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EDITORIAL COMMENT

Minding the Gap in Heart Failure

Understanding the Pulse Pressure in Reduced Versus Preserved Ejection Fraction*

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High pulse pressure (PP) is traditionally viewed as a marker of arterial stiffening resulting from the premature arrival of the reflected arterial pressure wave augmenting the central aortic pressure waveform. Indeed, a widened PP is a known risk factor for cardiovascular events, including new-onset heart failure (HF) (1). In established HF, however, the prognostic impact of PP is less straight forward: in asymptomatic and mildly symptomatic patients with HF with reduced ejection fraction (HFrEF) in SOLVD (Studies of Left Ventricular Dysfunction) (2), higher PP was linked to increased mortality; whereas in the advanced HFrEF populations of VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) (3), PRIME-II (Second Perspective Randomized Study of Ibopamine on Mortality and Efficacy) (4), CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study) (5), and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) study (6), lower PP was associated with higher mortality. To add to the complexity, left ventricular (LV) EF has recently been shown to importantly modify the association between PP and mortality in HF (7). In the first investigation of the prognostic value of PP in HF with preserved ejection fraction (HFpEF) from 22 of 31 studies in the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) meta-analysis, there was a highly significant interaction between EF category (HFrEF versus HFpEF, categorized at an EF cut off of 50%) and the relationship between PP and 3-year mortality (7). Lower PP was an independent predictor of mortality in HFrEF, but higher PP was related to higher crude mortality in HFpEF, an association that was attenuated after multivariable adjustment. Intriguingly, in subset analyses of acute (versus chronic) HFpEF, as well as HFpEF without atrial fibrillation, lower PP was related to increased mortality risk (**Table 1**).

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Against this backdrop of diverse findings in HF, the study by Laskey et al.(8) in this issue of *JACC: Heart Failure* is certainly welcome. In the large cohort of hospitalized patients with HF, regardless of EF in the Get With the Guidelines-Heart Failure (GWTG-HF) program, the authors showed that brachial PP at hospital discharge had a U-shaped relationship to 1-year mortality in both HFrEF and HFpEF (defined by an EF cut off of 40%) (**Figure 1**, top panels), with a risk nadir at a PP of 50 mm Hg. In HFrEF, higher PP was independently associated with lower mortality risk when PP was <50 mm Hg but higher mortality risk when PP was ≥50 mm Hg. In HFpEF, the association between PP and mortality risk did not reach statistical significance when PP was <50 mm Hg, but higher PP was independently related to increased mortality when PP was ≥50 mm Hg and systolic blood pressure (SBP)

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TABLE 1 Relationship Between Pulse Pressure and Mortality Risk

	HFrEF		HFpEF	
	GWTG-HF (8)	MAGGIC (7)	GWTG-HF (8,9)	MAGGIC (7)
HF setting	Hospitalized HF (Multicenter U.S. Registry)	Acute and Chronic HF (22 Observational Studies and Clinical Trials)	Hospitalized HF (Multicenter U.S. Registry)	Acute and Chronic HF (22 Observational Studies and Clinical Trials)
EF cut off	<40%	<50%	≥50%	≥50%
Sample size	15,716	22,038	18,897	5,008
Age, yrs	79	≈65	82	≈69
% of Women	40.0	25	67.3	49
% of Hypertension	73.1	43.5	81.3	63
% of Diabetes	39.3	25.6	40.6	27
% of Atrial fibrillation	36.1	14.8	40.6	23.4
PP, mm Hg	52 (median)	52	60	62
PP measurement	At or closest to discharge	Variable	At or closest to discharge	Variable
SBP, mm Hg	116 (range, 104–131)	≈128 (mean)	126 (range, 112–142)	≈139 (mean)
DBP, mm Hg	64 (range, 57–72)	≈76 (mean)	64 (range, 57–72)	≈79 (mean)
Crude % of mortality	37.5% at 1 yr	22.6% at 3 yrs	35.6% at 1 yr	16.5% at 3 yrs
Association between PP and mortality*	Nonlinear (inverse at PP <50 mm Hg, direct at PP ≥50 mm Hg)	Inverse (HR increased in quintile 3 [46–53 mm Hg], 2 [40–45 mm Hg], and 1 [2–39 mm Hg] relative to quintile 5)	Direct, significant interaction with SBP	Direct in unadjusted analysis; nonsignificant in adjusted models for overall cohort; significant inverse relationship in HFpEF without AF and acute HFpEF

*Adjusted for age, sex, ischemic cause, atrial fibrillation, hypertension, and diabetes (both studies), as well as race, insurance status, anemia, stroke/transient ischemic attack, hyperlipidemia, chronic obstructive pulmonary disease or asthma, peripheral artery disease, renal insufficiency, smoking, SBP on admission, heart rate, SBP on discharge, serum sodium, blood urea nitrogen, hospital characteristics (region, type, number of beds, rural vs. nonrural), and defect-free compliance score (GWTG-HF only).

AF = atrial fibrillation; DBP = diastolic blood pressure; EF = ejection fraction; GWTG-HF = Get With the Guidelines-Heart Failure; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; PP = pulse pressure; SBP = systolic blood pressure.

was ≥140 mm Hg. Furthermore, the effect of PP on mortality increased with increasing SBP. Thus the study by Laskey et al.(8) adds the following novel concepts in thinking about the PP gap in HF: 1) the existence of a nonlinear relationship with increased mortality risk at both ends of the PP distribution; 2) the independent prognostic value of PP in HFpEF; and 3) the important influence of SBP on the latter relationship. Of note, effect sizes were small (albeit with strong statistical significance due to large numbers), and results were not robustly achieved when PP was modeled as a categorical variable.

At face value, it may be difficult to reconcile the current GWTG-HF results with those of the prior MAGGIC meta-analysis. However close inspection of the 2 studies, using a similar EF cut off of 50% to define the HFpEF groups and based on prior published data from GWTG-HF (9), provides further insights (**Table 1**, **Figure 1**). Immediately obvious are the differences in patient populations studied. On average, the GWTG-HF cohort was older and sicker (with greater comorbidity burden and higher crude mortality) than the MAGGIC cohort regardless of EF group, consistent with real-world patients in the former and significant proportion of clinical trial patients in the latter. Other differences include variable timing of PP measurement, as well as differences in analytical methods and statistical modeling. However, side-by-side comparisons of the hazard plots from both studies revealed some consistencies (**Figure 1**): in HFrEF, the mortality risk starts to increase at a PP of <54 mm Hg in MAGGIC, consistent with the increased mortality with PP of <50 mm Hg in GWTG-HF. Above the risk nadir of ~50 mm Hg, the upsloping limb of the U-shaped relationship observed in GWTG-HF, but not in MAGGIC, may be related to enrichment by much older patients with the highest PP in GWTG-HF. Age-related increases in PP are well described and portend a poor prognosis in the elderly (10). In HFpEF, inspection of the hazards plots show similar patterns in both studies, where the HFpEF plots are of similar shape but shallower (lower gradients of risk) than the respective HFrEF hazards plots in each study. The independent prognostic impact of PP in GWTG-HF, but not in MAGGIC following multivariable adjustment, may be related to larger numbers of HFpEF in GWTG-HF (more than triple the number in MAGGIC). To address the issue of timing of PP measurement, it would have been useful to know whether consistent results were obtained using the PP on admission rather than at discharge in GWTG-HF.