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REGIONAL AND PHYSICIAN SPECIALTY-ASSOCIATED VARIATIONS IN THE MEDICAL MANAGEMENT OF ATHEROSCLEROTIC RENAL-ARTERY STENOSIS

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Abstract

For people enrolled in CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), we sought to examine whether variation exists in the baseline medical therapy of different geographic regions and if any variations in prescribing patterns were associated with physician specialty. Patients were grouped by location within the United States (US) and outside the US (OUS), which includes Canada, South America, Europe, South Africa, New Zealand, and Australia. When comparing US to OUS, participants in the US took fewer anti-hypertensive medications (1.9 ± 1.5 vs. 2.4 ± 1.4 , $p < 0.001$) and were less likely to be treated with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (46% vs. 62%, $p < 0.001$), calcium channel antagonist (37% vs. 58%, $p < 0.001$), and statin (64% vs. 75%, $p < 0.05$). In CORAL, the identification of

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Conflict of Interest/Disclosure Statement

None

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variations in baseline medical therapy suggests that substantial opportunities exist to improve the medical management of patients with atherosclerotic renal-artery stenosis.

Keywords

renal-artery stenosis; renovascular hypertension; antihypertensive medical therapy; geography; physician specialty

Introduction

Atherosclerotic renal-artery stenosis (RAS) is associated with secondary hypertension and cardiac morbidity and mortality worldwide (1,2). A lack of consensus exists regarding optimal treatment strategies for individuals with atherosclerotic RAS. However, the recently completed Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial found that stent revascularization conferred no further benefit to patient outcome in the setting of comprehensive, multifactorial medical therapy for patients with atherosclerotic RAS and either hypertension or chronic kidney disease (3). Thus, for the majority of these individuals, medical therapy is the preferred management strategy. While medical therapy remains an important foundation in the treatment of atherosclerotic RAS (4), the optimal anti-hypertensive regimen for patient management remains inconclusive. Limited work in this area suggests that renin-angiotensin inhibitors and HMG-CoA reductase inhibitors (statins) may be beneficial (5,6). Angiotensin blockade may reduce mortality in people with RAS (2,7–9), and observational studies have suggested that statin-treated individuals experience a lower rate of RAS progression (10) and improved prognosis (11). However, these data are derived mostly from retrospective observations.

Little is known specifically about the community use of anti-hypertensive, anti-platelet, and lipid-lowering medications in individuals with atherosclerotic RAS. In particular, questions remain regarding regional and worldwide trends in medication use and how physician specialty influences the medical management of this population.

Geographic region has been shown to influence clinical practice in the treatment of hypertension, with both inter-continental and intra-continental variations reported (12–20). Variations in non-clinical factors such as region and physician subspecialty may reflect potential barriers to the uniform adoption of recommended clinical guidelines (21). How exactly these trends apply to the more specific group of people with atherosclerotic RAS, a population with multiple co-morbidities, complex clinical scenarios, and clear indications to treat with certain medications, is unknown. Baseline demographic and medication data from the CORAL trial, a prospective, international, multi-center randomized clinical trial, was used to address these concerns. The CORAL trial enrolled participants with atherosclerotic RAS at sites throughout the United States, North and South America, Europe, South Africa, New Zealand, and Australia. Among the patients enrolled in the CORAL trial, we sought to determine whether variation exists in the use of medical therapy categories between regions and whether this variation was driven by participant characteristics or prescribing physician subspecialty. Specifically, in the current study we sought to determine if the type and number of baseline medications varied among (1) different regions from which the clinical

centers enrolled patients into the trial and (2) specialties of the physicians responsible for overseeing patient care in the trial.

Methods

The CORAL study was a prospective, international, multi-center, non-blinded, two-arm, randomized trial for which the study design, rationale, and methods have been previously reported (22). In people with hemodynamically significant atherosclerotic RAS who also received optimal medical therapy, the study assessed the effect of revascularization, accomplished through endovascular stenting, on cardiovascular and renal events (ClinicalTrials.gov identifier NCT00081731). All of the centers obtained institutional review committee approval and followed institutional guidelines. Participants provided written informed consent to join the study. The CORAL trial was undertaken in accordance with the Declaration of Helsinki.

Medication Information

Baseline medication data analyzed in the current study were obtained from the medication logs of the 931 participants randomized into the CORAL trial. The medications were categorized into 12 drug classes: 9 classes of anti-hypertensive agents and 3 separate, additional drug classes that included anti-platelets, lipid-lowering therapies, and nitrates. The anti-hypertensive category consisted of the following 9 medication classes: alpha beta blocker, vasodilator, alpha blocker, diuretic, aldosterone antagonist, beta blocker, ACEI or ARB, calcium channel blocker, and renin inhibitor. The number of patients on the renin inhibitor class was too few for appropriate analysis; its data was therefore excluded from presentation. Patients taking one or more medication(s) within a class were identified and counted as being on that class of medication. Medication use at baseline was recorded and classified (yes, no, or unknown). Unknown was designated if the start and stop dates could not be ascertained.

Kidney Function Measurement

Kidney function was assessed using serum creatinine (mg/dL), creatinine-based estimated glomerular filtration rate (mL/min/1.73m²) calculated using the modified diet in renal disease standard (MDRD-eGFR), and cystatin-C (mg/L). All measurements were centrally analyzed by the Biochemistry Core Lab at the University of Minnesota.

Blood Pressure Measurement and Goal

Blood pressure was measured at the baseline study visit. Participants were seated for 5 minutes in a quiet room and blood pressure was measured in triplicate separated by two-minute intervals with an automated, oscillometric manometer provided to the sites by the CORAL study. The mean of the last 2 measurements was taken as the baseline blood pressure. The goal for blood pressure control was based on the current clinical practice guidelines at the time the CORAL study was planned and conducted: <130/80 mmHg for those with diabetes and/or chronic kidney disease (CKD), or 140/90 mmHg if those conditions were not present (23–25).

Physician Specialty Determination

Study site principal investigator (PI) specialty was protocol-defined as hypertensionologist (HTN), interventional cardiologist (IC), interventional radiologist (IR), or vascular surgeon (VS). Each site also had a PI responsible for hypertension control (HTN PI) that was protocol-defined as either a cardiologist, nephrologist, or internal medicine-trained hypertension specialist.

Statistical Analysis

Continuous data are presented as mean $\pm$ SD and categorical data are presented as counts or percentages. All analyses were performed using R (version 3.0.0) and SAS (version 9.3). Statistical significance was defined as a p-value <0.05 . For continuous variables, univariate analyses were performed using Pearson correlation, two-sample t-tests, or ANOVA for more than 2 groups. Chi-square with Fisher's exact test for independence and/or Mantel-Haensel-Cochran test for odds ratio (OR) were calculated for categorical variables. The Shapiro-Wilk test was used to test for normal distribution of continuous data, and nonparametric analysis using two-group Mann-Whitney U rank test or Kruskal-Wallis test for more than 2 groups was employed if the assumption of normality was violated.

Sites were grouped by location within the United States (US) and outside the US (OUS). Additionally, three continent groups were established by combining countries as follows: Canada and the United States, North America (NA); Europe, Australia and New Zealand, Eurasia; and South America and South Africa (SA/SA). North America and Eurasia have been previously categorized in this manner (20); South America and South Africa were grouped together due to economic and health care system similarities, as well as latitude. Sites in the US were grouped according to the four federal census regions: the Midwest, Northeast, South, and West. Regional variations within the US as well as between the continent groups were examined.

The specialty affiliation of the site's principal investigator and geographic groups were examined with univariate logistic regression using pre-specified adjustment that controlled for age, gender, race and ethnicity. Significant variables ($p<0.05$) from the univariate analysis, along with the pre-specified covariates, were included in multiple variable analyses with stepwise logistic and linear regression.

Results

Baseline characteristics of clinical participants: US vs. OUS

At baseline, participants enrolled at clinical centers in the US ($n=772$) were heavier than those from OUS ($n=159$) (178 ± 37 vs. 163 ± 31 lbs., $p<0.001$) and had lower diastolic blood pressure (DBP) (78 ± 13 vs. 82 ± 13 mmHg, $p<0.001$) (Table 1). Baseline systolic blood pressure (SBP) for US participants was lower than that of OUS participants, but did not reach statistical significance (150 ± 23 vs. 152 ± 24 mmHg, $p=0.178$). People from the US were more likely to have a family history of premature atherosclerosis (39% vs. 29%, $p<0.05$), peripheral vascular disease (53% vs. 41%, $p<0.05$), and CKD as determined by MDRD-eGFR (64% vs. 55%, $p<0.05$) (Table 1). Location within or outside of the US was

not associated with any differences in core lab-determined stenosis severity, measured as percent stenosis, or the presence of bilateral renal-artery stenosis.

US participants took fewer anti-hypertensive medications (1.9 ± 1.5 vs. 2.4 ± 1.4 , $p < 0.001$) and were less likely to be treated with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) (46% vs. 62%, $p < 0.001$), calcium channel antagonist (37% vs. 58%, $p < 0.001$), and statin (64% vs. 75%, $p < 0.05$) (Table 1, Figure 1). Multivariate analysis adjusting for age, gender, race, and ethnicity determined that US location, when contrasted against OUS location, was independently and negatively associated with the number of anti-hypertensive medications utilized (slope estimate: -0.48 , $p < 0.001$) (Table 3a). Renal function was not predictive of the intensity of anti-hypertensive therapy.

Baseline characteristics of participants: 4 census regions of the US

Participants in the South ($n=283$, 37%) and West ($n=107$, 14%) had better renal function compared to those from the Midwest ($n=235$, 30%) and Northeast ($n=147$, 19%) as assessed by serum creatinine (1.18 ± 0.4 and 1.23 ± 0.4 vs. 1.30 ± 0.5 and 1.32 ± 0.5 mg/dL, respectively, $p=0.01$), cystatin-C (1.24 ± 0.4 and 1.25 ± 0.4 vs. 1.35 ± 0.5 and 1.38 ± 0.5 mg/L, $p=0.01$) and MDRD-eGFR (65 ± 24 and 63 ± 23 vs. 59 ± 23 and 58 ± 26 mL/min/1.73m², $p < 0.05$), and had a lower incidence of CKD (56% and 63% vs. 68% and 70%, $p < 0.05$) (Table 2). While location within the four regions of the US was not associated with any difference in core lab-determined percent stenosis, there was variability in the presence of bilateral renal-artery stenosis among the different regions (19%, 21%, 30% and 26%, $p=0.044$) (Table 2).

Significant heterogeneity was observed in medication use between the 4 census regions of the US (Figure 2). Individuals in the South were less likely than those in the Midwest, Northeast and West to take a calcium channel antagonist (27% vs. 39%, 53% and 41%, respectively, $p < 0.001$) and statin (58% vs. 60%, 73% and 73%, $p < 0.01$), and overall took fewer anti-hypertensive medications (1.7 ± 1.5 vs. 1.9 ± 1.5 , 2.1 ± 1.4 and 2.3 ± 1.5 , $p < 0.01$). Participants in the Midwest were less likely than participants from the Northeast, South and West to take an anti-platelet medication (62% vs. 73%, 70% and 76%, $p < 0.05$). Multivariate analysis adjusting for age, gender, race, and ethnicity found that participants in the South were taking fewer anti-hypertensive medications than the NE and West (slope estimates: 0.42, $p=0.005$ and 0.56, $p=0.001$, respectively) (Table 3b).

Physician specialty and medication use within the United States

Interventional cardiologists (IC) and vascular surgeons (VS) were more likely to prescribe anti-platelet medications than interventional radiologists (IR) and hypertensionologists (HTN) (76% and 78% vs. 60% and 55%, respectively, $p < 0.001$), while IR physicians prescribed fewer total medications than HTN, IC and VS physicians (2.9 ± 2.4 vs. 3.4 ± 2.6 , 4.0 ± 2.6 and 3.8 ± 2.2 , $p < 0.001$). No interaction was found between site PI and census region, nor was there any interaction between site PI and HTN PI with regards to the number of anti-hypertensive medications prescribed.

Baseline characteristics of clinical participants: continental zones

The distribution of the percent of participants enrolled by continent is displayed in Figure 3. North America accounted for the largest percentage of patient enrollment (88%) with the majority of North American participants enrolled in the US (n= 772). We observed variation in the use of several medication classes amongst the intercontinental groupings designated for this study: North America (NA, n=823, 88%); Europe, Australia and New Zealand (Eurasia, n=71, 8%); and South America and South Africa (SA/SA, n=37, 4%). Figure 4 demonstrates these differences. To summarize, participants in NA were less likely to be treated with an ACEI/ARB ($p<0.001$); those in SA/SA were less likely to be treated with a beta-blocker ($p<0.05$); and in Eurasia, participants were more likely to be treated with both a calcium channel antagonist ($p<0.01$) and statin ($p<0.05$), and were also on a higher total number of anti-hypertensive medications ($p<0.001$). Additionally, both systolic and diastolic blood pressures were higher in SA/SA than in either North America or Eurasia (systolic: 167 ± 24 vs. 149 ± 23 and 151 ± 22 mmHg, respectively, $p<0.001$; diastolic: 89 ± 12 vs. 78 ± 13 and 83 ± 12 mmHg, respectively, $p<0.001$).

Discussion

Current study findings

We observed several potentially important variations in baseline medical therapy of patients with atherosclerotic RAS between clinical centers in the US and OUS. US participants were less likely to be treated with an ACEI/ARB, calcium channel antagonist, and statin than their counterparts OUS. Moreover, individuals in the US were on fewer anti-hypertensive medications. Significant heterogeneity was also observed in medication use across the four census regions of the US. Individuals in the South were less likely than those in other regions to take calcium channel antagonists and statins, whereas patients from the Midwest were less likely than those in other regions to take anti-platelet medication. Within the US, medical specialty also appeared to influence medical therapy. As an example, interventional cardiologists and vascular surgeons, physicians who more commonly treat atherosclerosis or coronary heart disease equivalents, were more likely to prescribe anti-platelet medications than other medical specialties. Globally, significant variation also existed in the use of several medication classes between NA, Eurasia, and SA/SA. Altogether, these differences highlight inconsistencies in the medical management of atherosclerotic RAS. These inconsistencies may in part be due to differences in hypertension guidelines that exist between regions and countries. The majority of patients were recruited from the US. A possible explanation for our results would suggest that medical management of patients enrolled OUS may not reflect how care is provided outside the CORAL study protocol.

Geographic variations in blood pressure and medical therapy

Prior work has shown that geographic region influences clinical practice in the treatment of hypertension (26), with important regional variations reported in its prevalence and treatment in such places as the United States (18–20), England (15), Canada (14,16,17), Italy (13), and Belgium (12). In our study, some of the differences in systolic and diastolic blood pressure may reflect regional variation in blood pressure control. As an example, we observed that OUS participants were more likely to be on an ACEI/ARB and calcium

channel antagonist, were on more total anti-hypertensive medications, and also had higher blood pressure. Some of these regional differences in blood pressure control may be attributable to naturally occurring, population-dependent differences in blood pressure and effective response to medications (19,27). The more aggressive treatment strategies observed outside of the US and North America may reflect an attempt at overcoming these differences in blood pressure with more anti-hypertensive medications.

We also observed significant variation in the prescription pattern of statin medications. Use of statins was less common in the US than OUS. This phenomenon was noted despite observations that US patients had a higher average weight, an increased prevalence of peripheral vascular disease, and more commonly reported a family history of premature atherosclerotic disease. For elderly patients with renovascular disease, statin use has been associated with a reduction in the rate of primary cardiorenal events (e.g., myocardial infarction, stroke, heart failure, acute renal failure, dialysis, and death) (11). Statin-treated individuals may also experience lower rates of stenosis progression (10), and at times even regression (28). Given the association between atherosclerotic RAS and cardiac morbidity and mortality (1,2), as well as the known benefits of statin use, statins should be considered an important feature of medical therapy in the care of patients with atherosclerotic RAS.

Broad implications of geographic variability

Geographic region is a special concern in the implementation of medical therapy for individuals with atherosclerotic RAS. Variations in non-clinical factors, such as location, may reflect potential barriers to the uniform adoption of recommended clinical guidelines (21). In comparisons of US vs. OUS patients and between the four federal census regions of the US, location was an independent predictor of the quantity and nature of medical therapy. This finding was independent of physician specialty, and is consistent with several prior studies detailing global variations in hypertension with regards to its frequency, severity, treatment rate, and percent at goal (19,29,30). Differences in the quantity and nature of medical therapy, as seen in our study, may be reflective of these underlying global variations in hypertension. Region-dependent variations in blood pressure, superimposed upon the pathophysiological consequences of atherosclerotic disease, may complicate the development of a uniform treatment strategy and the ability to adequately control blood pressure (i.e., individuals in different regions require more medications or different medications). Harmonized national and international clinical practice guidelines may help to play a role in reducing regional variations in actual treatment practices, and may provide for better management of blood pressure control.

Limitations

We recognize that our study has several notable limitations. The biggest limitation is that relatively few patients were enrolled outside the United States, and that this provides for disproportionate sample sizes. Nevertheless, CORAL provides the best available contemporary view of medical therapy for atherosclerotic renal-artery stenosis. We also understand that there is no assurance that the few centers located outside of the United States are representative of medical management of patients with atherosclerotic RAS in their country or “region” of origin. Finally, we do not have data on patient referral sources or

duration of specialist care before enrollment that could influence study referral patterns and clinical management.

Conclusions

Utilizing data from the global enrollment of the CORAL trial we were able to obtain a contemporary perspective on the worldwide use of medical therapy in patients with atherosclerotic RAS. Significant region-, continent-, and physician specialty-dependent variation exists in the medical therapy of these individuals. These geographic and specialty-associated variations suggest that there are significant opportunities to improve the medical management of patients with atherosclerotic RAS.

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Abbreviations List

RAS	renal-artery stenosis
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
MDRD-eGFR	modified diet in renal disease estimated glomerular filtration rate
CKD	chronic kidney disease
PI	principal investigator
OR	odds ratio
DBP	diastolic blood pressure
SBP	systolic blood pressure
ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin II receptor blocker

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Figure 1.

Odds ratio (OR) and 95% confidence intervals (CI) for medical management in the United States (US) compared to outside the US (OUS) including anti-hypertensive, anti-platelet, nitrate and lipid-lowering therapies. Solid circles indicate OR estimates and lines with brackets indicate the lower and upper 95% CI limits for medication use by class.

Figure 2.

Medical management distributed within the 4 federal census regions of the US (the Midwest, Northeast, South, and West) displayed as average total anti-hypertensive medications and proportional use of non-antihypertensive and anti-hypertensive medication classes that demonstrated significant variation among census regions. Proportional results are shown for the non-antihypertensive lipid-lowering and anti-platelet agents, and the anti-hypertensive agent calcium channel blocker. Total anti-hypertensive medications are displayed as mean $\pm$ SD and overall comparison among the four regions was performed using one-way ANOVA with Fisher's PSLD for multiple pairwise comparisons between regions. Proportional use of medication is shown as the percent use in each census region for the drug class with regional percents compared using multiple proportions test for equality and test of equal proportions for pairwise regional comparisons.

Figure 3.

Distribution of the number of participants enrolled by continent, displayed as the percent of total worldwide enrollment including North America, South America, Europe, Australia, New Zealand, and South Africa.

Figure 4.

Therapeutic medication use is graphically represented within the three continent groups designated for the study formed by combining countries: North America (NA), Canada and the United States; Eurasia, Europe, New Zealand and Australia; and South America and South Africa (SA/SA). Data are presented as average total anti-hypertensive medications and proportional use of non-antihypertensive and anti-hypertensive medication classes that varied significantly among the continents. Percent medication use in the continent groups is shown by drug class for the non-antihypertensive lipid-lowering agent, and the anti-hypertensive agents calcium channel antagonist, renin-angiotensin inhibitor, and beta-adrenergic and alpha-adrenergic blockers. Total anti-hypertensive medications for the continents are depicted as mean $\pm$ SD and were compared using one-way ANOVA with Fisher's PSLD for pairwise comparisons between continents. Proportional use for each drug class is tested for equal proportions among multiple continent groups. Equal proportion analysis was performed between pairwise combinations of continents.

Table 1

Baseline characteristics and medical management of patients in the United States and those outside the United States.

Baseline Characteristics	OUS (n=159)	US (n=772)	P-Value [*]	Odds Ratio (CI) [†]
	Mean ± SD or n (%)			
Demographic/Physical Exam				
Age (years)	70 ± 9	70 ± 9	0.70	
Weight (kg)	74 ± 14	81 ± 17	<0.001	
BMI	27± 4	30 ± 6	<0.001	
SBP (mmHg)	152 ± 24	150 ± 23	0.178	
DBP (mmHg)	82 ± 13	78 ± 13	<0.001	
SBP (at goal)	36 (24)	207 (27)	0.422	1.20 (0.79, 1.9)
Laboratory Values				
Creatinine (mg/dL)	1.26 ± 0.2	1.25 ± 0.2	0.82	
MDRD-eGFR (mL/min/1.73m ²)	62 ± 24	61 ± 24	0.89	
Cystatin-C (mg/L)	1.23 ± 0.4	1.30 ± 0.5	0.08	
Risk Factors/Indications				
Premature atherosclerotic disease [‡]	40 (29)	247 (39)	0.033	1.55 (1.03, 2.38)
PVD	63 (41)	400 (53)	0.013	1.58 (1.1, 2.29)
CKD	87 (55)	492 (64)	0.041	1.43 (0.99, 2.05)
CKD stage				
Normal	28 (18)	104 (13)		
Mild	69 (45)	267 (35)	0.9	1.04 (0.61, 1.74)
Moderate	48 (32)	351 (46)	0.014	1.97 (1.13, 3.38)
Severe	7 (5)	45 (5)	0.30	1.73 (0.67, 5.03)
Angiographic Findings [×]				
Percent stenosis	68.9 ± 12.1	68.5 ± 11.4	0.75	
Bilateral disease [§]	26 (21)	148 (24)	0.56	1.16 (0.73, 1.86)
Treatment				
Total HTN Medications	2.4 ± 1.4	1.9 ± 1.5	<0.001	
Total All Medications	3.7 ± 1.9	3.2 ± 2.2	0.01	

SD, standard deviation; CI, confidence interval; US, United States; OUS, outside the United States; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDRD-eGFR, modified diet in renal disease glomerular filtration rate; HTN, hypertension; CAD, coronary artery disease; CVD, cerebrovascular disease; PVD, peripheral vascular disease; CKD, chronic kidney disease; CAD, coronary artery disease; and BMI, body mass index.

* P-value, odds-ratio for dichotomous variables, t-test or Mann-Whitney U rank test for continuous variables

[†] CI, confidence interval for lower and upper 95% limits

[‡] Premature atherosclerotic disease: CAD, CVD or PVD in male relatives <55 and/or female relatives <65 years old

[×] Findings based on assessments from the Angiographic Core Laboratory

[§] Bilateral disease: stenosis ≥60% in the diameter of at least one artery for each kidney

Table 2

Baseline characteristics for the four census regions of the United States.

Baseline Characteristics		Midwest (n=235)	Northeast (n=147)	South (n=283)	West (n=107)	P-Value*
		Mean ± SD or n (%)				
Demographic/Physical Exam						
Age (years)		71 ± 9**	69 ± 9	68 ± 9 ^{††} ,**	72 ± 9 ^{††}	<0.001
Height (cm)		168 ± 10 ^{//}	165 ± 10 ^{††}	168 ± 10 [#]	170 ± 10 ^{//,##,††}	0.004
Weight (kg)		83 ± 17 ^{//}	78 ± 16 ^{//}	80 ± 17	81 ± 17	0.03
BMI		31 ± 6 ^{//,##}	29 ± 5 ^{//}	30 ± 6	29 ± 5 [#]	0.012
SBP (mmHg)		150 ± 24	151 ± 21	149 ± 23	149 ± 22	0.92
DBP (mmHg)		77 ± 13	79 ± 13	77 ± 13	80 ± 13	0.08
SBP (at goal)		71 (30)	29 (20)	83 (29)	24 (23)	0.08
Laboratory Values						
Creatinine (mg/dL)		1.30 ± 0.5 [#]	1.32 ± 0.5 ^{//}	1.18 ± 0.4 ^{//,##}	1.23 ± 0.4	0.01
MDRD-eGFR (mL/min/1.73 ²)		59 ± 23 [#]	58 ± 26 ^{//}	65 ± 24 ^{//,##}	63 ± 23	0.011
Cystatin-C (mg/L)		1.35 ± 0.5	1.38 ± 0.5 ^{//}	1.24 ± 0.4 ^{//}	1.25 ± 0.4	0.01
Risk Factors/Indications						
Premature atherosclerotic disease [†]		78 (39)	43 (36)	82 (36)	34 (41)	0.87
Smoking (past year) ^{##}		55 (24) [§]	43 (29)	104 (37) [§]	31 (29)	0.01
PVD		105 (45) ^{//}	81 (57) ^{//}	153 (55)	62 (59) ^{//}	0.03
CKD		161 (68) ^{††}	103 (70) [§]	160 (56) ^{§,††}	68 (63)	0.011
CKD Stage						
Normal		26 (11)	18 (12)	47 (17)	13 (12)	0.25
Mild		76 (32)	38 (26)	109 (39)	45 (42)	0.017
Moderate		118 (50)	75 (51)	115 (41)	43 (40)	0.056
Severe		15 (6)	15 (10)	9 (3)	6 (6)	0.031
Angiographic Findings [‡]						
Percent stenosis		69.0 ± 11.0	70.7 ± 13.0 ^{‡‡}	67.2 ± 10.9 ^{‡‡}	68.4 ± 11.5	0.07

Baseline Characteristics	Midwest (n=235)	Northeast (n=147)	South (n=283)	West (n=107)	P-Value*
	Mean ± SD or n (%)				
Bilateral disease [×]	56 (30) [×] ×	30 (26)	45 (19) [×] ×	18 (21)	0.044

SD, standard deviation; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDRD-e GFR, modified diet in renal disease glomerular filtration rate; HTN, hypertension; CAD, coronary artery disease; CVD, cerebrovascular disease; PVD, peripheral vascular disease; CKD, chronic kidney disease; and BMI, body mass index.

* P-value, contingency table analysis for dichotomous variables, one-way ANOVA for continuous variables

[†] Premature atherosclerotic disease: CAD, CVD or PVD in male relatives <55 and/or female relatives <65 years old

[‡] Findings based on assessments from the Angiographic Core Laboratory

^x Bilateral disease: stenosis 60% in diameter of at least one artery for each kidney

^{##} Smoking status was self-reported as within the past year. Otherwise, length of time smoking or packs per year was not reported.

[§] P 0.001

^{//, #} P<0.05

^{**} P<0.01

^{††} P 0.005

^{‡‡} P<0.01 for comparison of Northeast and South

^{xx} P<0.05 for comparison of Midwest and South

Table 3a

Multivariable model using stepwise linear regression to predict total anti-hypertensive use applying significant clinical variables and controlled for age, gender, race, and ethnicity with location within the United States* as a covariate.

	Slope Estimate	Std. Error	P-Value
Age	0.01	0.005	0.11
Gender: Male	0.353	0.113	0.0023
Race: White	-0.133	0.183	0.483
Hispanic/Latino	0.083	0.223	0.733
Location: US	-0.473	0.143	<0.0013
PVD	-0.233	0.103	0.023
Diabetes	0.49	0.10	<0.001
CHF	0.35	0.15	0.02

Std., Standard; US, United States; PVD, Peripheral Vascular Disease; and CHF, Congestive Heart Failure

* Outside the US is the comparator reference

Table 3b

Multivariable model using stepwise linear regression to predict total anti-hypertensive use applying significant clinical variables and controlled for age, gender, race and ethnicity with the US census regions* as covariates.

	Slope Estimate	Std. Error	P-Value
Age	0.01	0.01	0.05
Gender: Male	0.273	0.113	0.0123
Race: White	−0.183	0.193	0.363
Hispanic/Latino	0.703	0.313	0.023
Midwest	0.233	0.133	0.0753
Northeast	0.423	0.153	0.0053
West	0.563	0.173	0.0013
BMI	0.013	0.013	0.1753
PVD	−0.233	0.113	0.043
Diabetes	0.49	0.12	<0.001
CHF	0.35	0.16	0.025

Std., Standard; US, United States; BMI, Body Mass Index; PVD, Peripheral Vascular Disease; and CHF, Congestive Heart Failure

* The South census region is the comparator reference for the Midwest, Northeast and West regions