Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study

Daniel G Hackam, Deva Thiruchelvam, Donald A Redelmeier

Summary

Background **Angiotensin-converting enzyme (ACE) inhibitors prevent the expansion and rupture of aortic aneurysms in animals. We investigated the association between ACE inhibitors and rupture in patients with abdominal aortic aneurysms.**

Methods **We did a population-based case-control study of linked administrative databases in Ontario, Canada. The sample included consecutive patients older than 65 (n=15 326) admitted to hospital with a primary diagnosis of ruptured or intact abdominal aortic aneurysm between April 1, 1992, and April 1, 2002.**

Findings **Patients who received ACE inhibitors before admission were significantly less likely to present with ruptured aneurysm (odds ratio [OR] 0·82, 95% CI 0·74–0·90) than those who did not receive ACE inhibitors. Adjustment for demographic characteristics, risk factors for rupture, comorbidities, contraindications to ACE inhibitors, measures of health-care use, and aneurysm screening yielded similar results (0·83, 0·73–0·95). Consistent findings were noted in subgroups at high risk of rupture, including patients older than 75 years and those with a history of hypertension. Conversely, such protective associations were not observed for β blockers (1·02, 0·89–1·17), calcium channel blockers (1·01, 0·89–1·14), α blockers (1·15, 0·86–1·54), angiotensin receptor blockers (1·24, 0·71–2·18), or thiazide diuretics (0·91, 0·78–1·07).**

Interpretation **ACE inhibitors are associated with a reduced risk of ruptured abdominal aortic aneurysm, unlike other antihypertensive agents. Randomised trials of ACE inhibitors for prevention of aortic rupture might be warranted.**

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Introduction

Abdominal aortic aneurysms develop in 4–8% of men and 0·5–1·5% of women older than 50 years.[1,2] The most catastrophic complication of this condition is rupture, which in the past occurred in up to a third of patients left untreated.[3] After rupture, 50% of patients die before reaching hospital.[4] Of the remainder, 24% die before surgery and 42% die after surgery, with a total mortality of 80–90%.[5,6] Elective surgical repair of unruptured abdominal aortic aneurysm carries a lower mortality rate (about 5%) but the overall rate of complications is 32%.[7] To date, no medical treatment has been shown to prevent aortic rupture or forestall the need for surgical repair.[8]

Activation of the renin-angiotensin system has been implicated in the genesis of several important cardiovascular pathologies, including heart failure, hypertension, and atherosclerosis.[9] Emerging evidence also links the renin-angiotensin system to the development of aortic aneurysms.[10] Angiotensin II is strongly upregulated in human aortic aneurysms, with increases mediated through pathways dependent on angiotensin-converting-enzyme (ACE) and chymase.[11–13] In genetic studies, polymorphisms at the ACE locus are associated with aortic, coronary, and cerebral aneurysms.[14–19] Data from studies in animals also suggest that ACE inhibitors might slow the progressive course of aortic aneurysms. In several animal models, ACE inhibitors prevented aortic expansion and rupture.[20–25] Such protective effects were not apparent for angiotensin receptor blockers, hydralazine, calcium channel blockers, or spironolactone, suggesting that the mechanism involved might not be related to reduction of blood pressure.[21–27]

We postulated that treatment with ACE inhibitors alters the risk of aortic aneurysm rupture in a population-based setting. We compared patients with ruptured and unruptured aortic aneurysm according to antecedent use of ACE inhibitors, taking into account important confounding factors. We tested for specificity by analysing the use of other antihypertensive and non-antihypertensive medications to ascertain whether the findings with ACE inhibitors were unique or were shared with other medications. We tested for selection bias by using a parallel cohort analysis and comparing the incidence of several important health-related outcomes in patients receiving and not receiving an ACE inhibitor.

Methods

Setting and data sources

We designed a retrospective, population-based, case-control study by linking several administrative health-care databases over 10 years in the province of Ontario. Throughout the study, Ontario was Canada's most populous province, with about 12 million people, of whom 1·6 million were aged 65 years or older. Elderly patients in Ontario had universal access to hospital care, doctors' services, and prescription drug coverage. Additionally, health-care records could be analysed using encrypted identifiers to track individuals over time. The study was

approved by the Sunnybrook Health Sciences Centre research ethics board and the University of Toronto Health Sciences research ethics board.

We used four large validated databases: the Ontario Drug Benefit database, which recorded prescription medications dispensed to all elderly patients in the province; the Canadian Institute for Health Information Discharge Abstract database, which recorded all hospital admissions, including diagnostic and procedural information; the Ontario Health Insurance Plan database, which provided information on all claims by doctors for inpatient and outpatient services; and the Ontario Registered Persons database, which contained vital statistics on all residents.[28–30] These four databases have been used extensively in past research to study population-based health outcomes.[31–34]

Patients and data collection

We included consecutive patients older than 65 years who were admitted to an Ontario hospital with a most responsible diagnosis of abdominal aortic aneurysm (International Classification of Diseases, ninth revision, clinical modification [ICD-9-CM] codes 441.3 and 441.4). The most responsible diagnosis was defined as "the one diagnosis which describes the most significant condition of the patient which causes his or her stay in hospital".[35] These codes have an accuracy of 94% for identifying patients with radiographically confirmed abdominal aortic aneurysm.[7] After accrual, patients were classified as cases or controls. Cases were individuals with identifiers for ruptured abdominal aortic aneurysm (ICD-9-CM code 441.3 or physician service code E627). Controls were the remaining individuals with unruptured abdominal aortic aneurysm. The primary outcome, therefore, was ruptured abdominal aortic aneurysm. We included patients admitted between April 1, 1992 and April 1, 2002 (10 years).

Demographic characteristics, risk factors for rupture, major comorbidities, and contraindications to ACE inhibitors were assessed by analysing inpatient and outpatient databases in the 3 years before admission for each patient. In accord with past research, the eight prespecified risk factors for aortic aneurysm rupture were older age, female sex, hypertension, emphysema, chronic renal insufficiency, ischaemic heart disease, peripheral arterial occlusive disease, and carotid stenosis.[36–43] Additional prespecified comorbidities were malignant disease, diabetes mellitus, dementia, heart failure, cerebrovascular disease, chronic liver disease, alcoholism, peptic ulcer disease, and cardiac dysrhythmias. The prespecified contraindications for ACE inhibitors were a history of hyperkalaemia, angioneurotic oedema, hypotension, and renal artery stenosis.[44]

We also assessed diverse measures of health-care use, since access to care might affect the course of abdominal aortic aneurysm by allowing opportunities for detection and repair.[45,46] Specifically, we noted the number of visits to cardiologists, cardiovascular surgeons, general surgeons, or vascular surgeons in the year before admission, as well as the total number of visits to any doctor in the year before admission. We identified any abdominal ultrasonography, abdominal computed tomography, abdominal magnetic resonance imaging, electrocardiography, echocardiography, and cholesterol testing in the 3 years before admission as additional objective events related to access and screening. We included three validated measures of overall health status as the number of hospital admissions in the preceding 3 years, the number of distinct medications prescribed in the past year, and the Charlson Comorbidity Index.[47–49]

The primary exposure of the study was the receipt of treatment with ACE inhibitors before admission. Filled prescriptions for ACE inhibitors were identified by searching the Ontario Drug Benefit database for each patient anywhere in the province. The coding accuracy of this database is excellent, with comprehensive inclusivity and an error rate of 0·7%.[30] Because patients received a maximum of 90 days treatment with each successive prescription, ACE inhibitor therapy was defined as two or more prescriptions in the year before admission with at least one prescription in the 3 months immediately before admission.[50] All ten ACE inhibitors available in Ontario were included in the analysis: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and trandolapril. We allowed patients to switch between different types and doses of ACE inhibitors without exclusion. Combination therapies containing ACE inhibitors were also included.

Analyses

The primary analysis used logistic regression to compute the association of ACE inhibitors and aortic rupture. Multivariable analyses adjusted for demographic characteristics, risk factors for rupture, other comorbidities, contraindications to treatment, health-care access, and screening. All tests were two-tailed with a p value of 0·05 deemed significant and an odds ratio of less than 1·0 indicating a protective association. The sample size was estimated to provide sufficient power to detect a 15% relative change in the risk of aortic rupture associated with ACE inhibitors. All analyses were done with SAS statistical software, version 8.2 (SAS Institute, Cary, NC, USA).

We did several additional analyses to test the robustness of our findings.

First, we repeated the main analysis by assessing the risk of rupture in relation to ACE inhibitor dosing, estimated according to the last prescription before admission.[51] Second, we investigated the risk of rupture according to the three most common ACE inhibitors in our sample: enalapril, lisinopril, and ramipril. Third, we assessed rupture and exposure to ACE inhibitors in 14 prespecified patient subgroups based on age, sex, socioeconomic status, history of hypertension, peripheral arterial disease, ischaemic heart disease, and emphysema. The intent of the latter analyses was to examine the

association of ACE inhibitors with aortic rupture in distinct settings that increase the risk of rupture.

As a test of specificity, we assessed exposure to five other major antihypertensive classes in relation to rupture: α blockers, angiotensin receptor blockers, β blockers, calcium channel blockers, and thiazide diuretics (webpanel 1). The intent of these tracer analyses was to check for the presence of an association where such an association might be expected. To test for selection bias, whereby healthier patients are more likely to receive preventive medications, we also assessed the relation between six commonly prescribed non-antihypertensive drug classes and rupture: antidepressants, gastric acid suppressants, thyroid hormone replacement, sedative-hypnotics, lipid-lowering agents, and anti-osteoporosis medications (webpanel 2). The intent of these analyses was to check for the absence of association where no association would be expected based on direct biological effects.

We also examined the risk of rupture in patients who were on ACE inhibitors but discontinued them more than 3 months before admission; we compared the risk of rupture in these patients with that in other patients who never received an ACE inhibitor. Since discontinued treatment with ACE inhibitors would probably not protect against aortic rupture, the intent of this analysis was to ascertain whether patients prescribed an ACE inhibitor had an innately lower risk of rupture than patients not prescribed an ACE inhibitor.

As a further test for confounding, we assessed the incidence of five distinct markers of health in follow-up, comparing users and non-users of ACE inhibitors. The five outcomes were subsequent admission for infection, respiratory disease, trauma, cataract repair, and cancer (webpanel 3). Follow-up for these analyses began on the date of discharge from the index admission and continued until death, the event, or March 31, 2002, if the patient's course was uneventful. The intent of these analyses was again to test whether patients receiving ACE inhibitors were inherently healthier than those not receiving ACE inhibitors.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

15 326 patients with abdominal aortic aneurysm were admitted to 231 hospitals during the 10-year accrual period. Of the sample, 22% had ruptured aneurysms and 78% had intact aneurysms (table 1). Overall, the mean age was 75 years (SD 6), and 78% of the patients were men. Contraindications to ACE inhibitor treament were rare (all ≤2%). Indications for ACE inhibitors were balanced between the two groups but, as expected, controls were more likely to have undergone abdominal imaging or surgical consultation before the index admission ($p<0·0001$ for both). The three measures of overall health status (number of drugs prescribed, Charlson index, and number of previous admissions) were similar between the two groups.

See Online for webpanels 1, 2, and 3

	Cases (n=3379)	Controls (n=11 947)
Demographics		
Age (years)	76·8 (7·0)	74·2 (5·5)
Income (Canadian $)	23 997 (8394)	24 432 (8349)
Male sex	2507 (74%)	9514 (80%)
Long-term care	123 (4%)	86 (1%)
Home care	630 (19%)	1373 (11%)
Rural residence	536 (16%)	2060 (17%)
Risk factors for rupture		
Emphysema	999 (30%)	3468 (29%)
Chronic renal failure	297 (9%)	931 (8%)
Hypertension	2220 (66%)	8112 (68%)
Ischaemic heart disease	1126 (33%)	4177 (35%)
Peripheral artery disease	1280 (38%)	6310 (53%)
Carotid artery disease	76 (2%)	356 (3%)
Other comorbidities		
Malignancy	294 (9%)	1321 (11%)
Diabetes mellitus	418 (12%)	1601 (13%)
Dementia	279 (8%)	480 (4%)
Heart failure	422 (12%)	1126 (9%)
Cerebrovascular disease	160 (5%)	448 (4%)
Chronic liver disease	30 (1%)	82 (1%)
Alcoholism	45 (1%)	198 (2%)
Peptic ulcer disease	314 (9%)	1413 (12%)
Cardiac dysrhythmias	605 (18%)	2361 (20%)
Contraindications to ACE inhibitors		
Hyperkalaemia	21 (1%)	34 (0·3%)
Angioedema	0 (0%)	5 (0·04%)
Hypotension	39 (1%)	135 (1%)
Renal artery stenosis	25 (1%)	282 (2%)
Health care and screening		
Cardiologist visits, past year	0·4 (2·0)	1·1 (2·5)
Cardiac surgeon visits, past year	0·1 (0·7)	0·6 (1·7)
Vascular surgeon visits, past year	0·3 (1·2)	1·4 (2·0)
General surgeon visits, past year	0·8 (2·9)	2·3 (3·2)
Total outpatient visits, past year	10·7 (8·8)	14·9 (8·7)
Admissions, past 3 years	0·9 (1·5)	0·9 (1·5)
Number of medications, past year	8·2 (6·5)	8·5 (5·9)
Charlson index, units	1·1 (1·5)	1·0 (1·3)
Cholesterol testing	1454 (43%)	7285 (61%)
Electrocardiography	2098 (62%)	10 310 (86%)
Echocardiography	599 (18%)	4447 (37%)
Abdominal ultrasound	1005 (30%)	9892 (83%)
Abdominal CT or MRI	419 (12%)	5807 (49%)

Data are mean (SD) for continuous variables, n (%) for categorical variables.

Table 1: **Baseline characteristics of patients**

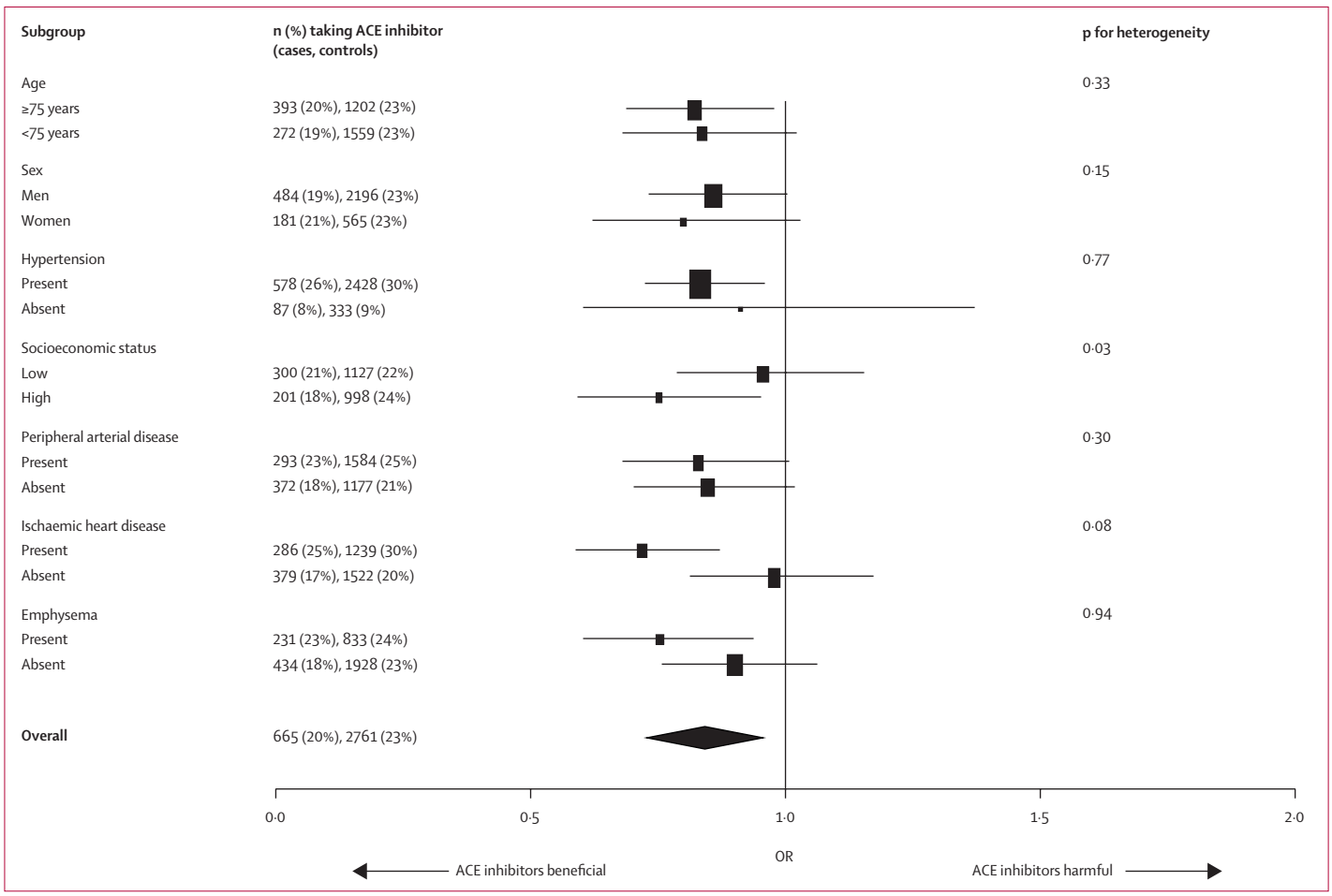

Figure 1: **Association of ACE inhibitors with aortic rupture in subgroups**
ORs for ruptured abdominal aortic aneurysm in patients receiving ACE inhibitors compared with patients not receiving ACE inhibitors. Subgroup ORs are shown as squares and overall ORs as diamonds, with size proportional to the amount of information contained in each analysis. Horizontal lines are 95% CI. N (%) refers to cases and controls receiving ACE inhibitors in each subgroup. All results adjusted for demographic characteristics, rupture risk factors, other comorbidities, contraindications to ACE inhibitors, and measures of health-care use and screening.

	Number (%) taking medication	OR (95% CI)†
Antihypertensives		
α blockers	497 (3%)	1·15 (0·86–1·54)
Angiotensin receptor blockers	132 (1%)	1·24 (0·71–2·18)
Thiazide diuretics	1705 (11%)	0·91 (0·78–1·07)
β blockers	2753 (18%)	1·02 (0·89–1·17)
Calcium channel blockers	3836 (25%)	1·01 (0·89–1·14)
Non-antihypertensives		
Antidepressants	871 (6%)	0·98 (0·79–1·21)
Gastric acid suppressants	2416 (16%)	0·95 (0·82–1·10)
Thyroid hormone replacement	1001 (7%)	0·96 (0·79–1·18)
Sedative-hypnotics	2637 (17%)	0·90 (0·78–1·03)
Lipid-lowering agents	2500 (16%)	1·03 (0·88–1·20)
Anti-osteoporosis agents	324 (2%)	1·00 (0·70–1·43)

OR<1·0 indicates protective association, 95% CIs that exclude 1·0 are statistically significant. †Adjusted for demographic factors, risk factors for rupture, other comorbidities, contraindications to ACE inhibitors, and measures of health-care use and screening.

Table 2: **Risk of ruptured abdominal aortic aneurysm in relation to other medications**

Overall, 3426 patients (22%) received ACE inhibitor therapy before admission, including 665 (20%) of the cases and 2761 (23%) of the controls. In the primary analysis, patients receiving ACE inhibitors had an 18% lower odds of aortic rupture than patients not receiving ACE inhibitors (odds ratio 0·82, 95% CI 0·74–0·90, p<0·0001). Adjustment for demographic characteristics, risk factors for rupture, other comorbidities, contraindications, measures of health-care use and screening gave similar results (0·83, 0·73–0·95, p=0·008). The predictive fit of this model was good (C statistic 0·87).

The protective association between ACE inhibitors and aortic rupture was further assessed by dose, agent, and setting. 720 (21%) of patients taking ACE inhibitors were prescribed the lowest available dose, with the remainder (2706, 79%) taking higher doses. Both dose groups had a lower risk of rupture than patients not receiving ACE inhibitor therapy: adjusted OR 0·74 (95% CI 0·57–0·94) for those taking the lowest dose and 0·82 (0·71–0·94) for those on higher doses. Findings for the three most

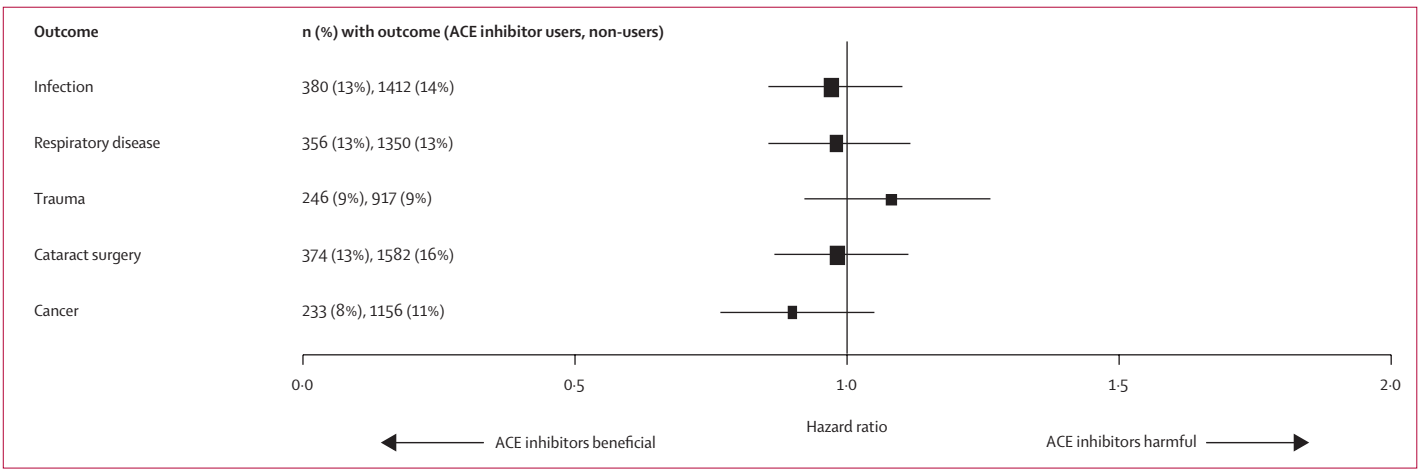

Figure 2: **Association of ACE inhibitors with other disease outcomes**
Hazard ratios for disease outcomes in patients receiving ACE inhibitors compared with patients not receiving ACE inhibitors. Data show point estimates as squares and 95% CIs as horizontal lines, with size proportional to the amount of information contained in each analysis. N (%) refers to ACE inhibitor users and non-users incurring each outcome. All results adjusted for demographic characteristics, rupture risk factors, other comorbidities, contraindications to ACE inhibitors, and measures of health-care use and screening.

prevalent ACE inhibitors were similar: enalapril (adjusted OR 0·67, 95% CI 0·56–0·80), lisinopril (0·82, 0·62–1·09), and ramipril (0·86, 0·61–1·22). ACE inhibitor therapy showed a protective association across most of the prespecified subgroups, although the results in several cases were not statistically significant (figure 1). Patients who were prescribed ACE inhibitors but discontinued them before admission were not protected from aortic rupture (adjusted OR 1·39, 95% CI 1·09–1·77). The mean time between the last prescription and hospital presentation in those who discontinued treatment was 5·9 months (SD 2·6).

Many patients in the sample were receiving other antihypertensive treatments at the time of admission. Unlike ACE inhibitors, none of these drugs was associated with a reduced risk of rupture (table 2); neither was any of the six common non-antihypertensive drugs that we assessed (table 2).

The five health-related outcomes we assessed all had high incidence (range of rates 9–15%). We noted no association between ACE inhibitor therapy and subsequent infection, respiratory disease, trauma, cataract repair, or cancer (figure 2). This balance suggests that patients who received ACE inhibitors were not inherently healthier than those who did not.

Discussion

We showed that ACE inhibitors were associated with a reduced risk of rupture in patients who have abdominal aortic aneurysms. This association was maintained after adjustment for measured confounders, was robust in sensitivity analyses of different agents and doses, and was consistent across predefined patient subgroups. Moreover, the relation between ACE inhibitors and aortic rupture was distinct and was not apparent for other antihypertensive medications or for drugs linked to preventive health care, such as lipid-lowering agents or anti-osteoporosis drugs; nor was it evident for discontinued ACE inhibitors. Finally, these data are congruent with preclinical evidence on ACE inhibitors and aortic aneurysms.[20–25]

The most important limitation of this study was potential selection bias, whereby healthier patients with a lower risk of rupture might be more likely to receive ACE inhibitors. However, five features of the study render such artifacts less likely. First, indications and contraindications for ACE inhibitor therapy were balanced between cases and controls, which would be expected, since all patients had manifest vascular disease. Second, multivariable adjustment for demographic characteristics, health-care access and screening, risk factors for rupture, other comorbidities, and contraindications did not substantially affect our findings. Third, patients who received ACE inhibitors but stopped them before admission were not protected from rupture. Fourth, selection bias would not explain the absence of association between other preventive medications and aortic rupture. Fifth, we found no evidence that users of ACE inhibitors were favoured on other health-related outcomes.

Several biological pathways provide a mechanism by which ACE inhibitors might prevent rupture of abdominal aortic aneurysms. Provision of angiotensin II to hyperlipidaemic mice increases aortic stiffness by 900%, reduces elastin content by 74%, and induces the formation of abdominal aortic aneurysms.[52] These effects are reversed by concomitant treatment with an ACE inhibitor. In patients with established abdominal aortic aneurysms, ACE inhibitors (but not other antihypertensive agents) augment systemic collagen synthesis and reduce stiffness of the aortic wall.[53] Augmentation index and pulse wave velocity are decreased under ACE inhibition, and arterial compliance improves.[54] In human beings and animals, ACE inhibitors reduce vascular inflammation, increase

elastin and fibrillin deposition, and inhibit matrix metalloproteinases.[21,54] Some of these mechanisms might also apply to angiotensin receptor blockers, but because only 1% of patients in our sample took such agents, we were unable to ascertain whether our findings with ACE inhibitors extend to angiotensin receptor blockers.

Hypertension is a risk factor for the development and rupture of aortic aneurysms, yet control of hypertension is often insufficient for stabilising the aneurysmal wall. In randomised trials of patients with aortic aneurysms, the β blocker propranolol lowered blood pressure but did not affect expansion of the aneuryms, the need for surgical repair, or mortality.[55–57] We also found no association between β blockers and the risk of aortic rupture. In experimental animal models, ACE inhibitors were substantially more effective at preventing aneurysm growth and rupture than were other antihypertensive agents, including calcium channel blockers, hydralazine, spironolactone, and angiotensin receptor blockers.[21–27] Taken together, these findings suggest that ACE inhibitors might be distinct in affecting the pathophysiology of abdominal aortic aneurysms.

We observed no dose-response relation for ACE inhibitors and aortic rupture in our study. Possibly, our dichotomisation of dosing might have missed an important threshold effect. Misclassification of dosing might have occurred if patients were instructed by their doctors to double up or take half of their prescribed doses. Alternatively, in view of the paucity of previous evidence on ACE inhibitor dosing and clinical outcomes, it might be that both dose levels protect against aortic rupture. Two additional limitations are the absence of detailed information on smoking status (a major risk factor for aortic aneurysm enlargement[58]) and our inability to include patients with ruptured aneurysm who died before reaching hospital. Unmeasured deaths in the community, however, would not explain why the reduced risk of rupture was associated only with ACE inhibitors and not with other antihypertensive agents.

Our findings could have implications for care of patients and research. First, patients with established abdominal aortic aneurysm who are not candidates for repair might benefit from treatment with ACE inhibitors; this approach is consistent with guidelines advocating intensive management of cardiovascular risk in this population.[59] Second, our findings emphasise the high incidence of unrelated diseases (such as infections and trauma) in patients with aortic aneurysms, which might have consequences for health promotion and prevention of illness in this population. Third, since no proven medical treatments exist for this disease, our results provide substantial motivation for clinical trials. Such a trial could proceed in two phases. An initial pilot study in patients with small aortic aneurysms could evaluate the effect of ACE inhibitor therapy on aneurysmal growth. If positive, a larger randomised trial might then assess whether ACE inhibitors truly modify the natural history of this disease.

Contributors

D G Hackam took part in study conception and design, interpretation of the results, and drafting of the manuscript. D Thiruchelvam took part in study design, statistical analyses, data acquisition, and revision of the manuscript. D A Redelmeier took part in study conception, design, interpretation of the results, and revision of the manuscript, and provided supervision and administrative support. All authors approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest related to this work.

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