Background: Angiotensin-converting enzyme (ACE) inhibitors slow renal disease progression and reduce cardiac morbidity and mortality in patients with diabetes. Patients’ out-of-pocket costs pose a barrier to using this effective therapy.

Objective: To estimate the cost-effectiveness to Medicare of first-dollar coverage (no cost sharing) of ACE inhibitors for beneficiaries with diabetes.

Design: Markov model with costs and benefits discounted at 3%.

Data Sources: Published literature and Medicare claims data.


Time Horizon: Lifetime.

Perspective: Medicare and societal.

Interventions: We evaluated Medicare first-dollar coverage of ACE inhibitors compared with current practice (no coverage) and the new Medicare drug benefit.

Outcome Measures: Costs (2003 U.S. dollars), quality-adjusted life-years (QALYs), life-years, and incremental cost-effectiveness.

Results of Base-Case Analysis: Compared with current practice, first-dollar coverage of ACE inhibitors saved both lives and money (0.23 QALYs gained and $1606 saved per Medicare beneficiary). Compared with the new Medicare drug benefit, first-dollar coverage remained a dominant strategy (0.15 QALYs gained, $922 saved).

Results of Sensitivity Analysis: Results were most sensitive to our estimate of increase in ACE inhibitor use; however, if ACE inhibitor use increased by only 7.2% (from 40% to 47.2%), first-dollar coverage would remain life-saving at no net cost to Medicare. In analyses conducted from the societal perspective, benefits were similar and cost savings were larger.

Limitations: Results depend on accuracy of the underlying data and assumptions. The effect of more generous drug coverage on medication adherence is uncertain.

Conclusions: Medicare first-dollar coverage of ACE inhibitors for beneficiaries with diabetes appears to extend life and reduce Medicare program costs. A reduction in program costs may result in more money to spend on other health care needs of the elderly.

The prevalence of diabetes and its complications is increasing substantially in the United States (1–4). As the population ages and the number of elderly Medicare beneficiaries increases relative to the rest of the population, so will the number of elderly persons with diabetes and the share of national health expenditures allocated to complications of diabetes. Angiotensin-converting enzyme (ACE) inhibitors slow the progression of renal disease (5–12) and reduce cardiac morbidity and mortality (13–15) in individuals with diabetes. Despite ample clinical (5–15) and economic (16–18) evidence of benefit, ACE inhibitors are underused in elderly individuals with diabetes (19–23).

A growing body of evidence suggests that drug copayments reduce the use of essential medications in the elderly (24–30). Specifically, elderly individuals with diabetes seem to curtail essential drug use as their drug coverage decreases (26, 31). In 1999, Medicare beneficiaries paid more than 40% of their drug costs out of pocket (32). Under the new Medicare drug benefit, out-of-pocket spending will continue to be substantial (33), causing an ongoing potential barrier to the use of known effective drugs. A policy that bases patients’ out-of-pocket copayments on clinical benefit rather than cost of drugs has been proposed to improve value in health care (34). We aimed to assess the cost-effectiveness to Medicare of first-dollar coverage (that is, no cost sharing) of ACE inhibitors for elderly beneficiaries with diabetes.

METHODS

Decision Analytic Model

We developed a Markov model simulating the natural history of renal and cardiovascular complications in diabetes and risk reduction due to ACE inhibition (Figure 1).
Model outcomes included progression of renal disease, cardiovascular events, life expectancy, quality-adjusted life expectancy, lifetime costs, and incremental cost-effectiveness ratios. Our model builds on previous models of ACE inhibition for diabetic nephropathy (16). However, the primary complication of type 2 diabetes is cardiovascular disease, accounting for more than 60% of deaths; thus, we extend these models by adding a cardiovascular events component based on recent data from the Heart Outcomes Prevention Evaluation (HOPE) trial. The HOPE trial demonstrated that ACE inhibitors improve both renal and cardiovascular outcomes, compared with placebo, in patients with diabetes (13, 14, 35).

A cohort of individuals 65 years of age with diabetes enters the model and transitions through renal disease states and cardiovascular event states with rate of disease progression modified by the use of ACE inhibitors. The time horizon of the analysis is divided into 1-year cycles and the cohort is followed over its lifetime.

**Initial Population Distribution**

The cohort was initially distributed across disease states (Table 1) on the basis of epidemiologic data obtained from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) (36), a nationally representative cross-sectional survey of the U.S. noninstitutionalized civilian population. Among individuals 65 years of age or older with self-reported diabetes, 28.2% had microalbuminuria, 18.3% had macroalbuminuria, 20.3%...
had previous myocardial infarction, and 14.5% had previous stroke.

**Likelihood of Events**

**Renal Disease**

We obtained baseline risk for developing and progressing through the stages of nephropathy (normoalbuminuria, microalbuminuria, macroalbuminuria, and end-stage renal disease [ESRD]) from the placebo groups of trials in patients with type 2 diabetes (5, 7, 37). We obtained risk reductions from ACE inhibitor treatment from clinical trials (5–7) (Table 1). While ACE inhibition may cause regression of diabetic nephropathy (8, 11, 46, 47), we assumed no regression to ensure conservative cost-effectiveness estimates.

**Cardiovascular Disease**

We obtained baseline cardiovascular risk and risk reduction with ACE inhibitors from the placebo and treatment groups, respectively, of the subset of individuals with diabetes who were enrolled in the HOPE trial (14) (Table 1). We obtained these rates after calibrating the model to HOPE composite end point.

---

### Table 1. Model Inputs: Disease Prevalence and Progression*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Range Tested†</th>
<th>Reference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial disease prevalence in cohort, %</strong></td>
<td></td>
<td></td>
<td></td>
<td>National sample of diabetics ≥ 65 y</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>53.5</td>
<td>30–75</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>28.2</td>
<td>15–45</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>18.3</td>
<td>10–25</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td>National sample of diabetics ≥ 65 y</td>
</tr>
<tr>
<td>Previous MI</td>
<td>15.3</td>
<td>10–20</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>9.5</td>
<td>5–15</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Previous MI and stroke</td>
<td>5.0</td>
<td>2–10</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

**Annual transition rates**

| Renal disease progression rates‡ | | | | |
| Normal to microalbuminuria | 0.035 | 0.015–0.05 (N) | 7, 16 | |
| Microalbuminuria to macroalbuminuria | 0.081 | 0.050–0.12 (N) | 37 | |
|Macroalbuminuria to ESRD | 0.056 | 0.025–0.08 (N) | 5, 16 | |
| Relative risk for renal progression with ACE§ | | | | |
| Normal to microalbuminuria | 0.32 | 0.25–0.60 (T) | 7, 16 | |
| Microalbuminuria to macroalbuminuria | 0.24 | 0.20–0.75 (T) | 7, 16 | |
|Macroalbuminuria to ESRD | 0.61 | 0.50–0.75 (T) | 5, 16 | |

**Cardiovascular event rates‡**

| Event mortality, % | | | | |
| MI | 30 | 20–40 (N) | 14 | |
| Stroke | 30 | 20–40 (N) | 14 | |

**CVD event relative risk with ACE§**

| MI | 0.755 | 0.65–0.85 (T) | 14 | Estimates obtained by calibrating model to HOPE composite end point |
| Stroke | 0.674 | 0.55–0.85 (T) | 14 | |

**Increase in cardiovascular event risk§**

| With history of MI | 2.65 | 1.80–3.40 (T) | 38 | |
| With history of stroke | 1.82 | 1.19–2.76 (T) | 39 | |
| Increased MI risk with macroalbuminuria | 2.73 | 1.95–3.81 (T) | 40 | |
| Increased stroke risk with macroalbuminuria | 2.33 | 1.28–4.24 (T) | 40 | |
| Increased other CVD mortality with microalbuminuria| 1.68 | 1.35–2.09 (T) | 40 | |
| Increased other CVD mortality with macroalbuminuria| 2.47 | 1.97–3.10 (T) | 40 | |

**Mortality**

| Non-CVD mortality | 0.28–0.54 | – | 41, 42 | Adjusted for diabetes |
| ESRD mortality (age-based) | – | 0.28–0.54 | 2, 43 | Annual ESRD mortality |

**ACE utilization rates**

| Current practice | 0.40 | – | 44 | NHANES 1999–2000 |
| First-dollar coverage | 0.60 | 0.40–1.00 (T) | 45 | Based on an arc elasticity of –0.25 |
| Practice after 2006 | 0.47 | 0.47–1.00 (T) | 46 | Base-case estimate is the conservative upper bound (biases against first-dollar coverage) |

* ACE = angiotensin-converting enzyme; CVD = cardiovascular disease; ESRD = end-stage renal disease; HOPE = Heart Outcomes Prevention Evaluation; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey.  
† Ranges tested were obtained from 95% CIs when available; otherwise they were derived by adding or subtracting ≥ 25% to or from the baseline estimate. Variables with a letter adjacent to the ranges were tested in probabilistic sensitivity analyses with the distributions used in parentheses: N = normal; T = triangular. Variable ranges with no adjacent letter were tested in 1-way sensitivity analyses.  
§ Presented as relative hazard rates.  
|| Other CVD mortality refers to cardiovascular deaths (such as from arrhythmias) that occur in the absence of a concomitant MI or stroke.
We based the age-dependent probability of death from causes other than cardiovascular disease or ESRD on year 2000 U.S. life table data (41, 42) multiplied by a standardized mortality ratio for diabetes in the elderly (2). We then applied a proportional hazards (that is, multiplicative) model to remove cardiovascular disease and ESRD mortality (42) from age-based diabetes hazards, because these were modeled separately in our model. We obtained age-dependent ESRD mortality rates from the U.S. Renal Data System (43).

### Utilities

Health state utilities, or measures of value for given health states, can be thought of as quality-of-life weights that are bounded by 1 for perfect health and 0 for death. When utilities are multiplied by the lengths of time individuals spend in their respective health states, the resultant metric is a quality-adjusted life expectancy (measured in quality-adjusted life-years [QALYs]), which reflects both the quantity and quality of remaining years of life (48). We obtained utilities for our study (Table 2) from published studies (49–53).

### Costs

Because we assessed a Medicare coverage decision, the base-case model took the Medicare perspective, including direct medical costs and future (related and unrelated) health care costs, because all are borne by Medicare. We performed additional analyses from the societal perspective to allow for comparison with other cost-effectiveness analyses. Because of

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**Table 2. Model Inputs: Utilities, Costs, and Discount Rate***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Utilities</th>
<th>Estimate</th>
<th>Range Tested†</th>
<th>Reference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health states</strong></td>
<td>Diabetes (baseline health)</td>
<td>0.88</td>
<td>0.8–1.0 (T)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>0.88</td>
<td>0.7–1.0 (T)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>0.64</td>
<td>0.5–0.8 (T)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>0.61</td>
<td>0.45–0.75 (T)</td>
<td>51, 52</td>
<td></td>
</tr>
</tbody>
</table>

**Annual costs, $**

| Event costs (annual cost in event year)‡ | Myocardial infarction, survive | 33 724 | 20 000–45 000 (LN) | |
| | Myocardial infarction, die | 38 471 | 25 000–50 000 (LN) | |
| | Stroke, survive | 22 112 | 15 000–30 000 (LN) | |
| | Stroke, die | 34 961 | 20 000–45 000 (LN) | |
| | MI and stroke, survive | 50 117 | 35 000–65 000 (LN) | |
| | MI and stroke, die | 51 370 | 35 000–65 000 (LN) | |
| | Noncardiovascular mortality | 25 365 | 15 000–40 000 (LN) | |

| **ESRD‡** | Beneficiary 65–74 y of age | 68 300 | – | 54 | Based on costs for ESRD due to diabetes |
| | Beneficiary ≥ 75 y of age | 74 772 | – | 54 | |

| **Ongoing costs of care§** | Baseline age- and sex-based costs | 1911–4285 | – | 55 | Based on a model developed for the CMS for risk adjustment on the basis of demographic and clinical characteristics of beneficiaries |

| **Incremental diagnosis-based costs§** | Diabetes, no complication | 1127 | 500–2000 (N) | 55 | |
| | Diabetes with microalbuminuria | 1965 | 1127–3000 (N) | 55 | |
| | Diabetes with renal complications | 4089 | 1127–6000 (N) | 55 | |
| | MI in previous year | 3680 | 2500–5000 (N) | 55 | |
| | MI ≥ 2 y ago | 2186 | 1000–3000 (N) | 55 | |
| | Stroke in any previous year | 4733 | 2000–7000 (N) | 55 | |
| | ACE inhibitor annual costs | 233 | 39–400 (T) | 56 | Lower bound from the federal supply schedule |

| **Discount rate** | 0.03 | 0–0.10 | 48 | |

* ACE = angiotensin-converting enzyme; CMS = Centers for Medicare & Medicaid Services; ESRD = end-stage renal disease; MI = myocardial infarction.
† Ranges tested were obtained from 95% CIs when available; otherwise they were derived by adding or subtracting ≥ 25% to or from the baseline estimate. Variables with a letter adjacent to the ranges were tested in probabilistic sensitivity analyses with the distributions used in parentheses: LN = log-normal distribution; N = normal; T = triangular. Variable ranges with no adjacent letter were tested in 1-way sensitivity analyses.
‡ Medicare expenditures for the entire year in which the event occurs.
§ Ongoing costs of care are applied to patients without ESRD and only in years when no clinical event occurs. They are calculated by summing baseline cost (based on age and sex) with the incremental costs associated with comorbid conditions. Costs associated with diabetes (that is, diabetes with no complication, with microalbuminuria, or with renal complications) are mutually exclusive and only 1 of these costs can apply in a given year to a patient with diabetes. Similarly, costs associated with having an MI in the previous year or having an MI ≥ 2 years earlier are mutually exclusive, with only 1 applying to a given patient in a given year.

We based the age-dependent probability of death from causes other than cardiovascular disease or ESRD on year 2000 U.S. life table data (41, 42) multiplied by a standardized mortality ratio for diabetes in the elderly (2). We then applied a proportional hazards (that is, multiplicative) model to remove cardiovascular disease and ESRD mortality (42) from age-based diabetes hazards, because these were modeled separately in our model. We obtained age-dependent ESRD mortality rates from the U.S. Renal Data System (43).
the well-known difficulties in measuring price changes in the medical sector (57, 58), we standardized costs to 2003 U.S. dollars by using the Consumer Price Index for all urban consumers (59). We based all costs, except medication costs, on Medicare claims data (Table 2).

**Event Costs**

We obtained Medicare expenditures occurring in the year of an event from the 2001 Medicare Standard Analytic Files, a nationally representative 5% random sample of fee-for-service Medicare beneficiaries, and limited them to beneficiaries 65 years or older with diabetes. We obtained annual expenditures associated with ischemic strokes, myocardial infarctions, and deaths (both cardiovascular and noncardiovascular) from these data. We assigned costs for the year of death on the basis of the costs incurred in the last year of life by beneficiaries who had a myocardial infarction, a stroke, both events, or neither event in the year of their death.

We obtained annual costs associated with treating patients with ESRD (including costs of dialysis; transplantation; and other health care, including cardiovascular event care) from the U.S. Renal Data System. The annual costs comprise Medicare payments for individuals with ESRD due to diabetes (54).

**Ongoing Care Costs**

We obtained ongoing costs of care (including medical costs of future years of life added) for years in which no discrete event occurred from a diagnostic classification system. This system was developed for the Centers for Medicare & Medicaid Services (CMS) to make risk-adjusted payments to Medicare managed care plans on the basis of patient demographic characteristics and clinical risk factors (55). Many expenditures depend on beneficiary demographic characteristics (age, sex, and percentage of Medicare enrollment), but incremental costs accrue for disease history (that is, history of stroke, myocardial infarction, and diabetes-related renal failure) (Table 2).

We based the annual cost of therapy ($233) on the average wholesale price of lisinopril, a once-daily, off-patent ACE inhibitor (56).

**Interventions**

The intervention of interest was Medicare first-dollar coverage of ACE inhibitors (that is, Medicare bears the full drug costs with no beneficiary cost sharing). The comparator was current practice (before the planned 2006 implementation of the new Medicare drug benefit) (60). For current practice, we assign a base rate of ACE inhibitor use from which Medicare accrues the benefits and cost offsets (that is, avoided costly health outcomes), but we assume that Medicare bears none of the costs for drugs in this comparator group. With first-dollar coverage, we very conservatively assume that 100% of the current practice drug costs get shifted to Medicare (that is, all third-party payers currently paying for ACE inhibitors will drop this coverage, effectively shifting all ACE inhibitor costs to Medicare).

**ACE Inhibitor Use**

The rates of ACE inhibitor utilization with current practice were set at 40% on the basis of national rates of use obtained from NHANES 1999–2000 data for individuals 65 years of age or older with diabetes (44). In the base case, we assumed that utilization rates with Medicare first-dollar coverage increased to 60% (from 40%), on the basis of recent studies examining the effect of changes in prescription cost sharing on medication use (31, 45). Because of the variability in the effect on medication use of changes in patient copayments (31, 45, 61–68), we vary this variable extensively in sensitivity analyses (Table 1).

**Base-Case Analyses**

We performed base-case analyses from the Medicare perspective (which was more conservative than the societal perspective), and data are reported for a 65-year-old beneficiary with diabetes. We discounted future costs and QALYs at an annual rate of 3% (48). We performed analyses by using DATA 4.0 (TreeAge Software, Inc., Williamstown, Massachusetts).

**Sensitivity Analyses**

To assess the robustness of our findings, we performed extensive 1-way sensitivity analyses (ranges in Tables 1 and 2). We obtained ranges tested from 95% CIs when available; otherwise, we derived them by adding or subtracting 25% to or from the baseline estimate. We performed several additional sensitivity analyses in which the context of the study was changed.

**Medicare Drug Benefit**

One key sensitivity analysis examined first-dollar coverage of ACE with an alternate comparator: coverage after the 2006 implementation of the new Medicare drug benefit (that is, practice after 2006). We made our best estimate of how the new Medicare drug benefit would influence ACE inhibitor use by assuming that the new drug bill’s effect would be proportional to the level of coverage provided. The Congressional Budget Office projected that Medicare will pay for approximately 35% of overall beneficiary drug costs through 2013 (69) (Appendix, available at www.annals.org). We therefore assumed that the Medicare drug benefit would achieve 35% of the increase in ACE inhibitor use achieved with first-dollar coverage, resulting in 47% ACE inhibitor use. This assumption is very conservative, since much of the 35% of drug spending that Medicare will cover represents shifts in spending from other payers to Medicare rather than truly new drug spending that might increase adherence to medications.

**Drug Pricing**

Because ACE inhibitor price varies depending on care setting and ACE inhibitor used, we performed sensitivity analyses varying the cost of ACE inhibitors. For our base case, we use the average wholesale price of a generic ACE inhibitor. We then examine the implications of purchasing the ACE inhibitor at the federal supply schedule price,
which is the substantially lower price that the U.S. Department of Veterans Affairs and U.S. Department of Defense pay, as a lower bound for ACE inhibitor cost.

**Societal Perspective**

In addition to analyses from the Medicare perspective, we examined the societal perspective to provide a reference case for comparison with other cost-effectiveness analyses (48). Direct medical costs included Medicare costs, as outlined earlier, and the average annual beneficiary out-of-pocket drug costs (70). As recommended by the U.S. Public Health Service’s Panel on Cost-Effectiveness (48), we included productivity gains and losses in the health-related quality-of-life measure (the QALYs). We included caregiver time costs, obtained from the literature on caregivers of elderly patients with diabetes (71), as monetary costs.

**Probabilistic Sensitivity Analysis**

We also conducted probabilistic sensitivity analyses, in which 38 parameters were varied simultaneously over their probability distributions. We used log-normal distributions for large costs; normal distributions for small costs and probabilities; and triangular distributions for utilities, relative risks, ACE inhibitor price, and increase in ACE inhibitor use. When distributions were asymmetric, we used the medians of the respective distributions. We ran 10,000 iterations to determine the distribution of incremental cost-effectiveness results.

The Appendix (available at www.annals.org) contains additional details about methods.

**Role of the Funding Source**

The Primary Care Research Fund of Brigham and Women’s Hospital partly funded this study. The funding source had no role in the design, conduct, or reporting of this study or in the decision to submit the manuscript for publication.

**RESULTS**

**Base-Case Analyses**

Under current practice, the total discounted lifetime cost per Medicare beneficiary 65 years of age with diabetes was $117,549. This strategy resulted in a discounted quality-adjusted life expectancy of 8.13 QALYs and corresponding life expectancy (without quality adjustment) of 10.30 life-years. With Medicare first-dollar coverage, discounted lifetime costs decreased to $115,943, quality-adjusted life expectancy increased to 8.36 QALYs, and life expectancy increased to 10.55 life-years. This resulted in a dominant strategy, meaning that Medicare first-dollar coverage of ACE inhibitors saved both lives and money (0.23 QALYs and $1606 per beneficiary). The savings from first-dollar coverage resulted entirely from medical events prevented and were offset by higher lifetime costs for ACE inhibitors and future unrelated health care (Table 3).

**Sensitivity Analyses**

In 1-way sensitivity analyses, our results were robust to a wide range of plausible estimates of renal and cardiac risks and risk reductions, costs, utilities, and discount rate. Cost savings persisted for the Medicare first-dollar coverage strategy in all univariate sensitivity analyses, except those examining increases in ACE inhibitor use. Since increase in ACE inhibitor use due to first-dollar coverage was the most uncertain estimate in our analysis, we considered the implications of substantially lower increases in use (Figure 2). Compared with current practice, first-dollar coverage remains cost-saving if ACE inhibitor use increases by 7.2% and remains less than $20,000 per QALY if use increases by 2.9% more than the baseline 40% rate of use.

When we compare first-dollar coverage of ACE inhibitors with anticipated practice after implementation of the new Medicare drug benefit in 2006, first-dollar coverage remains a dominant strategy but with lower savings than in the base-case comparison to current practice (Figure 2). For a typical 65-year-old Medicare beneficiary with diabetes, first-dollar coverage results in lifetime savings of 0.15 QALYs and $922 (Table 4). Compared with practice after 2006, first-dollar coverage remains cost-saving if ACE inhibitor use increases by 6.2% and remains less than $20,000 per QALY if use increases by 2.2% more than the baseline 47% rate of use.

If ACE inhibitors were purchased according to the federal supply schedule (government-negotiated prices for the U.S. Department of Veterans Affairs and U.S. Department of Defense), ACE inhibitor use would only need to increase from 40% to 41.1% (absolute increase of 1.1%) for first-dollar coverage to be cost-saving to Medicare. With a 20% increase in use (our base-case estimate), lifetime cost savings would increase to $2943 per 65-year-old beneficiary with diabetes.

Analyses performed from the societal perspective demonstrated benefits similar to those seen in the base-case analysis (0.23 QALYs saved) but at substantially increased cost savings, with $2501 in lifetime savings per 65-year-old beneficiary with diabetes (Table 4). These findings represent the implications of first-dollar coverage increasing ACE inhibitor use from 40% to 60%.

Table 3. Distribution of Base-Case Costs*

<table>
<thead>
<tr>
<th>Source of Lifetime Costs</th>
<th>First-Dollar Coverage, $</th>
<th>Current Practice, $</th>
<th>Incremental Costs, $†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor costs</td>
<td>1606</td>
<td>0</td>
<td>1606</td>
</tr>
<tr>
<td>Event-related costs‡</td>
<td>82 321</td>
<td>86 929</td>
<td>−4608</td>
</tr>
<tr>
<td>Unrelated health care costs</td>
<td>32 016</td>
<td>30 620</td>
<td>1396</td>
</tr>
<tr>
<td>Overall costs</td>
<td>115 943</td>
<td>117 549</td>
<td>−1606</td>
</tr>
</tbody>
</table>

* ACE = angiotensin-converting enzyme.
† Negative numbers denote incremental savings with first-dollar coverage of ACE inhibitors.
‡ Costs related to renal disease, cardiovascular disease, and cerebrovascular disease.
inhibitor use (vs. no ACE inhibitor use) in a 65-year-old with diabetes, resulted in incremental savings of $12,506 and 1.14 QALYs over an individual’s lifetime, with cost savings persisting at ACE inhibitor costs up to $1323 per year.

Probabilistic sensitivity analyses, simultaneously varying 38 model variables, showed our findings to be quite robust. First-dollar coverage was cost-saving compared with current practice and compared with practice under the 2006 Medicare drug benefit in 91% and 90% of simulations, respectively, and was less than $20,000 per QALY in 99% of simulations in both comparisons (see Table 4 for distributions).

**DISCUSSION**

Diabetes is a major cause of ESRD and cardiovascular disease in the United States. Angiotensin-converting enzyme inhibitors are effective at reducing these complications, but they are substantially underused (19–23). Prescription copayments are a barrier to use (64, 65). While concern mounts over increasing Medicare costs, our analysis suggests that Medicare adoption of first-dollar coverage of ACE inhibitors for beneficiaries with diabetes not only saves lives but actually decreases total Medicare costs. Cost savings remained even when we conservatively compared
first-dollar coverage of ACE inhibitors with prescription coverage provided by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

Cost-saving interventions are rare in medical practice (72). Examples include folic acid fortification of cereal grains (48) and pneumococcal vaccination in the population older than 65 years of age (73). In our study, considerable gains in health can be realized while also saving substantial Medicare resources. In an era of growing concerns over Medicare’s future financial viability, rare opportunities to improve quality while also saving money should not be treated lightly.

Our findings were robust to wide variation in model estimates. First-dollar coverage of ACE inhibitors resulted in cost savings provided that ACE inhibitor utilization rates increased in absolute terms by at least 7.2%, corresponding to a price elasticity (change in drug demand due to change in out-of-pocket cost) that is much less than most published estimates (31, 45, 61–68) (see Appendix, available at www.annals.org). Regardless of the savings, the health benefits resulting from first-dollar coverage were substantial and similar to those seen with improving adherence to β-blockers after myocardial infarction (74).

It is important to remember when interpreting our results that they represent the health and economic outcomes resulting from an increase in medication adherence due to a Medicare policy change. In most pharmacoeconomic studies, the question is not whether increasing adherence is cost-effective but whether use of the drug (compared with no use) is cost-effective from a societal perspective. Certainly, ACE inhibitors are cost-effective in elderly individuals with diabetes. By using a societal perspective, we found that 1.14 QALYs are gained and $12,500 is saved per patient 65 years of age with diabetes.

However, the principal question we address is not whether ACE inhibitor use is cost-effective to society but whether benefit redesign, a more subtle policy question, is cost-effective.

We address other policy issues as well. One clause in the legislation that enacted the new Medicare drug benefit prohibits Medicare from directly negotiating prices with drug manufacturers. If this controversial prohibition was repealed and Medicare purchased ACE inhibitors at the federal supply schedule price (the drug prices negotiated by the U.S. Department of Veterans Affairs and U.S. Department of Defense), ACE inhibitor use need only increase by 1.1% for first-dollar coverage to be cost-saving. In actual practice, ACE inhibitor price will probably be somewhere between the average wholesale price and federal supply schedule price because pharmacy benefits managers will presumably negotiate prices that are somewhat less than the average wholesale price, meaning that the threshold increase in use needed for first-dollar coverage to save money will probably be less than 7.2%. In contrast, if ACE inhibitor costs increase above the average wholesale price to the level of branded ACE inhibitors or angiotensin-receptor blockers, first-dollar coverage remains an efficient (cost-saving) use of Medicare resources. Past economic analyses have shown that both ACE inhibitors (17, 18) and angiotensin-receptor blockers (75) are cost-saving in high-risk individuals with diabetes. Clark and colleagues (18) found cost savings to the Canadian government for providing provincial coverage of ACE inhibitors for patients with type 1 diabetes and overt nephropathy. These previous studies reporting cost savings focused on patients who already had renal disease. Golan and colleagues (16) evaluated the cost-effectiveness of ACE inhibitor therapy for all individuals with type 2 diabetes, reporting a cost-effective-
ness ratio of $7500 per QALY. In contrast to our study, Golan and colleagues did not consider the cardiovascular benefits of ACE inhibitors. These benefits are of far more interest because in patients with diabetes, the risk for cardiovascular disease is higher than that of renal disease. Our results were more favorable because we modeled both the renal and cardiovascular benefits of ACE inhibitor therapy.

Our work extends previous economic analyses in other ways as well. We explored the cost-effectiveness of making Medicare coverage more generous (that is, decreased patient cost sharing) for a specific service, and we explicitly modeled suboptimal patient adherence to known effective therapies. The U.S. health care system uses many crude instruments to control costs. In the case of medications, cost sharing is often applied globally to reduce unnecessary use. Yet studies have demonstrated that cost sharing reduces the use of both essential (clear mortality or quality-of-life benefit) and less essential medications (24, 25, 27–31), and specifically, increased cost sharing has been shown to decrease use of medications in elderly Medicare beneficiaries with diabetes (26, 29). Our study shows that nontargeted cost sharing may actually have a detrimental effect on overall program costs by detracting the use of highly cost-effective or cost-saving drugs. While policy decisions about selective drug coverage may be difficult to put into practice, we may benefit from improving our use of cost-sharing tools to maximize the use of the most beneficial and high value drugs (34) and, therefore, maximize the health of the elderly within constrained resources. However, it is important to recognize that interventions do not need to be cost-saving to provide value or to merit interventions (such as reduced cost sharing) to increase use.

Our study had many limitations. Our knowledge of the effect of drug coverage on use and adherence is still in its infancy and merits further exploration. We, therefore, report extensive sensitivity analyses on increases in use. Drug spending and increased ACE inhibitor use after implementation of the new Medicare drug benefit are estimates, since this benefit is not yet in effect. While we used conservative estimates to bias the model against first-dollar coverage, future policy analyses must follow the actual impact of the Medicare drug benefit after its implementation. We did not examine social security pension costs because inclusion of such costs would be analogous to a death benefit for not treating patients. We did, however, examine future costs of added years of life, and despite varying these widely in sensitivity analyses, our findings remained robust.

We assumed that with first-dollar coverage of ACE inhibitors, all drug costs previously paid by other payers or out of pocket would be shifted to Medicare. This assumption leads to very conservative estimates of Medicare savings. We also did not model the effect of first-dollar coverage of ACE inhibitor use on beneficiaries’ use of other beneficial medications, such as aspirin, statins, or β-blockers. However, eliminating ACE inhibitor out-of-pocket costs would allow for more discretionary income to spend on other valuable drugs. Furthermore, our analysis excluded the potential benefits of ACE inhibition in preventing diabetic retinopathy and neuropathy (76–78) as well as the benefits of ACE inhibitors for other prevalent indications in elderly individuals with diabetes, such as heart failure. These assumptions likely underestimated the potential clinical benefits and cost savings of Medicare first-dollar coverage of ACE inhibitors.

Finally, the decision to make ACE inhibitor use contingent upon coverage does not mean that other interventions (such as creation of a new performance measure, academic detailing, or other quality improvement activities) might also be effective in increasing ACE inhibitor use and subsequently saving lives and Medicare expenditures for elderly individuals with diabetes. Indeed, in the base case, we assumed a maximal ACE inhibitor uptake of 60%, which leaves many patients untreated.

The prevalence of diabetes and its renal and cardiovascular complications is increasing substantially. As the population ages and the number of elderly Medicare beneficiaries increases relative to the rest of the population, so will the number of elderly persons with diabetes and the share of national health expenditures allocated to complications of diabetes. Drug copayments, which represent a barrier to the use of effective medications, can be redesigned to create incentives for using beneficial medications. In our study, Medicare first-dollar coverage of ACE inhibitors for beneficiaries with diabetes appears to extend life and reduce Medicare program costs. A reduction in program costs from a cost-saving intervention may mean more money to spend on other health care needs of the elderly in a time when Medicare solvency is a national health policy concern.

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References


38. Valmadril CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in per-


51. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group, JAMA. 1996;276:1409-15. [PMID: 8892716]


68. Smith DG. The effects of copayments and generic substitution on the use and costs of prescription drugs. Inquiry. 1993;30:189-98. [PMID: 8314607]


### Renal Disease Progression

Rates of renal disease progression and risk reduction due to ACE inhibitors are the same as the rates used in a recent cost-effectiveness model by Golan and colleagues (16) with 1 exception. We use a lower rate of progression from microalbuminuria to macroalbuminuria (annual transition rate of 0.081) compared with that reported by Golan and colleagues (annual transition rate of 0.11). We obtained our transition rate from the placebo group of a randomized, controlled trial of irbesartan in individuals with type 2 diabetes and microalbuminuria (37). By using this lower progression rates, our model better validates to population incidence rates of ESRD.

### Cardiovascular Event Rates

Because Framingham risk models underestimate cardiovascular disease risk associated with diabetes (79–81) and because the United Kingdom Prospective Diabetes Study risk equations were developed for individuals younger than 65 years of age, we obtained our baseline hazards for first myocardial infarction and first stroke from the placebo group of the subset of patients with diabetes in the HOPE trial. We varied these cardiovascular disease event rates extensively in sensitivity analyses.

### Noncardiovascular, Non-ESRD Mortality Rates

We obtained age-based mortality hazard rates from year 2000 U.S. life tables (41) and multiplied them by a standardized mortality ratio, obtained from a 5% Medicare sample, of 1.41 for diabetes (2). We then applied a proportional hazards (that is, multiplicative) model to remove cardiovascular disease and ESRD mortality (42) from age-based diabetes hazards because these are modeled separately in our model. A multiplicative hazard relationship, which results in a constant proportion of cause-specific deaths over time (82), is consistent with the literature on cardiovascular disease mortality (83).

### Utilities

We obtained utilities from published studies that used various utility elicitation methods, including time-tradeoff utilities and standard gamble utilities.
elicted from patients, utilities from the Health Utilities Index (based on community preferences using the standard gamble method), and values from the Quality of Well-Being Scale, transformed from its rating scale values to obtain utilities (49–53).

**Event Costs**

We obtained Medicare expenditures incurred during the year in which an event occurred from a 2001 nationwide 5% random sample of fee-for-service Medicare beneficiaries with diabetes (n = 228 272). Consistent with past studies (84, 85), individuals were classified as having diabetes if they had either 2 or more diabetes-related codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], codes 250.xx) on an outpatient claim or 1 or more diabetes-related codes on an inpatient claim in 2001. We identified ischemic strokes by ICD-9-CM codes 433.x1, 434.xx, or 436.xx and myocardial infarctions by ICD-9-CM codes 410.xx. Annual expenditures included the sum of amounts paid for inpatient, outpatient, physician or supplier, home health, and skilled nursing facilities and, as such, reflect the actual 2001 Medicare program payments made in the care of Medicare beneficiaries with diabetes having these events.

**Ongoing Care Costs**

We obtained ongoing costs of care from a diagnostic classification system developed for the CMS to allow for risk-adjusted payments to Medicare managed care plans. This Hierarchical Condition Categories model was developed on and then calibrated to a 1999–2000 5% nationwide sample of fee-for-service Medicare beneficiary expenditure data (55). The model is prospective in that patient diagnoses in a given year are used to predict expenditures in the following year.

**ACE Inhibitor Use**

In 1999 and 2000, up to 20 medications could be reported for each NHANES respondent. No respondent 65 years of age or older with diabetes had all 20 medication slots filled. We classified an individual as receiving ACE inhibitor therapy if any of their listed medications included an ACE inhibitor or an angiotensin-receptor blocker, because these are often used interchangeably for ACE inhibitors.

In the base case, we assumed that utilization rates with Medicare first-dollar coverage increased to 60% (from 40%) on the basis of a price elasticity of −0.25 from a recent study examining the effect of changes in prescription cost-sharing on spending and use of medications (45). This estimate is conservative, and while a follow-up study by the same investigators (31) suggested that price elasticity for medications is lower in chronically ill adults than in the general population, the one exception was patients with diabetes who had price elasticities similar to that of the overall population (the elasticity we used in our study). It is important to note that the price elasticity for medications reported in the literature substantially varies, with arc elasticities ranging from −0.11 to −1.6 (31, 45, 62–68). We selected the base-case estimate of −0.25 because it is a more conservative value between the price elasticities reported by Joyce and colleagues (−0.22 to −0.33) in their study examining the effect of cost-sharing (under 55 different benefits packages) by using more than 700 000 person-years of data (45).

**Sensitivity Analysis Examining the Societal Perspective**

We reran analyses from the societal perspective to improve comparability with other published cost-effectiveness analyses. Direct medical costs included the Medicare costs as outlined for the base case and the average annual out-of-pocket drug costs. We obtained average annual out-of-pocket drug costs for Medicare beneficiaries ($996 in 2003) from a Kaiser Family Foundation publication that used 2003 Congressional Budget Office estimates (70). As recommended by the U.S. Public Health Service’s Panel on Cost-Effectiveness (48), productivity gains and losses were reflected in the health-related quality-of-life measure in the denominator of the cost-effectiveness ratio (that is, the QALYs). We included annual caregiver time costs, obtained from the literature on caregivers of elderly patients with diabetes, as monetary costs ($1246 in 2003 U.S. dollars) (71).

**Sensitivity Analysis Comparing First-Dollar Coverage with New Medicare Drug Benefit**

One sensitivity analysis compared first-dollar coverage of ACE inhibitors with an alternate comparator: the new Medicare drug benefit (that is, current practice after 2006). To estimate current practice after 2006, we assumed that Medicare would pay 35% of drug costs. This is consistent with Congressional Budget Office testimony to Congress on the administration estimates of $534 billion in Medicare outlays to meet the $1.6 trillion in drug spending by Medicare beneficiaries from 2006 to 2013 (69). We then very conservatively assumed that ACE inhibitor use would increase proportionately 35% of the way toward the estimated increase in ACE inhibitor use with first-dollar coverage. Therefore, the utilization rate would be 47% with current practice after 2006 compared with 40% with current practice and, for both comparisons, first-dollar coverage will increase ACE inhibitor utilization rates to 60% nationally in elderly individuals with diabetes.

**Results**

**Sensitivity Analysis: Thresholds for ACE Inhibitor Utilization Rate and ACE Inhibitor Cost**

Compared with current practice, first-dollar coverage remains cost-saving if ACE inhibitor use increases by 7.2% (corresponding to an arc elasticity of −0.09) or more above the baseline 40% rate of use. If ACE inhibitors were purchased according to the federal supply schedule, ACE inhibitor use would only need to increase from 40% to 41.1% (absolute increase of 1.1%, corresponding to an arc elasticity of −0.014) for first-dollar coverage to be cost-saving to Medicare. Both of these arc elasticities are substantially lower than those traditionally reported in the literature (31, 45, 62–68), suggesting that the true response to elimination of the copayment would be higher than this threshold value (and therefore first-dollar coverage would be cost-saving).
Components of Base-Case Savings: Adherent Versus Nonadherent Beneficiaries

Base-case results can be broken down into the adherent and nonadherent groups of beneficiaries within each of the 2 policies: first-dollar coverage and current practice. As can be seen in the Appendix Figure, lifetime costs for a 65-year-old beneficiary with diabetes who is nonadherent to ACE inhibitors are substantially higher ($13,383 to $16,059 higher) than the lifetime costs incurred by an adherent beneficiary. Nonadherence is also marked by a substantially lower life expectancy (1.15 QALYs less than in an adherent beneficiary).
Appendix Figure. Breakdown of base-case results by adherence to angiotensin-converting enzyme inhibitors.

Squares indicate a decision between alternate policies. “Drug benefit” denotes first-dollar coverage of angiotensin-converting enzyme inhibitor, while “no drug benefit” denotes current practice. Circles represent chance events; circles with “M” denote entry into a Markov process. QALY = quality-adjusted life-year.