Aging, Blood Pressure, and Heart Failure
What are the Connections?
Stanley S. Franklin, Daniel Levy

The Role of Low DBP as a Predictor of CVD Risk With Aging
In Framingham Heart Study participants who were free of CVD and not receiving BP-lowering therapy, SBP and DBP (or mean arterial pressure and PP) in combination produced a model that was superior to any single BP component alone in predicting total CVD events (coronary heart disease, heart failure, and stroke); of the 4 BP components, only DBP was nonlinear and showed a J-shaped curve of CVD risk that could be related to a rise in PP and/or a fall in DBP, and these findings were independent of antihypertensive therapy. Furthermore, when CVD events were stratified by DBP <70 mm Hg versus ≥70 to 89 mm Hg to evaluate risk according to the Sixth Joint National Committee classification, those individuals with DBP <70 mm Hg had an increased cardiovascular event rate (Table). Importantly, data from the National Health and Nutrition Examination Survey (1999–2006) confirmed that DBP <70 mm Hg with a prevalence of 30% among untreated persons with ISH was associated with increased CVD risk; advanced age, female sex, and diabetes mellitus, but not treatment status, were associated with low DBP. Perhaps the finding of low DBP together with high SBP can be thought of as an indicator of accelerated aging of conduit arteries.

The Changing Pattern of BP as a Predictor of Risk in the Very Old
Many previous community-based studies of persons ≥85 years of age found that survival worsens in association with lower SBP and DBP, an observation that has been attributed to reversed causality. Reversed causality interferes with the usual lower-is-better relation that normally exists for both SBP and DBP in predicting CVD events. Unlike the solitary DBP J-shaped curve indicative of increased arterial stiffness, reversed causality explains the combined DBP and SBP J-shaped curves often seen with competing comorbidities, but one cannot make a distinction between those that are naturally occurring versus those that are treatment induced. Indeed, frail, elderly persons (often institutionalized) may have DBP <60 mm Hg and SBP <120 mm Hg in association with reduced survival and often without abnormal left ventricular function or antihypertensive drug therapy.

BP and Heart Failure Risk Assessment
In a Framingham Heart Study publication, hypertension antedated the overt heart failure in 91% of cases, and coronary heart disease was the second most common predisposing factor; often these 2 factors coexist and jointly contribute to heart failure risk. In contrast, low SBP and DBP are observed frequently in heart failure in association with severe systolic dysfunction. Furthermore, the Framingham Heart Study reported recently that classical manifestations of overt heart failure were hastened by noncardiac organ dysfunction. It is likely that the advanced age of the subjects with multiple competing comorbidities may have not only accelerated the onset but also modified the clinical manifestations of heart failure. Therefore, there may be an entirely different set of biomarkers that predict incident heart failure in the frail, elderly population with multiple comorbidities. Although combined SBP and DBP J-shaped curves have been observed in symptomatic heart failure in association with severe systolic dysfunction, to date no BP biomarker has been shown to be clinically useful for predicting the onset of heart failure in the presence of asymptomatic left ventricular systolic dysfunction.

It is the significance of low DBP as it pertains to heart failure that has been addressed in a study by Guichard et al in the present issue of Hypertension. Using the community-dwelling Cardiovascular Health Study population that was

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Heart Disease Prevention Program (S.S.F.), School of Medicine, University of California, Irvine, Irvine, CA; Framingham Heart Study (D.L.), National Heart, Lung, and Blood Institute, Framingham, MA; Center for Population Studies (D.L.), National Heart, Lung, and Blood Institute, Bethesda, MD.

Correspondence to Stanley S. Franklin, Heart Disease Prevention Program, School of Medicine, University of California, Irvine, Sprague Hall 112, Irvine, CA 92697-4101. E-mail ssfranklinmd@earthlink.net

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.111.179119
free of centrally adjudicated heart failure at baseline. Guichard et al\textsuperscript{17} identified isolated diastolic hypotension (defined as DBP $< 60$ mm Hg with SBP $\geq 100$ mm Hg) as a new biomarker of incident heart failure. They identified 5376 subjects free of heart failure, of whom 751 (14\%) fit the diagnosis of isolated diastolic hypotension. Propensity scores for isolated diastolic hypotension were estimated for each of the 5376 participants. Isolated diastolic hypotension was the dependent variable in a multivariable logistic regression model that used 58 baseline characteristics as covariates. The 751 individuals with isolated diastolic hypotension averaged 75 years of age at baseline and consisted of 21\% with ISH (SBP $\geq 140$ mm Hg), 38\% with prehypertension (SBP 120–139 mm Hg), and 41\% with SBP 100 to 119 mm Hg. Mean SBP and DBP values were identical regardless of the presence or absence of antihypertensive therapy. The novel finding of this study was that isolated diastolic hypotension was a risk factor for incident heart failure after adjusting for other relevant covariates; furthermore, when participants with ISH were excluded from the definition of isolated diastolic hypotension (limiting SBP to 100–139 mm Hg), the hazard ratio for incident heart failure was further strengthened.

The findings of this study by Guichard et al\textsuperscript{17} should be interpreted within the context of its limitations. The definition of isolated diastolic hypotension can be questioned. In this very elderly population (75 years of age at baseline and 87 years after a mean follow-up of 12 years), it would be unlikely for SBP of 100 to 119 mm Hg to be “normal,” especially in the presence of extensive competing CVD comorbidities. More likely, SBP of $< 120$ mm Hg, together with DBP $< 60$ mm Hg, represents combined SBP and DBP J-shaped curves that are indicative of a high burden of comorbidities, suggesting that the association with incident heart failure is attributed to reversed causality. In contrast, those persons with ISH (mean SBP of 155/53 mm Hg) or systolic prehypertension (mean SBP of 129/54 mm Hg) have solitary DBP J-shaped curves. Moreover, the cutoff value for SBP at 100 mm Hg was arbitrary and may have prevented an extension of the J-shaped curve to lower levels of SBP (the same may be said for the cutoff value of DBP). Not provided by the authors is the association of low DBP with outcome in untreated versus treated individuals. This is important because treatment to reduce SBP in people with ISH or systolic prehypertension will convert some of them to isolated diastolic hypotension; naturally occurring isolated diastolic hypotension and isolated diastolic hypotension because of antihypertensive treatment effects may carry quite different risks. Furthermore, the pathophysiology of very low DBP in relation to the wide range of SBP included in the definition of isolated diastolic hypotension remains unclear. The increased risk for incident heart failure may be related to increased arterial stiffness as reflected in increased PP in both hypertensives and prehypertensives, reversed causality in association with systolic dysfunction and comorbidities in persons with SBP $< 120$ mm Hg, or possibly impaired systolic or diastolic function secondarily to treatment-related low DBP-induced impairment of coronary blood flow.

Despite the potential limitations of the definition of isolated diastolic hypotension as formulated by Guichard et al\textsuperscript{17}, the prediction of incident heart failure on the basis of low DBP represents a novel finding. If these observations can be confirmed in future longitudinal studies, other important questions beg answers. Is the presence of isolated diastolic hypotension, as defined in this study, a reliable biomarker in asymptomatic individuals of risk for future heart failure? Will isolated diastolic hypotension as a biomarker influence the ordering of noninvasive diagnostic tests and/or the initiation of therapy? In addition, what therapeutic modalities might be useful to prevent the progression to overt heart failure? Lastly, is there potential for worsening of CVD risk with antihypertensive treatment in the presence of DBP $< 60$ mm Hg, in those with isolated diastolic hypotension in whom therapy is recommended to further lower elevated SBP?\textsuperscript{18} Unfortunately, low DBP tracks with many confounders, including age-related declining DBP and antihypertensive drug treatment of ISH, precluding a definitive answer regarding a treatment-induced DBP J-shaped curve. Although additional observational studies may provide useful information regarding treatment-induced J-shaped BP curves, only clinical trials can establish whether further BP lowering in patients with ISH and low DBP is safe and beneficial in preventing heart failure and other CVD events.

Disclosures
None.

References

Table. Prediction of Cardiovascular Disease Events by JNC-6 Staging

<table>
<thead>
<tr>
<th>JNC-6 Classification</th>
<th>BP Limits, mm Hg</th>
<th>SBP/DBP, mm Hg</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal BP</td>
<td>SBP $&lt; 120$</td>
<td>109/69</td>
<td>Ref=1.0</td>
</tr>
<tr>
<td></td>
<td>DBP $&lt; 80$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/high-normal BP</td>
<td>SBP 120–139</td>
<td>127/65</td>
<td>2.0 (1.5–2.6)*</td>
</tr>
<tr>
<td></td>
<td>DBP $&lt; 70$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 isolated systolic HTN</td>
<td>SBP 140–159</td>
<td>147/81</td>
<td>2.0 (1.6–2.5)*</td>
</tr>
<tr>
<td></td>
<td>DBP 70–89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 isolated systolic HTN</td>
<td>SBP 140–159</td>
<td>147/64</td>
<td>3.0 (2.1–4.3)*</td>
</tr>
<tr>
<td></td>
<td>DBP $&lt; 70$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 isolated systolic HTN</td>
<td>SBP 160–179</td>
<td>171/81</td>
<td>3.1 (2.4–4.1)*</td>
</tr>
<tr>
<td></td>
<td>DBP $&lt; 90$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 systolic-diastolic HTN</td>
<td>SBP 160–179</td>
<td>172/94</td>
<td>2.7 (2.0–3.6)*</td>
</tr>
<tr>
<td></td>
<td>DBP 90–99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 systolic-diastolic HTN</td>
<td>SBP 160–179</td>
<td>168/106</td>
<td>3.6 (2.5–5.1)*</td>
</tr>
<tr>
<td></td>
<td>DBP $\geq 100$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JNC-6 indicates Sixth Joint National Committee; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; Ref, referent.

*P<0.0001.

Adapted from Franklin et al.\textsuperscript{6}
Aging, Blood Pressure, and Heart Failure: What are the Connections?
Stanley S. Franklin and Daniel Levy

Hypertension. 2011;58:760-762; originally published online September 26, 2011; doi: 10.1161/HYPERTENSIONAHA.111.179119

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/58/5/760

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/