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Blood Pressure and Outcomes in Very Old Hypertensive Coronary Artery Disease Patients: An INVEST Substudy

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Abstract

BACKGROUND—Our understanding of the growing population of very old patients (aged ≥80 years) with coronary artery disease and hypertension is limited, particularly the relationship between blood pressure and adverse outcomes.

METHODS—This was a secondary analysis of the INternational VErapamil SR-Trandolapril Study (INVEST), which involved 22,576 clinically stable hypertensive coronary artery disease patients aged ≥50 years. The patients were grouped by age in 10-year increments (aged ≥80, n = 2180; 70–<80, n = 6126; 60–<70, n = 7602; <60, n = 6668). Patients were randomized to either verapamil SR- or atenolol-based treatment strategies, and primary outcome was first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS—At baseline, increasing age was associated with higher systolic blood pressure, lower diastolic blood pressure, and wider pulse pressure ($P < .001$). Treatment decreased systolic, diastolic, and pulse pressure for each age group. However, the very old retained the widest pulse pressure and the highest proportion (23.6%) with primary outcome. The adjusted hazard ratio for primary outcomes showed a J-shaped relationship among each age group with on-treatment systolic and diastolic pressures. The systolic pressure at the hazard ratio nadir increased with increasing age, highest for the very old (140 mm Hg). However, diastolic pressure at the hazard ratio nadir was only somewhat lower for the very old (70 mm Hg). Results were independent of treatment strategy.

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CONCLUSION—Optimal management of hypertension in very old coronary artery disease patients may involve targeting specific systolic and diastolic blood pressures that are higher and somewhat lower, respectively, compared with other age groups.

Keywords

Age; Blood pressure control; Coronary artery disease; Elderly; Epidemiology; Hypertension

Atherosclerotic coronary artery disease and systemic hypertension are age-dependent (incidence and prevalence), and for both disorders, aging independently increases risk for adverse outcomes.^{1–4} The prevalence of patients with the combination of advanced age (including the very old, aged ≥ 80 years), coronary artery disease, and hypertension is increasing.¹ While aging is irreversible, and coronary artery disease is capable of only limited regression,⁵ hypertension can be successfully treated. Successful hypertension treatment decreases risk for adverse outcomes among most lower-risk and younger patient groups.⁶ However, for the very old, results have been conflicting.^{7,8} Additionally, for the very old with hypertension *and* coronary disease, information is limited. To our knowledge, there are no reports of the association between blood pressure and adverse outcomes for this group and, consequently, their optimal blood pressure is unknown.

One trial of patients with coronary artery disease and hypertension (INternational Verapamil SR-Trandolapril Study [INVEST]) included a large number of very old patients.^{9,10} The main result was that beta-blocker and calcium antagonist-based treatment strategies were similarly effective for lowering blood pressure and equivalent for reducing risk.⁹ Among the 22,576 patients enrolled, 2180 were very old. We focus on detailed results of a prespecified aging substudy here, including associations between on-treatment blood pressure and adverse outcomes for the very old versus other age groups.

METHODS

The INVEST design, methods, and principal results have been published.^{9,10} The study was approved by local ethics committees, and all patients provided informed written consent. Briefly, clinically stable coronary artery disease patients with hypertension were randomly assigned to either a verapamil SR- or an atenolol-based treatment strategy. The treatment strategy recommended addition of trandolapril, with or without hydrochlorothiazide, when necessary to achieve blood pressure goals. Trandolapril also was recommended for patients with heart failure, diabetes, or renal insufficiency (defined as history of or current abnormal elevation in serum creatinine level, but <4 mg/dL [<354 μ mol/L]).⁹ Blood pressure treatment goals were $<140/90$ mm Hg or, for patients with diabetes or renal insufficiency, $<130/85$ mm Hg.

Primary and Secondary Outcomes

The primary outcome was first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included all-cause death, total myocardial infarction (fatal and nonfatal), total stroke (fatal and nonfatal), and revascularization (coronary bypass or percutaneous intervention).

Statistical Analyses

Statistical analyses were performed using SAS statistical software (Version 9.1, SAS Institute Inc, Cary, NC) with chi-squared tests for categorical variables and one-way analysis of variance for continuous variables. Statistical significance was assumed when P values were $<.05$ (2-tailed).

Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for outcomes by age group (10-year increments). Stepwise selection was used to identify risk factors for primary outcome among patients in each age subgroup. The following covariates were entered into the model: age (decades, age <60 years as the reference group), sex, race, prior myocardial infarction, prior class I-III congestive heart failure, body mass index (BMI), smoking status, history of peripheral vascular disease, renal insufficiency, stroke/transient ischemic attack, diabetes, left ventricular hypertrophy (using electrocardiographic or echo-cardiographic criteria, or both) and cancer (skin, prostate, and other cancers with long survival expectancy).⁹ Factors were retained in the final model if a *P* value $\leq .05$ was achieved. Average on-treatment systolic, diastolic, and pulse pressures were calculated for each patient using all post-baseline results, until adverse outcome or censoring. The distribution of primary outcome rate was evaluated as a function of systolic blood pressure, and the frequency distributions best fit a quadratic relationship. A quadratic stepwise Cox proportional hazards model was therefore formed for time to primary outcome for each blood pressure variable (factors for blood pressure and blood pressure²). A similar analysis was made for diastolic blood pressure. A systolic blood pressure of 140 mm Hg and diastolic blood pressure of 90 mm Hg were used as references within each subgroup (HR = 1.0).

RESULTS

Baseline Conditions

The very old patients had the highest proportion of females, US residency, white ethnicity, the lowest BMI, and lowest prevalence of smoking compared with other age groups (Table; *P* <.001). Moreover, the very old had the highest prevalence of prior myocardial infarction, stroke/transient ischemic attack, peripheral vascular disease, congestive heart failure, arrhythmia, and renal insufficiency (*P* <.001). Each of these proportions appears to be part of age-dependent continuums beginning at age <60 years, and which transition as a function of age. However, increasing age only to <80 years was associated with increasing history of unstable angina, coronary revascularization, and use of antiplatelet and lipid-lowering drugs (*P* <.001). Each of these demographics then decreased for the very old.

Blood Pressure and Treatment

At baseline, increasing age was associated with generally higher systolic and lower diastolic blood pressure (Figure 1; *P* <.001). As a consequence, pulse pressure increased with increasing age, widest for the very old (*P* <.001). However, the very old had only a slightly greater proportion of patients with blood pressure levels <140/90 mm Hg (*P* = .024). At 24 months, the very old were using the least number of anti-hypertensive drugs (1.7; for the remaining age groups, 1.8–2.0; *P* <.001), reflecting a progressive decrease in the number of antihypertensive drugs used with increasing age. At 24 months, the very old had the largest decrease in systolic and smallest decrease in diastolic blood pressure, resulting in the largest decrease in pulse pressure. Nonetheless, at 24 months the very old still had the highest systolic pressure (similar to age 70–<80 years), lowest diastolic pressure, and widest pulse pressure. While treatment improved blood pressure control for all age groups over time, the very old had the lowest proportion of patients achieving levels <140/90 mm Hg (Figure 1). For all age groups, the verapamil SR- and atenolol-based treatment strategies resulted in very similar control of blood pressure (data not shown).

Primary and Secondary Outcomes

After 61,835 total patient-years of follow-up, the very old had the highest proportion of the primary outcome (23.6%; Figure 2; *P* <.001), driven by all-cause death. The principal cause of death in each age group was cardiovascular (for the very old, 46.2%; for the remaining

age groups, 47.5%–55.6%). The incidence of the primary outcome showed a progressive increase with increasing age, driven by increases in death (Figure 2). Total myocardial infarction (fatal and nonfatal) and total stroke (fatal and nonfatal) also increased with increasing age, peaking in the very old. Among patients developing either a myocardial infarction or stroke, the event was more likely to be fatal with increasing age, and this shift in the proportion of fatal events also peaked among the very old (Figure 3). However, coronary revascularization did not differ between age groups. There was no difference in any outcome for any age group based upon treatment (Figure 4).

Other strong predictors ($P < .0001$) for primary outcome were: congestive heart failure (HR 1.95; 95% CI, 1.72–2.22); diabetes (HR 1.79; 95% CI, 1.65–1.96); prior myocardial infarction (HR 1.33; 95% CI, 1.21–1.45); peripheral vascular disease (HR 1.29; 95% CI, 1.15–1.43); renal insufficiency (HR 1.51; 95% CI, 1.24–1.83); prior stroke/ transient ischemic attack (HR 1.46; 95% CI, 1.29–1.65); and smoking (HR 1.38; 95% CI, 1.27–1.52).

Relationships between Blood Pressure and Primary Outcome

The adjusted HR for primary outcome in the very old (and remaining age groups) was related to on-treatment systolic and diastolic blood pressure as a quadratic, “J-shaped” curve (Figure 5). The quadratic terms for both systolic and diastolic blood pressure were statistically significant in all age groups (all $P < .001$, except for diastolic blood pressure in 60–70-year-olds, for whom $P = .006$). The systolic blood pressure at the HR nadir increased with increasing age and was highest for the very old (140 mm Hg; Figure 5). Interestingly, the next oldest age group, aged 70–<80 years, had only a somewhat lower systolic pressure (135 mm Hg) at its HR nadir, whereas the 2 youngest age groups each had a much lower systolic pressure (110 mm Hg) at their respective nadirs. The diastolic blood pressure at the HR nadir was similar for all age groups (75 mm Hg) excepting for the very old, for whom it was somewhat lower (70 mm Hg).

DISCUSSION

We have reported^{11,12} that the relationship between blood pressure (by 10-mm Hg strata) and outcome was J-shaped, particularly for diastolic blood pressure. However, the mean ages in each 10-mm Hg blood-pressure stratum were very similar (66–67 years), so our analyses concentrated on other covariates. Our initial analysis¹¹ showed a relative increase in the proportion of myocardial infarctions to strokes as diastolic blood pressure decreased, and that low diastolic blood pressure was associated with relatively less risk among patients with prior coronary revascularization versus no revascularization. We interpreted these data to support the hypothesis that the increase in risk at lower diastolic blood pressure may be related to decreased coronary perfusion. Our next analysis¹² found that pulse pressure predicts outcomes, but pulse pressure was a weaker predictor compared with either diastolic or systolic pressure. The current prespecified substudy extends our observations to a detailed analysis of the influence of aging, focusing on very old patients (≥ 80 years), who are increasing in our population.

The results of the current analysis indicate that very old hypertensive patients with coronary disease have baseline conditions and blood pressures that seem to be part of an age-dependent continuum beginning at age <60 years, and which transition as a function of age. For these very old patients, achievement of blood pressure control and decreases in pulse pressure also seem to be part of an age-dependent continuum. Within all age groups, very similar blood pressure control was achieved using either antihypertensive strategy, and with similar effects on outcomes. The very old had the greatest incidence of adverse outcomes—with the exception of revascularization—and these incidences similarly seem to be part of an age-dependent continuum. Finally, for the very old, the relationships between systolic and

diastolic blood pressures and adverse outcomes are in the form of “J-shaped” curves. Although J-shaped curves also occurred for the other age groups, there is a progressive increase in systolic blood pressure at the HR nadir with increasing age, with the highest pressure at the nadir (140 mm Hg) observed in the very old. The diastolic blood pressure at the HR nadir was similar for all age groups except for the very old, for whom it was somewhat lower (by 5 mm Hg: 70 mm Hg).

The progressive transition in prevalence of baseline conditions and blood pressures culminated in the very old patients having the greatest proportion of women, US residency, and white ethnicity, with the lowest BMI and smoking prevalence. However, the very old also had the highest prevalence of myocardial infarction, stroke/transient ischemic attack, peripheral vascular disease, congestive heart failure, arrhythmia, and renal insufficiency, as well as highest systolic pressure (similar to age 70-<80 years), lowest diastolic pressure, and widest pulse pressure. The transition in baseline conditions may indicate an age-dependent selection for survival of those patients who are the most resilient and perhaps have better access to health care.¹³ The transition in baseline blood pressures may be the result of the age-dependent increase in extent and severity of vascular disease as reflected by the prevalence of peripheral vascular disease and prior stroke/transient ischemic attack.

This age-dependent increase in extent and severity of vascular disease also might have influenced the rate of control for systolic and diastolic blood pressures, which decreased with increasing age (Figure 1). However, the decrease in number of antihypertensive medications with increasing age may have contributed to this observation, which was statistically significant but clinically small. Regardless, narrowing of pulse pressure occurred for each successive age group and, although the very old still had the widest pulse pressure, adequate blood pressure control was achieved using either antihypertensive strategy, and outcomes did not differ by strategy. The similarity of outcomes regardless of strategy is consistent with the results of a recent meta-analysis of randomized trials involving different regimens to lower blood pressure in mostly younger adults.¹⁴ Conversely, these results are inconsistent with those of previous studies of isolated hypertension, for which beta-blocker therapy was associated with less optimal outcomes.¹⁵ The explanation for this latter inconsistency may involve the addition of coronary disease and other high-risk baseline conditions for the very old patients enrolled in INVEST and the fact that atenolol was dosed twice daily for most patients assigned this strategy.⁹ Addition of coronary disease and other high-risk conditions also might account for the observation that the outcomes of myocardial infarction and stroke were more likely to be fatal with increasing age. However, in the very old, the proportion of fatal strokes (31.6%) was less than in similarly aged patients in the Hypertension in the Very Elderly Trial (57.5%),⁸ which compared indapamide with or without perindopril versus placebo.

The progressive increase in the incidence of adverse outcomes with increasing age culminated in the very old patients having the highest incidence of each adverse outcome, with the exception of revascularization. However, the incidence of revascularization remained relatively low for all age groups, including the very old, compared with the general coronary artery disease population (10% in 2007).¹⁶ Although revascularization is a management choice rather than a disease outcome, this low incidence may relate in part to the effective blood pressure control⁹ as well as be a direct effect of verapamil SR and atenolol on ischemia-related symptoms.^{17–19}

The systolic blood pressure at the HR nadir increased with increasing age, and the very old demonstrated the highest systolic pressure (140 mm Hg) at their respective HR nadirs. This observation is consistent with some prior reports relating blood pressure and outcome to age in lower-risk hypertensive patients. For example, regarding the diminishing risk of

excessively high systolic pressure with increasing age, a meta-analysis of 1 million subjects showed that the steepness of the relationship between increases in systolic pressure and adverse outcomes decreases or flattens with increasing age.⁴ Additionally, for the increasing risk of excessively low systolic blood pressure with increasing age, it was demonstrated in a meta-analysis of 1670 very old subjects in antihypertensive clinical trials that, despite a decrease in risk of cardiovascular outcomes, there appeared to be no beneficial effect on all-cause death.⁷ In fact, there was an overall 6% (nonsignificant) increase in all-cause death, and when the analysis was limited to double-blind studies, there was an 11% (nonsignificant) increase in risk of cardiovascular outcomes and a 14% (significant) increase in all-cause death. A recent retrospective cohort analysis of very old hypertensive patients, of whom 84.5% were receiving antihypertensive medication, suggested a lower survival for those with systolic blood pressure <140 mm Hg, even after adjustment for known predictors of death.²⁰ The addition of coronary artery disease and other high-risk baseline conditions in the very old patients enrolled in INVEST may have reduced their tolerance for excessively low systolic pressure.

In contrast, the diastolic blood pressure at the HR nadir was similar for all age groups (75 mm Hg) except for the very old, where it was 70 mm Hg.

Regardless of antihypertensive strategy, the different J-shaped curves observed suggest that, in very old hypertensive patients with coronary artery disease, optimal management should target specific ranges for systolic and diastolic blood pressure. Although not the focus of this analysis, the curves indicate that this suggestion also may apply to those in the 70-<80-year age group. Moreover, this suggestion contrasts with the management of “isolated” hypertension, where larger reductions in blood pressure have been shown to produce larger reductions in risk.²¹ If an appropriately powered randomized trial confirms that excessively low blood pressure (<120/60 mm Hg) indeed increases adverse outcomes compared with a higher blood pressure target (140/70 mm Hg), then it would be appropriate to update guidelines to improve outcomes in the expanding population of very old hypertensive patients with coronary artery disease.

Limitations

This study has several limitations. First, although it was prespecified, it was nonetheless a secondary analysis. Second, results apply to hypertensive patients with coronary artery disease managed using either a verapamil SR- or an atenolol-based strategy and may not necessarily apply to similar patients managed using other strategies, or to patients without coronary disease. Finally, excellent blood pressure control was achieved in the INVEST study, with >70% of patients achieving blood pressures <140/90 mm Hg, and the results may not apply with less rigid blood pressure control. Thus, whether or not the results are generalizable to other hypertension patient populations using alternative medical strategies will depend upon the results of future randomized trials.

CONCLUSIONS

The goal of reducing blood pressure is to prevent morbidity and mortality; randomized trials have focused on determining which antihypertensive drugs or drug classes provide optimal protection in middle-aged patients. In this aging substudy focusing on very old (aged ≥80 years) hypertensive coronary artery disease patients, no difference in morbidity and mortality between antihypertensive drug treatment strategies was identified, but a strong suggestion of amplification of increased risk associated with lower pressures—especially systolic—as age increased was confirmed. The amplification was greatest for the very old, and a similar finding also was observed in the age group 70-<80 years. This is important for the increasing population of very old patients as coronary disease and hypertension

prevalence are increasing, and it would seem that caution is in order when either systolic or diastolic blood pressure is lowered below 140 and 70 mm Hg, respectively, until more data become available.

CLINICAL SIGNIFICANCE

- The population of very old (aged ≥ 80 years) patients with coronary artery disease and hypertension is increasing.
- For coronary artery disease patients with hypertension, as age increases there appears to be increased risk associated with lower blood pressures, especially systolic blood pressure.
- Optimal management of hypertension in very old coronary artery disease patients may therefore involve targeting specific systolic and diastolic blood pressure ranges.

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Figure 1. Systolic blood pressure (A), diastolic blood pressure (B), and pulse pressure (C) as a function of age (in 10-year increments) and time.

Figure 2.
Primary and secondary outcomes as a function of age (in 10-year increments).

Figure 3.
Fatal myocardial infarction and stroke as a function of age (in 10-year increments).

Figure 4. Primary and secondary outcomes as a function of age (in 10-year increments) based upon treatment strategy.

Figure 5.

Adjusted hazard ratio as a function of age (in 10-year increments), systolic and diastolic blood pressure. Reference systolic and diastolic blood pressure for hazard ratio: 140 and 90 mm Hg, respectively. Blood pressures are the on-treatment average of all postbaseline recordings. The quadratic terms for both systolic and diastolic blood pressures were statistically significant in all age groups (all $P < .001$, except for diastolic blood pressure in 60–70-year-olds for whom $P = 0.006$). The adjustment was based upon sex, race, history of myocardial infarction, heart failure, peripheral vascular disease, diabetes, stroke/transient ischemic attack, renal insufficiency, and smoking.

Table 1

Patient Characteristics at Baseline by Age (10-Year Increments)

Demographic	Age			
	<60 Years (n = 6668)	60-<70 Years (n = 7602)	70-<80 Years (n = 6126)	≥80 Years (n = 2180)
Age (years, mean ± SD)	54.6 ± 2.8	64.6 ± 2.9	74.0 ± 2.8	83.8 ± 3.5
Male (%)	49.7	49.7	46.8	38.7
Body mass index (kg/m ² , mean ± SD)	30.6 ± 6.1	29.6 ± 8.6	28.1 ± 5.0	26.4 ± 8.1
United States residency (%)	72.3	72.6	79.2	89.1
Ethnicity (%)				
Caucasian	41.5	48.1	54.2	54.4
Black	18.1	12.7	10.4	10.0
Hispanic	37.4	36.4	33.3	34.2
Asian	0.7	0.7	0.5	0.5
Other/multiracial	2.3	2.0	1.6	1.1
Adverse condition (%)				
Myocardial infarction	26.9	32.1	35.6	36.6
Angina pectoris	73.7	66.5	60.5	62.7
Unstable angina	10.9	11.9	12.1	9.1
Stroke/transient ischemic attack	4.7	6.9	9.1	10.7
Coronary artery bypass grafting	10.5	16.4	20.6	16.7
Percutaneous coronary intervention	13.5	15.7	16.2	13.8
Left ventricular hypertrophy	20.8	22.3	22.1	23.7
Arrhythmia	4.9	6.5	8.7	11.6
Heart failure (class I–III)	3.7	5.2	6.3	10.4
Peripheral vascular disease	8.6	10.9	14.6	18.5
Past smoker	50.5	48.9	42.7	34.4
Current smoker	20.1	12.5	7.1	3.9
Diabetes	25.7	31.3	29.6	22.5
Renal insufficiency	1.1	1.8	2.3	3.3
Dyslipidemia	53.5	58.4	58.5	46.1
Active medication (%)				
Antiplatelet drug	50.1	59.5	61.1	54.5
Lipid-lowering drug	32.5	39.1	41.8	27.2

For each characteristic, $P < .001$ among 4 age groups, except left ventricular hypertrophy, $P = .021$.