Long-Term Mortality in Hypertensive Patients With Coronary Artery Disease

Results From the US Cohort of the International Verapamil (SR)/Trandolapril Study

Islam Y. Elgendy, Anthony A. Bavry, Yan Gong, Eileen M. Handberg, Rhonda M. Cooper-DeHoff, Carl J. Pepine

See Editorial Commentary, pp 1103–1105

Abstract—The dyad of hypertension and coronary artery disease is prevalent; however, data on systolic blood pressure (SBP) control and long-term all-cause mortality are lacking. Using extended follow-up data from the US cohort of the International Verapamil (SR)/Trandolapril Study (mean 11.6 years), subjects were categorized by age at enrollment (50 to <60 and ≥60 years). Cox proportional adjusted hazard ratios (HRs) were constructed for time to all-cause mortality according to achieved mean SBP. In those 50 to <60 years and using a referent SBP of <130 mm Hg, an achieved SBP of 130 to 140 mm Hg was associated with a similar risk of mortality (HR, 1.03; 95% confidence interval [CI], 0.87–1.23), whereas an achieved SBP of ≥140 mm Hg was associated with an increased risk of mortality (HR, 1.80; 95% CI, 1.53–2.11). Among subjects aged ≥60 years and using a referent SBP of <130 mm Hg, an achieved SBP 130 to 140 mm Hg was associated with a lower mortality risk (HR, 0.92; 95% CI, 0.85–0.98). There was an increased risk of mortality with an achieved SBP ≥150 mm Hg (HR, 1.34; 95% CI, 1.23–1.45), but not with an achieved SBP 140 to 150 mm Hg (HR, 1.02; 95% CI, 0.94–1.11). In hypertensive patients with coronary artery disease, achieving a SBP of 130 to 140 mm Hg seems to be associated with lower all-cause mortality after =11.6 years of follow-up.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00133692.

Key Words: adult ▪ blood pressure ▪ coronary artery disease ▪ hypertension ▪ mortality

In the United States, it is estimated that 1 in every 3 adults has hypertension.1 Hypertension is an established independent risk factor for coronary artery disease (CAD) irrespective of age or sex.2 Medicare data indicate that the dyad of hypertension and CAD is the most prevalent chronic disease dyad among adults.3 The former members of the Eighth Joint National Committee Panel (JNC-8) recommended pharmacological antihypertensive therapy for a target therapeutic goal <120 mm Hg for adults ≥60 years and <140 mm Hg in those aged <60 years.3 These recommendations are inconsistent with different society guidelines including: the 2013 European Society of Hypertension and the European Society of Cardiology, the 2014 American Society of Hypertension and the International Society of Hypertension, and the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension updated statement for the management of hypertension in patients with CAD, which recommended a target therapeutic goal <140 mm Hg in hypertensive patients with CAD.2,4,5 Furthermore, in the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension statement, the authors acknowledged that the optimal systolic blood pressure (SBP) in relation to long-term mortality is lacking among this cohort of high-risk patients.2 More recently, the SPRINT (Systolic Blood Pressure Intervention Trial) found that a goal SBP of <120 mm Hg was superior to <140 mm Hg among subjects aged ≥60 years with high cardiovascular risk, many of whom had CAD; however, details of this CAD cohort were not provided.2 Accordingly, additional information on long-term all-cause mortality according to early achieved SBP in hypertensive CAD patients would be useful. Using the extended follow-up data from the US cohort of the INVEST (International Verapamil [SR]/Trandolapril Study), we aimed to address this knowledge gap.

Received May 13, 2016; first decision May 25, 2016; revision accepted July 22, 2016.
From the Division of Cardiovascular Medicine, College of Medicine (I.Y.E., A.A.B., R.M.C, C.J.P.) and Department of Pharmacotherapy and Translational Research, College of Pharmacy (Y.G., R.M.C.), University of Florida, Gainesville; and Medical Service, Cardiology Section, North Florida/South Georgia Veterans Health System, Gainesville (A.A.B.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.orglookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.07854/-/DC1.

Correspondence to Islam Y. Elgendy, Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Florida, PO Box 100277, 1600 SW Archer Rd, Gainesville, FL 32610. E-mail islam.elgendy@medicine.ufl.edu

© 2016 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.116.07854
Methods

Study Design and Outcome Assessed

Briefly, the INVEST was a prospective multicenter randomized trial comparing clinical outcomes for 22,576 patients ≥50 years of age with CAD and hypertension assigned to either a β-blocker/hydrochlorothiazide or a calcium antagonist/angiotensin-converting enzyme inhibitor strategy. After active study follow-up (mean 2.7 years),2 subjects were informed of these findings and then they were treated with open-label medications according to provider discretion. The trial was initially designed such that an extended follow-up for the US cohort could be evaluated. In addition, the project was planned with sufficient power to analyze the US cohort separately. The inclusion and exclusion criteria, study design, and results have been previously reported. Institutional review boards and ethics committees at each site approved the protocol, which was conducted in accordance with the principles outlined in the Declaration of Helsinki. Data were collected through an Internet-based system, which provided for individualized prescribing of antihypertensive medications using a flexible treatment algorithm and express mail delivery. The primary outcome of INVEST was the first occurrence of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke, whereas the secondary outcomes were each outcome individually. Both strategies were equivalent in terms of prevention of adverse outcomes with excellent BP control (>71% with BP <140/90 mmHg).1,9

This study is a long-term observational analysis of the US cohort of INVEST. For the purpose of this analysis, we combined the randomization treatment strategies. Data on long-term all-cause mortality, for subjects enrolled from a US site, were assessed by searching the US NDI (National Death Index) ≤11 years after INVEST follow-up was completed. The NDI has been previously shown to be reliable in detecting alive and dead subjects.8 To be considered a confirmed death, 4 of 5 matches among the following were required: name, Social Security number, date of birth, city, and state.8 Subjects were categorized according to age at enrollment (50 to <60 and ≥60 years), then they were further divided according to achieved mean SBP during the study follow-up: SBP <130 mmHg (group 1), 130 to <140 mmHg, and ≥140 mmHg in those aged 50 to 60 years and SBP <130 mmHg, 130 to <140 mmHg, 140 to <150 mmHg, and ≥150 mmHg in those aged ≥60 years.10 Because we aimed to test the 2 different SBP targets recommended by both the former members of the JNC-8 panel and the other society recommendations,2,4 we categorized the subjects aged ≥60 years in multiple groups to reflect these targets.

Statistical Analysis

The baseline characteristics in each group were compared with χ² test for categorical variables and analysis of variance for continuous variables. The average SBP was calculated for each subject using all measurements (except the baseline measurement) until the visit before the subject experienced one of the components of the primary outcome or was censored. Patients who did not appear in the NDI were censored on the day the death index search was completed. Cox proportional hazard ratios (HRs) were constructed for time to all-cause mortality according to achieved mean SBP during the study follow-up: SBP <130 mmHg (group 1, referent group), 130 to <140 mmHg (group 2), and ≥140 mmHg (group 3) in those aged 50 to <60 years and SBP <130 mmHg (group 4, referent group), 130 to <140 mmHg (group 5), 140 to <150 mmHg (group 6), and ≥150 mmHg (group 7) in those aged ≥60 years. All Cox regression analyses adjusted for covariates such as age, sex, race and history of myocardial infarction, history of stroke/transient ischemic stroke, heart failure, renal insufficiency, and diabetes mellitus. A secondary analysis for all-cause mortality was performed for SBP as a continuous variable, with an SBP and age interaction, as well as the quadratic term for age to evaluate the nonlinear relationship of age and outcome. All P values were 2-tailed, with statistical significance set at 0.05. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

Results

Among all participants, 17,131 patients were recruited from the United States (Figure 1). Among those aged 50 to <60 years, 19,424 patients (11.3%) achieved SBP of <130 mmHg (group 1), 1636 patients (9.6%) achieved SBP of ≥130 to 140 mmHg (group 2), whereas 1460 patients (8.5%) achieved on-treatment SBP of ≥140 mmHg (group 3) by the end of the study follow-up. Among those aged ≥60 years, 3832 patients (22.4%) achieved on-treatment SBP of <130 mmHg (group 4), 4014 patients (24.4%) achieved SBP of ≥130 to 140 mmHg (group 5), 2398 patients (14.0%) achieved SBP of ≥140 to 150 mmHg (group 6), and 1849 patients (10.8%) achieved SBP of ≥150 mmHg (group 7). The mean age at enrollment was 66 years and 54% were female. Baseline characteristics of the different groups were summarized in the Table. The mean follow-up duration was 11.6 years with a total of 198,352 patient-years. There were 6031 deaths (35.2%) including those that occurred during the extended follow-up period (Figure 1).

Consistent with our early findings, there was no difference in long-term all-cause mortality comparing the β-blocker–based strategy versus the calcium antagonist–based strategy (P=0.73). There was an observed reduction in the slope of the all-cause mortality curve with both strategies around 9 years (online-only Data Supplement). Among the subjects aged 50 to <60 years, an achieved SBP of ≥130 to 140 mmHg (group 2) was associated with a similar risk of all-cause mortality (adjusted HR, 1.03; 95% confidence interval [CI], 0.87–1.23; P=0.74), compared with an achieved SBP of <130 mmHg (group 1). An achieved SBP of ≥140 mmHg was associated with an increased risk of all-cause mortality (adjusted HR, 1.80; 95% CI, 1.53–2.11; P<0.0001), compared with SBP of <130 mmHg (group 1; Kaplan–Meier curve shown in Figure 2).

Among older subjects (≥60 years), using a referent group with an achieved SBP of <130 mmHg (group 4), an achieved SBP of ≥150 mmHg (group 7) was associated with an increased risk of all-cause mortality (adjusted HR, 1.34; 95% CI, 1.23–1.45; P<0.0001), but no increased risk of all-cause mortality was observed with an achieved SBP of 140 to <150 mmHg (group 6; adjusted HR, 1.02; 95% CI, 0.94–1.11; P=0.59). An achieved SBP of 130 to <140 mmHg (group 5) was associated with a lower risk of all-cause mortality (adjusted HR, 0.92; 95% CI, 0.85–0.98; P=0.01) when compared with an achieved SBP of <130 mmHg (group 4; Kaplan–Meier curve shown in Figure 3). Figure 4 summarizes the adjusted HRs for all-cause mortality for the different groups by age category. In a secondary analysis, using SBP as a continuous variable, every 1 mmHg increase in SBP was associated with 1% increase in the risk of all-cause mortality over 12 years (adjusted HR, 1.01; 95% CI, 1.008–1.011; P<0.0001). In addition, age had a different effect on mortality depending on the values of SBP (P for age×SBP interaction: <0.0001).

Figure 1. Patient flow diagram. INVEST indicates International Verapamil (SP)/Trandolapril Study.
Discussion

To our knowledge, this is the first study to investigate the relationship between long-term all-cause mortality and achieved SBP among a cohort of hypertensive patients with documented CAD. With almost 200,000 person-years of follow-up, our large observational study showed that early treatment with a β-blocker–based or a calcium antagonist–based BP-lowering strategy that resulted in excellent BP control during the active study follow-up was associated with similar long-term benefit in terms of all-cause mortality. Furthermore, we observed that early intense treatment of hypertension in this high-risk population appeared to attenuate the mortality-time curve with both strategies after about 9 years. The ADVANCE-ON trial (Action in Diabetes and Vascular Disease) randomized hypertensive diabetic patients to either perindopril/indapamide versus placebo. Both arms had similar SBP at the conclusion of the initial follow-up period. At a median of 9.9 years, all-cause mortality was reduced in the group initially assigned to perindopril/indapamide (HR, 0.91; 95% CI, 0.85–0.99; P = 0.03), despite the fact that participants in both the groups returned to their usual care.11 Our results confirm those observations suggesting that the benefit of good BP control during the active phase of the trial persisted, despite possible loss of the excellent BP control, and also extend those results to CAD patients. This suggests a possible legacy effect that has been described in other areas of cardiovascular medicine, such as with atorvastatin in hypertensive patients.12 A similar long-term effect was demonstrated in patients with type 2 diabetes mellitus (ie, the UKPDS [United Kingdom Prospective Diabetes Study] and the VATS [Veterans Affairs Diabetes Trial]), in whom an intensive glucose–lowering strategy early during the active study period resulted in reduction in long-term mortality well after the active phase of the trial was completed.13,14

Table. Baseline Characteristic of the US Cohort According to Age Category at Enrollment and Achieved Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>50 to &lt;60 y</th>
<th>≥60 y</th>
<th>All, n=17131</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (&lt;130 mm Hg; n=1942)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54.2±2.9</td>
<td>54.5±3.0</td>
<td>54.5±2.8</td>
<td>50.4</td>
</tr>
<tr>
<td>Female</td>
<td>52.9</td>
<td>52.9</td>
<td>52.2</td>
<td>50.4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13.2</td>
<td>19.4</td>
<td>34.6</td>
<td>9.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>51.0</td>
<td>41.0</td>
<td>28.6</td>
<td>45.2</td>
</tr>
<tr>
<td>White</td>
<td>32.7</td>
<td>36.0</td>
<td>33.4</td>
<td>43.2</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>138.1±16.4</td>
<td>147.2±16.3</td>
<td>157.0±18.8</td>
<td>139.8±17.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.6±10.1</td>
<td>89.1±10.1</td>
<td>92.5±11.4</td>
<td>81.7±10.4</td>
</tr>
<tr>
<td>Heart rate</td>
<td>76.0±9.5</td>
<td>77.2±9.1</td>
<td>77.7±9.8</td>
<td>74.9±9.6</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24.4</td>
<td>27.8</td>
<td>32.1</td>
<td>29.7</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>53.7</td>
<td>53.6</td>
<td>50.9</td>
<td>55.8</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>47.2</td>
<td>47.9</td>
<td>49.7</td>
<td>45.2</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>75.8</td>
<td>73.8</td>
<td>72.3</td>
<td>68.2</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8.3</td>
<td>8.9</td>
<td>10.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>23.6</td>
<td>23.8</td>
<td>24.9</td>
<td>30.3</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>21.5</td>
<td>22.4</td>
<td>24.5</td>
<td>29.3</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>3.8</td>
<td>5.2</td>
<td>5.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Heart failure (NYHA class I–III)</td>
<td>3.5</td>
<td>2.9</td>
<td>4.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0.8</td>
<td>0.8</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>35.4</td>
<td>33.9</td>
<td>28.5</td>
<td>40.2</td>
</tr>
<tr>
<td>Nitrate</td>
<td>32.8</td>
<td>31.4</td>
<td>23.2</td>
<td>34.2</td>
</tr>
<tr>
<td>Aspirin or other antiplatelet</td>
<td>41.4</td>
<td>41.8</td>
<td>41.2</td>
<td>51.4</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>24.0</td>
<td>24.0</td>
<td>19.3</td>
<td>23.4</td>
</tr>
</tbody>
</table>

Values are reported as mean±SD or percentages. CABG indicates coronary artery bypass surgery; NSAIDs, nonsteroidal anti-inflammatory agents; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.
Our analysis suggests that an achieved SBP of <140 mmHg is associated with beneficial results in regard to long-term all-cause mortality among younger patients with CAD (50 to <60 years). Among older patients with CAD (≥60 years), an achieved SBP of 130 to <140 mmHg was associated with lower risk of all-cause mortality, when compared with those who achieved SBP targets of 140 to <150 mmHg and SBP of ≥150 mmHg. These findings further support the viewpoint of some members of the former JNC-8 panel who disagreed with the 2014 recommendations to relax the goal SBP for the management of hypertension in adults. Data from the Northern Manhattan Study showed that raising the SBP threshold from 140 to 150 mmHg as a new target for hypertension treatment in older individuals without diabetes mellitus or chronic kidney disease could have a detrimental effect on stroke risk reduction. This observation is further supported among patients with diabetes mellitus in the long-term follow-up of the ACCORDION (Action to Control Cardiovascular Risk in Diabetes Trial Follow-On Blood Pressure) study. Although the SPRINT showed that targeting an SBP of <120 mmHg, compared with <140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause in patients at high risk for cardiovascular events but without diabetes mellitus, there has been concern about the lack of observer during the automated BP measurements in that trial, suggesting that the actual SBP in the treatment arm may have been higher. Some authors have estimated this variation to be around 10 to 20 mmHg. Therefore, the actual SBP target in the SPRINT trial might have been close to 130 to 140 mmHg. A recent meta-analysis of 123 studies with 613,815 participants regardless of the baseline SBP (from <130 mmHg to any higher value) suggested that every 10 mmHg reduction in SBP was associated with significantly reduced risk of all-cause mortality (relative risk, 0.87; 95% CI, 0.84–0.91); therefore, a higher baseline SBP led to a higher benefit.

Previously, we observed that achieving an SBP of 140 to <150 mmHg was associated with increased risk of adverse events compared with an SBP of <140 mmHg in those aged >60 years at the end of the 24 months of active follow-up. Although the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) and ACTION (A Coronary disease Trial Investigating Outcome With Nifedipine GITS) trials have reported prognostic effects of achieved SBP, the mean follow-up in those studies was 4 years. This analysis of INVEST assessed the relationship between early achieved SBP and long-term all-cause mortality at almost 12 years. In this study, we observed that long-term all-cause mortality might be increased in those who achieved an SBP of 140 to <150 and ≥150 mmHg, compared with 130 to <140 mmHg. Although the results of this analysis suggest that an achieved SBP of 130 to <140 mmHg seems to have the best survival outcome among hypertensive patients with CAD aged ≥50 years, future randomized trials are needed in patients with CAD to further support these findings. This study is limited by the lack of data on BP treatment and control in the years since the INVEST active follow-up ended; however, there does not seem to be an on-treatment bias. Furthermore, this study is a post hoc analysis of a randomized trial and was not specifically designed to test various SBP targets, although the investigators had initially designed it such that an extended follow-up for the US cohort could be evaluated.

**Perspectives**

The former members of the JNC-8 recommended a target therapeutic goal <150 mmHg for adults aged ≥60 years, whereas the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension updated statement for the management of hypertension in patients with CAD recommended a target therapeutic goal of <140 mmHg in hypertensive patients with CAD. Moreover, data on optimal SBP and long-term mortality are lacking in this population. Therefore, we aimed to assess long-term all-cause mortality according to early achieved SBP in hypertensive CAD adults using extended follow-up data from the INVEST study. In summary, our findings suggest that in adult hypertensive patients with CAD, achieving
an SBP of 130 to <140 mm Hg is associated with a reduction in all-cause mortality after ≈11.6 years of follow-up. Future studies are needed to determine the risk of adverse events (eg, renal failure) associated with a lower SBP target in this population.

Acknowledgments
We thank Negar Nasiri-Kenari and Sarah M. Lima for their help with performing the search for the United States National Death Index used for this study.

Sources of Funding
The main INVEST (International Verapamil [SR]/Trandolapril Study) was funded by grants from BASF Pharma, Ludwigshafen, Germany; Abbott Laboratories, Abbott Park, IL; and the University of Florida Research Foundation and Opportunity Fund.

Disclosures
A.A. Bavry discloses the following relationship: Honorarium from American College of Cardiology. The other authors report no conflicts.

References

Novelty and Significance

What Is New?
• First study to investigate the relationship between long-term all-cause mortality and achieved systolic blood pressure among a cohort of older adult hypertensive patients with documented coronary artery disease.
• Early treatment with a β-blocker–based or a calcium antagonist–based antihypertensive-lowering strategy resulted in similar long-term outcomes in terms of all-cause mortality.

What Is Relevant?
• In adult hypertensive patients aged 50 to 60 years with coronary artery disease, achieving a systolic blood pressure of <140 mm Hg seems to be associated with a reduction in all-cause mortality.

In those aged ≥60 years, achieving a systolic blood pressure of 130 to <140 mm Hg seemed to be associated with the lowest risk for all-cause mortality.

Summary
In adult hypertensive patients with coronary artery disease, achieving a systolic blood pressure of 130 to <140 mm Hg seemed to be associated with reduction in all-cause mortality after ≥12 years of follow-up.
Supplemental Material

Long-term mortality in hypertensive patients with coronary artery disease: Results from the United States cohort of the INternational VErapamil/Trandolapril STudy

Islam Y. Elgendy, MD; Anthony A. Bavry, MD, MPH; Yan Gong, PhD; Eileen M. Handberg, PhD; Rhonda M. Cooper-DeHoff, PharmD, MS; Carl J. Pepine, MD

From the Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, Florida (I.Y.E., A.A.B., R.M.C, C.J.P.), North Florida/South Georgia Veterans Health System, Gainesville, Florida (A.A.B.), and the Department of Pharmacotherapy and Translational Research, College of Pharmacy (Y.G., R.M.C.), University of Florida, Gainesville, Florida.

Correspondence:
Islam Y. Elgendy, MD
Division of Cardiovascular Medicine, Department of Medicine
College of Medicine, University of Florida, PO Box 100277
1600 SW Archer Road, Gainesville, FL 32610, USA
Email: islam.elgendy@medicine.ufl.edu
Telephone: 352-273-9089, Fax: 352-392-3606
All cause mortality in Extended Followup in US

Kaplan-Meier curves for all-cause mortality in both the beta-blocker based strategy (green) and the calcium antagonist based strategy (red).

BB= beta-blocker; CA= calcium antagonist