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EDITORIAL COMMENT

Heart Failure Management Under Pressure*

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The potential benefits of medical therapy for heart failure with reduced ejection fraction (HFrEF) are extraordinary. However, there remains a large gap between medical therapy doses achieved in clinical trials and clinical practice (1). There are multiple explanations for this observation, including clinical inertia, access to medicines and associated costs, and medication intolerance related to overlapping side effects including hyperkalemia, renal dysfunction, and hypotension. An often-stated conundrum is the limitation imposed by blood pressure and tolerability of guideline-directed medical therapy (GDMT). The question becomes: what blood pressure goal should one target for the upper limit of medication titration for patients with HFrEF? For example, during a routine clinical encounter, if the blood pressure is 120/80 mm Hg on carvedilol 12.5 mg twice daily, sacubitril/valsartan 24/26 mg twice daily, and spironolactone 12.5 mg daily, have we achieved success? More aptly stated, does blood pressure serve as a surrogate marker for clinical efficacy of GDMT?

Heart failure (HF) guidelines recommend treatment and titration of evidenced-based beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and aldosterone receptor antagonists to doses targeted in clinical trials, as tolerated (2). These recommendations attempt to model clinical care according to clinical trial protocols, but few if any protocols either: 1) performed dose ranging studies; or 2) targeted a blood pressure to determine optimal dosing. Importantly, doses of medications studied were *not* determined by a patient's therapeutic response, but instead were increased until predetermined target doses were achieved. The guidelines do provide blood pressure targets (i.e., <130 mm Hg) for patients with HF and concomitant hypertension (3). For these patients, the guidelines acknowledge that clinical trials evaluating optimal blood pressure targets in the setting of HFrEF and concomitant hypertension have not been performed. However, the SPRINT (Systolic Blood Pressure Intervention Trial) compared the benefit of treatment of systolic blood pressure to a target of <120 versus <140 mm Hg for patients at high risk for HF (stage A), finding improved clinical outcomes with the intensive treatment strategy (4). This included a 38% lower relative risk of the first episode of HF. Notably, patients with a history of symptomatic HF within the past 6 months or reduced left ventricular ejection fraction were excluded from the SPRINT trial. However, few, if any, evaluations have tested goal blood pressure thresholds attributable to GDMT.

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In this issue of the *Journal*, Arundel et al. (5) provide data on the association of observed systolic blood pressures of <130 mm Hg with short- and long-term outcomes in patients with HFrEF being discharged after a hospitalization for acute HF. Using data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry linked to Medicare claims,

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the investigators compared outcomes for patients with a discharge systolic blood pressure of <130 mm Hg versus those with ≥130 mm Hg. Patients with differences between the admission and discharge systolic blood pressure of >20 mm Hg were excluded to identify patients with a seemingly stable blood pressure despite the episode of acute HF. The investigators utilized a propensity score for discharge blood pressure given the differences in baseline characteristics between the 2 groups, and performed a number of sensitivity analyses, such as excluding patients with a discharge systolic blood pressure <110 mm Hg. In this study, patients with a lower systolic blood pressure had worse outcomes compared with those with a higher systolic blood pressure, including increased 30-day all-cause mortality (hazard ratio: 1.76; 95% confidence interval: 1.24 to 2.48) and 1-year all-cause mortality (hazard ratio: 1.32; 95% confidence interval: 1.15 to 1.53).

There are important limitations to the study that the authors acknowledge, including that the data were limited to patients age ≥65 years and that discharge blood pressures may not represent chronic blood pressures. Also, patients were not randomly allocated to different blood pressure targets; there are multiple reasons for the observed blood pressures that would also affect outcomes. For example, prior to matching for the propensity score, patients with lower observed blood pressure had markers of more severe HF (e.g., lower left ventricular ejection fraction) and did not appear to have lower blood pressure due to intensified medical therapy for HFrEF.

These data are provocative and make clear that 2 very different questions are at play: for the patient with heart failure and hypertension, what is the goal blood pressure treatment threshold; and for the patient with HFrEF, what is the acceptable nadir of blood pressure that optimizes benefit and minimizes harm in response to GDMT? Clearly, additional research is needed to address this latter question and determine optimal blood pressure targets for patients with HFrEF. These data also specifically highlight a tension that is apparent in the art of contemporary treatment for HFrEF: how should we target doses or therapeutic response to GDMT including blood pressure and symptoms? This question has not been prospectively studied.

Fortunately, 2 contemporary movements within medicine will allow us to address this important issue. First, research focused on precision medicine in HF may help clinicians tailor therapy for individual patients based on detailed patient characterization, that is, the broad array of "-omics" (6). Second, with the advent of mobile health devices, including wearables, we now have the ability to capture and analyze physiological data outside of routine clinical encounters and, in fact, data beyond those acquired in clinical trials. It is likely that *new surrogates of true clinical responsiveness* may emerge. These devices, paired with appropriate data platforms and analytic approaches, should be the foundation of a better understanding of physiological response to medical therapy for HFrEF and should allow patients and clinicians to integrate data on medication dose and adherence, with variables that go beyond heart rate, blood pressure, and congestion. In the future, we should better understand how to identify responders from nonresponders to HF medications and recognize patient-level treatment targets instead of population-level surrogates including blood pressure goals.

For now, the charge to the HF community should remain to improve both blood pressure control as well as initiation and titration of medical therapy for HF. For patients with hypertension at risk for HF (stage A), we need improved efforts at blood pressure control. Data from NHANES demonstrate that >40% of patients with hypertension are uncontrolled. For patients with symptomatic HF (stage C), the guidelines are unequivocal: achieving target doses of medical therapy for HFrEF is the goal. Recent data also suggest low blood pressure is not the barrier. That is, an analysis from the CHAMP-HF (Change the Management of Patients With Heart Failure) registry evaluated the proportion of outpatients with HFrEF and systolic blood pressure ≥110 mm Hg who were at target doses of HF medications (7). Despite adequate blood pressure, the investigators found only 19% of patients at target doses for evidenced-based beta-blockers, 12% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 6% for aldosterone receptor antagonists, and 2% for angiotensin receptor neprilysin inhibitors. Studies such as this demonstrate that more work is needed for us to realize the benefits of medical therapy for HFrEF in clinical practice. In summary, targeting blood pressure per se is not the goal; the emphasis should be on prevention of HF in those with hypertension and on optimal medical therapy and optimized clinical outcomes in those with symptomatic HF. That is where the pressure should reside.

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