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Clinical Investigations

Global Differences in Blood Pressure Control and Clinical Outcomes in the INternational VErapamil SR-Trandolapril STudy (INVEST)

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Summary

Background: The INternational VErapamil SR-Trandolapril Study (INVEST), a prospective, randomized, antihypertensive trial, found that two different medication regimens produced similar blood pressure (BP) control with equivalent cardiovascular (CV) outcomes (death from any cause, nonfatal myocardial infarction [MI], or nonfatal stroke).

Hypothesis: The study was undertaken to investigate whether differences exist by global regions in demographics, treatment, and outcomes in the INVEST trial.

Methods: Data were analyzed for 22,576 patients with stable coronary artery disease (CAD) enrolled in INVEST. We investigated differences in patient characteristics, treatment approaches, BP control, and clinical outcomes by creating three global regions based on geographical location: Northern Americas (NA), Caribbean (CA), and Eurasia (EA).

Results: We observed significant regional differences in patient characteristics, treatment patterns, BP control, and CV outcomes. At baseline, patients from NA were older and had greater body mass index, higher rates of diabetes, peripheral vascular disease, and coronary revascularization, but lower rates of MI or left ventricular hypertrophy than patients in CA and EA. At 24 months, there were regional differences in both study and nonstudy antihypertensive drug use. Despite having higher mean baseline BP, patients from CA and EA achieved lower mean systolic BP throughout study follow-up. Furthermore, patients from both CA and EA had lower rates of all-cause mortality, fatal or nonfatal MI, fatal or nonfatal stroke, and newly diagnosed diabetes than patients from NA.

Conclusions: In INVEST, regional differences in medication utilization, BP control, and CV outcomes were identified. These disparities warrant further investigation to define appropriate care for patients with hypertension and stable CAD from an international public health perspective.

Key words: hypertension, blood pressure, coronary artery disease, international, practice patterns, regional differences, clinical outcomes, INVEST

Introduction

National and international differences in the management of coronary artery disease (CAD) and cardiovascular (CV) outcomes have been documented, particularly in the setting of acute coronary syndromes (ACS).[1–8] These data primarily come from registries of non-ST-elevation ACS and myocardial infarction (MI) where management is highly technical and complex.[2–4, 9–11] Regional differences in noncomplex CV care required for hypertension and diabetes management have also been documented.[9, 12–16] The reasons for regional management and outcome differences have not been fully explored, but differences in patient characteristics, variability in delivery of complex and noncomplex technology and/or guideline-driven chronic therapies, disparity in patient adherence to treatment, and discrepancies in outcomes assessment and adjudication may contribute.

Registry data offer insights into disease patterns, medication use, and resource utilization over time and allow for assess-

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ment of adherence to practice guidelines. However, limitations of registry data include heterogeneous definitions of diagnoses and cohorts, potential selection bias of included institutions, differences in patient care, and selective outcome reporting. Analysis of large controlled clinical trial data could offer additional insights into regional management and outcome differences in individuals with CAD.

The INternational VErapamil SR-Trandolapril STudy (INVEST) examined two different antihypertensive strategies in patients with hypertension and stable CAD.[17] Results showed excellent blood pressure (BP) control overall, and no significant difference in either BP control or all-cause death, nonfatal MI, or nonfatal stroke comparing a verapamil-sustained release (SR)-based and an atenolol-based antihypertensive treatment strategy.[18] With participation of more than 22,000 patients from 14 countries and over 60,000 patient-years of accrued follow-up, this data set provides an opportunity to investigate differences in BP control, medication utilization, and clinical outcomes among different international regions.

Methods

The design of INVEST has been previously described.[17] Briefly, this trial enrolled hypertensive patients with clinically stable CAD to investigate BP control and adverse outcomes comparing a verapamil SR-based and an atenolol-based antihypertensive treatment strategy. Blood pressure treatment goals were < 140/90 or < 130/85 mmHg for patients with diabetes or renal impairment.[19] Standard of care nonpharmacological recommendations based on the sixth report of the Joint National Committee (JNC VI) guidelines[19] and secondary prevention according to the National Cholesterol Education Program[20] were provided online in a printable format that could be given to patients. Institutional review boards and ethics committees at participating sites approved the protocol and patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Patients were considered to have adequate BP control at 24 months if they achieved a BP within the appropriate range as defined by JNC VI. To investigate international differences for this analysis, the 14 participating countries were grouped into one of three geographic regions: Northern Americas (United States [including Puerto Rico] and Canada); Caribbean (Mexico, Cuba, Panama, El Salvador, Guatemala, and Dominican Republic); and Eurasia (Germany, Italy, Hungary, Turkey, Australia, and New Zealand).

Statistical Analysis

Baseline characteristics, BP reduction and BP control, and the primary outcome were compared among the three regions. The primary outcome was compared using a Cox proportional hazards model adjusting for treatment strategy, five prespecified baseline covariates (age, gender, race, prior MI, prior congestive heart failure [CHF]), and other baseline characteristics identified as significant in a stepwise model ($p < 0.1$). Data were captured and stored in database tables (Version 7.1, Oracle, Redwood Shores, Calif.). Data management and statistical analyses were performed using SAS statistical software (Version 8.2, SAS Institute Inc., Cary, N.C.).

Results

Regional Differences in Patient Characteristics

In all, 17,583 patients were enrolled from NA, 3,466 from CA, and 1527 from EA. Baseline characteristics are summarized in Table I. Patients from NA were older (mean age 66.7 ± 9.9 years) than those from CA (64.0 ± 9 years) or EA (63.3 ± 8.1 years) and had higher body mass indices (BMIs) (mean BMI 29.5 ± 5.8) than CA (28.0 ± 10.2) or EA (28.3 ± 10.6) patients. In addition, there were more women (53.4 vs. 49.9 or 43.3%) and black patients (15.2 vs. 10.2 or 0.1%) in NA compared with CA or EA ($p < 0.001$ for NA vs. both CA and EA for all above comparisons). As expected, CA had the highest proportion of Hispanic patients (52.2% of CA group), while EA had the highest proportion of Caucasians (96.7% of EA group).

Analysis of baseline comorbidities by region reveals that rates of diabetes, peripheral vascular disease, and previous revascularization were higher in NA than in the other regions. On the other hand, CA had the highest percentages of unstable angina, stable angina pectoris, prior CHF, and left ventricular hypertrophy (LVH), while having the lowest rate of previous stroke. Patients from CA also had higher percentages of current or past smoking history, but lower rates of hypercholesterolemia. Mean number of comorbidities also differed by region with NA patients having higher percentages than other regions (overall $p < 0.01$).

Baseline antihypertensive use differed by geographic region (Table II). The mean number of BP-lowering medications at entry was 1.5 ± 1.0 in NA, 1.26 ± 0.8 in CA, and 1.21 ± 1.0 in EA ($p < 0.001$). In addition, 88.4% of NA, 83.1% of CA, and 73.9% of EA were taking at least one antihypertensive agent at study entry ($p < 0.001$). Aspirin or other antiplatelet drug use (51.1%) and nitrate use (30.4%) was lowest in the NA region, while hormone replacement therapy (21.8%) and nonsteroidal anti-inflammatory drug (NSAID) use other than aspirin (21.2%) was highest in this group. Patients from NA and EA had similar overall use of lipid-lowering agents (38.1 and 37.1%, respectively, $p = 0.44$), while those from CA had significantly lower lipid-lowering drug use compared with the other two regions (29.9%, $p < 0.001$). Differences in other relevant nonstudy drugs are also summarized in Table II.

Regional Differences in Blood Pressure

At baseline, patients from both CA and EA had significantly higher mean systolic and diastolic BPs than NA patients (160/96 mmHg for CA; 161/94 mmHg for EA; 148/85 mmHg for NA, $p < 0.001$ vs. NA). However, by the first follow-up visit (Week 6), CA had the lowest mean systolic blood

TABLE I Baseline characteristics by geographical region

Characteristic	Region		
	Northern Americas (NA) (n = 17,583)	Caribbean (CA) (n = 3,466)	Eurasia (EA) (n = 1,527)
Mean age, years (SD)	66.7 (9.9) [a]	64.0 (9.0)	63.3 (8.1)
Mean BMI, kg/m^2 (SD)	29.5 (5.8) [a]	28.0 (10.2)	28.3 (10.6)
Female (%)	53.4 [a]	49.9	43.3
Race/ethnicity (%)			
Caucasian	46.5	36.8	96.7
Black	15.2	10.2	0.1
Hispanic	35.5	52.2	0
Asian	0.7	0.3	1.4
Other	2.2	0.5	1.8
SBP, mmHg (SD)	148 (19)	160 (19)	161 (18)
DBP, mmHg (SD)	85 (11)	96 (12)	94 (10)
Myocardial infarction (%)	29.5	41.3 [b]	39.0
Stable angina pectoris (%)	66.1	72.6 [a]	60.0
CABG (%)	17.9 [a]	6.0	13.6
Angioplasty (%)	16 [a]	11.3	12.0
Stroke (%)	5.6	2.9 [a]	5.0
Left ventricular hypertrophy (%)	16.3	46.2 [a]	31.6
Unstable angina (%)	10.7	17.8 [a]	5.7
Heart failure (%)	5.3	6.8‡	5.6
Peripheral vascular disease (%)	13.3 [a]	8.2	4.5
Past smoker (%)	45.1	53.4 [a]	43.6
Current smoker (%)	12.2	14.6 [a]	10.2
Diabetes† (%)	29.5 [a]	24.5	23.3
Renal dysfunction (%)	2.0	1.2 [b]	1.6
Hypercholesterolemia† (%)	56.2	52.9 [c]	57.3
Number of risk factors‡			
0–1	41.2	43.9	48.3
2–4	53.8	53.3	49.8
≥5	5.0	2.7	1.9

† denotes history of, or taking antidiabetic or lipid-lowering medications; ‡ risk factors included: prior renal impairment, heart failure, smoking, diabetes, age > 70, MI, revascularization, stroke/TIA, and PVD. All p values among all three groups < 0.001, except heart failure and renal dysfunction p = 0.002, and mean number of risk factors p < 0.01.

[a] p < 0.001 vs. other 2 regions.

[b] p < 0.001 vs. NA.

[c] p < 0.001 vs. NA, p = 0.004 vs. EA.

Abbreviations: SD = standard deviation, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, CABG = coronary artery bypass graft, MI = myocardial infarction, TIA = transient ischemic attack, PVD = peripheral vascular disease.

pressure (SBP) at 135 mmHg, and by Week 12 both CA and EA had significantly lower mean SBP than NA (p < 0.001 vs. NA). This SBP trend continued throughout 36 months of follow-up (Fig. 1).

At baseline, NA had the highest proportion of patients (22%) with BP controlled to JNC VI goals (Fig. 2), compared with just 8% in CA and 5% in EA (p < 0.001). However, by 12 months, NA had the lowest proportion of patients with JNC VI BP control (56%), compared with 81% in CA and 70% in EA (p < 0.001). At 24 and 36 months, NA still had the lowest percent of patients with JNC VI control at approximately 60%, while CA and EA maintained between 70 and 80% of patients at goal (p < 0.001). Differences in BP control were similar when looking at the proportion of patients achieving BP of < 140/90 mmHg. At baseline, 27% of patients in NA had BP < 140/90 mmHg compared with 9 and 6% in CA and EA, respectively (p < 0.001). Between 1 and 3 years of follow-up, 65–69% of NA patients achieved BP < 140/90 mmHg, compared with 84–88% of CA patients and 77–79% of EA patients (p < 0.001 for all comparisons).

Regional Differences in Study Antihypertensive Drug Use

At 24 months, NA, CA, and EA patients were taking a mean of 2.63, 2.46, and 2.63 antihypertensive agents, respectively (p < 0.001); these included both study and nonstudy agents. The majority of patients in each region were taking at least two antihypertensive drugs (Fig. 3). Specifically, 89% of

TABLE II Baseline medication use

Variable	Region		
	Northern Americas (NA) (n = 17,583)	Caribbean (CA) (n = 3,466)	Eurasia (EA) (n = 1,527)
Antihypertensive medications (%)	88.4	83.1	73.9
Mean number antihypertensive medications (SD)	1.5 (0.95)	1.26 (0.82)	1.21 (1)
Aspirin/antiplatelet (%)	51.1	76.7	75.9
Lipid-lowering medications (%)	38.1	29.9	37.1
Antidiabetic medications† (%)	24.0	17.2	17.4
Nitrates (%)	30.4	58.5	49.7
Digoxin (%)	7.7	7.4	3.7
Other NSAIDs (%)	21.2	5.3	6.4
HRT‡ (%)	21.8	3.4	3.6

† denotes insulin and/or oral hypoglycemics; ‡ data for women only; p < 0.001 among all three groups for all variables.
Abbreviations: SD = standard deviation, NSAIDs = non-steroidal anti-inflammatory drugs, HRT = hormone replacement therapy.

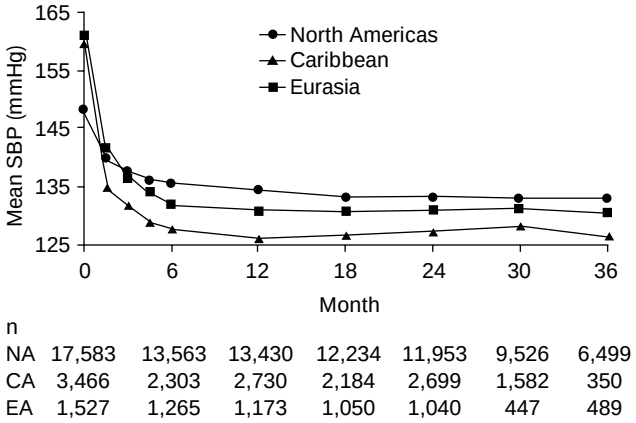

FIG. 1 Regional differences in mean systolic blood pressure during follow-up. P < 0.001 from baseline to end of follow-up for regional comparisons.

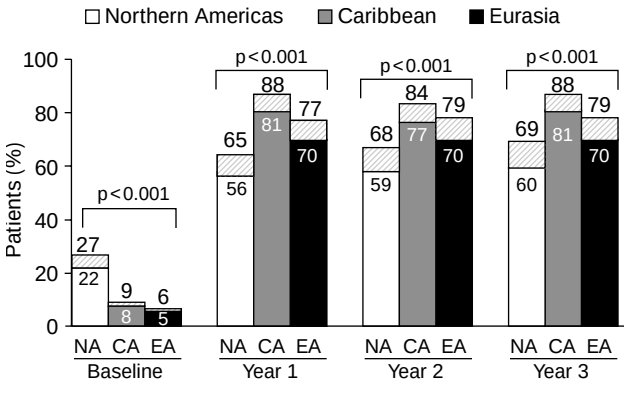

FIG. 2 Regional comparison of blood pressure control over study follow-up. Dashed lines = < 140/90 mmHg; solid lines = JNC VI blood pressure goal of < 140/90 or < 130/85 mmHg for diabetes or renal impairment. P < 0.001 for both < 140/90 mmHg and JNC VI blood pressure goals.

patients in the CA group were taking two or more antihypertensive drugs, compared with 81% in NA and 79% in EA. Fifty-two percent of NA and EA patients were taking three or more BP-lowering drugs, while 45% of patients in the CA group were taking at least three drugs. With respect to study drug use, CA had the highest proportion of patients treated with verapamil SR, atenolol, trandolapril, and hydrochlorothiazide (HCTZ) at 24 months (Fig. 4).

Regional Differences in Other Medications

As an index of quality of care, we examined absolute percent changes in use from baseline to 24 months for several drug classes including aspirin/antiplatelet agents, lipid-lowering therapy, and NSAIDs (Fig. 5). Aspirin use increased by 0.7% in NA, 9.7% in CA, and 6.4% in EA. Among patients with hypercholesterolemia, use of lipid-lowering agents increased by 4, 6, and 6% in NA, CA, and EA, respectively. The use of NSAID remained constant at 21.2% in NA, and was also similar to baseline in CA and EA (5.3 vs. 5.1% and 6.4 vs. 6.9%, respectively).

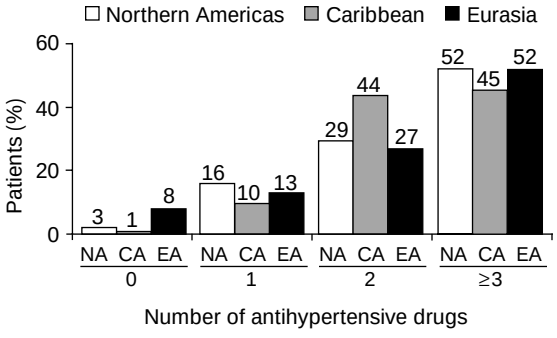

FIG. 3 Regional comparison of number of study and nonstudy antihypertensive drugs at 24 months. P < 0.001 for regional differences in mean number of antihypertensive drugs (see text).

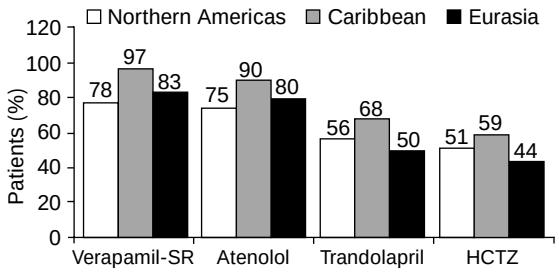

FIG. 4 Proportion of patients prescribed each study medication at 24 months by region. Mean daily doses ± standard deviation of verapamil-SR in NA, CA, and EA were 300 ± 104, 254 ± 89, and 272 ± 93 mg, respectively; doses for atenolol were 78 ± 36, 74 ± 30, and 73 ± 30 mg, respectively; doses for trandolapril were 4 ± 2, 3 ± 1, and 3 ± 1 mg, respectively; doses for hydrochlorothiazide (HCTZ) were 30 ± 15, 27 ± 10, and 25 ± 8 mg, respectively.

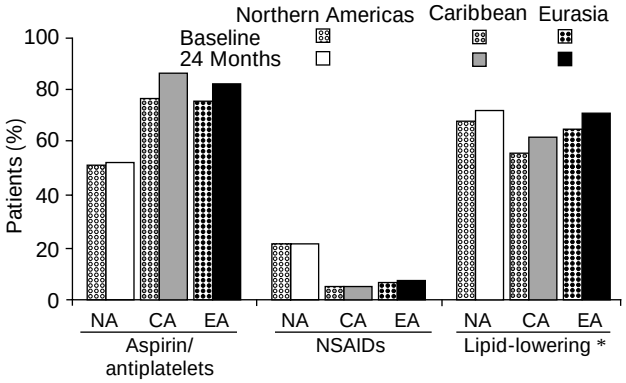

FIG. 5 Quality of care indices at baseline and 24 months by region; *denotes among patients with hypercholesterolemia. NSAIDS = nonsteroidal anti-inflammatory drugs.

Regional Differences in Outcomes

Within each region, there were no significant differences between patients comparing treatment strategies for rates of primary or secondary outcomes with the exception of new onset of diabetes mellitus (DM), which is described below. Specifically, in NA the primary outcome rates were 40 and 41 events per 1000 patient-years in the verapamil-SR and atenolol strategies, respectively ($p = 0.70$). In CA, the primary outcome rate was 22 and 24 events per 1000 patient-years in the verapamil-SR and atenolol strategies, respectively ($p = 0.49$). Finally, in EA the primary outcome rates were identical by antihypertensive strategy (13 events per 1000 patient-years, $p = 0.98$). Figure 6 summarizes the primary and secondary outcomes by region after a mean follow-up of 2.7 years per patient. Patients in NA had the highest rate of the primary outcome at 41 events per 1000 patient-years, those in CA had an intermediate primary outcome rate at 23 events per 1000 patient-years, and those in EA had the lowest rate at 13 events per 1000 patient-years ($p < 0.001$ for all comparisons). Similarly, NA had the highest risk of all-cause mortality at 31 deaths per 1000 patient-years, while CA had 19 deaths and EA had 9 deaths per 1000 patient-years ($p = 0.018$ for NA vs. CA; $p = 0.021$ for NA vs. EA). For fatal or nonfatal MI, NA demonstrated the highest rates with 15 MIs per 1000 patient-years, CA had 12 MIs per 1000 patient-years ($p < 0.001$ vs. NA), and EA demonstrated the lowest rates at 6 MIs per 1000 patient-years ($p = 0.001$ vs. NA). The rates for fatal or nonfatal stroke were highest in the NA group at seven strokes compared with three strokes for CA and two strokes for EA (all per 1000 patient-years). After adjustment for treatment strategy, age, gender, race, prior MI, prior heart failure (HF), and other baseline characteristics identified as significant in a stepwise model, the hazard ratio (HR) for the primary outcome comparing EA to NA was 0.39 (CI 95% 0.29–0.53), and the HR comparing CA to NA was 0.70 (CI 95% 0.60–0.82).

For all patients without diabetes at entry, the cumulative rates of new onset diabetes per 1000 patient-years were 30 for NA, 18 for CA, and 19 for EA, and were significantly different irrespective of treatment strategy ($p < 0.001$ for NA vs. CA; $p = 0.001$ for NA vs. EA). For patients randomized to the atenolol strategy who did not have diabetes at baseline, the rates of new diabetes cases were 32, 22, and 20 per 1000 patient-years for the NA, CA, and EA regions, respectively ($p = 0.018$ for NA vs. CA; $p = 0.021$ for NA vs. EA). For patients randomized to the verapamil-SR strategy without diabetes at entry, rates of new diabetes cases were 28, 14, and 18 per 1000 patient-years for the NA, CA, and EA regions, respectively ($p < 0.001$ for NA vs. CA; $p = 0.025$ for NA vs. EA).

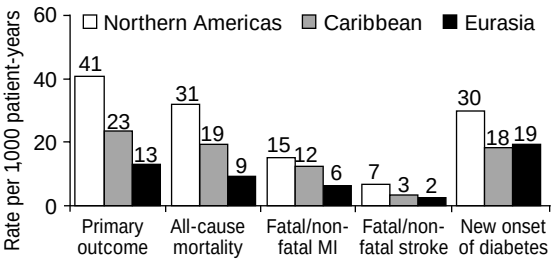

FIG. 6 Major outcomes by region (per 1000 patient years). MI = myocardial infarction.

Discussion

Differences in care of patients with CAD among international regions have been identified but not fully explored. It has been extensively documented that delivery of complex technologies, such as angiography and percutaneous coronary interventions (PCI), and use of drug therapies for acute coronary syndromes varies widely across geographical regions. For example, data from the Global Registry of Acute Coronary Events (GRACE) of ST-segment elevation MI and non-ST-segment elevation ACS management revealed that when comparing the U.S., Australia/New Zealand/Canada, Europe, and Argentina/Brazil, significant geographical differences were

seen for in-hospital use of aspirin, beta blockers, glycoprotein IIb/IIIa inhibitors, low-molecular weight heparin, and PCI.[6] Significant interregional differences were also seen for discharge prescribing for angiotensin-converting enzyme (ACE) inhibitors, antiplatelet/anticoagulant agents, beta blockers, and statins. In some settings, as suggested by a recent analysis of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) data, disparities in CV outcomes may almost exclusively be a function of differences in delivery rates of early aggressive care (i.e., surgical revascularization for acute MI).[21] However, in some cases these interregional differences are not only limited to management of complex, acute ischemic syndromes, but also to noncomplex management and treatment success of such modifiable diseases as hypertension.[16]

Variability in practice patterns within geographical regions is also heterogeneous. For example, in the U.S. performance of PCI and use of beta blockers and glycoprotein IIb/IIIa inhibitors are higher in teaching than in nonteaching hospitals. Intraregional variability in cardiovascular disease management has also been suggested in Europe.[5] While differences in delivery of both complex and noncomplex interventions for CV disease management are important, differences in the nonpharmacologic aspects of these interventions, as well as patient characteristics at baseline may also contribute.[7, 8, 22]

Data from INVEST provide an opportunity to investigate global differences in patient characteristics, care for stable hypertensive patients with CAD, and outcomes in these patients. While many of these results are consistent with historical expectations, several surprising findings may have broad implications.

First, despite having higher mean SBP at baseline, the CA and EA regions had significantly lower mean SBP than the NA region throughout the course of follow-up. In addition, they also had significantly higher rates of guideline-defined BP control (< 140/90 or < 130/85 mmHg for diabetes or renal impairment). Second, contrary to expectations, the NA group had two- to three-fold higher rates of adverse outcomes than the CA or EA groups. This was seen not only for the primary outcome of first occurrence of all-cause death, nonfatal MI, and nonfatal stroke, but also for each outcome considered separately, and these differences persisted with adjustments for differences in covariates among regions.

Several explanations for these regional observations are possible. For differences in control of SBP, baseline characteristics reveal that prior management of hypertension differed by geographic region, as evidenced not only by regional differences in medication use, but also by the higher proportion of patients with LVH in CA and EA where baseline BP was significantly higher. These baseline differences may contribute to differential study treatment effects, such as the more precipitous response to initiation of study medications in CA and EA compared with NA. Specifically, it has been shown that higher baseline BP is a major predictor of greater magnitude of BP response to antihypertensive treatment.[23, 24] As such, it could be hypothesized that higher baseline SBP in the CA and EA groups partially explains the difference in treatment effect when compared with patients in NA.

Racial differences may also affect response to hypertensive treatment. In general, hypertension in black patients appears more difficult to control, and blacks have an increased CV risk associated with hypertension;[25–31] there was a significantly higher proportion of blacks in NA than in CA and especially EA. Specifically, black patients are more likely to have low-renin hypertension and more frequently carry variant genotypes and haplotypes of the beta-1 adrenergic receptor, making them generally less likely to respond to ACE inhibitors and beta blockers, respectively.[23, 32–34] Consequently, given the higher number of black patients in the NA group, a multidrug approach using ACE inhibitors and beta blockers might have resulted in less effective BP control than in the other two geographical regions. Likewise, Hispanic patients in general appear to have hypertension of the low-renin type.[35, 36] Therefore, given that the highest ACE-inhibitor and beta-blocker use was in the CA group, one might expect poor BP control in the CA group (i.e., as with the NA group). However, medications such as calcium antagonists and diuretics usually have a greater effect upon low-renin hypertension. In our study, CA had a significantly higher proportion of patients on verapamil-SR and HCTZ, which may have accordingly produced a greater decrease in SBP.

The observed regional discrepancies in outcomes are more difficult to explain. The disparities in optimal management of hypertension probably account for a portion of the lower regional risk in CA and EA compared with NA. Given that BP at baseline was higher in patients in EA and CA, the greater reduction in mean SBP among CA and EA patients could produce a greater improvement in CV outcomes, as we observed. In addition, baseline characteristics reveal that NA may have been a higher-risk group at baseline, as NA patients were older, heavier, and had more diabetes than those in the other two regions, and were more likely to have multiple comorbid risk factors. Racial/ethnic differences, in part, may also account for the outcome differences. Furthermore, NA patients at baseline had a significantly lower percentage taking aspirin but a higher proportion taking hormone replacement therapy (HRT) and NSAIDs, a therapeutic milieu which could be associated with somewhat increased CV risk.[37–39] In addition, when looking at concomitant medical therapies as an index of quality of care, aspirin use significantly increased in CA and EA over time while remaining relatively constant in the NA group. In addition, lipid-lowering therapy use increased to a slightly greater extent in CA and EA compared with NA. Also, high NSAID use persisted in the NA group over 24 months of follow-up. These differences in use of nonstudy drugs may, in part, explain the regional variability in outcomes.

Based on this analysis, it appears that hypertension is globally undertreated. Furthermore, improved BP control is achievable with aggressive multidrug strategies that are either verapamil SR or atenolol based. In summary, CA and EA had better BP control and outcomes than NA in the setting of a large clinical trial. Thus, the previously recognized differences in regional or international care for patients with CAD may in

part be due to a disparity in access to healthcare providers or appropriate medications. When certain aspects of regional health care system or socioeconomic inequalities are minimized, as they were in INVEST (e.g., all medications were provided to patients free of charge during the study), patients outside of NA actually do better than NA patients with respect to both utilization of noncomplex standard care and reduction of CV morbidity and mortality.

Limitations

By analyzing data from a prospective, randomized controlled trial, we have circumvented many of the limitations inherent in clinical registries. However, several limitations of this analysis should be mentioned. Most notably, these data represent outcomes based on practice patterns and pretreatment characteristics of patients managed through INVEST participating sites and may not be representative of practice patterns and demographics for an entire region. As an extension, while we have gained insights into treatment choices by investigators in a particular geographical cluster, caution must be exercised in extrapolating these regional data. This is especially important given the heterogeneity in access to care even within a given region.[40] In addition, any grouping of regions for analysis can be seen as arbitrary in a sense. Population genetics studies indicate tremendous heterogeneity even within a particular geographic region.[41] As such, nonmodifiable, nonenvironmental predictors of antihypertensive response and outcomes (e.g., genetic variability) may by unevenly distributed within regions, leading to population stratification and confounding even within a seemingly homogeneous group. Finally, as this was not an epidemiologic study per se, our findings should be seen as offering additional information on possible factors that contribute to regional variability in treatment, treatment effects, and outcomes. The results should be interpreted against the backdrop of intrinsic limitations of retrospective and subgroup analyses. However, this does not diminish the significance of the results; namely, that differences in patient characteristics and secondary treatments should be taken into account when analyzing data from large, prospective trials. These differences might impact clinical practice and regional health policy.

Conclusion

Within INVEST, regional differences in medication utilization, BP control, and CV outcomes were identified. International disparities in the management of CV conditions represent a major public health concern. Our findings emphasize that differences in population characteristics, availability of drug therapy, pharmacologic treatment decisions, and intensity of patient follow-up may all contribute to this variability.

These disparities warrant further investigation and discussion of appropriate care for patients with hypertension and stable CAD from an international public health policy perspective. As data from clinical trials and registries continue to emerge, systematic adoption of evidence-based CV practices, considered in context of regional and international differences, should be implemented.

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