Dilemmas of Blood Pressure Management for Heart Failure Prevention

Vasiliki V. Georgiopoulou, MD; Andreas P. Kalogeropoulos, MD; Javed Butler, MD, MPH

More than 5.5 million individuals in the United States have heart failure (HF), more than a half-million individuals are diagnosed annually, and more than 1 million HF hospitalizations occur yearly.1 Outcomes remain poor, with approximately 50% of patients dying within 5 years of diagnosis.2 These trends will worsen when aging of the 78 million baby boomers will result in 1 in 5 Americans to be over the age of 65 years by the year 2050.3 HF incidence and prevalence are highest in the elderly. Incidence rate is 10 per 1000 individuals after age 65 years, and 80% of patients hospitalized with HF are over 65 years of age.1 A recent statement from the American Heart Association suggests that if the current trend continues, then by 2030 HF prevalence will increase by 25%, as opposed to 16.6% and 9.9% increase in coronary heart disease and hypertension, respectively, leading to a rise in estimated direct and indirect cost of care to 95 billion dollars annually.4 These trends underscore the importance of population-based strategies to prevent HF.

Case Histories

Patient 1 was a 66-year-old woman with a body mass index of 24, who was examined at a routine annual visit to her primary care physician. Her blood pressure was 148/94 mm Hg after 5 minutes in sitting position. She did not have diabetes mellitus or history of cardiovascular (CV) disease, and she did not smoke. Her routine laboratory tests were unremarkable, including normal renal function. She was asymptomatic.

Patient 2 was a 74-year-old man with a body mass index of 32, who was examined at a routine clinic visit to his cardiologist. His blood pressure was 148/94 mm Hg after 5 minutes in sitting position. He did not have diabetes mellitus. He had a history of non–Q-wave myocardial infarction 3 years previously. His last echocardiogram showed normal ejection fraction 1 year previously. He smoked one-half a pack of cigarettes a day. His routine laboratory tests showed a serum creatinine level of 1.6 mg/dL. He was asymptomatic.

Management Dilemma

To reduce the risk of HF, should both these patients be treated to a blood pressure reduction target of <140/90?

Systolic blood pressure (SBP) increases with age.5 By age 75 years, almost all hypertensive individuals have isolated systolic hypertension.6 Diastolic blood pressure (DBP) is a more important predictor of risk until age 50 years, and thereafter SBP assumes more importance.7 Antecedent hypertension is present in the majority of HF patients.8 In the Framingham Study, the population-attributable risk of hypertension for HF was 39% in men and 59% in women,9 whereas in the Health, Aging, and Body Composition (Health ABC) Study, the attributable risk of hypertension was 21.3% in white elderly individuals and 30.1% in black elderly individuals (Table).10 Risk for HF rises continuously with increasing BP.9,10 The lifetime risk for HF doubles in those with BP >160/100 versus <140/90 mm Hg; this risk gradient is seen in both sexes.11 The progression from hypertension to structural cardiac changes and eventually systolic and diastolic ventricular dysfunction is demonstrated in Figure 1. Considering that (1) the lifetime risk of hypertension is close to 90%;12; (2) hypertension prevalence in the population is currently between 25% to 60%;13 and (3) there is a projected increase in hypertension prevalence, based on the aging trends of the population, sedentary lifestyle, and worsening obesity and diabetes epidemic14; the importance of hypertension as an HF prevention target at the population level cannot be overemphasized.

The Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC-7) classifies hypertension as SBP ≥140 or DBP ≥90 mm Hg, and the treatment targets are set accordingly.15 However, alternative options have been suggested.16,17 Specifically related to HF risk, 4 management options to treat SBP exist.

Treatment Per Current Guidelines

The JNC-7 recommends treatment of SBP as the primary target for CV risk reduction in the elderly and recommends a therapeutic target of <140 mm Hg with stricter goals for individuals with diabetes mellitus or renal disease.15 In individuals over 50 years of age, the desired DBP is usually met once SBP is at goal, thus making SBP the primary focus of treatment in the elderly. Reduction in left ventricular hypertrophy (LVH) and HF risk with treatment to these goals.
has been shown. The Systolic Hypertension in the Elderly Program (SHEP) demonstrated that hypertension treatment exerted a strong protective effect on HF risk. A meta-analysis of 12 hypertension trials, including 4 studies with LVH as end point, demonstrated significant treatment benefits. The incidence of LVH was decreased by 35%, and HF was reduced by 52%; coronary heart disease, vascular events, and stroke rates were also reduced.

On the basis of these data, if the current guideline-based recommendations for SBP control were to be achieved at the population level, the HF burden could be reduced substantially. There are, however, several limitations to this approach. Most importantly, the association between SBP and HF risk is continuous with no threshold defining a “step” in the risk and demarcating need for antihypertensive therapy. High risk for HF was seen in men with SBP/H1140 mm Hg in the Physicians Health Study. In the Health ABC Study, HF risk increased substantially in elderly with increasing SBP among individuals not on any antihypertensive medications, and the absolute number of cases contributed by the partic-

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>White (n=1686)</th>
<th>Black (n=1167)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>PAR, %</td>
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<tr>
<td>Modifiable</td>
<td></td>
<td></td>
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<tr>
<td>SBP ≥140 mm Hg</td>
<td>1.80 (1.27–2.55)</td>
<td>21.3</td>
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<td>Coronary heart disease</td>
<td>2.72 (1.89–3.90)</td>
<td>23.9</td>
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<td>Glucose ≥126 mg/dL</td>
<td>2.08 (1.35–3.22)</td>
<td>11.3</td>
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<tr>
<td>LVH</td>
<td>0.90 (0.44–1.84)</td>
<td>. . .</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.04 (1.15–3.64)</td>
<td>5.5</td>
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<tr>
<td>Modifiable fraction</td>
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<tr>
<td>Potentially modifiable</td>
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<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
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<td>Albumin &lt;3.8 g/dL</td>
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<td>Heart rate &gt;75 bpm</td>
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<td>Potentially modifiable</td>
<td>20.5</td>
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</tr>
</tbody>
</table>

RR indicates rate ratio; CI, confidence interval; PAR, population-attributable risk; and eGFR, estimated glomerular filtration rate.

PARs are not additive and do not add up to 100%. Reproduced from Arch Intern Med 2009;169:708–715, with permission from the American Medical Association.
pants with baseline SBP <140 mm Hg was >50% (Figure 2A and 2B). The association between SBP and both HF and CV risk extending to levels <140 mm Hg has led to increased recognition of the importance of prehypertension.20,21 In the general population, prehypertension is more common than hypertension among untreated individuals (44.5% in men and 27.6% in women versus 13.7% in men and 13.5% in women, respectively).22 Because there are more people with prehypertension than hypertension and HF risk extends to SBP below 140 mm Hg, a large fraction of individuals who will have development of HF will not be addressed by the current JNC-7 recommendations. Thus, following the JNC-7 guidelines, although significant benefit can be expected in terms of reducing HF risk in individuals with uncontrolled hypertension, we will nevertheless miss out on a considerable opportunity to further lower the incidence of HF among those with SBP to within an acceptable range by current standards, at least for those who are still at a higher risk.

Currently, only lifestyle modification is recommended for prehypertension. Drug therapy, however, with an angiotensin receptor blocker has been shown to significantly prevent the transition of prehypertension to hypertension.23 However, outcomes from large clinical trials are currently lacking to address the question of whether lowering SBP in “prehypertensives” is effective strategy to prevent HF in the elderly. A recent randomized trial evaluating the effect of usual versus tight (<130 mm Hg) control of SBP in nondiabetic hypertensive individuals with LVH did demonstrate additional benefit with tighter control.24 In particular, LVH was less frequent, but also the composite outcome of all-cause mortality, CV events, and HF was lower in the tight control group.24 In addition, a recent meta-analysis has shown that treatment with antihypertensive medication of individuals with a history of CV disease but with BP levels in the range of normal and prehypertension is associated with reduced risk for HF, CV events, and mortality.25

The current BP control rates at the population level remain far below the Healthy People 2010 goal of 50%, with 30% of individuals still being unaware of their hypertension status.22 Although the reasons and potential solutions for these trends are many and complicated, side effects and intolerance to medication, complicated regimen and costs, and limited provider time availability complicates effective management. Clearly, the population-based health care goals of the current guidelines are not met with optimal success.

**Treatment on the Basis of Presence of Subclinical Disease Burden**

The observational link between BP and HF risk identifies hazards that may be impressive from a population perspective but is misleading when dealing with individuals. If a certain BP level is associated with a higher risk of HF in a large population, how one uses this information in a clinical setting is uncertain. Should a physician treat 2 individuals with the same BP but otherwise significantly varied risk profile the same or differently? What population risk hazards should define need for therapy? On the basis of this crude approach to decision-making, when extrapolating population data to individuals, some authorities have argued that risk factors are risk factors and not the disease. For widely prevalent risk factors, the sensitivity for predicting disease will be high but the specificity will be low. How does a provider use this information in the clinical setting? Also, if we withhold treatment until SBP reaches guideline thresholds, then it is likely that many patients will have subclinical disease or events in the interim.

On the basis of these concerns, some fields (eg, oncology) rely more on identifying early disease in asymptomatic individuals by screening, for example, mammography, colonoscopy, and Pap smears. However, screening for early CV disease, for example, by coronary artery calcium or carotid intima-media thickness assessment, remains controversial. Atherosclerosis and LVH antedate adverse events by years, and noninvasive testing can recognize both. On the basis of these data, Cohn et al26 have developed the Rasmussen score for assessing vascular (arterial elasticity, resting and exercise BP, fundus photography, carotid intima-media thickness, and microalbuminuria) and cardiac (ECG, echocardiography for left ventricular volume and mass, and N-terminal pro–B-type natriuretic peptide levels) health and early disease. The total score ranges from 0 to 20, and each test is scored as normal, borderline, or abnormal. They reported that one-third of participants in their study had a score >6, which is considered high risk.26 Rasmussen score was superior to risk factor assessment and Framingham 10-year risk scores in identifying those destined for morbid events.27 Additionally valsartan, in the Detection and Treatment of Early CV Disease Trial: Intervention with Valsartan study, reduced the score in asymptomatic high-risk individuals with prehypertension.28 This score may be relevant to HF because atherosclerosis, natriuretic peptides, and left ventricular mass are all related to HF risk.
However, the data on such an approach are preliminary, especially for HF. How to optimally treat BP in individuals with high scores and to what extent is unknown. To what extent an individual must have derangement in physiological parameters to be classified as having “early disease” is not easily definable in many cases because all these parameters tend to be continuous. In this era of cost containment, costs for when an approach is applied to populations that include multiple tests and how to assess risk or early disease recurrently over time must be studied. An implicit hope in the risk factor–based approach is to avoid development of subclinical disease in first place. Is it optimal to wait for individuals to develop subclinical disease before treating risk factors? Alternatively, is detection of subclinical disease better suited as a selection tool to more aggressively treat individuals who already meet the guideline-based criteria for treatment? Will this approach swing the balance from high sensitivity and low specificity to the converse? Is subclinical disease always reversible? Are there race, sex, or other groups in which a strategy based on subclinical disease detection would put them at higher risk because of a high propensity to develop subclinical disease (eg, BP and LVH in black patients)? Although an attractive alternative, this approach needs further study.

**Population-Based Therapy Irrespective of Absolute Levels**

At the population level, because most risk factors have a normal distribution, more events occur cumulatively in individuals at low to intermediate risk for most diseases. Because the distribution of BP is normal in the population, more events occur among the majority with intermediate values than among the smaller proportion with extreme values. The distribution of BP exhibits a wide overlap between those who have adverse events and those who do not, making it difficult to separate individuals who will have future events simply by measuring BP. These facts have prompted the suggestion that treatment decisions for BP should not be targeted to specific individual targets; instead, considering the high burden of risk factors in general and lifetime risk among populations, attempts should be made to move the mean for the entire population.

Proponents of the “polypill” containing 3 antihypertensive agents at moderate doses have recommended that not only classification of BP but also measurement of BP should be abandoned in favor of BP lowering in demographically defined populations at CV risk. It is suggested that the results of BP-lowering trials are compelling in that universal treatment with moderate-dose antihypertensive drugs is recommended for everyone above a sex-specific age, without even measuring BP. This approach is also thought to potentially improve the cost-effectiveness of treatment by using only generically available drugs, combined in a single pill, and avoiding expensive interactions with health care providers.

Although attractive, this approach has its limitations. First, there are limited data on both the safety and efficacy of this approach, especially for clinical outcomes, as opposed to BP reduction at the population level. Should be there any target set for populations to be treated? What doses of drugs in what combination should be used? How do we assess and modify regimen on the basis of side effects? How do we account for comorbidity that influences antihypertensive therapy choices? Because many individuals at all BP levels, high or low, will not have HF or other CV-adverse outcomes, exposing all such individuals to the costs and side effects, not only of one but multiple drugs simultaneously, may raise ethical issues. Also, HF prevention efforts are likely to be most cost-effective in the elderly. Elderly individuals, however, also have more complicated medical regimens and comorbidity burden and have a higher risk of intolerance and side effects. Exposing them to multiple simultaneous medications without any individual risk assessment may cause a shift in the risk-versus-benefit ratio balance. Finally, most antihypertensive agents require periodic assessment of either liver or renal function or other physiological parameters. How this would affect this paradigm needs further study.

**Targeted Treatment on the Basis of Individualized Risk Profiles**

The above discussion underscores that (1) individuals with the worst severity of SBP are at the highest risk for adverse events; (2) there is a considerable overlap in BP ranges among groups who do and do not have HF; (3) the risk extends to below the currently defined guidelines; and (4) a large proportion of HF occur in those with intermediate SBP. This "prevention paradox" has been described for other diseases, for example, cholesterol and coronary heart disease, or ejection fraction and sudden cardiac death. Disease-based (eg, hypertension) therapeutic goals in isolation do not take into account the cumulative risk burden for a particular outcome (eg, HF) for any given individual who tends to present with multiple risk factors at varying severity. Currently, treatment goals for hypertension are not individualized. On the contrary, treatment targets for cholesterol for coronary disease prevention are not solely based on the lipid values but in the context of overall risk profile for an individual. Similarly, 2 individuals with the same SBP may have different HF risk, depending on age or the presence or absence of other risk factors. For example, among the participants in the Health ABC study, who were not receiving antihypertensive medications at baseline, the recently developed Health ABC HF Risk Score overlapped significantly between those with normal BP, prehypertension, and stage 1 and stage 2 hypertension (Figure 3); the average score in these groups was $-1.4 \pm 2.9$, $0.3 \pm 2.8$, $2.0 \pm 2.9$, and $4.2 \pm 3.5$, respectively (unpublished data). Treatment strategies based on an individual’s cumulative risk factor profile may be more likely to maximize intervention benefit.

Such data have been interpreted in several different ways. Several groups have pointed out that elevated BP is but one predictor of CV disease, and age is a much more powerful risk factor. Not everyone with elevated BP will have an event, and regrettably, not every person with “normal” BP will be spared. It may, therefore, be recommended that treatment decisions should be based on a person’s absolute risk, which can be easily estimated using one of several risk estimators. Whether an HF-specific score, for example, the Health ABC HF Score, should be used to target therapy for HF prevention needs further study. Interestingly, the Health ABC HF Score was diverse in all
SBP groups and overlapped considerable between them. On the basis of the success of targeting lipid therapy for coronary disease risk prevention, this option holds promise.

Perspective on Case Management
The two cases described in the beginning highlight all the issues raised in this review. It is self-evident that the patient described in case 1 is at significantly lower risk of development of HF compared with case 2. The latter patient is much older, is a smoker, has renal dysfunction, and is obese; but most importantly, this patient has clinically manifest coronary artery disease. Despite the vastly different profiles, there are two noncontroversial recommendations for these cases. First, both need treatment. Second, case 1 can probably be initially treated with a thiazide diuretic, whereas the patient in case 2, if not already taking it, needs initial treatment with an angiotensin-converting enzyme inhibitor and a β-blocker, along with other therapies appropriate for a postinfarction patient. However, several other management decisions are uncertain or controversial. Considering that the risk for future development of HF differs considerably among these individuals, should their therapeutic targets be different? Would a lower SBP target for case 2 than current recommendation further decrease the risk of HF? As stated earlier, data from a recent randomized trial evaluating the effect of usual versus tight SBP control (<130 mm Hg) in nondiabetic hypertensive individuals with LVH demonstrated additional benefit with tighter control, including improvement in LVH, all-cause mortality, CV events, and HF. These data suggest but do not prove that it might be better to assess the cumulative risk burden of an individual and vary treatment targets. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, lowering blood pressure below the currently recommended levels did not reduce the combined risk of fatal or nonfatal CV events. Specifically, the risk of fatal or nonfatal HF with intensive treatment was 0.94 (95% confidence interval, 0.70 to 1.26). These patients, however, were not enrolled on the basis of stratified HF risk specifically. More concerning are the results of the Randomized Olmesartan and Diabetes Microalbuminuria Prevention Study (ROADMAP) trial, which showed higher incidence of fatal myocardial infarction with olmesartan among patients with preexisting coronary heart disease when blood pressure was targeted to <130/80 mm Hg in individuals with diabetes mellitus. Again, these patients were not stratified by their risk for HF per se. It is hoped that significantly more insight will be gained into these issues when results of the ongoing Systolic Blood Pressure Intervention Trial (SPRINT) trial are available.

Conclusion
There is no debate that uncontrolled SBP is a highly prevalent and effectively intervenable HF risk factor. How to optimally approach SBP to maximally reduce HF risk at the population level, however, needs further consideration. Targeting those at the worst end of the spectrum does not address the prevention paradox, and many individuals at risk, despite SBP in less-than-elevated range, will not benefit. With the concern about the long-term safety profile and risks associated with many of the medications, population-based treatment strategies need evaluation. Screening for subclinical disease has significant cost-effectiveness concerns that must be addressed. An individual risk prediction tool to target therapy to those at high risk, based on overall risk burden, is an attractive but unproven strategy. Comparative effectiveness, risks, and costs of the various approaches to population-based risk reduction, however, must be studied, considering the aging and the worsening risk factor profile of the population. Although we provide management of blood pressure as an illustrative case example, similar dilemmas occur regarding other individual risk factor management, and whether or not management of any individual risk factor should be based on cumulative risk burden in an individual remains an open question. What is not an open question is the fact that the looming worsening HF epidemic necessitates more targeted prevention efforts.

Disclosures
None.

References
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