Predictors of Development of Diabetes Mellitus in Patients With Coronary Artery Disease Taking Antihypertensive Medications (Findings from the INternational VErapamil SR-Trandolapril STudy [INVEST])

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Knowledge of predictors of diabetes mellitus (DM) development in patients with coronary artery disease (CAD) who use antihypertensive therapy could contribute to decreasing this adverse metabolic consequence. This is particularly relevant because the standard of care, β blockers combined with diuretics, may contribute to adverse metabolic risk. The INternational VErapamil SR-trandolapril STudy compared a calcium antagonist-based (verapamil SR) and a β-blocker–based (atenolol) strategy with trandolapril and/or hydrochlorothiazide added to control blood pressure (BP) in patients with CAD. The 16,176 patients without DM at entry were investigated with regard to newly diagnosed DM during follow-up. Newly diagnosed DM was less frequent in the verapamil SR versus atenolol strategy (7.0% vs 8.2%, hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). Characteristics associated with risk for newly diagnosed DM included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, coronary revascularization, hypercholesterolemia, greater body mass index, and higher follow-up systolic BP. Addition of trandolapril to verapamil SR decreased DM risk and addition of hydrochlorothiazide to atenolol increased risk. In conclusion, clinical findings associated with more severe vascular disease and Hispanic ethnicity identify a group at high risk for developing DM, whereas lower on-treatment BP and treatment with verapamil SR-trandolapril attenuated this risk. **(Am J Cardiol 2006;98:890–894)**

Patients with hypertension are >2 times as likely to develop diabetes mellitus (DM) than those with normal blood pressure (BP).[1,2] Risk for DM is particularly high among hypertensive patients with coronary artery disease (CAD) and risk for adverse outcomes is substantially increased.[3,4] Recent evidence has indicated that DM can be prevented or delayed by lifestyle or pharmacologic intervention.[5] Identifying patients at increased risk for DM could also be important in the choice of antihypertensive treatment and BP goals in terms of limiting DM development. Standard of care for controlling BP in CAD patients is β blockers, often with thiazide diuretics.[6] However, in many trials, β blockers and diuretics compared with other agents increased DM risk in hypertensive patients.[7] Controlled studies comparing various antihypertensive treatments in stable patients with CAD are lacking and knowledge of conditions predicting DM risk is incomplete. Accordingly, data from the INternational VErapamil SR-trandolapril STudy (INVEST) were analyzed to determine clinical characteristics predictive of newly diagnosed DM among patients with CAD.

Methods

Patient population: INVEST was a randomized trial of 2 antihypertensive treatment strategies in patients with clinically stable CAD who were ≥50 years old. Details of study design, exclusion criteria, and main outcomes were previously published.[8,9] The protocol was conducted in accordance with principles outlined in the Declaration of Helsinki, institutional review committees at participating sites approved the protocol, and patients provided written informed consent. Treatment for BP and other medical care were defined according to guidelines.[6,10]

The DM status of each patient was determined by the site investigators from review of all available patient data, including antidiabetic medication. Among the 22,576 randomized patients, the 16,176 without DM at entry are the subject of this report. DM status and new antidiabetic med-

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Table 1
Selected patient characteristics at baseline

Characteristic	Verapamil SR Strategy (n = 8,098)	Atenolol Strategy (n = 8,078)	p Value
Age (yrs), mean ± SD	66 ± 10	66 ± 10	0.65
Age >70 yrs	2,707 (33%)	2,762 (34%)	0.31
Women	4,150 (51%)	4,165 (52%)	0.69
Caucasian	4,070 (50%)	4,061 (50%)	0.69 (for overall race)
Black	1,018 (13%)	1,012 (13%)	
Hispanic	2,820 (35%)	2,794 (35%)	
Asian	43 (1%)	57 (1%)	
Multiracial/other	147 (2%)	154 (2%)	
BP (mm Hg), mean ± SD	151/88 ± 19/12	151/88 ± 20/12	0.27/0.70
Body mass index (kg/m^2), mean ± SD	29 ± 7	29 ± 8	0.41
Previous myocardial infarction	2,563 (32%)	2,478 (31%)	0.18
History of			
Angina pectoris	5,361 (66%)	5,396 (67%)	0.42
Stroke/transient ischemic attack	550 (7%)	491 (6%)	0.06
Left ventricular hypertrophy	1,674 (21%)	1,719 (21%)	0.34
Heart failure (class I–III)	349 (4%)	386 (5%)	0.15
Peripheral vascular disease	804 (10%)	779 (10%)	0.54
Smoking (ever)	3,776 (47%)	3,758 (47%)	0.89
Hypercholesterolemia*	4,344 (54%)	4,297 (53%)	0.57
Renal impairment	93 (1%)	97 (1%)	0.76
Antihypertensive drugs used			
ACE inhibitor	3,300 (41%)	3,283 (41%)	0.89
Centrally acting†	337 (4%)	370 (5%)	0.19
Calcium antagonist	2,889 (36%)	2,892 (36%)	0.87
Diuretic	2,475 (31%)	2,537 (31%)	0.25
α blocker/other vasodilator	567 (7%)	570 (7%)	0.89
β blocker‡	0	0	
Aspirin or other antiplatelet drug	4,527 (56%)	4,468 (55%)	0.45
Other NSAIDs	1,354 (17%)	1,400 (17%)	0.30
Any lipid-lowering drug	2,823 (35%)	2,780 (34%)	0.55
Nitrates	2,715 (34%)	2,814 (35%)	0.08
Potassium supplement	473 (6%)	476 (6%)	0.89

* History of hypercholesterolemia/lipid-lowering medications.
† Included clonidine, methyldopa, and moxonidine.
‡ Patients taking β blockers within 2 weeks of planned randomization or for a myocardial infarction that occurred in the previous 12 months were ineligible for enrollment to avoid possible withdrawal phenomena in patients randomized to the verapamil SR-based strategy.
ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

ications were collected at each follow-up visit. Early during the trial enrollment period, information became available that angiotensin-converting enzyme inhibitors may decrease risk of developing DM; therefore, newly diagnosed DM was added as a secondary outcome to the analysis plan.

The objective of this investigation was to determine the relative contribution of clinical conditions that influence risk for developing DM among patients with clinically stable CAD who require hypertension treatment.

Statistical analysis: Baseline characteristics were compared between randomized treatment strategies. Categorical variables were compared with chi-square statistics, and continuous variables were compared using *t* tests. A p value ≤0.05 was considered statistically significant. Kaplan-Meier analysis was used to examine the proportion of patients alive and free of DM by treatment strategy, and results were compared by log-rank statistic.

To identify conditions independently associated with newly diagnosed DM, a stepwise Cox proportional hazards model was developed to analyze time to onset of newly diagnosed DM. Age, race/ethnicity (Caucasian as reference), gender, previous myocardial infarction, heart failure, and treatment strategy were forced entries. The remaining covariates were retained in the model if the p

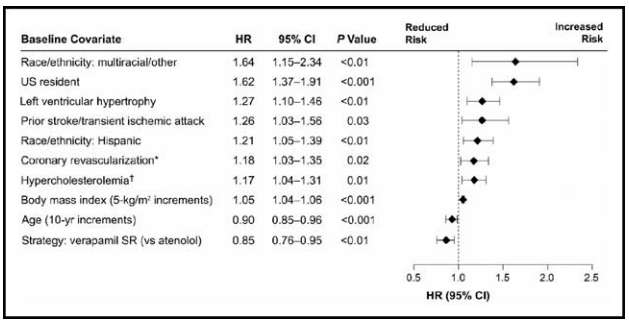

Figure 1. Statistically significant multivariable predictors of DM (stepwise Cox's proportional hazards model). *Coronary artery bypass graft/percutaneous coronary intervention; †history or use of lipid-lowering medications. CI = confidence interval; HR = hazard ratio.

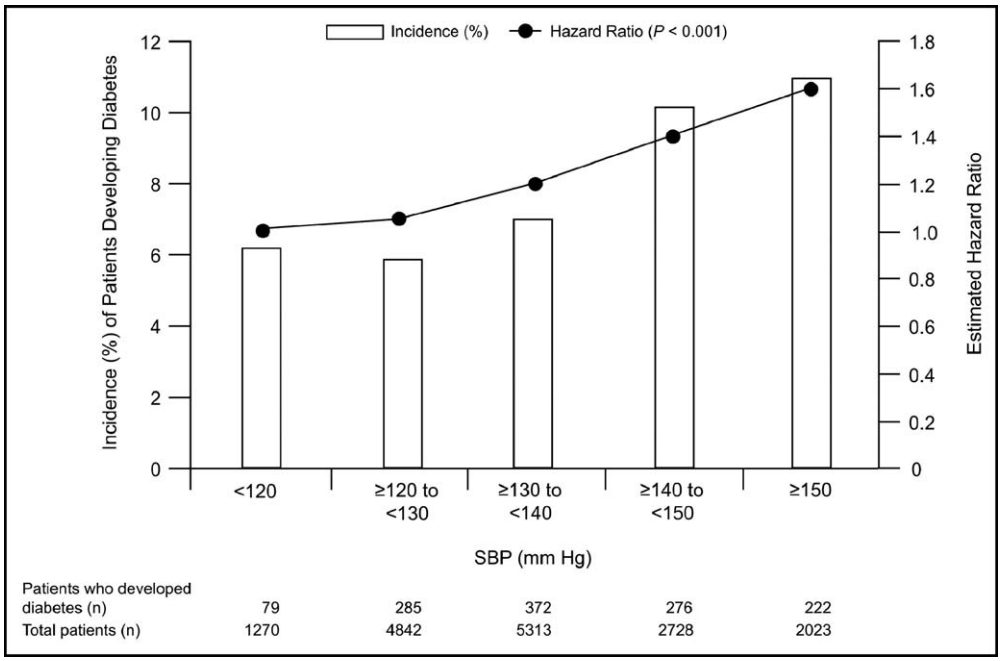

Figure 2. Relation between follow-up systolic BP (SBP) and DM development shows relative hazard for follow-up systolic BP (mean of measurements before DM development or censoring) with a reference (hazard ratio 1.0) of 120 mm Hg. A systolic BP <120 mm Hg is associated with a 6.2% incidence of new DM, whereas a systolic BP ≥150 mm Hg is associated with an 11.0% incidence of new DM. From the stepwise model, a systolic BP equal to 150 mm Hg is associated with 53% excess risk for DM compared with a systolic BP equal to 120 mm Hg.

value was ≤0.1. Covariates included residence (United States vs not United States), body mass index, angina pectoris, coronary revascularization, previous stroke/transient ischemic attack, left ventricular hypertrophy, peripheral vascular disease, hypercholesterolemia, smoking, renal impairment, arrhythmia, and unstable angina. The percentage of newly diagnosed diabetic patients having ≥1 of the risk conditions selected by the model (i.e., percent attributable risk) was calculated.

A stepwise Cox proportional hazards model for time to new DM was fit to estimate the relative hazard of specific mean follow-up systolic BPs to a reference (hazard ratio 1.0) of 120 mm Hg. Systolic BP was averaged over all follow-up BP measurements before developing DM or censoring and was included as a continuous variable. Baseline systolic BP was used if there were no follow-up BP measurements before developing DM or censoring.

The electronic data collection system developed for INVEST provided details of study medications at each visit.[11] By using a previously described drug-dose model statistical approach,[12] an exploratory time-dependent Cox proportional hazards model was developed for risk of newly diagnosed DM associated with the study drugs.

Results

Among patients without DM at entry, 8,098 were assigned to the verapamil SR-based strategy and 8,078 to the atenolol-based strategy, and totals of 22,328 and 22,304 patient-years were accumulated, respectively. With <1% lost, mean follow-up ± SD in this cohort was 2.8 ± 0.85 years in each strategy. Patient characteristics did not differ by randomized treatment strategy (Table 1). Patients using the verapamil SR strategy had a significantly lower rate of DM development (7.0%, 569 patients) than those using the atenolol strategy (8.2%, 665 patients) during follow-up (unadjusted hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). There were 25 cases of newly diagnosed DM/1,000 patient-years with the verapamil SR strategy and 30 with the atenolol strategy. More patients were alive and free of DM during follow-up in the verapamil SR strategy (log-rank test, p <0.01).

Modeling identified United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, coronary revascularization, hypercholesterolemia, and greater body mass index as independently associated with increased risk for DM (Figure 1). Multiracial or other race/ethnicity was also identified as a predictor of DM, but this subgroup was relatively small (n = 301) and most (72%, 218 of 301) categorized as multiracial were part Hispanic. Older age was associated with lower risk of new DM. Adjusting for these differences in characteristics did not change the finding that patients randomized to the verapamil SR strategy had a lower risk for newly diagnosed DM compared with those randomized to the atenolol strategy (adjusted hazard ratio 0.85, 95% confidence interval 0.76 to 0.95, p <0.01). Attributable risk was 68%. Incidence of new DM was directly and independently associated with follow-up systolic BP (p <0.001; Figure 2). Sen-

sitivity analysis using systolic BP as a time-dependent covariate produced consistent results.

At 24 months, in the verapamil SR- and atenolol-based strategies, uses of verapamil SR were 82% and 0% (4,682 and 0 patients, respectively), whereas uses of atenolol were 0% and 78% (0 and 4,454 patients), uses of trandolapril were 60% and 48% (3,404 and 2,735 patients, $p < 0.001$), and uses of hydrochlorothiazide were 41% and 59% (2,343 and 3,383 patients, $p < 0.001$) in totals of 5,721 and 5,701 patients, respectively. At 24 months, mean number of study drugs ± SE was 2.0 ± 0.03 for patients who developed DM versus 1.8 ± 0.01 for those who did not ($p < 0.001$). Mean number of study plus nonstudy antihypertensive drugs was 2.8 versus 2.4, respectively ($p < 0.001$). Need for 3 study drugs was more frequent in patients with new DM than in nondiabetic patients (40% [400 of 1,001] vs 29% [2,991 of 10,421], respectively, $p < 0.001$). Data were similar at 12 and 36 months, with no differences between strategies.

With 50 mg/day of atenolol as reference (hazard ratio 1.0), adding hydrochlorothiazide to atenolol was associated with increased DM risk (12.5 and 50 mg/day, respectively, hazard ratio 1.07, 95% confidence interval 0.84 to 1.35; 25 and 100 mg/day, respectively, hazard ratio 1.38, 95% confidence interval 1.06 to 1.80) and addition of trandolapril (2 and 4 mg/day) did not significantly change this increased risk. Addition of trandolapril to verapamil SR was associated with decreased DM risk (2 and 180 mg/day, respectively, hazard ratio 0.56, 95% confidence interval 0.43 to 0.74; 4 and 240 mg/day, respectively, hazard ratio 0.58, 95% confidence interval 0.44 to 0.78), which was maintained when adding hydrochlorothiazide (12.5 to 25 mg/day, hazard ratio 0.63 to 0.72, 95% confidence interval 0.48 to 0.96).

Discussion

Our study confirms that several conditions previously associated with new DM, such as increased body mass index, Hispanic ethnicity, left ventricular hypertrophy, hypercholesterolemia, and United States residence[2,5,13] are also important risk conditions for patients with CAD. Conditions such as previous stroke/transient ischemic attack and coronary revascularization are newly identified and could help better identify those likely to benefit from optimized metabolic evaluation during follow-up. Because DM was associated with approximately 80% excess risk of death, myocardial infarction, or stroke in INVEST,[3] identifying conditions with adverse metabolic consequences could be important in decreasing risk in patients with CAD.

It can be hypothesized that patients who developed DM during follow-up were likely to already have had impaired glucose tolerance at entry. Because impaired glucose tolerance is a risk factor for cardiovascular disease,[14] it is not surprising that conditions reflecting more severe vascular disease, such as coronary revascularization, stroke/transient ischemic attack, and left ventricular hypertrophy, were associated with a higher risk of developing DM. The lower risk of newly diagnosed DM associated with older age is consistent with data suggesting a plateau in risk of developing DM beginning around the seventh decade of life, because mean age was 66 years in our study patients.[15] Because our cohort was relatively old, the number developing DM likely was minimized, so the magnitude of the difference between treatment strategies might be greater in younger cohorts. Trials that restricted enrollment to those who were ≥70 years of age reported fewer cases of new DM and smaller treatment differences.[16,17]

Our data suggest that BP may have been more difficult to control in those destined to develop DM compared with those who did not develop DM, which is probably due to insulin resistance. The number of antihypertensive drugs required to lower BP in those who developed DM was higher compared with those who did not develop DM. Also, this number was similar to that in those with DM at baseline (24 months, mean number of study drugs ± SE 2.0 ± 0.02, mean number of study and nonstudy antihypertensive drugs ± SE 2.9 ± 0.03).[3]

On-treatment systolic BP >120 mm Hg predicted increased DM risk and, to our knowledge, this has not been previously emphasized in patients with CAD. Excellent BP control was achieved (>70% at 24 months had BPs <140/90 mm Hg), and this may have minimized possible influences of baseline BP and limited the number of new DM cases.[9] Because baseline BP, on-treatment BP over 4 years, and percentage of patients achieving BPs <140/90 mm Hg were not different between treatment strategies, differences in BP cannot explain the difference observed between treatment strategies in newly diagnosed DM. The significant relation between on-treatment systolic BP and DM risk is important because many trials have not achieved the same BP in each treatment group.[18–20] Because BP influences not only death, myocardial infarction, and stroke but also risk for DM, differences in achieved BPs between treatments make it difficult to interpret the overall effects on clinical outcome and DM in other trials.

Many trials have suggested that, compared with an angiotensin active drug or calcium antagonist, β blockers and/or diuretics are more frequently associated with DM development.[7] Similar to INVEST, many of these trials included additional antihypertensive drugs. The increased risk for DM we observed with atenolol and hydrochlorothiazide and decreased risk with trandolapril added to verapamil SR are consistent with several of these previous studies.[7] However, protection against increased risk for new DM observed when hydrochlorothiazide was added in those already taking verapamil SR and trandolapril is new information, as is the apparent lack of protection when hydrochlorothiazide was used with atenolol and trandolapril.

Explanations proposed for the observed associations between antihypertensive drugs and DM focus on thiazide diuretics and β blockers decreasing serum potassium and insulin secretion and/or increasing insulin resistance.[21,22] Protective effects of blockers of angiotensin II may relate to less interference with insulin signal transduction[23] and/or

more bradykinin to improve glucose delivery by facilitating the microcirculation.[24]

Some limitations of this analysis deserve mention. Laboratory data used to classify newly diagnosed DM at sites were not systematically collected. DM diagnosis was based on investigator reports, but the accuracy of such reporting has been verified[25] and has been used in other recent trials.[26–28] Because a placebo-controlled, single-agent trial is not ethical in these patients, it is not possible to determine whether verapamil SR or trandolapril alone conferred protection and whether atenolol or hydrochlorothiazide alone accelerated DM onset. The data suggest trandolapril had a protective effect in the verapamil SR strategy, whereas hydrochlorothiazide increased DM risk in the atenolol strategy. Consistent with the protocol, patients using the atenolol strategy were, on average, exposed to hydrochlorothiazide for a longer duration than were patients using the verapamil SR strategy; however, hydrochlorothiazide duration and dose were accounted for in the model.

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