A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly


ABSTRACT

BACKGROUND
Treatment of hypertension with diuretics, beta-blockers, or both leads to improved outcomes. It has been postulated that agents that inhibit the renin–angiotensin system confer benefit beyond the reduction of blood pressure alone. We compared the outcomes in older subjects with hypertension who were treated with angiotensin-converting–enzyme (ACE) inhibitors with the outcomes in those treated with diuretic agents.

METHODS
We conducted a prospective, randomized, open-label study with blinded assessment of end points in 6083 subjects with hypertension who were 65 to 84 years of age and received health care at 1594 family practices. Subjects were followed for a median of 4.1 years, and the total numbers of cardiovascular events in the two treatment groups were compared with the use of multivariate proportional-hazards models.

RESULTS
At base line, the treatment groups were well matched in terms of age, sex, and blood pressure. By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE-inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient-years; the hazard ratio for a cardiovascular event or death with ACE-inhibitor treatment was 0.89 [95 percent confidence interval, 0.79 to 1.00]; P=0.05). Among male subjects, the hazard ratio was 0.83 (95 percent confidence interval, 0.71 to 0.97; P=0.02); among female subjects, the hazard ratio was 1.00 (95 percent confidence interval, 0.83 to 1.21; P=0.98); the P value for the interaction between sex and treatment-group assignment was 0.15. The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE-inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE-inhibitor group).

CONCLUSIONS
Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure.
PLACEBO-CONTROLLED STUDIES OF THE
drug treatment of mild-to-moderate hyper-
tension have demonstrated that the reduc-
tion of blood pressure is associated with a reduced
risk of cardiovascular events and death.1-7 This
benefit was first shown with diuretics, beta-block-
ers, or both as initial therapy.1-6 Since those studies
were conducted, newer classes of antihypertensive
agents, including angiotensin-convertase–enzyme
(ACE) inhibitors, calcium-channel antagonists, and
angiotensin II antagonists, have become widely ac-
cepted into practice. When our study began, no data
were available indicating whether therapy involving
these newer agents would have the same benefit in
persons with hypertension. However, evidence of a
benefit of treatment with ACE inhibitors in the im-
provement of impaired cardiac function8-10 sug-
gested that they conferred additional benefit beyond
their ability to lower blood pressure, possibly be-
cause of effects on independent cardiovascular risk
factors.11-13 It had earlier been suggested that ex-
cessive activity of the renin–angiotensin system had
deleterious cardiovascular effects beyond its influ-
ence on blood pressure.14
During the past three to four years, results have
been published of studies evaluating differences be-
tween regimens based on conventional agents and
regimens based on newer drugs in terms of out-
comes in hypertensive subjects.15-18 None of the
studies involving ACE inhibitors or calcium-channel
antagonists has yet demonstrated a clear difference
in outcome between treatment groups.19 The recent
Heart Outcomes Prevention Evaluation (HOPE)
study reported that ACE inhibitors confer a benefit in
terms of outcome despite the fact that they result
in little or no change in blood pressure in high-risk
subjects.20 Further supportive evidence comes from
the Losartan Intervention for Endpoint Reduction
(LIFE) study, which demonstrated that antihyper-
tensive therapy with the angiotensin II antagonist
losartan prevented more cardiovascular events and
deaths than did therapy with the beta-blocker atenolol,
which led to a similar reduction in blood pressure.21
Our study was undertaken to address the ques-
tion of possible regimen-specific benefit with re-
spect to the outcome of the treatment of
hypertension. We investigated whether there was
any difference in outcome between hypertensive
subjects who are actively treated with an ACE-inhib-
itor–based regimen and those treated with a diuret-
ic-based regimen. Unlike many previous studies,
our study enrolled older subjects with hyperten-
sion who had had few previous cardiovascular
events. The study was conducted at family practices
throughout Australia and thus reflects routine clinical
practice for the management of hypertension.

METHODS

STUDY DESIGN
The study design and recruitment strategies have
been published previously.22-24 In brief, the study
was conducted at 1594 family medical practices
throughout Australia, with the use of a prospective,
randomized, open-label design, with blinded as-
sessments of end points.25
At screening, blood pressure was measured by
trained study nurses using a mercury sphygmo-
nometer in all eligible subjects 65 to 84 years of
age.26 Suitable subjects had two subsequent study-
entry visits at least one week apart. In subjects who
were taking antihypertensive drugs, medication was
discontinued under medical supervision. Subjects
were required to be free of antihypertensive drugs
for at least one week before the study-entry visits.

CRITERIA FOR INCLUSION AND EXCLUSION
Criteria for inclusion in the study were an average
systolic blood pressure, measured at the two study-
entry visits while the subject was sitting, of at least
160 mm Hg or an average diastolic blood pressure
of at least 90 mm Hg (if the systolic blood pressure
was at least 140 mm Hg); the absence of recent car-
diovascular events (within the previous six months);
and willingness to give informed consent. Criteria
for exclusion included any life-threatening illness,
contraindication to an ACE inhibitor or diuretic, a
plasma creatinine concentration of more than 2.5
mg per deciliter (221 µmol per liter), malignant hy-
pertension, or dementia. Subjects were randomly
assigned centrally by telephone to either ACE-inhib-
itor–based or diuretic-based treatment. Random-
ization began in April 1995 and was completed in
June 1998.

GOALS AND TREATMENTS
Family practitioners were responsible for the man-
agement of antihypertensive therapy, which was to
conform to the randomized treatment assignment
and the study’s blood-pressure goals. The guide-
lines were based on the aim of achieving a reduction
of the systolic blood pressure by at least 20 mm Hg
to less than 160 mm Hg, with a further reduction to
less than 140 mm Hg if tolerated, and a reduction
of the diastolic blood pressure by at least 10 mm Hg
to less than 90 mm Hg, with a further reduction to
less than 80 mm Hg if tolerated. The ACE inhibi-
tor enalapril and the diuretic hydrochlorothiazide
were recommended as initial therapy; however, the
choice of the specific agent and dose was made by
the family practitioner.

To achieve the blood-pressure goals, the addition
of beta-blockers, calcium-channel blockers, and al-
pha-blockers was recommended in both groups. Blood
pressure was recorded annually by study
nurses and at each patient visit by the general practi-
tioner, using routine mercury sphygmomanometry.
Case records, hospital notes, and death certificates
were reviewed by study nurses for documentation of
end points every six months throughout the study.

END POINTS
The primary end point was all cardiovascular events
or death from any cause. Both initial and subsequent
fatal and nonfatal cardiovascular events were in-
cluded. Cause-specific cardiovascular events in-
cluded the following: coronary events, including
myocardial infarction, sudden or rapid death from
cardiac causes, other deaths from coronary causes,
or coronary events associated with therapeutic pro-
cedures involving the coronary arteries; other car-
diovascular events, including heart failure, acute oc-
cclusion of a major feeding artery in any vascular bed
other than cerebral or coronary, death from non-
coronary cardiac causes, dissecting or ruptured aor-
tic aneurysm, or death from vascular causes; and
cerebrovascular events, including stroke and tran-
sient ischemic attacks. An end-point committee
whose members were unaware of the treat-
ment-group assignments adjudicated all potential end
points.

APPROVAL, SUPPORT, AND CONDUCT
OF THE STUDY
The protocol was approved by the ethics committee
of the Royal Australian College of General Practi-
tioners and conducted in accordance with the Hel-
sinki Declaration. All subjects gave written in-
formed consent. The study is a project of the High
Blood Pressure Research Council of Australia that
was initiated, designed, and conducted by the inves-
tigators. Although it was funded by a joint venture
of the Commonwealth Government of Australia,
the National Health and Medical Research Coun-
cil, Merck Sharp & Dohme, and academic institu-
tions, all data analysis and writing were performed
independently by the publications committee, with-
out the involvement of representatives of Merck
Sharp & Dohme.

STATISTICAL ANALYSIS
Three thousand subjects were required in each
group for the study to achieve a power of 90 percent
to detect a 25 percent difference between the treat-
ment groups in the rate of cardiovascular events
during a five-year period, assuming a rate of 21
events per 1000 person-years in the diuretic group and
allowing for a 15 percent loss to follow-up. The
management committee decided to stop the trial
because the observed total number of events had
well exceeded the number required on the basis of
the estimate of sample size and because resources
became limited as the result of an extension of the
recruitment period. No comparison of the treatment
groups in terms of data on outcomes was performed
before the study was terminated.

Cox regression was used to model multiple times
to events, with the treatment-group assignment as
the principal predictor. An event was defined as
any cardiovascular event or death from any cause.
Robust estimates of variance were used to allow for
the clustering of subjects according to practitioner,
and potential confounding by risk factors was ex-
plored by analysts who were unaware of changes in
P values or of the direction of changes in esti-
mates. Only age and sex changed estimates sub-
stantially and were therefore adjusted for in the
model. Cumulative hazard functions were plotted to
check for proportional hazards. Simulation meth-
ods were used to validate estimates of the hazard ra-
tios and confidence intervals.

The two primary comparisons (all events and
any first events) were tested at the 0.05 level of sig-
ificance. Hazard ratios with 95 percent confidence
intervals and two-sided P values are presented. Haz-
ard ratios from secondary comparisons of cause-
specific first events and subgroups defined accord-
ing to sex are also shown with 95 percent confidence
intervals and P values unadjusted for multiple test-
ing, in order to facilitate comparisons with results
from other studies. However, the significance of
these secondary results should be judged cautious-
ly. The number needed to treat to avoid one addi-
tional event was estimated from survival functions
based on the proportional-hazards model. All re-
S hortly.
**RESULTS**

**STUDY SUBJECTS**

A total of 54,288 subjects presented for the initial screening visit. Fifty-eight percent (31,255) either were currently being treated for hypertension (25,926 subjects [48 percent]) or had untreated blood pressure in the range specified by the eligibility criteria (5329 subjects [10 percent]). A total of 8316 subjects (4682 previously treated subjects and 3634 untreated subjects) had study-entry visits, and 6083 subjects (95 percent of whom were white) were subsequently randomly assigned to the ACE-inhibitor group (3044 subjects) or the diuretic group (3039 subjects) (Fig. 1). Subjects were recruited over a 3-year period and were followed for a median of 4.1 years, for a total of 24,702 patient-years of observation. As indicated in Figure 1, all subjects who underwent randomization were included in the final analysis. For subjects who were lost to follow-up monitoring, we used the last available data; vital status was ascertained for all but two subjects.

![Figure 1. Summary of Screening, Randomization, and Loss to Follow-up.](image-url)

ACE denotes angiotensin-converting enzyme.
The two treatment groups were similar in terms of sex, age, blood pressure, body-mass index (the weight in kilograms divided by the square of the height in meters), plasma cholesterol concentration, tobacco and alcohol use, the level of physical activity, and the extent of previous treatment with antihypertensive drugs (Table 1). Eight percent of subjects had previously had a coronary event, 5 percent had previous cerebrovascular disease, and 7 percent had received a diagnosis of diabetes. Mean (±SD) systolic blood pressure at entry was 168±13 mm Hg; mean diastolic blood pressure at entry was 91±8 mm Hg.

Outcomes
The overall rates of all cardiovascular events or death in the two treatment groups are shown in Table 2. The hazard ratio for all cardiovascular events or death from any cause among subjects in the ACE-inhibitor group as compared with those in the diuretic group was 0.89 (95 percent confidence interval, 0.79 to 1.00; P=0.05); in other words, there was an 11 percent reduction in the total burden of events between the groups in the change in diastolic blood pressure at any time point. The pattern of blood-pressure reduction with the two treatments was similar among men and among women.

Table 1. Base-Line Characteristics of the Subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACE-Inhibitor Group (N=3044)</th>
<th>Diuretic Group (N=3039)</th>
<th>All Subjects (N=6083)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td>Male 50</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Female 50</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>Mean 72.0</td>
<td>71.9</td>
<td>71.9</td>
</tr>
<tr>
<td></td>
<td>65–74 yr 70</td>
<td>70</td>
<td>70</td>
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<tr>
<td></td>
<td>75–84 yr 30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Blood pressure at randomization (mm Hg)</td>
<td>Systolic 167±13</td>
<td>168±13</td>
<td>168±13</td>
</tr>
<tr>
<td></td>
<td>Diastolic 91±8</td>
<td>91±8</td>
<td>91±8</td>
</tr>
<tr>
<td>Blood-pressure grade (%)</td>
<td>1 20</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>2 65</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>3 15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Previously treated (%)</td>
<td>62</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>27±4</td>
<td>27±4</td>
<td>27±4</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>Current 7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Previous 46</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>Current 74</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Previous 6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>78</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>38</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Receiving lipid-lowering drugs</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Coronary heart disease included myocardial infarction, angina, coronary-artery bypass grafting, and percutaneous transluminal coronary angioplasty; cerebrovascular disease included stroke and transient ischemic attack. The blood-pressure grade was according to the criteria of the World Health Organization and the International Society of Hypertension.† Because of rounding, not all percentages total 100. ACE denotes angiotensin-converting enzyme.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.
cardiovascular events or death from any cause. The difference between treatment groups appeared early and remained consistent throughout the duration of the study. From a clinical perspective, 32 subjects of either sex in this age group or 23 men would need to be given ACE-inhibitor–based therapy in order to prevent one additional first cardiovascular event or death within the first five years after treatment began.

There were almost twice as many events in male subjects (907 events) as in female subjects (524 events). The beneficial effects of ACE-inhibitor treatment were more evident in male subjects, among whom there was a 17 percent reduction in the rates of both all cardiovascular events and first cardiovascular events (hazard ratio for both end points, 0.83 [95 percent confidence interval, 0.71 to 0.97]; P=0.02) (Fig. 3). Among female subjects, the hazard ratio for all cardiovascular events and first cardiovascular events was 1.00 (95 percent confidence interval for all events, 0.83 to 1.21; 95 percent confidence interval for first events, 0.83 to 1.20;

![Figure 2. Systolic and Diastolic Blood Pressure after Randomization.](image)

The numbers above the curves indicate the numbers of subjects whose blood pressure was measured. ACE denotes angiotensin-converting enzyme.

### Table 2. Primary End Points and Cause-Specific First Events. *

<table>
<thead>
<tr>
<th>Event</th>
<th>ACE-Inhibitor Group (N=3044)</th>
<th>Diuretic Group (N=3039)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>Rate per 1000 Patient-yr</td>
<td>No. of Events</td>
<td>Rate per 1000 Patient-yr</td>
</tr>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cardiovascular events or death from any cause</td>
<td>695</td>
<td>56.1</td>
<td>736</td>
<td>59.8</td>
</tr>
<tr>
<td>First cardiovascular event or death from any cause</td>
<td>490</td>
<td>41.9</td>
<td>529</td>
<td>45.7</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>195</td>
<td>15.7</td>
<td>210</td>
<td>17.1</td>
</tr>
<tr>
<td><strong>Cause-specific first events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cardiovascular event †</td>
<td>394</td>
<td>33.7</td>
<td>429</td>
<td>37.1</td>
</tr>
<tr>
<td>Coronary event</td>
<td>173</td>
<td>14.3</td>
<td>195</td>
<td>16.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>58</td>
<td>4.7</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>Other cardiovascular event</td>
<td>134</td>
<td>11.0</td>
<td>144</td>
<td>11.9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>69</td>
<td>5.6</td>
<td>78</td>
<td>6.4</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>152</td>
<td>12.5</td>
<td>163</td>
<td>13.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>112</td>
<td>9.2</td>
<td>107</td>
<td>8.8</td>
</tr>
</tbody>
</table>

* Hazard ratios are for the event in the group assigned to angiotensin-converting–enzyme (ACE) inhibitors as compared with the diuretic group and are adjusted for age and sex. CI denotes confidence interval.
† Myocardial infarction is a subcategory of coronary events; heart failure is a subcategory of other cardiovascular events; and stroke is a subcategory of cerebrovascular events. Patients were counted once for each type of first cardiovascular event they had, but patients who had more than one type of event were counted only once for the overall category of first cardiovascular event.
P=0.98 for both comparisons). The P value for the interaction between sex and treatment-group assignment was 0.15 for all cardiovascular events or death from any cause and 0.14 for first cardiovascular events.

The hazard ratio for all first cardiovascular events in the ACE-inhibitor group as compared with the diuretic group was 0.88 (95 percent confidence interval, 0.77 to 1.01; P=0.07); this ratio represents a 12 percent reduction over the study period (Table 2). There was no significant difference between treatments in terms of the rate of first coronary events, but there was a reduction in the rate of first myocardial infarctions in the ACE-inhibitor group: the adjusted hazard ratio was 0.68 (95 percent confidence interval, 0.47 to 0.98; P=0.04).

There was no significant difference between the two treatment groups in the rates of fatal cardiovascular or noncardiovascular events (Table 3). The rates of cause-specific fatal events did not differ significantly between the treatment groups, with the exception of the rate of fatal strokes, which was higher with ACE-inhibitor treatment (adjusted hazard ratio, 1.91 [95 percent confidence interval, 1.04 to 3.50]; P=0.04).

There was a 14 percent reduction in the rate of first nonfatal cardiovascular events with ACE-inhibitor treatment (adjusted hazard ratio, 0.86 [95 percent confidence interval, 0.74 to 0.99]; P=0.03) and a 32 percent reduction in the rate of first nonfatal myocardial infarctions (adjusted hazard ratio, 0.68 [95 percent confidence interval, 0.47 to 0.99]; P=0.05) (Table 3). There was no significant difference between treatments in terms of any other first nonfatal cardiovascular events. As with the main outcomes of the study, differences between treatment groups in cause-specific fatal and nonfatal events were observed only among male subjects.

**DISCUSSION**

Our study has demonstrated that outcomes are better when hypertension in the elderly is treated with an ACE inhibitor than when it is treated with a diuretic agent, with the difference being observed primarily among male subjects. In contrast to other recent trials in the elderly, the subjects in this trial were relatively healthy and active and, overall, had few previous cardiovascular events; one would therefore expect the benefit to be smaller than that found in the other trials, but the results should be more generally applicable to elderly populations. The benefit was a reduction in the rate of total cardiovascular events or death from any cause, with a
particular reduction in the rate of nonfatal events. There was also a reduced likelihood of a first cardiovascular event or death.

Since we conducted the study in the family-practice setting, our results reflect the probable effects among relatively healthy elderly persons with hypertension in typical care settings. For example, 15 to 16 percent of subjects in both groups did not immediately begin receiving medication, because the family practitioner and the patient preferred to delay treatment. Faced with an elderly hypertensive patient with blood pressure just above 140/90 mm Hg (satisfying the criteria for study entry), a primary care physician may choose not to begin treatment immediately despite established evidence of benefit. However, all but 3 to 4 percent of subjects were treated during the study. The finding that approximately 60 percent of subjects continued to receive the treatment to which they were assigned for the duration of the study is consistent with findings in other trials focused on hypertension in elderly subjects and suggests what is likely to happen in practice.4,7,15

Three other published studies have compared ACE-inhibitor–based therapy for hypertension with conventional treatment: the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study,15 the Captopril Prevention Project (CAPPP),16 and the United Kingdom Prospective Diabetes Study (UKPDS).34 The results of these studies are consistent with our findings, but our trial also demonstrates differences of a clinically and statistically relevant magnitude. The design of the trial, the entry criteria, the definition of end points, and the alpha error are factors that may have contributed to the differences between our findings and those of other studies. Although a prospective meta-analysis has concluded that “there were no detectable differences between randomized groups in the risks of any of the outcomes studied,”19 our study and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)35 will be in-

Table 3. Cause-Specific First Events (Fatal and Nonfatal).*  

<table>
<thead>
<tr>
<th>Event</th>
<th>ACE-Inhibitor Group (N=3044)</th>
<th>Diuretic Group (N=3039)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>Rate per 1000 Patient-yr</td>
<td>No. of Events</td>
<td>Rate per 1000 Patient-yr</td>
</tr>
<tr>
<td>Fatal events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>84</td>
<td>6.8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>Coronary event</td>
<td>40</td>
<td>3.2</td>
<td>52</td>
<td>4.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9</td>
<td>0.7</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>Other cardiovascular event</td>
<td>15</td>
<td>1.2</td>
<td>15</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
<td>0.2</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>29</td>
<td>2.3</td>
<td>15</td>
<td>1.2</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>111</td>
<td>9.0</td>
<td>128</td>
<td>10.4</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events</td>
<td>338</td>
<td>28.9</td>
<td>380</td>
<td>32.8</td>
</tr>
<tr>
<td>Coronary event</td>
<td>141</td>
<td>11.6</td>
<td>149</td>
<td>12.4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>50</td>
<td>4.1</td>
<td>71</td>
<td>5.8</td>
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<tr>
<td>Other cardiovascular event</td>
<td>120</td>
<td>9.9</td>
<td>137</td>
<td>11.3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>68</td>
<td>5.5</td>
<td>77</td>
<td>6.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>91</td>
<td>7.5</td>
<td>94</td>
<td>7.8</td>
</tr>
</tbody>
</table>

* Myocardial infarction is a subcategory of coronary events; heart failure is a subcategory of other cardiovascular events. For nonfatal events, patients were counted once for each type of event they had, but patients who had more than one type of event were counted only once for the overall category of nonfatal cardiovascular events. Hazard ratios are for the event in the group assigned to angiotensin-converting–enzyme (ACE) inhibitors as compared with the diuretic group and are adjusted for age and sex. CI denotes confidence interval.
cluded in the next cycle of this meta-analysis, which will provide a more definitive comparison of outcomes with ACE-inhibitor–based and diuretic-based regimens.19,36,37

The observation in our study that the relative benefits of an ACE-inhibitor–based regimen were restricted to men is of interest but should be interpreted with caution, since it represents a post hoc analysis of the data and requires confirmation. The observation that the rate of events among male subjects was almost twice that among female subjects is highly consistent with current data on morbidity and mortality.38 Men have a higher cardiovascular risk than women, and ACE-inhibitor treatment may be of particular advantage in subjects with high cardiovascular risk because of factors that influence the atherosclerotic process, such as stability of plaque and endothelial function.39 This possibility is consistent with results from the HOPE trial showing that ACE inhibitors are beneficial in subjects with high cardiovascular risk, despite minimal change in blood pressure.20 Other possible mechanisms include the absence of any adverse effect on circulating lipids,12,13 reduction of left ventricular hypertrophy,11 greater likelihood of survival in the presence of cardiac failure,9 reduced left ventricular function,40 enhanced insulin sensitivity,13 and preservation of the glomerular filtration rate.41-43 Substudies of our study concerning ambulatory monitoring of blood pressure, left ventricular hypertrophy, and vascular compliance may provide evidence clarifying the mechanisms of the putative benefits of ACE-inhibitor therapy beyond its effect on blood pressure.

The reason for discrepant observations concerning the relation between ACE-inhibitor treatment and cause-specific end points — with a greater likelihood that a stroke will be fatal but a lower likelihood of myocardial infarction — is not obvious. An indication that the benefit of treatment does relate to the reduction of the effects of angiotensin II comes from the results of the LIFE study,21 which demonstrated a reduction in cardiovascular events or death from cardiovascular causes of 13 percent (95 percent confidence interval, 2 to 23 percent) with losartan as compared with atenolol, despite an equivalent reduction in blood pressure.

In conclusion, in elderly subjects with hypertension, particularly among male subjects, ACE-inhibitor–based therapy resulted in an outcome advantage over a diuretic-based regimen, despite similar reductions in blood pressure. This finding was observed in family practices, where most elderly persons with hypertension receive their care. The question of whether the relative benefit of beginning treatment with an ACE-inhibitor–based regimen is confined to men requires examination in large, ongoing trials.

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APPENDIX


The list of family-practice investigators who participated in the study can be found in Supplementary Appendix 1 (available with the complete text of this article at http://www.nejm.org).

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