Cost-effectiveness of full Medicare coverage of angiotensin-converting enzyme inhibitors for beneficiaries with diabetes

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
First-dollar coverage (no cost sharing) of angiotensin-converting enzyme (ACE) inhibitors was compared with current practice (no coverage) and the new drug benefit for elderly Medicare beneficiaries with diabetes.

Type of intervention
Secondary prevention and treatment; Other (medication coverage policy design).

Economic study type
Cost-utility analysis.

Study population
The target population for the model was a hypothetical cohort of individuals aged 65 years old with diabetes.

Setting
The setting was primary and secondary care. The economic study was carried out in the USA.

Dates to which data relate
The studies used for the effectiveness evidence dated from 1985 to 2004. For the cost data, the studies dated from 2001 to 2004. The price year was 2003.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies, and estimates based on authors’ assumptions.

Modelling
A Markov (state transition) decision model was used to simulate the natural history of renal and cardiovascular complications in diabetes, and risk reduction due to ACE inhibition. The model was described in detail. A cohort of individuals aged 65 old with diabetes entered the model and transitions through renal disease states and cardiovascular event states were assessed, with the rate of disease progression (renal and cardiovascular) modified by the use of ACE inhibitors. The cohort was initially distributed across disease states on the basis of epidemiologic data, and followed yearly over a lifetime horizon. The model also took non-adherence with ACE inhibitor use into consideration.

The model assumed that Medicare bore none of the costs for drugs in the comparator group. With first-dollar coverage, the model very conservatively assumed that 100% of the current practice drug costs were shifted to Medicare.
Outcomes assessed in the review
The model inputs included data about disease prevalence and progression, as well as the health utility of different health states. The selected parameters assessed for disease prevalence and progression were:

- initial disease prevalence in the cohort for renal disease (different stages of renal disease from normoalbuminuria to macroalbuminuria) and cardiovascular disease (prior myocardial infarction (MI) and/or prior stroke);
- the annual transition rates for the stages of renal disease, and the relative risk for renal progression and cardiovascular disease (CVD) with ACE inhibitors;
- the cardiovascular event rates (first MI, first stroke, and over CVD mortality);
- event mortality (MI, stroke), and CVD and end-stage renal disease (ESRD) mortality;
- different cardiovascular risk modifiers in selected sub-groups (e.g. history of MI or stroke); and
- the rates of ACE inhibitor use under the different strategies.

Study designs and other criteria for inclusion in the review
The authors reported that they used randomised controlled trials (RCT), cohort studies, observational studies and published literature.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Sixty-four studies were included as sources of effectiveness.

Methods of combining primary studies
A narrative method was used to combine the primary studies.

Investigation of differences between primary studies
The authors do not appear to have investigated differences between the primary studies.

Results of the review
The initial disease prevalence in the cohort was 53.5% for normoalbuminuria, 28.2% for microalbuminuria and 18.3% for macroalbuminuria.

For CVD, the initial prevalence was prior MS 15.3%, prior stroke 9.5%, and prior MI and stroke 5.0%.

The annual renal disease progression rates were 0.035 from normal to microalbuminuria, 0.081, from microalbuminuria to macroalbuminuria, and 0.056 from macroalbuminuria to ESRD.
The relative risk for renal progression with ACE inhibitors was 0.32 from normal to microalbuminuria, 0.24 from microalbuminuria to macroalbuminuria, and 0.61 from macroalbuminuria to ESRD.

The cardiovascular event rates obtained by calibration were first MI 0.0287, first stroke 0.0133, and other CVD mortality 0.0040.

The event mortality was 30% for MI and stroke.

The CVD event relative risk with ACE inhibitors was 0.755 for MI and 0.674 for stroke.

The increase in cardiovascular event risk was 2.65 with a history of MI and 1.82 with history of stroke.

With macroalbuminuria, the increased MI risk was 2.73 and the increased stroke risk was 2.33.

The increased risk of other CVD mortality was 1.68 with microalbuminuria and 2.47 with macroalbuminuria.

The non-CVD mortality rate was age-based and the ESRD mortality rate (age-based) was between 0.28 and 0.54.

The rate of ACE inhibitor use was 0.40 for current practice, 0.60 for first-dollar coverage, and 0.47 for the practice after 2006.

The utilities for health states were 0.88 for diabetes (baseline health), 0.88 for MI, 0.64 for stroke and 0.61 for ESRD.

For all model parameters included, the authors adequately referenced their base-case value, the range used in the sensitivity analysis and their source.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
Key model assumptions were reported in an appendix. These included assumptions about base-case patient characteristics, renal and CVD, ACE inhibitor use and adherence to treatment. The authors stated that when published estimates were not available, they assumed a conservative estimate of the parameter.

Among the main assumptions, the authors stated that while ACE inhibition might cause regression of diabetic nephropathy, they assumed no regression to ensure conservative cost-effectiveness estimates. In the base-case, they assumed that rates of ACE inhibitor use with Medicare first-dollar coverage increased to 60% from 40% in current practice, on the basis of recent studies examining the effect of changes in prescription cost sharing on medication use. Also, they assumed that the Medicare new drug benefit would achieve 35% of the increase in ACE inhibitor use achieved with first-dollar coverage, resulting in 47% ACE inhibitor use.

Measure of benefits used in the economic analysis
The authors used quality-adjusted life-years (QALY) as a measure of benefit, and also reported life-years. The utilities were obtained from published studies that used various utility elicitation methods. For example, time trade-off utilities elicited 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. The authors provided a list of utilities and the range tested in the sensitivity analysis around each point estimate. The health benefits were discounted at a rate of 3% per year.

Direct costs
All the costs, except medication costs, were obtained from Medicare claims data, 2001 Medicare Standard Analytic Files, for expenditures occurring in the year of an event. Annual expenditures included those associated with ischaemic
strokes, MIs and deaths (both cardiovascular and non-cardiovascular). Annual costs associated with treating patients with ESRD due to diabetes were obtained from the US Renal Data System. These included the costs of dialysis, transplantation and other health care, including cardiovascular event care. The ongoing costs of care (including medical costs of future years of life added) for years in which no discrete event occurred were obtained from a diagnostic classification system developed for the Centres for Medicare & Medicaid Services (CMS). In addition, the societal perspective included the cost of caregiver time obtained from the literature on caregivers of elderly patients with diabetes.

The annual cost of therapy was based on the average wholesale price of a generic ACE inhibitor (lisinopril, a once-daily off-patent ACE inhibitor). The implications of purchasing the ACE inhibitor at the federal supply schedule price were also explored because it was a substantially lower price for the government. All the costs were discounted at a rate of 3% per year. The quantities and the costs were analysed separately but were not reported in full. All the cost estimates were updated to 2003 US dollars by using the Consumer Price Index for all urban consumers. The price year was 2003.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
No indirect costs were reported. The authors examined the societal perspective and stated that they included productivity gains and losses in the health-related quality of life measure (QALYs), measure as recommended by US Public Health Service's Panel on Cost-Effectiveness.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors investigated areas of uncertainty related to variability in the data through one-way and probabilistic sensitivity analyses. The ranges selected and reported were based on published literature or authors' assumptions. The parameters investigated were a wide range of plausible estimates of renal and cardiac risks and risk reductions, costs, utilities, discount rate and ACE inhibitor use. Probabilistic sensitivity analyses were carried out in which 38 model parameters were varied simultaneously, and the variable distributions used were adequately reported (10,000 iterations used).

**Estimated benefits used in the economic analysis**
The current practice strategy resulted in a discounted quality-adjusted life expectancy of 8.13 QALYs and a crude life expectancy of 10.30 life-years.

With Medicare first-dollar coverage, quality-adjusted life expectancy increased to 8.36 QALYs, and life expectancy increased to 10.55 life-years. This represented incremental QALYs of 0.23 (95% credible interval, CrI: 0.05 - 0.58) and incremental life-years of 0.25 (95% CrI: 0.06 - 0.60).

The usual practice after 2006 (new drug benefit strategy) resulted in a discounted quality-adjusted life expectancy of 8.21 QALYs and a crude life expectancy of 10.39 life-years. This represented incremental QALYs of 0.15 (95% CrI: 0.04 - 0.50) and incremental life-years of 0.16 (95% CrI: 0.06 - 0.52) in comparison with the first-dollar coverage strategy.

**Cost results**
The current practice strategy resulted in a total discounted lifetime cost per Medicare beneficiary aged 65 years old with diabetes of $117,549 from the Medicare perspective. With Medicare first-dollar coverage, the discounted lifetime
costs decreased to $115,943, representing incremental savings of $1,606 (95% CrI: -588 - 6,874). The usual practice after 2006 (new drug benefit strategy) resulted in a total discounted lifetime cost of $116,865, from the Medicare perspective, representing incremental costs of $922 (95% CrI: -463 - 6,095) in comparison with the first-dollar coverage strategy.

**Synthesis of costs and benefits**
The Medicare first-dollar coverage strategy was a dominant strategy, meaning that it saved both lives and money. 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. 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 $2,501 (95% CrI: -215 - 7,468) in lifetime savings per 65-year-old when compared with the current practice.

These results represented the increasing ACE inhibitor use from 40 to 60% due to the first-dollar coverage strategy. Analyses of ACE beneficiary with diabetes inhibitor use (versus 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. The cost-savings persisted at ACE inhibitor costs up to $1,323 per year.

All univariate sensitivity analyses showed that the Medicare first-dollar coverage strategy was cost-saving, except for increases in ACE inhibitor use. Compared with current practice, first-dollar coverage remained cost-saving if ACE inhibitor use increased by 7.2% and remained less than $20,000 per QALY if use increased by 2.9% more than the baseline 40% rate of use. The probabilistic sensitivity analyses showed that first-dollar coverage was cost-saving, compared with current practice and practice after 2006, in 91% and 90% of simulations, respectively. In addition, it was less than $20,000 per QALY in 99% of simulations in both comparisons.

**Authors’ conclusions**
Medicare adoption of first-dollar coverage of angiotensin-converting enzyme (ACE) inhibitors for beneficiaries with diabetes not only saved lives but actually decreased total Medicare costs. Cost-savings remained even when they conservatively compared first-dollar coverage of ACE inhibitors with prescription coverage provided by the Medicare Prescription Drug Improvement and Modernization Act of 2003.

**CRD COMMENTARY - Selection of comparators**
The authors justified the comparators on the grounds of the barriers imposed by co-payments and the potential impact of non-targeted cost sharing policies. That might actually have a detrimental effect on the overall programme costs by deterring the use of highly cost-effective or cost-saving drugs, and thus preventing the maximisation of the health of the elderly within constrained resources. You should judge whether the coverage strategies compared are relevant in your own setting, or whether other comparator policies could also be relevant.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used. The authors used data from high-quality studies when available, but one cannot be sure that all relevant literature was identified. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, experts’ opinions and their own assumptions. The sources of effectiveness evidence were derived from RCTs and cohort studies, which are adequate sources to estimate effectiveness. The authors justified their assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses using ranges from the literature. The authors justified the ranges selected and reported.

**Validity of estimate of measure of benefit**
The authors used life-years and QALYs as measures of benefit. These measures enable cross health technology
comparisons. The authors stated that the utilities used were obtained from published studies that used various elicitation methods. For example, time trade-off utilities elicited 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.

Validity of estimate of costs
The authors reported that they carried out the study from third-party payer (Medicare) and societal perspectives. Consequently, direct and indirect costs were included although they were not reported in sufficient detail. In addition, the indirect costs were included in the health-related quality of life measure, as recommended by the US Public Health Service’s Panel on Cost-Effectiveness. Therefore, no monetary values were assigned to the indirect costs. The unit costs were taken from published sources. The quantities were not thoroughly reported, thus the analysis could not be easily reworked for other settings. The total costs were reported only in a discounted version. Sensitivity analyses of the drug costs were conducted and reported, and the cost parameters were incorporated in the probabilistic sensitivity analysis. Discounting was appropriately carried out since the time horizon exceeded two years. The price year was reported, which will aid any future reflation exercises.

Other issues
The authors compared their findings with those from other studies but they were not reported in full. The conclusions reflected the scope of the analysis. The authors did not explicitly address the generalisability of the results but they did consider other limitations.

The limitations stated were as follows. First, drug spending and increased ACE inhibitor use after implementation of the new Medicare drug benefit were estimates, as this benefit was not yet in effect. Second, social security pension costs were not examined. Third, it was assumed that all drug costs previously paid by other payers or out-of-pocket costs would be shifted to Medicare. Fourth, the effect of first-dollar coverage of ACE inhibitor use on beneficiaries’ use of other beneficial medications was not modelled. Fifth, the analysis excluded the potential benefits of ACE inhibition in preventing diabetic retinopathy and neuropathy, as well as the benefits of ACE inhibitors for other prevalent indications in elderly individuals with diabetes (e.g. heart failure). Finally, it was decided to make ACE inhibitor use contingent upon coverage, which did not mean that other interventions might not also be effective in increasing ACE inhibitor use, subsequently saving lives and Medicare expenditures for elderly individuals with diabetes.

Most of these estimates and assumptions biased the model against first-dollar coverage strategy and underestimated the potential clinical benefits and cost-savings of Medicare first-dollar coverage of ACE inhibitors.

Implications of the study
The authors addressed policy issues about legislation that prohibited Medicare from directly negotiating prices with drug manufacturers, and the resulting impact on prices and ACE inhibitor use. Future policy analyses must follow the actual impact of the Medicare drug benefit after its implementation. In current practice, the threshold increase in use needed for first-dollar coverage to save money would 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.

The authors’ study showed that non-targeted cost sharing might actually have a detrimental effect on overall programme costs, by deterring the use of highly cost-effective or cost-saving drugs. Improving the use of cost-sharing tools to maximise the use of the most beneficial and high value drugs might be beneficial, particularly to maximise the health of the elderly within constrained resources. However, the authors recognised that interventions do not need to be cost-saving to provide value or to merit interventions (such as reduced cost sharing) to increase use.

The authors reported also that the knowledge of the effect of drug coverage on use and adherence is still in its infancy and merits further exploration.
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