Comment. To my knowledge this is the first study to report that smokers of mentholated cigarettes, and in particular women and non–African Americans, have significantly increased odds of stroke compared with nonmentholated cigarette smokers. Although potential causal links cannot be established and further research is required to confirm the findings, the association between mentholated cigarette smoking and stroke is noteworthy, given that the results are based on large population-level data, with data spanning nearly a decade, and given that the relationship is independent of multiple sociodemographic, smoking behavior, and health status confounders. The mentholated cigarette–stroke association may even be underestimated because this analysis included only current smokers and not former smokers. Increased cigarette particulate matter entering the lungs because of facilitation of reflex breath-holding through menthol-induced upper airway cold receptor stimulation serves as a potential mechanism for how mentholated cigarettes might potentially cause increased stroke over nonmentholated cigarettes. It is curious why smoking mentholated cigarettes would not result in an increase in forms of cardiovascular disease, other than stroke, like myocardial infarction and hypertension. A possible explanation is that mentholated cigarettes exert some selective effects on the cerebrovascular system. Potentially in support of this theory, smoking mentholated cigarettes has been found to result in increased carotid artery stiffness compared with smoking nonmentholated cigarettes, whereas equal decreases in coronary artery reserve flow were observed between the 2 cigarette types.

Other potential explanations for the mentholated cigarette–stroke relationship deserve mention. First, smokers with stroke may have a greater predisposition for smoking mentholated cigarettes than regular cigarettes (ie, reverse causality). Second, confounders not included in the analysis may potentially explain the association (eg, the presence or not of medical therapy). Third, the mentholated cigarette–stroke relationship may be erroneous, as a result of several sources of potential bias associated with the analysis (eg, recall bias, prevalence bias). Finally, there is less than 5% probability that the association found between mentholated cigarette smoking and stroke is one of chance. The fact that multiple disease outcomes were examined increases to some degree the finding of a “chance” association.

These results highlight the need for further review of the last legally allowed tobacco additive in North America, given that mentholated cigarettes may be placing individuals at even greater risk of potentially devastating cerebrovascular disease than regular cigarettes.

Nicholas T. Vozoris, MHSc, MD, FRCPC

Author Affiliations: Division of Respirology, Department of Medicine, St Michael’s Hospital, Toronto, and Division of Internal Medicine, Department of Medicine, Kingston General Hospital and Queen’s University, Kingston, Ontario, Canada.

Financial Disclosure: None reported.


Use of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers and Cardiovascular Outcomes in Chronic Dialysis Patients: A Population-Based Cohort Study

Routine use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for the treatment of cardiovascular disease is well established. However, because most randomized controlled trials have excluded patients with advanced chronic kidney disease, the role of ACEIs/ARBs in chronic dialysis patients remains poorly defined. Our objective was to determine whether ACEI/ARB use is associated with a reduction in mortality and major adverse cardiovascular events in older chronic dialysis patients.

Methods. We conducted a retrospective, population-based cohort study using linked health care databases in Ontario, Canada. To minimize bias, we used a new-user study design. The study population was composed of older chronic dialysis patients in Ontario (age ≥66 years) who were newly treated with ACEIs/ARBs, calcium channel blockers (CCBs), or statins between July 1, 1991, and July 31, 2007. We selected new treatment with ACEIs/ARBs as the exposure group and new treatment with CCBs or statins as the comparator groups to minimize confounding by indication and because CCBs and statins have not been shown to be clearly beneficial in this population. We excluded patients with missing demographic information or incomplete drug records.
Patients were stratified into 1 of 3 mutually exclusive treatment groups (ACEI/ARB, CCB, or statin) and were prospectively observed for up to 5 years, or March 31, 2010. The primary outcome was a composite of all-cause mortality, hospitalization for myocardial infarction (MI), stroke, heart failure (HF), or coronary revascularization. Secondary end points included each component of the primary end point. We used an intention-to-treat approach. We estimated event-free survival by the Kaplan-Meier method and used the log-rank test for comparison. We used standardized differences to compare baseline characteristics in the 3 treatment groups, and Cox proportional hazards regression, adjusting for age, sex, diabetes, hypertension, coronary artery disease, HF, dialysis duration, and the Deyo-Revised Charlson Comorbidity score.5-7

Results. During the study period, we identified 1950 older chronic dialysis patients in Ontario who initiated treatment with 1 of the study drug classes. There were no systematic differences in the baseline characteristics between the treatment groups (Table 1). There was no significant difference in event-free survival among the 3 groups (log-rank P = .12). In multivariable analysis, the use of ACEIs/ARBs was not independently associated with a reduction in the primary outcome (hazard ratio, 0.97; 95% CI, 0.84-1.13) or secondary outcomes compared with the CCB group (Table 2). Similar results were obtained when the ACEI/ARB group was compared with the statin-only group. 

Comment. In this population-based cohort study of chronic dialysis patients older than 65 years, new use of ACEIs or ARBs was not independently associated with an overall reduction in major adverse cardiovascular events. Data from previous randomized controlled trials and observational studies have been conflicting. This study offers unique insights into the use of ACEIs/ARBs in chronic dialysis patients through its new-user study design.4 Although this new-user study design has not been used extensively in chronic dialysis patients, it allows for a less biased evaluation of the “real world” safety and effectiveness of secondary prevention therapies in such patients, in contrast to randomized controlled trials, which often recruit highly selected healthier patients.8,9

Table 1. Baseline Characteristics of Study Patients in the Different Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACEI/ARB (n = 679)</th>
<th>Statin (n = 847)</th>
<th>CCB (n = 424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76.2 (5.4)b</td>
<td>77.0 (5.8)</td>
<td>76.4 (6.0)</td>
</tr>
<tr>
<td>Women</td>
<td>244 (35.9)b</td>
<td>356 (42.0)</td>
<td>180 (42.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>266 (39.2)c</td>
<td>374 (44.2)</td>
<td>124 (29.2)d</td>
</tr>
<tr>
<td>Hypertension</td>
<td>525 (77.3)c</td>
<td>669 (79.0)</td>
<td>346 (81.6)</td>
</tr>
<tr>
<td>Coronary artery disease (including angina)</td>
<td>434 (63.9)b</td>
<td>549 (64.8)</td>
<td>243 (57.3)d</td>
</tr>
<tr>
<td>Previous MI</td>
<td>91 (13.4)b</td>
<td>155 (18.3)</td>
<td>43 (10.1)d</td>
</tr>
<tr>
<td>Heart failure and cardiomyopathy</td>
<td>338 (49.8)b</td>
<td>408 (48.2)</td>
<td>158 (37.3)d</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>118 (17.4)</td>
<td>180 (21.3)</td>
<td>84 (19.8)</td>
</tr>
<tr>
<td>Dialysis vintage, median (IQR), y</td>
<td>1.9 (0.3-3.3)b</td>
<td>1.4 (0.7-2.4)</td>
<td>1.9 (1.1-3.4)d</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>558 (82.2)b</td>
<td>611 (72.1)</td>
<td>336 (79.2)d</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>99 (14.6)a</td>
<td>208 (24.6)</td>
<td>42 (9.9)d</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; MI, myocardial infarction.

a Unless otherwise noted, data are reported as number (percentage) of patients.

b Significant standardized difference (>|0.1) between the ACEI/ARB and statin groups.

c Significant standardized difference (>0.1) between the ACEI/ARB and CCB groups.

d Significant standardized difference (>0.1) between the CCB and statin groups.

Table 2. Study Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ACEI/ARB (n = 679)</th>
<th>Statin (n = 847)</th>
<th>CCB (n = 424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up, mean (SD), y</td>
<td>2.4 (1.6)</td>
<td>2.1 (1.4)</td>
<td>2.6 (1.6)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>474 (0.97 [0.84-1.13])</td>
<td>564 (1.08 [0.94-1.25])</td>
<td>300 [Referent]</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>441 (0.92 [0.79-1.06])</td>
<td>524 (1.05 [0.91-1.22])</td>
<td>288 [Referent]</td>
</tr>
<tr>
<td>Heart failure</td>
<td>140 (0.83 [0.63-1.09])</td>
<td>129 (0.73 [0.55-0.96])</td>
<td>90 [Referent]</td>
</tr>
<tr>
<td>MI</td>
<td>85 (1.02 [0.72-1.46])</td>
<td>96 (1.05 [0.76-1.50])</td>
<td>50 [Referent]</td>
</tr>
<tr>
<td>Stroke</td>
<td>33 (0.97 [0.56-1.70])</td>
<td>37 (1.08 [0.62-1.88])</td>
<td>21 [Referent]</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>23 (0.87 [0.46-1.69])</td>
<td>30 (1.08 [0.57-2.07])</td>
<td>15 [Referent]</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MI, myocardial infarction.

a Unless otherwise noted, data are reported as number (adjusted hazard ratio [95% CI]) of patients.
critical trials. Despite their high baseline cardiovascular risk, as evidenced by the high event rate in our study, treatment benefit with ACEIs/ARBs was not observed. Another strength of our study was the large unselected cohort of incident dialysis patients observed for longer periods to more accurately assess the cardiovascular effects of ACEIs/ARBs.

Important limitations of our study are that drug therapy was not randomly assigned, and we analyzed classes of drugs rather than individual drugs. We selected our control groups with the expectation that these would serve as nonactive comparators. If statin or CCB use can indeed confer cardiovascular protection in chronic dialysis patients, our comparative analysis may have attenuated any observed benefit of ACEIs/ARBs.

In conclusion, our data suggest that use of ACEI or ARB therapy in chronic dialysis patients may not favorably impact cardiovascular outcomes. Compared with patients with normal kidney function, chronic dialysis patients may not derive the same cardiovascular benefit from ACEI/ARB use. Given the substantial cardiovascular morbidity and mortality in the expanding chronic dialysis patient population, a large definitive randomized controlled trial of ACEIs/ARBs is warranted.

Ravi R. Bajaj, MD
Ron Wald, MD, MPH
Daniel G. Hackam, MD, PhD
Tara Gomes, MHSc
Jeffrey Perl, MD, SM
David N. Juurlink, MD, PhD, BPharm
Michael Manno, MSc
Amit X. Garg, MD, PhD
Abhijit Kitchlu, MD
Muhammad M. Mamdani, MPH, MA
Andrew T. Yan, MD

Author Affiliations: Terrence Donnelly Heart Centre (Drs Bajaj and Yan), Division of Nephrology (Drs Wald and Perl), and Applied Health Research Centre, Li Ka Shing Knowledge Institute (Mr Mamdani), St Michael’s Hospital, Toronto, Ontario, Canada; Department of Medicine (Drs Bajaj, Wald, Perl, Juurlink, and Yan and Mr Mamdani), Leslie Dan Faculty of Pharmacy (Ms Gomes), and Department of Health Policy, Management, and Evaluation (Dr Juurlink), University of Toronto, Toronto; Divisions of Clinical Pharmacology (Dr Hackam) and Nephrology (Drs Garg and Kitchlu), Department of Medicine, and Department of Epidemiology and Biostatistics (Dr Garg), University of Western Ontario, London; and Institute for Clinical Evaluative Sciences, Toronto (Ms Gomes, Drs Juurlink and Garg, and Mr Manno).

Correspondence: Dr Yan, Division of Cardiology, St Michael’s Hospital, 30 Bond St, Room 6-030 Queen, Toronto, ON M5B 1W8, Canada (yana@smh.ca).

Author Contributions: Study concept and design: Wald, Hackam, Gomes, Juurlink, Garg, Kitchlu, Mamdani, and Yan. Acquisition of data: Juurlink and Kitchlu. Analysis and interpretation of data: Bajaj, Wald, Hackam, Gomes, Perl, Manno, Kitchlu, Mamdani, and Yan. Drafting of the manuscript: Bajaj and Kitchlu.

Critical revision of the manuscript for important intellectual content: Bajaj, Wald, Hackam, Gomes, Perl, Juurlink, Manno, Garg, Kitchlu, Mamdani, and Yan.

Statistical analysis: Gomes, Juurlink, Manno, Kitchlu, and Mamdani. Obtained funding: Juurlink. Administrative, technical, and material support: Gomes, Kitchlu, and Mamdani. Study supervision: Wald and Yan.

Financial Disclosure: None reported.

Funding/Support: Dr Yan is supported by a New Investigator Award from the Heart and Stroke Foundation of Canada.


EDITOR’S NOTE

Do the Benefits of Medications Outweigh the Burdens for Hemodialysis Patients?

A recent study reported that patients on hemodialysis are prescribed an average of 11 different medications with a mean daily burden of 19 pills. Yet few randomized controlled trials support the efficacy of these medications in the dialysis population, in part because these patients are usually excluded from trials. Angiotensin converting enzyme inhibitors are commonly used in the dialysis population to control hypertension and heart failure; lisinopril was the seventh most commonly prescribed drug among hemodialysis patients in the United States in 2008, according to the 2011 Annual Data Report from the United States Renal Data System. Thus, the “real world” data reported by Bajaj et al, which suggest that ACEIs might not provide the benefits to dialysis patients that have been demon-