Factors Influencing Blood Pressure Response to *Trandolapril* Add-On Therapy in Patients Taking *Verapamil SR* (from the International *Verapamil SR/Trandolapril* [INVEST] Study)

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Factors such as age and race/ethnicity might influence blood pressure (BP) response to drugs. Therapeutic response to the angiotensin-converting enzyme inhibitor trandolapril used as add-on therapy to stable calcium channel blocker therapy with verapamil sustained release 240 mg was addressed in a racially/ethnically diverse group of 1,832 hypertensive patients with coronary artery disease. Furthermore, the association with a polymorphism (1166A→C) in the angiotensin II type 1 receptor gene (*AGTR1*) was tested. BP response was compared between groups using analysis of covariance after adjustment for covariates associated with BP response. Genotyping was performed using polymerase chain reaction and pyrosequencing. Trandolapril decreased mean unadjusted systolic and diastolic BPs by −9.1 ± 17.3 (SD) and −4.1 ± 10.1 mm Hg, respectively. The percentage of patients with BP under control (<140/90 mm Hg) increased from 6.7% to 41.3% ($p < 0.0001$). Adjusted BP response was significantly associated with age and baseline systolic and diastolic BP ($p < 0.0001$). Whereas the decrease in systolic BP was more pronounced in younger patients, the opposite was observed for diastolic BP decrease. Diastolic BP response was also significantly associated with race. Specifically, the adjusted diastolic BP decrease was significantly smaller in Hispanics and blacks than whites ($p = 0.0032$ and $p = 0.0069$, respectively). However, Hispanics achieved a decrease in systolic BP and an increase in BP control similar to the other ethnic groups. There was no genetic association between *AGTR1* 1166A→C genotype and BP response. In conclusion, trandolapril add-on therapy was effective in increasing BP control, with age and baseline BP associated with both systolic and diastolic BP response. Race was associated with diastolic BP response, although the difference is likely not to be clinically significant and *AGTR1* genotype was not associated with BP response. **(Am J Cardiol 2007;99:1549–1554)**

We assessed factors associated with the response to add-on therapy with the angiotensin-converting enzyme (ACE) inhibitor trandolapril, including race/ethnicity, angiotensin II type 1 receptor (*AGTR1*) genotype, age, and clinical factors in hypertensive patients with coronary artery disease. Patients were selected from the INternational VErapamil SR/Trandolapril STudy (INVEST), an ethnically diverse multicenter trial that included white and black patients with hypertension and 1 of the largest Hispanic patient populations reported.

Methods

The INVEST rationale, design, inclusion and exclusion criteria, treatment strategies, and main results were published in detail elsewhere. Briefly, after an extensive cardiovascular history and physical examination, patients were randomly assigned to either a verapamil sustained release (SR)–trandolapril– or atenolol-hydrochlorothiazide–based antihypertensive strategy. Patients were evaluated every 6 weeks for the first 6 months and then biannually for ≥2 years to assess blood pressure (BP) and adverse outcomes. The detailed BP measurement method was published previously.[1,2] The INVEST on-line data system provided detailed tracking of study medication prescriptions.[3] From 1997 to 2003, follow-up of 61,835 patient-years was accumulated, and each strategy provided excellent BP control (>70% of patients achieved BP <140/90 mm Hg) without differences in BPs between strategies. The strategies were

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Table 1
Patient baseline characteristics

	INVEST (n = 1,832)	INVEST GENES (n = 551)
Age, mean (yrs)	66.3 ± 10.0	65.8 ± 9.8
Women	975 (53.2%)	317 (57.5%)
Ethnicity		
White	792 (43.2%)	193 (35.0%)
Black	332 (18.1%)	80 (14.5%)
Hispanic	641 (35.0%)	242 (43.9%)
Other	67 (3.7%)	36 (6.5%)
Body mass index (kg/m^2)	29.6 ± 5.7	29.7 ± 5.8
Baseline Systolic BP (mm Hg)	150.5 ± 17.6	151.3 ± 17.4
Baseline diastolic BP (mm Hg)	86.7 ± 10.9	87.5 ± 10.3
Baseline heart rate (beats/min)	75.8 ± 9.5	75.1 ± 9.4
Myocardial infarction	542 (29.6%)	125 (22.7%)
Angina pectoris	1,225 (66.9%)	410 (74.4%)
Stroke/transient ischemic attack	110 (6.0%)	38 (6.9%)
Peripheral vascular disease	207 (11.3%)	56 (10.2%)
Smoker		
Past	790 (43.1%)	208 (37.8%)
With in last 30 d	235 (12.8%)	58 (10.5%)
Diabetes mellitus*	525 (28.6%)	159 (28.9%)
Hypercholesterolemia†	940 (51.3%)	278 (50.5%)
Aspirin or other antiplatelet drug	859 (46.9%)	228 (41.4%)
Other nonsteroidal anti-inflammatory drugs	315 (17.2%)	125 (22.7%)
Antidiabetic medication	448 (24.5%)	132 (24.0%)
Any lipid-lowering drug	685 (37.4%)	205 (37.2%)

INVEST-GENES patients represent a subgroup of INVEST patients who were genotyped for *AGTR1* 1166A→C. Data presented as number (percentage of population) or mean ± SD.

* History of diabetes or antidiabetic medication use.

† History of hypercholesterolemia or lipid-lowering medication use.

equally effective in preventing the composite primary outcome of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.[1]

Genetic samples were collected as part of the GENEtic Substudy of INVEST (INVEST-GENES) of 5,979 subjects from 184 sites in mainland United States and Puerto Rico to elucidate the contribution of genetic variants to interpatient and interdrug variations in response and outcome during antihypertensive drug therapy.[4] Both studies were approved by appropriate institutional review boards and, in the case of INVEST-GENES, by the University of Florida, which served as the central institutional review board for all participating sites in the genetic substudy. Written informed consent for participation in both the main INVEST and the genetic substudy was provided by each patient.

A total of 1,832 INVEST patients randomly assigned to the verapamil SR strategy who received monotherapy with verapamil SR 240 mg and had trandolapril (1, 2, or 4 mg) added to their treatment because of failing to meet BP goals were included in this analysis. Response to ACE-inhibitor addition was assessed by comparing BP readings from 2 visits, the first reading obtained at the visit that led to prescription of trandolapril and the second reading obtained at the next follow-up visit. In other words, BP change was assessed before and after the addition of trandolapril. Only patients with BP readings at these 2 visits were included in

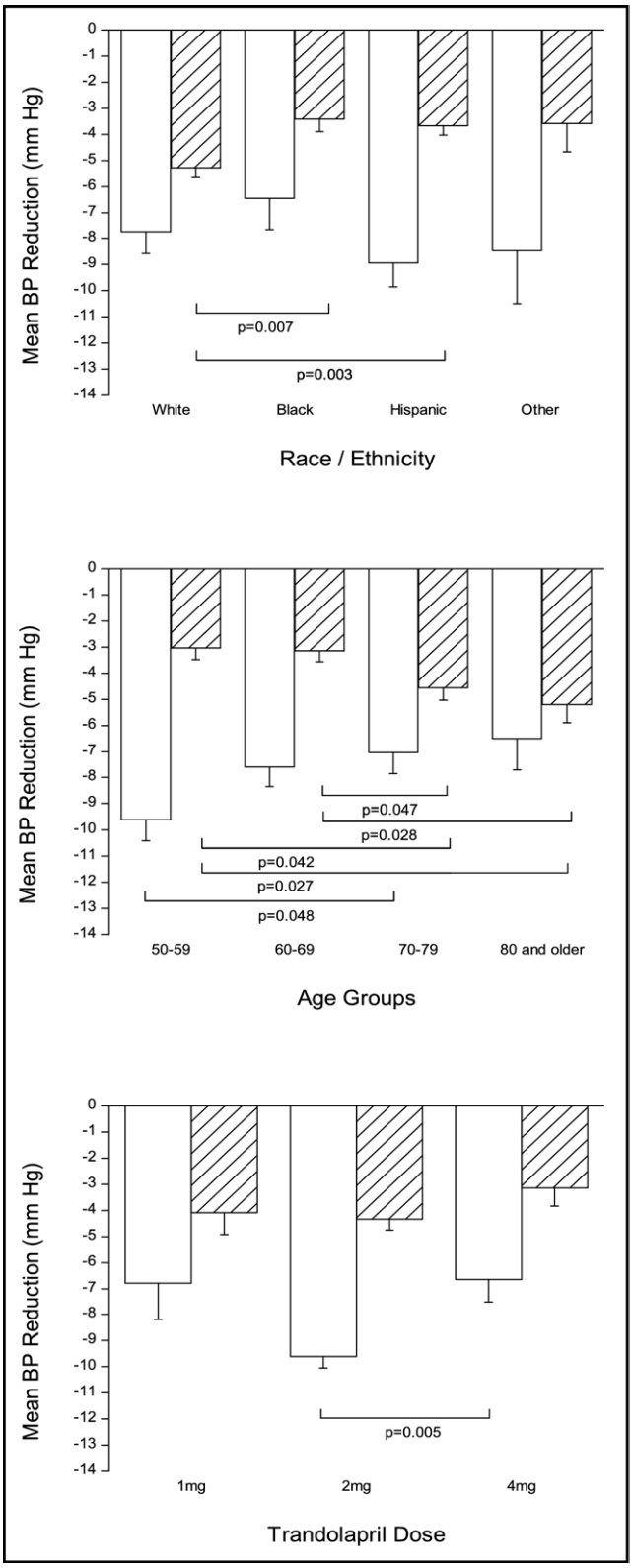

Figure 1. Systolic *(open bars)* and diastolic *(filled bars)* BP decreases (mm Hg) after the addition of trandolapril to verapamil SR 240 mg monotherapy according to race/ethnicity *(upper panel)*, age groups *(middle panel)*, and trandolapril dose *(lower panel)* and adjusted for systolic and diastolic BP before trandolapril addition and other covariates found to be associated with BP response (age, gender, race, trandolapril dose, diabetes mellitus, and body mass index). Results presented as mean ± SE.

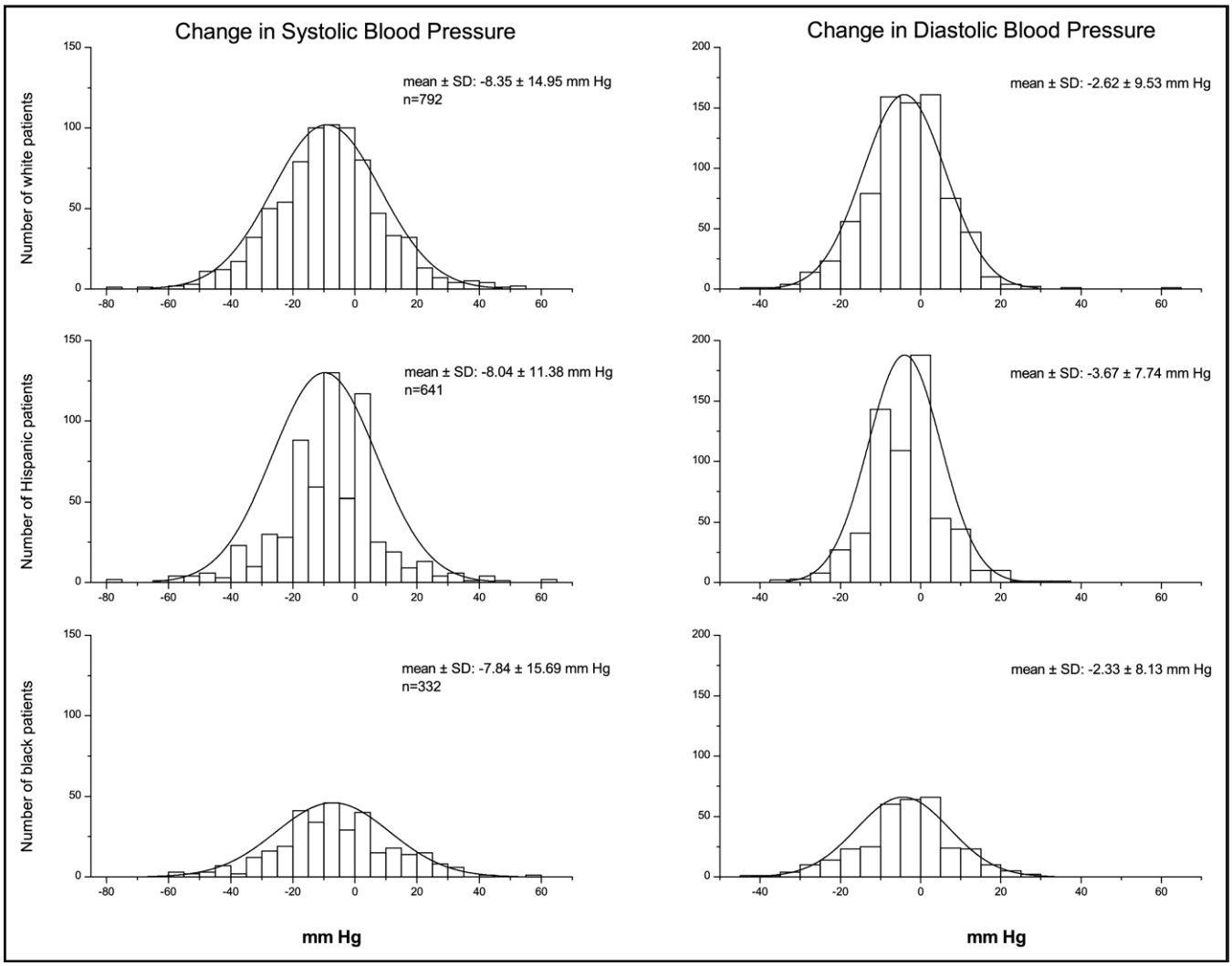

Figure 2. Ranges of systolic *(left column)* and diastolic BP *(right column)* responses after the addition of trandolapril to verapamil SR 240 mg monotherapy in whites *(upper row)*, Hispanics *(middle row)*, and blacks *(lower row)*. Histograms show changes in BP in equal-sized bins of 5 mm Hg for the respective number of patients. The superimposed curve shows the normal distribution of the data sets.

the final analysis. BP control is defined as achieving BP $<$140/90 mm Hg at the follow-up visit.

Determination of race/ethnicity was self-identified using patient report with interaction by the site investigator, choosing all that were applicable of the options on the INVEST data collection form of white, black, Hispanic, Asian, and "other." Patients of mixed race/ethnicity could choose $>$1 category. Hispanic was used as a race rather than ethnicity term. Due to comparably small sample sizes, Asians and the multiracial group were defined as other for analysis. Of these 1,832 INVEST patients, 551 also consented to participate in INVEST-GENES, provided genetic samples, and were subsequently genotyped for *AGTR1* 1166A$\rightarrow$C.

Genomic DNA was isolated from buccal genetic samples using commercially available kits (PureGene, Gentra Systems Inc, Minneapolis, Minnesota) and normalized to 20 ng/μl. Genotyping for the *AGTR1* 1166A$\rightarrow$C polymorphism was performed using polymerase chain reaction (PCR) followed by pyrosequencing (PSQ; Pyrosequencing, Uppsala, Sweden). Primers used for PCR reaction and PSQ were 5′-CCCCTCAGATAATGTAAGC-3′ (PCR forward), 5′-Bio-GTCGGTTCAGTCCACATAATG-3′ (PCR reverse), and sequencing primer 5′-ACTTCACTACCAAATGAGC-3′. The PCR mixture (12.50 μl) consisted of 6.25 μl of HotStarTaq Master Mix Kit (Qiagen Inc, Valencia, California), 1 μl of PCR primers (10 pmol/μl), 1 μl of dimethyl sulfoxide, 1.25 μl of water, and 40 ng of DNA. PCR was performed under the conditions of 95°C for 15 minutes; 40 cycles consisting of denaturation at 95°C for 30 seconds, annealing at 54°C for 30 seconds, and extension at 72°C for 30 seconds; and final extension for 7 minutes. PSQ was performed under standard conditions for sequence determination and allele designation in a Biotage PSQ HS 96 System (Biotage AB, Uppsala, Sweden), and data were captured using PSQ HS 96 SNP software.

Analysis of covariance was used to compare BP response to ACE inhibitor addition adjusting for systolic or diastolic BP before ACE inhibitor addition and covariates found to be associated with BP response using a stepwise selection

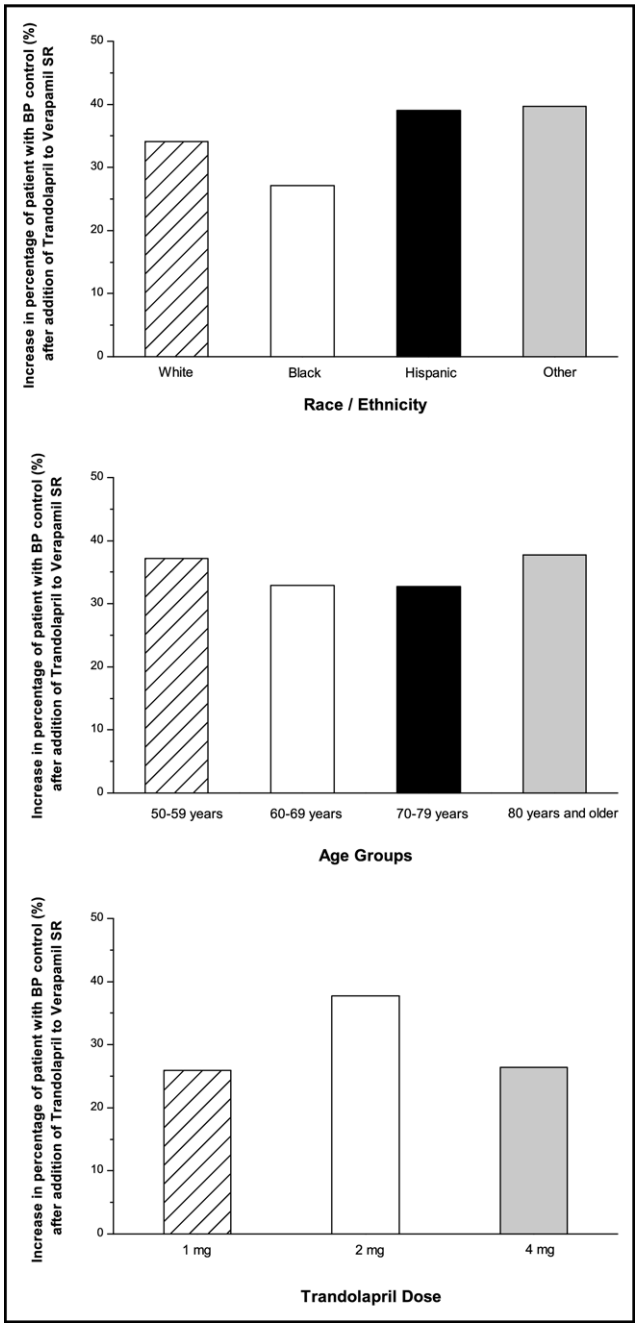

Figure 3. Increase in BP control (<140/90 mm Hg) after the addition of trandolapril to verapamil SR 240 mg monotherapy according to race/ethnicity *(upper panel)*, age groups *(middle panel)*, and trandolapril dose *(lower panel)*. Results given as percentage of the different subgroups.

method. Age was considered a continuous variable with 1 degree of freedom. For presentation purpose, patients were also categorized into four 10-year age groups. BP control before and after trandolapril treatment was compared using McNemar's test for matched pairs. The *t* test was used for continuous variables and chi-square test was used for categorical variables. A p value <0.05 was considered statistically significant. Hardy-Weinberg equilibrium was tested using chi-square test with 1 degree of freedom. Due to the small number of patients homozygous for the C allele, A/C and C/C genotypes were collapsed for further analysis.

Results

Detailed demographic and baseline characteristics for the main study population and subgroup of patients with genotype data are listed in Table 1.Separated according to decade, 544 patients were aged 50 to 59 years, 590 were 60 to 69 years, 502 were 70 to 79 years, and 196 were >80 years. Mean time from trandolapril addition to BP response assessment was 74.5 ± 89.1 days. Median duration of verapamil monotherapy before the addition of trandolapril was 51 days (interquartile range 42 to 97 days). Most whites (84.0%), Hispanics (90.5%), and others (88.1%) were treated with 2 mg of trandolapril, whereas in 85.2% of African-American patients, trandolapril was initiated at 4 mg, in addition to verapamil SR 240 mg/d, as suggested by the INVEST protocol.

ACE inhibitor addition decreased mean unadjusted systolic and diastolic BPs by −9.1 ± 17.3 and −4.1 ± 10.1 mm Hg to mean unadjusted systolic and diastolic BPs of 139.7 ± 17.5 and 80.1 ± 10.3 mm Hg, respectively. After adjusting for covariates and multiple comparisons, no statistically significant differences were observed for systolic BP decreases in different races/ethnicities, whereas diastolic BP decrease was significantly smaller in Hispanics and blacks than whites (Figure 1). The adjusted systolic BP decrease was significantly greater in younger patients (50 to 59 years) compared with those aged 70 to 79 years (Figure 1). It is of interest to note that the effect of age is in opposite directions for systolic and diastolic BP, with younger patients having better systolic BP response and older patients having better diastolic BP response. Figure 2 shows ranges of systolic and diastolic BP responses after trandolapril addition in the different racial/ethnic groups and that both ranges and average responses are similar by race/ethnicity. It also highlights the wide range of responses around the mean. Overall, trandolapril therapy significantly increased the percentage of patients with BP under control from 6.7% before trandolapril addition to 41.3% after add-on therapy ($p < 0.0001$). Figure 3 shows increases in percentages of patients with BP control according to race/ethnicity, age group, and trandolapril dose. There were no differences among these groups.

In the cohort with DNA samples provided, minor allele frequencies for *AGTR1* 1166A→C were 0.30 for whites, 0.06 for blacks, 0.24 for Hispanics, and 0.28 for others. Genotype frequencies did not deviate from Hardy-Weinberg equilibrium. Adjusted mean systolic/diastolic BPs after the addition of trandolapril to verapamil SR monotherapy were 142.6 ± 1.3/82.0 ± 0.7 mm Hg for A/A homozygotes and 140.6 ± 1.4/81.4 ± 0.8 mm Hg for C-allele carriers ($p = 0.17$ and $p = 0.48$). The corresponding adjusted mean systolic BP decreases for A/A and C/C genotypes were −5.9 ± 1.3 and −7.9 ± 1.5 mm Hg ($p = 0.17$). Adjusted mean diastolic BP decreases were −2.9 ± 0.7 and −3.4 ± 0.8 mm Hg, respectively ($p = 0.47$). After adjusting for covariates, *AGTR1* genotype was not significantly associated with either systolic or diastolic BP response ($p = 0.17$ and $p = 0.48$, respectively). In whites, the lowest adjusted

Table 2
Adjusted mean systolic and diastolic blood pressure (BP) and systolic and diastolic BP decreases after the addition of trandolapril to verapamil sustained release monotherapy in different races/ethnicities according to *AGTR1* 1166 A→C genotype (n = 551)

	Adjusted Systolic/Diastolic BP (mm Hg)		
	A/A	C Allele Carriers	p Value (systolic/diastolic BP)
White	139.9 ± 2.5/77.7 ± 1.4	141.0 ± 2.4/79.5 ± 1.4	0.63/0.12
Black	143.9 ± 6.3/82.8 ± 3.3	137.1 ± 7.8/80.1 ± 4.1	0.22/0.36
Hispanic	144.6 ± 2.7/85.3 ± 1.4	141.3 ± 3.0/83.9 ± 1.2	0.11/0.19
	Systolic/Diastolic BP Decrease (mm Hg)		
	A/A	C Allele Carriers	p Values (systolic/diastolic BP decrease)
White	−8.5 ± 2.5/−5.6 ± 1.4	−7.4 ± 2.4/−3.7 ± 1.4	0.63/0.16
Black	−7.0 ± 6.3/−3.1 ± 3.4	−13.9 ± 7.8/−6.3 ± 4.2	0.22/0.29
Hispanic	−3.3 ± 2.7/−0.5 ± 1.4	−6.6 ± 3.0/−1.9 ± 1.5	0.11/0.12

C Allele carriers were combined in 1 group. p Values were adjusted for multiple comparisons. Results presented as mean ± SE.

systolic and diastolic BP values after trandolapril addition were seen in patients homozygous for the A allele (Table 2). In blacks and Hispanics, the opposite was observed (Table 2). Due to the small number of others, this patient group is not reported in the final analysis.

Discussion

In the present study, we address the therapeutic response to an ACE inhibitor used as add-on therapy to a calcium channel blocker in a large ethnically diverse population. We show that diastolic BP response is modestly influenced by race/ethnicity and age, whereas race/ethnicity does not influence systolic BP response. *AGTR1* 1166 genotype also was not associated with BP response.

To our knowledge, these are the first data for the combination of trandolapril and verapamil SR in a Hispanic patient population with hypertension and coronary artery disease. These patients responded well to add-on therapy with 2 mg of trandolapril and achieved a decrease in systolic BP (Figures 1 and 2) and an increase in BP control (Figure 3) similar to those of other racial/ethnic groups when analysis was adjusted for confounding factors. However, compared with whites, trandolapril addition led to a statistically smaller diastolic BP decrease, although this difference could be argued to be of limited clinical significance given the small absolute difference and that diastolic BP tends to be easier to control than systolic BP. That the diastolic BP response difference in Hispanics is of limited clinical significance is also supported because Hispanics had the numerically highest increase in percentage of BP control with trandolapril addition (39.0%) versus increases of 34.1% in whites and 27.1% in blacks. In a recent publication, the Hispanic cohort of INVEST also yielded better BP control compared with the non-Hispanic cohort after 24 months of treatment with a mean of 2.4 drugs required to achieve BP control.[5] From the present analysis, one might conclude that a substantial proportion of BP control after 24 months can be attributed to trandolapril addition to verapamil SR, which justifies the administration of these drug classes in Hispanics. The Hispanic subpopulation of the present study was recruited from countries in North and Central America and the Caribbean, with a high percentage from Puerto Rico. Thus, our results may not be fully generalizable to Hispanics with other ancestry, which is emphasized by recent studies showing variable prevalences of hypertension among Hispanic patients from the United States, Mexico, and Europe.[6]

Although Hispanics have not been well represented in hypertension trials to date, there are many examples of differences between blacks and whites with respect to prevalence, pathophysiological characteristics, target-organ damage, and responses to hypertension treatment.[7,8] For black patients with hypertension, for example, a decreased therapeutic response to ACE inhibitor treatment was reported,[9] although more aggressive dosing compensated for the observed differences and led to similar BP decreases in blacks and whites.[10] The present study is in line with these findings, showing no significant differences in systolic BP decreases and BP control in blacks compared with the other races/ethnicities when trandolapril was added to verapamil. However, black patients received a higher trandolapril dose (4 mg) according to the INVEST protocol,[2] which increased the percentage of blacks with BP <140/90 mm Hg by approximately 30% (Figure 3). To further increase the percentage of patients with controlled BP, black patients are likely to require >2 drugs, shown in a previous subanalysis of INVEST that reported that 62.1% of black patients in the verapamil SR arm of the trial achieved BP control at 24 months, most of them with ≥3 antihypertensive drugs.[11]

Finally, to test whether genetic variants affect BP response to trandolapril addition, we assessed the contribution of the most frequently studied *AGTR1* single-nucleotide polymorphism (rs5186), which shows an adenine (A) to cytosine (C) transversion (1166A→C). This was based on studies reporting associations between 1166A→C genotype, hypertension, and/or cardiovascular disease,[12–15] although sometimes with conflicting results.[16,17] Compared with other genetic studies that usually concentrated on white and black subjects/patients, the present study additionally

provides genetic data for a comparatively large Hispanic population and shows that allele frequencies in Hispanics were similar to those reported for Caucasians, with the majority of patients homozygous for the wild-type A allele.[13] Although we failed to show an association between *AGTR1* 1166A→C genotype and BP response, there were suggestions that the magnitude of BP decrease was influenced by genotype and race (Table 2). These findings are consistent with previous studies reporting higher systolic[18] and diastolic BPs[19] in white patients with the C/C genotype, but higher BPs in black carriers of the A allele.[18] 1166A→C single-nucleotide polymorphism is located in an untranslated region of the *AGTR1* gene and might not be functional itself. The genotype-driven discordance of BP data in different populations suggests that 1166A→C might be in linkage disequilibrium with 1 or several mutations of functional importance, and the linkage disequilibrium might differ between whites, blacks, and Hispanics. Data from the International HapMap Project showed racial/ethnic differences in linkage disequilibrium structure for the *AGTR1* gene.[20] Furthermore, to overcome the limitations of candidate single-nucleotide polymorphism studies, race/ethnicity-specific linkage disequilibrium and haplotype patterns should be taken into account, for example, through a tag–single-nucleotide polymorphism approach.[21] Ultimately, approaches that consider multiple genes together in a statistical model will be needed to help understand the role of genetics on variable antihypertensive response.[22]

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