

Epidemiology and Management of Hypertension in the Hispanic Population

A Review of the Available Literature

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Abstract

Hispanics are the fastest growing ethnic minority in the USA. Among Hispanics, lack of hypertension awareness and lack of effective blood pressure (BP) control are problematic, as are higher incidence rates of hypertension-related co-morbidities compared with non-Hispanic populations. Moreover, there are currently no hypertension treatment guidelines that address the unique characteristics of this ethnic group. This article discusses ethnic differences in hypertension and cardiovascular risk factors and reviews the literature on the efficacy of antihypertensive agents in Hispanic patients, with a focus on the role of renin-angiotensin-aldosterone system (RAAS) inhibition in the management of hypertension in these patients. Hypertension in Hispanic patients can be challenging to manage, in part because this population has a higher prevalence of obesity, diabetes, and metabolic syndrome compared with non-Hispanic whites. The presence of these co-morbidities suggests that RAAS-inhibitor-based therapies may be particularly beneficial in this population. However, few studies have evaluated the efficacy of antihypertensive treatments in Hispanic patients. Two outcomes studies in hypertensive patients have shown the benefits of treating Hispanic patients with antihypertensive therapy and included RAAS inhibitors as part of the treatment regimen. In addition, BP-lowering trials have shown the antihypertensive efficacy of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and direct renin inhibitors, although data on the latter are more limited. Additional studies are needed to more thoroughly evaluate the effects of RAAS inhibitors (and other drug classes) on outcomes and BP lowering in the Hispanic hypertensive population.

1. Introduction

Hispanic Americans (i.e. individuals of Mexican, Cuban, Puerto Rican, Dominican, South American, or Central American descent, or descendants of other Spanish cultures or races) are the youngest and fastest growing ethnic minority in the USA. In 2006, Hispanics made up 15% of the US population, and this number is expected to grow to 24% by 2050.^[1] Studies have shown that Hispanic Americans have an increased cardiovascular risk compared with non-Hispanic Whites.^[2,3] Therefore, it is important for US healthcare providers to be aware of cardiovascular health characteristics that may be unique to this subset of the population. As this segment of the population continues to grow, the financial burden of managing cardiovascular disease will increase as well. Cardiovascular disease accounts for the single largest proportion of both direct and indirect US healthcare costs annually, with costs estimated at roughly \$300 billion in 2008 and rising rapidly.^[4] By 2030, these costs are projected to exceed \$800 billion annually.^[4]

Hypertension is the most common risk factor for cardiovascular disease, surpassing smoking, obesity, and diabetes mellitus, and is a significant predictor of premature death and cardiovascular disability.^[4] According to 2008 estimates, 18% of Hispanic adults ≥ 18 years of age have been diagnosed with hypertension compared with 27% of non-Hispanic Whites and 32% of non-Hispanic Blacks.^[5] However, in middle-aged and older adults (45–84 years), the crude incidence rate of hypertension per 1000 person-years was higher in Hispanics compared with non-Hispanic Whites (65.7 vs 56.8).^[6] Moreover, compared with non-Hispanics, Hispanics are less likely to be aware of their hypertension, and are less likely to have their blood pressure (BP) adequately controlled.^[2,7] Consequently, hypertension-related mortality rates have been increasing faster for certain Hispanic subgroups than for other ethnic groups. For example, between 1995 and 2002, hypertension-related mortality rates increased by 31% among Mexican Americans and by 46% among other Hispanic Americans (excluding Puerto Ricans and Cubans) compared with 27% among non-Hispanic Whites.^[8]

Unless steps are taken to increase the awareness of hypertension among Hispanics, this trend of increasing hypertension-related mortality is likely to continue. This appears to be the case particularly in younger individuals. Bersamin and colleagues,^[9] for example, observed that Mexican Americans between 25 and 34 years of age were less likely to be aware of their hypertension compared with Mexican Americans between 75 and 84 years of age (odds ratio, 5.5 [95% confidence interval (CI), 1.7, 17.5], $p < 0.001$).

There are abundant data regarding the treatment of hypertension in the general population and in the Black population, which have resulted in the development of evidence-based treatment guidelines for these groups.^[10,11] However, relatively few studies have evaluated Hispanic populations or have been adequately powered for *post hoc* analyses of Hispanic subsets, and no specific treatment guidelines exist for this demographic group.^[12] While it is clear that antihypertensive therapy to lower BP reduces cardiovascular morbidity and mortality in all hypertensive populations, it is unclear which antihypertensive medications are safest and most effective in Hispanics. In many cases, treatment with two or more different classes of antihypertensive medications is necessary, and very few data are available about which combinations are most beneficial in Hispanics.^[12]

This article discusses ethnic differences in BP and cardiovascular risk factors, reviews the literature on the efficacy of antihypertensive agents in Hispanic patients, and describes the role of renin-angiotensin-aldosterone system (RAAS) inhibitors, including direct renin inhibitors (DRIs), in the treatment of Hispanic patients with hypertension.

2. Ethnic Differences in Cardiovascular Disease Risk Factors, the Epidemiology of Cardiovascular Disease, and Lifestyle Factors

2.1 Cardiovascular Disease Risk Factors: Obesity, Diabetes, and Metabolic Syndrome

In addition to hypertension, there are high incidences of the cardiovascular disease risk factors of obesity, diabetes, and metabolic syndrome among Hispanics.^[4] Several studies have shown that, compared with non-Hispanic Whites, Hispanics have a higher prevalence of these conditions and they are more likely to be diagnosed at a younger age.^[2,3,7,13] This clustering of co-morbidities increases patients' overall risk of cardiovascular morbidity and mortality, and also complicates the management of hypertension. According to data from the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES), more than 50% of Mexican Americans with hypertension are obese or overweight and nearly 25% are both obese or overweight and diabetic.^[9] Future projections predict that over the next 10–20 years, the prevalence of obesity and diabetes in Hispanic Americans will increase at a faster rate than in non-Hispanic Whites,^[14] making it even more imperative that strategies are developed to effectively manage hypertension in these patients.

The prevalence of obesity, diabetes, and metabolic syndrome is particularly high among Hispanic women compared with their non-Hispanic counterparts.^[4,13] The American Heart

Association 2012 update on heart disease and stroke statistics reports that among Mexican-American women and non-Hispanic White women, respectively, the prevalence of diabetes is 17% versus 8%, the prevalence of metabolic syndrome is 41% versus 32%, and the proportion of women who are obese or overweight is 75% versus 59%.^[4] Given the high prevalence of these co-morbid conditions, it is not surprising that only 38% of Mexican-American women treated for hypertension achieve optimal BP control, and 27% of women continue to have uncontrolled stage 2 hypertension (i.e. systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg).^[9]

2.2 Epidemiology of Cardiovascular Disease

Several epidemiologic studies have shown that despite higher rates of obesity, diabetes, and metabolic syndrome, poorer socioeconomic status, and reduced access to health care, Hispanic ethnicity is associated with lower rates of all-cause and cardiovascular mortality compared with non-Hispanic White ethnicity.^[15-17] Explanations for this observation, which is often referred to as the ‘Hispanic Paradox,’ are somewhat controversial. Some have cited misclassification of ethnicity in trials and differential ascertainment of deaths by ethnicity as possible explanations.^[15,16,18,19] Others have proposed that health-selective and return immigration, positive health-related behaviors, better social support and culture-specific resiliency in Hispanic-American communities, and lower levels of subclinical cardiovascular disease contribute to these findings.^[20-24]

In contrast with the above, long-term findings from the San Antonio Heart Study refute the notion of a ‘Hispanic Paradox.’^[25] In this study, Mexican-American ($n = 1438$) and non-Hispanic White ($n = 921$) men and women between 45 and 64 years of age at enrollment were followed for up to 20 years to examine the relationship between ethnicity and mortality. After adjustment for age and sex, Mexican Americans had a 50% greater risk of all-cause mortality, a 60% greater risk of mortality because of coronary artery disease, and a 70% greater risk of cardiovascular mortality relative to non-Hispanic Whites. Further, even after adjusting for biomedical risk factors and socioeconomic status, these mortality hazard ratios remained above 1.^[25] When mortality data from the San Antonio Heart Study were analyzed in the subset of participants with diabetes, US-born Mexican Americans ($n = 554$) had 66% greater risks of both all-cause and cardiovascular mortality compared with US-born non-Hispanic Whites ($n = 178$).^[26] Diabetes and insulin use modified the mortality differential such that Mexican Americans with diabetes who did not require insulin therapy had the greatest mortality risks (figure 1).^[25]

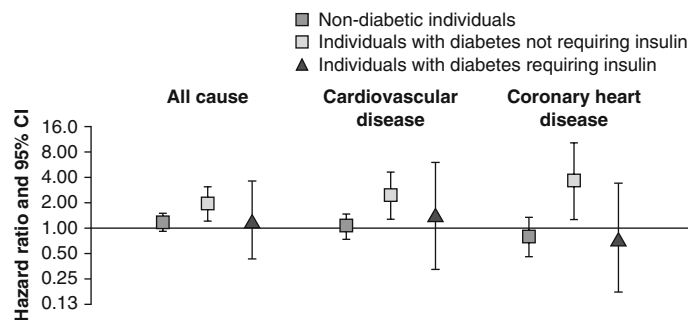


Fig. 1. San Antonio Heart Study: Cox hazard ratio models predicting all-cause, cardiovascular disease, and coronary heart disease mortality in a comparison of Mexican Americans with non-Hispanic Whites, stratified by diabetes mellitus/insulin use. Reprinted from Hunt et al.^[25] by permission of Oxford University Press.

Studies evaluating the prevalence of other cardiovascular and renal diseases based on ethnicity have found that Hispanics are more likely than non-Hispanic Whites to suffer from congestive heart failure^[3] and end-stage renal disease.^[27] Mexican-American men and women are also more likely to have higher low-density lipoprotein and triglyceride levels and lower high-density lipoprotein levels than non-Hispanic White men, and Mexican Americans are less likely to be aware of their hypercholesterolemia than their non-Hispanic White counterparts.^[4] Results of the Brain Attack Surveillance in Corpus Christi Project have also shown that stroke is more common in Mexican Americans than in non-Hispanic Whites.^[28]

2.3 Lifestyle Factors

In the general patient population, Hispanics tend to have poorer BP control than non-Hispanics;^[2,7] however, based on the results of controlled clinical trials, it is unlikely that the differences in BP control rates between Hispanics and non-Hispanics are a result of biologic differences. In controlled clinical trial settings, where external factors are equal and all patients have the same access to medical care and no-cost medication, it has been observed that BP control rates among Hispanics can be equal to or better than those of non-Hispanic Whites.^[29-31] Thus, in many cases, lifestyle, economic, and cultural factors likely contribute to Hispanic Americans’ overall level of risk for uncontrolled hypertension. Effective patient education strategies are necessary to increase awareness of risk factors associated with hypertension and to help patients learn to modify unhealthy behaviors.

As an example, according to NHANES data from 2001 to 2006, about one-third of Mexican Americans reported no participation in leisure-time physical activity.^[7] This rate was twice as high as that reported in non-Hispanic Whites and 15%

higher than that reported in non-Hispanic Blacks.^[7] Results from the Racial and Ethnic Approaches to Community Health Across the US 2009 risk factor survey^[32] showed that fruit and vegetable consumption was lower in Hispanic communities than in other ethnic minority communities throughout the USA, including non-Hispanic Black, Asian/Pacific Islander, and American Indian communities. In this study,^[32] Hispanics also had the lowest rates of cholesterol screenings and management of high BP with antihypertensive therapy.

Acculturation and language barriers may also negatively affect access to health care and treatment in Hispanic communities. In a study of 131 277 patients in Kaiser Permanente's Northern California Diabetes Registry, Traylor and colleagues^[33] found that Hispanic patients were less likely than non-Hispanic Whites to adhere to their cardiovascular medications (49% vs 58%; $p < 0.001$); equally, Spanish-speaking patients were less likely to adhere to their cardiovascular medications compared with English-speaking patients (51% vs 57%; $p < 0.001$). Eamranond and colleagues^[34] observed that Hispanics with low levels of acculturation to American language, values, beliefs, and ways of life have higher rates of diabetes and hypertension, and are more likely to have poorly controlled hypercholesterolemia.

Patient trust is higher when healthcare providers are of the same ethnicity as the patient and when physicians can communicate in the patient's native language.^[35] As of 2001, only 3.3% of internal medicine physicians and 3.8% of cardiologists in the USA were Hispanic,^[36] suggesting that most Hispanic Americans do not have access to physicians of the same ethnicity and may choose to rely on the advice of trusted family and friends instead of healthcare professionals. Hispanics have also been shown to have a strong sense of fatalism, believing that the course of their cardiovascular disease is out of their control and making them less motivated to adopt healthy lifestyle changes, seek medical care, or adhere to treatment.^[37] Physician access may also be limited by the cost of care, lack of health insurance, and limited access to regular health care.^[38] According to US Census Bureau data, in 2009, per capita income for Hispanics was approximately half that of non-Hispanic Whites (US\$15 063 vs US\$30 941, respectively), the poverty rate among Hispanics was 25.3%, and 32.4% of Hispanics did not have health insurance compared with 12.0% of non-Hispanic Whites.^[39]

3. Efficacy of Antihypertensive Agents in Hispanics: Review of the Literature

In landmark clinical trials of antihypertensive agents for the management of high BP and/or cardiovascular disease, patients of Hispanic ethnicity have been under-represented.^[12] Results

Table I. Full trial names of study acronyms used in this article

Acronym	Name
ACQUIRE	Aliskiren Alone or in Combination With Hydrochlorothiazide in Patients With Stage 2 Hypertension to Provide Quick Intensive Control of Blood Pressure
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ASCENT	Aliskiren+Amlodipine+HCTZ in Minority Patients With Stage 2 Hypertension
ATTAIN	Aliskiren/HCTZ vs Ramipril in Obese Patients with Stage 2 Hypertension
EVALUATE	Evaluation of Valsartan's Uniqueness and 24-Hour Blood Pressure Efficacy
INCLUSIVE	Irbesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations
INVEST	International Verapamil SR/Trandolapril Study
TRINITY	Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study
Val-MARC	Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in High-Sensitivity C-Reactive Protein

from the small number of antihypertensive trials that enrolled significant numbers of Hispanic patients are also limited because ethnicity and/or race were usually self-reported,^[40-42] which may have affected the uniformity of data capture, and in most cases no distinctions were made between Hispanic Whites and Hispanic Blacks.

In an effort to identify available data from randomized controlled trials that reported on the efficacy of antihypertensive agents in Hispanic patients, a search of PubMed was conducted for English-language articles classified as clinical trials or randomized controlled trials published through 26 August 2011 using the terms “(Hispanic* or Latino*) and hypertension.” This search yielded 148 articles. Analysis of these articles identified 17^[30,31,40-54] publications involving 15 different studies that specifically reported on the efficacy and safety of antihypertensive agents in Hispanic patients. Additional data from the INVEST study (table I provides full names of trial acronyms used in this article) was also included from a publication not identified in this search.^[29] In addition, the author was aware of and included relevant data from four studies that were presented as abstracts^[55-58] at scientific meetings. The main results from all identified articles ($n = 18$) and abstracts ($n = 4$) presenting data from 19 studies are summarized in table II.^[29-31,40-58]

Only two of the studies identified were outcomes trials that reported results for the subset of Hispanic participants:

Table II. Studies reporting on the efficacy of antihypertensive agents in the Hispanic population (PubMed findings)

Study reference	Design	No. of Hispanic patients	Daily treatment	Duration	Main findings in Hispanics at endpoint
Outcomes trials					
INVEST ^(29,31)	Randomized, open-label in hypertensive patients with coronary artery disease	8045 (14 531 non-Hispanics), including 5107 Hispanic women (4710 non-Hispanic white women)	Verapamil SR 240 mg or atenolol 50 mg; other drugs added if needed to achieve BP goal	2 years	<ul style="list-style-type: none"> At baseline, Hispanics had a higher prevalence of angina pectoris and diabetes vs non-Hispanics and a lower prevalence of MI, CABG/PCI, stroke/TIA, unstable angina, HF, and hypercholesterolemia Baseline BP: 148/87 mmHg in Hispanics and 151/86 mmHg in non-Hispanics In Hispanics vs non-Hispanics, either treatment strategy resulted in greater SBP reduction (-21.3 mmHg vs -17.4 mmHg; $p < 0.001$) and lower risk for experiencing the primary outcome of death, non-fatal MI, or non-fatal stroke (HR 0.87; 95% CI 0.78, 0.97); analysis in women showed similar findings Hispanic ethnicity was associated with an increased risk of new-onset diabetes (HR 1.19; 95% CI 1.04, 1.36), though treatment with trandolapril in the verapamil SR strategy reduced the risk
ALLHAT ⁽³⁰⁾	Randomized, double-blind in hypertension with ≥ 1 coronary heart disease risk factor	5239 Hispanic Whites and 1090 Hispanic Blacks (15705 non-Hispanic Whites and 10608 non-Hispanic Blacks)	Chlorthalidone 12.5–25 mg, amlodipine 2.5–10 mg, lisinopril 10–40 mg, or doxazosin 2–8 mg; other drugs added if needed to achieve BP goal	4 years	<ul style="list-style-type: none"> At baseline, Hispanics had more diabetes mellitus, less atherosclerotic disease, and were slightly younger than non-Hispanic Whites Baseline BP 144.5–146.7/81.8–87.1 mmHg across ethnic groups At baseline, Hispanics were less likely to have BP controlled (<140/90 mmHg), but by 6 months, BP control among Hispanics was similar to or higher than that of non-Hispanics At 4 years, BP goal (<140/90 mmHg) was achieved by 72% of Hispanic Whites, 69% of Hispanic Blacks, 67% of non-Hispanic Whites, and 59% of non-Hispanic Blacks
BP-lowering efficacy trials not involving RAAS inhibitors					
β-Blocker					
Punzi and colleagues ⁽⁴⁰⁾	Randomized, double-blind in stage 1 or 2 hypertension	277	Titration up to nebivolol 40 mg or placebo	8 weeks	<ul style="list-style-type: none"> Baseline BP: 155.8/100.3 mmHg for nebivolol and 156.5/100.6 mmHg for placebo BP was reduced by -14.1/-11.1 mmHg with nebivolol and -9.3/-7.3 mmHg with placebo ($p \leq 0.001$) AE rates were 17% with nebivolol and 22% with placebo
CCB					
Herrera and colleagues ⁽⁴³⁾	Randomized, double-blind in stage 1 or 2 hypertension	118	Titration up to diltiazem 300 mg or placebo	8 weeks	<ul style="list-style-type: none"> Baseline BP: 148.7/98.6 mmHg for diltiazem and 153.6/99.8 mmHg for placebo BP was reduced by -7.8/-8.2 mmHg with diltiazem and -0.1/-4.1 mmHg with placebo ($p < 0.01$) Treatment-related AE rates were 15% for diltiazem and 19% for placebo

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Table II. Contd

Study reference	Design	No. of Hispanic patients	Daily treatment	Duration	Main findings in Hispanics at endpoint
Prisant and colleagues ^[44]	Open-label (randomized dose) in stage 1 or 2 hypertension	101 (1700 Whites and 466 Blacks)	Titration up to verapamil 400 mg as chronotherapy	12 weeks	<ul style="list-style-type: none"> Baseline BP: 156.8/94.7 mmHg in Hispanics, 155.1/94.2 mm Hg in Whites, 154.1/96.6 mmHg in Blacks Target BP (<140/90 mm Hg) was achieved by 58% of Hispanics, 63% of Whites, and 60% of Blacks AE rates were similar across all ethnic groups; the most common AE was constipation (31%)
Black and colleagues ^[45]	Randomized, double-blind in stage 1 isolated hypertension	51 (84 Whites and 21 Blacks)	Felodipine ER 2.5–10 mg or placebo	1 year	<ul style="list-style-type: none"> Baseline BP: 149/83 mmHg for felodipine and 150/84 mmHg for placebo Overall, BP was reduced by –11.7/–3.0 mmHg with felodipine and by –2.0/–0.1 with placebo ($p < 0.01$) Subgroup analyses showed that significant BP reductions were achieved with felodipine vs placebo regardless of ethnicity
Fuenmayor and colleagues ^[46,47]	Randomized, open-label, 2-way crossover in mild to moderate uncomplicated hypertension	30	Verapamil IR or verapamil SR 240–480 mg	8 days per treatment	<ul style="list-style-type: none"> Baseline BP range: 153–160/108–110 mmHg across all treatment groups Maximum BP change was –34/–27 mmHg for both verapamil IR and verapamil SR 480 mg 73% of patients treated with verapamil SR 240 mg and 83% of patients treated with verapamil SR 480 mg achieved normotension Incidence of AEs was dose dependent; 73% of patients treated with verapamil 480 mg reported headache, palpitations, flushing, and/or tiredness
α_2-Agonist or α_1-antagonist					
Dias and colleagues ^[48]	Open-label in stage 1 or 2 hypertension	73 (280 Blacks)	Titrated up to clonidine 0.3 mg (transdermal patch)	12 weeks	<ul style="list-style-type: none"> Baseline BP: 158.5/99.5 mmHg BP was reduced by –16/13 mmHg in Hispanics and –15/12 mmHg in Blacks (numbers estimated from graph) Overall AE rate was 21%
Harris and Alvarez ^[49]	Randomized, double-blind in stage 1 or 2 hypertension	34 (44 total)	Titrated up to clonidine 0.3 mg (transdermal patch) or terazosin 5 mg (oral)	8 weeks	<ul style="list-style-type: none"> Baseline BP: 156.0/100.6 mmHg for clonidine and 154.0/100.3 for terazosin Overall, BP was reduced by –10.2/–11.6 mmHg with clonidine and by –7.1/–9.6 mmHg with terazosin ($p = \text{NS}$) Overall AE rates were 30% with clonidine and 48% with terazosin
BP-lowering efficacy trials involving RAAS inhibitors					
ACE inhibitor					
Weir and colleagues ^[50]	Salt-sensitive patients with stage 1–2 hypertension	63 (232 White and 96 Black)	Enalapril 10–40 mg, isradipine 10–20 mg or placebo; alternating high- and low-salt diet	20 weeks	<ul style="list-style-type: none"> BP difference between enalapril and placebo on high-salt diet: –11.4/–9.6 mmHg in Hispanics, –15.0/–10.9 mmHg for Whites, and –10.3/–8.6 mmHg for Blacks; on low-salt diets: –13.3/–7.5 mmHg for Hispanics, –12.7/–9.0 mmHg for Whites, and –7.7/–5.5 mmHg for Blacks

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Study reference	Design	No. of Hispanic patients	Daily treatment	Duration	Main findings in Hispanics at endpoint
ATTAIN ^[55] (abstract)	See results under DRI section below				<ul style="list-style-type: none"> BP difference between isradipine and placebo on high-salt diet: -13.7/-8.9 mmHg in Hispanics, -14.8/-9.4 mmHg for Whites, and -15.9/-12.1 mm Hg for Blacks; on low-salt diets: -10.0/-6.0 mmHg for Hispanics, -7.6/-4.2 mmHg for Whites, and -7.1/-5.9 mmHg for Blacks Controlling for salt sensitivity decreased ethnicity-related differences in antihypertensive efficacy of enalapril and isradipine
ARB					
TRINITY ^[56] (abstract)	Randomized, double-blind in stage 1 or 2 hypertension	369 (2122 non-Hispanic/non-Latino)	Olmesartan/amlodipine/HCTZ 40 mg/10/25 mg, olmesartan/amlodipine 40 mg/10 mg, olmesartan/HCTZ 40 mg/25 mg, or amlodipine/HCTZ 10 mg/25 mg	12 weeks	<ul style="list-style-type: none"> BP was reduced to a significantly greater extent ($p < 0.05$) in the triple-therapy group vs the dual-therapy groups (actual BP values/reductions not reported) 57% of Hispanic/Latino patients treated with triple therapy vs 41-51% with dual therapy achieved BP <140/90 mmHg (<130/80 mmHg if diabetic or with chronic renal or cardiovascular disease) AEs were comparable between treatment groups and mostly mild or moderate in severity (actual data not reported)
Ofili and colleagues ^[53]	Randomized, double-blind in systolic hypertension (predominantly stage 2)	165 (474 non-Hispanic Whites and 198 non-Hispanic Blacks)	Forced titration to amlodipine/valsartan/HCTZ 10 mg/320 mg/12.5 mg or 5 mg/160 mg/12.5 mg	12 weeks	<ul style="list-style-type: none"> BP was reduced from 162.0/92.5 mmHg at baseline to 138.1/81.4 mmHg at week 4 with amlodipine/valsartan 10/320 mg and from 164.2/91.1 mmHg to 144.8/82.7 mmHg with amlodipine/valsartan 5 mg/160 mg At week 8, 73% of Hispanics, 64% of Whites, and 56% of Blacks achieved BP <140/90 mmHg with amlodipine/valsartan/ HCTZ 10 mg/320 mg/12.5 mg 22.4% of Hispanic patients in the amlodipine/valsartan 10 mg/320 mg group and 23.5% in the 5 mg/160 mg group experienced AEs
INCLUSIVE ^[42,54]	Open-label in hypertensive patients uncontrolled on monotherapy	110 (454 Whites and 157 Blacks), including 72 Hispanic women (242 White women and 115 Black women)	Titration up to irbesartan 300 mg/HCTZ 25 mg	18 weeks	<ul style="list-style-type: none"> At baseline, Hispanics had a higher prevalence of diabetes and metabolic syndrome vs Blacks and Whites Baseline BP: 154.5/89.5 mmHg for Hispanics, 154.0/91.0 mmHg for Whites, and 155.9/93.6 mmHg for Blacks BP was reduced by -22.9/-10.6 mmHg in Hispanics, -21.5/-10.6 mmHg in Whites, and -20.7/-9.4 mmHg in Blacks ($p < 0.001$ vs baseline) AE rates were 48% in Hispanics, 57% in Whites, and 56% in Blacks Analysis in women showed similar findings

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Table II. Cont'd

Study reference	Design	No. of Hispanic patients	Daily treatment	Duration	Main findings in Hispanics at endpoint
Vai-MARC ^[51]	Randomized, open-label in stage 2 hypertension	109 (1129 Whites and 392 Blacks)	Forced titration to valsartan 320 mg/HCTZ 12.5 mg or valsartan 320 mg	6 weeks	<ul style="list-style-type: none"> • Baseline BP 165/100 mmHg for valsartan/HCTZ and 164/100 mm Hg for valsartan • In Hispanics, SBP was reduced by -21.7 mmHg with valsartan/HCTZ and -16.3 mmHg with valsartan (p = NS); -21.4 mmHg and -12.6 mmHg, respectively, in Blacks (p ≤ 0.01) • In Hispanics, AE rates were 37% with valsartan/HCTZ and 31% with valsartan; 45% and 43%, respectively, in Whites and 38% and 36%, respectively, in Blacks
EVALUATE ^[41]	Randomized, double-blind in stage 2 hypertension	86 (256 Whites and 79 blacks)	Forced titration to valsartan 320 mg/HCTZ 25 mg or amlodipine 10 mg/HCTZ 25 mg	10 weeks	<ul style="list-style-type: none"> • At baseline, Hispanics were younger and more likely to be obese and female vs Whites • Baseline ABP: 148/87 mmHg for Hispanics, 146/86 mmHg for Whites, and 148/90 mmHg for Blacks • In Hispanics, 24-hour ABP was reduced by -17.9/-9.7 mmHg with valsartan/HCTZ and -14.2/-7.2 mmHg with amlodipine/HCTZ (p = NS); -21.9/-12.7 mmHg and -17.6/-9.5 mm Hg, respectively, in Whites (p < 0.001) and -17.3/-10.6 mmHg and -17.9/-9.5 mmHg, respectively, in Blacks (p = NS) • In Hispanics, AE rates were 37% with valsartan/HCTZ and 33% with amlodipine/HCTZ; 43% and 45%, respectively, in Whites and 29% and 42%, respectively, in Blacks
Phillips and colleagues ^[52]	Randomized, double-blind in stage 1 or 2 hypertension	66 'other' of whom 82% were Hispanic (298 Whites and 64 Blacks)	Titrated up to amlodipine 10 mg or losartan 50 mg/HCTZ 12.5 mg	16 weeks	<ul style="list-style-type: none"> • Baseline BP: 153.4/100.3 mmHg for amlodipine and 154.5/99.7 mmHg for losartan/HCTZ • In the 'other' race/ethnic category (82% Hispanic), DBP response (≤90 mmHg) was achieved by 68% with amlodipine and 54% with losartan/HCTZ (p < 0.05); 63% and 41%, respectively, in Blacks (p < 0.05) • Overall AE rates were 58% with amlodipine and 55% with losartan/HCTZ
DRI ACQUIRE ^[57] (abstract)	Randomized, double-blind in stage 2 hypertension	230 (688 total)	Forced titration to aliskiren 300 mg/HCTZ 25 mg or aliskiren 300 mg	12 weeks	<ul style="list-style-type: none"> • Baseline BP: 167.1/94.1 mmHg for aliskiren/HCTZ and 167.0/93.6 mmHg for aliskiren • BP was reduced by -35.8/-15.8 mmHg with aliskiren/HCTZ and -23.4/-9.5 mmHg with aliskiren (p < 0.0001) • Safety not reported for Hispanics

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Table II. Cont'd

Study reference	Design	No. of Hispanic patients	Daily treatment	Duration	Main findings in Hispanics at endpoint
ATTAIN ^[55] (abstract)	Randomized, double-blind in obese patients with stage 2 hypertension	71 (380 total)	Forced titration to aliskiren 300 mg/HCTZ 25 mg or ramipril 10 mg	8 weeks	<ul style="list-style-type: none"> • Baseline BP: 169.7/92.8 mmHg for aliskiren/HCTZ and 168.2/96.6 mmHg for ramipril • BP was reduced by -27.7/-10.7 mmHg with aliskiren/HCTZ and -20.1/-4.9 mmHg with ramipril (p<0.004 for DBP) • BP goal (<140/90 mmHg) was achieved by 64.3% with aliskiren/HCTZ and 44.8% with ramipril (p=NS) • Between-group differences in SBP change and BP goal rates were significant for Whites and Blacks but not Hispanics • Safety not reported for Hispanics
ASCENT ^[58] (abstract)	Randomized, double-blind in minority patients with stage 2 hypertension	131 (411 total)	Forced titration to aliskiren 300 mg/amlodipine 10 mg/HCTZ 25 mg or aliskiren 300 mg/amlodipine 10 mg	8 weeks	<ul style="list-style-type: none"> • Baseline BP: 166.7/92.4 mmHg for triple therapy and 167.9/92.5 mmHg for dual therapy • BP was reduced by -37.1/-14.7 mmHg with triple therapy and -27.5/-11.0 mmHg with dual therapy (p<0.0001/p=0.0054) • Safety not reported for Hispanics

ABP = ambulatory BP; **ACE** = angiotensin-converting enzyme; **AE** = adverse event; **ARB** = angiotensin II receptor blocker; **BP** = blood pressure; **CABG** = coronary artery bypass graft; **CCB** = calcium-channel blocker; **CI** = confidence interval; **DBP** = diastolic BP; **DRI** = direct renin inhibitor; **ER** = extended release; **HCTZ** = hydrochlorothiazide; **HF** = heart failure; **HR** = hazard ratio; **IR** = immediate release; **MI** = myocardial infarction; **NS** = not significant; **PCI** = percutaneous coronary intervention; **RAAS** = renin-angiotensin-aldosterone system; **SBP** = systolic blood pressure; **SR** = slow release; **TIA** = transient ischemic attack.

ALLHAT^[30] and INVEST.^[29,31] Of these, only INVEST reported statistical comparisons of efficacy in the Hispanic cohort compared with the non-Hispanic cohorts.^[29,31] INVEST was an important trial because it provided evidence-based findings on the efficacy of antihypertensive agents in Hispanic patients compared with non-Hispanic patients. When hypertensive patients with coronary artery disease were treated with either calcium channel blocker (CCB)-based therapy (verapamil + trandolapril) or β -adrenoceptor antagonist (β -blocker)-based therapy (atenolol + diuretic), Hispanic patients achieved better BP control than non-Hispanic patients, and Hispanic patients had a significantly lower risk of experiencing adverse cardiovascular outcomes, including non-fatal myocardial infarction, non-fatal stroke, or death (figure 2). Addition of an angiotensin-converting enzyme (ACE) inhibitor to CCB therapy was associated with a decreased risk of new-onset diabetes in Hispanic patients, while increasing doses of β -blocker and diuretic therapy increased the risk of new-onset diabetes.^[29] Results of a separate analysis of women participating in the INVEST trial^[31] were similar to those of the overall study population.^[29] Hispanic women receiving antihypertensive therapy were more likely to achieve BP control compared with non-Hispanic White women (75% vs 68%, respectively; p<0.001), and Hispanic women were less likely to experience non-fatal myocardial infarction, non-fatal stroke, or all-cause death compared with non-Hispanic White women (5.7% vs 12.3%, respectively; adjusted hazard ratio, 0.84 [95% CI 0.71, 0.98]).^[31] The majority ($\geq 79\%$) of both Hispanic and non-Hispanic patients in the INVEST trial required multiple agents to achieve BP goals,^[29,31] and this finding is similar to what has been shown in other studies of populations with high levels of cardiovascular risk.^[59]

In the ALLHAT study, hypertensive patients with at least one other coronary heart disease risk factor were randomized to receive an ACE inhibitor, a CCB, an α_1 -blocker, or a thiazide diuretic, with step-up to combination therapy as necessary.^[30] In an analysis of the effects of Hispanic ethnicity on study results, Margolis and colleagues^[30] observed that Hispanic patients were less likely than non-Hispanics to have controlled BP (<140/90 mm Hg) at baseline, but within 6–12 months of follow-up, the proportion of Hispanic patients with controlled BP exceeded that of non-Hispanics. At 4 years of follow-up, BP was controlled in 72% of Hispanic Whites, 69% of Hispanic Blacks, 67% of non-Hispanic Whites, and 59% of non-Hispanic Blacks. Thus, the authors of this study concluded that Hispanic ethnicity was not associated with inferior BP control when patients had equal access to medications and health care at no cost.^[30]

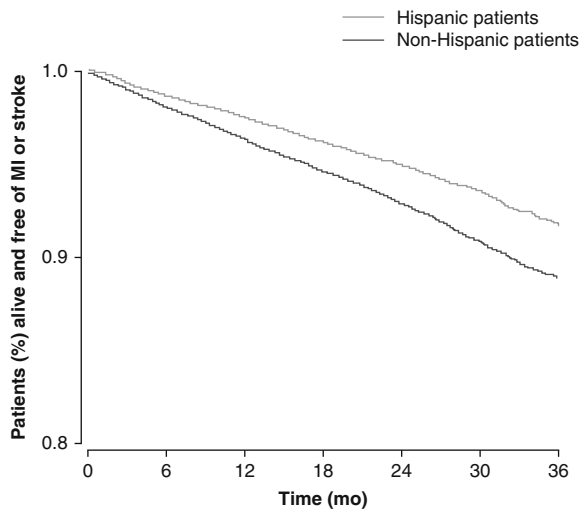


Fig. 2. INVEST (International Verapamil SR/Trandolapril Study): Kaplan-Meier survival curve of time to primary outcome event (composite of death, non-fatal myocardial infarction, or non-fatal stroke) by Hispanic status. Reprinted from Cooper-DeHoff et al.^[29], with permission from Elsevier. **MI** = myocardial infarction.

Results from non-cardiovascular outcomes, BP-lowering efficacy trials identified from the search are also summarized in table II.^[40-58] In general, all of the different classes of antihypertensive drugs substantially reduced BP in Hispanic patients, and greater BP reductions were observed with combination therapy than with monotherapy. In most cases, a RAAS inhibitor (ACE inhibitor, angiotensin II receptor blocker [ARB], or DRI) was used, either alone or in combination with another antihypertensive agent.

3.1 Benefits of Renin-Angiotensin-Aldosterone System Inhibitor Therapy

RAAS inhibitors may be more beneficial than other classes of antihypertensive therapy in reducing complications related to obesity, diabetes, and metabolic syndrome, which as discussed previously are significant concerns for many Hispanic patients.^[60] Over-activation of the RAAS results in increased vasoconstriction, increased sodium reabsorption, and increased aldosterone secretion, all of which elevate BP. In addition, increased RAAS activity can contribute to the pathophysiology of diabetes and metabolic syndrome. Increased aldosterone production has been shown to impair insulin signaling and increase insulin resistance, and angiotensin II-mediated oxidative stress can damage pancreatic islet cells.^[60,61] Excess food intake

has also been linked to increased angiotensin II formation in adipocytes, and body mass index is positively correlated with plasma aldosterone and plasma renin activity levels, suggesting a pathophysiologic association between RAAS activation and obesity.^[60] Therefore, in addition to lowering BP, antihypertensive therapy with RAAS inhibitors may also improve glucose metabolism and delay or prevent the onset of diabetes.^[60,61] RAAS inhibitors have also been shown to reduce tissue injury and microvascular damage in patients with hypertension and hyperglycemia.^[62] For these reasons, RAAS inhibitors are an appropriate component of first-line therapy in hypertensive patients at risk for obesity, diabetes, and/or metabolic syndrome.^[60]

3.1.1 Angiotensin-Converting Enzyme (ACE) Inhibitors

Data from randomized controlled trials reporting on the BP-lowering efficacy of ACE inhibitors in Hispanic patients are very limited. In a study examining the effects of dietary salt intake on the efficacy of the ACE inhibitor enalapril or the CCB isradipine, when Hispanic patients consumed more than 190 mmol of sodium per day, treatment with enalapril reduced BP by $-11.4/-9.6$ mmHg and treatment with isradipine reduced BP by $-13.7/-8.9$ mmHg compared with placebo. When Hispanic patients consumed 88 mmol or less of sodium per day, treatment with enalapril reduced BP by $-13.3/-7.5$ mmHg and treatment with isradipine reduced BP by $-10.0/-6.0$ mmHg compared with placebo.^[50]

Although the ALLHAT trial included the ACE inhibitor lisinopril as one of four assigned treatments,^[30] analysis of the efficacy of the different classes of drugs (i.e. ACE inhibitor, CCB, α_1 -blocker, or a thiazide diuretic) in Hispanic patients has not been reported. In the ATAIN trial,^[63] (discussed further in the DRI section below), treatment with the ACE inhibitor ramipril reduced mean sitting BP by $-20.1/-4.9$ mmHg in Hispanic patients ($n = 29$), and 44.8% of these patients achieved BP control.^[55] Further studies are necessary to adequately evaluate the efficacy of ACE inhibitor monotherapy or combination therapy in Hispanic patients.

3.1.2 Angiotensin II Receptor Blockers (ARBs)

Several studies were identified that reported the efficacy of ARB monotherapy or combination therapy in Hispanic patients. These studies indicate that substantial proportions of Hispanic patients treated with ARBs as part of their treatment regimen can achieve BP goals. The largest, TRINITY (NCT00654745; complete results posted on ClinicalTrials.gov),^[64] included a prespecified subgroup analysis of 369 Hispanic/Latino and 2122 non-Hispanic/non-Latino hypertensive patients that has

been published in abstract form.^[56] Regardless of ethnicity, triple therapy with olmesartan/amlodipine/hydrochlorothiazide (HCTZ) resulted in significantly ($p < 0.05$) greater reductions in systolic BP relative to dual therapy with olmesartan/amlodipine, olmesartan/HCTZ, or amlodipine/HCTZ.^[56,64] At 12 weeks, 57% of Hispanic/Latino participants in the triple-therapy group versus 41–51% in the dual-therapy groups achieved BP goals ($<140/90$ mmHg or $<130/80$ mmHg for those with diabetes or chronic renal or cardiovascular disease). In non-Hispanics/non-Latinos, the corresponding results were 66% versus 34–47%.^[56] In the INCLUSIVE trial, after 18 weeks of treatment with irbesartan/HCTZ, 70% of non-Hispanic Whites, 66% of non-Hispanic Blacks, and 65% of Hispanics achieved BP goals.^[42] The Val-MARC study comparing valsartan versus valsartan/HCTZ found that in Hispanic patients with stage 2 hypertension, combination therapy lowered systolic BP by -21.7 mmHg, compared with -16.3 mmHg with monotherapy.^[51] Similarly, the EVALUATE trial showed that combination therapy with either valsartan/HCTZ or amlodipine/HCTZ effectively lowered BP in Hispanic patients with stage 2 hypertension (reductions of $-17.9/-9.7$ mmHg and $-14.2/-7.2$ mmHg, respectively).^[41] In a study evaluating triple therapy with amlodipine/valsartan/HCTZ 10/320/12.5 mg in Hispanic patients, 8 weeks of treatment reduced mean systolic BP by -36.7 mmHg in Hispanic patients and 73% of patients achieved target BP $<140/90$ mmHg.^[53]

3.1.3 Direct Renin Inhibitors (DRIs)

The only DRI currently approved for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents, is aliskiren. In clinical studies, aliskiren monotherapy and combination therapy with other agents (e.g. diuretics or amlodipine) have all been shown to significantly reduce BP and plasma renin activity in patients with stage 1 or stage 2 hypertension.^[63,65-67] There are currently no cardiovascular outcomes data available on the use of aliskiren in Hispanic patients, and BP-lowering data are limited to subgroup analyses from clinical trials. Three subgroup analyses^[55,57,58] on the BP-lowering efficacy of aliskiren monotherapy or combination therapy with HCTZ in Hispanics were reported in the form of abstracts. In the 12-week ACQUIRE study (NCT00705575; complete results posted on ClinicalTrials.gov),^[66] Hispanic patients had mean BP reductions of $-35.8/-15.8$ mmHg with aliskiren/HCTZ and $-23.4/-9.5$ mmHg with aliskiren monotherapy.^[57] In the ATTAIN study (NCT00772577; complete results posted on ClinicalTrials.gov),^[55,63] 8 weeks of treatment with aliskiren/HCTZ reduced BP by $-27.7/-10.7$ mmHg in Hispanic patients, compared with $-20.1/-4.9$ mmHg with ramipril monotherapy ($p < 0.004$ between treatment groups for

change in diastolic BP).^[55] In the 8-week ASCENT study (NCT00942994; complete results posted on ClinicalTrials.gov),^[67] self-identified Hispanic patients had least-square mean systolic BP reductions of -37.1 mmHg with aliskiren/amlodipine/HCTZ versus -27.5 mmHg with aliskiren/amlodipine ($p < 0.0001$).^[58] Corresponding results for diastolic BP were -14.7 mmHg versus -11.0 mmHg ($p = 0.0054$).^[58]

4. Considerations for Treating the Hypertensive Hispanic Patient

For most patients, regardless of ethnicity, multiple antihypertensive agents are needed to attain BP goal.^[59] For example, current guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure^[10] state that two or more antihypertensive medications are usually required to achieve BP goals in patients with diabetes and chronic kidney disease, and for patients whose BP is more than 20 mmHg above the systolic BP goal or more than 10 mmHg above the diastolic BP goal. For these patients, current guidelines recommend initiation of therapy with two agents, one of which is usually a thiazide diuretic. The choice of a thiazide diuretic as part of an initial treatment regimen is based on the well established observations that drugs in this class are generally well tolerated, can prevent cardiovascular complications associated with hypertension, and are usually cost effective.^[10]

The combination of a diuretic with a RAAS inhibitor is often recommended as first-line therapy in patients with stage 2 hypertension, given that the RAAS is the central mediator of the majority of hypertension-related complications and that the RAAS is activated in response to pressure-related target-organ damage.^[10,11] Compelling indications for RAAS-inhibitor-based combination treatment regimens in the general population include co-morbid cardiovascular disease, diabetes, chronic kidney disease, stroke prevention, heart failure, and coronary artery disease risk.^[10] Although data evaluating the efficacy of RAAS-inhibitor-based therapy in Hispanics are limited, the high prevalence of obesity, diabetes, and metabolic syndrome in this population provides rationale for the use of this class of antihypertensive drugs.

When treating hypertension in the Hispanic patient, physicians should be aware of the typical cardiovascular clustering that is common in this ethnic group and the treatment challenges that this creates. Results from the INVEST study suggest that combination therapy is necessary for the majority of hypertensive Hispanic patients with coronary artery disease to achieve target BP goals and that achieving these BP goals is

associated with significantly lower risks of adverse cardiovascular events.^[29]

5. Summary and Conclusions

Hypertension control and hypertension-related co-morbidities are substantial problems in the US Hispanic population. Given that Hispanics are the fastest growing and youngest ethnic population in the USA, strategies to prevent hypertension-related morbidity and mortality are essential, including hypertension education programs and attention to economic issues when prescribing to this demographic group. Aggressive anti-hypertensive strategies are needed; however, not enough has been done to include Hispanic Americans in clinical studies in sufficient representative numbers. Therefore, very little evidence-based information is available in this population, and current guidelines do not provide specific guidance for treating hypertension in Hispanic patients. Given the clustering of hypertension with obesity, diabetes, and metabolic syndrome in Hispanics and the role of the RAAS in the pathogenesis of these conditions, RAAS-based treatments should be a cornerstone of therapy. Studies that included subgroup analyses of Hispanic patients have shown that treatment with RAAS inhibitors in combination with other antihypertensive agents is associated with substantial BP lowering; however, more data are needed to determine whether RAAS-based treatment regimens improve cardiovascular outcomes in this growing patient population.

Acknowledgments

Technical assistance with editing, figure preparation, and styling of the manuscript for submission was provided by Cherie Koch, PhD, and Michael S. McNamara, MS, of Oxford PharmaGenesis Inc., and was funded by Novartis Pharmaceuticals Corporation. The author was fully responsible for all content and editorial decisions and received no financial support or other form of compensation related to the development of this manuscript. The opinions expressed in the manuscript are those of the author, and Novartis Pharmaceuticals Corporation had no influence on the contents.

Author disclosure: Dr Guzman has served as a Consultant and faculty member for Novartis Pharmaceuticals Corporation.

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