Characteristics and Outcomes of Revascularized Patients With Hypertension
An International Verapamil SR-Trandolapril Substudy

Scott J. Denardo, Franz H. Messerli, Efrain Gaxiola, Juan M. Aranda, Jr, Rhonda M. Cooper-DeHoff, Eileen M. Handberg, Yan Gong, Annette Champion, Qian Zhou, Carl J. Pepine

Abstract—Our understanding of the growing population of revascularized patients with hypertension is limited. We retrospectively analyzed the International Verapamil SR-Trandolapril Study, which randomized coronary artery disease patients with hypertension to either verapamil SR- or atenolol-based treatment strategies, focusing on characteristics and outcomes of 6166 previously revascularized patients compared with 16 410 nonrevascularized patients. Revascularized patients had a history of coronary artery bypass grafting (45.2%), percutaneous coronary intervention (42.1%), or both (12.8%). Compared with nonrevascularized patients, revascularized patients at baseline demonstrated a higher prevalence of coronary artery disease risk factors and risk conditions ($P<0.001$). This higher prevalence was the principal cause of a higher incidence of primary outcome (death, nonfatal myocardial infarction, or nonfatal stroke) among revascularized patients (14.2% versus 8.5% for nonrevascularized patients; $P<0.001$). However, both patient groups demonstrated a relatively low incidence of subsequent revascularization (5.1% versus 1.5% respectively; $P<0.0001$). Associations between adjusted hazard ratio for primary outcome and follow-up blood pressure appeared “J shaped” for both patient groups. Because, as a group, revascularized patients with hypertension had worse outcomes compared with nonrevascularized patients, management of blood pressure to a specific target in future studies could result in improved outcomes. (Hypertension. 2009;53:624-630.)

Key Words: hypertension ■ blood pressure ■ coronary artery disease ■ revascularization ■ coronary artery bypass grafting ■ percutaneous coronary intervention ■ epidemiology

Despite advances in prevention, pharmacotherapy, and revascularization, atherosclerotic coronary artery disease (CAD) remains the leading cause of death in adults.1,2 Revascularization procedures (coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI]) have increased in use as effective treatments for CAD.2 For example, during 2004, 1 700 000 coronary revascularization procedures were performed compared with 900 000 in 1994.2 Hypertension (HTN) is a major risk factor for the development and progression of CAD,2 and previous revascularization is also a risk factor for progression of CAD.3 Among CAD patients, the prevalence of HTN is $\approx60\%$ to $69\%$,2,4 and this prevalence is predicted to increase.5 The annual incidence of revascularization among CAD patients is 10%.2 and, in certain subpopulations, revascularization improves survival.5–9 Although the population of CAD patients with HTN and previous revascularization is growing, our understanding of the characteristics of this population and their associations with outcomes is incomplete. The International Verapamil SR-Trandolapril Study (INVEST) provides an opportunity to address these gaps in our knowledge base.

INVEST was a randomized, open-label, blinded end-point study of 22 576 CAD patients with HTN aged $\geq50$ years that compared outcomes of patients managed with verapamil SR-versus atenolol-based antihypertensive strategies.10 The main results were that both of these strategies provided excellent BP control (>70% patients achieved <140/90 mm Hg) and were equivalent for reducing mortality and major morbidity.11 We report here the results of a prespecified analysis focusing on patients with previous revascularization compared with those without revascularization.

Methods

The INVEST design, methods, and principal results have been described in detail.10,11 The study was performed in accordance with the Declaration of Helsinki and was approved by local ethics committees. The pilot phase of INVEST (30 selected sites) started in September 1997. Full-scale site recruitment and patient enrollment began in January 1998, and patient follow-up was completed in

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February 2003. All of the patients provided informed written consent. Briefly, clinically stable CAD patients with HTN were randomly assigned to either a verapamil SR or an atenolol treatment strategy. The addition of trandolapril with or without hydrochlorothiazide was recommended if needed for blood pressure (BP) control. Trandolapril was also recommended for heart failure, diabetes mellitus, or renal insufficiency. BP treatment goals were <140/90 mm Hg or, for patients with diabetes mellitus or renal insufficiency, <130/85 mm Hg. The primary outcome was the first occurrence of all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke. Secondary outcomes were death, fatal and nonfatal MI, fatal and nonfatal stroke, and revascularization (CABG and/or PCI). Standard-of-care nonpharmacological recommendations based on the Sixth Report of the Joint National Committee Guidelines3 and secondary prevention according to the National Cholesterol Education Program14 were provided online in printable format that could be given to patients.

This analysis was prespecified, focusing on patients with previous coronary revascularization. Patients undergoing revascularization <1 month before enrollment were excluded. Data on revascularization ≥1 month before enrollment were collected at baseline, including specific technique of revascularization (CABG only [CABG], PCI only [PCI], and both CABG and PCI [CABG+PCI]).

Statistical Analyses
As specified in the protocol, all of the analyses were made on the intention-to-treat population. Data management and statistical analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc). Univariate analysis was performed with χ² tests for categorical variables and 1-way ANOVA for continuous variables. ANCOVA model (adjusted for baseline) was used for comparing BP changes from baseline. Statistical significance was assumed when P values were <0.05 (2 tailed).

Kaplan-Meier analysis was used to assess time to first event for the primary and secondary outcomes. Unadjusted Cox proportional hazard models were used to estimate the hazard ratios (HR) and CIs between groups according to revascularization status for primary and secondary outcomes. The sample size of 6166 revascularized and 16410 nonrevascularized patients provided 80% power to detect an HR of >1.15 at an α level of 0.05.

Stepwise Cox proportional hazard model was used to identify the factors associated with the primary outcome among patients with and without revascularization. The following covariates were forced into the model: treatment strategy, age (decades), gender, race, previous MI, and previous congestive heart failure (CHF, class I through III). Other factors were retained in the final model if a P value ≤0.10 was achieved. Interaction between ethnicity and revascularization for the risk of primary outcome was also tested.

Baseline data for each patient group were summarized as mean and SD for continuous variables and as number and percentage for categorical variables. Baseline and “on-treatment” BP data from protocol follow-up visits were summarized as average systolic BP (SBP) and diastolic BP (DBP) for each patient. The latter values were calculated for each patient using all of the follow-up BP measurements, up to the date of a primary outcome or censoring. The baseline value was used for patients with no follow-up BP measurements (n=1154). In this exploratory analysis, patients were grouped by 10-mm Hg strata of average follow-up SBP, and the distribution of primary outcome rate by follow-up BP was evaluated to determine whether the relationship was linear. Because the frequency distributions were most consistent with a quadratic function, a quadratic stepwise Cox proportional hazard model was formed for the time to primary outcome for each BP variable (factors for BP and BP²). A similar analysis was conducted for DBP. A SBP of 140 mm Hg and a DBP of 90 mm Hg were used as the reference point (HR: 1.0) within each group.

To control for nonrandom assignment of patients to the revascularization and nonrevascularization groups, we calculated the predicted probability for each patient to be in one group or another (ie, propensity score), adjusting for all of the demographic and clinical characteristics available for each patient at baseline as explanatory variables.15 SAS Logistic procedure was used to create propensity scores. The propensity scores were then used as a variable in Cox proportional hazard model to adjust for any group membership differences attributable to the variables used to create the propensity score. This analysis was performed as a sensitivity analysis to assess whether the difference in baseline characteristics for each group explained the difference in risk for primary outcome.

Results
Of the 22 576 patients who enrolled in INVEST, a total of 6166 (27.3%) had a history of previous coronary revascularization: CABG, 2784 (45.2%); PCI, 2594 (42.1%); and CABG+PCI, 788 (12.8%). The revascularized patients, compared with the nonrevascularized patients, were older, more frequently male, residents of the United States, and white, with a higher prevalence of characteristics associated with risk for adverse outcomes, including previous MI, CHF, stroke/transient ischemic attack, and peripheral vascular disease (P<0.001; Table). As expected, the nonrevascularized patients more frequently had angina and left ventricular hypertrophy (P<0.001).

BP and Treatment
At baseline, revascularized patients had lower BP than nonrevascularized patients (148.0/83.5 versus 151.9/88.5 mm Hg; P<0.001 for SBP and DBP; Figure 1) and more patients with BP in control (<140/90 mm Hg: 29.0% versus 20.2%, P<0.001; within Sixth Report of the Joint National Committee guidelines: 24.1% versus 16.9%, P<0.001). At 24 months, BP was decreased in both groups (adjusted for baseline BP: revascularized, −17.6/−10.9 versus nonrevascularized, −19.4/−9.8 mm Hg), with SBP somewhat higher and DBP somewhat lower among revascularized patients compared with nonrevascularized patients (132.9/75.7 versus 131.7/78.0 mm Hg; P<0.001 for SBP and DBP). As a consequence, pulse pressure decreased less for revascularized patients than for nonrevascularized patients (adjusted for baseline BP: −6.5 versus −9.6 mm Hg; P<0.001). For all of the patients, the greatest decrease in BP was seen during the first 6 weeks of treatment, followed by additional decreases during the subsequent 5 months, which were maintained through 24 months (Figure 1). Fewer revascularized patients had adequately controlled BP (<140/90 mm Hg: 69.5% versus 71.9%, P<0.01; within Sixth Report of the Joint National Committee guidelines: 59.7% versus 63.8%, P<0.001). However, among revascularized patients, the verapamil SR- and atenolol-based treatment strategies resulted in similar control of BP (at 24 months: SBP 133.2 versus 132.6 mm Hg, P=0.29; DBP 75.8 versus 75.7 mm Hg, P=0.75). At 24 months, significant decreases in BP had occurred for all of the revascularized patients, regardless of technique of revascularization (CABG: −14.8/−7.4, PCI: −15.7/−8.2, CABG+PCI: −13.8/−7.3 mm Hg; P<0.0001 for SBP and DBP).

Primary and Secondary Outcomes
The revascularized patients had a proportionately higher incidence of primary and secondary outcomes than the nonrevascularized patients (Figure 2), and the difference between the cumulative primary outcome rates increased over
The unadjusted risk for primary outcome was higher for revascularized patients compared with nonrevascularized patients (HR: 1.46; 95% CI: 1.34 to 1.59). However, after adjustment for baseline conditions, this increased risk diminished (HR: 1.15; 95% CI: 1.05 to 1.26), and with propensity score analysis it resolved (HR: 1.06; 95% CI: 0.93 to 1.22). In a fourth analysis that adjusted for baseline conditions and follow-up BP, the results were similar to the adjustment for baseline conditions only (HR: 1.17; 95% CI: 1.06 to 1.28). There was no significant change in these latter results when the 1154 "no-follow-up-BP" patients were excluded from analysis (HR: 1.15; 95% CI: 1.05 to 1.26).

Similar to the entire INVEST population, there was no difference in primary outcome for the revascularization patients based on treatment strategy (data not shown).\textsuperscript{11} The interaction between the ethnicity and revascularization on the risk for primary outcome was not significant (all $P$ values $>0.05$).

The most frequent secondary outcome for all of the patients was death, followed by total MI (fatal and nonfatal; Figure 2). Revascularization during follow-up occurred in only 557 (2.5%) of all of the enrolled patients. However, it was 3.4 times more likely in the revascularized patients (5.1%, versus 1.5% for nonrevascularized patients; $P<0.0001$). Both in patients with and without previous revascularization, there were no differences in the revascularization rates during follow-up based on treatment strategy (2.49% for verapamil SR- versus 2.43% for atenolol-based strategies; $P=0.80$).\textsuperscript{11}

### Relationships Between Primary Outcome and BP

Relationships between the incidence of primary outcome and mean follow-up SBP and DBP for the revascularized and nonrevascularized patients were quadratic, or J shaped. (Figure 4). A J-shaped curve was also apparent for both patient groups, to a lesser degree for SBP and a greater degree for DBP, for the relationships between the adjusted HR for primary outcome and mean follow-up SBP and DBP. These relationships persisted after propensity score analysis (Figure 5). The SBP/DBP nadirs were 135/70 and 125/75 mm Hg, respectively.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Previous Revascularization</th>
<th>Previous Revascularization</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.6±9.9</td>
<td>67.3±9.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Age $&gt;70$ y</td>
<td>31.6</td>
<td>38.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>29.2±6.7</td>
<td>29.1±8.1</td>
<td>&lt;0.001</td>
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<tr>
<td>Male</td>
<td>40.8</td>
<td>66.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>US residency</td>
<td>73.7</td>
<td>81.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>39.0</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15.1</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>43.1</td>
<td>15.7</td>
<td></td>
</tr>
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<td>Asian</td>
<td>0.6</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Other/multiracial</td>
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<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>25.1</td>
<td>50.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>78.2</td>
<td>35.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina ($\geq 1$ mo pre-enrollment)</td>
<td>7.5</td>
<td>22.0</td>
<td>&lt;0.001</td>
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<td>Heart failure (class I through III)</td>
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<td>6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
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<td>18.7</td>
<td>&lt;0.001</td>
</tr>
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<td>Arrhythmia</td>
<td>6.7</td>
<td>8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>6.6</td>
<td>9.0</td>
<td>&lt;0.001</td>
</tr>
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<td>Peripheral vascular disease</td>
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<td>&lt;0.001</td>
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<td>Cigarette smoking</td>
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<td></td>
</tr>
<tr>
<td>Past</td>
<td>41.6</td>
<td>58.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>During $\leq1$ mo pre-enrollment</td>
<td>12.6</td>
<td>11.9</td>
<td>0.158</td>
</tr>
<tr>
<td>Never</td>
<td>58.4</td>
<td>41.3</td>
<td>&lt;0.001</td>
</tr>
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<td>Diabetes mellitus</td>
<td>27.1</td>
<td>31.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.5</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>48.5</td>
<td>75.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>46.4</td>
<td>84.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>27.3</td>
<td>61.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or percentage.
Discussion

This is the first detailed analysis of the characteristics and outcomes of revascularized CAD patients with HTN, and there are a number of interesting findings. The revascularized compared with nonrevascularized patients had more characteristics at baseline that were associated with increased risk for adverse outcomes, and they indeed suffered a higher rate of adverse outcomes despite adequate BP control. Implicating more severe vascular disease, their SBP (but not DBP) was somewhat more difficult to control, and their pulse pressure decreased less compared with those patients without revascularization. Their mortality and morbidity were affected primarily by baseline conditions, and there was also a J-shaped association with follow-up SBP and DBP.

This substudy of INVEST showed that the ability to medically control SBP was somewhat more difficult in revascularized patients compared with nonrevascularized patients. However, the ability to control DBP was equivalent, resulting in an attenuated decrease in pulse pressure for the revascularized patients. The difficulty in controlling SBP may have involved otherwise subclinical peripheral atherosclerosis in the revascularized patients, as suggested by the attenuated decrease in pulse pressure, and, in turn, the result of adverse baseline conditions. Our analysis indicates that the relatively minor differences in follow-up BP were not responsible for the increase risk for adverse outcomes among

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### Figure 1. BP control for revascularized and nonrevascularized patients. The mean follow-up period was 32.9 ±10.3 months.

### Figure 2. Risk for clinical outcomes for revascularized and nonrevascularized patients.

### Figure 3. Survival without primary outcome as a function of time and revascularization status.
revascularized patients and that the verapamil SR- and atenolol-based strategies were similarly effective in achieving control of SBP and DBP among those patients.

The increased primary and secondary outcomes for revascularized patients shown in this study were independent of treatment strategy.11 However, the incidence of the secondary outcome of subsequent revascularization for revascularized patients (and nonrevascularized patients; 5.1% and 1.5%, respectively) was relatively low compared with that described in recent revascularization studies.16,17 This lower incidence of revascularization may have been the result of the verapamil SR- and atenolol-based therapies used in INVEST, both of which have been shown to reduce the rates of repeat revascularization in patients with CAD.18–20

The relationship between the adjusted risk for primary outcome and follow-up SBP and DBP was in the form of a J-shaped curve. For both the revascularized and nonrevascularized patients, this J-shaped curve was less pronounced for SBP compared with DBP, consistent with our previously published analysis of the entire INVEST population.21 The results of this retrospective analysis cannot clarify the cause and effect of this relationship. However, future studies that manage BP to a specific target for revascularized patients (and nonrevascularized patients) could clarify the cause and effect and result in improved outcomes.

**Limitations**

This substudy has one principle limitation. Although patients with previous revascularization represented a prespecified population of interest, randomization was not stratified to account for this baseline characteristic, nor was there any stratification of the revascularization procedure used. Therefore, imbalances between patient groups may exist beyond what we could adjust for in our analyses.

**Perspectives**

Revascularized compared with nonrevascularized CAD patients with a history of HTN had more adverse cardiovascular conditions at baseline, which contributed to a higher incidence of the primary outcome (death, nonfatal MI, or nonfatal stroke) and secondary outcomes, including revascularization. The increased risk for adverse outcomes for revascularized patients appeared to be attributable more to differences in baseline conditions rather than the relatively minor differences in follow-up BP. Importantly, revascularization rates were relatively low for both revascularized and nonrevascularized patients, and these low rates may be the result of the verapamil SR- and atenolol-based treatment strategies.18–20

Associations between adjusted HR and follow-up BP appeared J shaped. Should an appropriately powered random-
Figure 5. Comparison of HR (adjusted for baseline conditions) without and with propensity score analysis as a function of SBP and DBP in patients with and without previous revascularization. Reference SBP and DBP for HR: 140 and 90 mm Hg, respectively.

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