New Issues in the Treatment of Isolated Systolic Hypertension

Norman M. Kaplan, MD

The newest hot issue in the field of hypertension relates to the oldest—isolated systolic hypertension (ISH) in the elderly. The article by Fagard et al. in this issue of *Circulation* provides important evidence about the response of ISH to antihypertensive therapy. Moreover, the implications of the evidence extend to the management of hypertension of any nature at any age.

Before commenting on the findings in this article, I will provide a bit of background. ISH is the most common form of hypertension in those older than 65 years. Because this segment of the population is expanding so rapidly, ISH will soon be the most prevalent form of hypertension.

Over the last few years, a paradigm shift has occurred, away from the prior concern over an elevation of diastolic pressure to our current awareness that an elevation of systolic pressure and, to an even greater extent, the combination of higher systolic and lowered diastolic pressures (i.e., a widening of the pulse pressure) are the major determinants of cardiovascular risk in the elderly. This should come as no surprise because the widening pulse pressure reflects atherosclerotic stiffening of the aorta and large capacitance vessels. This provides a smaller, rigid reservoir wherein systolic inflow raises pressure and diastolic emptying lowers pressure to a greater degree than occurs with more compliant, elastic vessels. In addition, pulse-wave velocity is faster through stiff vessels, so that the usual reflection of the pressure wave back from the periphery occurs in midsystole rather than diastole, augmenting the already elevated systolic pressure and removing the major support of diastolic pressure. Therefore, the widened pulse pressure so typically found in the elderly reflects both a rise in systolic levels and a fall in diastolic levels.

The dangers of high systolic pressure are well known, and unequivocal evidence shows that the treatment of ISH provides significant protection against cardiovascular mortality and morbidity. Attention must obviously be paid to expanding the number of elderly patients with ISH whose blood pressure is well controlled. Such control will prolong life a bit and, more importantly, it will reduce the strokes, heart attacks, and episodes of heart failure that are so burdensome to the elderly. In one of the trials of ISH treatment, the onset of dementia was also reduced, holding promise for even more benefit from such therapy.

However, lower diastolic pressure is also dangerous. In the analysis of the course of >7500 elderly patients with ISH who were left on placebo during multiple randomized controlled trials (RCTs), a continually higher death rate was seen, as expected, with progressively higher systolic pressures on entry but, surprisingly, similar increases in mortality were seen with progressively lower diastolic pressures on entry. When diastolic pressures are lowered too much by antihypertensive therapy, similar increases in events have also been seen. Therefore, the high systolic pressure must be lowered, but caution is needed not to lower the already low diastolic pressure much further.

Therefore, as more attention is directed toward the control of ISH, the following 3 questions must be addressed:

1. At what level of systolic blood pressure should treatment with drugs begin? Nondrug therapies to lower blood pressure, although they may be even more effective in the elderly than in the young, are often not adequate.
2. Which drugs should be used?
3. To what level should the blood pressure be lowered?

Data from the Systolic Hypertension in Europe trial, including that contained in the article by Fagard et al., can help answer these questions.

Regarding the first question, all of the RCTs for ISH have used a systolic blood pressure of 160 mm Hg taken in the office or clinic as the lower limit for entry. However, in the side project of the Systolic Hypertension in Europe trial described by Fagard et al., ambulatory blood pressure monitoring was done (for the first time in an RCT) in 695 of the 4695 patients enrolled. As noted by others in elderly patients with either ISH or combined systolic and diastolic hypertension, the out-of-the-office daytime systolic readings in most of the patients were considerably lower than the average of 6 clinic readings (this average was 173 mm Hg). In almost 25% of the patients, the average out-of-the-office daytime systolic blood pressure was <140 mm Hg and, in another 45%, it was <160 mm Hg. These patients had “white-coat” hypertension.

When the effects of drug therapy were examined by repeat ambulatory blood pressure monitoring, ECGs, and the numbers of cardiovascular events, there was no evidence of any significant change in out-of-the-clinic blood pressures, ECG voltage, or cardiovascular events in those who were treated compared with those on placebo if their initial ambulatory...
blood pressure readings were <160 mm Hg. These data cover only 1 year and may not reflect longer effects, but they strongly suggest that before rushing to treat all those who have office systolic readings >160 mm Hg, out-of-office readings should be obtained to identify white-coat hypertension.

In keeping with the data in this article, increasingly strong evidence indicates that those with white-coat hypertension do not experience an increase in cardiovascular events, at least over the 10 years of follow-up now available in a few hundred such patients. Therefore, in view of the fact that the further lowering of the diastolic blood pressure that usually accompanies the treatment of systolic hypertension may be harmful, caution is needed. Ambulatory blood pressure monitoring would prove whether the hypertension is white-coat in 24 hours, but because third-party payers in the United States misguidedly refuse to pay for the procedure, self-taken home readings are a readily available and quite satisfactory alternative. Such readings should be obtained, if at all possible, on all patients with a systolic blood pressure >160 mm Hg in the absence of obvious target organ damage or overt cardiovascular disease that would mandate drug therapy, even if a significant white-coat effect is found. Without any evidence that treating those with systolic pressure levels <160 mm Hg is beneficial and with evidence that lowering their already low diastolic levels further may be harmful, this precaution seems advisable.

Regarding the second question, once the usual systolic blood pressure is found to be >160 mm Hg, the form of drug therapy now recommended in all of the expert guidelines is low-dose diuretics or dihydropyridine calcium-channel blockers. These recommendations are based on the cardiovascular protection found in the RCTs in which these drugs were used. In older patients with combined systolic and diastolic hypertension, therapy based on an angiotensin-converting enzyme inhibitor has recently been shown to be as good, if not better, than that based on diuretics or calcium-channel blockers. Whether this applies to ISH patients is unknown.

Concerns exist regarding inadvertently lowering the already low diastolic pressures in patients with ISH. Very limited data suggest oral nitrates may slow the augmentation of the pulse wave that is largely responsible for the high systolic pressures in the elderly. The pulse wave would thereby have less effect on the diastolic pressure or, if the augmentation was high enough, it could even cause the diastolic pressure to rise. More controlled trials with nitrates or other drugs that may improve the hemodynamic faults of ISH are obviously needed.

The third question, how much should blood pressure be lowered, is perhaps the most disturbing in view of evidence that serious consequences are seen with low diastolic blood pressures. These low pressures may occur naturally, as part of the atherosclerotic process (as shown by Staessen et al), or as part of antihypertensive therapy. In the Rotterdam Study involving 2351 elderly hypertensives, the risk of stroke was significantly higher in those given antihypertensive drugs whose diastolic blood pressure was <65 mm Hg compared with those who had a diastolic blood pressure between 65 and 74 mm Hg. In the recent reanalysis of data from the Systolic Hypertension in the Elderly Program, those who experienced a cardiovascular event while on antihypertensive drug therapy had lower diastolic levels than those who did not have an event. Overall, a further decrease of 5 mm Hg in a diastolic blood pressure (which initially averaged 77 mm Hg) among those who were treated resulted in statistically significant 11% to 14% increases in stroke and cardiovascular events.

Thus, there may very well be a J-curve of increasing cardiovascular disease when the diastolic pressure is lowered below the level needed to maintain perfusion to vital organs. Even among patients with initially high diastolic pressures, such as those in the massive Hypertension Optimal Treatment trial in which all participants began the trial with a diastolic blood pressure >100 mm Hg, an apparent increase in cardiovascular mortality occurred among those whose diastolic blood pressure was reduced to a level ≤70 mm Hg. Therefore, caution is advised in treating those with ISH, who obviously start with already low diastolic blood pressures.

In conclusion, the need for effective antihypertensive therapy for the many millions of elderly patients with ISH has been reconfirmed by Fagard et al. However, their data warn of the need to first establish the presence of out-of-the-office hypertension. Once established, ISH should be treated gently by bringing the systolic blood pressure to near 140 mm Hg while ensuring that the diastolic pressure is not lowered much below 70 mm Hg. Those with even lesser elevations of systolic pressure may require active therapy if they are at high risk because of concomitant diabetes, renal dysfunction, heart failure, etc.

In the future, drugs other than those currently recommended may have a more selective effect, lowering the elevated systolic levels but not reducing the already low diastolic levels. Nonetheless, with appropriate caution, protection can be provided to these vulnerable patients.

References

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