRCs in ISAR-REACT 5 trial, patients recruited at LRCs were younger, had fewer comorbidities, including hypercholesterolemia, and were less sick, with fewer cases of cardiogenic shock or history of prior revascularization. The authors concluded that the recruitment of patients with lower baseline risk at LRCs was most likely responsible for the differences in all-cause death and numerical trends in the lower incidence of the primary composite end point. Of note, follow-up was incomplete in 3.1% of patients recruited at LRCs and 2.0% of patients recruited at HRCs ( $P=0.038$ ).

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The findings of this study have several important implications. First, baseline risk profiles of patients recruited at LRCs ought to be more carefully analyzed before inclusion of patients in randomized clinical trials. This is not the first analysis of a clinical trial that has found differential outcomes between patients enrolled in low versus high recruitment sites; in fact, it is one of several. As the authors point out, the GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation) trial has previously reported the impact of recruitment volume on all-cause mortality and found similarly low baseline risk among patients recruited at LRCs. In contrast, a post hoc analysis of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial showed low enrolling sites had worse outcomes and higher rates of death compared with high enrolling sites.<sup>9,10</sup> Although the differences did not reach significance, together with the results of this present study, these studies reveal the spectrum of clinical outcomes observed across sites with low recruitment volumes.<sup>9,10</sup> Moreover, they beg the question of whether a novel standardized approach is required for patient recruitment across low (and high) recruitment centers. Although the randomization process should have prevented any site-by-site heterogeneity, statistically, there was significant effect modification for all-cause death between the two treatment arms based on high versus low recruitment volume, suggesting the potential for a real difference. Perhaps training and support aimed at recruiting patients with similar risk profiles in line with the intent of the trial protocol should be provided to all site investigators from the get-go. This may prevent the inadvertent enrollment of patients who are lower risk than intended, which can compromise the statistical power of a trial. It can, however, be difficult to tease out any impact that LRC status may have on other aspects of trial conduct, such as completeness of follow-up or adherence to guideline-directed therapies that could affect event rates in all arms of a trial.

Second, central remote patient recruitment and consent may assist in recruiting a larger number of patients with appropriate risk profiles for clinical trials. Over the past 2 decades, both social media and digital health platforms have been leveraged to reach a larger network of diverse participants who meet inclusion criteria of trials.<sup>3,11–13</sup> However, despite introduction of these novel technologies and methods, they have not been routinely implemented. The COVID-19 pandemic has helped provide some of the much needed activation energy for this process as in-person recruiting and consent were limited by stay-at-home and quarantine requirements, but more work is needed for sustainable change.<sup>2,3,13,14</sup>

Finally, and perhaps most importantly, this study serves as a reminder that clinical trial results should be

analyzed carefully before implementation into clinical practice. Decisions to start treatment should be personalized to each patient and his/her needs. Physicians must ensure that their patients fit the risk profile of trial participants driving the outcomes of a trial. These efforts will prevent overtreatment and preclude unwanted sequelae of new therapies, whether they be drugs or devices.

A few limitations to be noted include the single trial data set, arbitrary cutoffs used for HRCs versus LRCs, and lack of analyses that correct for all baseline differential risk profiles, potentially influencing clinical outcomes.

In conclusion, this insightful study by Ndrepepa et al underscores the need for a relook, reevaluation, and central standardization of recruitment processes for multicenter clinical trials, especially LRCs. Efforts are needed at both the central and local level for sustainable change. We are now equipped with sophisticated technologies that allow easy and immediate remote communication. It is our imperative to leverage these resources, in addition to existing resources, to build a better, more unified, and higher quality future for our patients. Ongoing studies of other multicenter clinical trials will help to continue to inform this process.

## ARTICLE INFORMATION

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### Disclosures

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