Systolic Swing of the Pendulum
Relation Between Hypertension and Heart Failure Revisited

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Heart failure (HF) is a dreadful condition, a common final pathway of varied heart diseases. The lifetime risk of developing HF is 20%. Once diagnosed, HF carries a substantial risk of mortality. More than 70% of men and women at the age ≥65 years die within 8 years of the diagnosis. It has been estimated that, in 2009, the total direct and indirect costs of HF in the United States alone will exceed $37 billion despite the advances in therapeutic approaches that took place in the past 30 years. Clearly, a lot of effort still needs to be directed to fighting the modifiable risk factors. Among these, hypertension (HT) has long been recognized as a crucial one, predating development of HF in 75% of cases. Thus, virtually all recent expert recommendations place prevention, early detection, and treatment of HT high on the priority list of actions with high potential to avert the constant trend toward increased incidence of HF. However, HT is a disorder with many faces. For instance, for most of the past 20 years it has been far from decided whether it is systolic blood pressure (SBP) or diastolic blood pressure (DBP) that carries most of the blood pressure–associated risk.

Nineteen years ago, a seminal meta-analysis was published that, based on the collection of a large number of data, proved the relation between DBP and cardiovascular risk but disregarded SBP altogether. This was in line with the approach at that time, which based decisions regarding diagnosis and treatment of HT primarily on DBP. However, with time it became evident that SBP plays a great role. An analysis of data from the Framingham Heart Study showed that, in the general population, SBP may be a better predictor of cardiovascular outcome, including HF, than DBP. For the elderly patients with isolated systolic HT (ISH), this was true especially with respect to stroke, for which it became evident that adequate treatment was benefiting patients. Three large-scale, placebo-controlled trials were designed and conducted in the United States, Europe, and China to check the hypothesis that treatment of ISH would reduce incidence of stroke. In the Systolic Hypertension in the Elderly Program, 4736 patients were randomly assigned to receive treatment based on chlorthalidone or were receiving matching placebos. SBP was reduced by active treatment by 11.5 mm Hg, and this was reflected by a 39% reduction in the incidence of stroke. The Systolic Hypertension in Europe Trial enrolled 4695 elderly patients with ISH. The active treatment, which was based on the dihydropyridine calcium channel blocker nitrendipine, as compared with placebo, lowered SBP by 10.2 mm Hg and reduced the incidence of stroke by 42%. Finally, the Systolic-China Trial, a Chinese counterpart of the Systolic Hypertension in Europe Trial, confirmed the beneficial effects on the risk of stroke of antihypertensive treatment of ISH patients in the Chinese population.

In 2000, a group of researchers liaised with the Study Coordinating Centre, Hypertension Unit, University of Leuven, published a report of combined analyses of individual data of all of the ISH patients who up, to that date, had been included in 8 trials testing antihypertensive therapies. The median duration of follow-up ranged from 1.9 through 6.1 years. A 10-mm Hg higher SBP was associated with 14% higher risk of all-cause mortality, 12% higher risk of cardiovascular mortality, 8% higher risk of all cardiovascular events, and 12% higher risk of stroke. Notably, the analyses did not reveal a statistically significant increase in the risk of fatal and nonfatal coronary events with higher SBP (Table). In these analyses, DBP was not associated with an increase in cardiovascular risk. On the contrary, a borderline significant negative trend was noted for the relation between DBP and all-cause mortality.

The present issue of Hypertension brings forth a report by Ekundayo et al., who, using data from Cardiovascular Health Study, assessed the relation between ISH and incidence of HF. In an elegant analysis, they first assessed the relation between ISH status and the risk of HF using a classic propensity-matched analysis. The rate of increase in risk was 90 mm Hg) had a 22% higher risk of developing HF (in propensity-matched analysis). The rate of increase in risk was 1% per 1-mm Hg higher baseline SBP. They were also able to reproduce earlier observations that ISH is associated with higher incidence of cerebrovascular disease but were unable to show the link between ISH and mortality.

The confirmation of a relation between ISH and HF is important, thus firmly introducing HF into the group of complications of ISH (Table). However, several issues must carefully be taken into account when considering these results, as acknowledged by the authors. First, the relation between ISH status and HF incidence may heavily depend on...
the definition of the former. Thus, the relation between ISH or level of SBP and risk of HF and other outcomes (notably, total and cardiovascular mortality) may have been diluted by using the 140-mm Hg and not the 160-mm Hg cutoff value for SBP. Previously published analysis of data from the Framingham Heart Study indicates that, in older individuals, the risk of cardiovascular mortality increases from an SBP of \( \approx 160 \text{ mm Hg} \). This is also important in view of the apparent discrepancy between the finding by Ekundayo et al\(^6\) that ISH does not predict HF in individuals \( \geq 72 \) years of age and a recent observation from the Hypertension in the Very Elderly Trial that antihypertensive treatment based on perindopril and indapamide of octogenarian and older hypertensives reduces the risk of HF by 64\%. Indeed, in the Hypertension in the Very Elderly Trial, baseline SBP had to be \( > 160 \text{ mm Hg} \), and one third of participants had ISH.\(^8\)

Another issue of concern is that, in the study by Ekundayo et al,\(^6\) the relation between ISH and incidence of HF was mainly driven by small subsamples of participants at particularly high risk, like diabetic or renal failure patients.\(^6\) However, the authors were unable to account for such factors as incident ISH and changes in medication status, which may have diluted the risks associated with ISH in the per-baseline-status analyses, especially in groups of individuals at lower risk, ie, nondiabetic or patients with preserved renal function.\(^6\) Similarly, allowance for the regression dilution bias could have steepened a relation between SBP and outcome. Previously, it has been estimated that, in ISH patients, such steepening of the slope of relation reaches \( \approx 90\%.\)\(^5\)

An already mentioned meta-analysis showed an unequivocally beneficial effect of antihypertensive treatment in ISH.\(^5\) Thus, 59 elderly patients with ISH needed to be treated for 5 years to prevent 1 death of any cause and 79 elderly patients with ISH needed to be treated equivalently to prevent a cardiovascular fatality. Corresponding numbers needed to treat for fatal and nonfatal events were 26 for all cardiovascular, 48 for stroke, and 64 for coronary events.\(^5\) However, whether antihypertensive treatment of elderly patients with ISH can prevent HF and which regimen should be preferred remains a matter of uncertainty. The above-mentioned trials in the elderly patients with ISH yield somewhat conflicting evidence. Although in the Systolic Hypertension in the Elderly Program Trial chlorthalidone significantly reduced incidence of HF (by 49\%), in the Systolic Hypertension in Europe Trial, the trend toward reduction of incident HF (by 26\%) in patients treated with nitrendipine did not reach statistical significance.\(^10\) Recently some light was shed by the Hypertension in the Very Elderly Trial;\(^9\) however, neither of the trials mentioned was specifically designed to answer the question posed here, and patients included were healthier than those we usually see in everyday practice. Clearly, we need to wait for more evidence, if not from new trials then at least from ISH-focused analyses of existing data.

Disclosures

None.

References

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_Hypertension_. 2009;53:452-453; originally published online February 2, 2009;
doi: 10.1161/HYPERTENSIONAHA.108.125633

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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