Enayet K. Chowdhury, Zanfina Ademi, John R. Moss, Lindon M.H. Wing, Christopher M. Reid, on behalf of the Second Australian National Blood Pressure Study Management Committee

Cost-utility of angiotensin-converting enzyme inhibitor-based treatment compared with thiazide diuretic-based treatment for hypertension in elderly Australians considering diabetes as comorbidity

Medicine, 2015; 94(9):e590-1-e590-9

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Originally published at:
http://doi.org/10.1097/MD.0000000000000590

http://hdl.handle.net/2440/99435
Cost–Utility of Angiotensin-Converting Enzyme Inhibitor-Based Treatment Compared With Thiazide Diuretic-Based Treatment for Hypertension in Elderly Australians Considering Diabetes as Comorbidity

Enayet K. Chowdhury, PhD, Zanfina Ademi, PhD, John R. Moss, MSocSci, Lindon M.H. Wing, FRACP, Christopher M. Reid, PhD, on behalf of the Second Australian National Blood Pressure Study Management Committee

Abstract: The objective of this study was to examine the cost-effectiveness of angiotensin-converting enzyme inhibitor (ACEI)-based treatment compared with thiazide diuretic-based treatment for hypertension in elderly Australians considering diabetes as an outcome along with cardiovascular outcomes from the Australian government’s perspective.

We used a cost–utility analysis to estimate the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained. Data on cardiovascular events and new onset of diabetes were used from the Second Australian National Blood Pressure Study, a randomized clinical trial comparing diuretic-based (hydrochlorothiazide) versus ACEI-based (enalapril) treatment in 6083 elderly (age ≥65 years) hypertensive patients over a median 4.1-year period. For this economic analysis, the total study population was stratified into 2 groups. Group A was restricted to participants diabetes free at baseline (n = 5642); group B was restricted to participants with preexisting diabetes mellitus (type 1 or type 2) at baseline (n = 441). Data on utility scores for different events were used from available published literatures; whereas, treatment and adverse event management costs were calculated from direct health care costs available from Australian government reimbursement data. Costs and QALYs were discounted at 5% per annum. One-way and probabilistic sensitivity analyses were performed to assess the uncertainty around utilities and cost data.

After a treatment period of 5 years, for group A, the ICER was Australian dollars (AUD) 27,698 (€ 18,004; AUD 1–€ 0.65) per QALY gained comparing ACEI-based treatment with diuretic-based treatment (sensitive to the utility value for new-onset diabetes). In group B, ACEI-based treatment was a dominant strategy (both more effective and cost-saving). On probabilistic sensitivity analysis, the ICERs per QALY gained were always below AUD 50,000 for group B; whereas for group A, the probability of being below AUD 50,000 was 85%.

Although the dispensed price of diuretic-based treatment of hypertension in the elderly is lower, upon considering the potential enhanced likelihood of the development of diabetes in addition to the costs of treating cardiovascular disease, ACEI-based treatment may be a more cost-effective strategy in this population.

INTRODUCTION

Hypertension or high blood pressure (BP) is a major risk factor for cardiovascular diseases such as stroke or coronary heart disease. The incidence and prevalence of hypertension increases with age. Worldwide >60% of those aged 65 years and older are hypertensive. Evidence suggests that diabetes and hypertension often coexist, substantially increasing the risk of cardiovascular disease and all-cause mortality. According to recent Australian data, the prevalence of hypertension in people aged 65 years and older was 70% and of diabetes 14%. Management and treatment of these conditions pose a large burden on the health care system. This burden is expected to increase due to an ageing society and increasing levels of obesity and other comorbidities. In 2010, the estimated cost related to managing hypertension in the United States was about US$ 93 billion. In Australia, antihypertensive drugs constituted ~9.5% of the total annual drug expenditure for 2011–2012 (Australian dollar [AUD] 9.2 billion) under the Australian Pharmaceutical Benefits Scheme (PBS).
Therefore, understanding and determining the financial impact of the treatment of hypertension and diabetes is of major importance for planning health care expenditure. Lowering of high BP is one of the effective ways to reduce the incidence of subsequent cardiovascular events; evidence shows that there are no major differences in BP lowering between different antihypertensive drug classes as monotherapy. In addition, the BP Lowering Treatment Trialist’s Collaboration has shown that there are no differences in cardiovascular outcomes associated with treating hypertension using regimens based on different classes of antihypertensive drugs. The current European Society of Hypertension management guideline recommends in people aged 65 years and older the initial use of a BP lowering drug from any one of the following classes: thiazide-type diuretics (thiazide diuretics), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel antagonists, or angiotensin receptor antagonists, depending on other compelling and comorbid conditions in the individual patient. In contrast, the recent hypertension management guideline of the American Society of Hypertension and the International Society of Hypertension recommends the use of either calcium channel antagonists or thiazide diuretics as an initial treatment in people aged 60 years and older.

Among the different antihypertensive drug classes, a thiazide diuretic has been claimed to be the preferred first-line and most cost-effective antihypertensive drug if not otherwise contraindicated. However, despite their cost-effectiveness, thiazide diuretics are not recommended as first-line therapy in younger hypertensive patients, as their long-term use is associated with an increased incidence of new-onset diabetes compared with some other commonly used drugs such as ACEIs, angiotensin receptor antagonists, and calcium channel antagonists. Recently, thiazide diuretic-based treatment regimens have also been shown to be associated with an increased incidence of new-onset diabetes in treated elderly hypertensive patients compared with ACEI-based treatments. Therefore, to assess the cost-effectiveness of hypertension treatment in clinical practice, in addition to the BP lowering effect and drug dispensing price, the metabolic changes caused by long-term use of drug therapy need to be considered. Studies conducted to evaluate the cost-effectiveness of ACEI-based treatments over thiazide diuretic-based treatments in a general population have demonstrated that diuretic-based treatment is more cost-effective, but there is limited information on the comparative cost-effectiveness of ACEI-based versus diuretic-based treatment of hypertension in an elderly population with diabetes as an outcome event in addition to cardiovascular disease or as a comorbid condition, which is highly prevalent in elderly hypertensive patients. It is therefore important to compare the cost-effectiveness of ACEI-based treatment with diuretic-based treatment of hypertension considering diabetes as a comorbid condition. The aim of our study was to determine the cost-effectiveness of ACEI-based treatment compared with thiazide diuretic-based treatment in the Australian context, using data from the Second Australian National BP (ANBP2) study, which was carried out in elderly hypertensive patients irrespective of whether diabetes was a comorbid condition.

**METHODS**

**Study Participants and Setting**

The ANBP2 study was a prospective randomized open label blinded endpoint study. Six-thousand eighty-three hypertensive patients aged between 65 and 84 years were enrolled through 1594 family medical practices throughout Australia and then randomized to receive either ACEI (mainly enalapril, n = 3044) or thiazide diuretic (mainly hydrochlorothiazide, n = 3039) based BP-lowering treatment. Among the inclusion criteria were an average untreated sitting BP at the 2 “study entry” visits of ≥160 mm Hg systolic and/or ≥90 mm Hg diastolic (if systolic was ≥140 mm Hg), having no cardiovascular morbidity within 6 months, and willingness to give informed consent. Exclusion criteria included any life-threatening illness, contraindication to an ACEI or a thiazide diuretic, serum creatinine concentration >2.5 mg/dL (≥221 µmol/L), malignant hypertension, or dementia.

**Interventions**

Subjects were centrally randomized to either ACEI- or diuretic-based treatment. The ACEI, enalapril, and the diuretic, hydrochlorothiazide, were recommended as initial therapy; however, choice of the specific agent and dose was determined by the subject’s family practitioner. The study subjects were followed for a median 4.1 years. During this follow-up period, detailed information on each subject’s BP, medication use, relevant laboratory values (eg, plasma cholesterol, serum creatinine, blood glucose), and cardiovascular morbidity and mortality were collected through follow-up visits. These visits were conducted on average every 6 months. The study focused on the clarification and differentiation of the effects of antihypertensive treatment on the incidence of cardiovascular events. Key findings from the ANBP2 study have been published previously. The ANBP2 study was approved by the Ethics Committee of the Royal Australian College of General Practitioners and conducted according to the Helsinki Declaration of the World Medical Association.

**Economic Analysis**

We carried out a cost–utility analysis using patient-level data collected as part of the ANBP2 study to compare the 2 strategies: thiazide diuretic-based and ACEI-based treatments of hypertension. The perspective of the Australian government was taken into account while analyzing the data. The outcome of interest was the incremental cost-effectiveness ratio (ICER) in terms of AUD per quality-adjusted life-year (QALY) gained. The ANBP2 study provides real-life data on cardiovascular adverse events and new-onset diabetes in the elderly treated hypertensive population for the economic analysis. The decision model used for the economic analysis is illustrated in Figure 1. All costs are given in AUD (AUD 1=€ 0.65). The total patient population was stratified into 2 groups based on the presence of diabetes at baseline (randomization): group A participants were free from diabetes at baseline (n = 5642) and group B participants were known to have preexisting diabetes mellitus (type 1 or type 2) at baseline (n = 441). Both groups were followed on-treatment after being randomized for a median 4.1 years (maximum 5 years) until death or closeout of the study.

**Health Outcomes**

Individual information on any cardiovascular events (non-fatal events and deaths) was collected by study nurses from the family practice case records during 6-monthly follow-up visits and from hospital notes and death certificates. All information was then reviewed for end point documentation and adjudicated for all potential study end points throughout the trial by an end
point committee blinded to drug treatment. We considered the following events (if experienced) for a participant in the ANBP2 study to calculate the utility values at the end of each year and associated costs (inpatient hospital costs of complication management). These events were nonfatal myocardial infarction (MI), nonfatal stroke, nonfatal heart failure (HF) hospitalization, and death from any cause. For group A, in addition to above events, “new-onset diabetes” was considered as an additional event (if developed). Overall during the ANBP2 trial period an incidence rate of 1.45% per annum for diabetes was observed. The “new-onset diabetes” event was based on observed new development of diabetes during the follow-up period, defined as the participant being diagnosed or treated for diabetes by their family practitioner, or first incidence of a random plasma glucose concentration ≥11.1 mmol/L (≥200 mg/dL).

Resource Use and Unit Costs (in AUDs)

The Australian government subsidizes family physician (GP) and specialist consultations (through Medicare Australia), and the costs of many prescribed pharmaceuticals (under the Australian PBS) together with funding public hospital care jointly with the individual states. Patient copayments were not considered in the current analysis. Moreover, indirect costs (ie, productivity costs) were not included in the analysis as these patients were all ≥65 years, and so relatively few were still undertaking paid work. The cost parameters used for this analysis are shown in Table 1. Prices were updated to reflect recent values.

Pharmaceutical Use and Related Costs

In ANBP2, GPs were responsible for prescribing the drugs and their doses for treating hypertension in the participants enrolled in the study. At the time of either prescribing or dispensing of the medication by a pharmacist, substitution of a different product from the assigned drug class may have been provided to the patient, and also there were a variety of doses of each drug within a recommended dosage range. Therefore, we used estimated drug costs for each antihypertensive drug class by calculating the sum of each drug dose and its proportional contribution within the PBS for the drug class. The pharmaceutical costs were derived from the PBS reimbursement data for the calendar year 2012 (January to December). For costing antidiabetic therapy, we used the proportion of patients treated with diet alone, oral therapy alone, insulin alone, or both insulin and oral therapies based on estimates derived from the AusDiab data and also the cost of routine diagnostic testing (ie, home glucose strip, 1 pathology test per year, 1 Haemoglobin A1c test quarterly).

General Practice Visits and Related Costs

In ANBP2, the number of GP consultations for each participant was recorded, but not the type and duration of consultation. Both the latter can affect the amount of reimbursement to the treating doctor. The cost of each GP visit was based on the Australian Medicare Benefit Schedule for the 2012 calendar year. The cost (100% schedule fee) for a standard consultation with a GP in a primary care setting was AUD 36.30. However, the schedule fee can vary from AUD 16.60 to AUD 106.75 depending on the type and duration of consultation. Therefore, a weighted average of the schedule fees for GP services for people aged 65 years or older was used.

Costs of Inpatient Complication Management

The costs of inpatient management of nonfatal MI, nonfatal stroke, nonfatal HF, and fatal events (deaths) were derived from published data for the relevant Australian Refined Diagnosis-Related Groups (AR-DRGs) for public sector hospitals. Each AR-DRG represents a class of patients with similar clinical conditions requiring similar hospital services constructed using information in the hospital morbidity record. Australian national cost weight data were used for each DRG and adjusted for high outliers with regard to the length of stay. We calculated a weighted mean cost for each clinical event. As these derived costs represent the event management cost for the year 2009, we used the Australian total health price index to estimate the 2012 values.

Utilities

Utility values range from 0 to 1 and are commonly used in health economics to reflect an individual’s preferences for different health outcomes and to measure QALYs. The “0”
utility score reflects states of health equivalent to death, whereas “1” reflects perfect health. We have used utility values for nonfatal MI, stroke, hospitalization for HF, and new-onset diabetes from published sources (Table 1).27,28,33 In the present analysis, hypertensive patients without diabetes were considered to have a utility value of “1” at baseline. We used this value assuming that there were no significant differences as all patients were hypertensive and randomized to receive treatment. For group A, we used this value for all participants at the start. For group B, the utility value of participants with preexisting diabetes at baseline was assumed to be 0.86 considering the selective inclusion criteria of the ANBP2 study participants. At any time during the follow-up period, if a participant experienced 2 or more events, the utility value was obtained by multiplying individual event utilities.28

**Incremental Cost-Effectiveness Analysis**

We conducted the cost-effectiveness analyses for a representative 1000 subjects (simulated at commencement) and calculated the corresponding events, QALYs and costs for each year based on observed event rates for ANBP2 participants in each treatment group following enrolment. An annual discount rate of 5% was applied to both costs and outcomes.34 The ICER was calculated as the difference in cost divided by the difference in QALYs between the treatment groups for a maximum 5 years of follow-up using the formula: ICER = (Cost ACEI-based treatment – Cost diuretic-based treatment)/(QALY ACEI – QALY thiazide diuretics). The Australian government has a cost-effectiveness threshold of less than AUD 50,000 per QALY gained as being cost-effective.

**Sensitivity Analyses**

We conducted 1-way sensitivity analyses by, in turn, changing the utility parameter through the ranges listed in Table 1 and with the cost of complication management increased/reduced by 20%. We also did a 1-way sensitivity analysis using a 3% discount rate. The purpose of this was to assess the credible range for the ICER per QALY gained for ACEI compared with diuretic-based therapy. We also conducted 1-way sensitivity analysis by varying all outcome utilities or all costs of adverse outcomes together at their upper and lower limits of their respective ranges. In addition, to enable a direct comparison with previous studies, a further sensitivity analysis was conducted across all trial participants disregarding both preexisting diabetes at baseline and new-onset diabetes during follow-up, and the costs of diabetes management during follow-up. Separate probabilistic sensitivity analyses of groups A and B were also undertaken via Monte Carlo simulation with 5000 iterations. In these sensitivity analyses, related costs of interest were entered within ±25% uniform uncertainty ranges; utility values were entered with beta distributions; costs of treatment and GP visits were used as fixed parameters (Table 1). Results of these analyses were presented using cost-effectiveness acceptability curves. @RISK version 6.2 (Palisade Corporation, Ithaca, NY) was used for the probabilistic sensitivity analyses. In addition, Stata version 11.2 for Windows (StataCorp LP, College Station, TX) and Microsoft Excel (Microsoft Corporation, Redmond, WA) were used for the economic analysis.

**RESULTS**

As reported previously, the mean (SD) age of the 6083 ANBP2 subjects at baseline was 72(±5) years, and 49% were

| TABLE 1. Key Input Data: Costs and Health State Utilities |
|----------------------------------------------------------|
| **Variables**                                           | **Base Case (Range for 1-Way Sensitivity Analysis)** | **Uncertainty Ranges (for Probabilistic Sensitivity Analysis)** | **Source** |
| Costs (AUD, Australian government perspective)           |                                                      |                                                                |          |
| Medication cost (annual cost/person)                     | ACEI 191                                             | Not varied                                                     | 24        |
| Diuretics                                               | 74                                                   | Not varied                                                     | 24        |
| Diabetes management                                     | 487                                                  | Not varied                                                     | 24        |
| Cost of complication management (once off/person)       | Nonfatal MI 8177                                      | ±25% (uniform)                                                | 25        |
|                                                          | Nonfatal stroke 12818                                  | ±25% (uniform)                                                | 25        |
|                                                          | Nonfatal HF hospitalization 7789                      | ±25% (uniform)                                                | 25        |
|                                                          | Fatal event (death from any cause) 1754                | ±25% (uniform)                                                | Assumption |
|                                                          | General practice visit cost/person 41                  | ±25% (uniform)                                                | 26        |
| Health state utilities                                  | Hypertension (on treatment) 1.00                      | Not varied                                                     | Assumption |
|                                                          | Diabetes (baseline) 0.86 (0.80–0.95)                   | Not varied                                                     | Assumption |
|                                                          | Nonfatal MI 0.76 (0.50–0.87)                           | Betta distribution                                             | 27,28     |
|                                                          | Nonfatal stroke 0.63 (0.26–0.92)                       | Betta distribution                                             | 27,28     |
|                                                          | Nonfatal HF hospitalization 0.71 (0.43–0.84)           | Betta distribution                                             | 27,28     |
|                                                          | New-onset diabetes 0.73 (0.60–0.98)                    | Betta distribution                                             | 29        |
|                                                          | Discount rate 5% (3% as an alternative)                | Not varied                                                     |          |
| ACEI = angiotensin-converting enzyme inhibitor, AUD = Australian dollar, HF = heart failure, MI = myocardial infarction. |
| *Actual cost for management of fatal event (death) if hospitalized is AUD 3508.25 Because not all patients were hospitalized for fatal events, we used 50% of the cost for all fatal events.*  

---

**Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.**
males. There were few significant differences in baseline characteristics between the treatment groups, including when comparing subgroups based on presence of diabetes at baseline, except for a higher random blood sugar in the ACEI group overall, and there were more males in the ACEI group among patients with diabetes at baseline (Table 2).

The duration of diabetes in the preexisting diabetes group at the commencement of the clinical trial was 9.4 years (median). Overall, during a maximum follow-up period of 5 years (median 4.1 year), the ANBP2 patients experienced 505 non-fatal cardiovascular events (diuretic group 260 and ACE-I group 245), 339 were newly diagnosed with diabetes (diuretic group 200 and ACE-I group 139), and there were 396 deaths (diuretic group 206 and ACE-I group 190). The number of observed events for groups A and B by antihypertensive treatment group is summarized in Supplementary Table 1, http://links.lww.com/MD/A217.

### Cost-Effectiveness

The results of the cost-effectiveness analyses are summarized in Table 3. For group A, restricted to participants diabetes group 245), 339 were newly diagnosed with diabetes (diuretic group 200 and ACE-I group 139), and there were 396 deaths (diuretic group 206 and ACE-I group 190). The number of observed events for groups A and B by antihypertensive treatment group is summarized in Supplementary Table 1, http://links.lww.com/MD/A217.

### Cost-Effectiveness

The results of the cost-effectiveness analyses are summarized in Table 3. For group A, restricted to participants diabetes

#### Table 2. Baseline Characteristics of the Participants by Treatment Group and Presence of Diabetes

|                         | Overall | ACEI | Diuretics | Group A: No Diabetes at Start | Group B: Diabetes at Start |
|-------------------------|---------|------|-----------|-------------------------------|---------------------------|
|                         | Total   | ACEI | Diuretics | ACEI                          | ACEI                      |
| **Number**              | 6083    | 3044 | 3039      | 2815                          | 229                       |
| **Age (mean ± SD, y)**  | 71.9 ± 4.9 | 72.0 ± 4.9 | 71.9 ± 5.0 | 72.0 ± 4.9                  | 71.8 ± 5.0                  |
| Age 75, %               | 30.2    | 30.4 | 30.1      | 30.4                          | 30.6                      |
| Male, %                 | 49.8    | 49.5 | 48.2      | 48.5                          | 60.9                      |
| Systolic BP             | 168 ± 13 | 167 ± 13 | 168 ± 13 | 167 ± 13                     | 169 ± 13                   |
| Diastolic BP            | 91 ± 8  | 91 ± 8 | 91 ± 8    | 91 ± 8                        | 89 ± 9                     |
| BMI                     | 27 ± 4  | 27 ± 4 | 27 ± 4    | 27 ± 4                        | 28 ± 4                     |
| Previous history        |         |      |           |                               |                           |
| Antihypertensive therapy, % | 62.2    | 62.0 | 62.4      | 60.9                          | 75.1                      |
| Preexisting diabetes, % | 7.2     | 7.5  | 7.0       | —                             | 100                       |
| Coronary heart disease, % | 7.9    | 7.8  | 8.0       | 7.7                           | 9.6                       |
| Cerebrovascular disease, % | 4.5   | 4.6  | 4.4       | 4.7                           | 4.4                       |
| Raised cholesterol, %   | 22.2    | 22.7 | 21.8      | 23.1                          | 17.7                      |
| Current smoker, %       | 7.1     | 6.9  | 7.3       | 6.9                           | 6.6                       |
| Increased plasma creatinine, % | 11.9 | 11.8 | 12.0      | 11.6                          | 14.4                      |
| High RBS, %             | 2.3     | 2.7  | 1.9       | 0.7                           | 27.9                      |

ACEI = angiotensin-converting enzyme inhibitor, BMI = basal metabolic index, BP = blood pressure, RBS = random blood sugar.

Significant differences ($P < 0.05$) for the comparison of ACEI group versus diuretics group. One-way analysis of variance used for continuous variables and $\chi^2$ used for categorical variables.

#### Table 3. Results of the Cost-Effectiveness Analysis Simulated in 1000 Participants at Start

|                         | Based on 1000 Patients (Discounted) | Costs (in AUD) | ICERs | AUD/ QALY |
|-------------------------|-------------------------------------|----------------|-------|-----------|
|                         | Nonfatal Events                      | Complication Management | Treatment | GP Visits | Total Cost | AUD/ QALY |
|                         | CV | New-Onset Diabetes | Death | QALYs | Costs | GP Visits | Total Cost | AUD/ QALY |
| Group A, hypertensive patients free from diabetes at start | | | | | | | | |
| ACEI                    | 77 | 49 | 66 | 4089 | 803,402 | 875,635 | 1,357,918 | 3,036,955 |
| Diuretic                | 76 | 72 | 69 | 4069 | 784,099 | 412,789 | 1,301,341 | 2,498,229 |
| Difference              | 19 | 9  | 7  | 2  | 19.5   | 538,725 | 539       | AUD 27,698 |
| Difference/subject      | 0.019 | | | | | | | |
| Group B, hypertensive patients with preexisting diabetes at start | | | | | | | | |
| ACEI                    | 103 | — | 78 | 3467 | 1,059,417 | 2,844,547 | 1,721,735 | 5,625,699 |
| Diuretic                | 198 | — | 116 | 3378 | 1,992,992 | 2,321,439 | 1,477,780 | 5,792,211 |
| Difference              | 89.4 | | | | | | | |
| Difference/subject      | 0.089 | | | | | | | |

ACEI = angiotensin-converting enzyme inhibitor, AUD = Australian dollar, CV = cardiovascular, GP = family physician, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year.

Costs are less and effectiveness is greater for ACEI-based treatment.
free at baseline, the overall net cost (discounted) was AUD 539 (£350) per person with 0.019 QALY gained (discounted) per person. The ICER for ACEI-based treatment compared with thiazide-based treatment was AUD 27,698 (£18,004) per QALY gained. For group B, restricted to participants with preexisting diabetes at baseline, ACEI-based treatment was a dominant strategy, being both more effective and less expensive than thiazide diuretic-based (mainly hydrochlorothiazide) treatment during the trial period. Here, there was an overall net saving (discounted) of AUD 167 (£109) per person with 0.089 QALY (discounted) gained per person (Table 3). Detailed information on the QALYs gained and costs for the ACEI-based and diuretic-based treatment by year for group A and group B cost-effectiveness analysis is summarized in Supplementary Table 2, http://links.lww.com/MD/A217.

**Sensitivity Analyses**

The findings of the 1-way sensitivity analyses are presented in Table 4. The results are sensitive to the utility value for new-onset diabetes. In the probabilistic sensitivity analysis, the 95% confidence interval for the ICER for group A ranged from AUD 13,769 (£8950) to AUD 101,557 (£66,012) and for group B from AUD −5239 (−£3,405) (saving) to AUD 633 (£411). The results of the probabilistic sensitivity analysis are shown as cost-effectiveness acceptability curves in Figure 2. Based on our assumed cost-effectiveness threshold ICER value of AUD 50,000 per QALY gained, for group A, there was an 85% probability that use of ACEI compared with thiazide diuretic as a first-line antihypertensive drug would be cost-effective. For group B, use of ACEI-based treatment compared with diuretic-based

**TABLE 4. One-Way Sensitivity Analyses for ICER per QALY**

| Description of Inputs                        | Value | Group A (in AUD) | Group B (in AUD) |
|---------------------------------------------|-------|------------------|------------------|
| Base case                                   | —     | 27,698           | −1864            |
| Sensitivity analysis—changing only 1 parameter |       |                  |                  |
| Health utilities                            |       |                  |                  |
| Preexisting diabetes                        |       |                  |                  |
| Lower limit of range                        | 0.80  | —                | −1914            |
| Upper limit of range                        | 0.95  | —                | −1679            |
| Nonfatal myocardial infarction              |       |                  |                  |
| Lower limit of range                        | 0.50  | 24,436           | −1925            |
| Upper limit of range                        | 0.87  | 29,195           | −1838            |
| Nonfatal stroke                             |       |                  |                  |
| Lower limit of range                        | 0.26  | 29,766           | −1508            |
| Upper limit of range                        | 0.92  | 24,942           | −2298            |
| Nonfatal heart failure hospitalization      |       |                  |                  |
| Lower limit of range                        | 0.430 | 30,359           | −1961            |
| Upper limit of range                        | 0.840 | 26,538           | −1821            |
| New-onset diabetes                          |       |                  |                  |
| Lower limit of range                        | 0.60  | 19,312           | —                |
| Upper limit of range                        | 0.98  | 185,974          | —                |
| Costs                                       |       |                  |                  |
| Nonfatal MI                                 |       |                  |                  |
| Cost reduced by 20%                         | 6542  | 28,061           | −1649            |
| Cost increased by 20%                       | 9813  | 27,335           | −2078            |
| Nonfatal stroke                             |       |                  |                  |
| Cost reduced by 20%                         | 10,254| 27,187           | −867             |
| Cost increased by 20%                       | 15,381| 28,209           | −2860            |
| Nonfatal HF hospitalization                 |       |                  |                  |
| Cost reduced by 20%                         | 6231  | 27,600           | −1113            |
| Cost increased by 20%                       | 9346  | 27,795           | −2614            |
| Death (from any cause)                      |       |                  |                  |
| Cost reduced by 20%                         | 1403  | 27,745           | −1736            |
| Cost increased by 20%                       | 2104  | 27,651           | −1991            |
| Annual discount rate                        | 3%    | 26,912           | −1708            |
| Sensitivity analysis—changing all utilities/cost parameters together |       |                  |                  |
| Health utilities                            |       |                  |                  |
| Lower limit of all utility range            | —     | 19,873           | −1704            |
| Upper limit of all utility range            | —     | 114,669          | −1964            |
| Costs                                       |       |                  |                  |
| Lower limit of all cost range               | —     | 27,499           | 226              |
| Upper limit of all cost range               | —     | 27,896           | −3953            |

AUD = Australian dollar, HF = heart failure, ICER = incremental cost-effectiveness ratio, MI = myocardial infarction, QALY = quality-adjusted life-year.
treatment was always cost-effective, and there was an 86% probability that it would be a “dominant” strategy. The sensitivity analysis disregarding both preexisting and new-onset diabetes and the costs of diabetes management during follow-up suggested an ICER of AUD 64,112 (£41,673) for the trial participants overall for ACEI-based treatment compared with thiazide-based treatments.

**DISCUSSION**

Our cost-effectiveness analyses from the Australian government’s perspective suggest that commencing antihypertensive treatment with an ACEI (mainly enalapril) rather than a thiazide diuretic (mainly hydrochlorothiazide) would be cost-effective in the elderly who are free from diabetes at the initiation of treatment, if an implicit threshold of AUD 50,000 per QALY gained is chosen. For elderly hypertensive patients with preexisting diabetes, commencing treatment with an ACEI rather than a thiazide diuretic would be a dominant approach (ie, both more effective and cost saving).

Economic evaluations conducted in general populations considering only cardiovascular events and mortality have suggested that commencing antihypertensive treatment with an ACEI is not cost-effective when compared with commencing treatment with a thiazide diuretic. These previous studies were not undertaken in relation to an elderly population and did not consider new onset of diabetes as an outcome of antihypertensive treatment. The results of our study have demonstrated the impact of the important comorbidity of diabetes on the management of elderly hypertensive patients. This is illustrated by our sensitivity analysis disregarding both preexisting and new-onset diabetes and the costs of diabetes management during follow-up being in line with earlier findings suggesting ACEI not to be cost-effective compared with thiazide diuretics as a first-line antihypertensive drugs despite our base case results indicating the opposite. Current practice guidelines for the management of hypertension recommend the use of a thiazide diuretic, an ACEI, an angiotensin receptor antagonist, or a calcium channel antagonist in the elderly as the preferred first-line drug in the absence of comorbidities. These clinical guidelines have mostly been based on clinical trial findings; however, there is some less robust evidence for better effectiveness of ACEI compared with diuretics as first-line antihypertensive drugs. Moreover, only a limited number of studies have been undertaken on the elderly comparing the outcome of treatment with ACEI and diuretics, and then analyzing the cost-effectiveness of these treatments. A study using a health economic model in a 65-year-old population with an annual diabetes risk of 1.1% showed that a calcium channel antagonist is the most cost-effective initial drug for high BP. This study reported a minimal absolute difference between calcium channel antagonists and ACEI. The available cost-effectiveness analyses for ACEI compared with placebo conducted in high risk hypertensive patients show that the use of ACEI is a cost-effective approach.

The global cardiovascular disease burden is increasing over time, and hypertension is an important risk factor. Previous findings have demonstrated the beneficial effects of ACEI on reducing cardiovascular events, as well as a lowered incidence of new-onset diabetes, and suggest that, despite the higher dispensed price of ACEI-based treatment, it will become cost-effective once the trade-off between health outcomes and resource costs is considered. Our findings confirm that, despite the higher dispensed price, ACEI-based treatment will be more cost-effective compared with diuretics in treating elderly hypertensive patients when new-onset diabetes is considered. Some of the previous studies suggested that switching from diuretics to another antihypertensive drug once diabetes has developed can be a cost-effective approach. However, conclusions derived from these studies may be controversial, because once diabetes develops it can give rise to many complications along with an increased risk of mortality in the long term.

The cost-effectiveness analyses that we have used had several limitations. Firstly, we did not incorporate treatment adherence in the analysis, because we had only limited information on this. However, in a subanalysis using the limited data available, we did not observe any differences in treatment adherence between the ACEI and thiazide diuretic-based treatment groups. Moreover, we observed that about 58% and 62% of the participants remained in their assigned ACEI and diuretic groups, respectively, at the end of the ANBP2 study. In comparison, among those who developed diabetes during the trial period, 63% and 61% of remained in their assigned ACEI and diuretic groups, respectively. This suggests that there was little contamination bias. Secondly, we did not consider any add-on drug cost in the analysis, and we made the assumption that the add-on drug costs were similar in both treatment groups. At the end of the study, the add-on drugs in both the treatment group participants were similar: the number of participants on monotherapy in the ACEI group was 65% and in the diuretic group was 67%. However, 6% in the ACEI group and 5% in the diuretic group were on 3 or more antihypertensive agents. Third, other cardiovascular and noncardiovascular events that might have affected the cost-effectiveness were not considered in these analyses. For example, chronic kidney disease is one of the common health problems in hypertensive patients other than diabetes, and available literature suggests that ACEI-based treatment may be better in preserving kidney function. Inclusion of such a condition may favor initiating treatment with an ACEI even more. Fourthly, we did not consider any

![FIGURE 2. Probabilistic sensitivity analysis presented as cost-effectiveness acceptability curves per QALY gained by ACEI-based treatment versus diuretic-based treatment.](Image)
specialist consultations, by either medical or allied health professionals, although for instance such costs might have been incurred in relation to the management of diabetes. We also did not consider any posthospitalization cost such as for rehabilitation following nonfatal cardiovascular events. Finally, our cost-effectiveness analysis has been conducted from the Australian health care perspective using predominantly white participants. Therefore, our findings may only be generalizable to countries with similar health care systems and racial backgrounds. However, ANBP2 was a pragmatic “real-world” study performed on a large number of elderly hypertensive people, and used information from actual observed events. Therefore, the identified findings will be relevant when treating physicians make treatment decisions on a day-to-day basis.

In conclusion, the use of ACEI-based treatment as a first-line antihypertensive drug for those aged 65 years or older instead of thiazide diuretic-based (mainly hydrochlorothiazide) treatment appears to be a cost-effective strategy for the prevention of adverse cardiovascular outcomes when diabetes is present or subsequent on-treatment development of diabetes is considered.

ACKNOWLEDGMENTS

We are indebted to the participants, family practitioners, study staff, data management centres and the ANBP2 Management Committee.

REFERENCES

1. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet. 2000;355:865–872.
2. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum—current outcomes and control in the community. JAMA. 2005;294:466–472.
3. Whelton PK. Epidemiology of hypertension. Lancet. 1994;344:101–106.
4. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365:217–223.
5. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease. Hypertension. 2001;37:1053–1059.
6. Alderman MH, Cohen H, Madhavan S. Diabetes and cardiovascular events in hypertensive patients. Hypertension. 1999;33:1130–1134.
7. Australian Health Survey: Health Service Usage and Health Related Actions, 2011–12 (4364.0.55.002). Australian Bureau of Statistics; 2013. http://www.abs.gov.au/AUSSTATS/abs@.nsf/276295845417acca25706e00834fae322DB1B539ACC6C-CA257B3900F316C7?opendocument. Accessed November 21, 2013.
8. Australian Institute of Health and Welfare. Diabetes Prevalence in Australia: Detailed Estimates for 2007–08. Diabetes series no. 17. Cat. no. CVD 56. Canberra: AIHW 2011.
9. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123:933–944.
10. Department of Health and Ageing—Medicines Australia. Expenditure and Prescriptions Twelve Months to 30 June 2012. Canberra: PBS Information Management Section Pharmaceutical Policy Branch; 2013. http://www.pbs.gov.au/info/statistics/expenditure-and-prescriptions-30-06-2012
11. Fahey T, Schroeder K, Ebrahim S. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2006. Article: CD005182.
12. Turnbull F, Neal B, Algert C, et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overview of randomised trials. Lancet. 2003;362:1527–1535.
13. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281–1357.
14. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens. 2014;32:3–15.
15. Tran K, Ho C, Noorani H, et al. Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-analysis and Economic Evaluation Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.
16. National Collaborating Centre for Chronic Conditions (UK). Hypertension: Management in Adults in Primary Care: Pharmacological Update. London, UK: Royal College of Physicians; 2006. (NICE Clinical Guidelines, No. 34). http://www.ncbi.nlm.nih.gov/books/NBK45886/.
17. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. J Hypertens. 2006;24:3–10.
18. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. Diabetes Care. 2006;29:1065–1070.
19. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981–2997.
20. Chowdhury EK, Owen A, Ademi Z, et al. Short- and long-term survival in treated elderly hypertensive patients with or without diabetes: findings from the Second Australian National Blood Pressure Study. Am J Hypertens. 2014;27:199–206.
21. Heidenreich PA, Davis BR, Cutler JA, et al. Cost-effectiveness of chlorthalidone, amlodipine, and lisinopril as first-step treatment for patients with hypertension: an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Gen Intern Med. 2008;23:509–516.
22. Nordmann AJ, Krahn M, Logan AG, et al. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. Pharmacoeconomics. 2003;21:573–585.
23. Wing LMH, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med. 2003;348:583–592.
24. Pharmaceutical Benefits Scheme. http://www.pbs.gov.au. Accessed Mar 02, 2013.
25. Public Sector Estimated Cost Weights Round 13 AR-DRG v5.2 http://www.health.gov.au/internet/main/publishing.nsf/Content/ Round_13-cost-reports. Accessed March 3, 2013.
26. Medicare Benefits Schedule (MBS). http://www.mbsonline.gov.au/. Accessed February 10, 2013.
27. National Collaborating Centre for Chronic Conditions (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. Available from:
http://www.ncbi.nlm.nih.gov/books/NBK83274/. 2011. Accessed June 10, 2013.

28. Ara R, Wailoo AJ. NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models. Decision Support Unit, School of Health and Related Research, University of Sheffield; 2011. http://www.nicesdsu.org.uk.

29. Howard K, Salkeld G, White S, et al. Cost-Effectiveness of Early Detection and Intervention to Prevent Progression of Chronic Kidney Disease in Australia. Kidney Health Australia; 2006. http://www.kidney.org.au.

30. Ademi Z, Liew D, Hollingsworth B, et al. The economic implications of treating atherothrombotic disease in Australia, from the government perspective. Clin Ther. 2010;32:119–132.

31. Dunstan D, Zimmet P, Welborn T, et al. Diabesity and Associated Disorders in Australia, 2000: The Accelerating Epidemic. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Melbourne: International Diabetes Institute; 2001.

32. Australian Institute of Health and Welfare (AIHW). Health Expenditure Australia 2011–12 [Cat. no. HWE 59]. Canberra: AIHW; 2013. https://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129544656. Accessed January 11, 2014.

33. Smith SM, Campbell JD. Cost-effectiveness of renin-guided treatment of hypertension. Am J Hypertens. 2013;26:1303–1310.

34. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health. 2004;7:397–401.

35. Harris AH, Hill SR, Chin G, et al. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994–2004. Med Decis Mak. 2008;28:713–722.

36. George B, Harris A, Mitchell A. Cost effectiveness analysis and the consistency of decision making—evidence from pharmaceutical reimbursement in Australia (1991 to 1996). Pharmacoeconomics. 2001;19:1103–1109.

37. Wright JM, Musini VM. First-line drugs for hypertension (Review). Cochrane Database Syst Rev. 2009. Article: CD001841.

38. Lamy A, Yusuf S, Pogue J, et al. Cost implications of the use of ramipril in high-risk patients based on the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation. 2003;107:960–965.

39. Briggs A, Mihaylova B, Sculpher M, et al. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart. 2007;93:1081–1086.

40. World Health Organization. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. Geneva, Switzerland: World Health Organization; 2009.

41. Gupta AK, Dahlof B, Dobson J, et al. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial-blood pressure lowering arm and the relative influence of antihypertensive medication. Diabetes Care. 2008;31:982–988.

42. Kostis JB, Wilson AC, Freudenberger RS, et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. Am J Cardiol. 2005;95:29–35.

43. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet. 2005;366:2026–2033.

44. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244–252.