

Characteristics of Contemporary Patients with Hypertension and Coronary Artery Disease

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Summary

Background: Despite a high prevalence of hypertension in the population with CAD, there are limited data describing the clinical characteristics and treatments, as well as their interrelations in these patients. This is particularly true for black and Hispanic patients who have been underrepresented in randomized CAD trials.

Hypothesis: There exist racial and ethnic differences that define the characteristics of patients with both coronary artery disease (CAD) and hypertension.

Methods: This report describes the characteristics of Caucasian, Hispanic, and black patients enrolled in the International Verapamil SR/trandolapril Study (INVEST), a prospective trial undertaken exclusively in patients with CAD and hypertension.

Results: In all, 10,925 Caucasian, 8,045 Hispanic, and 3,029 black patients are described. An abnormal angiogram or documented myocardial infarction was observed more fre-

quently in Caucasian patients (73%), while angina pectoris was more prevalent in Hispanic patients (87%). Diabetes and left ventricular hypertrophy were most common in black patients (33 and 29%, respectively), while hypercholesterolemia and prior revascularization (coronary artery bypass graft or angioplasty) were most common in Caucasian patients (64 and 41%, respectively). More than 60% of Hispanic and black patients were women—a unique characteristic for randomized CAD trials. Comparing race/ethnic cohorts, there were significant differences for all characteristics. More than 80% of patients in all race/ethnic groups were receiving antihypertensive therapy; however, only fewer than 25% had controlled blood pressure according to guidelines from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

Conclusions: This high-risk population of hypertensive patients with CAD has been undertreated and does not have well-controlled BP. Race/ethnic differences were observed for clinical characteristics and medication use.

Key words: coronary artery disease, hypertension, comorbidity, blood pressure control, Hispanic, black

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Introduction

Patients with coronary artery disease (CAD) are a complex population that is increasing in size.¹ Historically, patients with CAD and hypertension have not been well described in the literature, and patients with CAD have been underrepresented in most previous, large hypertension treatment trials.^{2–8}

The International Verapamil SR/trandolapril Study (INVEST) evaluated blood pressure (BP) control and cardiovascular (CV) outcomes in patients with CAD and hypertension. The demographic data collected during recruitment for INVEST provide particularly important information to char-

acterize and understand better this growing population so that perhaps they can be more effectively treated in clinical practice. This report focuses on the racial/ethnic differences that define the characteristics of this group of patients. A large number of black and Hispanic patients were enrolled and, as a result, this report provides valuable prospective registry-type information collected in a uniform fashion on the management of hypertension in these race/ethnic groups, as well as their characteristics. These characteristics include demographics, comorbidities, the use of antihypertensive and other medications, and BP measurements.

Methods

Rationale, Study Design, and Study Population

The rationale, design, and primary results of INVEST are published elsewhere.^{9, 10} Briefly, INVEST was an international, prospective trial evaluating management of BP in hypertensive patients with CAD. Inclusion criteria included patients aged ≥ 50 years with essential hypertension¹¹ who required drug therapy and had documented CAD. Coronary artery disease was defined as any of the following: remote (≥ 3 months prior to enrollment) confirmed myocardial infarction (MI), coronary angiogram with $> 50\%$ narrowing of at least one major coronary artery, diagnosis of classic angina pectoris, or concordant abnormalities on two different types of signals (electrocardiograms, echocardiograms, and/or radionuclide scans) from stress tests, provided that two different signals showed findings consistent for ischemia. Recruitment began in September 1997 and was completed in December 2000 at 862 sites in 14 countries (Australia, Canada, Cuba, Dominican Republic, El Salvador, Germany, Guatemala, Hungary, Italy, Mexico, New Zealand, Panama, Turkey, and the United States). Patients were randomized to either a verapamil SR-based or an atenolol-based antihypertensive treatment strategy. Trandolapril and/or hydrochlorothiazide were also allowed to achieve BP goals according to guidelines from the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) of < 140 mmHg (systolic) and < 90 mmHg (diastolic); and < 130 mmHg (systolic) and < 85 mmHg (diastolic) if diabetes or renal impairment was present.⁹⁻¹¹ The ethics committee of each locality approved the protocol, and the trial was conducted according to principles of the Declaration of Helsinki. All recruited patients provided voluntary written informed consent.

Patients underwent a baseline medical history and examination during which BP and heart rate (HR) were measured according to procedures described in JNC VI.¹¹ Blood pressure was measured in duplicate in both arms, separated by at least 2 min, and if there was more than a 5 mmHg difference between arms, measurements from the higher arm were recorded for the baseline and subsequent protocol visits. Investigators entered relevant demographic and other data into an Internet-based data collection system.

Data were summarized as means and standard deviations or percent, where appropriate, according to race/ethnicity. Cohorts were defined as Caucasian, Hispanic, and black. Chi-square tests were used to compare categorical measures, and one-way analysis of variance (ANOVA) models were used to compare continuous measures. Odds ratios and associated 95% confidence intervals were presented for three baseline conditions of interest (taking angiotensin-converting enzyme [ACE] inhibitors, taking diuretics, and BP not in control) by selected baseline characteristics.

Results

Clinical Characteristics

In all, 10,925 Caucasian patients, 8,045 Hispanic patients, and 3,029 black patients were recruited. There were significant differences ($p < 0.001$) between race/ethnic cohorts for comparisons of all of the characteristics discussed below. It is interesting that the majority of Hispanic and black patients (61%) were women, while women made up only 43% of the Caucasian population. Hispanic and black patients tended to be younger (mean age 66 [SD 9.8] and 64 [SD 9.7] years, respectively) while Caucasians had a mean age 67 (SD 9.7) years. Mean body mass index was 29 kg/m² in Caucasians and Hispanics and 31 kg/m² in blacks. Classic angina pectoris was present in 87% of Hispanics, 71% of blacks and 50% of Caucasians; however, mean angina frequency was higher in Caucasians (1.9 episodes/week during the preceding month) than in Hispanics and blacks (1.1 and 1.5, respectively). Either an abnormal coronary angiogram or documented prior was observed in the majority of Caucasians (73%) but in a minority of Hispanic and black patients (28 and 47%, respectively).

The prevalence of left ventricular hypertrophy (LVH) (documented by findings from electrocardiogram or echocardiogram) and congestive heart failure (CHF) (New York Heart Association class I-III, documented by findings in medical records) was highest in blacks (28 and 9%, respectively) compared with 20 and 7% in Caucasians and 22 and 3% in Hispanics, respectively. Diabetes (defined as a history of or taking antidiabetic medications) was present more often in Hispanic (30%) and black (33%) than in Caucasian (26%) patients, while hypercholesterolemia (defined as a history of or taking lipid-lowering medications) was more prevalent in Caucasian (64%) than in either Hispanic (48%) or black (46%) patients. Renal impairment (defined as a history of or serum creatinine between normal for lab to < 4 mg/dl) was more common in black (3%) than in Caucasian (2%) or Hispanic (1%) patients. Caucasian patients reported the highest incidence of past smoking (54%), while black patients reported the highest incidence of current (within the past 30 days) smoking (18%). In addition, Caucasian patients reported feeling good or excellent more frequently (72%) than either black (67%) or Hispanic (65%) patients.

Use of Medication

The Caucasian cohort was less likely to be taking antihypertensive therapy (83%) than other cohorts (Hispanics 91% and blacks 89%). Of those receiving antihypertensive therapy, black patients were more likely to be taking two or more medications (54%) than either Caucasian (44%) or Hispanic (37%) patients. Angiotensin-converting enzyme inhibitors were the most frequently prescribed class of drugs in Caucasian (42%) and Hispanic (50%) patients, while diuretics were the most frequently prescribed class of drugs in blacks (50%). Patients most likely to be treated with ACE inhibitors were those with CHF, diabetes, LVH, and prior MI. Hispanics were more likely to be treated with ACE inhibitors than Caucasians, as were men and those ≤ 70 years old compared with women and patients aged > 70 years (Fig. 1A). Also, patients with BP in control were more likely to receive ACE inhibitors than those with BP out of control. Patients most likely to be treated with diuretics were those with CHF, LVH, diabetes, and prior MI, and were more likely to be black than Caucasian and to have BP in control (Fig. 1B). Lipid-lowering medications were prescribed more frequently in Caucasian (46%) compared with Hispanic (30%) and black (24%) patients. The use of nitrates was most frequent in Hispanic patients (41%) compared with 34% in both Caucasian and black pa-

tients. The use of aspirin or other antiplatelet agents was reported in 72% of Caucasian patients but in $< 50\%$ of Hispanic and black patients. Finally, other nonsteroidal anti-inflammatory drugs were used more often by Hispanic and black (22%) than by Caucasian patients (14%).

Blood Pressure Measurements and Control

Figure 2A summarizes mean BP and HR values; rates of BP control for the race/ethnic cohorts are summarized in Figure 2B. When assessed by race/ethnicity, mean systolic and diastolic blood pressures (SBP and DBP) were significantly different ($p < 0.001$). Caucasian patients had the highest mean SBP (151.9 mmHg [SD \pm 19.5]) and black patients had the highest mean DBP (89.2 mmHg [SD \pm 12.5]). The proportion of patients with SBP and DBP in control was also significantly different according to race/ethnicity ($p < 0.001$); SBP control was highest in Hispanic patients while DBP control was highest in Caucasian patients. Characteristics strongly associated with BP not in control included diabetes or LVH, while Hispanic ethnicity, prior MI, male gender, presence of CHF, and taking ≥ 2 antihypertensive medications were associated with BP less likely to be out of control (Fig. 3). The frequencies of SBP and DBP by category are listed in Table I. The frequency of significantly elevated SBP (≥ 160 mmHg) and

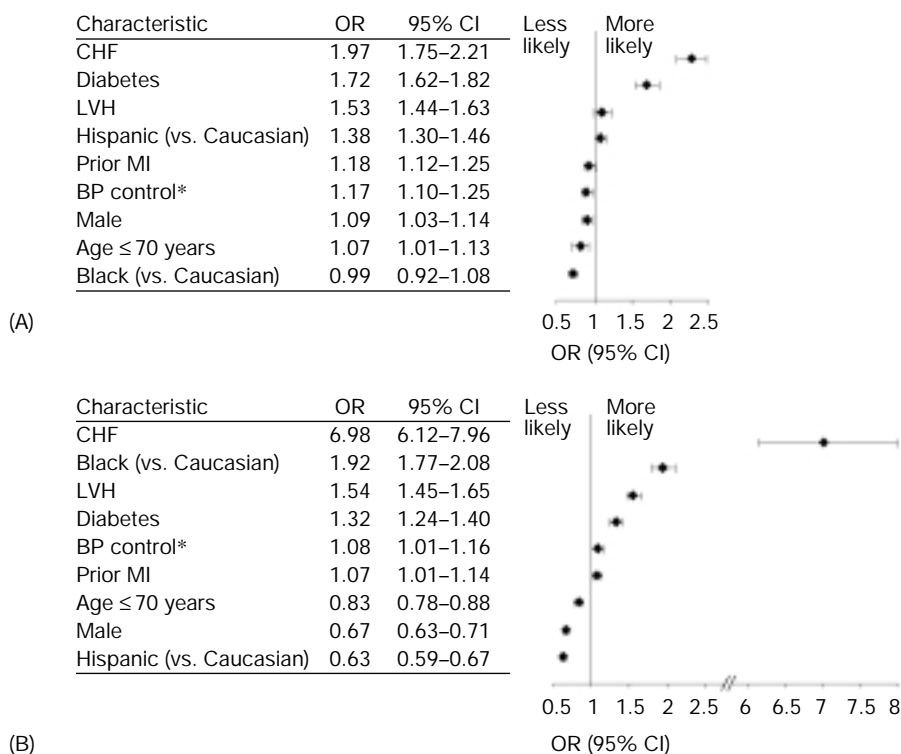


FIG. 1 Odds of taking an angiotensin-converting enzyme inhibitor (ACE-I) (A) and a diuretic (B) at baseline by selected baseline characteristics. *Control according to JNC VI guidelines ($< 130 / < 85$ mmHg for patients with diabetes and renal impairment, and $< 140 / < 90$ mmHg for others). CHF = congestive heart failure, LVH = left ventricular hypertrophy, MI = myocardial infarction, BP = blood pressure, vs. = versus, OR = odds ratio, CI = confidence interval.

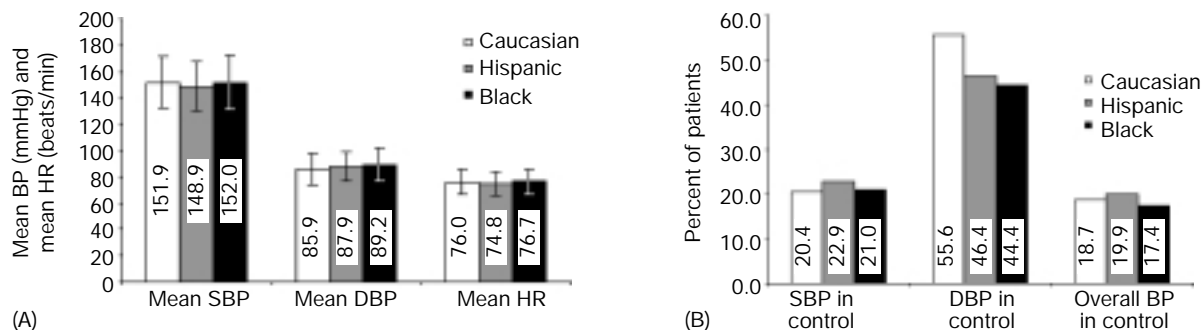


FIG. 2 Mean (\pm standard deviation) blood pressure and heart rate values (A), and rates of blood pressure control (B) at baseline according to race/ethnicity. DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure. Error bars = standard deviation. Caucasian n = 10,925, Hispanic n = 8045, black n = 3029. Blood pressure control as defined in Figure 1.

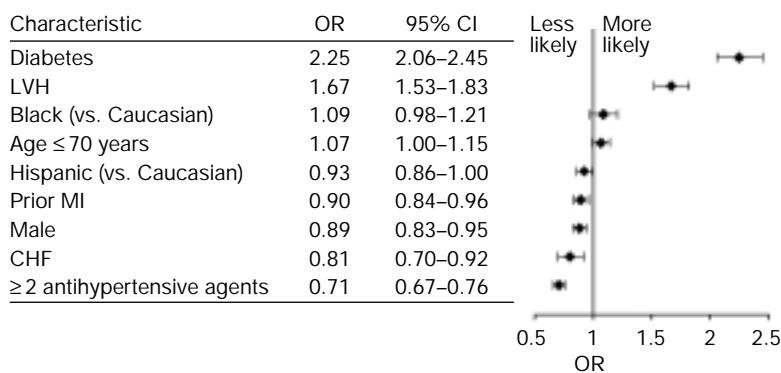


FIG. 3 Odds of blood pressure not in control by selected baseline characteristics. Abbreviations and blood pressure control as defined in Figure 1.

DBP (\geq 100 mmHg) was highest in black patients (36 and 23%, respectively) compared with Caucasian (34 and 15%) and Hispanic (30 and 18%, respectively) patients.

Discussion

Until now there have been few published data on the clinical characteristics of contemporary ambulatory patients with both CAD and hypertension, particularly for the black and Hispanic populations. Our data demonstrate that patients with CAD and hypertension, regardless of race/ethnicity, often have uncontrolled BP and moderately frequent angina symptoms, despite treatment with one or more antihypertensive medications. Several additional CV risk factors are also present. These data emphasize important race/ethnic differences in the clinical characteristics and treatment of this patient population.

The INVEST study is the only large antihypertensive trial exclusively in patients with CAD. Only a small proportion of patients from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),^{5,6} Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE),^{7,8} and Losartan Intervention for Endpoint reduction in hypertension study (LIFE)^{12,13} had con-

TABLE I Systolic (SBP) and diastolic blood pressure (DBP) categories according to race/ethnicity (%)

| | Caucasian N = 10,925 | Hispanic N = 8,045 | Black N = 3,029 |
|----------------------------|-------------------------|-----------------------|--------------------|
| SBP category (mmHg) | | | |
| < 130 | 11.4 | 12.2 | 11.5 |
| 130–139 | 12.5 | 15.7 | 14.7 |
| 140–159 | 42.1 | 42.5 | 38.0 |
| \geq 160 | 34.1 | 29.6 | 35.9 |
| DBP category (mmHg) | | | |
| < 80 | 28.2 | 16.7 | 19.5 |
| 80–89 | 30.4 | 33.4 | 29.3 |
| 90–99 | 26.1 | 32.3 | 28.7 |
| \geq 100 | 15.3 | 17.5 | 22.6 |

comitant CAD (7.5–32.7%). The INVEST study included a high proportion of Hispanic patients (36%), and was second only to ALLHAT in the number of black patients. Thus, INVEST represents a substantial addition to the available demographic information on patients with CAD, particularly for these race/ethnic groups. Other recent hypertension trials such

as the Nordic Diltiazem study (NORDIL), Intervention as a Goal in Hypertension Treatment (INSIGHT), and Hypertension Optimal Treatment (HOT) included even fewer patients with CAD (<7%) and, because enrollment in these trials was limited primarily to patients in Europe and Scandinavia, very few, if any, non-Caucasian patients were enrolled.²⁻⁴

There are notable similarities and differences in characteristics between the patients in INVEST and patients with CAD contained in other reports. Previous investigators concluded that conventional CV risk factors (smoking, diabetes, hyperlipidemia, and hypertension) were not prevalent in the population with CAD.^{14, 15} Data from INVEST and others suggest otherwise. In a meta-analysis of over 120,000 patients with coronary heart disease, Khot *et al.* reported hyperlipidemia in 40% of women and 34% of men, while diabetes was present in 23% of women and 15% of men. Prevalence rates for current smoking (30% women, 42% men) were somewhat higher than those in the current study, and 43% of patients reported hypertension.¹⁶ Although the Heart Outcomes Prevention Evaluation (HOPE) study was not exclusive to patients with CAD, the majority (80%) had CAD.¹⁷ Hypertension, diabetes, and hyperlipidemia were common (47, 38, and 66%, respectively), supporting data observed in INVEST and described by Khot *et al.*¹⁶ In addition to clinical data for the overall population with CAD, our patients demonstrate race/ethnic differences in the clinical characteristics of patients with hypertension and CAD. Caucasian patients were more likely to have experienced a prior MI than black or Hispanic patients. In contrast, black patients were more likely to have LVH and diabetes.

The hypertension data show that BP remained elevated in this high-risk population despite the use of at least one antihypertensive medication in most cases. This finding is comparable with data from ALLHAT^{5, 6} and CONVINCe,^{7, 8} which included hypertensive patients at increased risk for or with heart disease. In these studies, only 27 and 20% of patients, respectively, had controlled BP at baseline.

In addition, the frequency of hypercholesterolemia is in keeping with that reported by Khot *et al.*¹⁶ More important, only two-thirds of our hypercholesterolemic patients were receiving lipid-lowering therapy. Aspirin or other antiplatelet agents appear to be underutilized, but this may relate to the uncertainty about the protective benefit in women. Also, the use of other nonsteroidal anti-inflammatory drugs (NSAIDs), all of which are labeled with warnings against concurrent aspirin use and which are frequently used by the elderly, likely contributes to this lower than expected use of aspirin.

There are limitations to the generalizability of these data. Since INVEST was a randomized trial with exclusion criteria, the results will not necessarily reflect all of the other characteristics of a general population with CAD and hypertension. In particular, patients taking a beta blocker within 2 weeks of randomization or taking a beta blocker for an MI that occurred in the previous 12 months were excluded to avoid withdrawal phenomena in patients randomized to the verapamil-SR-based strategy. However, since it is likely that many of these patients had taken a beta blocker prior to enrollment, it was more likely that investigators slowly withdrew these agents. In addition,

patients who had unstable angina, had undergone percutaneous coronary intervention or coronary artery bypass graft, or had a stroke within 1 month of enrollment were excluded. Furthermore, these patients were enrolled from diverse geographic regions with varying standards of medical practice, available medical care, and costs of medications. This may, in part, explain some of the differences seen in patient characteristics, particularly medication use and prior revascularization procedures. Nevertheless, these data provide valuable information on this understudied population.

Conclusion

These data from a modern population of hypertensive patients with CAD have important clinical implications. Most important is that a majority (>80%) of these patients have less than optimal blood pressure control which, taken alone, has profound negative clinical implications for their long-term survival and well being (stroke and MI). Information on the characteristics of modern high-risk minorities also provides valuable insights into these subpopulations. Finally, in addition to uncontrolled hypertension, these patients also had multiple other uncontrolled comorbidities, which underscores the need for better recognition and management of risk factor conditions in all cohorts of this high-risk patient population.

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