Predicting Stroke Risk in Hypertensive Patients With Coronary Artery Disease
A Report From the INVEST

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Background and Purpose—Our understanding of factors influencing stroke risk among patients with coronary artery disease is incomplete. Accordingly, factors predicting stroke risk in hypertensive, clinically stable coronary artery disease patients were determined with data from the INternational VERapamil SR-trandolapril STudy (INVEST).

Methods—The effect of baseline characteristics and on-treatment blood pressure (BP) were analyzed to determine the risk of stroke (fatal or nonfatal) among the 22 576 patients enrolled. Cox proportional-hazards models (unadjusted, adjusted, and time dependent) were used to identify predictors of stroke among subgroups with these characteristics present at entry and on-treatment BP.

Results—Excellent BP control (at 24 months, >70% <140/90 mm Hg) was achieved during 61 835 patient-years of follow-up, as 377 patients had a stroke (6.1 strokes/1000 patient-years) and 28% of those patients had a fatal stroke. Increased age, black race, US residency, and history of prior myocardial infarction, smoking, stroke/transient ischemic attack, arrhythmia, diabetes, and coronary bypass surgery were associated with an increased risk of stroke. Achieving a systolic BP <140 mm Hg and a diastolic BP <90 mm Hg was associated with a decreased risk of stroke. There was no statistically significant difference in stroke risk comparing the verapamil SR–based with the atenolol-based treatment strategy (adjusted hazard ratio = 0.87; 95% CI, 0.71 to 1.06; P = 0.17).

Conclusions—Among hypertensive patients with chronic coronary artery disease, stroke was an important complication associated with significant mortality. Black race, US residency, and conditions associated with increased vascular disease severity and arrhythmia predicted increased stroke risk, whereas achieving a BP <140/90 mm Hg on treatment predicted a reduced stroke risk. (Stroke. 2008;39:343-348.)

Key Words: atenolol ■ coronary artery disease ■ hydrochlorothiazide ■ hypertension ■ stroke ■ trandolapril ■ verapamil SR

Stroke is a major cause of death and disability and its incidence is increasing, which greatly impacts healthcare costs. The propensity for increased blood pressure (BP) and coronary artery disease (CAD) to increase stroke risk has been known for >2 decades, yet our understanding of factors associated with stroke risk in patients with these conditions is incomplete. Most prior work in this area has focused on stroke in the acute coronary syndrome (ACS) period, and information on the association of patient characteristics and BP control with stroke risk in the increasing numbers of patients with chronic CAD is limited. The INternational VERapamil SR-trandolapril STudy (INVEST) provided an opportunity to investigate factors associated with stroke in a large, chronic-CAD patient population in whom BP was well controlled with 2 different treatment strategies. The main INVEST results found that a verapamil SR–based strategy was equivalent to an atenolol-based strategy in reducing mortality and morbidity. Unlike other recent large, randomized, hypertension studies, the reductions in BP and BP control achieved (>70% <140/90 mm Hg) between treatment strategies were also very similar, eliminating the need to attempt to adjust for differences in BP reduction between the strategies to examine the effects of BP on outcomes.

Using the INVEST database, we sought to investigate factors associated with risk for stroke among hypertensive patients with CAD. We included analyses of baseline conditions and on-treatment BP on the risk of stroke during follow-up.
Subjects and Methods

Study Design
The design and primary outcomes of INVEST have been previously described. In brief, INVEST was a randomized trial of a verapamil SR–versus an atenolol-based antihypertensive treatment strategy in CAD patients with hypertension to determine their effects on all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke (primary outcome). Patients <50 years old, those with recent (within 1 month) stroke or coronary revascularization, or those with recent (within 3 months) MI were not eligible. The protocol specifically excluded patients with sick sinus syndrome, bradycardia, heart block, and atrial fibrillation/flutter with Wolf-Parkinson-White syndrome because of the risk of adverse reactions to either verapamil SR or atenolol. Trandolapril and/or hydrochlorothiazide were added as needed to achieve BP goals for patients with heart failure, diabetes, or renal impairment. The study was approved by local ethics committees and conducted according to principles of the Declaration of Helsinki, and all patients provided voluntary, written, informed consent.

Outcomes
The individual component events of the primary outcome were prespecified secondary outcomes, and the focus of this investigation was total stroke (hereafter referred to as stroke) taken as either fatal or nonfatal stroke. The diagnosis of stroke was based on either sudden onset of an ischemia-related neurologic deficit involving the carotid, verteobasilar, or cerebral arterial territories that persisted for at least 24 hours, unless terminated earlier by thrombolytic intervention, or a new neurologic deficit, such as speech impediment (up to aphasia), alexia, agraphia, focal paresis, hemiparesis, visual field deficits, unilateral or total blindness, vertigo, nausea, or drop attacks. The 3-member events committee, masked to treatment assignment, adjudicated all strokes by reviewing documentation and other pertinent patient records.

Statistical Analyses
Univariate analyses were performed with $\chi^2$ tests for categorical variables and $t$ tests for continuous variables. Statistical significance was assumed when $P<0.05$ (2-tailed). Risk for stroke associated with baseline characteristics, treatment strategy, and on-treatment BP was assessed with Cox proportional-hazards regression analyses. To assess the risk for stroke among the randomized treatment strategies, an unadjusted Cox proportional-hazards model was used with strategy as the only term. Baseline factors associated with stroke risk were identified with a stepwise Cox proportional-hazards model that included age (10-year increments), sex, race/ethnicity (white, Asian, black, Hispanic, multiracial/other), US residency, body mass index (5-kg/m$^2$ increments), sex, race/ethnicity (white, Asian, black, Hispanic, multiracial/other), US residency, body mass index (5-kg/m$^2$ increments), prior stroke/TIA, arrhythmia, heart failure, peripheral vascular disease, smoking history, diabetes, and renal dysfunction; and be taking aspirin or other antplatelet agents.

Stepwise Cox modeling identified baseline conditions and time-dependent SBP >140 mm Hg as independently associated with increased stroke risk (Figure 1). Not unexpectedly, the risk for stroke was -2-fold higher in patients with prior stroke or TIA (HR = 2.33; 95% CI, 1.78 to 3.04; P = 0.0001). Stroke risk also increased with increasing age (in 10-year increments ≥50 years old; HR = 1.55; 95% CI, 1.38 to 1.75), US residency, black (versus nonblack) race, and history of arrhythmia, CABG, diabetes, smoking, and prior MI. After adjusting for baseline conditions, no significant difference in stroke risk was detected between the verapamil SR and the atenolol strategy (HR = 0.87; 95% CI, 0.71 to 1.06; P = 0.17).

Influence of BP
Baseline SBP was similar in those with and without stroke during follow-up. Baseline DBP was lower in those with stroke during follow-up (the Table). As previously reported, BP control (<140/90 mm Hg) was achieved in >70% patients in both treatment strategies at month 24. However, the mean SBP was higher in patients with stroke during follow-up compared with patients without stroke during follow-up (142 vs 135 mm Hg, respectively; P = 0.0001). Based on the average follow-up BP, the percentage of patients who achieved a mean follow-up BP <140/90 mm Hg was lower in those with stroke during follow-up (46.5%) than in those without a stroke (69.4, P = 0.001).

Overall, patients who achieved a mean follow-up SBP of <140 mm Hg had a lower rate of stroke than did patients with a mean follow-up SBP ≥140 mm Hg (1.1% vs 2.9%, P = 0.001). The stroke rate in patients with a mean follow-up DBP <90 mm Hg was 1.5% and was 3.7% in those with a DBP ≥90 mm Hg (P = 0.0001). When adjusted for baseline covariates, a time-dependent mean follow-up SBP <140 mm Hg compared with ≥140 mm Hg was associated with a reduced risk for stroke (HR = 0.63; 95% CI, 0.51 to 0.78; P = 0.001). A time-dependent mean follow-up DBP <90 mm Hg was also associated with decreased risk (HR = 0.50; 95% CI, 0.38 to 0.66; P = 0.001).
Achieving an SBP <140 mm Hg was associated with a decreased risk for stroke in patients with the high-risk characteristics summarized earlier (Figure 2). The effect was greatest among those with prior CABG, prior stroke/TIA, age >70 years, US residency, and a history of smoking. None of the probability values for interaction between SBP category and any high-risk subgroup reached statistical significance, suggesting a similar risk reduction when SBP is <140 mm Hg, whether the high-risk characteristic was present or absent (data not shown). Very similar findings were noted for achieving a DBP <90 mm Hg (data not shown). There was no apparent increase in crude stroke rates among patients with low DBP.

### Impact of Initial and Subsequent Drug Combinations

Drug class and dose were not found to be important determinants of stroke risk. With verapamil SR at 180 mg/d, the stroke HR was 0.88 (95% CI, 0.54 to 1.41) and at 240 mg/d, the HR was 0.94 (95% CI, 0.55 to 1.59). In combination with trandolapril at 180/2 mg/d, the HR was 0.81 (95% CI, 0.48 to 1.37); at 240/4 mg/d, the HR was 0.97 (0.49 to 1.93); with trandolapril/hydrochlorothiazide at 180/2/12.5 mg/d, the HR was 0.57 (95% CI, 0.29 to 1.11); and at 240/4/25 mg/d, the HR was 0.48 (95% CI, 0.16 to 1.40). An increase in atenolol from 50 to 100 mg/d was associated with an HR of 1.25 (95% CI, 0.97 to 1.59); in combination with hydrochlorothiazide at 50/12.5 mg/d, the HR was 0.77 (95% CI, 0.45 to 1.33); at 100/25 mg/d, the HR was 0.87 (95% CI, 0.41 to 1.87); with trandolapril/hydrochlorothiazide at 50/2/12.5 mg/d, the HR was 0.73 (95% CI, 0.41 to 1.30); and at 100/4/25 mg/d, the HR was 0.78 (95% CI, 0.35 to 1.74).

### Discussion

INVEST afforded the opportunity to better understand the characteristics associated with stroke outcomes among hypertensive patients with CAD. In addition to identification of a number of risk conditions present at entry, because >70% of INVEST patients achieved a BP <140/90 during follow-up, we were able to estimate the effect of attainment of BP control on stroke risk. In these CAD patients, an increased risk of stroke was associated with a number of nonmodifiable conditions present at study entry, but attainment of BP control during the study was associated with a similar decreased risk of stroke, whether or not these conditions were present. Our time-dependent analyses suggest that lower BP is associated with reduced risk of stroke in CAD patients and strengthens the relevance of achieving BP control in very high-risk patients.

We identified age, black race, and female sex as nonmodifiable risk factors for stroke, which extends findings noted by others to a population with chronic CAD. Also, smoking, diabetes, and arrhythmias were identified to be modifiable predictors of stroke, which also extends these risk conditions for stroke to a CAD population. Additional risk factors for stroke included US residency and prior CABG. The presence of CAD has been strongly associated with cerebrovascular disease. Although the increased stroke risk associated with CAD necessitating prior CABG was not unexpected, prior reports dealt with the revascularization procedure or CABG in ACS, and remote CABG in patients with stable CAD has not been emphasized as an important risk factor for subsequent stroke. In patients with a history of MI, there was an increased risk of stroke, consistent with prior reports showing that stroke risk, while high during the first few days after an MI, declines very rapidly thereafter. Patients who had an MI within 3 months or unstable angina within 1 month of screening were not eligible for INVEST. Our data provide evidence for a link with increased stroke risk many months after an MI in CAD patients with hypertension. Others have reported a stroke rate of 22.6/1000 person-months during the first 30 days after MI, which remained increased for ~3 years, and older age, previous stroke, and
diabetes increased the risk. Beyond 3 years, the stroke rate declined to 0.9/1000 person-months. The 0.51/1000 person-months that we observed may be related to good BP control. The observation of CABG as a predictor of stroke risk long after the procedure deserves additional comment. Patients with different revascularization procedures (CABG, PCI, and CABG/PCI) were entered in our statistical model separately. Only CABG alone was significantly associated with risk of stroke. These data are summarized in Figure 1 among factors independently associated with increased risk of stroke. Stroke in patients with revascularization procedures and in patients with non–ST-segment elevation ACS is important and is reviewed here to avoid misinterpretation. In brief, patients with non–ST-segment elevation ACS as described by Cronin et al were excluded from INVEST (ie, non–ST-segment elevation MI for at least 3 months and unstable angina for at least 1 month). Cronin et al have shown that most of the stroke hazard occurs in the first several months after presentation for ACSs, which were treated with CABG. The fact that CABG was a significant predictor of stroke many years after the procedure and that a history of prior unstable angina was not selected by our model suggests that CABG is likely just a marker of patients with more severe vascular disease. Also of interest is that prior MI increased the risk of stroke independent of CABG. Why patients who had undergone both CABG and PCI were not at increased risk is difficult to explain, unless these patients had less severe vascular disease than those with CABG alone. Finally, PCI is not neutral in terms of stroke risk, and the reported rates are 0.3% to 0.4% at 30 days. However, most patients in those reports had ACS or were very elderly. In clinically stable patients, the reported rate is 0.1%. In those reports, BP control was not a topic of interest.

The relation between stroke and BP has been documented in groups of patients with a low frequency of CAD. The results of our analyses strongly support the importance of

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Independent predictors of increased risk for stroke during follow-up. Baseline characteristics associated with stroke during follow-up were selected by the procedure and included in the model when \( P \leq 0.10 \). Two baseline revascularization variables were input into the stepwise model: CABG with or without PCI and PCU only.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Adjusted HR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke/transient ischemic attack</td>
<td>2.33 (1.78–3.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>United States residency</td>
<td>1.75 (1.24–2.47)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Race: black vs non-black</td>
<td>1.64 (1.25–2.14)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Time-dependent SBP ( \geq 140 ) mm Hg</td>
<td>1.59 (1.29–1.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (10-yr increments)</td>
<td>1.55 (1.38–1.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1.55 (1.14–2.13)</td>
<td>0.0059</td>
</tr>
<tr>
<td>CABG vs no CABG</td>
<td>1.47 (1.15–1.88)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.43 (1.14–1.78)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Smoker (ever)</td>
<td>1.33 (1.06–1.66)</td>
<td>0.0131</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>1.29 (1.04–1.61)</td>
<td>0.0208</td>
</tr>
</tbody>
</table>

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Risk of stroke by category of SBP during follow up. HR for SBP <140 mm Hg from a stepwise Cox proportional-hazards model within each subgroup is shown. Adjusted HR (95% CI) for SBP <140 mm Hg vs SBP \( \geq 140 \) mm Hg in a Cox model with time-dependent SBP in each subgroup after stepwise selection, excluding SBP measurements within 6 weeks before stroke/censoring.
good BP control in reducing stroke risk in patients with established but clinically stable CAD. Reduction of SBP to <140 mm Hg during follow-up was associated with a reduced risk of stroke in patients with any of the high-risk characteristics identified, including prior stroke/TIA, older age, diabetes, and prior history of MI. This finding suggests that BP reduction is important, even in patients with so-called “nonmodifiable” risk factors.

In these patients with CAD, we observed a doubling in stroke risk in patients with a history of stroke or TIA, supporting recently published data in patients with a prior stroke or TIA but a low prevalence of CAD.24 Consistent with our findings in CAD patients, these data also confirm that hypertension is a strong predictor of recurrent stroke, supporting the recommendation for aggressive steps to control BP.

The goal of reducing BP is to prevent cardiovascular morbidity and mortality. Attention, in the form of randomized clinical trials, has been focused on determining which antihypertensive drugs and/or drug classes provide optimal protection, but few differences have been reported.25,26 At the initiation of INVEST, Joint National Committee VI guidelines recommended a diuretic or β-blocker as the initial choice for treating hypertension.28 Recently, a meta-analysis of patients with uncomplicated hypertension found that β-blockers were less effective at preventing stroke than diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists.29 This meta-analysis is consistent with a recent network meta-analysis30 suggesting that diuretics were more effective than β-blockers in reducing stroke risk. The network meta-analysis also showed no difference in stroke risk between calcium antagonists and diuretics,30 supporting a previous meta-analysis.26 Collectively, these observations suggest that calcium antagonists, as a class, may offer some stroke-protective benefits to patients with hypertension. However, none of these reports used time-dependent analyses for the effects of on-treatment BP or included a CAD population. Although no statistically significant difference was detected between the drug treatment strategies, the stroke HR observed in favor of the verapamil SR–based strategy supports the point estimates from the meta-analyses, but they also indicate that most of the beneficial effect is likely related to BP control.

INVEST was a large multinational study, and as such, there are several limitations that deserve comment. Although the data supporting all of the outcomes in INVEST (hospital records, test results, death records, neurology consultations, etc) were reviewed by the events committee, the actual scans were not read centrally. Thus, the events committee chose not to attempt to differentiate between ischemic stroke and intracerebral hemorrhage. Second, because ECGs were not collected at entry, the baseline characteristic of arrhythmia was a history of arrhythmia diagnosis. Because a history of most other arrhythmias was an exclusion in these otherwise clinically stable patients, we assumed that most of these were secondary to atrial fibrillation or flutter. These latter 2 arrhythmias are highly prevalent in elderly patients with CAD and hypertension and are well known to increase stroke risk.

As the first, large trial of hypertensive patients with clinically stable CAD, INVEST afforded the opportunity to investigate this patient population relative to stroke risk. In general, characteristics associated with more severe vascular disease (eg, aging, diabetes, prior stroke/TIA, need for CABG, etc) were associated with increased stroke risk. Our results strongly support the importance of reducing BP to <140/90 mm Hg for stroke prevention in CAD patients, and the effect of BP control to reduce stroke risk was noted in patients with any of these high-risk characteristics. An increased stroke risk with very low on-treatment BP was not observed. Finally, antihypertensive drug class was not found to be a significant determinant of stroke risk in this analysis, but rather the attainment of BP control is likely responsible for most of the benefit toward stroke reduction in these CAD patients.

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Disclosures
Q.Z. and A.C. are employees of Abbott Laboratories. All of the other authors report no conflicts of interest.

References


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