Cost-effectiveness of lowering blood pressure with a fixed combination of perindopril and indapamide in type 2 diabetes mellitus: an ADVANCE trial-based analysis

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Reducing the vascular complications of type 2 diabetes mellitus is a global health priority; worldwide the number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. Most people with diabetes will die from or be disabled by macrovacular and microvascular complications that can be reduced by blood pressure (BP)-lowering therapy. Traditional strategies have set BP thresholds and targets for treatment. While effective, these strategies are resource intensive, requiring multiple patient visits, careful monitoring of BP and side effects, and the management of complex drug regimens. Hence, few patients ever achieve recommended BP goals. This strategy also neglects patients with diabetes whose BP is not high enough for the arbitrary label of “hypertension” but is still a major determinant of their risk of vascular disease.

A simpler approach in patients with diabetes may be routine BP-lowering therapy, additional to any current treatment and irrespective of initial BP. This is more inclusive and less resource intensive than the target-setting strategy. In testing this alternative strategy, the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial recently demonstrated the benefits of a fixed-dose combination of an angiotensin-converting enzyme inhibitor, perindopril, and a diuretic, indapamide, versus placebo in preventing macrovascular and microvascular events in participants with type 2 diabetes, irrespective of their BP at inclusion. This approach was found to reduce cardiovascular mortality (relative risk reduction, 18%; \( P < 0.03 \)) and all-cause mortality (relative risk reduction, 14%; \( P < 0.03 \)). However, concerns have been raised about the expense if it is widely implemented.

We undertook a prospective cost-effectiveness analysis within the ADVANCE trial and report here on the health-related quality of life, resource utilisation, and cost-effectiveness of treatment with perindopril–indapamide compared with placebo.

**ABSTRACT**

**Objective:** To determine the cost-effectiveness of routine administration, irrespective of blood pressure (BP), of a fixed-dose combination of perindopril and indapamide to patients with type 2 diabetes mellitus.

**Design, setting and participants:** Prospective cost-effectiveness analysis within the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial, an international, multicentre, randomised controlled trial of 11 140 participants with type 2 diabetes randomly allocated to receive perindopril plus indapamide (4 mg–1.25 mg/day) or placebo.

**Main outcome measures:** Health-related quality-of-life measured by the EuroQol-5D, resource utilisation, and cost-effectiveness (cost per death averted at 4.3 years’ average follow-up, and estimated cost per life-year gained, by extrapolation).

**Results:** The mean health-related quality-of-life score of survivors was 0.80 (on a 0–1 scale [death to full health]), with no difference between treatment groups. Active treatment reduced hospital admissions for coronary heart disease and coronary revascularisation by 5%. For the Australian participants, perindopril–indapamide cost $A1368 per patient during the trial period, but reduced total hospitalisation costs by $A410 and other medication costs (mainly other BP-lowering drugs) by $A332. The absolute reduction in all-cause mortality for the active treatment group was 1.1%, giving a cost per life saved of $A49 200. Lifetime extrapolation gave an estimated cost per life-year saved of $A10 040 (discounted at 5% per year).

**Conclusion:** The combination of perindopril and indapamide in patients with type 2 diabetes appears to be cost-effective.

**Trial registration:** United States National Library of Medicine NCT00145925.

**METHODS**

**Study design and population description**

The ADVANCE trial was a 20-country, randomised controlled, 2 × 2 factorial trial involving 11 140 participants with type 2 diabetes. One arm of the study compared routine BP lowering based on a fixed-dose (4 mg–1.25 mg per day) perindopril–indapamide combination or matching placebo on top of whatever other hypertensive treatment was being used, if any. The study began in June 2001 and patient recruitment ended in March 2003; the BP-lowering treatment arm closed in June 2007. Data on mortality, morbidity, quality of life, and hospitalisation came from the main ADVANCE study. We also performed a substudy of the 978 Australian participants, which provided additional information on outpatient resource usage, including outpatient diagnostic investigations and procedures.

People with type 2 diabetes were eligible for the ADVANCE trial if they had been diagnosed at the age of 30 years or older, were aged 55 years or older on entry to the study, and had established vascular disease or at least one other major risk factor for cardiovascular diseases. There were no BP criteria for inclusion.

**Economic evaluation**

We undertook an incremental cost-effectiveness analysis from the perspective of the health care purchaser. Only direct health service costs were included. The analysis was by “intention-to-treat” for both effects and costs: that is, all events and resources were attributed according to a patient’s initial randomisation. Thus, perindopril–indapamide...
The aim of the cost-effectiveness analysis was to estimate the cost per death averted within the trial, and the cost per life-year gained (estimated by extrapolating for individual survivors beyond the mean follow-up period). There were four major data elements: survival to the end of the study; measurements of quality of life; resource usage; and costs for each of the resources used (unit costs).

Outcomes and survival
All-cause mortality and cardiovascular mortality from the clinical trial have previously been reported. We calculated the survival time within the study for each treatment group from survival curves. Life expectancy of survivors beyond the close of the study was based on multistate life tables under the assumption of no continuing benefits from the within-trial treatment. These life tables were constructed from parametric survival models, and estimates were based on information about all ADVANCE participants who were alive 2 years after randomisation, including age, sex, smoking status, duration of diabetes and history of major cardiovascular disease.

Quality of life
To measure health-related quality of life, we administered the EuroQol-5D (EQ-5D) instrument to all participants from the 20 participating countries. For comparison, version 2 of the 36-item short-form health questionnaire (SF-36v2) was also used with the Australian subgroup of participants. Both questionnaires were administered at baseline, and at 2 years and 4 years after randomisation. A comparison of the baseline data found that the EQ-5D appeared to be as reliable and valid for measuring utility as the SF-36v2, hence the final analysis used the EQ-5D alone.

Resource usage
Hospitalisation data for participants from all 20 countries were included in an assessment of resource usage, and costs were based on diagnosis-related-group (DRG) categories using core grouping computer software (casemix expert release 2.3.1 AR [Australian revision]-DRG 5.1, 3M Australia, Sydney, NSW), together with information extracted from the National Hospital Cost Data Collection (NHCDC) in Australia. Of the 978 Australian participants, 948 (97%) consented to retrieval of Medicare claims data on medical services they received outside of hospital. Data on long-term (out-of-hospital) medications were collected as part of the main study, but information about dispensed medications and dosage were only collected for the Australian subgroup.

Unit costs
Unit costs of resources were allocated as suggested by the Australian Pharmaceutical Benefits Schedule manual of costs. The principal sources for establishing the unit costs of resources were:
- for hospitalisations — DRG costs,
- for outpatient visits and outpatient diagnostic testing — the Australian Medicare Benefits Schedule; and
- for the costs of medications — the Pharmaceutical Benefits Schedule.

All costs are reported in Australian dollars at 2007 values (Box 1).

Statistical analysis
Our analysis comprised a descriptive phase and a cost-effectiveness analysis. A generalised negative binomial regression was used to compare the numbers of medications, DRG episodes, and out-of-hospital visits and procedures between the two treatment groups (as the variance was greater than the mean). Quality-of-life utility scores from the EQ-5D were also compared at the end of the study. No adjustment was made to P values for multiple comparisons.

Mean values for both cost and outcomes with 95% confidence intervals were reported, as well as cost-effectiveness ratios. A non-parametric bootstrap process, in which participants were sampled with replacement, was used to estimate uncertainty in the estimated results. We report undiscounted 2007 costs and outcomes, along with amounts expressed in net present values using discount rates of 0 (ie, undiscounted) 3%, 5% and 10% per year. The effect on our main results of uncertainty surrounding some aspects was examined using sensitivity analyses.

RESULTS
At baseline, characteristics of the 11 140 participants allocated to the two treatment groups were similar. About a third had a prior history of cardiovascular disease. Participants’ mean age was 66 years (SD, 6 years); mean number of years since diagnosis was 8 (SD, 6); 43% were women; 46% were from Europe, 37% from Asia, 9% from Australia, and 4% each from Canada and New Zealand. At the first (registration) visit, their mean BP was 145/81 mmHg. Forty-one per cent had a systolic BP less than 140 mmHg and diastolic BP less than 90 mmHg, and 25% were using antihypertensive medication.

Mean follow-up was 4.3 years, during which allocated treatment was continued for 9293 patient-years (83% of the time) in the active treatment group and 20 849 patient-years (87%) in the placebo group.

During the study, 879 participants died: 408 (7.3%) in the active treatment group and 471 (8.5%) in the placebo group (relative risk reduction, 14% [95% CI, 2%–25%]; P = 0.025). This overall mortality difference was primarily due to the reduction in cardiovascular deaths (Box 2) with active treatment (relative risk reduction, 18% [95% CI, 2%–32%]; P = 0.027).

Quality of life
Based on the EQ-5D, the mean quality-of-life utility assessment (on a scale from 0 [dead] to 1 [full health]) in survivors was...
Hospitalisation across all countries, was somewhat higher than costings based on Australian DRGs, for both the Australian substudy and all countries, are presented in Box 3. The overall difference in hospital costs between placebo and active treatment groups (placebo minus active) in all countries combined was just over A$1 million (about 4% of total hospital costs), with most of this arising from reductions in hospitalisations for cardiovascular episodes. Active treatment reduced hospital admissions for coronary heart disease and coronary revascularisation by 5%. There was a statistically significant reduction in cardiovascular events for participants in the active treatment group, with an average cost reduction of A$222 per patient. However, there were wide variations in hospital resource use by ADVANCE study participants in different regions of the world. In the Australian subgroup, the costs of hospitalisation were about double the average (Box 3), and the cost difference between treatment groups larger, at A$410 per patient (Box 2). This was somewhat higher than costings based on hospitalisation across all countries, mainly due to higher rates of hospitalisation in Australia.

### Outpatient costs

The 948 Australian participants for whom data were retrieved reported an average of 10.2 visits per year to a GP, 3.4 to a medical specialist, and 17.4 to other outpatient services (including diagnostic testing). Over the duration of the trial, none of the differences in outpatient services costs between the perindopril–indapamide and placebo groups were statistically significant (Box 5).

### Medication costs

At the end of follow-up, treatment adherence was 73% and 74% in the active and placebo treatment groups, respectively. Participants assigned to perindopril–indapamide used it for an average of 43.1 months (of 52 months’ duration of the trial), none of the differences in medication costs between the perindopril–indapamide and placebo groups were statistically significant (Box 5).
difference per patient treated was A$555. Hence the cost per death prevented was around A$49 200.

Predicted survival times for both treatment groups were substantially shorter than those for the general population of the same age. Within the period of follow-up, participants allocated to the perindopril–indapamide intervention lived a mean of 4.17 years (95% CI, 4.15–4.18 years) compared with 4.14 years (95% CI, 4.12–4.16 years) for the placebo group — an incremental gain in life expectancy of 0.03 years (95% CI, 0.00–0.05 years) (Box 6). Based on the observed within-trial treatment effects of perindopril–indapamide, the modelled mean life expectancy of 0.04 years (95% CI, 0.03–0.05 years) (95% CI, 0.06–0.12 years), or 0.05 years (95% CI, 0.03–0.06 years) when discounted at 5%.

With no discounting, this is about A$8470 per life-year saved, and at a 5% discount rate, the incremental average cost in the perindopril–indapamide group was A$502 more per patient and the discounted benefits gained were 0.05 life-years, giving a cost-effectiveness ratio of A$10 040 per discounted life-year gained. Analysis of uncertainties showed there is a 30% chance the treatment is cost-neutral or cost-reducing (cost per quality-adjusted life-year [QALY] less than 0), and a 95% chance the cost per QALY is less than A$40 000. Applying the average EQ-5D utility score of 0.80 would mean the cost per QALY is around $10 600.

Sensitivity analysis
When we used only the cost of the therapy and hospitalisations for all Australian participants, the incremental cost of the therapy was A$1176 (A$1368–A$192 [the offset by a reduction in hospital costs]). When costs and effects were discounted at 3%, the incremental cost-effectiveness ratio was around A$19 800 per life-year saved.

In the United Kingdom and United States, the price for 30 days’ medication is £14.49 and US$42, respectively. Assuming a similar proportional reduction in hospital and other costs, the UK and US costs per QALY would be about £4 085 and US$11 842 per discounted life-year saved.

DISCUSSION
Our cost-effectiveness analysis of data from the ADVANCE trial found that the cost offset attributable to the intervention was roughly two-thirds of the total costs of perindopril–indapamide dispensed during the trial. The resultant cost-effectiveness of A$49 200 per premature death prevented is within a range generally considered acceptable and is comparable to that of many other interventions. There was no difference in quality of life between groups, but applying the average quality-of-life score results in a cost per QALY of around $10 600.

These findings are comparable to previous studies of BP reduction in patients with diabetes and patients at high risk of cardiovascular events. For example, in the UK Prospective Diabetes Study, the estimated cost per QALY was £1049 (in 1998 pounds). For participants with stable cor-
ornary disease in the EUROPA trial, the estimated cost per QALY of perindopril alone was £9700.18 Similar relative risk reductions were found across different age, sex, and lipid profile groupings.17,18 Absolute risk, and hence cost-effectiveness, is therefore largely dependent on individual predicted risk.

Although we could make some approximation of cost-effectiveness in the UK and US from the ADVANCE trial data, differences in health care systems would require additional analyses to extend this analysis to other countries in more detail. The absolute benefit is unlikely to be substantially influenced by country-specific factors and, given a similar price for perindopril–indapamide in other countries, the cost offsets are unlikely to repay the medication costs. However, such country-specific variations are still likely to leave perindopril–indapamide in the cost-effective range.

If the monthly costs of medication were reduced to around $12, then this intervention would reduce net costs as well as being clinically important. However, as it is, from the Australian payer’s perspective, perindopril–indapamide is clearly cost-effective for patients with type 2 diabetes mellitus, independent of their BP level.

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COMPETING INTERESTS

Paul Glasziou was reimbursed by the George Institute for travel to management committee meetings. John Chalmers is paid as a Board Member of the Servier International Diabetes Advisory Board. John Chalmers, Anushka Patel, Neil Poultier and Mark Woodward have received honoraria from Servier for speaking at scientific meetings. Mark Woodward has been paid by Roche as a member of the dal-PLAQUE steering committee and as a consultant by Servier, AstraZeneca and GlaxoSmithKline.

REFERENCES


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