Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients With Abdominal Aortic Aneurysms
Nation-Wide Cohort Study

Karl Emil Kristensen, Christian Torp-Pedersen, Gunnar Hilmar Gislason, Martin Egfjord, Henrik Berg Rasmussen, Peter Riis Hansen

Objective—The renin–angiotensin system is thought to play a pivotal role in the pathogenesis of abdominal aortic aneurysms (AAAs). However, effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) on human AAAs remain unclear. We therefore examined whether treatment with ACEIs or ARBs influenced hard clinical end points in a nation-wide cohort of patients with AAA.

Approach and Results—All patients diagnosed with AAA during the period 1995 to 2011 were identified from the Danish nation-wide registries. Subjects were divided according to ACEI and ARB treatment status and followed up for an average of 5 years. Study outcomes were evaluated by time-dependent Cox proportional hazard models. Of 9441 patients with AAA, 12.6% were treated with ACEIs and 5.0% received ARBs. Incidence rates of death from AAA per 100 patient-years were 3.7, 3.6, 4.0, and 4.7 for treatment with ACEIs or ARBs, ACEIs, ARBs, and no ACEI/ARB, respectively. Hazard ratios of death from AAA were 0.64 (95% confidence interval, 0.51–0.80; P<0.001) for patients receiving ACEIs and 0.65 (95% confidence interval, 0.48–0.88; P=0.006) for those receiving ARBs, respectively (P for difference=0.944). The risk of surgery for AAA was significantly reduced in patients receiving ACEIs (hazard ratio, 0.86 [95% confidence interval, 0.74–0.99]; P=0.040) but not in patients receiving ARBs (hazard ratio, 1.02 [95% confidence interval, 0.84–1.23]; P=0.867; P for difference=0.119).

Conclusions—In this observational study, treatment with ACEIs or ARBs was associated with a comparable reduction in mortality but not in surgery for AAA among patients with AAA. Randomized controlled trials are warranted to confirm these findings. (Arterioscler Thromb Vasc Biol. 2015;35:00-00. DOI: 10.1161/ATVBAHA.114.304428.)

Key Words: aneurysm | angiotensins | cardiovascular diseases | hypertension | pharmacoepidemiology

Abdominal aortic aneurysms (AAAs) are characterized by progressive luminal dilatation of the artery, scarcity of symptoms, and, ultimately, a high risk of rupture with frequent fatal outcomes.1 The prevalence of AAA in northern Europe ranges from 1.6% to 2.2% for men >65 years of age and ≈0.4% for women >70 years of age, respectively.2–5 In addition, AAAs are responsible for ≥10,000 deaths and ≈65,000 hospital admissions annually in the United States.6 Despite efforts aimed at finding pharmacological therapy for inhibition of AAA growth and rupture, open surgical treatment or endovascular artery repair remains the only validated interventions for AAAs.7–9

Activation of the renin–angiotensin system has been suggested to play a central role in the pathogenesis of AAA, although limited studies have indicated that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) can inhibit the growth and rupture of AAAs.8–10 However, there are experimental and clinical data to suggest that these 2 drug classes may not offer comparable protection, and in contemporary clinical practice guidelines for medical management of AAAs, these 2 classes of renin–angiotensin system inhibitors have received a weak recommendation with a low level of evidence.11–16 These conflicting data have led to calls for clinical trials in this area of research, and although randomized trials with ACEIs and ARBs in patients with AAA are ongoing with AAA growth rates as primary outcomes, studies powered for detection of effects on mortality from AAA and head-to-head randomized
comparisons of ACEIs and ARBs are less likely ever to be performed.16 Therefore, we used the Danish nation-wide registries to examine whether treatment with ACEIs or ARBs was associated with a reduction of hard clinical end points in patients with AAAs and the possibility of a difference in treatment effects between these 2 pharmacological regimens.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Ethics

Retrospective registry studies do not require ethical approval in Denmark. This project was approved by the Danish Data Protection Agency (no. 2007-58-0015/GEH-2014–015, I-Suite 02733).

Results

Study Population

During 1995 to 2011, 21791 patients with AAA were identified from the Danish registries of whom 3924 (18.0%) died, 4996 (22.9%) underwent surgery for AAA, and 3430 (15.7%) were diagnosed with congestive heart failure within the 60-day qualifying period. Consequently, 9441 patients were enrolled in the study. Of these, 1186 (12.6%) received ACEIs and 467 (5.0%) were treated with ARBs at baseline (Figure 1). In general, patients treated with ACEIs and ARBs were burdened with more comorbidity and received more concomitant treatment, but they were younger and with higher socioeconomic class than patients not treated with ACEIs or ARBs at baseline. Other baseline characteristics are listed in Table 1.

At study entry (date of AAA diagnosis plus 60 days), 5572 (59.0%) of the patients received ≤1 (group A), 2280 (24.2%) ≥2 (group B), and 1589 (16.8%) ≥3 (group C) antihypertensive drugs, respectively. In the time-dependent analysis, 3661 (38.8%), 2880 (30.5%), and 2900 (30.7%) patients were accumulated in groups A, B, and C, respectively (Figure 2). At 1, 3, and 5 years after study entry, the proportion of patients treated with ACEIs (21.1%, 26.3%, and 29.7%) and ARBs (9.4%, 12.4%, and 14.0%) increased, and mean adherence to treatment with ACEIs and ARBs was 3.1 (SD, 3.3) and 3.2 (SD, 3.3) years. A total of 527 patients switched from ACEIs to ARBs or vice versa during the follow-up period. The mean follow-up for the total study population and for patients who underwent surgery for AAA was 4.9 (SD, 4.0) and 1.7 (SD, 2.2) years, respectively.

Outcomes

Incidence rates per 100 patients-years for all study outcomes are shown in Table 2, and results from the adjusted Cox proportional analyses are listed in Table 3. Treatment with ACEIs and ARBs was associated with decreased risks of death from AAA, with hazard ratios (HRs) 0.64 (95% confidence interval [CI], 0.51–0.80; P<0.001) and 0.65 (95% CI, 0.48–0.88; P=0.006), respectively (Figure 3). The difference between treatment with ACEI or ARB was not significant (P=0.944).

As shown in Table 4, HRs for death from AAA and all-cause death, respectively, were significantly increased in patients treated with ≥2 antihypertensive drugs, and this risk increased with hypertension severity as determined by the number of antihypertensive drugs, whereas an opposite trend was observed for the risk of undergoing surgery for AAA. Furthermore, when data from patients treated with ACEIs or ARBs were combined, we found protective effects of these agents in all predefined subgroups (Figure 4). As for the secondary study outcomes, treatment with ACEIs or ARBs was associated with a significant decreased risk of all-cause death (Table 3 and Figure 3). However, outcomes for risk of surgery for AAA and for the composite of surgery for AAA or death from AAA, respectively, were only significant in patients receiving ACEIs (HR, 0.86 [95% CI, 0.74–0.99]; P=0.040 and HR, 0.82 [95% CI, 0.73–0.93]; P=0.001) and not significant for patients receiving ARBs (HR, 1.02 [95% CI, 0.84–1.23];
Sensitivity Analyses
When adjusting for treatment with ACEIs and ARBs at baseline only, ie, so that treatment with these agents was not allowed to change within 60 days before the event, results were comparable with those found in the time-dependent Cox analyses with HRs 0.65 (95% CI, 0.52–0.82; P<0.001) and 0.70 (95% CI, 0.52–0.94; P=0.019) for patients treated with ACEIs and ARBs, respectively. The differences between ACEIs and ARBs were not significant in these 2 sensitivity analyses (P=0.832 and P=0.700). When patients who underwent surgery for AAA were not censored, HRs of death from AAA were 0.64 (95% CI, 0.52–0.79; P<0.001) and 0.71 (95% CI, 0.54–0.93; P=0.014) for ACEIs and ARBs, respectively (P for difference=0.520).

### Table 1. Baseline Characteristics of Patients With Abdominal Aortic Aneurysms Treated With ACEIs, ARBs, or No ACEI/ARB

<table>
<thead>
<tr>
<th></th>
<th>ACEIs (n=1186)</th>
<th>ARBs (n=467)</th>
<th>No ACEI/ARB (n=7788)</th>
<th>Total (n=9441)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>765 (64.5%)</td>
<td>290 (62.1%)</td>
<td>5326 (68.4%)</td>
<td>6381 (67.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD), age, y</td>
<td>71.4 (10.4)</td>
<td>71.2 (9.2)</td>
<td>71.9 (10.5)</td>
<td>71.8 (10.5)</td>
<td>0.062</td>
</tr>
<tr>
<td>Year of inclusion</td>
<td></td>
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</tr>
<tr>
<td>1995–2000</td>
<td>271 (23.5%)</td>
<td>67 (14.3%)</td>
<td>2789 (35.7%)</td>
<td>3127 (33.1%)</td>
<td>...</td>
</tr>
<tr>
<td>2001–2005</td>
<td>284 (24.6%)</td>
<td>147 (31.5%)</td>
<td>2118 (27.1%)</td>
<td>2549 (27.0%)</td>
<td>...</td>
</tr>
<tr>
<td>2006–2011</td>
<td>600 (51.9%)</td>
<td>253 (54.2%)</td>
<td>2912 (37.2%)</td>
<td>3765 (39.9%)</td>
<td>...</td>
</tr>
<tr>
<td>Socioeconomic class</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>585 (50.6%)</td>
<td>213 (45.6%)</td>
<td>4174 (53.4%)</td>
<td>4972 (52.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>High</td>
<td>570 (49.4%)</td>
<td>254 (54.4%)</td>
<td>3645 (46.6%)</td>
<td>4469 (47.3%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension severity group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group A</td>
<td>294 (25.5%)</td>
<td>95 (20.3%)</td>
<td>5183 (66.3%)</td>
<td>5572 (59.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>433 (37.5%)</td>
<td>153 (32.8%)</td>
<td>1694 (21.7%)</td>
<td>2280 (24.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group C</td>
<td>428 (37.1%)</td>
<td>219 (46.9%)</td>
<td>942 (12.0%)</td>
<td>1589 (16.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>956 (82.8%)</td>
<td>402 (86.1%)</td>
<td>3221 (41.2%)</td>
<td>4579 (48.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>128 (11.1%)</td>
<td>70 (15.0%)</td>
<td>882 (11.3%)</td>
<td>1080 (11.4%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>40 (3.5%)</td>
<td>22 (4.7%)</td>
<td>238 (3.0%)</td>
<td>300 (3.2%)</td>
<td>0.115</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>288 (24.9%)</td>
<td>77 (16.5%)</td>
<td>1100 (14.1%)</td>
<td>1465 (15.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>179 (15.5%)</td>
<td>84 (18.0%)</td>
<td>1226 (15.7%)</td>
<td>1489 (15.8%)</td>
<td>0.398</td>
</tr>
<tr>
<td>Carotid artery stenosis</td>
<td>35 (3.0%)</td>
<td>16 (3.4%)</td>
<td>108 (1.4%)</td>
<td>159 (1.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>111 (9.6%)</td>
<td>33 (7.1%)</td>
<td>415 (5.3%)</td>
<td>559 (5.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>138 (11.9%)</td>
<td>69 (14.8%)</td>
<td>1212 (15.5%)</td>
<td>1419 (15.0%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>96 (8.3%)</td>
<td>36 (7.7%)</td>
<td>441 (5.6%)</td>
<td>573 (6.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>1 (0.1%)</td>
<td>0 (0.0%)</td>
<td>55 (0.7%)</td>
<td>56 (0.6%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Liver disease</td>
<td>10 (0.9%)</td>
<td>14 (3.0%)</td>
<td>143 (1.8%)</td>
<td>167 (1.8%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>149 (12.9%)</td>
<td>55 (11.8%)</td>
<td>1029 (13.2%)</td>
<td>1233 (13.1%)</td>
<td>0.680</td>
</tr>
<tr>
<td>Arhythmia</td>
<td>212 (18.4%)</td>
<td>61 (13.1%)</td>
<td>946 (12.1%)</td>
<td>1219 (12.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Statin</td>
<td>359 (31.1%)</td>
<td>159 (34.0%)</td>
<td>1231 (15.7%)</td>
<td>1749 (18.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blocker</td>
<td>413 (35.8%)</td>
<td>146 (31.3%)</td>
<td>1902 (16.7%)</td>
<td>1861 (19.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thiazide</td>
<td>292 (25.3%)</td>
<td>133 (28.5%)</td>
<td>779 (10.0%)</td>
<td>1204 (12.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>364 (31.5%)</td>
<td>162 (34.7%)</td>
<td>1410 (18.0%)</td>
<td>1936 (20.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>69 (6.0%)</td>
<td>5 (1.1%)</td>
<td>332 (4.2%)</td>
<td>406 (4.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral antidiabetic drugs</td>
<td>82 (7.1%)</td>
<td>30 (6.4%)</td>
<td>279 (3.6%)</td>
<td>391 (4.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>410 (35.5%)</td>
<td>157 (33.6%)</td>
<td>1721 (22.0%)</td>
<td>2288 (24.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>74 (6.4%)</td>
<td>27 (5.8%)</td>
<td>372 (4.8%)</td>
<td>473 (5.0%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>53 (4.6%)</td>
<td>20 (4.3%)</td>
<td>148 (1.9%)</td>
<td>221 (2.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P value for difference between the 3 groups

P=0.867 and HR, 0.92 [95% CI, 0.78–1.08]; P=0.313; P for difference=0.119 and 0.209, respectively.

**Sensitivity Analyses**
When adjusting for treatment with ACEIs and ARBs at baseline only, ie, so that treatment with these agents was not allowed to change over time, HRs for death from AAA were 0.80 (95% CI, 0.62–1.01; P=0.061) and 0.83 (95% CI, 0.58–1.19; P=0.304), respectively. Adjusting for treatment with ACEIs and ARBs 60 days before death from AAA, ie, treatment was not allowed to change within 60 days before the event, results were comparable with those found in the time-dependent Cox analyses with HRs 0.65 (95% CI, 0.52–0.82; P<0.001) and 0.70 (95% CI, 0.52–0.94; P=0.019) for patients treated with ACEIs and ARBs, respectively. The differences between ACEIs and ARBs were not significant in these 2 sensitivity analyses (P=0.832 and P=0.700). When patients who underwent surgery for AAA were not censored, HRs of death from AAA were 0.64 (95% CI, 0.52–0.79; P<0.001) and 0.71 (95% CI, 0.54–0.93; P=0.014) for ACEIs and ARBs, respectively (P for difference=0.520),
and in analyses exclusively restricted to patients who received surgery for AAA during follow-up, we found comparable results (HR, 0.69 [95% CI, 0.42–1.11; P=0.121] and HR, 0.96 [95% CI, 0.51–1.77; P=0.867]; P for difference=0.370). Similar results were also found when patients with congestive heart failure were included in the model, with HRs 0.87 (95% CI, 0.78–0.97; P=0.016) and 0.78 (95% CI, 0.66–0.93; P=0.006) for treatment with ACEIs and ARBs, respectively (P for difference=0.265). These results were corroborated in analyses that were not adjusted for hypertension severity group, with HRs 0.77 (95% CI, 0.62–0.95; P=0.014) and 0.79 (95% CI, 0.59–1.06; P=0.122) for treatment with ACEIs and ARBs, respectively (P for difference=0.853). Moreover, we found no association between risk of death from AAA and treatment with β-blockers (HR, 1.02 [95% CI, 0.92–1.32; P=0.290]) or calcium channel blockers (HR, 0.89 [95% CI, 0.74–1.07; P=0.211] when compared with patients not treated with β-blockers or calcium channel blockers, respectively. In addition, we repeated the main analyses with added adjustments for use of statins and found comparable results (not shown).

### Discussion

In this nation-wide cohort study, we examined the effects of ACEIs and ARBs on hard clinical end points in patients with AAA, with an average follow-up of 5 years. We found that ACEIs and ARBs were associated with a comparable reduction in risk of death from AAA and all-cause death but not surgery for AAA in the total study population and in all predefined subgroups of patients. This association was consistent in sensitivity analyses conditioned on ACEI and ARB treatment defined at baseline and at 60 days before death from AAA, respectively. Importantly, comparable results were found when we did not censor patients at the time of surgery for AAA, as well as in a subgroup analysis of patients who underwent surgery for AAA during follow-up. The main study results were further corroborated by analyses not censored for congestive heart failure and in models that were not adjusted for hypertension severity group, respectively. Also, the risk of death from AAA was not significantly modified by treatment with β-blockers or calcium channel blockers. These results suggest that ACEIs and ARBs may provide comparable protection against fatal outcomes in patients with AAA, as well as against AAA-related death in patients who have not yet undergone surgery for AAA.

In this study, an observed reduced risk of undergoing surgery for AAA in patients receiving ACEIs was only of borderline significance and no association was found between ARBs and surgery for AAA, which may be at odds with the apparent protective effects of ACEIs and ARBs otherwise found in our study. In this regard, it is important first to emphasize that in the main analysis, patients who underwent surgery for AAA were censored at the time of surgery and therefore did not contribute with risk-time for fatal outcomes, ie, these patients did not influence our findings for the primary study end point. Furthermore, as shown in Table 4, the probability of undergoing surgery for AAA declined with increasing hypertension severity as represented by the number of antihypertensive drugs used by the patients, whereas the risk of death from AAA and all-cause death both increased with an increased number of drugs. Therefore, patients who underwent surgery for AAA probably represented a selected subgroup burdened with less comorbidity. The mean duration of follow-up for these patients, ie, the time from AAA diagnosis to surgery was also notably shorter than for the total study population as AAAs are more likely to be diagnosed when symptomatic and hence ripe for surgery. Because of these considerations, surgery for AAA may not be a suitable proxy for AAA progression and the results for AAA surgery should be interpreted with caution. In attempt to model isolated effects of ACEIs and ARBs on AAA outcomes independent of blood pressures, we repeated the main analyses conditioned on ACEI and ARB treatment defined at baseline and at 60 days before death from AAA, respectively.

### Table 2.  IRs and Numbers of Study End Points Per 100 Patient-Years in Subjects With AAAs That Received ACEIs, ARBs, or No ACEI/ARB During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>ACEIs</th>
<th>No ACEI</th>
<th>ARBs</th>
<th>No ARB</th>
<th>ACEI/ARB</th>
<th>No ACEI/ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from AAA</td>
<td>3.6 (229)</td>
<td>4.9 (1260)</td>
<td>4.0 (111)</td>
<td>4.7 (1398)</td>
<td>3.7 (336)</td>
<td>4.9 (1173)</td>
</tr>
<tr>
<td>Surgery for AAA</td>
<td>6.3 (403)</td>
<td>6.9 (1812)</td>
<td>6.9 (193)</td>
<td>6.8 (2022)</td>
<td>6.4 (576)</td>
<td>6.9 (1639)</td>
</tr>
<tr>
<td>Surgery or death from AAA</td>
<td>9.8 (628)</td>
<td>11.7 (3067)</td>
<td>10.8 (304)</td>
<td>11.3 (3391)</td>
<td>10.1 (908)</td>
<td>11.8 (2787)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>9.1 (722)</td>
<td>13.3 (4389)</td>
<td>8.3 (300)</td>
<td>12.9 (4811)</td>
<td>8.9 (1008)</td>
<td>13.9 (4103)</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; and IR, incidence rate.
AAA Pathogenesis in Animal Models

AAA pathogenesis is thought to involve the activation of proinflammatory signaling pathways that mediate a shift in the extracellular matrix homeostasis of the abdominal aortic wall favoring the degradation of matrix proteins by matrix metalloproteases. Concomitantly, inflammatory cytokines mediate infiltration of macrophages and lymphocytes, which amplify proinflammatory cascades that weaken the artery wall and promote AAA growth, thrombus formation, and rupture. The renin–angiotensin system can play a pivotal role in these processes, and subcutaneous infusion of angiotensin II in atherosclerosis-prone apolipoprotein E–deficient mice rapidly leads to development of AAA. There are several small rodent models of AAA, and both ACEIs and ARBs markedly attenuate the development of AAAs in the models induced by angiotensin II infusion or intra-aortic elastase infusion. However, although an ACEI was also found to have protective effects in the model of aortic dissection in rats induced by feeding with β-aminopropionitrile monofumarate (an agent that inhibits cross-linking of collagen fibers), an ARB conferred no benefit in this model, possibly because of preferential upregulation of angiotensin II type 2 receptors in the diseased aortas. Although the 2 drug classes have different pharmacodynamic effects and, for example, ACEIs also inhibit bradykinin generation and current ARBs can lead to stimulation of the unblocked angiotensin II type 2 receptor, we are not aware of other reports of differential effects of these agents in experimental models of AAA.

### Human Data on Renin–Angiotensin System Inhibition and AAA Progression

In accordance with the results of this study, a previous retrospective cross-sectional case–control study of patients admitted to hospital with ruptured or intact AAAs found it less likely for ACEI-treated patients to present with ruptured AAA when compared with patients treated with other antihypertensive drugs, and the latter included ARBs, which were not associated with protection from rupture. In that study, however, only 1% patients received ARBs, which provided limited statistical power. On the other hand, in a study of patients participating in an AAA screening and surveillance program, ARBs but not ACEIs were associated with slower...
AAA growth rates, although this effect was not independent of all confounders. Moreover, a retrospective cohort study of 1701 patients with AAA found a significant increase in an AAA diameter growth rate of 0.67 mm/year in patients treated with ACEIs compared with no ACEI treatment. However, these findings were limited by variability of ultrasound imaging measurements, a small number of ACE-treated subjects (n=169), differences in baseline characteristics between the 2 groups, and lack of adjustment for changes of baseline drug therapy during the study period. By showing that ACEIs and ARBs were associated with comparable protective effects in a nation-wide cohort of patients with AAA, our results therefore add significantly to the existing evidence. Results of small and medium-scale (n<400) randomized trials of effects of ACEIs and ARBs on AAA growth rates are awaited, but as studies powered for detection of effects on mortality from AAA and head-to-head randomized comparisons of ACEIs and ARBs are less likely ever to be performed, it is possible that higher

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (CI)</td>
<td>HR (CI)</td>
<td>HR (CI)</td>
</tr>
<tr>
<td>Death from AAA</td>
<td>1.00</td>
<td>1.46 (1.24–1.71)</td>
</tr>
<tr>
<td>Surgery for AAA</td>
<td>1.00</td>
<td>0.96 (0.85–1.09)</td>
</tr>
<tr>
<td>Surgery or death from AAA</td>
<td>1.00</td>
<td>1.05 (0.95–1.16)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.00</td>
<td>1.13 (1.11–1.35)</td>
</tr>
</tbody>
</table>

Group A: ≤1 antihypertensive drug (reference), group B: 2 antihypertensive drugs, and group C: ≥3 antihypertensive drugs. CI: confidence interval; and HR: hazard ratio.

*P value for the overall effect of hypertension, using group A (≤1 antihypertensive drug) as reference.
levels of clinical evidence in this specific area of research may not be achievable.

**Strengths and Limitations**

In addition to methodological aspects discussed above, other considerations also apply to the interpretation of our results. By including all Danish patients with incident AAAs during the study period, we avoided selection bias related to, for example, subject sex, age, socioeconomic status, and labor market association. All medications examined in this study were dispensed only on prescription, and the National Prescription Register that is directly linked to the system for reimbursement of drug expenses has been found to be accurate.25 However, inaccuracies may have been introduced by our method of estimation of the average daily treatment dosage, as well as in the calculations of periods with and without treatment, respectively. Despite adjustment for some but not all factors known to influence AAA growth and rupture, residual confounding is inherent to observational studies and epidemiological associations do not per se represent causal relationships. Furthermore, results might have been affected by limited sensitivity of the diagnostic codes by which these risk factors were defined and confounding may have been introduced by the unequal distribution of baseline parameters of our patients, although most of these parameters were adjusted for in the Cox analyses. Furthermore, as Danish registries lack information about actual blood pressure, a proxy based on pharmacological treatment was used to differentiate between strata of hypertension severity. However, these surrogate measures of blood pressure were pragmatic and may have underestimated the true effect of hypertension. A major limitation in this study was the inability to adjust for smoking and cholesterol levels which both have been associated with AAA development.26,27 However, adjustment for chronic obstructive pulmonary disease/emphysema may have captured some effects of the former. Prescription data were additionally applied as proxies for congestive heart failure and diabetes mellitus, respectively, to strengthen the sensitivity of these international classification of diseases codes provided from hospital admissions, although this method does not account for cases treated with nonpharmacological therapies alone. In addition, as we found the positive predictive value of international classification of diseases codes related to AAAs to be 89%, limited data accuracy in this study may have influenced our results. Finally, the Danish population is predominantly of white descent and extrapolation of results to other ethnicities should be done with caution.

**Conclusions**

In this nation-wide pharmacoepidemiological study of patients with AAA, treatment with ACEIs and ARBs was associated with a comparable reduction of all-cause death and death from AAA in patients who had not yet undergone surgery for AAA, compared with patients not treated with these agents. The results support a role for the renin–angiotensin system in human AAA pathogenesis and suggest that ACEIs and ARBs may have comparable efficacy in patients with AAAs. Randomized controlled trials are warranted to confirm or refute these findings.

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**Disclosures**

None.

**References**


**Significance**

The renin–angiotensin system has been suggested to play a pivotal role in the pathogenesis of abdominal aortic aneurysms (AAAs). However, the capacity of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to limit AAA progression is unclear. We therefore conducted a Danish nation-wide cohort study of 9441 patients with AAA and a mean follow-up of 5 years and found a comparable reduction in risk of death from AAA associated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, respectively. Sensitivity analyses provided similar results, and other frequently used antihypertensive drugs, i.e., β-blockers and calcium channel blockers, did not modify the risk of death from AAA. These findings support the role of renin–angiotensin system in human AAA pathogenesis and add weight to use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for medical management of AAA.
Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients With Abdominal Aortic Aneurysms: Nation-Wide Cohort Study
Karl Emil Kristensen, Christian Torp-Pedersen, Gunnar Hilmar Gislason, Martin Êgfjord, Henrik Berg Rasmussen and Peter Riis Hansen

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Material and Methods

Registries

Each resident in Denmark has a unique and permanent ten digit identification number which enables linkage of information from the Danish nation-wide registries on an individual level. Since 1978, all admissions to Danish hospitals are collected in the Danish National Patient Registry according to the International Classification Code (ICD) and the Nordic classification of surgical procedures (NCSP), respectively. All redeemed prescriptions since 1995 are enumerated in The Danish Registry of Medicinal Product Statistics (the Prescription Registry), according to the Anatomical Therapeutic Chemical (ATC) classification system. This registry holds specific information on prescription date, package size, amount of packages, and strength of the medication. Causes of death are registered in the National Causes of Death Registry and information on birth date, vital status, sex, annual income and migration is collected in the Central Person Registry.

Study population and outcomes

During 1995–2011, we obtained information on all patients with AAAs (ICD8 441 and ICD10 DI 714, 716, 719, 719A, 790), identified in the National Patient Registry. We validated the AAA codes in a sample of 100 patients randomly selected from 3 separate Danish hospitals and found an overall positive predictive value of 89%. Diagnoses were substantiated by imaging techniques including ultrasound and computer tomography in 90% of the cases. We applied a 60-day qualifying period starting at the day of the AAA diagnosis to avoid an anticipated high risk of AAA complications in temporal proximity of establishment of the AAAs diagnosis and to allow sufficient time for patients to claim their prescriptions from pharmacies. Only patients, who survived the qualifying period without undergoing surgery for AAA (including endovascular aortic repair) were included in the study. Patients undergoing surgery for AAA within the follow up period were censored at the time of the surgical intervention and patients permanently leaving the country were censored at the time of emigration. Also, patients with congestive heart failure (CHF) were censored at the time of CHF diagnosis to decrease the probability of confounding by indication with ACEI and ARB treatment. The cohort was followed until occurrence of a study outcome or for a maximum of 10 years. The primary outcome of the study was death from AAA (ICD8 441 and ICD10 DI71). Secondary outcomes were surgery for AAA (procedure codes KPCG, KPCP, KPCQ, KPDG, KPDN, KPDP, KPDQ, KFCD and KPDC10), the composite of surgery for AAA or death from AAA, and all-cause death, respectively. We did not censor patients at time of surgery for AAA in our statistical modeling of all-cause death. The procedure codes for surgery for AAA have previously been validated in the Danish National Vascular Registry to have a reproducibility of 90-100%. The risk of surgery for AAA was defined as the probability of undergoing surgery for AAA within 10 years of diagnosis, the maximal time of follow up. Patients only contributed with one of the above-mentioned outcomes, whichever came first.

Concomitant medication, comorbidity and socioeconomics

Administration of ACEIs (ACT C09A), ARBs (C09B) and other medications were determined by prescription redemptions from the Danish pharmacies. The Danish Prescription Registry does not supply information on daily dosage or duration of treatment; therefore, we estimated an average daily dosage on the basis of up to four consecutive prescriptions. To avoid prediction on the future, calculations were exclusively based on previous prescription claims. By applying knowledge of the minimum, maximum, and ‘default’ (standard) treatment dose for each tablet strength of the specific drug of interest, we calculated whether the drug quantity dispensed to each individual was sufficient to allow for uninterrupted treatment between one prescription and the next. If this was not achievable, the treatment period was taken to be terminated at the
last day of treatment that was calculated from the on-going collection of consecutive prescriptions. If at a later point in time a new prescription was redeemed, a new treatment period was, by definition, initiated and the same scheme for determination of treatment periods was subsequently applied, so that several treatment periods were calculated for each individual patient. This method for determination of whether or not a drug was available to an individual at a particular time during follow-up has been used and validated by our group previously.6,7 To increase the sensitivity of the diagnostic codes, prescriptions of glucose-lowering drugs (A10), and loop diuretics (C03C) were used as proxies for diabetes and CHF, respectively.8,9 Similarly, we defined hypertension by treatment with two or more antihypertensive drugs within a period of three months, or any hospital admission with a hypertension diagnosis (ICD 8: 400-404; ICD10: D110-15).9 Because the severity of hypertension is thought to play a role for AAA growth and rupture, and because the Danish registries lack blood pressure data, patients were classified in three hypertension severity groups by use of the surrogate of number of antihypertensive drugs (including ACEIs, ARBs, centrally acting adrenergic agents, beta blockers, calcium channel blockers and diuretics), i.e., those receiving ≤1 (group A), 2 (group B), and ≥3 (group C) drugs, respectively.10 Furthermore, we gathered information on the following comorbidities which previously have been linked to an increased risk of AAA rupture: chronic obstructive pulmonary disease/emphysema (ICD 8: 491, 492; ICD 10: DJ42-44), chronic kidney disease (ICD 8: 403-4, 581-84; ICD 10: DN00-01, DN11-12, DN14, DN18-19, DN26, DN158-159, DN160, DN162-164, DN168, DQ612-613, DQ615, DQ619, DE102, DE112, DE132, DE142, DI120, DM300, DM313, DM319, DM321B), ischemic heart disease (ICD8: 410-414; ICD 10: DI20-DI25), peripheral artery disease (ICD 8: 440; ICD 10: DI702-709) and carotid artery stenosis (ICD 10: DI652).10-17 We also divided the study population into high and low socioeconomic class based on the individual average annual gross income throughout the 5-year period prior to inclusion.

Statistics

Crude incidence rates (IRs) for each study outcome per 100 person-years were calculated for patients treated with ACEIs or ARBs. Differences in baseline characteristics were tested with Student’s t-test and Chi-square test for continuous and categorical covariates, respectively. Adherence to a given drug was calculated as the sum of on-treatment years for the total study population divided by the number of treated patients. Cox proportional hazard models were used to model survival and other endpoints. Each observation was split at the occurrence of any change in covariates (including [on- or off-] treatment status with ACEIs, ARBs and the other reported drugs) and after each year. Thus all covariates were considered in a time-dependent fashion and patient time ‘at risk’ with or without ACEIs and ARBs (and with respect to the other reported covariates) was fragmented in to periods with different risk. Analyses were adjusted for age, sex, calendar year, socioeconomic class, diabetes, hypertension severity (group A, B, and C), chronic obstructive pulmonary disease, chronic kidney disease, ischemic heart disease, peripheral artery disease and carotid artery stenosis.18

To examine if study outcomes were influenced by premature termination of treatment due to advanced age or comorbidity, results were tested in sensitivity analyses adjusted for treatment status at baseline or 60 days before an event. As the main analysis of death from AAA was censored at the time of surgery for AAA, we also examined this endpoint in a model not censored for AAA surgery as well as in a subgroup of patients who underwent surgery for AAA during follow-up. To further examine the role of confounding, we included a sensitivity analysis that did not censor for patients diagnosed with CHF. In addition, risk of death from AAA was tested for two other frequently used antihypertensive agents, i.e., beta-blockers and calcium channel blockers, by applying the exact same statistical model as used in the main analysis. To assess the impact of blood pressure control on our results, the primary endpoint was tested in a model not adjusted for hypertension severity group. We further investigated outcomes for 17 pre-specified subpopulations dependent on sex, age >
or ≤ 70 years, socioeconomic class, hypertension severity (groups A, B, and C), and presence of diabetes, chronic obstructive pulmonary disease, ischemic heart disease and peripheral artery disease, respectively. The proportional hazard assumption, linearity of continuous variables and absence of interaction between variables were fulfilled if not otherwise specified. A two-sided P value of 0.05 or less was considered significant. Analyses and data management were performed in SAS version 9.2 (SAS Institute Inc. Cary, North Carolina).