

University of Groningen

An economic assessment of losartan-based versus atenolol-based therapy in patients with hypertension and left-ventricular hypertrophy

Boersma, Cornelis; Carides, George W.; Atthobari, Jarir; Voors, Adriaan; Postma, Maarten

Published in:
Clinical Therapeutics

DOI:
[10.1016/j.clinthera.2007.05.014](https://doi.org/10.1016/j.clinthera.2007.05.014)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2007

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Boersma, C., Carides, G. W., Atthobari, J., Voors, A. A., & Postma, M. J. (2007). An economic assessment of losartan-based versus atenolol-based therapy in patients with hypertension and left-ventricular hypertrophy: Results from the Losartan Intervention For Endpoint reduction (LIFE) study adapted to The Netherlands. *Clinical Therapeutics*, 29(5), 963-971. DOI: 10.1016/j.clinthera.2007.05.014

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

An Economic Assessment of Losartan-Based Versus Atenolol-Based Therapy in Patients with Hypertension and Left-Ventricular Hypertrophy: Results from the Losartan Intervention For Endpoint reduction (LIFE) Study Adapted to The Netherlands

Cornelis Boersma, MSc¹; George W. Carides, PhD²; Jarir Atthobari, MD, PhD¹; Adriaan A. Voors, MD, PhD³; and Maarten J. Postma, PhD¹

¹Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, The Netherlands; ²Merck Research Laboratories, North Wales, Pennsylvania; and ³Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Background: The Losartan Intervention For Endpoint reduction (LIFE) study was a randomized, double-blind trial that compared the effects of losartan-based treatment with those of atenolol-based treatment on cardiovascular disease (CVD)-related morbidity and mortality in 9193 patients with hypertension and left-ventricular hypertrophy (LVH). Compared with atenolol, losartan reduced the combined risk for CVD-related morbidity and mortality by 13% ($P = 0.021$), and reduced the risk for stroke by 25% ($P = 0.001$), with comparable blood pressure control in both trial arms.

Objective: The aim of this study was to analyze the cost-effectiveness of losartan compared with atenolol in the treatment of stroke from the Dutch health care perspective.

Methods: Utilization of losartan and atenolol within the trial period (mean, 4.8 years) and an estimation of direct medical costs of stroke for The Netherlands were combined with estimates of reduction in life expectancy through stroke. Medication costs and stroke incidence during 5.5 years of patient follow-up were estimated separately, adjusted for the baseline degree of LVH and Framingham risk score. To estimate lifetime stroke costs, the cumulative incidence of stroke was multiplied by the lifetime direct medical costs attributable to stroke. All costs are in 2006 Dutch prices and discounted following the former (4% costs and effects) and new Dutch guideline (4% costs, 1.5% effects) for conducting pharmacoeconomic analyses.

Results: With 4% discounting, prevention of stroke was associated with a gain of 3.7 life-years. As a conse-

quence, losartan treatment was associated with 0.059 life-year gained (LYG) per patient treated with losartan. Losartan reduced stroke-related costs by €1076 (US \$1349) per patient. After inclusion of study medication cost, net cost per patient was €51 (\$64) higher for losartan than atenolol. The net cost per LYG was €864 (\$1083), which is below the Dutch pharmacoeconomic threshold of €20,000/LYG (~\$25,000/LYG) for accepting interventions. The corresponding probability of a cost-effectiveness ratio below this Dutch threshold was 0.95. Discounting money and health following the new Dutch guideline resulted in an even more favorable cost-effectiveness for losartan.

Conclusions: 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. (*Clin Ther.* 2007;29:963-971) Copyright © 2007 Excerpta Medica, Inc.

Key words: angiotensin-II receptor blocker, losartan, stroke, cost-effectiveness.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of mortality and morbidity in The Netherlands as well as in

Accepted for publication March 13, 2007.

doi:10.1016/j.clinthera.2007.05.014

0149-2918/\$32.00

Printed in the USA. Reproduction in whole or part is not permitted. Copyright © 2007 Excerpta Medica, Inc.

many other countries.¹ Due to aging of the population, CVDs present a heavy and growing burden to society.^{2,3} In The Netherlands, costs of CVDs amount to up to 10% of the total health care budget, of which ~28% is related to stroke.⁴ Stroke accounts for ~3% per year of the total health care costs in some countries, including The Netherlands.^{2,5,6} Based on demographic changes and treatment improvements associated with improved life expectancies for surviving patients with stroke, an increase in the prevalence of future strokes can be expected.⁷⁻⁹ Direct costs for stroke consist mainly of costs for institutional care (eg, hospitalization, nursing home, rehabilitation center), of which costs for hospitalizations are dominant in the first year after stroke and nursing home costs are dominant in the remaining lifetime.^{2,5,10-16} Despite improvements, only a few effective treatments are available for managing stroke. Hypertension is an important risk factor that contributes to the risk for CVDs, including stroke.^{17,18} Thus, primary prevention in patients with hypertension using blood pressure-lowering agents may offer a relevant opportunity to reduce the medical and economic burden caused by stroke.^{17,19}

The Losartan Intervention For Endpoint reduction (LIFE) study^{20,21} was designed to assess the long-term effects of the angiotensin-II receptor blocker (ARB) losartan compared with those of the β -blocker atenolol in hypertensive patients with left-ventricular hypertrophy (LVH) on the combined end point of CVD-related morbidity and mortality. Losartan resulted in a statistically significant effect on the combined end point, notably associated with a 25% reduction in the incidence of stroke (relative risk [RR] = 0.75; P = 0.001).²¹ The LIFE study found that losartan may prevent stroke and stroke-associated morbidity, despite comparable blood pressure control for both atenolol and losartan. Based on a literature review, Díez²² suggested that losartan (and other ARBs) possibly has properties, independent of the antihypertensive effects, that are associated with a lower prevalence of strokes as found during the LIFE study. In this economic analysis, the findings of the LIFE study were adapted to the Dutch situation to estimate the cost-effectiveness of preventing stroke by means of treatment with losartan compared with treatment with atenolol.

In The Netherlands, losartan has been approved for treatment of essential hypertension, type 2 diabetes with comorbid proteinuria (to delay progression of kidney failure), and hypertension in patients with LVH

(to reduce the risk for cardiovascular morbidity and mortality). Our study analyzed the pharmacoeconomic profile of losartan. Next to evidence with respect to the effectiveness of treatment, costs and cost-effectiveness become more and more important not only for reimbursement costs of the medications used but also reductions in other direct costs (ie, hospitalizations, rehabilitation, etc.) contribute to possible lower total costs or even cost savings within a health care system. For the treatment of essential hypertension, antihypertensive agents other than ARBs (eg, losartan) are recommended in treatment guidelines for general practitioners,²³ as these generally less expensive agents have been associated with sufficient blood pressure control. In patient groups with more severe disease, significantly favorable results—in terms of lower risk for cardiovascular and renal disease—were found for ARBs compared with other antihypertensive agents. Previous comparable analyses of losartan and other ARBs have found economic favorability (cost savings) in patients with type 2 diabetes with nephropathy.^{24,25} To calculate the cost-effectiveness of losartan treatment in patients with LVH, results from the LIFE study were applied to The Netherlands.

MATERIALS AND METHODS

Design of the LIFE Study

The study design and results of the LIFE study have been reported elsewhere.^{20,21} It was a randomized, double-blind trial that compared the effects of the ARB losartan with those of the β -blocker atenolol on CVD-related morbidity (stroke and myocardial infarction) and mortality. The LIFE population consisted of 9193 hypertensive patients included from >800 clinical centers in different countries (Scandinavian countries, the United Kingdom, and the United States) were included. Eligible participants were aged 55 to 80 years, had essential hypertension (systolic/diastolic blood pressure 160–200/95–115 mm Hg) and LVH (ascertained by electrocardiography) and were assigned to once-daily treatment with losartan or atenolol, administered for a mean (SD) duration of 250 (47) weeks. For at least 4 years, doses of losartan and atenolol (mean [SD] doses, 82 [24] and 79 [26] mg, respectively) were increased in an attempt to lower blood pressure to a target of <140/<90 mm Hg. Patients were regularly monitored and followed up for at least 4 years, and until then 1040 patients had reported a primary end point (stroke, myocardial infarction, and/or cardiovascular

death). Baseline demographic, clinical characteristics, and medical history of participating patients are presented in **Table I**, which shows that the losartan and atenolol groups closely matched with respect to the baseline characteristics.

The LIFE study found a statistically significant reduction with losartan in the combined end point of incidence of stroke, myocardial infarction, and cardiovascular death of 13% compared with atenolol with comparable blood pressure control (RR = 0.87; 95% CI, 0.77–0.98; $P = 0.021$). For the single end points of myocardial infarction (RR = 1.07; 95% CI, 0.88–1.31; $P = \text{NS}$) and CVD-related death (RR = 0.89; 95% CI, 0.73–1.07; $P = \text{NS}$), no statistically significant differences were found between losartan and atenolol. However, for the single end point of stroke, losartan was associated with a significantly (25%) lower incidence (RR = 0.75; 95% CI, 0.63–0.89; $P = 0.001$) compared with the atenolol-treated group.²¹ In addition, the incidence of new-onset diabetes was 25% lower with losartan than with atenolol (RR = 0.75; 95% CI, 0.63–0.88; $P = 0.001$), the adverse-event profile was more favorable, and the number of patients remaining on treatment was higher (84% vs 80% of follow-up) in the losartan-treated group.²¹ The present economic study focused on the findings for stroke only.

Economic Assessment

The present study was an incremental cost-effectiveness comparison of losartan and atenolol in costs per life-year gained (LYG) from the Dutch health care perspective. The between-treatment difference in total costs form the numerator of the incremental cost-effectiveness ratio, with *total costs* defined as those of the study medication and direct lifetime medical costs attributable to strokes observed during the 5.5-year trial period of the LIFE study. The denominator was the number of LYGs for losartan versus atenolol. Costs and health were discounted against 4%.

In sensitivity analysis, we applied different discount rates based on the recent change in the discounting procedure in the Dutch guidelines for pharmacoeconomic research. In particular, it was just decided that updated guidelines would advocate differential discount rates for money and health, at 4% and 1.5%, respectively.^{26–31} To investigate the effects of applying discount rates according to both options, both procedures were applied. Additionally, we conducted a

Table I. Baseline demographic and clinical characteristics of the Losartan Intervention For Endpoint reduction (LIFE) study population.²¹

Characteristic	Losartan (n = 4605)	Atenolol (n = 4588)
Age, mean (SD), y	66.9 (7.0)	66.9 (7.0)
Sex, no. (%)		
Female	2487 (54)	2476 (54)
Male	2118 (46)	2112 (46)
Blood pressure, mean (SD), mm Hg		
Systolic	174.3 (14.2)	174.5 (14.4)
Diastolic	97.9 (8.8)	97.7 (9.0)
Framingham risk score, mean (SD)	0.223 (0.095)	0.225 (0.096)
Medical history, no. (%)		
Cardiovascular disease*	1203 (26)	1104 (24)
Coronary heart disease*	771 (17)	698 (15)
Isolated systolic hypertension†	660 (14)	666 (15)
Cerebrovascular disease	369 (8)	359 (8)
Peripheral vascular disease	276 (6)	244 (5)
Atrial fibrillation	150 (3)	174 (4)
Diabetes mellitus	586 (13)	609 (13)

Data from Dahlöf et al.

* $P < 0.05$.

†Defined as $\geq 160/90$ mm Hg.

sensitivity analysis on the major cost driver in our analysis—stroke.

Cumulative Incidence of Stroke

In the LIFE trial, a 25% RR reduction in first stroke was found with losartan. To use the reduced stroke incidence in our economic assessment, the absolute risk for stroke after a 5.5-year within-trial period was calculated. This absolute risk reduction reflects the difference in cumulative incidence of stroke between the losartan- and atenolol-treated groups. The cumulative incidence of stroke after the 5.5-year within-trial period was estimated using the cumulative incidence competing risk method to account for the possibility of non-stroke-related death without prior stroke.³² Based on the clinical assessment in the LIFE study, we adjusted for baseline severity of LVH and Framingham risk

score.²¹ To account for censoring due to incomplete patient follow-up, up to the 5.5 years within trial period, the mean duration of study medication administration (in days) was estimated using a 2-stage method, to determine the relationship between cumulative number of days on each dose of study medication and survival.³³ In particular, in patients with a duration of follow-up <5.5 years, medication use was extrapolated up to the full period based on the mean use during actual follow-up.

Unit Costs of Medical Resource Use

To estimate costs from the Dutch health care perspective, all randomized patients in the trial were included based on the intent-to-treat principle. *Total direct costs* were defined as the sum of costs of study medication during the 5.5-year within-trial period and estimated lifetime costs attributable to strokes.

Costs for study medication were estimated by multiplying study medication utilization during the LIFE study by unit costs in The Netherlands. In patients who experienced stroke, study medication costs after the stroke were excluded. Study medication utilization was based on the exact durations and doses of the study medications, as recorded during the patient-specific follow-up within LIFE. Unit costs for study medication were based on 2006 Dutch prices³⁴ for losartan 50 and 100 mg at €0.63 (US \$0.79) and €1.07 (\$1.34), respectively, and for atenolol 50 and 100 mg at €0.08 (\$0.10) and €0.12 (\$0.15), respectively. In addition, 6% value-added tax and the pharmacists' prescription fee (€6.10; \$7.65) were included.

The costs for stroke used in this analysis were based on a specific estimate of the stroke-related costs in The Netherlands,¹⁰ verified by means of other estimates for stroke costs.^{2,5,6,11-14,16,35} Total stroke costs were estimated by multiplying the lifetime costs due to managing stroke with the cumulative incidence of stroke over 5.5 years in the LIFE trial.

Life Expectancy

Gender- and age-specific life expectancy without stroke was estimated using Dutch life tables matched to the LIFE patient population.³⁶ Life expectancy with stroke was estimated with a Weibull model³⁷ applied to data from LIFE, with baseline severity of LVH, Framingham risk score, sex, and age as covariates. LYGs for losartan versus atenolol due to stroke risk reduction were estimated by multiplying the absolute

risk reduction in stroke during the 5.5-year LIFE study by the number of additional life-years expected by preventing a stroke.

Cost-Effectiveness Analysis

For cost-effectiveness analysis, all costs and effects were respectively discounted according to both discounting options (4% costs and effects vs 4% costs and 1.5% effects). The 95% CIs and acceptance probabilities were based on a log-normal stroke cost distribution and the nonparametric bootstrap (1000 replicates).^{33,38} Acceptance probabilities were calculated using the informal Dutch willingness-to-pay (WTP) threshold of €20,000/LYG (~\$25,000/LYG) for accepting pharmacotherapeutic interventions. All costs are reported in 2006 Euros.

RESULTS

Overview

First-year and lifetime costs of stroke were estimated at €16,775 (\$21,025) and €46,445 (\$58,213) per patient, respectively. Compared with that of atenolol, the costs per patient of losartan was €1128 (\$1414) higher during the LIFE-trial follow-up. However, losartan was associated with a significantly lower stroke-related cost per patient by €1076 (\$1349). The reduction in stroke-related per-patient cost offset 95% of the increase in medication cost and was due to a lower incidence of stroke for losartan at 5.5 years (4.9%) compared with atenolol (6.5%) ($P = 0.003$). **Table II** shows the results of per-patient direct costs and incidence of stroke.

In patients who did not experience stroke, we estimated a discounted mean life expectancy of 11.6 years, whereas patients with stroke had an estimated discounted life expectancy of 7.9 years. Thus, prevention of stroke was associated with 3.7 discounted (4%) LYGs per stroke patient, implying 0.059 LYGs per patient with losartan treatment (0.016×3.7). **Table III** shows the results.

After inclusion of stroke-related costs and study medication costs, the net cost per patient was €51 (\$64) higher with losartan compared with that of atenolol. The net cost per LYG was €864 (\$1083), which is below the Dutch threshold of €20,000/LYG (~\$25,000).⁴¹

Figure 1 shows the plane of bootstrap replicates for incremental direct costs and LYGs. Fifty-four percent of the replicates were in the upper right hand, indicating

Table II. Per-patient direct costs (€ [US \$]) and incidence of stroke (no. [%] of patients) during follow-up of the Losartan Intervention For Endpoint reduction (LIFE) study population.²¹ Data are mean (SD) unless otherwise noted.

Parameter	Losartan	Atenolol	Difference
Costs			
Study medication	1265 (1586)	138 (173)	1128 (1414)
Stroke	3317 (4157)	4393 (5506)	-1076* (-1349)
Net	4582 (5743)	4531 (5679)	51 (64) (95% CI, -601 to 703)
Cumulative incidence of stroke (at 5.5 years)	0.049	0.065	0.016 (95% CI, 0.006 to 0.026)

*Negative costs indicate cost savings.

Table III. Life expectancy (LE), life-years gained (LYG), and incremental cost per LYG.

Parameter	Former PE Guideline ³⁹	New PE Guideline ⁴⁰
Discounted LE without stroke, mean, y	11.6	14.0
Discounted LE with stroke, mean, y	7.9	8.9
Expected LYG by preventing a stroke, mean, y	3.7	5.1
LYG for losartan due to stroke risk reduction, mean (95% CI), y	0.059 (0.020 to 0.097)	0.081 (0.029 to 0.134)
Incremental cost per LYG for losartan, mean (95% CI)		
€	864 (-7308 to 27,607)	630 (-5245 to 20,158)
\$	1003 (-9162 to 34,611)	790 (-6575 to 25,272)

PE = pharmacoeconomic.

an intervention with increased cost and improved effectiveness. However, the remaining replicates were in the lower right-hand quadrant, indicating cost savings.

Figure 2 presents the probability of cost-effectiveness for a range of pharmacoeconomic thresholds. From the Dutch health care perspective, the probability of a cost-effectiveness ratio below the Dutch threshold of €20,000/LYG (~\$25,000/LYG) was estimated at 0.95.

In the sensitivity analysis, outcomes of the incremental cost-effectiveness of losartan versus atenolol for the change in discount rate for health gains in The Netherlands was compared. Discounting LYG at 1.5% resulted in a mean discounted life expectancy without stroke of 14 years, whereas patients who experienced stroke would have an average discounted life expectancy of 8.9 years. The 5.1-years' difference reflects the expected LYGs resulting from preventing a

stroke. LYGs with losartan—as the product of the absolute risk reduction for stroke (1.6%) and expected LYGs by preventing stroke (5.1 years)—is estimated at 0.081 ($P = 0.002$). The estimated incremental cost per LYG with losartan was €630 (\$790) (**Table III**). **Figure 2** shows results for discounting health gains at 1.5%. The suggested probability of a cost-effectiveness ratio below the Dutch threshold of €20,000/LYG (\$25,000/LYG) was estimated at 0.97. Sensitivity analysis on the major cost driver—stroke costs (+25% and -25%)—indicated a range of cost savings to €5441 (\$6822).

DISCUSSION

The LIFE study found a significantly lower prevalence of stroke in losartan-treated patients compared with atenolol-treated patients for comparable blood pres-

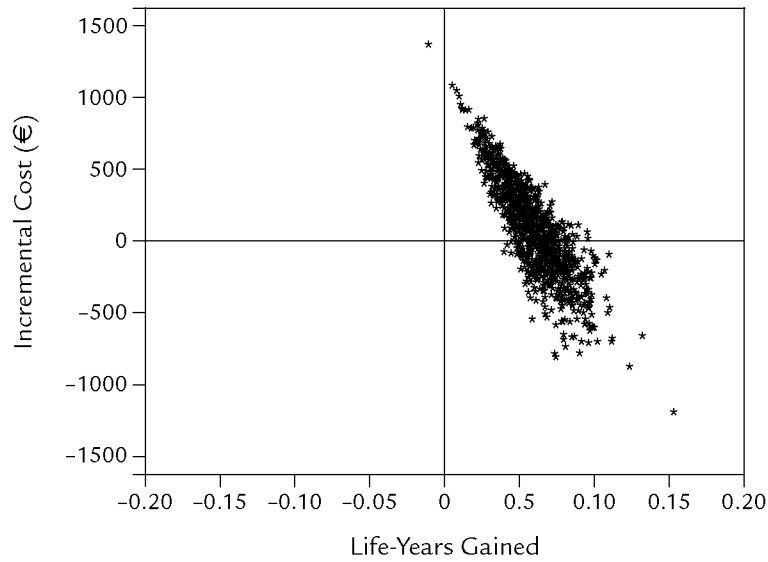


Figure 1. Cost-effectiveness plane showing bootstrap replicates for incremental direct costs and life-years gained.

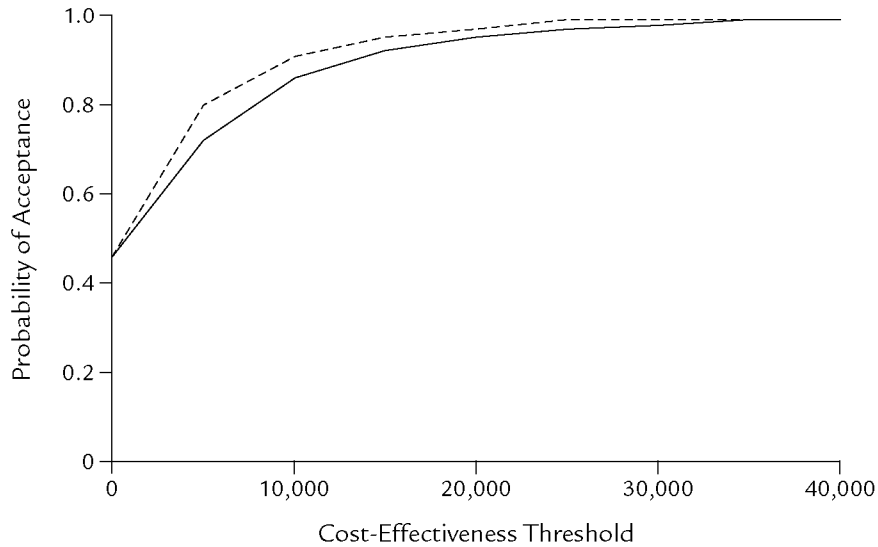


Figure 2. Cost-effectiveness probability curve for a range of pharmacoeconomic thresholds (losartan vs atenolol [1 € = US \$1.25372]). Dashed line indicates 1.5% discounting of effects; solid line indicates 4% discounting of effects.

sure control.²¹ In this economic assessment of the LIFE study adapted to The Netherlands, stroke costs were €1076 (\$1349) lower in the losartan-treated group, corresponding with €51 (\$64) net incremental direct costs. With an extended estimated life expectancy due to the reduction in stroke associated with losartan

treatment, estimated incremental cost-effectiveness was €864/LYG (\$1083/LYG). For losartan, the estimated likelihood of falling below the Dutch threshold of €20,000/LYG (\$25,000/LYG) was 95%.

Comparable economic assessments based on the LIFE study have been conducted in Switzerland,

Sweden, the United Kingdom, and Canada. These studies also found favorable estimated economic outcomes with losartan, with potential per-patient cost-savings of €19 (\$25) in Switzerland⁴² and cost-effectiveness of €4188 (\$5249), €3195 (\$4005), and Can \$1337 (US \$1003) per quality-adjusted life year (QALY) gained in Sweden,⁴³ the United Kingdom,⁴⁴ and Canada,⁴⁵ respectively. Despite differences in pharmacoeconomic guidelines (eg, regarding perspective, discount rates, type of analysis, model used), costs included and purpose of the study (eg, registration, justification of prescribing practice of health care professionals, reimbursement decisions, clinical guidelines), country-specific results were in the same direction varying from net cost savings for losartan in Switzerland to low net costs per LYG or QALY gained in the other countries.

Several limitations of the present study should be acknowledged. Because the data were derived from a clinical trial, the period to which the data referred was limited and lacked long-term follow-up, so model-based extrapolations were necessary, with uncertainty obviously surrounding such extrapolations for LYGs and QALYs. Also, treatment compliance may not fully reflect what happens in clinical practice. Furthermore, no survival data were available that exactly matched the cohort in the clinical trial. Finally, perspective of the present study was limited to that of the health care sector only, rather than analyzing the full scope within a societal perspective.

In addition to the efficacy of losartan found in the LIFE study, the results of the present cost-effectiveness analysis for this drug may be partly explained by a lower rate of adverse events and greater tolerability of losartan, which may have resulted in better treatment compliance with losartan compared with atenolol. Results from an observational study by Conlin et al⁴⁶ support this suggestion with regard to ARBs, such as losartan, by claiming a substantially greater persistence for ARBs compared with other classes of antihypertensives, including atenolol.

In The Netherlands, β -blockers and diuretics are recommended as first-line treatment of hypertension in the general practitioners' guidelines. This, together with relatively high use (~30% of all prescriptions in The Netherlands in 2005⁴⁷)—compared with other classes of antihypertensive agents (ie, diuretics and calcium channel blockers)—suggests that atenolol is a proper comparator for losartan.^{48–50} However, the results of clinical trials in general provide evidence for

selected patient groups, which may not allow for direct extrapolation to the general patient population in clinical practice.⁵¹

In the present analysis, we included only stroke-related costs and excluded costs related to comorbidities and related use of drugs other than study drugs. The inclusion of stroke-related costs only could, however, be a concern in the relatively high-risk patients in the LIFE study. However, there were almost no statistical differences in prevalence of comorbidities between the losartan- and atenolol-treated groups. Differences found were related to compliance/persistence and new-onset diabetes, with losartan being associated with higher and lower rates, respectively. The prevalence of new-onset diabetes was 25% lower in the losartan-treated group compared with the atenolol-treated group ($P = 0.001$).²¹ This finding suggests that the results of the present study may show a further cost advantage of losartan if we also included (direct) costs associated with additional cardiovascular events and (co-)morbidity, such as new-onset diabetes and adverse events.

In the sensitivity analysis, discounting health gains lower at 1.5% versus 4% as in the baseline analysis was associated with a favorable pharmacoeconomic outcome for losartan, with the probability of being below the Dutch threshold at 97%. The new pharmacoeconomic guideline favors pharmacoeconomic outcomes of (primary) prevention programs, compared with the old one, in which costs and effects were both discounted at 4%. In literature there is discussion about the choice of applying the same or different discount rates for costs and effects.⁵² Varying the major cost driver also resulted in a favorable pharmacoeconomic outcome following the Dutch WTP threshold.

The present study included LIFE study data from various countries, due to the multinational approach of the LIFE study. A limitation of the present economic assessment was the assumption that findings from the LIFE study would be similar in Dutch patients, whereas no Dutch patients were included in the LIFE trial. In short, imperfections can be found in the transferability of data from a clinical trial such as LIFE to The Netherlands due to, for example, epidemiologic and demographic factors. However, the present study can at least be seen as providing an indication for positive health effects at a low additional cost per LYG. The results from the present analysis suggest that drug prices alone do not provide the full economic picture;

in particular, downstream savings may cause that the initially more expensive option is in the end still a cost-effective option. Trials tailored to the Dutch situation are needed to confirm the present findings for The Netherlands.

CONCLUSIONS

In the present cost analysis, treatment with losartan could be considered a cost-effective intervention compared with atenolol based on the reduced risk for stroke observed in the LIFE study for The Netherlands. This notion should be considered in the development of clinical guidelines, in addition to clinical efficacy, tolerability, and experience with treatment options in general clinical practice.

ACKNOWLEDGMENT

This study was financially supported by an unrestricted grant from Merck Sharp & Dohme, Haarlem, The Netherlands.

REFERENCES

1. Reitsma JB, Dalstra JA, Bonsel GJ, et al. Cardiovascular disease in The Netherlands, 1975 to 1995: Decline in mortality, but increasing numbers of patients with chronic conditions. *Heart*. 1999;82:52-56.
2. van Exel J, Koopmanschap MA, van Wijngaarden JD, Scholte op Reimer WJ. Costs of stroke and stroke services: Determinants of patient costs and a comparison of costs of regular care and care organised in stroke services. *Cost Eff Resour Alloc*. 2003;1:1-11.
3. Niessen LW, Barendregt JJ, Bonneux L, Koudstaal PJ, for the Technology Assessment Methods Project Team. Stroke trends in an aging population. *Stroke*. 1993;24:931-939.
4. Polder JJ, Takken J, Meerding WJ, et al. Costs of diseases in The Netherlands. Available at: www.rivm.nl/kostenvanziekten/site_en. Accessed November 15, 2006.
5. Evers SM, Engel GL, Ament AJ. Cost of stroke in The Netherlands from a societal perspective. *Stroke*. 1997;28:1375-1381.
6. Evers SM, Struijs JN, Ament AJ, et al. International comparison of stroke cost studies. *Stroke*. 2004;35:1209-1215.
7. Peeters A, Bonneux L, Barendregt JJ, Mackenbach JP, for The Netherlands Epidemiology and Demography Compression of Morbidity Research Group. Improvements in treatment of coronary heart disease and cessation of stroke mortality rate decline. *Stroke*. 2003;34:1610-1614.
8. Struijs JN, van Genugten ML, Evers SM, et al. Modeling the future burden of stroke in The Netherlands: Impact of aging, smoking, and hypertension. *Stroke*. 2005;36:1648-1655.
9. Hannerz H, Nielsen ML. Life expectancies among survivors of acute cerebrovascular disease. *Stroke*. 2001;32:1739-1744.
10. Bergman L, van der Meulen JH, Limburg M, Habbema JD. Costs of medical care after first-ever stroke in The Netherlands. *Stroke*. 1995;26:1830-1836.
11. Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): Predicting long-term costs from functional status. *Stroke*. 1999;30:2574-2579.
12. Caro JJ, Huybrechts KF, Duchesne I, for the Stroke Economic Analysis Group. Management patterns and costs of acute ischemic stroke: An international study. *Stroke*. 2000;31:582-590.
13. Spieler JF, Lanoe JL, Amarenco P. Costs of stroke care according to handicap levels and stroke subtypes. *Cerebrovasc Dis*. 2004;17:134-142.
14. Payne KA, Huybrechts KF, Caro JJ, et al. Long term cost-of-illness in stroke. An international review. *Pharmacoeconomics*. 2002;20:813-825.
15. van Straten A, van der Meulen JH, van den Bos GA, Limburg M. Length of hospital stay and discharge delays in stroke patients. *Stroke*. 1997;28:137-140.
16. Evers SM, Driessen GA, Ament AJ. The use of mental health care facilities after stroke. A cost analysis. *Int J Technol Assess Health Care*. 2002;18:33-45.
17. Mancia G, Ambrosioni E, Rosei EA, et al, for the ForLife Study Group. Blood pressure control and risk of stroke in untreated and treated hypertensive patients screened from clinical practice: Results of the ForLife study. *J Hypertens*. 2005;23:1575-1581.
18. Donnan GA, Davis SM, Thrift A. The role of blood pressure lowering before and after stroke. *Curr Opin Neurol*. 2003;16:81-86.
19. Mancia G. Prevention and treatment of stroke in patients with hypertension. *Clin Ther*. 2004;26:631-648.
20. Dählof B, Devereux R, de Faire U, et al, for the LIFE Study Group. The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: Rationale, design, and methods. *Am J Hypertens*. 1997;10:705-713.
21. Dählof B, Devereux RB, Kjeldsen SE, et al, for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet*. 2002;359:995-1003.
22. Díez J. Review of the molecular pharmacology of losartan and its possible relevance to stroke prevention in patients with hypertension. *Clin Ther*. 2006;28:832-848.
23. Dutch General Practitioners Society. Dutch General Practitioner Guidelines [Dutch General Practitioners Society Web site; in Dutch]. Available at: <http://nhg.artsennet.nl>. Accessed May 14, 2007.

24. Boersma C, Atthobari J, Gansevoort RT, et al. Pharmacoeconomics of angiotensin II antagonists in type 2 diabetic patients with nephropathy: Implications for decision making. *PharmacoEconomics*. 2006;24:523–535.
25. Carides GW, Shahinfar S, Dasbach EJ, et al, for the RENAAL Investigators. The impact of losartan on the lifetime incidence of end-stage renal disease and costs in patients with type 2 diabetes and nephropathy. *PharmacoEconomics*. 2006;24:549–558.
26. Oostenbrink JB, Koopmanschap MA, Rutten FF. Guideline for costing research, methods and guideline prices for economic evaluations in health care. Amstelveen, The Netherlands: Health Care Insurance Board; 2000.
27. Oostenbrink JB, Bouwmans CA, Koopmanschap MA, Rutten FF. Guideline for costing research, methods and standardized prices for economic evaluations in health care. Diemen, The Netherlands. Health Care Insurance Board; 2004.
28. Klok RM, Brouwer WB, Annemans LJ, et al. Towards a healthier discount procedure. *Expert Rev Pharmacoeconomics Outcomes Res*. 2005;5:59–63.
29. Brouwer WB, Niessen LW, Postma MJ, Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analysis. *BMJ*. 2005;331:446–448.
30. Claxton K, Sculpher M, Culyer A, et al. Discounting and cost-effectiveness in NICE—stepping back to sort out a confusion. *Health Econ*. 2006;15:1–4.
31. Gravelle H, Brouwer W, Niessen L, et al. Discounting in economic evaluations: Stepping forward towards optimal decision rules. *Health Econ*. 2007;16:307–317.
32. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York, NY: Wiley; 1980.
33. Carides GW, Heyse JF, Iglewicz B. A regression-based method for estimating mean treatment cost in the presence of right-censoring. *Biostatistics*. 2000;1:299–313.
34. Dutch drug prices [in Dutch]. Available at: <http://www.medicijnkosten.nl>. Accessed May 15, 2006.
35. Niessen LW, Dippel DW, Limburg M. Calculation of costs of stroke, cost effectiveness of stroke units and secondary prevention in patients after a stroke, as recommended by revised CBO practice guidelines 'stroke' [in Dutch]. *Ned Tijdschr Geneesk*. 2000;144:1959–1964.
36. Voorburg/Heerlen. Central Institute of Statistics Web site [in Dutch]. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed October 2, 2005.
37. Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. Chichester, UK: Wiley; 1993.
38. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. New York, NY: Chapman and Hall; 1993.
39. Health Care Insurance Board. Dutch Guideline for Pharmacoeconomic Research [in Dutch]. Amstelveen, The Netherlands; 1999.
40. Health Care Insurance Board. Dutch Guideline for Pharmacoeconomic Research [in Dutch]. Available at: <http://www.cvz.nl>. Accessed May 12, 2006.
41. Bos JM, Postma MJ. Using pharmacoeconomics for policy making: Is rational decision making enhanced by applying thresholds for cost-effectiveness? *Expert Rev Pharmacoeconomics Outcomes Res*. 2004;4:247–250.
42. Szucs TD, Burnier M, Erne P. Cost-effectiveness of losartan versus atenolol in treating hypertension—an analysis of the LIFE study from a Swiss perspective. *Cardiovasc Drugs Ther*. 2004;18:391–397.
43. Jonsson B, Carides GW, Burke TA, et al, for the LIFE Study Group. Cost effectiveness of losartan in patients with hypertension and LVH: An economic evaluation for Sweden of the LIFE trial. *J Hypertens*. 2005;23:1425–1431.
44. McInnes G, Burke TA, Carides G. Cost-effectiveness of losartan-based therapy in patients with hypertension and left ventricular hypertrophy: A UK-based economic evaluation of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. *J Hum Hypertens*. 2006;20:51–58.
45. Anis AH, Sun H, Singh S, et al. A cost-utility analysis of losartan versus atenolol in the treatment of hypertension with left ventricular hypertrophy. *PharmacoEconomics*. 2006;24:387–400.
46. Conlin PR, Gerth WC, Fox J, et al. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clin Ther*. 2001;23:1999–2010.
47. Prescription database [in Dutch]. Available at: <http://www.gipdatabank.nl>. Accessed May 2, 2007.
48. Wiersma T, Walma EP, Thomas S, Assendelft WJ. Summary of the practice guidelines 'hypertension' (third division) from the Dutch College of General Practitioners [in Dutch]. *Ned Tijdschr Geneesk*. 2004;148:923–931.
49. Greving JP, Denig P, van der Veen WJ, et al. Does comorbidity explain trends in prescribing of newer antihypertensive agents? *J Hypertens*. 2004;22:2209–2215.
50. Van Gilst WH. The Netherlands in reverse thanks to the *Lancet*? [in Dutch]. *Hart Bull*. 2006;37:2–3. Editorial.
51. Vandenbroucke JP. Benefits and harms of drug treatments. *BMJ*. 2004;329:2–3.
52. Bos JM, Postma MJ, Annemans L. Discounting health effects in pharmacoeconomic evaluations: Current controversies. *PharmacoEconomics*. 2005;23:639–649.

Address correspondence to: Cornelis Boersma, MSc, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: c.boersma@rug.nl/m.j.postma@rug.nl