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Clinical Investigation

Relationship Between Clinical Trial Site Enrollment With Participant Characteristics, Protocol Completion, and Outcomes

Insights From the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) Trial

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Objectives The study investigated whether the number of participants enrolled per site in an acute heart failure trial is associated with participant characteristics and outcomes.

Background Whether and how site enrollment volume affects clinical trials is not known.

Methods A total of 4,133 participants enrolled among 359 sites were grouped on the basis of total enrollment into 1 to 10, 11 to 30, and >30 participants per site and were compared for outcomes (cardiovascular mortality or heart failure hospitalization).

Results Per-site enrollment ranged from 0 to 75 (median 6; 77 sites had no enrollment). Regional differences in enrollment were noted between North and South America, and Western and Eastern Europe ($p < 0.001$). Participants from sites with fewer enrollments were more likely to be older and male, have lower ejection fraction and blood pressure as well as worse comorbidity and laboratory profile, and were less likely to be on angiotensin-converting enzyme inhibitors or aldosterone antagonists. During a median follow-up of 9.9 months, 1,700 (41%) participants had an outcome event. Compared to event rate at sites with >30 participants (32%), those with 1 to 10 (51%, hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 1.56 to 2.02) and 11 to 30 (42%, HR: 1.44, 95% CI: 1.28 to 1.62) participants per site groups had worse outcomes. This relationship was comparable across regions ($p = 0.43$). After adjustment for risk factors, participants enrolled at sites with fewer enrollees were at higher risk for adverse outcomes (HR: 1.26, 95% CI: 1.08 to 1.46 for 1 to 10; HR: 1.22, 95% CI: 1.07 to 1.38 for 11 to 30 vs. >30 participant sites). Higher proportion of participants from site with >30 participants completed the protocol (45.5% for <10, 61.7% for 11 to 30, and 68.4% for sites enrolling >30 participants; $p < 0.001$).

Conclusions Baseline characteristics, protocol completion, and outcomes differed significantly among higher versus lower enrolling sites. These data imply that the number of participant enrolled per site may influence trials beyond logistics. (J Am Coll Cardiol 2013;61:571–9) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AHF = acute heart failure
CI = confidence interval
HF = heart failure
HR = hazard ratio

Heart failure (HF) remains a major global health concern (1). The overall prevalence of HF and the number of hospitalizations for acute heart failure (AHF) are high, and outcomes for these patients remain poor (1–3). Although many therapies have been evaluated in the last decade, none of them reduced mortality or readmission rates among AHF patients (4,5). The reasons behind this are complex including issues related to the therapies studied and trial conduct (6). AHF patients constitute a heterogeneous group and patient characteristics affect outcomes. Moreover, important differences between continents, and regions within continents, in HF etiology, severity, and management exist, which affect patient outcomes as well (7–10).

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Recently, attention has been focused on the difficulties of enrolling participants in clinical trials in the United States (11). In order to enroll the required number of participants, it is increasingly common for trials to have several hundred sites in operation. The performance and the number of participants enrolled by these sites vary widely. In a clinical trial, slower enrollment rate affects the duration of the trial, however the participants are expected to be clinically homogenous due to the pre-specified strict inclusion and exclusion criteria. Therefore the overall enrollment by sites may not affect outcomes of the trial besides costs and logistics. Conversely, if outcomes of participants from high versus low enrollment sites are different, this may have significant implications for trial design and conduct. To assess whether the site enrollment affects outcomes, we performed a post hoc analysis of the data from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial.

Methods

Study population. The design of the EVEREST trial has been described previously (3,12,13). Briefly, EVEREST was a prospective, international, randomized, double blind, placebo-controlled program that examined the short- and long-term efficacy and safety of tolvaptan added to optimal medical therapy in participants hospitalized for worsening HF. The EVEREST program included 2 identical short-term clinical status trials during hospitalization (trials A and B) embedded within the long-term post-discharge outcome study that combined all participants. Adults ≥18 years of age with left ventricular ejection fraction ≤40% who were hospitalized primarily for worsening HF and with 2 or more signs or symptoms of fluid overload (i.e., dyspnea, pitting edema, or jugular venous distension) were randomized within 48 h of admission to oral tolvaptan (30 mg/day) or matching placebo in addition to conventional therapy. Exclusion criteria included cardiac surgery within 60 days of enrollment, cardiac mechanical support, biventricular pacemaker placement within 60 days, expected survival of <6 months, acute myocardial infarction at the time of hospitalization, hemodynamically significant uncorrected valvular disease, end-stage HF, dialysis, systolic blood pressure <90 mm Hg, serum creatinine >3.5 mg/dl, serum potassium >5.5 mEq/l, and hemoglobin <9 g/dl. Background therapy was at the discretion of the treating physician, but recommendations for guideline-based therapy were included in the protocol.

Clinical trial sites. In the EVEREST trial, overall 4,133 participants were randomized from 359 sites in 20 countries across North America, South America, and Europe between October 7, 2003, and February 3, 2006. Countries were grouped as follows: North America (United States and Canada), South America (Argentina and Brazil), Western Europe (Italy, Belgium, Norway, Netherlands, Germany, Spain, France, United Kingdom, Sweden, and Switzerland), and Eastern Europe (Poland, Romania, Czech Republic, Russia, Bulgaria, and Lithuania).

Study groups. The participants were divided into the following groups on the basis of overall participants enrolled by an individual site into those sites that enrolled 1 to 10, 11 to 30, and >30 participants. This grouping was virtually identical to sample tertiles on the basis of total numbers of participants enrolled within these sites (1 to 11, 12 to 30, and ≥30) and was selected for ease of communication. Outcomes for patients within these 3 individual groups were homogeneous and further subdivision did not improve overall model fit to the data. Hence these larger groups were used for all further analysis and reporting of the data.

Outcomes events. For this analysis the primary outcome was defined as a composite of cardiovascular death or HF hospitalization, 1 of the 2 coprimary endpoints in EVEREST. All-cause mortality, the other coprimary endpoint in EVEREST, was also compared among the 3 groups. Multiple other clinical outcomes were also assessed in secondary analysis including modes of death, other cardiovascular outcomes, and hospitalizations. An independent event committee adjudicated the mode of death and the cause of hospitalizations for all participants. An independent and blinded adjudication committee determined the cause of all hospitalizations and deaths during follow-up. Rehospitalization was defined as a nonelective hospital admission for medical therapy with a

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