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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.

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Abbreviations: ANBP2 = Second Australian National Blood Pressure, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year.

INTRODUCTION

Hypertension or high blood pressure (BP) is a major risk factor for cardiovascular diseases such as stroke or coronary heart disease.[1] The incidence and prevalence of hypertension increases with age.[2,3] Worldwide >60% of those aged 65 years and older are hypertensive.[4] Evidence suggests that diabetes and hypertension often coexist, substantially increasing the risk of cardiovascular disease and all-cause mortality.[5,6] According to recent Australian data, the prevalence of hypertension in people aged 65 years and older was 70% and of diabetes 14%.[7,8] 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.[9] 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).[10]

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From the Centre of Cardiovascular Research and Education in Therapeutics (EKC, ZA, CMR), Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Institute of Pharmaceutical Medicine (ZA), University of Basel, Basel, Switzerland; School of Population Health (JM), The University of Adelaide; and Department of Clinical Pharmacology (LMHW), School of Medicine, Flinders University, Adelaide, Australia.
Correspondence: Enayet Karim Chowdhury, School of Public Health & Preventive Medicine, Monash University, 6th Floor, Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia (e-mail: enayet.chowdhury@monash.edu).
The management committee consists of the following members: LMHW (Chair), CMR, LJ Beilin, MA Brown, GLR Jennings, CI Johnston, JJ McNeil, JE Marley, TO Morgan, P Ryan, J Shaw (deceased), MJ West, and G MacDonald.
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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.[11] 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.[12] 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.[13] 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.[14]

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.[15,16] 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.[17,18] 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.[19,20] 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,[21,22] 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.[23] 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 (nonfatal 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

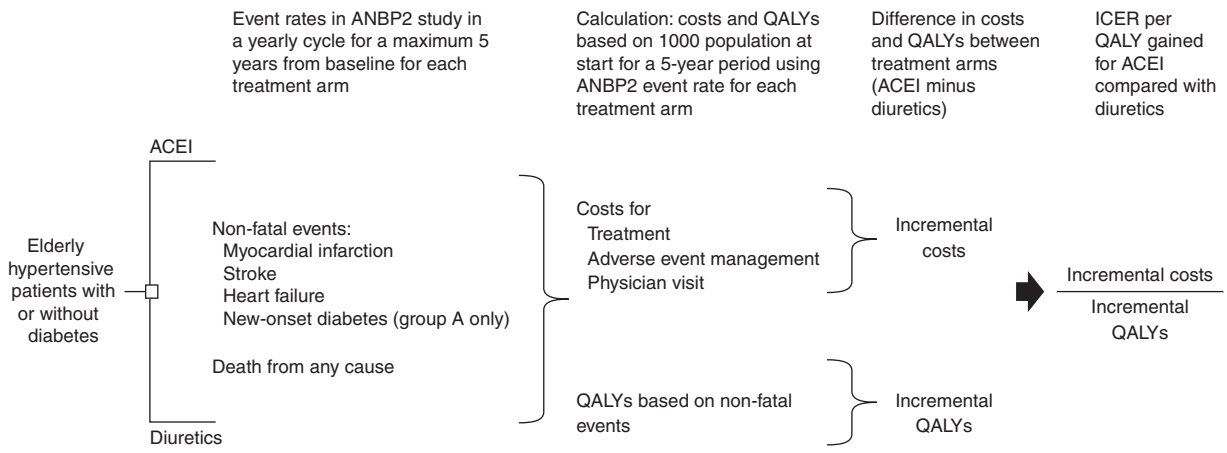

FIGURE 1. Outline of the decision model for the cost-effectiveness analysis of ACEI-based treatment versus diuretic-based treatment of hypertension in an elderly population. ACEI = angiotensin-converting enzyme inhibitor, ANBP2 = Second Australian National Blood Pressure, Group A = hypertensive patients without preexisting diabetes at start, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year.

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.[18] 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 $\geq$11.1 mmol/L ($\geq$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 $\geq$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.[30] The pharmaceutical costs were derived from the PBS reimbursement data for the calendar year 2012 (January to December).[24] 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[29,31] 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.[26] 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.[25] 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.[32]

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''

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)	Beta distribution	[27,28]
Nonfatal stroke	0.63 (0.26–0.92)	Beta distribution	[27,28]
Nonfatal HF hospitalization	0.71 (0.43–0.84)	Beta distribution	[27,28]
New-onset diabetes	0.73 (0.60–0.98)	Beta 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.

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).[27,29,33] 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 not revealed any threshold value for cost-effectiveness in funding new drugs or treatments for subsidy. However, several studies have claimed a relationship between the value of the ICER and the probability of being listed for subsidy.[35,36] Based on their findings, as a rough guide, we have used 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 2. Baseline Characteristics of the Participants by Treatment Group and Presence of Diabetes

	Overall			Group A: No Diabetes at Start		Group B: Diabetes at Start	
	Total	ACEI	Diuretics	ACEI	Diuretics	ACEI	Diuretics
Number	6083	3044	3039	2815	2827	229	212
Age (mean ± SD, y)	71.9 ± 4.9	72.0 ± 4.9	71.9 ± 5.0	72.0 ± 4.9	71.8 ± 5.0	71.8 ± 5.0	72.1 ± 4.9
Age 75, %	30.2	30.4	30.1	30.4	30.1	30.6	30.7
Male, %	48.9	49.5	48.2	48.5	48.0	62.0*	50.1
Systolic BP	168 ± 13	167 ± 13	168 ± 13	167 ± 13	168 ± 12	169 ± 13	172 ± 14
Diastolic BP	91 ± 8	91 ± 8	91 ± 8	91 ± 8	91 ± 8	89 ± 9	88 ± 9
BMI	27 ± 4	27 ± 4	27 ± 4	27 ± 4	27 ± 4	28 ± 4	28 ± 4
Previous history							
Antihypertensive therapy, %	62.2	62.0	62.4	60.9	62.0	75.1	67.9
Preexisting diabetes, %	7.2	7.5	7.0	—	—	100	100
Coronary heart disease, %	7.9	7.8	8.0	7.7	7.8	9.6	9.9
Cerebrovascular disease, %	4.5	4.6	4.4	4.7	4.2	4.4	7.5
Raised cholesterol, %	22.2	22.7	21.8	23.1	22.0	17.7	18.6
Current smoker, %	7.1	6.9	7.3	6.9	7.3	6.6	7.6
Increased plasma creatinine, %	11.9	11.8	12.0	11.6	12.1	14.4	10.4
High RBS, %	2.3	2.7*	1.9	0.7	0.4	27.9	21.1

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 χ^2 used for categorical variables.

males.[23] 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 nonfatal 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

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

	Based on 1000 Patients (Discounted)								
	Nonfatal Events				Costs (in AUD)				ICERs
	CV	New-Onset Diabetes	Death	QALYs	Complication Management	Treatment	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				19.5				538,725	AUD 27,698
Difference/subject				0.019				AUD 539	
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				−166,512	Dominant*
Difference/subject				0.089				−AUD 167	

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.

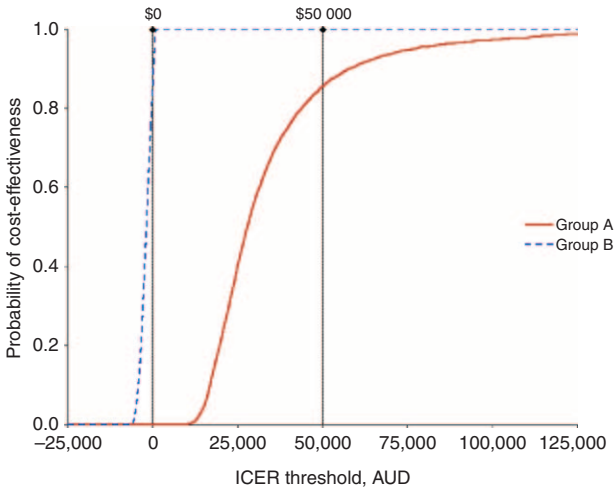

FIGURE 2. Probabilistic sensitivity analysis presented as cost-effectiveness acceptability curves per QALY gained by ACEI-based treatment versus diuretic-based treatment. ACEI = angiotensin-converting enzyme inhibitor, AUD = Australian dollar, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted 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.[15,21] 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 importance of considering 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.[13,14] 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.[37] 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.[16] 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.[38,39]

The global cardiovascular disease burden is increasing over time, and hypertension is an important risk factor.[40] Previous findings have demonstrated the beneficial effects of ACEI on reducing cardiovascular events, as well as a lowered incidence of new-onset diabetes,[17–20,41] 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.[20,42]

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%, whereas 6% in the ACEI group and 5% in the diuretic group were on 3 or more antihypertensive agents.[23] 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.[43,44] Inclusion of such a condition may favor initiating treatment with an ACEI even more. Fourthly, we did not consider any

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.

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