Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors Versus β-Blockers as Second-Line Therapy for Hypertension

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Background—Trials comparing hypertension monotherapies have found either no difference or modest differences in blood pressure (BP) and cardiovascular events. However, no trial has assessed the comparative effectiveness of 2nd-line therapy in patients whose BP was not controlled with a thiazide diuretic.

Methods and Results—This was an observational study conducted with a hypertension registry of adults enrolled in 3 large integrated health care delivery systems from 2002 to 2007. Patients newly started on thiazide monotherapy whose BP remained uncontrolled were observed after addition of either an angiotensin-converting enzyme (ACE) inhibitor or β-blocker for subsequent BP control and cardiovascular events. Patients for whom either add-on drug was indicated or contraindicated were excluded. After adjustment for patient characteristics and study year, BP control during the subsequent 6 to 18 months was comparable for the 2 agents (70.5% ACE, 69.0% β-blockers; P = 0.09). Rates of incident myocardial infarction (hazard ratio, 1.05; 95% confidence interval, 0.69 to 1.58) and stroke (hazard ratio, 1.01; 95% confidence interval, 0.68 to 1.52) were also similar for the ACE inhibitor and β-blocker groups during an average of 2.3 years of follow-up. There were also no differences in heart failure or renal function.

Conclusions—ACE inhibitors and β-blockers are equally effective in lowering BP and preventing cardiovascular events for patients whose BP is not controlled with a thiazide diuretic alone and who have no compelling indication for a specific 2nd-line agent. (Circ Cardiovasc Qual Outcomes. 2010;3:453-458.)

Key Words: hypertension ■ comparative effectiveness ■ diuretics ■ cardiovascular diseases

Hypertension affects 29% of US adults.1 There is a strong and linear association between the level of blood pressure (BP) and subsequent risk of cardiovascular events.2 Prior studies have also clearly demonstrated that hypertension treatment reduces morbidity and mortality.3 The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study found that thiazide diuretics are efficacious for reducing BP and cardiovascular events, and thiazides are currently recommended as 1st-line therapy for patients with essential hypertension.4,5 However, control of BP to guideline-recommended levels often requires 2 or more agents, and the optimal 2nd-line agent for patients whose BP is not adequately controlled on a thiazide alone is unknown.6 Selection of optimal add-on therapy to a thiazide diuretic was identified as a key question for which there is currently insufficient data by the National Heart Lung, and Blood Institute working group on future directions in hypertension research.7

The objective of this study was to assess the comparative effectiveness of 2 commonly used 2nd-line antihypertensive agents: angiotensin-converting enzyme (ACE) inhibitors and β-blockers. We hypothesized that after controlling for baseline BP level, there would be no difference between ACE inhibitors and β-blockers in BP control at 1 year. Similarly, we hypothesized that there would be no difference in the incidence of myocardial infarction, stroke, congestive heart failure, or chronic kidney disease between patients receiving ACE inhibitors versus β-blockers as 2nd-line therapy.

Methods

Study Setting

The study was conducted in 3 large, integrated health care delivery systems that collectively care for more than 4 million people: Kaiser Permanente Colorado, Kaiser Permanente Northern California, and HealthPartners in Minneapolis. Kaiser Permanente Colorado has more than 460,000 enrollees in the Denver, Colo, metropolitan area and contracts with more than 600 physicians to deliver care in 18...
outpatient clinics. HealthPartners serves more than 620,000 members in the Minneapolis, Minn, metropolitan area, with more than 200 physicians who work in 22 clinics. Kaiser Permanente Northern California provides care to more than 3.2 million members and contracts with a medical group of more than 6000 physicians who treat patients at 39 clinics. Electronic data on longitudinal BP measurements, medication dispensings, laboratory test results, diagnoses, and health care utilization was available from electronic health records and administrative data bases at all sites dating back to January 2000. Data from each of the health plans were restructured into a common, standardized format with identical variable names, formats, and specifications and identical variable definitions, labels, and coding.

WHAT IS KNOWN

- The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study found that thiazide diuretics are efficacious for reducing blood pressure and cardiovascular events, and thiazides are currently recommended as 1st-line therapy for patients with essential hypertension.
- However, control of blood pressure to guideline-recommended levels often requires 2 or more agents, and the optimal 2nd-line agent for patients whose blood pressure is not adequately controlled with thiazide alone is unknown.

WHAT THE STUDY ADDS

- The objective of this study was to assess the comparative effectiveness of 2 commonly used 2nd-line antihypertensive agents: angiotensin-converting enzyme inhibitors and β-blockers.
- We found that that angiotensin-converting enzyme inhibitors and β-blockers are equally effective in lowering blood pressure and preventing cardiovascular events for patients whose blood pressure was not controlled with a thiazide diuretic alone and who have no compelling indication for a specific 2nd-line agent.

To confirm that algorithms designed to identify hypertensive patients were valid and the degree to which the analytic data were identical to the source data, a chart review of 450 randomly selected charts (150 from each site) was conducted of patients who had been continuously enrolled with pharmacy coverage for 12 months before the date of entry into the registry. To confirm that hypertension was in fact incident on the date assigned by the algorithm, the auditors examined whether there was mention of hypertension in the physician note, a hypertension diagnosis code, or evidence of an antihypertensive drug treatment at the visit preceding the incident date or before. Five (1%) audits showed evidence of a hypertension diagnosis and 16 (4%) audits revealed use of an antihypertensive drug for hypertension before the incident date, indicating 96% accuracy of this method for excluding preexisting hypertension. Chart auditors also recorded the BP values in the vital signs field or in the physician notes from the electronic medical record on that date. The BP was an exact match between the analytic and source data in all 300 audits from HealthPartners and Kaiser Permanente Colorado and all 34 audits from 2007 at Kaiser Northern California. In Northern California, the electronic BP data were recorded in categories before 2007; the electronic categorical data matched the BP in the chart in 109 of 116 audits (94%), for an overall agreement rate of 98%.

Study Population

The study population included all patients 18 years or older with incident hypertension during 2002 to 2007 who were started on an ACE inhibitor or β-blocker after failure of initial thiazide therapy (Figure 1). To assemble this cohort, we first identified all patients with a diagnosis code of hypertension during the study period. To identify those with incident hypertension, we excluded patients with prior diagnoses or treatment for hypertension based on pharmacy dispensing data. We also excluded patients who did not have continuous health plan membership with a pharmacy benefit for at least 1 year before their first hypertension diagnosis because prevalent hypertension could not be reliably excluded in this group.

Among the patients with incident hypertension, we identified those initially treated with a thiazide diuretic as 1st-line therapy. We excluded patients without a pharmacy benefit, those not treated with any antihypertensive medication, and those started on an antihypertensive agent other than a thiazide diuretic (including those initiated on multiple antihypertensive agents or combination therapy). The vast majority of patients initiated on a thiazide were prescribed hydrochlorothiazide. The initial dose of hydrochlorothiazide was 25 mg in 63% of patients and 50 mg in 17% of patients.

Next, we identified patients who were started on an ACE inhibitor or β-blocker as 2nd-line therapy. To ensure that the medication was prescribed for uncontrolled BP, we excluded patients who did not have elevated BP at the time of the addition of the 2nd agent. We also excluded patients who were prescribed a 2nd-line agent other than an ACE inhibitor or β-blocker and those who did not continue on their thiazide after the new antihypertensive agent was started (because the prescription of the ACE inhibitor or β-blocker for patients may represent a medication substitution rather than an add-on therapy).

To reduce potential confounding bias, we excluded all patients with a specific indication or contraindication for either an ACE inhibitor or β-blocker. Patients with a history of any of the following conditions were excluded: diabetes, chronic kidney disease, asthma, albuminuria, myocardial infarction, heart failure, 2nd- or 3rd-degree heart block, atrial fibrillation, other arrhythmias (ie, ventricular or atrial tachycardia), peripheral vascular disease, a history of percutaneous coronary intervention or coronary artery bypass graft procedures, cerebrovascular disease, migraine headaches, pregnancy, or angioedema. The presence of these conditions was determined based on ICD-9 diagnosis codes, problem list entries, medications, and laboratory data according to prespecified algorithms. The final analytic sample of patients with incident hypertension who were started on a 2nd-line agent after failure of initial thiazide therapy was 9622 receiving ACE inhibitors and 5918 receiving β-blockers.

Outcomes

The primary outcome of the study was BP control at 1 year after initiation of the 2nd-line agent. BP was considered controlled if it was <140/90 mm Hg. The BP measurement closest to 1 year after initiation of the 2nd-line agent was used for this assessment. Overall, 5245 patients (3698 in the ACE inhibitor group and 1544 in the β-blocker group) were excluded from the analysis of BP control because they did not have a BP measurement recorded in the 6 to 18 months after initiation of the 2nd-line agent. Of those who were excluded because of a lack of BP measurement, the majority (60%) were enrolled in health plan for <1 year after initiation of the 2nd-line agent.

Secondary outcomes included incident cases of myocardial infarction, congestive heart failure, stroke, and chronic kidney disease after initiation of the 2nd-line agent. The study cohort was followed for a maximum of 6 years, with most persons followed for just over 2 years (median, 2.3 years; interquartile range, 1.2 to 3.7 years). We also performed a sensitivity analysis, looking at these outcomes within the 1st year. The results of the sensitivity analysis were consistent with the results of the primary analysis and therefore are not presented. Primary hospital discharge diagnoses were used to identify incident cases of myocardial infarction (ICD-9 codes 410.xx), congestive heart failure (ICD-9 codes 428.xx), and stroke (ICD-9 codes 430.xx-434.xx, 436.xx, 852.0, 852.2, 852.4, 853.0).
Both diagnosis data and laboratory measures of renal function were used to identify incident cases of chronic kidney disease. Patients with previously normal renal function were considered to have progressed to chronic kidney disease if, after initiation of 2nd-line therapy, they had a new diagnosis of kidney disease (ICD-9 codes: 585.1 to 585.9) or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m².

Additional outcomes assessed included the proportion of patients in each group with (1) no change (additions or substitutions) to their antihypertensive medication regimen; (2) addition of a 3rd-line antihypertensive agent; and (3) persistence of the 2nd-line agent at 1 year. Persistence at 1 year was reported as a dichotomous variable, and a patient was considered “persistent” if they filled a prescription for the 2nd-line agent between 10 to 14 months after initiation of initial prescription.

Statistical Analyses
We used an intention-to-treat approach to assess the comparative effectiveness of ACE inhibitors versus β-blockers as 2nd-line antihypertensive agents. To characterize the study population at baseline, we calculated descriptive statistics using means and standard deviations for continuous variables and compared the 2 groups using t tests. For categorical variables, we calculated percents and compared the 2 groups using χ² tests. The proportions of patients in each group with no change to their antihypertensive medication regimen, addition of a 3rd-line antihypertensive agent, and persistence at 1 year were also compared using χ² tests.

We used logistic regression to compare the proportion of patients in the ACE inhibitor and β-blocker groups achieving BP control at 1 year. Because the outcome of BP control is not rare, we present estimated relative risks using the method of Zhang et al instead of odds ratios. To adjust for differences in baseline demographic and clinical factors, we performed a propensity score analysis and created inverse probability-weighted estimators. Propensity scores were created using all the covariates in Table 1. Because of changing prescription patterns over time, interactions with the initiation year of the 2nd agent and all covariates were also included in the models creating the propensity scores. Stabilized inverse probability weights were created and used to adjust for covariates in the outcome models. Stabilized weights reduce the possibility of large changes to estimates being caused by a few, unusual observations. Stabilized weights also realign weights to range 0 to 1 so that the resulting sample size is comparable to the original population and standard errors are more appropriate. The consistency of ACE inhibitor versus β-blocker results within subgroups of site, age, sex, and year was tested by interactions tests in the full model and estimated within strata effects.
Table 1. Comparisons of Persons Initiated on ACE Inhibitor Versus β-Blocker as a Second Agent

<table>
<thead>
<tr>
<th>Year of 2nd agent start</th>
<th>ACE Inhibitor (n=9622)</th>
<th>β-Blocker (n=5918)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>30.8%</td>
<td>69.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2003</td>
<td>39.9%</td>
<td>60.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2004</td>
<td>51.4%</td>
<td>48.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2005</td>
<td>62.8%</td>
<td>37.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2006</td>
<td>81.8%</td>
<td>18.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2007</td>
<td>85.1%</td>
<td>14.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for year of 2nd agent start

Age, y 55.9 55.3 0.006
Male sex 47.7% 42.2% <0.001
Mean No. of days on thiazide before 2nd agent start 336 308 <0.001
Average No. of visits during year before thiazide initiation 1.7 1.7 0.57
Mean systolic BP‡ (closest measure before or same day as 2nd agent start) 151.8 152.7 <0.001
Mean diastolic BP‡ (closest measure before or same day as 2nd agent start) 89.0 90.0 <0.001
Chronic obstructive pulmonary disease 0.6% 0.4% 0.09
Hyperlipidemia 4.0% 5.0% 0.005
Cancer 1.7 2.3 0.01
Dementia 0.03% 0.06% 0.35
Chronic liver disease 0.1% 0.2% 0.44
Depression 13.6% 14.5% 0.11
Minimum of 1-year enrollment after 2nd-line initiation† (n=12,371) 80.0% 79.6% 0.61
BP measured 12 months after 2nd-line agent start‡ (n=10,298) 83.7% 83.0% 0.36

Table 2. Blood Pressure Control at 12 Months* by ACE Inhibitor Versus β-Blocker (n=10,298)

<table>
<thead>
<tr>
<th>Estimated Percentage With BP Controlled at 12 Months</th>
<th>Relative Risk (95% Confidence Interval)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>β-Blocker</td>
</tr>
<tr>
<td>Univariate</td>
<td>72.0%</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

*Closest BP to 12 months after 2nd-line initiation (range, 6 to 18 months).
†Estimated relative risk and 95% confidence interval from logistic regression models with non-rare outcome.
‡Adjusted by inverse propensity score weights.

Results

The baseline characteristics for the ACE inhibitor and β-blocker groups are shown in Table 1. In the study cohort, β-blockers were much more commonly prescribed in the earlier years of the study period, whereas ACE inhibitors were more commonly prescribed in the latter years. After adjusting for the year the 2nd-line agent start, the remaining baseline patient characteristics were similar in the 2 groups, though some statistical differences were evident in this relatively large cohort. Mean age was slightly higher for ACE inhibitor users than those taking β-blockers (55.9 versus 55.3 years). BP was slightly higher for patients started on β-blockers (152.7/90.0 versus 151.8/89.0), and ACE inhibitor users were on average treated with thiazide monotherapy for longer time periods before being started on a 2nd agent. ACE inhibitor users had a higher percentage of men, whereas β-blocker users had a higher percentage of persons with a diagnosis of hyperlipidemia.

Table 2 presents results for the outcome of BP control at 12 months. Crude results suggested a slightly higher BP control rate for ACE inhibitors; however, in the adjusted models, the rates of BP control were comparable for the 2 agents (70.5% for ACE inhibitors; however, in the adjusted models, the rates of BP control were comparable for the 2 agents (70.5% for ACE inhibitors; 69.0% for β-blockers; P=0.09). Interactions tests and results by subgroup strata were similar by sex, age (±65 years), site, and year (probability values all >0.20). Adjusted BP control rates for ACE inhibitor and β-blocker groups by year are shown in Figure 2. This figure shows increasing BP control rates in later years but comparable rates of control for ACE inhibitor versus β-blocker groups within each year.

Outcomes of hypertension sequelae (myocardial infarction, stroke, congestive heart failure, and kidney disease) are reported in Table 3. Rates of incident myocardial infarction and stroke were similar for the ACE inhibitor and β-blocker

Figure 2. Percentage with BP controlled at 12 months by year of 2nd agent start.

We used the Cox proportional hazards model to assess the association between the specific 2nd-line agent and outcomes of incident myocardial infarction, stroke, heart failure, and progression to kidney disease.1–16 Stabilized inverse propensity scores were similarly used to adjust for potential confounders and differing prescription patterns over time in these models. For models predicting incident kidney disease, the closest estimated glomerular filtration rate measure preceding the 2nd-line agent was also incorporated into the propensity model.
groups, as evidenced by hazard ratios close to 1. Rates of incident congestive heart failure were not significantly different by 2nd-line agent; however, we had limited statistical power to find a difference due to the low incidence of congestive heart failure. There was also no difference in subsequent kidney disease in the ACE inhibitor group compared with those in the \( \beta \)-blocker group (hazard ratio=0.95; 95% confidence interval, 0.85 to 1.05).

The proportion of patients who were dispensed a new BP-lowering agent over a 1-year time frame was slightly higher for patients in the ACE inhibitor group compared with the \( \beta \)-blocker group (24.0% versus 21.9%, \( \chi^2 \) \( P \)=0.003). Among persons with a new antihypertensive agent prescribed within 1 year, the new agent was more often an apparent substitution (2nd agent no longer dispensed) for ACE inhibitors than \( \beta \)-blockers (18.9% versus 9.3%) and less often an addition (ie, 2nd agent dispensed after new agent started) (5.2% ACE-inhibitors, 12.6% \( \beta \)-blockers).

### Discussion

The objective of the present study was to assess the comparative effectiveness of ACE inhibitors versus \( \beta \)-blockers as 2nd-line therapy in patients whose BP was not controlled with a thiazide diuretic alone and did not have a compelling indication for a specific 2nd-line agent. This is an important clinical question that has not been addressed in any trials to date. BP control rates were similar when either ACE inhibitors or \( \beta \)-blockers were added to a thiazide diuretic. Furthermore, rates of hypertension sequelae, including incident myocardial infarction, stroke, and kidney disease, were also comparable between the ACE inhibitor and \( \beta \)-blocker groups.

The findings of our study are consistent with the results of randomized controlled trials of hypertension monotherapy that have found either no difference or only a modest differences in the degree of BP and cardiovascular disease risk reduction in patients treated with any of the major classes of antihypertensive medications.\(^3\,17\) Our results are also consistent with a meta-analysis of clinical trials that concluded that each of the main classes of hypertensive agents reduce BP to the same extent and the degree of BP reduction alone accounts for the effect of these drugs in preventing coronary heart disease and stroke in patients with uncomplicated hypertension.\(^18\,19\) The finding of a somewhat higher rate of substitution of another agent for ACE inhibitors than for \( \beta \)-blockers is also consistent with the relatively high incidence of chronic dry cough with ACE inhibitors. In several blinded trials, ACE inhibitors had higher discontinuation rates than placebo or comparator drugs.\(^3\,20\,21\)

Most clinical trials of BP-lowering medications have focused on the choice of initial hypertension agent. Based on the totality of the evidence, the JNC7 guidelines recommend thiazide diuretics as initial therapy for uncomplicated hypertension, either alone or in combination with other agents.\(^22\) Two recent clinical trials (VALUE and ASCOT) explicitly tested adding different 2nd agents in a stepped-care regimen.\(^23\,24\) However, neither of these trials used thiazide monotherapy as the initial drug treatment. Another large trial (ACCOMPLISH) has compared 2 different combination therapy regimens in which both drugs were started simultaneously (ACE inhibitor plus calcium channel blocker compared with ACE inhibitor plus thiazide).\(^25\) Although this trial, published in late 2008, found a statistically significant difference in the important composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, the trial design has been criticized for its use of low-dose hydrochlorothiazide (12.5 mg).\(^26\) In contrast, the present study specifically addresses the question of optimal add-on therapy for patients whose BP is not controlled by a thiazide alone (primarily moderate-dose hydrochlorothiazide, 25 to 50 mg), a question designated as high priority by experts in hypertension research.\(^3\) Our findings that ACE inhibitors and \( \beta \)-blockers are equally effective in lowering BP and preventing cardiovascular events suggest that either is a reasonable choice for add-on therapy for patients not controlled with a thiazide monotherapy.

We would like to acknowledge several potential limitations of this study. Patients were not randomly assigned to 2nd-line antihypertensive therapy. The decision to choose one agent instead of another may be related to factors associated with BP control or cardiovascular outcomes. To reduce the impact of potential confounding by indication bias, we restricted the study cohort to incident cases of hypertension and patients without indications or contraindications to either ACE inhibitors or \( \beta \)-blockers. We also used propensity matching to compare the effectiveness of ACE inhibitors versus \( \beta \)-blockers in strata within which patients were comparable with regard to baseline covariates and on the predicted probability of receiving each treatment. Nevertheless, despite the methodological rigor of our study design and analysis, we may not have been able to eliminate the impact of unmeasured confounding.

### Table 3. Adjusted Hazard Ratios* for Incident Myocardial Infarction, Stroke, Chronic Kidney Disease, or Congestive Heart Failure Comparing ACE Inhibitor Versus \( \beta \)-Blocker Second-Line Initiation (n=15 532†)

<table>
<thead>
<tr>
<th>Incident</th>
<th>No. of Events</th>
<th>Adjusted Hazard Ratio*</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>96</td>
<td>1.05</td>
<td>(0.69 to 1.58)</td>
<td>0.83</td>
</tr>
<tr>
<td>Stroke</td>
<td>101</td>
<td>1.01</td>
<td>(0.68 to 1.52)</td>
<td>0.95</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23</td>
<td>1.71</td>
<td>(0.69 to 2.43)</td>
<td>0.25</td>
</tr>
<tr>
<td>Chronic kidney disease‡</td>
<td>1445</td>
<td>0.95</td>
<td>(0.85 to 1.05)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Adjusted by inverse propensity score weights.
†Eight persons missing initial BP measurements or comorbidity information.
‡Additionally adjusted for estimated glomerular filtration rate (n=14 080).
Additional considerations include limited generalizability due to the geographic location of study sites and selection effects related to enrollment for care in the participating health plans. However, the study populations were broadly representative of their geographic regions, and the results of subgroup analyses were consistent with the primary analysis. Because of the available sample size and follow-up period, we had somewhat limited statistical power to detect differences in cardiovascular events between in the ACE inhibitor and β-blocker groups. We ascertained clinical outcomes using data captured in the electronic medical records and through insurance claims. Finally, because of the composition of health plan formularies, we were unable to assess for differences in the effectiveness of individual drugs within the ACE inhibitor and β-blocker groups, and, because of their low use in the participating health plans, we were unable to evaluate the effectiveness of calcium channel blockers and angiotensin-receptor blockers as 2nd-line agents.

In conclusion, we found that that ACE inhibitors and β-blockers are equally effective in lowering BP and preventing cardiovascular events for patients whose BP is not controlled with a thiazide diuretic alone and who have no compelling indication for a specific 2nd-line agent. This suggests that both ACE inhibitors and β-blockers are a reasonable choice for add-on therapy for patients with essential hypertension not controlled with a thiazide monotherapy.

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Disclosures
None.

References
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