Use of Renin-Angiotensin Inhibitors in People with Renal Artery Stenosis

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Abstract

Background and objectives People with atherosclerotic renal artery stenosis may benefit from renin-angiotensin inhibitors, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers, but little is known about the factors associated with their use.

Design, setting, participants, & measurements The Cardiovascular Outcomes in Renal Atherosclerotic Lesions study (ClinicalTrials.gov identifier: NCT00081731) is a prospective, international, multicenter clinical trial that randomly assigned participants with atherosclerotic renal artery stenosis who received optimal medical therapy to stenting versus no stenting from May 2005 through January 2010. At baseline, medication information was available from 853 of 931 randomly assigned participants. Kidney function was measured by serum creatinine-based eGFR at a core laboratory.

Results Before randomization, renin-angiotensin inhibitors were used in 419 (49%) of the 853 participants. Renin-angiotensin inhibitor use was lower in those with CKD (eGFR<60 ml/min per 1.73 m²) (58% versus 68%; P=0.004) and higher in individuals with diabetes (41% versus 27%; P<0.001). Presence of bilateral renal artery stenosis or congestive heart failure was not associated with renin-angiotensin inhibitor use. Although therapy with renin-angiotensin inhibitors varied by study site, differences in rates of use were not related to the characteristics of the sites participating. Participants receiving a renin-angiotensin inhibitor had lower systolic BP (mean±SD, 148±23 versus 152±23 mmHg; P=0.003) and more often had BP at goal (30% versus 22%; P=0.01).

Conclusions Kidney function and diabetes were associated with renin-angiotensin inhibitor use. However, these or other clinical characteristics did not explain variability among study sites. Patients with renal artery stenosis who received renin-angiotensin inhibitor treatment had lower BP and were more likely to be at treatment goal.


Introduction

Atherosclerotic renal artery stenosis (RAS) is associated with increased mortality, and treatment remains complex. Prior estimates have placed the prevalence of atherosclerotic RAS as high as 7% in elderly individuals (1) and as low as 0.5% in the Medicare population (2,3). RAS, through the release of renin, activates the renin-angiotensin-aldosterone system (4). Increased angiotensin II, a major bioactive product of activation of this system, is implicated in damage to both kidneys (5) and heart (6). Angiotensin II is believed to be a key component of the hypertensive response to ischemia of the kidney (7,8) as well as an important mechanism for the high rate of adverse cardiovascular events in people with RAS (9,10).

This evidence would appear to support the use of renin-angiotensin inhibitors in individuals with RAS. However, the potential for AKI does exist, particularly in patients with bilateral disease or high-grade stenosis to a solitary functioning kidney (11). Because of these concerns, some physicians avoid or discontinue use of renin-angiotensin inhibitors in patients with RAS (11,12). More recent studies have demonstrated safety and tolerability, as well as renoprotective effects, of these medications in this group (13–15). Furthermore, several studies suggest that renin-angiotensin inhibitor use for RAS may reduce risk of progression to ESRD and death (15–17). Renin-angiotensin inhibitors are also regularly used for common comorbid conditions of RAS, including resistant hypertension (18,19), CKD (20–22), and congestive heart failure (23–26).

Despite evidence for benefits, the frequency of renin-angiotensin inhibitor use in recent studies of people with RAS was 50%–55% (15,17). Lower use rates may be due to individual characteristics or, alternatively, the prescribing habits of physicians. For individuals with RAS, patient factors associated with antihypertensive agent selections are not known. The aim of the present study was to identify the factors associated with angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blocker (ARB) use...
before entry into the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) clinical trial.

Materials and Methods

The CORAL study design and methods have been described previously (27). This prospective, international, multicenter, unblinded, two-group, randomized trial enrolled participants with atherosclerotic RAS from May 2005 through January 2010. The study assessed effects of optimal medical therapy plus stenting versus no stenting for effects on cardiovascular disease and CKD events (ClinicalTrials.gov identifier NCT00081731). Data analyzed in the current study include baseline characteristics obtained from 931 of the 947 participants enrolled in the CORAL study. Sixteen individuals were administratively withdrawn, as previously explained (28). Participants with missing baseline characteristics (n=8) and those in whom the use of ACEI/ARB could not be ascertained at baseline (n=70) were excluded, leaving 853 of 931 for the primary analysis. All the centers obtained approval of their respective institutional review committees and followed institutional guidelines. Participants provided written informed consent to join the study. The CORAL trial was conducted in accordance with the Declaration of Helsinki.

BP Measurement and Goal

BP was measured at the baseline study visit. Participants were seated for 5 minutes in a quiet room, and BP was measured in triplicate (separated by 2-minute intervals) with an automated, oscillometric manometer provided to the sites for the CORAL study. The mean of the last two measurements was taken as the baseline BP. Goal BP control was defined as <130/80 mmHg for patients with diabetes and/or CKD or <140/90 mmHg for patients without these conditions (19,29,30).

Antihypertensive Medication

Baseline information for antihypertensive agents was obtained from the medication logs of CORAL study participants. Medications were categorized into 13 drug classes: 10 classes of antihypertensive agents and 3 separate drug classes that included nitrates, antiplatelets, and lipid-lowering agents. Medication use at baseline was recorded and classified (yes, no, unknown). “Unknown” was designated if the start and stop dates for the ACEI or ARB could not be ascertained. Sensitivity analyses were performed including participants in whom the use of ACEIs or ARBs could not be ascertained at baseline (unknowns), placing these individuals (n=70) into both the ACEI/ARB group and the non-ACEI/ARB group to assess the effects on participant characteristics associated with drug use. Participants taking more than one medication within a class were identified and were counted as receiving that class.

Kidney Function Measurement

Kidney function was assessed using serum creatinine (mg/dl), creatinine-based eGFR (ml/min per 1.73 m²) calculated using the Modification of Diet in Renal Disease standard-eGFR, and cystatin C (mg/L). All measurements were centrally analyzed by the Biochemistry Core Lab at the University of Minnesota.

Statistical Analyses

Study data are presented as continuous (mean±SD), categorical (number and percentage), and median (with interquartile range) data. For comparisons of continuous variables, Pearson correlation coefficient and two-sample t tests were used, while for categorical variables, the Fisher exact test for independence or Mantel-Haenszel-Cochran test for odds ratios (ORs) was calculated. The Shapiro-Wilk test was used to test for normal distribution of continuous data, and nonparametric analysis using the Mann–Whitney U rank test was used if the assumption of normality was violated. The main outcome variable was whether a participant was receiving treatment with an ACEI/ARB at study entry, as recorded at the baseline assessment. Participants were categorized as taking an ACEI only, an ARB only, an ACEI plus an ARB, or neither an ACEI nor an ARB. Variables with P<0.05 in univariate correlations were included in multiple variable analyses with stepwise logistic regression. Age, sex, and study site location (United States versus outside the United States) using logistic regression were prespecified covariates entered into multiple variable analyses. The rate of ACEI/ARB use was calculated for sites and aggregated into three groups of therapeutic use (low, intermediate, or high), respectively, based on rates of ≤25%, >25 to ≤75%, or >75%. Analyses were performed using R software (version 3.0.0) and SAS software (version 9.3). Statistical significance was defined with a two-sided P value <0.05. To assess systolic BP, participants were matched according to diabetes and CKD status, along with concomitant antihypertensive medications. BP was then examined as an outcome comparing use of an ACEI/ARB (individuals receiving ACEI/ARB versus individuals not receiving ACEI/ARB).

Results

Factors Associated with ACEI/ARB Use

Before randomization, ACEI/ARB agents were used in 419 (49%) of the 853 participants (Table 1). Rates of use were lower in participants with CKD (58% versus 68%; P=0.004) (Figure 1) and in those enrolled in the United States (78% versus 87%; P<0.001). Participants with a history of diabetes were more commonly treated with these agents (41% versus 27%; P<0.001). Baseline use of ACEI/ARB did not differ by presence of history of congestive heart failure or bilateral RAS (confirmed by renal angiogram) independent of kidney function and diabetes status. ACEI/ARB users were slightly, but significantly, less likely to have dipstick-positive proteinuria, defined by a protein level of 100 mg/dl (3% versus 7%; P=0.01). Potassium levels were marginally higher in ACEI/ARB users (4.2±0.6 versus 4.1±0.6 mmol/L; P=0.04) and were negatively correlated with eGFR for both ACEI/ARB users and nonusers (r=−0.19 [P<0.001] and r=−0.23 [P<0.001], respectively). After sensitivity analysis, the inclusion of unknowns in either group did not change inferences of the primary analysis. Multiple logistic regression analyses adjusted for age, sex, and study site were performed and demonstrated findings consistent with nonadjusted results in Table 1. (For additional details, see Supplemental Table 1.)
Table 1. Baseline clinical characteristics and medication use among participants in the CORAL clinical trial stratified by use of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker

<table>
<thead>
<tr>
<th>Demographic/physical examination</th>
<th>Non-ACEI/ARB (n=434)a</th>
<th>ACEI/ARB (n=419)</th>
<th>P Valueb</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70 ± 9</td>
<td>71 ± 9</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>203 (47)</td>
<td>222 (53)</td>
<td>0.07</td>
<td>1.28 (0.97 to 1.7)</td>
</tr>
<tr>
<td>White race</td>
<td>395 (91)</td>
<td>386 (92)</td>
<td>0.62</td>
<td>1.15 (0.69 to 1.94)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>20 (5)</td>
<td>34 (8)</td>
<td>0.04</td>
<td>1.83 (1.0 to 3.42)</td>
</tr>
<tr>
<td>United States as country origin</td>
<td>378 (87)</td>
<td>326 (78)</td>
<td>&lt;0.001</td>
<td>0.52 (0.35 to 0.76)</td>
</tr>
<tr>
<td>Height (in)</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>174 ± 38</td>
<td>178 ± 35</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9 ± 34.0</td>
<td>29.6 ± 30.3</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>152 ± 23</td>
<td>148 ± 23</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79 ± 14</td>
<td>78 ± 13</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Systolic BP at goal</td>
<td>96 (22)</td>
<td>124 (30)</td>
<td>0.01</td>
<td>1.49 (1.08 to 2.05)</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.31 ± 0.5</td>
<td>1.21 ± 0.4</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>MDRD-eGFR (ml/min per 1.73 m²)</td>
<td>58 ± 24</td>
<td>64 ± 24</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>1.33 ± 0.5</td>
<td>1.25 ± 0.4</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.1 ± 0.6</td>
<td>4.2 ± 0.6</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Dipstick proteinuria &lt;100 mg/dl</td>
<td>386 (93)</td>
<td>389 (96)</td>
<td>0.01</td>
<td>0.45 (0.23 to 0.85)</td>
</tr>
<tr>
<td>Dipstick proteinuria ≥100 mg/dl</td>
<td>31 (7)</td>
<td>14 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors/indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature atherosclerotic diseasec</td>
<td>129 (36)</td>
<td>129 (37)</td>
<td>0.94</td>
<td>1.02 (0.74 to 1.4)</td>
</tr>
<tr>
<td>Smoking (past year)</td>
<td>124 (29)</td>
<td>118 (28)</td>
<td>0.88</td>
<td>0.97 (0.71 to 1.33)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>384 (90)</td>
<td>374 (90)</td>
<td>0.73</td>
<td>1.1 (0.68 to 1.76)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>114 (27)</td>
<td>123 (30)</td>
<td>0.36</td>
<td>1.16 (0.85 to 1.6)</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>91 (21)</td>
<td>76 (18)</td>
<td>0.30</td>
<td>0.83 (0.58 to 1.2)</td>
</tr>
<tr>
<td>Angina</td>
<td>41 (11)</td>
<td>46 (13)</td>
<td>0.04</td>
<td>1.56 (1.0 to 2.5)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>256 (63)</td>
<td>236 (63)</td>
<td>0.94</td>
<td>0.99 (0.73 to 1.34)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>221 (52)</td>
<td>197 (48)</td>
<td>0.24</td>
<td>0.85 (0.64 to 1.12)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>115 (27)</td>
<td>169 (41)</td>
<td>&lt;0.001</td>
<td>1.9 (1.41 to 2.57)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>52 (12)</td>
<td>66 (16)</td>
<td>0.11</td>
<td>1.38 (0.91 to 2.08)</td>
</tr>
<tr>
<td>CKD</td>
<td>295 (68)</td>
<td>245 (58)</td>
<td>0.004</td>
<td>0.66 (0.50 to 0.89)</td>
</tr>
<tr>
<td>CKD stages 1–2</td>
<td>55 (13)</td>
<td>60 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage 3</td>
<td>139 (32)</td>
<td>169 (41)</td>
<td>0.66</td>
<td>1.11 (0.71 to 1.75)</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>205 (47)</td>
<td>172 (42)</td>
<td>0.24</td>
<td>0.77 (0.49 to 1.19)</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>33 (8)</td>
<td>13 (3)</td>
<td>&lt;0.01</td>
<td>0.36 (0.16 to 0.80)</td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td>84 (19)</td>
<td>71 (17)</td>
<td>0.38</td>
<td>0.85 (0.59 to 1.22)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>106 (26)</td>
<td>225 (57)</td>
<td>&lt;0.001</td>
<td>3.8 (2.78 to 5.15)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>12 (3)</td>
<td>14 (3)</td>
<td>0.69</td>
<td>1.21 (0.51 to 2.91)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>175 (43)</td>
<td>252 (63)</td>
<td>&lt;0.001</td>
<td>2.19 (1.63 to 2.93)</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>64 (15)</td>
<td>70 (17)</td>
<td>0.51</td>
<td>1.14 (0.78 to 1.69)</td>
</tr>
<tr>
<td>αβ-Blocker</td>
<td>49 (12)</td>
<td>43 (10)</td>
<td>0.58</td>
<td>0.88 (0.56 to 1.4)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>113 (30)</td>
<td>199 (53)</td>
<td>&lt;0.001</td>
<td>2.64 (1.94 to 3.61)</td>
</tr>
<tr>
<td>Renin inhibitor</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>&gt;0.99</td>
<td>1.04 (0.14 to 7.78)</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>26 (6)</td>
<td>16 (4)</td>
<td>0.15</td>
<td>0.62 (0.30 to 1.22)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>72 (18)</td>
<td>91 (23)</td>
<td>0.08</td>
<td>1.37 (0.95 to 2.0)</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>232 (62)</td>
<td>277 (75)</td>
<td>&lt;0.001</td>
<td>1.88 (1.36 to 2.61)</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>176 (49)</td>
<td>303 (83)</td>
<td>&lt;0.001</td>
<td>4.91 (3.45 to 7.04)</td>
</tr>
<tr>
<td>Total hypertension medications</td>
<td>1 (0, 2)</td>
<td>3 (2, 4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total all medications</td>
<td>3 (1, 4)</td>
<td>5 (4, 7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as the mean ±SD or number (percentage) of patients. Data not normally distributed are expressed as median (interquartile range). ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; 95% CI, 95% confidence interval; MDRD-eGFR, Modification of Diet in Renal Disease-eGFR; TIA, transient ischemic attack; RAS, renal artery stenosis.

aExcludes unknowns (n=70) and those with missing baseline characteristics (n=8).

bP value, odds ratio for dichotomous variables, t test, or ANOVA for continuous variables and nonparametric Mann–Whitney U test if data are not normally distributed.

cPremature atherosclerotic disease: coronary artery disease, cerebrovascular disease, or peripheral artery disease in male relatives age <55 years or female relatives age <65 years.
Variation of ACEI/ARB Use among Sites

Site variations in ACEI/ARB use is shown in Figure 2. The rate of ACEI/ARB use ranged from 39% to 91% among sites that enrolled 10 or more participants. Sites with high, intermediate, and low use did not differ by participant characteristics, such as diabetes or CKD. Furthermore, specialty affiliation of the principal investigator did not differ among sites with high, intermediate, and low use. (For details, see Supplemental Figure 1 and Supplemental Table 2, a–c.)

Multiple Variable Analyses of Adjusted Data

Stepwise logistic regression adjusted for age, sex, and study site location was applied to baseline covariates to develop a multivariable model to understand ACEI/ARB use. Exploratory variables that met the criteria for entry into the model included body mass index, serum creatinine, history of myocardial infarction, diabetes, and CKD. BP as a response variable was not included (Table 2). (For additional details, see Supplemental Table 3). Serum creatinine level (1 unit mg/dl increments) and location in the United States were negatively associated with ACEI/ARB use (OR, 0.55 [95% confidence interval (95% CI), 0.39 to 0.76; \( P < 0.001 \)) and 0.51 [95% CI, 0.35 to 0.75; \( P < 0.001 \)], respectively), while male sex and diabetes were positively associated with ACEI/ARB use (OR, 1.51 [95% CI, 1.12 to 2.02; \( P = 0.006 \)) and 2.14 [95% CI, 1.58 to 2.90; \( P < 0.001 \)], respectively).

ACEI/ARB Use and BP Control

Participants receiving an ACEI/ARB had lower systolic BP (SBP) at baseline (148±23 versus 152±23 mmHg; \( P = 0.003 \)) and were more frequently at SBP treatment goal compared with nonusers (30% versus 22%; \( P = 0.01 \)). Individuals treated with an ACEI/ARB also received more non-ACEI/ARB antihypertensive agents (median, 3 [interquartile range, 2, 4] versus 1 [interquartile range, 0, 2]; \( P < 0.001 \)) and were more likely to be treated with a diuretic (57% versus 26%; \( P < 0.001 \)), \( \beta \)-blocker (63% versus 43%; \( P < 0.001 \)), and calcium-channel blocker (53% versus 30%; \( P < 0.001 \)). The use of antiplatelet and lipid-lowering drugs was also more common in participants receiving ACEI/ARB therapy (75% versus 62% [\( P < 0.001 \)] and 83% versus 49% [\( P < 0.001 \)], respectively) (Figure 3). After sensitivity analysis, the inclusion of unknowns in the ACEI/ARB or the non-ACEI/ARB group did not change inferences of the primary analysis. Participants were grouped according to treatment with or without an ACEI/ARB and were also paired within each group corresponding to the presence or absence of diabetes and CKD, as well as all exclusive medications. After matching for diabetes, CKD, and concomitant medications, participants who used an ACEI/ARB had lower SBP than patients not taking an ACEI/ARB (146±22 versus 152±21 mmHg; \( P < 0.01 \)).

Discussion

ACEI/ARB use was examined in individuals with atherosclerotic RAS who enrolled in the CORAL clinical trial. These data represent contemporary clinical management across an international range of study sites. ACEI/ARB use was more common in people with diabetes and less common in those with decreased kidney function. We found that the use of ACEI/ARB was not associated with
the presence of congestive heart failure or bilateral RAS independent of kidney function or diabetes status. Of note, there was significant heterogeneity among study sites, with lower rates of ACEI/ARB use in the United States than in other countries.

RAS is commonly managed without revascularization. The relative balance of potential benefits versus harms of renin-angiotensin inhibitor use in RAS has long been debated. However, three randomized clinical trials comparing medical therapy with stenting demonstrated no difference in BP, kidney or cardiovascular events, or mortality (28,31,32). Most recently, the CORAL trial demonstrated no benefit of renal artery stenting when added to optimal medical therapy that included an ARB (28). Thus,

**Figure 2.** Variation in ACEI/ARB use by site. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for site use of ACEI/ARB grouped by low (≤25%), intermediate (>25 to ≤75%), and high (>75%) proportional use, indicated in red, blue, and green, respectively. The non-ACEI/ARB group was the comparator reference at each site. Dark squares indicate OR estimates, with lines indicating 95% CIs for renin-angiotensin inhibitor use in logarithmic scale. Size of square indicates number of patients enrolled at the respective site. Sites outside of the United States are indicated by an asterisk.

**Table 2.** Model for ACEI/ARB use applying only significant variables controlled for age, sex, and location

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (per 1 unit mg/dl)</td>
<td>0.55 (0.39 to 0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.14 (1.58 to 2.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.51 (1.12 to 2.02)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Location: United States</td>
<td>0.51 (0.35 to 0.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
medical therapy, including renin-angiotensin inhibitors, remains a cornerstone of treatment for RAS. Additionally, these agents are indicated for treatment of overt diabetic kidney disease (33–35), but whether similar benefit extends to diabetic persons who have RAS or nonproteinuric CKD is not established. Use of renin-angiotensin inhibitors in people with RAS has been reported to reduce risk of progression to ESRD and death (15,17). However, such data may be considerably confounded. As an example, ACEI/ARB use in this study was associated with higher baseline eGFR, which predicts lower risk of ESRD and death. Furthermore, dipstick-positive proteinuria was less frequent in ACEI/ARB users, consistent with known biologic effects of these agents to reduce proteinuria. Thus, residual confounding by indication and treatment effects is likely.

A perception of increased risk for occurrence of AKI may be responsible for lower use of ACEI/ARB in people with RAS and low eGFR in the present study. Indeed, in a study examining the risk factors for AKI in people with RAS, CKD was associated with a 4-fold higher risk and the addition of a renin-angiotensin inhibitor was associated with a 2-fold higher risk (17). Hyperkalemia is also a potential adverse effect, particularly in individuals with low eGFR, a common occurrence in this setting. In this study, potassium levels were marginally higher in ACEI/ARB users and were inversely related to eGFR. Thus, the diagnosis of RAS presents a therapeutic conundrum: use an ACEI or ARB to reduce BP and potentially improve long-term outcomes, or avoid their use because of potentially harmful adverse effects upfront.

Participants treated with an ACEI/ARB had lower BP and were more likely to be at BP goal. This observation could be accounted for by increased use of antihypertensive medications in the ACEI/ARB treatment group. However, after matching patients for CKD, diabetes, and up to three medication combinations, the initial finding of lower BP in the ACEI/ARB treatment group was still present. Men were more likely than women to be using an ACEI/ARB; the reasons for this sex difference remain
unclear but may involve biases in prescribing patterns. Our results are similar to another study examining sex differences in BP control, which found that older women (age 65–80 years) are less likely than older men to use an ACEI for BP control but are similar to men in the use of an ACEI for secondary prevention of cardiovascular disease (36). Significant heterogeneity among study sites in ACEI/ARB use was independent of kidney function, diabetes, and other baseline characteristics. Interestingly, at highervolume sites and sites in the United States, ACEI/ARB use was lower than at other sites. This observation suggests that local prescribing patterns, rather than characteristics of individuals with RAS, are largely associated with ACEI/ARB use.

This secondary analysis of the CORAL trial has several notable limitations. First, as a cross-sectional study it is hypothesis-generating and does not establish causality. Second, although we controlled for recognized confounders, residual confounding by unmeasured aspects of participants’ characteristics is possible. Third, this study was also limited by lack of data on medication dosage. Fourth, data are derived from participants enrolled in a clinical trial for management of RAS, who may not generally represent patients treated in usual clinical practices. However, the CORAL study population is similar to other study populations in US Food and Drug Administration–approved trials of renal artery stents (37–39). Finally, we do not have data on referral sources or duration of specialist care data that could influence study referral patterns and clinical management.

Renin-angiotensin inhibition may improve clinical outcomes in people with RAS. Whether renal artery stenting reduces potential risks of these medications is an unanswered question. In a recent cohort study examining renin-angiotensin inhibitor intolerance, including documented deterioration of renal function, 13 of 74 people with RAS who were initially intolerant to therapy underwent revascularization; of those, 12 had renin-angiotensin inhibition safely reinstated (15).

In conclusion, this study of the entry characteristics of CORAL participants demonstrated wide variability in the use of renin-angiotensin inhibitors for people with RAS. Better kidney function and diabetes were associated with higher odds of renin-angiotensin inhibitor use; however, neither these nor other baseline characteristics explained the variability observed among sites. Notably, people with renal artery stenosis who received renin-angiotensin inhibitor treatment had lower BP and were more likely to be at the treatment goal.

Acknowledgments

Part of this work was presented in abstract format at the American Heart Association Annual Scientific Sessions, November 16–20, 2013, Dallas, Texas.

The present work benefited from the input of Diane Reid of the National Heart, Lung, and Blood Institute, who provided valuable assistance in the undertaking of this research.

Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (5U01-HL071556). S.T.H. is supported by the National and Ohio Valley Affiliate of the American Heart Association (13POST16660035). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Drug for this study was provided by AstraZeneca, device support was provided by Cordis Corporation, and supplemental financial support was granted by Cordis Corporation and Pfizer, Inc.

Disclosures
None.

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Received: November 18, 2013 Accepted: February 24, 2014

Published online ahead of print. Publication date available at www.jASN.org.

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.11611113/-/DCSupplemental.