“The Lower the BP the Better” Paradigm in the Elderly Vanished by VALISH?

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If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties.
—Francis Bacon, The Advancement of Learning, year 1605

Hypertension is a growing public health problem in elderly people, with a prevalence up to 80% in individuals aged ≥70 years. Isolated systolic hypertension accounts for 60% to 75% of cases, systolic blood pressure (BP) being the dominant prognostic marker. Unfortunately, the rate of hypertension control only minimally improved over last year’s in elderly subjects when compared with the younger people.

Treating Hypertension in Elderly

Several randomized clinical trials tested the benefit of treatment in elderly patients with isolated systolic hypertension or systolic-diastolic hypertension. Staessen et al reviewed 8 randomized clinical trials carried out in patients with isolated systolic hypertension and aged ≥60 years. Active treatment reduced total mortality by 13%, cardiovascular (CV) mortality by 18%, all CV complications by 26%, stroke by 30%, and coronary events by 23%. The benefits of treatment in octogenarians remained unproved for years up to the results of the Hypertension in the Very Elderly Trial, in which 3845 patients aged ≥80 years with systolic BP ≥160 mm Hg were randomized to indapamide or placebo. Perindopril or matching placebo was added if necessary to achieve the target BP of 150/80 mm Hg. The trial was stopped after less than 2 years of follow-up because of a beneficial effect of treatment on several outcomes including all-cause mortality, although the primary study outcome, fatal or nonfatal stroke, was only marginally reduced (by 30%; P=0.06). At study end, BP was lower by 15.0/6.1 mm Hg in the treatment group than in the placebo group. The results of Hypertension in the Very Elderly Trial extend the benefits of treatment to octogenarians with systolic BP ≥160 mm Hg. More recently, the Blood Pressure Lowering Treatment Trialists’ Collaboration reviewed 31 trials, for a total of 190,606 participants, and concluded that, for any given reduction in systolic BP, the protection afforded by antihypertensive treatment is comparable in younger (<65 years) and older (≥65 years) adults.

It is now generally accepted that, despite some minor differences between different classes of antihypertensive drugs in the risk of stroke and coronary artery disease, most of the outcome benefit of antihypertensive treatment is explained by the degree of systolic BP reduction. A recent meta-analysis of 147 randomized trials showed that a reduction in systolic BP by 10 mm Hg leads to a 25% relative risk reduction in coronary heart disease and a 35% to 40% relative risk reduction in stroke.

Does Evidence Support an Aggressive Systolic BP Target in the Elderly?

Although the current guidelines suggest that systolic BP should be lowered below 140 mm Hg in the elderly, supporting evidence is scanty. As suggested by Zanchetti et al, 3 points should be considered: (1) not a single trial was specifically conducted in elderly hypertensive patients with systolic BP <160 mm Hg; (2) in none of the available placebo-controlled trials did systolic BP fall below 140 mm Hg in the control group; and (3) in none of the available placebo-controlled trials was 140 mm Hg the pre-specified BP target of treatment.

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients was conducted in hypertensive patients aged 60 to 85 years with systolic BP ≥160 mm Hg. Patients were randomized to a more tight (<140 mm Hg) or less tight (140 to 160 mm Hg) systolic BP target and followed for 2 years. The primary end point, a composite of CV disease and renal failure, did not differ between the 2 groups. This study cannot be considered as definitive because of the relatively short duration of follow-up, the inclusion of patients with complicated hypertension, and the underuse of diuretics (12.1%). In the Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control, a more aggressive systolic BP target (<130 mm Hg) was superior to a less aggressive target (<140 mm Hg) in reducing left ventricular hypertrophy, the primary outcome of the study, in a relatively younger population (≥55 years of age; mean age: 67 years) of patients with systolic BP >150 mm Hg. In this study, coronary revascularization (P=0.032) and new-onset atrial fibrillation (P=0.044), 2 secondary outcomes, were less common in patients randomized to the more aggressive target.

The picture is complicated by the results of the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) Study.
Main features

Design: Multicenter, parallel-group, Prospective, open study with blind assessment of end-points (PROBE)

Inclusion criteria: Elderly subjects (70-84 years of age) with systolic BP > 160 mmHg and diastolic BP < 90 mmHg

Comparison: Two target systolic BP levels (<140 mmHg vs 140-149 mmHg)

First line drug: Valsartan

Primary outcome: Composite of sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death due to heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, renal dysfunction

Median follow-up: 3.07 years

Enrolled patients: 3,260

Difference in achieved BP between the groups: 5.4/1.7 mmHg (systolic/diastolic)

Potential Limitations

Angiotensin receptor blocker at relatively low dose as initial treatment in elderly subjects

Less than expected statistical power:

● Expected incidence of primary outcome: 21.4 (aggressive target) and 29.1 (standard target) per 1,000 patient-years
● Observed incidence of primary outcome: 10.6 (aggressive target) and 12.0 (standard target) per 1,000 patient-years

Figure. Main features and limitations of the VALISH Trial.

published in the present issue of Hypertension. Overall, 3260 patients aged 70 to 84 years were randomized to a more tight (<140 mm Hg) or less tight (140 to 150 mm Hg) systolic BP control. Valsartan was the first-line drug in all of the patients, with possible combination with other drugs, except other angiotensin receptor blockers, to achieve the assigned BP target (Figure). At the end of the study (median follow-up: 3 years), systolic BP decreased by 5.4 mm Hg more in the tight BP control group, but the primary outcome, a composite of fatal and nonfatal CV disease and renal failure, was only modestly reduced in the more tight control group (10.6 versus 12.0 per 1000 patient-years; P=0.38). One potential limitation of the VALISH Study was the observed rate of primary outcome, which was half of that expected (10.6 versus 21.4 per 1000 patient-years in the more tight and 12.0 versus 29.1 per 1000 patient-years in the less tight BP control group). This could have reduced the power of the study to detect significant outcome differences between the groups, if truly present. The relatively low event rate might be explained by a low prevalence of patients with established CV disease at entry (Figure).

Another point that deserves mention is the use of an angiotensin receptor blocker (valsartan) at relatively low daily doses as initial therapy for all of the patients (40 to 80 mg once daily). Calcium-channel blockers and diuretics may be preferential drugs for older hypertensive patients when compared with drugs that inhibit the renin-angiotensin system.12 Furthermore, low daily doses of angiotensin receptor blockers, as those used in the VALISH Study,11 are generally considered scarcely effective in US and European patients, and, hence, the extrapolation of these data to non-Asian populations may not be automatic.

What to Conclude, Then?

On balance, none of the available intervention trials provided strong support for ambitious BP targets in elderly patients with systolic hypertension. It is clear that the absolute CV risk is higher in elderly patients than in the younger ones, particularly in the presence of comorbidities or other risk factors. Consequently, if we assume that the relative benefit of treatment does not change with age, then the absolute benefit of treatment in the elderly for any given reduction of BP would be greater, and the number of patients to treat to prevent one event would be lower. The outcome benefits of systolic BP reduction in the elderly are well established. The current uncertainty surrounding the definition of the most appropriate systolic BP target, highlighted by the few available trials including VALISH, should be perceived as a stimulus for future research, not as an argument vanishing or questioning the benefit of treatment. Paraphrasing Sir Francis Bacon, we should be content to enter this arena with doubts, not with certainties. The systolic BP target of 140 mm Hg in the elderly, although recommended by guidelines, remains largely unsupported. More stringent targets, although reasonable and potentially affordable, require evidence from clinical trials.

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None.

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