

Original Research

Analysis of Published Economic Evaluations of Angiotensin Receptor Blockers

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Key words:
Cost-effectiveness,
hypertension,
angiotensin receptor
blockers.

Manuscript received:
February 10, 2009;
Accepted:
February 23, 2009.

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Introduction: In this study we reviewed the published literature on the economic evaluation of the use of angiotensin receptor blockers (ARBs) for the treatment of hypertension, either primary or due to diabetes.

Methods: An extensive literature review was undertaken. The HEED (Health Economic Evaluations Database) of the Office for Health Economics and the NHS-EED (NHS Economic Evaluation Database) databases were searched. Keywords used were “losartan”, “irbesartan”, “valsartan”, “candesartan”, “olmesartan”, “telmisartan”, “eprosartan”, “primary hypertension” and “diabetes”. The study included all articles retrieved from 2001 onwards. Exclusion criteria included economic evaluations of ARBs for other indications (e.g. heart failure, myocardial infarction, etc.), an underage population, as well as prevalence studies of hypertension for a disease-specific population.

Results: Of the 63 studies retrieved in the literature search, 35 were included in the review. The majority of the studies were of irbesartan (16) or losartan (8). In each study, the model used country-specific data to project and evaluate the clinical and cost outcomes of the treatment arms. The most common method undertaken was cost-consequence analysis (52.94%) followed by cost-effectiveness analysis (32.35%). In most cases, costs and benefits results were not synthesised. Results failed to show a clear advantage in favour of specific therapy, as the outcomes suffered from heterogeneity, referred to specific circumstances and were rather difficult to compare. For different treatment comparators, all the analyses demonstrated an improved life expectancy and a cost-saving choice. The robustness of results was tested with a series of sensitivity analyses, which showed a statistically significant result in each case.

Conclusions: The evidence from this review suggests that the available ARBs represent a cost-saving and cost-effective treatment compared with other conventional treatment options for patients with hypertension and associated conditions. However, there are no meaningful differences between available ARBs, as the design of clinical and economic studies makes it difficult to find any such differences.

Approximately 600 million individuals worldwide are hypertensive, while 7.14 million deaths are caused annually by hypertension, according to the World Health Organisation (WHO).¹ An elevated blood pressure has long been considered as a major risk factor for several cardiovascular diseases –such as heart failure, myocardial infarction, cerebrovascular disease and others– accounting annually for millions of deaths overall.²⁻⁴ Given the fact that the rates of cardiovascular mortality

have increased in most European countries, including Greece, the assessment, control and modification of risk factors such as hypertension is considered imperative.

The results of several international cross-sectional or cohort epidemiological studies show that the prevalence of hypertension varies significantly.⁵⁻¹⁸ Based on the results of a systematic review,⁸ the prevalence of hypertension in Europe is 44.2% on average, almost twice that in Canada and the USA (27.4% and 27.8%, respectively).

Antihypertensive treatment can reduce the risk of cerebrovascular disease by 40%, coronary heart disease by 25% and heart failure by 50%, especially in the middle-aged and elderly population. The benefits of antihypertensive drugs have been confirmed by a variety of clinical trials that have been undertaken. Many classes of drug are available for treatment, and debate has raged about whether the benefits of treatment are purely a function of the quality of blood pressure control or whether the type of drug used might also be a powerful determinant of outcome. The difference in cost between the “newer” classes of angiotensin receptor blockers (ARBs) and the “older” drugs (β -blockers) is substantial, while overall the costs of cardiovascular drugs account for almost 20% of the entire worldwide drug expenditure. It is not surprising, therefore, that recently there has been increasing interest in the economic aspects of health care in general and the economic evaluation of pharmaceuticals for hypertension in particular.

The economic evaluation of antihypertensive therapy entails several methodological challenges. Hypertension clinical trials are of limited duration, and in this context modelling is necessary to capture the long-term consequences in terms of both costs and survival. An assessment of the long-term risk of developing cardiovascular disease as a result of hypertension requires long-term epidemiological data from studies such as the Framingham study. Such data are not specifically designed to evaluate the effectiveness of individual drug classes, however, which also makes it important to have access to clinical trial data that are relatively long-term. Modelling is not always straightforward in this context and poses several challenges. It is sometimes problematic to estimate the relative risks for the subpopulations involved, their quality of life, and the reductions from hypertension treatments. The objective of the present study was to review published economic evaluations of all ARBs for the treatment of hypertension, primary or due to diabetes, and to summarise their methods and results.

Methods

An extensive literature review was undertaken. The HEED (Health Economic Evaluations Database) of the Office for Health Economics and the NHS-EED (NHS Economic Evaluation Database) databases were searched. The latter was accessed via the Centre for Reviews and Dissemination of the University of

York or via the Cochrane Library website. Both databases were searched by drug name and the results of the searches were filtered according to the patient population of relevance for the aim of this study.

The keywords used were “losartan”, “irbesartan”, “valsartan”, “candesartan”, “olmesartan”, “telmisartan”, “eprosartan”, “primary hypertension” and “diabetes”. The study included all articles retrieved from 2001 and onwards. The cut-off date was the end of January 2008. Exclusion criteria included economic evaluations of ARBs for other indications (e.g. heart failure, myocardial infarction, etc.), an underage population, as well as prevalence studies of hypertension for a disease-specific population. No restrictions were imposed regarding the types of articles included in the review or the study design.

Once the literature review was finished, an experienced researcher applied the inclusion and exclusion criteria, and data were extracted in an Excel format. Papers were reviewed for quality by two independent researchers. In the case that a full record was not provided on the NHS-EED or HEED website, an attempt was made to extract any available and substantial data from the abstracts of the papers.

Results

Of the 63 studies retrieved in the literature search, 35 satisfied the inclusion criteria; the majority were of irbesartan (16) or losartan (8). The table presents the studies included in the analysis for both the hypertensive and diabetic populations. No economic evaluations assessing eprosartan were retrieved.

The majority of the studies were conducted in either a European setting or in the USA and followed the corresponding NHS-setting or third-party-payer perspective. Cost-consequence analysis (48.6%) was the most commonly employed analysis in the review, followed by cost-effectiveness analysis (37.1%). It is noteworthy that analysis based on Quality Adjusted Life Years (QALYs) was undertaken in only two studies.

Olmesartan

As indicated in Table 1, two studies were retrieved from the databases. Saito et al, 2005,¹⁹ assessed the cost-effectiveness of Olmesartan for the treatment of mild to moderate hypertension in Japanese patients with or without diabetes. The authors employed a deterministic Markov model to assess the cost-effectiveness of six treatment regimens: initial ARB with addi-

tional calcium antagonist if monotherapy was insufficient; initial calcium antagonist with additional ARB; initial ARB with additional diuretic; initial calcium antagonist with additional diuretic; initial diuretic with additional calcium antagonist; and initial diuretic with additional ARB. Among patients without diabetes, expected survival and costs were similar in the 6 treatment groups. The analysis showed that for hypertensive patients with concomitant diabetes, the cost-effectiveness in the initial olmesartan plus calcium antagonist group was noticeably higher in terms of both lower costs and better survival over the patient's lifetime, suggesting that this regimen was superior to the others. The robustness of the results was tested with a series of one-way sensitivity analyses.

Simons et al, 2003,²⁰ was a multiple ARB comparator study including olmesartan and will be reviewed below.

Telmisartan

The search yielded one economic evaluation of telmisartan.²¹ This was a cost-consequences analysis of the drug compared to four other antihypertensive medications – hydrochlorothiazide, atenolol, enalapril and amlodipine – when used for the treatment of patients with uncontrolled mild-to-moderate uncomplicated hypertension. The study was carried out in the USA. The authors employed a decision model to measure the costs and outcomes (i.e. time to hypertension control and the probability of a drug being chosen as first line therapy) over a 15-month period of time. The model was populated with data from literature review and clinical experts' opinion. The evaluation showed that telmisartan reduced the time to hypertension control and costs, relative to other commonly prescribed therapies, for the treatment of patients with mild-to-moderate hypertension. This conclusion was robust to wide variations performed in the sensitivity analyses.

Candesartan

Fujikawa K et al, 2005,²² performed a cost-effectiveness analysis of low-dose candesartan combined with controlled release nifedipine compared to candesartan monotherapy in patients with essential hypertension uncontrolled by the latter. Efficacy data were derived from a double-blind, parallel-arm, randomised clinical trial in Japan (Nifedipine and Candesartan Combination-NICE Combi-study).²³ Outcomes were

measured as achievement rates of target blood pressure (i.e. <130/85 mmHg for patients aged under 60 years, <140/90 mmHg for those aged 60 to 69 years, and <150/90 mmHg for those aged 70 years and over) and rates of adverse events. The incremental cost-effectiveness of each treatment during the 8-week period was compared from the perspective of a third-party payer. The economic analysis showed that combination therapy with controlled-release nifedipine and low-dose candesartan is “dominant” compared to candesartan monotherapy for the treatment of essential hypertension, since it demonstrates higher efficacy and lower incremental costs. The stability of the initial findings over a range of sensitivity analyses supports the conclusions.

Irbesartan

Sixteen studies were included in the review for irbesartan, of which 11 based their efficacy data on the “Irbesartan in Diabetic Nephropathy Trial” (IDNT). The IDNT demonstrated that irbesartan would lead to greater reductions in end-stage renal disease (ESRD) or death compared to control or amlodipine arms in patients with hypertension, type-II diabetes and nephropathy.²⁴ A Markov model was used to simulate the progression of the aforementioned diseases and to estimate the incremental cost and benefits among treatment choices. This model was adapted to the specific countries by using regional data of resource use and costs and all employed the third-party-payer perspective. Three different assessments were carried out, and will be outlined in detail below.

Irbesartan vs. amlodipine and standard care

In particular, 7 studies had as an objective to assess the cost-effectiveness of treating patients with hypertension, type-II diabetes and/or nephropathy with irbesartan, amlodipine or standard blood pressure control.²⁵⁻³¹ Standard care was assumed to be any antihypertensive treatment but ARBs, ACE inhibitors and calcium channel blockers (CCB). The time horizon ranged from 10 to 25 years. Only in the UK were the costs combined with the benefits. In all cases, it was shown that irbesartan, compared with amlodipine and standard care, improved life expectancy whilst reducing treatment costs, thus being cost-saving. These findings were supported by a wide range of sensitivity analyses.

Authors Country	Study population	Methodology Time horizon	Type Evaluation Perspective	Outcomes	Costs	ICER measure	Conclusions
OLMESARTAN							
Saito, 2005 Japan	Moderate hypertension with or without diabetes, ≥55 years	Deterministic Markov model over patient's lifetime	Cost-consequence 3 rd party payer	Expected survival (discounted): longest in A+C (without/with diab) M: 17.38/17.07yrs; F: 20.06/19.47yrs & shortest in the D+A (without/with) M: 17.33/16.81yrs; F: 19.97/19.03	Expected Cost (discounted JPYmill) highest in A+C (without diabetes) M/F: 5,59/5,68 & C+A (with) M/F: 10,57/12,01 & lowest in D+A (without) M/F: 5,21/5,28 & A+C (with) M/F: 9,41/10,54	N/A	Cost-effectiveness in the A+C group was noticeably high in terms of both the costs and survival, suggesting that this regimen was superior to the others
VALSARTAN							
Smith, 2004 USA	Type II diabetes and albuminuria	MARVAL data into Markov model to simulate disease states and outcome for 8 years	Cost-Utility 3 rd party payer	QAS: advantage for valsartan increases with time, difference yr1: 0.011yrs vs. yr8: 0.555yrs	Costs increased less for patients in valsartan with time. Difference yr1: \$1,006 vs. yr8 \$32,412 (p<0.01)	CE ratio/year of QAS (valsartan vs. amlodipine): yr1: \$12,444 vs. 13,653 yr8: \$14,407 vs. 21,332	No specific recommendation. Future research should try to further compare the use of ARBs
CANDESARTAN							
Fujikawa, 2005 Japan	Mild to severe hypertension, adult population	To estimate cost effectiveness alongside NICE-Combi trial	Cost-effectiveness 3 rd party payer	combi vs. up-titrated mono target rate: SBP 28.5% vs. 17.2% & DBP 40.8% vs. 27.3% (p=0.0225 and p=0.0164, respectively,)	*ATC / patient: combi vs. monoth JPY 29,943 vs. JPY 33,182 *ATC/patient reaching target BP: JPY 105,063 vs. JPY 192,916	Combination therapy (cand+nife) was dominant	Combination therapy with controlled-release nifedipine and low-dose candesartan (8 mg) is "dominant" to up-titrated candesartan monotherapy for the treatment of essential hypertension
TELMISARTAN							
Richter, 2001 USA	Mild-to-moderate uncomplicated hypertension	Decision model to evaluate the costs and consequences of treatments for 15 months	Cost-consequence 3 rd party payer	Time (mths) to control: CCB 2.83 vs. BB 3.04 vs. ACE 3.75 vs. Diuretic 3.41 vs. Telmis 2.73	Total costs US\$: Telmisartan 2,392 vs. Diuretic 2,057 vs. BB 2,426 vs. ACE 2,838 vs. CBB 3,018	N/A	Telmisartan reduced time to hypertension control and costs, relative to other therapies, for patients with mild-to-moderate hypertension. This conclusion was robust to wide sensitivity analyses
IRBESARTAN							
Palmer, 2004 USA	Patients with type II diabetes, hypertension & microalbuminuria	Markov model to simulate disease progression over a 25-year horizon	Cost-effectiveness 3 rd party payer	*Years free of ESRD: control 12.4, early 14.4, late 12.7. *LYG (discounted) / patient: early vs. control 0.96; late vs. control 0.05 early vs. late 0.92	Cost savings / patient (25 yrs): early vs. control US\$11,922; late vs. control US\$3,252 early vs. late US\$8,670	Early irbesartan was dominant over control & late irbe. Late irbesartan is also superior to control.	The model supports the use of irbesartan in hypertensive type-2 diabetic patients with microalbuminuria (early intervention) or overt nephropathy (late intervention). The model showed life and cost-savings in both
Palmer, 2005 Spain	Patients with type II diabetes, hypertension & microalbuminuria	Markov model to simulate disease progression over a 25-year horizon	Cost-effectiveness 3 rd party payer	*Years free of ESRD: CT 13.44 vs. irbes. 15.66. *LYs (discounted): CT 11.53 vs. irbesartan: 12.371 diff 0.84±0.15	25-yr costs / patient (discounted): CT €25,119 vs. Irbesartan: €14,038; difference €11,082	Irbesartan was dominant	Irbesartan added to standard care for diabetic hypertensive individuals with microalbuminuria was found projected to reduce the incidence of end-stage renal disease, extend life, and reduce costs for the Spanish third party payer
Palmer, 2004 Spain	Patients with type II diabetic nephropathy	Markov model to extrapolate IDNT study results for 10 & 25 yrs	Cost-consequence NHS	*Time to ESRD (yrs): irbes 8.23 vs. aml 6.82 vs. CT 6.88. *ESRD incidence (%) at 10/25yrs Irbes 36/47 vs. aml 49/59 vs. CT 59/55 *LE (discounted yrs): Irbes 7.23 vs. Aml 7.11 vs. CT 6.95	*MeanTC / patient (lifetime): Irbe 50,456 € vs. Aml 64,129 €, CT: 58,088 € *Cost savings (25yrs): Irbes vs aml 13,673€; Irbes vs. CT 7,632€.	N/A	The delay in progression to ESRD in hypertensive patients with type 2 diabetic nephropathy, using irbesartan as treatment, produced reductions in the total costs and improved the life expectancy compared to the treatment with amlodipine, or with anti-hypertensive treatment alone
Palmer, 2004 UK	Patients with type II diabetes, hypertension & nephropathy	Markov model to extrapolate IDNT study results for 10 years	Cost-consequence NHS	*Life expectancy improvement (discounted yrs): Irbes vs. Aml 0.07 vs. control 0.21 *Time free to ESRD (yrs): Irbes 8.2 vs. aml 6.8	*µTC (10yrs): Irbes £20,882 vs. Aml £27,417 vs. control £24,642 *Cost savings /patient (ESRD delay) Irbes vs Amlodipine: £3125; Irbes vs. control: £2919	N/A	Treating patients with hypertension, type II diabetes and overt nephropathy with irbesartan was cost saving over a 10-year period compared to Amlodipine and control

Authors Country	Study population	Methodology Time horizon	Type Evaluation Perspective	Outcomes	Costs	ICER measure	Conclusions
Palmer, 2007 UK	Patients with type II diabetes, hypertension & nephropathy	Markov model to simulate disease progression over lifetime	Cost-consequence NHS	*ESRD free (yrs): control 12.25 vs. early 14.29 vs. late 12.47 *LE (discounted yrs): C 10.18 vs. Early 11.00 vs. late 10.20 *LYG (discounted yrs): 0.83 over control	*Mean TC (discounted): early irbe €6735 vs. late irbe €9045 vs. Control £10536 *Cost-savings / patient: early vs. late £2310 & early vs. control £3801	Irbesartan was dominant	Irbesartan is predicted to improve survival and reduce costs in hypertensive patients with type 2 diabetes and microalbuminuria compared to control. Early irbesartan treatment is more effective than late irbesartan
Coyle, 2004 Canada	Patients with type II diabetes, hypertension & proteinuria	Markov model to extrapolate IDNT study results for 25 years	Cost-effectiveness 3 rd party payer	LYG irbe: 6.82 (95% CI:6.2-7.44); Aml0 6.48 (95% CI:5.9-7.06); Control: 6.40 (95% CI:5.68-7.17)	Total costs Can\$: Irbes 89,304 vs. aml0 109,280 vs. Control 101,688	Irbesartan was dominant	The analysis provided strong evidence that, compared with amlodipine and standard care, irbesartan led to a reduction in the medical costs and an increase in life expectancy.
Coyle, 2007 Canada	Patients with type II diabetes, hypertension & microalbuminuria	Markov model to simulate disease progression over a 25-year horizon	Cost-effectiveness NHS	LYG: Early Irbes vs late: 0.45 Early vs. control 0.62 LYG	Cost-saving (Can \$): Early irbes vs. late irbes \$54,100; early vs. control \$68,400	N/A	Early use of irbesartan for patients with hypertension and type 2 diabetes is effective and cost saving and that the earlier is added to conventional treatment, the greater the delays in the onset of ESRD and the overall savings from the perspective of the Canadian health and socialcare system
Palmer, 2006 Switzerland	Patients with type II diabetes, hypertension & microalbuminuria	Markov model to simulate disease progression over a 25-year horizon	Cost-consequence 3 rd party payer	*LE (discounted yrs): CT 9.80 vs irbes 10.37 LYG 0.57yrs *Years free of ESRD: CT 12.90 vs. Irbes 15.04	*TC / patient (CHF): Irbes 25,469 ; control 46,956 *Cost-savings vs. control: CHF21,487	N/A	Compared with conventional therapy, the use of irbesartan to treat type 2 diabetes patients with hypertension and microalbuminuria improved life expectancy and reduced total costs for the Swiss health care system
Palmer, 2003 France-Belgium	Patients with type II diabetes, hypertension & nephropathy	Markov model to simulate disease progression over lifetime	Cost-consequence 3 rd party payer	*Mean time(yrs) to ESRD: Irbes 8.23 vs. Aml0 6.82 vs. cont 6.88 *LE (discounted yrs): Belgium Irbes vs. aml0 0.46; vs. control 0.62; France Irbes vs. aml0 0.45; vs. control 0.61	*Lifetime TC (discounted): Belgium: Irbes €76,777 vs. Aml0 €97,940 vs. Control €88,662; France: Irbes €93,240 vs. Aml0 €120,284 vs. Control €109,585	N/A	Under the analysis assumptions, irbesartan remained both cost and life saving compared with amlodipine and control
Palmer, 2006 France	Patients with type II diabetes & hypertension	Markov model to simulate disease progression over a 25-year horizon	Cost-utility 3 rd party payer (health insurance)	*LE improvement (discounted): 0.2 yrs *QALYs (discounted): no screening 8.58±3.73 vs. screening & optimal tx 8.87±4.02; diff 0.29±0.32 QALYs	*TC / patient (discounted 25-yrs): no screening €17,968 vs. with screening €13,155; diff €4,812 *Cost-saving occurred after 8 years	not performed	Early irbesartan treatment improved quality and length of life and reduced costs in hypertensive patients with type 2 diabetes and microalbuminuria in France. Late irbesartan therapy is also beneficial, but earlier irbesartan leads to better outcomes. Sensitivity analysis showed repeated the results
Palmer, 2005 Italy	Patients with type II diabetes, hypertension & nephropathy	Markov model to simulate disease progression for 10 & 25 years	Cost-consequence Health care payer	*Mean time to ESRD(yrs): Irbe 8.23 vs. aml0 6.82 vs. pbo 6.88; in 10-years the cumulative improvement in LE (in 10 yrs): Irbes 0.15 vs. aml0 0.31 vs. placebo 0.31	*TC / patient (discounted) (10yrs): Irbe €41,692 vs. aml0 €55,222 vs. placebo €49,825 *Cost-savings / patient (10yrs): Irbe vs. aml0 € 13,530; vs. placebo € 8,133.	N/A	Including both cost and effectiveness aspects is that irbesartan is a life-saving and cost- saving drug in patient with type 2 diabetes compared to amlodipine and standard treatment
Palmer, 2007 Hungary	Patients with type II diabetes & hypertension	Markov model to simulate disease progression over lifetime	Cost-consequence 3 rd party payer (health insurance)	*LY (discounted): usual care 7.62yrs vs. Irbe 8.16; diff 0.54 yrs	*25-yr TC(HUF): usual 1,770,197 vs. Irbes 1,250,204; difference 519,993 in favour of Irbesartan *Irbesartan cost-saving after 13 years of therapy	N/A	Irbesartan was projected to improved life expectancy and reduce costs compared to placebo in the Hungarian setting in hypertensive patients with type 2 diabetes and microalbuminuria
Rodby, 2003 USA	Patients with type II diabetes, hypertension & nephropathy	Markov model to extrapolate study results (IDNT) for 10 & 15 yrs	Cost-consequence 3 rd party payer (medicare)	*LE (25-yrs): Irbe 8.225 vs. aml0 7.601 vs. pbo 7.484 *LE (10-yrs): Irbe 6.41 vs. aml0 6.241 vs. pbo 6.136	*Cost savings (over 25 years): Irbes vs. pbo \$15,607; vs. aml0 \$26,290 *Cost savings (over 10yrs): Irbes vs. pbo \$16,026; vs. pbo \$23,817	N/A	Irbesartan may increase life expectancy and decrease costs of care in patients with type 2 diabetic nephropathy and thus it may potentially reduce the clinical and economic burdens of type 2 diabetic nephropathy

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Authors Country	Study population	Methodology Time horizon	Type Evaluation Perspective	Outcomes	Costs	ICER measure	Conclusions
Palmer, 2007 UK	Patients with type 2 diabetes, hypertension, and overt nephropathy	Markov model to extrapolate study results (IDNT) for 10 & 15 yrs	Cost-consequence	LG (months) at 25 years: irbesartan vs. placebo 8.9; vs. amlodipine 7.5	Cost savings (over 25 years): Irbesartan vs. placebo \$15,607; vs. amlodipine \$26,290	N/A	Irbesartan treatment is predicted to improve survival and reduce costs in hypertensive patients with type 2 diabetes and microalbuminuria compared with 'control'. Early treatment is more effective than late. Irbesartan is a valuable treatment in this group in the UK setting.
Palmer, 2004 Germany	Patients with type II diabetes, hypertension & nephropathy	Markov model to simulate disease progression over a 10-year horizon	Cost-consequence NHS	Cumulative incidence of ESRD (after 10yrs): irbe 36% vs. aml 49% vs. control 45%	Cost savings: irbe vs. aml €14,424; irbe vs. control €8,720	N/A	Treating patients with hypertension, type 2 diabetes and nephropathy using irbesartan lowers the cumulative incidence of ESRD and is cost-saving compared to amlodipine or control.
LOSARTAN							
Melnes, 2006, UK/USA	Essential hypertension; 55-80 years	Model was used to extrapolate the results of LIFE clinical trial for patient's lifetime	Cost-effectiveness, Cost-Utility NHS	*LY saved by stroke prevention: 4.4 & stroke reduction: 0.070. *QoL reduction due 1st stroke: 7.6 *QALYs gained through stroke reduction: 0.054.	*Drug costs: Los: £1,128 vs. Aten £44 (95% CI diff: 1,054 to 1,114). *Stroke costs: Los £2,984 vs. Aten £3,953 (95% CI diff: -1,931 to -5). *Total: Los £4,112; Aten £3,997 (95% CI diff: -846 to 1,076).	*IC per LY saved £1,643 (95% CI: -10,104 to 27,181) *IC per QALY £1,643 (95% CI: -12,549 to 34,875)	The clinical benefit of losartan-based therapy in hypertensive patients with left ventricular hypertrophy (LVH) has been demonstrated. This was achieved at a cost well within the range considered cost-effective.
Jonsson, 2005, Sweden	Essential hypertension & LVH; 55 - 80 years.	LIFE trial data were extrapolated for lifetime	Cost-Utility, NHS & Societal	*LYG: 0.092 (95% CI: 0.038 to 0.146) *QALYs gained: 0.069 (95% CI: 0.028 to 0.109) compared with aten, respectively	Direct TC/patient: Losartan €5,097 Atenolol€4,808	IC per QALY: *HC system pers. €4,188 (95% CI: -3,546 to 33,009) *societal pers: €11,710	Losartan is cost-effective in preventing stroke in hypertensive patients with LVH from both the perspective of a national health care system and a societal perspective
Szucs, 2004 Switzerland	Essential hypertension, 60-years old	LIFE trial data were extrapolated using the declining exponential approximation to the life expectancy model (DEALE)	Cost-effectiveness 3rd party payer	* Incremental LE / patient: los vs. aten 0.0495 yrs	*Cost saving (discounted TC): CHF24,227 (95% CI: CHF940,356 to add. cost CHF 1145,589)	Losartan was dominant over atenolol	The use of a losartan-based regimen in hypertensive patients in Switzerland was not cost-saving when compared with an atenolol-based regimen
Beersma, 2007 Netherlands	Patients with hypertension & LVH	Clinical trial data from LIFE were extrapolated to a life time horizon	Cost-effectiveness 3rd party payer	* LYG by stroke prevention: 3.7 *LYG / patient: 0.059	Reduction of stroke-related costs: US\$1,076 per patient	Net cost per LYCS864(1083)	Results from the present analysis suggest that, in The Netherlands, treatment with losartan compared with atenolol may well be a cost-effective intervention based on the reduced risk for stroke observed in the LIFE trial
Jonsson, 2002 Sweden	Elderly mild-to-moderate hypertensive; mean age 55 yrs old	Economic evaluation of double-blind, randomised clinical trial for 26 months	Cost-consequence Not stated	no benefit measure used	*Cost-savings were SEK38,000. Savings ranged from SEK10,800 - 65,200 depending time required. *Cost-savings over ICTZ SEK28,500	N/A	Losartan produces improvements in cognitive function among hypertensive patients, which lead to cost-savings. However, due to the limitations of the analysis, further studies should be carried out to confirm the results, particularly among patients aged older than 75
Stafilas, 2005, Greece	Uncomplicated hypertension	Decision model to simulate clinical decisions & outcomes of disease for 5 years	Cost-minimisation Social security system	*RR: 0.90 (CI: 0.85 - 0.95) for total mortality *5-year NNT 143 (95% CI: 97 - 833) for total mortality	*5-yr drug costs: los €1,657.10 vs. enal €548.41 vs. aml €1,005.05 vs. €78.4 chlor *inclusive of all costs chlor is still cheapest €485.87	N/A	Chlorthalidone was the most cost-effective agent in the treatment of mild-to-moderate uncomplicated hypertension in Greece. Prescribing newer agents as first-line therapy for uncomplicated hypertension is not cost-effective, unless the acquisition costs of these agents become lower.

Authors Country	Study population	Methodology Time horizon	Type Evaluation Perspective	Outcomes	Costs	ICER measure	Conclusions
Anis, 2006 Canada	Hypertension & LVH; 67 years old	Markov state transition model to extrapolate outcomes for patients' lifetime	Cost-Utility Societal	not reported separately	not reported separately	Cost per QALY gained losartan: US\$1002.75	Losartan appears to be a cost-effective alternative to atenolol in patients with hypertension and LVH. The ICERs were within the range of those for other funded interventions in many unities
Jonsson, 2005 Denmark-Finland-Norway-Sweden	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 4 years	Cost-saving Health care payer	No benefit measures used	Cost-savings / patients due to reduced ESRD incidence with losartan: Denmark €5,591; Finland €6,842; Norway €7,025; Sweden €6,776		The nephroprotective effects of losartan may be associated with important cost savings in the Nordic region
Souchet, 2003 France	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 4 years	Cost-consequence Health care payer	ESRD free days / patients with losartan after 3.5 yrs: 33.6days (95% CI: 10.9 - 56.3) & after 4yrs: 46.9 (95% CI: 19.1-74.7; p=0.009 against pbo)	Net savings / patient (4 yrs): 5,834 (CI 95%: 1,407 euros - 10,301 euros, p=0.01)	N/A	
Vora, 2005 UK	Patients with type II diabetes & nephropathy	Extrapolation of results of REENAL study for 4 years	Cost-effectiveness NHS	*expected LYs: los 7.82 vs. control 7.38; difference 0.44 (95% CI: 0.16 to 0.71; p=0.002) *Cumulative ESRD incidence: los 0.193 vs. control 0.296; diff -0.102 (95% CI: -0.157 to -0.047)	TC / patient: los £14,777 vs. control £21,339; difference -£6,622 (95% CI: -10,591 to -2,653; p=0.001)	Losartan dominated control treatments	The results are in line with other studies indicating that losartan is a cost saving treatment option. Caution is needed in trying to generalise the study results to other settings
Alexander, 2004 USA	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 3.5 years	Cost-consequence 3 rd party payer	Reduction in the risk of the development of ESRD with losartan: 28.6% (p=0.002)	*ESRD-related cost saving: los vs. pbo \$5,144 (95% CI \$1,701-\$8,586, P=0.003) *Net savings: los vs. pbo \$3,522 (\$143-\$6,900, P=0.041)	N/A	Treatment with losartan in patients with type 2 diabetes and nephropathy reduces the incidence of ESRD and from a US perspective leads to cost savings over the 3.5-year duration of the trial across all levels of baseline albuminuria
Gerth, 2002 EU countries	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 3.5 years	Cost-consequence Not explicitly stated	*Risk reduction of ESRD with losartan 28% (95% CI: 11 to 42; p=0.002)	Saving/patient €3,730 at 3.5 yrs & €5,206 at 4 years Savings/target population of EU: 2.6 bil at 3.5 yrs & 3.6bil at 4 yrs	N/A	
Herman, 2003 USA	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 3.5 years	Cost-consequence Health care payer	Risk reduction of ESRD 29% vs. pbo (p=0.002)	*µESRD-related costs: Los \$12,714 vs. Control \$17,858, diff \$5,144 (95% CI: 1,701 - 8,586; P=0.003).	N/A	Losartan should be added to the treatment regimens of patients with type 2 diabetes and nephropathy and recommend research to ascertain whether cost-savings observed in the study would be sustained over the long run
Burgess, 2004 Canada	Patients with type II diabetes & nephropathy	Extrapolation of results of REENAL study for 3.5 yrs	Cost-effectiveness NHS	Reduction of estimated # days with ESRD: 33.6 (95% CI: 10.9 - 56.3) at 3.5 yrs & 46.9 (95% CI: 19.1 - 74.7) at 4 yrs	*Net cost-savings at 3.5 yrs Can\$3,675& 4 yrs Can\$4,445. *Cost-diff significant only after 3.5yrs	losartan dominated placebo	From the perspective of the Canadian health care payer, losartan represents a cost-effective treatment for type 2 diabetes patients with nephropathy
Carides, 2006 USA	Patients with type II diabetes & nephropathy	Extrapolation of results of REENAL study	Cost-effectiveness NHS	Lifetime incidence of ESRD losartan (66%) placebo (83%). LYG per patient 0.99 (0.70 discounted)	Lifetime net saving of \$US24 632 per patient	Losartan dominated control treatments	Treatment with losartan plus CT in patients with type 2 diabetes and nephropathy reduced the within-trial incidence of ESRD and is projected to result in lifetime reductions in ESRD and associated costs, and increased survival, versus placebo

→ continued on next page

Authors Country	Study population	Methodology Time horizon	Type Evaluation Perspective	Outcomes	Costs	ICER measure	Conclusions
Seng, 2005 Asia	Patients with type II diabetes & nephropathy	Cost evaluation alongside RENAAL study for 3.5 years	Cost-saving NHS	μ ESRD days saved: 37.9 95%CI: -24.3 to 100	*Cost savings / patient at 3.5yrs by ESRD reduction alone, ranged from US\$910 in Malaysia up to US\$4346 in Japan *Net cost savings / patient at 3.5 yrs: ranged from US\$ -943 in Hong Kong to US\$-6271 in Japan	N/A	Treatment with losartan in patients with type 2 diabetic nephropathy reduced the incidence of ESRD among Asian patients and the direct medical cost in countries or regions representing Asia
MULTIPLE							
Simons, 2003 USA	Hypertension	Clinical trial data (Oparril, 2001), MCOs cost data combined using Framingham model	Cost-saving Managed care	Increased reduction in mortality, CHD events, CVD, MI, stroke over the years with olmesartan over losartan; valsartan; irbesartan	Cost savings from a reduction in the number of cases of CHD, MI and stroke were incurred from treatment with olmesartan instead comparators	N/A	Based on comparative antihypertensive efficacy data, treatment of hypertensive patients with olmesartan medoxomil instead of other leading ARBs potentially may reduce overall cost of medical care in a US managed care setting
Anderson, 2000 South Africa	Hypertension	Probabilistic model based on meta-analysis of clinical trial results	Cost-effectiveness Payers and Private Sector	Reduction in sitting diastolic blood pressure with candesartan, losartan, valsartan and irbesartan	Direct cost of treatment	Candesartan generated a cost savings relative to losartan	After having stressed that there are significant differences in the clinical effectiveness and costs of ARB drugs in terms of reducing SDBP, the authors concluded that candesartan may be the most cost-effective regimen, potentially resulting in significant savings

Irbesartan plus standard care vs. standard care alone

This type of analysis refers to the comparison of irbesartan combined with standard antihypertensive treatment versus the conventional treatment alone in patients with type-II diabetes, hypertension and microalbuminuria. Three studies were retrieved that followed the same analysis and modelling approach.³²⁻³⁴

A Markov model was employed to simulate disease progression from microalbuminuria to early overt nephropathy, advanced overt nephropathy, doubling serum creatinine, ESRD treated with early dialysis or renal transplant, and death. Country-specific adaptation was performed, especially when considering resource use and cost data. The model was populated with clinical data from the IDNT and IRMA-2 studies.³⁵ Outcome measures were life years gained, life expectancy, cumulative incidence of ESRD and years free of ESRD. All analyses led to the conclusion that the addition of irbesartan to standard care for diabetic hypertensive individuals with microalbuminuria was projected to reduce the incidence of ESRD, extend life, and reduce costs from the health care payer perspective. The sensitivity analyses demonstrated that the base-case results were unchanged when variations in key assumptions and parameters were made.

Early irbesartan vs. late irbesartan and standard care

Four studies retrieved were based on trials where irbesartan treatment was provided to patients at different time points according to the progression of the disease.³⁶⁻³⁹ These were diabetic patients with hypertension and microalbuminuria. The three strategies were standard antihypertensive treatment, late irbesartan treatment and early irbesartan treatment. Standard care was any antihypertensive treatment but ARBs, ACE inhibitors and CCBs. Early irbesartan treatment consisted of 300 mg irbesartan daily, started when patients were in the state of microalbuminuria. Late irbesartan treatment referred to standard care when patients were in the states of microalbuminuria and early overt nephropathy and in combination with 300 mg irbesartan daily once patients reached the state of advanced overt nephropathy.

A Markov decision model was used to simulate the progression of the associated disease through the aforementioned states. A number of analyses were carried out using country specific data for resource use and costs. All country-specific analyses showed that the addition of irbesartan (early or late) may lead to signifi-

cant cost savings. However, the early addition of the drug during microalbuminuria was found to be more cost-saving than both late treatment on advanced overt nephropathy or standard care. This was due to greater delays in the onset of ESRD and thus greater overall savings in health care resource utilisation. Sensitivity analyses confirmed the robustness of the study results.

Losartan

Eight studies focused on the use of Losartan in hypertension and nine in diabetes patients. These studies are summarised in Table 1 and are discussed below.

Economic evaluation of losartan vs. atenolol

Several studies were based on the efficacy data from the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) clinical trial.⁴⁰⁻⁴³ The LIFE study assessed the cardiovascular mortality and morbidity associated with losartan and atenolol. It was a double-blind, randomised, parallel-group trial undertaken in six European countries and the USA. It involved patients with essential hypertension (sitting blood pressure 160-200/95-115 mmHg) and electrocardiographic evidence of left ventricular hypertrophy (LVH).⁴⁴ A model was used to extrapolate the results of the trial to patient lifetime. In all cases the model was adapted using country-specific resource use and cost data. In all analyses, a third-party-payer perspective was used and direct costs were measured: i.e. medication costs and costs of myocardial infarctions and strokes, which included interventions, hospitalisation, outpatient treatment and rehabilitation. Only in Sweden⁴¹ were indirect costs expressed as consumption/production and production losses due to morbidity/mortality were also included in the sensitivity analysis. The cost and benefits were combined in all studies using incremental cost-effectiveness ratios, either with QALYs or Life Years Gained (LYG). The analyses found that losartan is cost-effective in preventing stroke in hypertensive patients with LVH, irrespective of the perspective employed. In the case of Switzerland,⁴² losartan even proved to be dominant. Sensitivity analyses were performed to test the accuracy and sensitivity of the results.

Losartan and improvement in cognitive function

Johnson et al, 2002,⁴⁵ assessed the potential economic consequences of losartan vs. hydrochlorothiazide due to the cognitive improvement of hypertensive patients

in Sweden. The effectiveness data came from a double-blind, randomised, controlled trial that evaluated improvement in the cognitive function and quality of life of hypertensive patients.⁴⁶ Cognitive function was evaluated, at baseline and after 26 months, by psychometric tests consisting of items from the Mini-Mental State Examination (MMSE). Regression analyses were performed to evaluate the impact of the MMSE score on resource utilisation and to evaluate the relationship between the MMSE score and the total cost of care. The resources included in the economic analysis were hospitalisation, accommodation, home help, and drug consumption. The analysis demonstrated an inverse relationship between the MMSE score and the total costs of care. The improvements in cognitive function obtained with losartan, compared with hydrochlorothiazide, were associated with economic benefits, larger than expected, in terms of blood pressure control among patients with hypertension.

Economic evaluation of losartan in Greece

Stafilas et al, 2005,⁴⁷ examined the clinical and economic impact of several antihypertensive treatments of mild to moderate hypertensive patients in Greece. This was a cost minimisation analysis of losartan, propranolol, amlodipine, enalapril and chlorthalidone. A decision model was constructed to simulate clinical decisions and outcomes of the disease. Clinical evidence was extracted from seven studies (6 randomised, controlled trials, and a meta-analysis). The analysis of costs was carried out from the third-party-payer perspective and thus only direct costs were included. The study concluded that prescribing older agents as first-line treatment for uncomplicated hypertension is more cost-effective, since their drug costs are lower. Sensitivity analyses were performed and further enhanced the results of the analysis.

In diabetic patients, a number of economic evaluations of losartan were carried out.⁴⁸⁻⁵⁸ All studies were based on the results of the RENAAL (Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) clinical trial.⁵⁹ The trial compared losartan combined with standard care with the latter alone in the prevention of ESRD. Standard care included all antihypertensive treatment but ACE inhibitors or ARBs. The outcomes in the economic analyses were measured as incidence of ESRD, life years gained, or time without ESRD. For the economic analyses, the clinical data and resource use data from the trial were used. The study period was

4 years on average. Only one economic evaluation⁵⁶ projected the results of the trial to a lifetime horizon. In all the analyses, it was demonstrated that the combination of losartan and standard care may lead to significant improvements in renal outcomes overall, whilst being cost-saving. This was evident in all country-specific analyses. In fact, in all studies the costs and benefits were not combined because losartan dominated the comparative treatments. These findings were validated by the results of sensitivity analyses.

Valsartan

Smith et al, 2004,⁶⁰ conducted a cost utility analysis of valsartan versus amlodipine in type-II diabetic and microalbuminuria patients in the USA. A Markov model was used to assess the costs and outcomes of both treatments over an 8-year period. The patients could progress within the model between different states, such as from normal albumin levels to microalbuminuria, nephropathy, ESRD, cardiovascular disease, or death. The clinical data to populate the model were obtained from the MARVAL study.⁶¹ The results of the economic analysis were favourable to valsartan, since it was found to be both less costly and more effective compared to amlodipine. A range of sensitivity analyses were performed. The authors did not provide any specific recommendation based on the results of this study. However, they suggest that future research should try to compare further the use of angiotensin II receptor blockers and angiotensin converting enzyme (ACE) inhibitors, especially generic ones.

Multiple ARB comparators

Two studies reviewed the cost effectiveness of different angiotensin receptor blockers. Anderson et al, 2000,⁶² examined the clinical and cost-effectiveness of candesartan, losartan, valsartan and irbesartan used for the treatment of mild to moderate hypertension in South Africa. The analysis and the choice of comparators were based on the assumption that the decision to treat patients with ARBs was already made, and therefore no other class of antihypertensive drug was included in the study. Synthesis of data from a review of clinical papers was used to populate the parameters in the analysis. The summary benefit measure used was the reduction in sitting diastolic blood pressure. Resource use only accounted for drugs used. Average cost-effectiveness ratios for each drug were

calculated, demonstrating that candesartan was the most cost-effective regimen, potentially resulting in significant savings.

Simons et al, 2003,²⁰ compared the cost-effectiveness of olmesartan, losartan, valsartan and irbesartan for the treatment of hypertension, from the perspective of a managed care setting in the USA over a 5-year time period. The evaluation was based on a prospective, randomised, double-blind clinical trial.⁵⁸ Incremental differences in blood pressure reduction were translated into a reduction in the annual risk of cardiovascular disease and morbidity. Only direct costs were included in the analysis, including hospitalisation, emergency room visits, visits to a general practitioner, and drug costs. Based on the results of this study, it was argued that treatment of patients with olmesartan in a managed care setting in the USA may reduce the overall cost of medical care for patients with uncontrolled hypertension to a greater extent than its comparators. However, sensitivity analysis was not performed.

Discussion

Nowadays, hypertension has been recognised as one of the most common risk factors for cardiovascular disease. Given the fact that the rates of cardiovascular mortality have increased in most European countries, including Greece, the assessment, control and modification of risk factors such as hypertension is considered imperative. The cost of cardiovascular drugs is growing rapidly worldwide and there has therefore been an increasing interest in the economic aspects of hypertension in Greece and elsewhere. In the present study we set out to review published economic evaluations of several ARBs, including losartan, irbesartan, valsartan, candesartan, olmesartan, telmisartan and eprosartan, for the treatment of hypertension, primary or due to diabetes. For the purposes of this review we searched the HEED (Health Economic Evaluations Database) of the Office for Health Economics and the NHS-EED (NHS Economic Evaluation Database).

Several studies fulfilled the inclusion criteria. Most studies employ decision modelling to extrapolate from large multinational clinical trials to various country-specific settings.

The review of economic evaluations revealed that the use of this class of drugs for the treatment of primary or diabetic hypertension may result in cost-effective use of scarce health care resources. In fact, in almost all of the economic evaluations identified, the use

of ARBs could save money, in addition to being more effective compared to their alternatives. The authors of all the economic evaluations concluded that the use of these drugs might be a cost-effective alternative to standard antihypertensive treatments. This reflected the scope of the analyses. However, some of them pointed out that future research could address issues such as the inclusion of different comparators, or methodological aspects such as extrapolation of the results beyond the duration of clinical trials, or address structural uncertainties around the models.

Regarding the methodological elements of the analyses in general, the review suggests a good adherence to recommended principles of economic evaluations. Elements such as the perspective used for the analyses, the discount methods and discount rates, and the time-horizon of the analysis were reported in the majority of the evaluations. Due to the nature of this review, it was not possible to assess whether the authors had presented visual representation of the models in the publications.

Almost all the studies performed extensive sensitivity analyses. These were performed to address the uncertainty around the estimation of parameters or the assumptions made in the models. A high number of those performed deterministic sensitivity analyses by altering the values of one or more parameters at a time. A few studies employed probabilistic sensitivity analyses.

The economic evaluations used a range of outcomes based on which the effectiveness of ARBs was measured. The most common outcomes measured for primary hypertension were time (measured in months) to hypertension control, overall survival, target rates of blood pressure and in two studies QALYs (Quality Adjusted Life Years). For diabetic patients, the most common outcomes were life expectancy, time to progression to ESRD, cumulative and incidence of ESRD. In terms of the costs, in all the studies but one they were estimated from the third-party-payer (either the health care system or the health insurer) perspective; hence the indirect costs (loss of productivity) were not included. It should be noted that all the analyses (apart from candesartan and telmisartan) extrapolated clinical trial results for a time horizon up to 25 years.

The economic evaluation of hypertension, and in particular of ARBs, is a dynamic methodological field. The studies included in this review can be used as a reference point for economic evaluations of hypertension treatments in the future; however, any new

economic evaluation should address the methodological challenges and uncertainties of previous analyses in order to make the best use of the available data for the specific decision problem in the context of health care environment.

In conclusion, as far as the findings are concerned, the evidence from this review suggests that the available ARBs represent a cost-saving and cost-effective treatment compared with other conventional treatment options for patients with hypertension and associated conditions. However, we found no meaningful differences between available ARBs, since the design of clinical and economic studies makes it difficult to detect any such differences.

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