Economic Implications of Evidence-Based Prescribing for Hypertension
Can Better Care Cost Less?

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Context Deviation from evidence-based guidelines in hypertension treatment is common, but its economic impact has not been rigorously studied. Suboptimal prescribing patterns contribute to the high cost of medications for elderly patients as well as the difficulty in providing affordable prescription drug benefits for older Americans.

Objective To calculate the potential savings from the perspective of health care payers that would result from increased adherence to evidence-based recommendations for managing hypertension in patients older than 65 years.

Design Comparative analysis of medications prescribed vs potential regimens suggested by evidence-based guidelines tailored to each patient’s medical history, with calculation of the costs of both the actual and the evidence-based regimens.

Setting and Patients A total of 133,624 patients being treated for hypertension during 2001 who were enrolled in a large state pharmaceutical assistance program that provides prescription drug insurance for elderly persons.

Main Outcome Measure Cost difference between medications actually prescribed and regimens suggested by evidence-based guidelines.

Results The patients studied filled more than 2.05 million prescriptions for antihypertensive medications in 2001, at an annual program cost of $48.5 million ($363 per patient). We identified 815,316 prescriptions (40%) for which an alternative regimen appeared more appropriate according to evidence-based recommendations. Such changes would have reduced the costs to payers in 2001 by $11.6 million (nearly a quarter of program spending on antihypertensive medications), as well as being more clinically appropriate overall. Replacement of calcium channel blockers resulted in the largest potential savings. Use of pricing limits similar to those in the Medicaid program would have resulted in even larger potential savings of $20.5 million (42% of program costs).

Conclusions Adherence to evidence-based prescribing guidelines for hypertension could result in substantial savings in prescription costs for elderly patients with hypertension that would amount to savings of about $1.2 billion nationally. Identification of similar areas in which prescribing can be improved will be critical for the affordability of prescription drug benefit programs.

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most effective in controlling systolic blood pressure as well as in preventing heart failure and stroke; it was also the least costly. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) recommended thiazide-type diuretics as first-line agents for uncomplicated hypertension in most patients. Although some trials offer evidence for angiotensin-converting enzyme (ACE) inhibitors, a comprehensive meta-analysis emphasized strong evidence for thiazides as the preferred agents for the majority of patients with this condition. Specific comorbidities (eg, diabetic nephropathy or coronary artery disease) constitute indications for other agents (ACE inhibitors and β-blockers, respectively), although even in these conditions, guidelines state that thiazide-type diuretics could still be considered first-line therapy.

We investigated the economic impact that would result from better adherence to evidence-based therapeutic guidelines. To do this, we analyzed medication use patterns in more than 130,000 hypertensive patients in a state drug assistance program for elderly patients. We evaluated every antihypertensive regimen in light of the clinical history of each patient and then estimated the potential cost savings to the health care delivery system that could have been realized through adherence to evidence-based recommendations.

**METHODS**

**Sources of Data**

Pennsylvania’s Pharmaceutical Assistance Contract for the Elderly (PACE) program provides prescription drug coverage for a large population of that state’s elderly patients who are not indigent enough to qualify for Medicaid but have annual incomes of less than $14,000 for single persons or $17,200 for married persons. The program covered all drug costs, minus a $6 copayment for each prescription, for 201,000 beneficiaries in 2001. Prior publications have studied medication use in the PACE program. Medication claims were available from 1994 through 2001. Data on filled prescriptions were linked to Medicare part A and B files containing additional data on all diagnoses and comorbidities, both outpatient and inpatient, recorded for these patients through the end of 2000. All personal identifiers were transformed to anonymous untraceable coded study numbers to protect patient confidentiality. Institutional review board approval was obtained for review of the claims records. Data analyses were performed using SAS software. Prior research has validated the accuracy of computerized claims data for determining medication exposure. The PACE program receives rebates averaging about 16% from drug manufacturers; this was considered in all cost analyses.

**Identification of Patients**

We identified every patient who filled a prescription for antihypertensive medications during 2001 and who had been an active user of the PACE program for at least 1 year prior to his/her first antihypertensive prescription. To avoid considering antihypertensive drugs prescribed for other indications, we required that study patients have a recorded diagnosis of hypertension.

We recorded data on all other PACE prescriptions filled by these patients since 1994, as well as all diagnoses recorded in all outpatient and inpatient encounters or reflected in medications used (eg, insulin for diabetes) during the period 1994-2001. In this way, we identified the presence of diabetes mellitus, congestive heart failure (CHF), history of myocardial infarction (MI), asthma, chronic obstructive pulmonary disease (COPD), angina, nephropathy, or benign prostatic hypertrophy.

**Substitution Analysis**

In keeping with current guidelines, we considered thiazides to be appropriate first-line hypertension therapy for patients without specific contraindications or indications for another drug. The JNC VII report includes specific indications for certain classes of antihypertensives, which we incorporated. For patients with CHF or diabetes and nephropathy, we considered ACE inhibitors to be indicated as first-line therapy. For patients with a history of ischemic heart disease, we considered β-blockers as first-line therapy, except in patients with diagnoses of asthma, COPD, or CHF. Angiotensin receptor blockers were considered acceptable first-line agents in patients with diabetes and nephropathy. We followed JNC VII in allowing α-blockers as potentially favorable treatment for hypertensive patients with prostatic disease, although some evidence suggests that this may be a problematic strategy. For patients with hypertension and angina, we classified calcium channel blockers as an acceptable therapeutic choice based on JNC-VII guidelines, although other recommendations suggest use of β-blockers for most such patients.

For each patient, we considered all comorbid conditions in assigning alternative antihypertensive medications when appropriate. If there were any current or prior prescriptions for a given medication, we assumed that the drug class was currently being used or had been tried previously and was abandoned due to ineffectiveness or adverse effects, and we did not assign it as a substitute. Medications were replaced on a prescription-for-prescription basis, assuming that compliance with the substitute regimen would be the same as compliance with the prescriptions actually filled, in keeping with recent data. The FIGURE summarizes the basic logic used in assigning this replacement therapy. For patients without a significant comorbidity and with no history of thiazide use, we assigned thiazide as replacement therapy; we did the same for additional prescriptions for patients with comorbid conditions. For any patient with a relevant comorbidity who had no history of using the indicated first-line agent, we assigned that agent as a re-
For patients with no relevant comorbidity, guidelines recommend initial treatment with a thiazide-type diuretic. For patients with a relevant comorbidity, guidelines recommend initial treatment with a specific drug based on the comorbidity.

We then calculated the amount paid by the PACE program in the study year for each patient’s actual regimen and compared it with the total amount that the evidence-based regimen would have cost the health care system for each patient.

Alternate Cost Calculations

In Medicaid, the prices of generically available drugs are fixed at a lower level by “maximum allowable cost” (MAC) pricing. In secondary analyses, we evaluated the additional impact of using MAC-level pricing for ACE inhibitors. In other analyses, we also varied the percentage of patients taking thiazide diuretics who would require potassium supplements.

RESULTS

Existing Antihypertensive Regimens

Of approximately 201,000 PACE participants, 133,624 (66%) had a diagnosis of hypertension and filled 205,281 antihypertensive drug prescriptions during the study year, an average of 15.4 prescriptions per patient. Table 1 shows the basic demographic characteristics of this population and the frequency of major comorbid conditions. Table 1 also shows the earliest
year for which PACE data were available for these patients. Nearly two thirds of patients (n = 85551) had a history in PACE extending to 1994; an additional 32322 (24.2%) had 3 to 6 years of prior history in PACE. The 2001 program expenditure for antihypertensives (after adjustment for rebates) was $48.5 million, or $363 per patient. For prescriptions costing less than the $6 per-prescription co-payment, the program paid nothing, but data on medication type and quantity were recorded. Including co-payments, total spending for antihypertensive medications by the program and patients was about $60 million.

Table 2 summarizes by class the number of prescriptions, amount paid, and average cost across all prescriptions. Calcium channel blockers had the highest average cost ($33.39 per prescription) and the highest total spending ($17 million); ACE inhibitors were the second costliest class ($10.5 million). β-Blockers were the most commonly prescribed antihypertensive drug, but average cost ($15.62) and total spending ($8.0 million) were lower than for ACE inhibitors or calcium channel blockers. Thiazides were among the least expensive medications ($5.33 per prescription) but accounted for only 4.3% of prescriptions.

Table 3 presents the numbers of patients in several major clinical categories who were and were not prescribed first-line antihypertensive medications. Among patients with CHF, ischemic heart disease, and diabetes with nephropathy, we found no history of use of a first-line medication for 33% to 38%. Of patients with no major comorbidities, 82% had no history of use of a thiazide-type diuretic.

Substitution Analysis
For 815316 prescriptions (40% of total), an evidence-based replacement medication appeared clinically appropriate after review of all of a patient’s recorded diagnoses and drug use history. The algorithm identified a lower-cost agent for 631951 of these prescriptions (31% of total). In 183365 prescriptions (9% of the total), the replacement (primarily ACE inhibitors) would have cost more than the existing prescription. If all of the substitutions were made, spending on antihypertensive medications and associated laboratory tests would have decreased by $11.6 million in the study year (24% of the program’s antihypertensive drug spending), an annual cost reduction of $8.7 million per 100000 patients treated for hypertension.

Table 4 summarizes the projected changes in drug use by drug class. Substitution appeared appropriate for about half of calcium channel blocker prescriptions (244745 [48%]); the greatest savings came from 140600 prescriptions that could have been replaced with thiazides, saving $4.32 million. Of existing ACE inhibitor prescriptions, 94060 (23%) appeared replaceable by thiazides, with associated spending reduction of $2.05 million (20% of spending on ACE inhibitors). In 71885 β-blocker prescriptions (14%), there was an indication for substitution by an ACE inhibitor, which would have increased spending by $570000. Most of the $701622 spending reduction for combination agents was accounted for by calcium channel blocker–ACE inhibitor combinations that could have been replaced with combinations containing thiazides.

Alternative Analyses
Over time, the price of generic ACE inhibitors should continue to fall, so we also considered the potential impact of MAC-level pricing, as used by Medicaid in most states, by recalculating the potential costs if all replacement ACE inhibitors had been priced at the average cost paid by the Pennsylvania Medicaid program for a generic ACE inhibitor. This resulted in a larger reduction in spending of $15.8 million, or 33% of program spending on hypertension. If the MAC price had been used not just for substitution but in place of all brand-name ACE inhibitor prescriptions (analogous to a reference-pricing approach), spending would have declined by another $4.7 million, increasing the total savings to $20.5 million, or a potential reduction of 42% of spending for antihypertensive medications.

If all thiazide users required potassium replacement, the potential savings would have decreased slightly to $10.20 million; if only 20% required potassium replacement, the potential savings would have increased to $11.85 million.

COMMENT
We reviewed the medication choices and costs of antihypertensive regimens in typical elderly patients in a
large state drug assistance program over a 1-year period and measured the cost implications of evidence-based drug substitution when clinically appropriate in light of their medical histories. A large proportion of existing prescribing for hypertension was outside of published guidelines. Adherence to established guidelines for treating hypertension would have resulted in considerable savings to the health care delivery system ($11.6 million per year, or nearly a quarter of program antihypertensive medication costs). While some controversy persists regarding the precise details of which agents are best for first-line therapy, the broad outline of the approach presented herein would be applicable to most currently proposed evidence-based guidelines with only minor modifications.

There are many possible reasons for this large divergence between routine practice on the one hand and clinical trial data and evidence-based recommendations on the other. Foremost among these is the vigorous marketing of newer, more costly agents compared with virtually no marketing for older, off-patent drugs. Such marketing affects both physician prescribing choices and patient preferences. It is not clear from these analyses to what extent patient vs physician factors cause these findings; this is an important area for future research.

These findings could have considerable national impact. We found potential savings of $87.14 per patient treated for hypertension; the level of per-patient spending on antihypertensive medication in our population is similar to that found in other research. According to the National Center for Health Statistics, in 2000 almost 22 million older hypertensive patients had hypertension. Survey data indicate that 63% of older hypertensive patients are being treated, translating to more than 13.5 million elderly patients taking antihypertensive medication. Applying our findings to that population corresponds to a decrease in spending for antihypertensive medications of about $1.2 billion per year.

The ALLHAT results indicate that these changes would have been preferred on clinical as well as financial grounds, although some controversy persists about the role of ACE inhibitors vs thiazides in some subgroups. As lower-priced ACE inhibitors become more widely available, such evidence-based prescribing would reduce the cost of antihypertensives by at least $2 billion to $3 billion annually.

These data must be viewed in light of several considerations. While we made many conservative assumptions in our estimates of potential therapeutic substitution, we did not interview or examine the patients, review their primary medical records, or communicate with their physicians. As a result, we were not able to completely

Table 3. Prevalence of Previous or Current First-Line Medication Use by Clinical Category

<table>
<thead>
<tr>
<th>Condition (First-Line Therapy)</th>
<th>No. of Patients</th>
<th>No. (%) With No Previous or Current Use of First-Line Therapy</th>
<th>No. Receiving First-Line Therapy in 2001</th>
<th>No. Who Received First-Line Therapy Before 2001 but Not in 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (ACE inhibitor)</td>
<td>74,284</td>
<td>28,233 (38.0)</td>
<td>31,568 (42.5)</td>
<td>14,493 (19.5)</td>
</tr>
<tr>
<td>Ischemic heart disease (β-blocker)</td>
<td>61,302</td>
<td>23,031 (37.6)</td>
<td>29,716 (48.5)</td>
<td>8,555 (14.0)</td>
</tr>
<tr>
<td>Diabetes with nephropathy (ACE inhibitor)</td>
<td>19,054</td>
<td>6,288 (33.0)</td>
<td>8,246 (43.3)</td>
<td>4,520 (23.7)</td>
</tr>
<tr>
<td>No major comorbidity (thiazide)</td>
<td>28,442</td>
<td>23,240 (81.7)</td>
<td>3,456 (12.2)</td>
<td>1,746 (6.1)</td>
</tr>
</tbody>
</table>

Abbreviation: ACE, angiotensin-converting enzyme.

Table 4. Potential Savings by Drug Class

<table>
<thead>
<tr>
<th>Originally Prescribed Drug Class</th>
<th>No. of Prescriptions</th>
<th>More Expensive Than Initial Medication</th>
<th>Less Expensive Than Initial Medication</th>
<th>Initial Spending, $</th>
<th>Alternative Spending, $</th>
<th>Potential Reduction (Increase) in Spending, $ (% Reduction, Increase), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>508,991</td>
<td>27,432</td>
<td>217,213</td>
<td>16,996,846</td>
<td>11,367,475</td>
<td>5,639,371 (32.2)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>413,590</td>
<td>4279</td>
<td>116,123</td>
<td>10,460,811</td>
<td>7,961,446</td>
<td>2,509,365 (24.0)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>514,810</td>
<td>80,957</td>
<td>111,328</td>
<td>8,043,137</td>
<td>7,097,307</td>
<td>945,830 (11.8)</td>
</tr>
<tr>
<td>All combination products</td>
<td>259,991</td>
<td>2927</td>
<td>43,931</td>
<td>5,569,422</td>
<td>4,867,800</td>
<td>701,622 (12.6)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>128,418</td>
<td>5584</td>
<td>87,481</td>
<td>4,266,738</td>
<td>2,645,424</td>
<td>1,621,314 (38.0)</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>59,648</td>
<td>7871</td>
<td>22,204</td>
<td>1,524,164</td>
<td>1,102,132</td>
<td>422,032 (27.7)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>40,688</td>
<td>12,782</td>
<td>19,998</td>
<td>805,457</td>
<td>502,370</td>
<td>303,087 (37.6)</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td>88,032</td>
<td>22,845</td>
<td>1862</td>
<td>469,567</td>
<td>825,492</td>
<td>(355,925) (75.8)</td>
</tr>
<tr>
<td>Other</td>
<td>26,804</td>
<td>11,953</td>
<td>10,799</td>
<td>314,409</td>
<td>372,746</td>
<td>(58,337) (18.6)</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>10,309</td>
<td>6,735</td>
<td>1012</td>
<td>41,074</td>
<td>124,934</td>
<td>(83,860) (204)</td>
</tr>
<tr>
<td>Total*</td>
<td>2,051,281</td>
<td>183,365</td>
<td>631,951</td>
<td>48,491,626</td>
<td>36,847,126</td>
<td>11,644,500 (24.0)</td>
</tr>
</tbody>
</table>

*Data may not sum because of rounding.
eliminate the possibility of contraindications for a substitute regimen or hidden indications for the regimens actually prescribed. Diagnoses based on visits, hospitalizations, and filled prescriptions are not as accurate as those measured by review of the primary medical record, but they are a useful way to track whether a given patient ever had a diagnosis of the conditions we studied. We included data on prior prescriptions back to 1994 but could not exclude the possibility that some patients may have taken a first-line agent prior to 1994. We did not define a patient-specific replacement dose when switching a given patient to an evidence-based regimen, and we used the average dose of all prescriptions for each major drug class. Finally, we did not directly address issues of patient adherence but assumed that a given patient would comply approximately the same with one regimen as with another. This assumption has been borne out by the results of the ALLHAT study, which even showed a slight adherence advantage for thiazides.

The JNC VII guidelines on which we based this analysis were published in 2003. However, these were quite similar to the recommendations published in JNC VI, which appeared in 1997. The main difference was that JNC VII no longer recommended β-blockers as equivalent to thiazides as first-line treatment for uncomplicated hypertension. While our findings focus on the potential savings from application of the JNC VII recommendations, the results apply equally well if the JNC VI guidelines, which were current at the time of the prescriptions studied, are used as the basis for the analysis.

While we cannot conclude that a given substitution would have been appropriate in any given patient, it is overwhelmingly likely based on extensive clinical trial data that the proposed substitutions would have been clinically reasonable in a large proportion of hypertensive patients. Not all patients will tolerate first-line therapy. In ALLHAT, the 1-year cessation rates were 12.9% for thiazide-type diuretics and 17.6% for ACE inhibitors, and in recent trials of β-blockers, the cessation rate was about 27%. Applying these rates to our projections and assuming that the same proportions of patients who switched to these regimens would revert to their previous medications would reduce the potential savings by $1.7 million, to $9.9 million. This amount still represents a 20.5% decrease in program spending for antihypertensive medications.

These estimates of potential savings are conservative in several ways. Since many thiazides cost less than 8¢ per tablet, patients filling these prescriptions would pay less than the $6 co-payment required for costlier prescriptions. Thus, for many of the 430,514 prescriptions for which thiazide replacement was suggested, patients would also have paid less out of pocket, in addition to the program savings described.

We were also conservative in making exceptions for recommended therapy. We excluded patients from substitution if they had filled even 1 previous thiazide prescription. Many of these patients likely did not have intolerable adverse effects and may well have been able to use thiazides instead of more expensive antihypertensives, resulting in greater savings, but we did not consider this possibility. Similarly, we followed the JNC VII guidelines and considered any diagnosis of angina as an acceptable indication for maintaining calcium channel blocker treatment, even though other guidelines prefer β-blockers as in such patients. Likewise, patients with a diagnosis of benign prostatic hypertrophy may have prostatic enlargement without urinary symptoms or may have already had surgical correction of the condition. Nevertheless, we used the JNC VII guidelines, which considered α-blockers an acceptable therapeutic choice in such patients, although evidence from ALLHAT would suggest replacing many of these α-blocker prescriptions with thiazides.

Bringing medication use closer to established practice guidelines would require some initial costs for physician education as well as some additional office visits at first as patients’ prescriptions are converted to new antihypertensive medications. Recent research addressed this problem directly in examining the effect of a reference-pricing system and found that the costs of additional physician visits associated with switching patients’ antihypertensive therapy were very small in relation to the savings achieved. Although additional costs might be incurred when patients switch drug classes, the savings from these changes would continue over years of subsequent drug use, offsetting these modest initial implementation and transition costs.

Overall drug spending for Medicare beneficiaries in 2002 was projected at $87 billion, and addition of a Medicare prescription drug benefit will add substantially to this cost; estimates of the eventual cost of this program have already increased dramatically from $400 billion over 10 years to more than $530 billion. Initiatives to improve prescribing could result not only in better clinical outcomes but also in lower spending on medications for hypertension and, potentially, for other conditions as well. Such rationalization of prescribing could make the difference between programs that are fiscally viable and those that are not.

Author Contributions: Dr Fischer and Avorn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fischer, Avorn.

Acquisition of data: Avorn.

Analysis and interpretation of data: Fischer, Avorn.

Drafting of the manuscript: Fischer.

Critical revision of the manuscript for important intellectual content: Avorn.

Obtained funding: Avorn.

Administrative, technical, or material support: Avorn.

Supervision: Avorn.

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REFERENCES