Optimal decongestive therapy in acute decompensated heart failure syndromes: Far from being solved

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Dear Editor,

We have read with great interest the article entitled “Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) Trial” [1]. First, we would like to commend the authors for their effort in carrying out this investigator-initiated clinical trial by testing the prognostic effect of three decongestive strategies in the management of patients with acute decompensated heart failure (ADHF). The analysis of the data revealed no significant differences in the in-hospital and post-discharge outcomes between high (HDF) vs low-dose furosemide infusion (LDFD); the addition of low-dose dopamine infusion to LDFD-group was not associated with any beneficial effects.

Not infrequently, trials comparing different decongestive modalities in ADHF have produced negative results [2–4] leading to a great uncertainty about the optimal treatment in ADHF syndromes. We would like to highlight some potential explanations for these and other recent findings and also, exert caution in their interpretation.

1. Lack of statistical power: This trial was designed to have 150 patients in each group in order to reject the null hypothesis of no difference (effect size of 16%), with an alpha of 0.025, and a power of 80%. However, due to safety concerns, the trial was stopped prematurely, leading to a final sample for the analysis of 50, 56 and 55 patients for HDF, LDFD and LDF groups, respectively. The consequence is a dramatic drop in power when comparing the groups between them. For instance, if we assume a mortality rate for LDF (control group) of 32.7% while keeping the same alpha and effect size, the estimated power to detect a significant difference with the LDFD group is 29.4%. This high rate of false negatives (Type II error = 70.6%) precludes to attribute these negative results to a true lack of therapeutic differences. This concern is also valid for other recent clinical trials that have enrolled small number of patients [2–4].

2. Ignoring the complexity of ADHF: ADHF syndromes have a complex and heterogeneous pathophysiology that translates into a variety of clinical presentations. Even though fluid overload (FO) is the most common cause of heart failure hospitalizations, its degree varies from simply fluid redistribution to generalized edema [5]. Adding more complexity to this puzzle, the definition of the syndrome itself is not straightforward, allowing the inclusion of a mixture of risk profiles, etiologies, and precipitant factors. For instance, classical criteria for defining ADHF used in most trials have included natriuretic peptides, dyspnea, and classical signs of FO, ignoring the fact that they have shown limited accuracy to quantify the degree of congestion [5]. It seems reasonable to us to evaluate in further studies other tools such as clinical scores, novel biomarkers, and/or newer diagnostic methods for a more accurate quantification of FO [5,6]. In addition, other special (and prevalent) characteristics deserve special attention, in particular cardiorenal syndrome type I. This syndrome identifies a subgroup of patients at higher risk for renal changes (either worsening or improvement) and adverse clinical outcomes [7]. In this trial, patients with glomerular filtration rate < 30 ml/min/1.73 m², were excluded, decreasing the odds for detecting significant differences in renal parameters during intervention. We believe, that the entry criteria should account not only for the current definition of ADHF but also including other important players such as age, gender, etiology, left ventricular function, comorbidity-burden, degree of renal impairment, and FO severity. This will ensure a more homogeneous ADHF groups available for the analysis.

3. Too many expectations: Despite the high rate of mortality and readmission once the patient is discharged, most of them, however, show symptomatic improvement following the administration of loop diuretics. In our opinion, further studies evaluating in-hospital alternatives to loop diuretics or concomitant treatments, should mainly focus in those with real diuretic resistance, a situation where there is unmet need in finding therapeutic approaches or alternatives to loop diuretics.

4. Short intervention: In this trial, the duration of the intervention was shorter (8 h) than other trials, and no information was given regarding treatment beyond this period [1]. We believe, that the prognostic effect of these symptomatic interventions diluted over time. Theoretically, patients with a chronic condition and who remain at higher risk of adverse outcome following hospitalization, would require therapeutic strategies not only circumscribed to hospitalization but also at post-discharge.

5. Study endpoints: The true value of some surrogate endpoints used to evaluate the efficacy in ADHF is a matter of debate. For instance, recent studies suggest that worsening renal function during hospitalization may serve either as a marker for aggressive decongestion or for true renal impairment [8]. Regarding clinical endpoints, recent initiatives claim for analyzing repeated events instead of time to first event [9]. There is great interest in applying novel statistical approaches that account for the number of repeated events during follow-up, which at the end, would better serve for dissecting the natural history of the disease, and better measuring the impact of any intervention [9].

References

Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: A subanalysis of the ORIGIN trial

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Type 2 diabetes (DM2) and lesser degrees of dysglycemia currently affect approximately 600 million people worldwide. These individuals are at high risk for future cardiovascular (CV) events and the presence of other well-established CV risk factors further increases their risk [1]. Muscle strength has been identified as an index of future CV risk and mortality [2–5]. Studies of the relationship between strength and CV outcomes have mainly been done in non-Hispanic Caucasians from high-income countries [6] and little data are available regarding this relationship in a wider, more heterogeneous sample of people with dysglycemia. We report the relationship between handgrip strength and CV events, and all-cause mortality based on a subanalysis of the ORIGIN (Outcomes Reduction with an Initial Glargine Intervention) clinical trial, the design and results of which have been previously published [7,8]. The ORIGIN trial recruited 12,537 people from 40 countries aged 50 and older with impaired fasting glucose/impaired glucose tolerance (12%) or DM2 (88%), who were either taking no glucose lowering agents or only 1 oral glucose lowering agent.

Three measurements of handgrip strength (HGS) were taken at baseline in 12,516 people (99.83% of total sample) using a Jamar Dynamometer (Sammons Preston Inc., Bolingbrook, IL) and mean HGS (kg) was calculated. The primary composite CV outcome of nonfatal myocardial infarction, stroke or CV death, and the individual components of this outcome, all-cause mortality, cardiac, carotid or peripheral revascularization and hospitalisation for heart failure were analysed. All HGS analyses (SAS software, version 9.1 for Solaris) were done using age adjusted handgrip strength (HGSA) for men and for women. The relationship between baseline characteristics and fifths of HGSA divided by quintiles was assessed using linear regression. The relationship between baseline HGSA and subsequent outcomes was assessed using Cox regression models before and after adjustment for body mass index (BMI), and waist (WC) and hip (HC) circumferences. Interactions of HGSA with gender were assessed by including an interaction term of gender and grip strength. Interactions of HGSA with region (South America, North America, Western Europe, Eastern Europe, Asia, India and Australia) were similarly assessed by including an interaction term of region and grip strength overall and by gender. Event curves for each fifth of HGSA for the primary composite and log-rank tests were used to compare each fifth to the highest fifth. The nominal level of significance for all analyses was p < 0.05.

12,516 individuals (35% women) of mean (SD) age 63.6 (7.8) years had a baseline HGS and were followed for a median of 6.2 years. As there was an interaction between gender and HGSA with respect to prior CV disease (p = 0.001), all analyses were done separately for men and women (Tables 1A, 1B). In both men and women, higher fifths of HGSA were associated with a progressively lower prevalence of previous CVD (p < 0.001), positively related to weight, BMI and WC (p < 0.001) and inversely related to age, systolic blood pressure and creatinine (p < 0.001). There was an interaction between gender and HGSA for all of the incident outcomes except stroke (p < 0.006). Therefore, results are presented separately for men and women. As both unadjusted and adjusted Cox regression analyses yielded similar results, only the adjusted data are presented (Fig. 1). The relationship between baseline HGSA divided into fifths and the incidence of the composite outcome is shown in Fig. 2. A nominal interaction (p = 0.03) was noted for HGSA to cardiovascular death by region for men but no other significant region interactions of the relationship of HGSA to outcomes were noted.