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Different relationships between pulse pressure and mortality in heart failure with reduced, mid-range and preserved ejection fraction☆

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ABSTRACT

Objectives/Background: In heart failure (HF), pulse pressure (PP) may reflect both vascular stiffness and left ventricular function, but its prognostic role in relation to ejection fraction (EF) is poorly understood.
Methods: In the Swedish Heart Failure Registry, we investigated the association between PP and 1-year mortality in patients with HF and reduced (HFrEF, <40%), mid-range (HFmrEF, 40–49%) and preserved EF (HFpEF, ≥50%), using multivariable logistic regression and restricted cubic splines.
Results: Among 36,770 patients discharged alive or enrolled as out-patients with 1-year follow-up (mean age 74 ± 12 years, 63% men, 56% HFrEF, 21% HFmrEF, 23% HFpEF), crude one-year mortality was 18%. Mean PP increased across EF groups: 51 ± 16 in HFrEF, 57 ± 18 in HFmrEF, 60 ± 19 mm Hg in HFpEF. In crude regression splines, the association between PP and mortality was U-shaped in HFmrEF and HFpEF, but curvilinear with only low PP associated with mortality in HFrEF. In multivariable analyses, a significant interaction by EF group and PP was observed ($p_{interaction} = 0.015$): low PP was associated with higher mortality in HFrEF (adjusted OR [1st vs. 4th quintile] = 1.40, 95% CI 1.18–1.67) and HFpEF (1.43, 1.14–1.81) but only by trend in HFmrEF; high PP had a trend towards higher mortality in HFmrEF (5th vs. 3rd quintile = 1.30, 1.00–1.69) and HFpEF (1.25, 0.98–1.61).
Conclusions: The association between PP and mortality in HF was influenced by EF. Low PP was independently associated with mortality in HFrEF and HFpEF and by trend in HFmrEF. High PP was independently associated with mortality by trend in HFmrEF and HFpEF.

Clinical perspectives and translational outlook

Pulse pressure is a simple, inexpensive and commonly available clinical measurement, which can provide incremental risk assessment beyond the traditional cardiovascular risk factors. High PP is traditionally viewed as a marker of arterial stiffening, which contributes to left ventricular afterload. On the other hand, low PP may reflect reduced stroke volume/impaired left ventricular systolic function in heart failure (HF).
In our large population-based study of HF, we found that PP associated differently with mortality in the three HF groups (HF with preserved, mid-range, and reduced ejection fraction [HFpEF, HFmrEF, HFrEF respectively]). Low PP was independently associated with mortality in HFrEF and HFpEF, whereas there was a trend for high PP to be associated with mortality in HFmrEF and

Abbreviations: PP, Pulse pressure; HF, Heart failure; HFrEF, Heart failure with reduced rejection fraction; HFmrEF, Heart failure with mid-range ejection fraction; HFpEF, Heart failure with preserved ejection fraction; SwedeHF, Swedish Heart Failure Registry; SBP, Systolic blood pressure; GWTG-HF, Get With The Guidelines-Heart Failure; LVEF, Left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; OR, Odds ratio.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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HFpEF. These real world data serve as a call to carefully consider both arterial and ventricular hemodynamic significance of PP in HF, and to recognize the prognostic implications of both low and high values in HFrEF, HFmEF and HFpEF.

Wide pulse pressure (PP), an index primarily of arterial stiffening, is well-recognized as a powerful independent predictor of adverse outcomes in healthy individuals and those with cardiovascular risk factors such as hypertension [1–5]. In patients with established heart failure (HF) and reduced ejection fraction (HFrEF) however, the association of PP with all-cause mortality is more complex [6–10]. Low PP in advanced HF, but high PP in asymptomatic left ventricular systolic dysfunction and mild HF, have separately been linked to higher mortality [7,8,11,12], whereas a U-shaped relationship, independent of SBP, has most recently been reported in the Get With The Guidelines-Heart Failure (GWTG-HF) cohort [13]. Furthermore, the importance of left ventricular ejection fraction (LVEF) in modifying the relationship between PP and mortality has been recently recognized [6], where lower PP independently correlated with mortality in HF with reduced EF (HFrEF), yet higher PP was associated with mortality in HF with preserved EF (HFpEF) – the latter an association that was rendered non-significant following multivariable adjustment [6].

The differences in prior reports may have been due to low sample size, significant patient heterogeneity, or cutoffs used to define HFpEF versus HFrEF [14,15]. We therefore aimed to assess the relationship between PP and mortality in the large population-based cohort of the Swedish Heart Failure Registry (SwedeHF). Importantly, we recognized the lack of prognostic information on PP especially in patients with mid-range EF (HFmrEF, 40–49%) [16,17]. Given the known differences in ventricular-arterial interaction in HFrEF, HFmrEF and HFpEF [18], we hypothesized that PP, reflective of arterial stiffness/ventricular afterload on the one hand, and left ventricular systolic function/stroke volume on the other, would associate differently with mortality in the three EF groups.

1. Methods

1.1. Data sources and study design

The Swedish Heart Failure Registry (SwedeHF) [19,20] was used to address the research aims. This ongoing population-based quality registry was founded in 2000 and comprised patients ≥18 years old, with clinician-judged HF registered at time of hospital discharge or out-patient consultation. For this study we included first registrations between 11 May 2000 and 31 December 2012. We excluded: a) 617 patients with missing pulse pressure; b) 8281 with missing EF; c) 685 in-hospital deaths, d) 4707 patients who were registered in 2012 and had not completed 1-year follow-up. The final cohort comprised 36,770 HF patients (see Supplementary Fig. 1) from 70 of a total of 80 hospitals and 100 out-patient primary care clinics in Sweden.

The Patient Registry, maintained by the Swedish Board of Health and Welfare (http://www.socialstyrelsen.se) provided further information on baseline comorbidities and additional baseline data on socioeconomic data was provided by Statistics Sweden (http://www.scb.se/en_/). This yielded comprehensive data of 78 baseline variables, including demographics, medical comorbidities, EF, New York Heart Association functional class, vital signs on physical examination, blood chemistries, and pharmacological and non-pharmacological interventions.

Echocardiography was routinely performed with standardized and accredited protocols and reported by the local investigators as EF <30%, 30–39% (together, defined as HFrEF), 40–49% (HFmrEF), and ≥50% (HFpEF).

Pulse pressure (PP) was defined as the difference between arterial systolic and diastolic pressure. PP taken at or closest to index hospital discharge or out-patient consultation was used.

1.2. Outcome measures

The outcome was all-cause mortality at one-year from hospital discharge or out-patient visit. Deaths were obtained by linkage to the Population Registry, which is maintained by the Swedish Tax Agency (http://www.skatteverket.se/).

1.3. Statistical analyses

Descriptive statistics for the overall cohort at baseline were compared across PP quintiles (depicted in Table 1). Continuous variables were presented as mean ± SD and categorical variables presented as counts and percentages. A linear trend across PP quintiles was tested using linear regression or the Mann-Whitney test.

To determine if the association between PP and mortality was different between EF groups, we tested for interaction effect between PP and EF subgroup in univariable analysis. Because of a significant interaction, subsequent analyses were performed in the 3 stratified EF groups. For associations between PP and mortality, restricted cubic regression splines, with knots specified at the respective quintiles, were used to assess the (crude) functional form of PP with mortality in the 3 separate groups, comparing against a linear fit. For multivariable analyses, Cox models violated the proportional hazards assumption; therefore, logistic regressions with PP stratified in quintiles as the independent variable, and mortality at one year as the outcome, were used. Important clinical and demographic predictors of mortality, including SBP, which were included in multivariable models are marked with * in Table 1. Variables with >10% missing data and patients with incomplete data on the factors for adjustment were excluded from the multivariable analyses.

Due to the fundamentally different phenotypes of in- vs. out-patients, we also tested the interaction between in- vs. out-patient status and PP. This was non-significant ($p = 0.140$) so we did not perform any additional sub-group analyses. All statistical analyses were performed using Stata version 14.0. For all analyses, reported p-values are two-sided, and significant at 5% level.

1.4. Ethics approvals

The establishment of the registry and this study were approved by a multisite Ethics Committee and conform to the ethical guidelines of the Declaration of Helsinki. Individual patient consent was not provided but patients are informed of registration in Swedish national registries and allowed to opt out.

2. Results

2.1. Clinical characteristics

Among 36,770 patients (mean age 74 ± 12 years, 63% men), HFrEF, HFmrEF and HFpEF were present in 56%, 21% and 23% respectively. Overall, PP was mean 55 ± 18 mm Hg and median 50 (IQR 40–65) mm Hg. Table 1 shows characteristics based on quintiles of PP. Patients in the higher PP quintiles were older and more likely to have hypertension, diabetes, coronary artery disease, anaemia, peripheral arterial disease and chronic kidney disease; but less likely to have atrial fibrillation (all $p < 0.001$) (Table 1). Across PP quintiles, the proportion of HFpEF increased sharply (12.8% in 1st quintile to 34.7% in the 5th quintile), whereas the proportion of HFmrEF increased less sharply (15.9% in 1st quintile to 25.3% in the 5th quintile) and that of HFrEF decreased (71.3% in 1st quintile to 40.0% in the 5th quintile) (Table 1). Accordingly, mean PP increased across EF groups (51 ± 16 mm Hg in HFrEF, 57 ± 18 mm Hg in HFmrEF, and 60 ± 19 mm Hg in HFpEF). Increases in PP between the EF groups were largely driven by higher SBP, rather than lower DBP (Supplementary Table 1). Clinical characteristics by EF group are shown in Supplementary Table 1. Patients with HFmrEF were intermediate in many regards but resembled HFrEF in many others, most notably regarding high prevalence of ischemic heart disease.

Patients who were excluded due to missing EF values tended to be older, female, receiving care at inpatient, have comorbidities such as hypertension, atrial fibrillation, anaemia and were less often treated with