

# 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  $\geq 80$  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 SStudy (INVEST), which involved 22,576 clinically stable hypertensive coronary artery disease patients aged  $\geq 50$  years. The patients were grouped by age in 10-year increments (aged  $\geq 80$ ,  $n = 2180$ ;  $70 < 80$ ,  $n = 6126$ ;  $60 < 70$ ,  $n = 7602$ ;  $< 60$ ,  $n = 6668$ ). 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.

**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.

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**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.<sup>1-4</sup> The prevalence of patients with the combination of advanced age (including the very old, aged

$\geq 80$  years), coronary artery disease, and hypertension is increasing.<sup>1</sup> While aging is irreversible, and coronary artery disease is capable of only limited regression,<sup>5</sup> hypertension can be successfully treated. Successful hypertension treatment decreases risk for adverse outcomes among most lower-

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risk and younger patient groups.<sup>6</sup> However, for the very old, results have been conflicting.<sup>7,8</sup> 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.<sup>9,10</sup> 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.<sup>9</sup> 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.<sup>9,10</sup> 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 [ $<354$   $\mu$ mol/L]).<sup>9</sup> 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 echocardiographic criteria, or both) and cancer (skin, prostate, and other cancers with long survival expectancy).<sup>9</sup> 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 pressure<sup>2</sup>). 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.

## CLINICAL SIGNIFICANCE

- The population of very old (aged  $\geq 80$  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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