ORIGINAL ARTICLE

Cost-effectiveness of Chlorthalidone, Amlodipine, and Lisinopril as First-step Treatment for Patients with Hypertension: An Analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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OBJECTIVE: To evaluate the cost-effectiveness of first-line treatments for hypertension.

BACKGROUND: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found that first-line treatment with lisinopril or amlodipine was not significantly superior to chlorthalidone in terms of the primary endpoint, so differences in costs may be critical for optimizing decision-making.

METHODS: Cost-effectiveness analysis was performed using bootstrap resampling to evaluate uncertainty.

RESULTS: Over a patient's lifetime, chlorthalidone was always least expensive (mean $4,802 less than amlodipine, $3,700 less than lisinopril). Amlodipine provided more life-years (LYs) than chlorthalidone in 84% of bootstrap samples (mean 37 days) at an incremental cost-effectiveness ratio of $48,400 per LY gained. Lisinopril provided fewer LYs than chlorthalidone in 55% of bootstrap samples (mean 7-day loss) despite a higher cost. At a threshold of $50,000 per LY gained, amlodipine was preferred in 50%, chlorthalidone in 40%, and lisinopril in 10% of bootstrap samples, but these findings were highly sensitive to the cost of amlodipine and the cost-effectiveness threshold chosen. Incorporating quality of life did not appreciably alter the results. Overall, no reasonable combination of assumptions led to 1 treatment being preferred in over 90% of bootstrap samples.

CONCLUSIONS: Initial treatment with chlorthalidone is less expensive than lisinopril or amlodipine, but amlodipine provided a nonsignificantly greater survival benefit and may be a cost-effective alternative. A randomized trial with power to exclude "clinically important" differences in survival will often have inadequate power to determine the most cost-effective treatment.

KEY WORDS: hypertension; cost-effectiveness; diuretic; angiotensin-converting enzyme inhibitors; calcium channel blockers.
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INTRODUCTION

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolled 33,357 patients (Fig. 1) and found that outcome for patients initially treated with amlodipine or lisinopril was not clearly superior to outcome for those treated with chlorthalidone.[1] Some secondary outcomes, such as incidence of heart failure, favored chlorthalidone. Furthermore, the daily cost of chlorthalidone is less than the cost of amlodipine or lisinopril, so it has been recommended as first-step hypertension treatment because of a better presumed cost-effectiveness.[2] However, the best estimate of cost-effectiveness must consider all cost differences and compare them with differences in survival. It is possible that small, nonstatistically significant differences in outcome may have an important impact on the cost-effectiveness of a treatment if the difference in cost is also not large.

Using the cost of care and quality of life for patients treated with chlorthalidone, lisinopril, and amlodipine in ALLHAT, we sought to compare the cost-effectiveness of these 3 agents as first-step therapy for hypertension in the context of the nonsignificant differences in survival observed in this trial.[1]

METHODS

In ALLHAT,[1] patients 55 years old or greater with hypertension and at least 1 additional risk factor for coronary heart disease were randomized to initial treatment with chlorthalidone, lisinopril, or amlodipine. The study received institutional review board approval, and participants provided written informed consent. A fourth arm of the trial that evaluated

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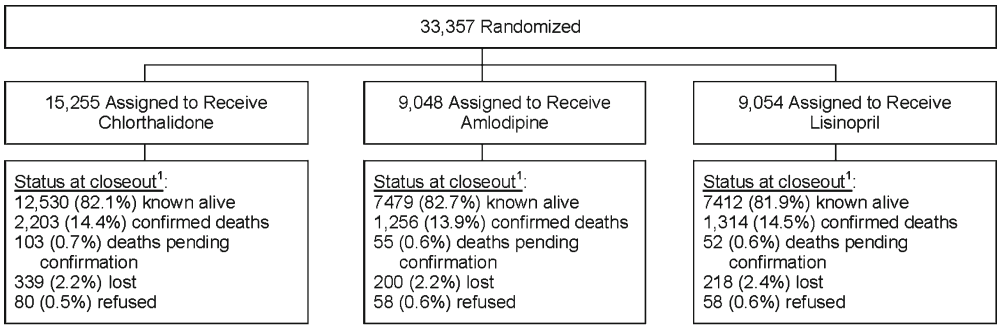

Figure 1. Randomization and follow-up of ALLHAT participants.

doxazosin was stopped early and not included in this analysis. We compiled the resource use, survival, and quality of life data collected during the course of the trial, and supplemented this information with claims data on patients who were enrolled in Medicare or received care in the Veterans Administration (VA) Health Care System. Using costs and survival during the trial, we projected post trial costs and outcomes to estimate lifetime cost of care and survival for initial treatment with chlorthalidone, lisinopril, or amlodipine.

Health Outcomes

We determined the mean survival times during the initial 6 years of ALLHAT by calculating the area under the Kaplan–Meier survival curve. To estimate survival after the conclusion of the trial, we calculated the relative risk of death for chlorthalidone-treated patients compared with the U.S. population (matched to gender and mean age) during the course of the trial (Table 1) and assumed this risk (0.65) remained constant over the patient's lifetime. We then used a proportional hazards model to determine the risk ratio for death during the trial for lisinopril versus chlorthalidone and for amlodipine versus chlorthalidone. We assumed that differences in mortality would approach 0 at a relative rate of 10% per year. In sensitivity analyses, we varied the persistence of the drug effects after the trial from 0 years to the patient's lifetime.

Quality of Life

Twenty-eight thousand five hundred thirty-four (86%) patients completed at least 1 annual analog scale estimate of their quality of life (0–100). This value was transformed (Torrance transformation) so that the distribution of quality of life utilities better matched the standard utility values such as the time-tradeoff or standard gamble.[3,4] The mean value over the time in the trial was determined for each patient, and the overall mean was determined for each trial arm. Quality-adjusted survival was determined by multiplying this mean utility by the survival during the trial. After the trial period, we assumed that quality of life remained constant until death.

Costs

We analyzed a reference-case assuming a universal payer's perspective (Table 1). Indirect costs were not incorporated.[5] Medical costs were measured as the sum of hospital costs, drug costs, and outpatient visits. ALLHAT recorded the use of medication and number of outpatient visits. Medicare (MEDPAR) and VA (Patient Treatment File) hospitalization data were obtained for trial participants. The cost of hospitalization was determined by multiplying the diagnosis-related group-specific

Table 1. Main Model Inputs used to Determine Outcomes and Costs Beyond the Trial

Model variables	Baseline value	Range tested	Source for baseline estimate
Relative risk of death			
Chlorthalidone arm versus U.S. population (age- and sex-adjusted)	0.65	0.5–1.0	U.S. life table data; ALLHAT
Amlodipine versus chlorthalidone arm	0.96	*	ALLHAT
Lisinopril versus chlorthalidone arm	1.001	*	ALLHAT
Duration of drug differences after the trial	Decreases by 10% per yr	0–10 yrs	Assumed
Quality of life			ALLHAT average over 6 yrs
Amlodipine	0.8517	*	
Lisinopril	0.8480	*	
Chlorthalidone	0.8484	*	
Drug cost per day ($)			Average wholesale price (Redbook 2004)
Amlodipine (10 mg)	$2.47	$1.50–2.47	
Lisinopril (40 mg)	$1.65	$1.50–1.65	
Chlorthalidone (25 mg)	$0.19	$0.05–0.19	
Cost of office visits ($)	$50	$25–100	Level 3 CPT for established patient Medicare allowed charge (CPT 99213)
Annual discount rate for costs and utilities	3%	0–5%	Assumed[5]

**Uncertainty evaluated with bootstrap sampling using trial data.*
CPT: current procedural terminology

Medicare case weight times the conversion factor for 2004. We did not make further adjustments for outlier costs, geographic wage differences, indirect medical education, or disproportionate share of indigent patients. We accounted for professional fees by increasing the hospital costs by 25%.[6] For the 5,574 (17%) patients not in Medicare or the VA system, we estimated hospital cost using a multistep procedure. The probability of having inpatient costs was determined for the Medicare and VA patients adjusting for age, gender, race, diabetes, and use of the VA system. The logistic model was used to determine the probability of inpatient costs for those not in the VA or Medicare. For Medicare and VA patients with hospitalizations, we estimated a log-linear regression model of annual hospital costs that included age, race, gender, diabetes, and use of the VA health system. Log costs were transformed to costs using a smearing algorithm.[7] We then multiplied the estimated costs from this model by the probability of having hospital costs to estimate hospital costs for those not in Medicare or the VA system.

Drug costs were determined using the median wholesale price as listed in the 2004 Drug Topics Red Book for the most common dosage of each medication. A dispensing fee of $7.00 was added for each 100 doses.[8] We tabulated the specific antihypertensive medications for participants in each study arm whose blood pressure could not be controlled with first-line therapy with chlorthalidone, amlodipine, or lisinopril, grouped by drug class to estimate their costs: alpha-blocker (cost of doxazosin), beta-blocker (cost of atenolol), calcium antagonist (cost of amlodipine), angiotensin-converting enzyme inhibitor (cost of lisinopril), diuretic (cost of chlorthalidone), clonidine, reserpine, hydralazine, and other antihypertensive agents (mean cost of all listed medications). Medications other than for hypertension were not recorded, except for potassium. The cost of an office visit was determined from Medicare reimbursement for an intermediate intensity follow-up office visit ($50). Cumulative medical costs during the trial were calculated using the product of the yearly cost of care for survivors and the Kaplan–Meier estimate of survival to adjust for censoring.[9] To determine the lifetime cost of care, we assumed that inpatient, outpatient, and drug costs remained constant after year 6 of the trial. We included an additional cost per patient per year to account for the cost of nonhypertension-related care. This value increased with age (range 2,900–4,200) and was based on U.S. national health care expenditure data.[10]

We adjusted all costs to 2004 dollars using the medical component of the Consumer Price Index (Bureau of Labor Statistics). All cost and survival outcomes were discounted at 3% per year.[5]

Cost-effectiveness

We compared the cost of care for the 3 treatment arms. For each analysis, we ranked the strategies by increasing cost and compared the cost-effectiveness between the lowest cost strategy with the strategy that has the next highest cost. Cost-effectiveness was calculated as the difference in cost divided by the difference in LYs by the formula $\mathrm{CE} = \left[\mathrm{Cost}_{\mathrm{DrugA}} - \mathrm{Cost}_{\mathrm{DrugB}}\right] / \left[\mathrm{LY}_{\mathrm{DrugA}} - \mathrm{LY}_{\mathrm{DrugB}}\right]$. A similar analysis was performed using quality-adjusted LYs (QALYs).

To evaluate the uncertainty in the incremental cost-effectiveness ratios, we repeated the analysis on 500 bootstrapped samples.

Sensitivity Analysis. We varied all parameters through the ranges listed in Table 1. A parameter was considered sensitive if the cost-effectiveness ratio doubled above the baseline. Subgroup analyses were done by patient's race (black versus nonblack) and by age groups. In a separate analysis, we assumed that patients with new-onset diabetes had an increased risk of death (RR=2.0)[11–14] and increased annual costs ($2,000 per year) after the trial.[15] Although there is no universally accepted threshold for cost-effectiveness,[5] $50,000 per QALY gained is commonly used.[16] All statistical analyses were performed using STATA version 9, (College Station, TX, USA).

RESULTS

Economic

Within Trial Costs. The cost of drug therapy (Table 2) was lowest for chlorthalidone. Differences in the cost of study drug

Table 2. Cost of Care during ALLHAT and Estimated Lifetime Cost

	Mean cost chlorthalidone	Increase in cost (95%CI) versus chlorthalidone	
		Amlodipine	Lisinopril
In trial			
Drug cost ($)			
Study drug	618	2,681 (2,649, 2,714)	1,383 (1,360, 1,405)
Other antihypertensive drug	1,168	17 (−15, 48)	241 (209, 277)
Total drug cost	1,786	2,698 (2,631, 2,762)	1,624 (1,586, 1,664)
Hospitalization ($)			
Heart failure	368	68 (20, 123)	18 (−34, 71)
Ischemic heart disease	1,876	58 (−95, 216)	87 (−67, 253)
Stroke	240	−3 (−45, 37)	54 (6, 100)
Other cardiovascular	988	1 (−101, 101)	50 (−47, 148)
Cancer	1,069	26 (−67, 113)	225 (130, 307)
Other noncardiovascular	4,063	−320 (−558, −40)	138 (−150, 449)
Total hospitalization cost	8,604	−170 (−535, 235)	572 (150, 1038)
Outpatient visit cost ($)	1,057	−9 (−34, 15)	28 (−3, 57)
Total in trial cost ($)	11,447	2,519 (2,154, 2,934)	2,224 (1,797, 2,692)
Lifetime cost ($)	53,536	4,802 (3,862, 6,092)	3,700 (2,676, 5,000)

Cost of care discounted at 3% per year. Individual costs may not sum to totals as a result of rounding.

treatment accounted for 80% of the differences in total costs. Additional antihypertensive treatment was greatest for patients treated with lisinopril. Although hospitalizations accounted for 80% of follow-up costs, differences between trial arms were small compared to the differences in costs of antihypertensive treatment. Total hospitalization costs were similar for amlodipine and chlorthalidone with amlodipine having higher heart failure costs, but less noncardiovascular hospitalization costs. Total hospital costs were higher for lisinopril than for chlorthalidone-treated patients with significantly higher costs for stroke- and cancer-related hospitalizations. Outpatient visits and their associated costs were nearly identical among arms.

Lifetime Costs

The lifetime discounted cost of care was approximately $53,500 for the patients initially treated with chlorthalidone (Table 2). Costs were $4,800 higher for patients initially treated with amlodipine and $3,700 higher for patients treated with lisinopril. With bootstrap resampling, chlorthalidone-treated patients had the lowest in trial and lifetime costs in all (500 of 500) samples (Figs. 2 and 3).

Survival during the Trial

When compared with the chlorthalidone group, the hazard ratio for total mortality was 0.96 (95%CI=0.89–1.02) for the amlodipine arm and 1.00 (95%CI=0.94–1.08) for the lisinopril arm. Discounted survival was 5.20 years for chlorthalidone patients, slightly less (2 days; 95%CI=10-day loss to 6-day gain) for lisinopril-treated patients, and slightly greater (6 days, 95%CI= 2-day loss to 14-day gain) for amlodipine-treated patients during the initial 6 years of the trial (Table 3).

Lifetime Survival

Survival for the chlorthalidone-treated patients was estimated to be 13.2 years (discounted, Table 4). Amlodipine patients were estimated to live 37 (95%CI=−29 to 95) days longer and lisinopril patients 2 days less (95%CI=67-day loss to 62-day gain) than chlorthalidone-treated patients. During 500 bootstrap samples, survival was greatest for the amlodipine group in 73% of the samples, for the chlorthalidone group in 14%, and for the lisinopril group in 13%.

Quality-adjusted Survival

The mean quality of life value (0–100) over the 6 years of the trial was not significantly different among trial arms (74.3±14 for amlodipine, 74.0±15 for chlorthalidone, and 73.8±15 for lisinopril). After applying the Torrance transformation, the utility value was 0.864±0.12 for the amlodipine group, 0.862± 0.12 for the chlorthalidone group, and 0.861±0.12 for the lisinopril group (p=.36).

Quality-adjusted survival during the 6 years of the trial was 4.51±0.62 years for the amlodipine group, 4.48±0.62 years for

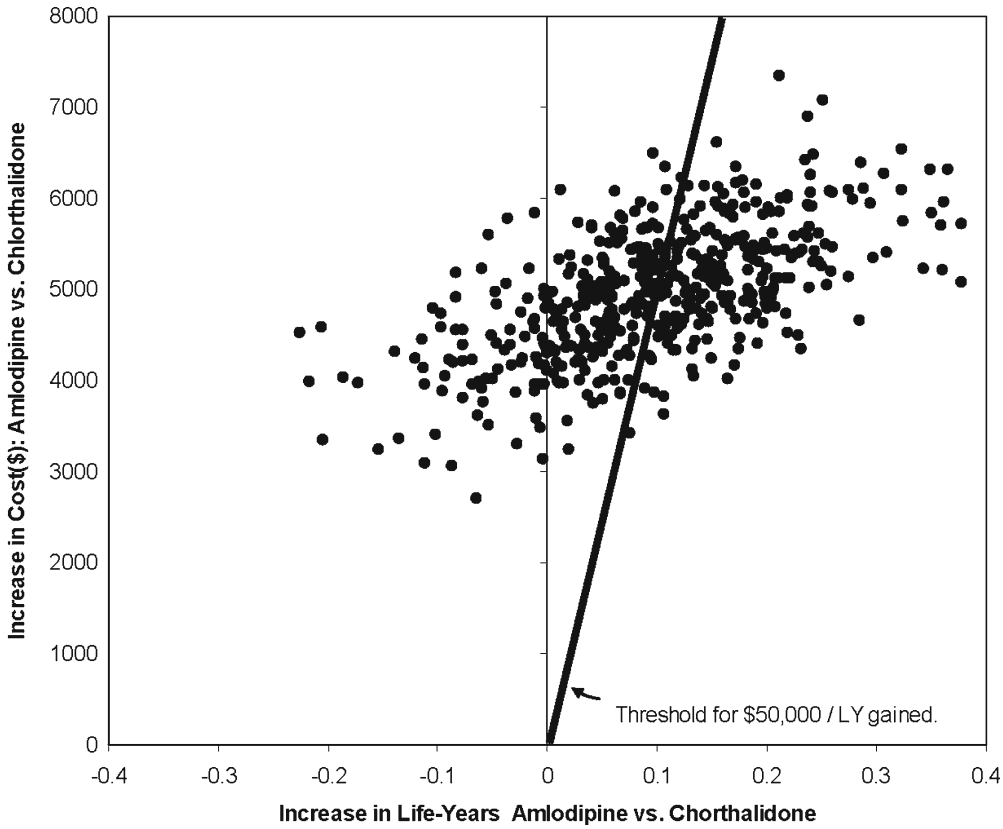

Figure 2. Incremental costs and outcomes of initial treatment with amlodipine versus chlorthalidone for 500 bootstrap samples. Amlodipine was more expensive in all (100%) samples, amlodipine had a better outcome in 84%, and the cost per LY gained was less than $50,000 in 49%. *Points to the right of the diagonal line* indicate samples where amlodipine was cost-effective at a threshold of $50,000 per LY gained.

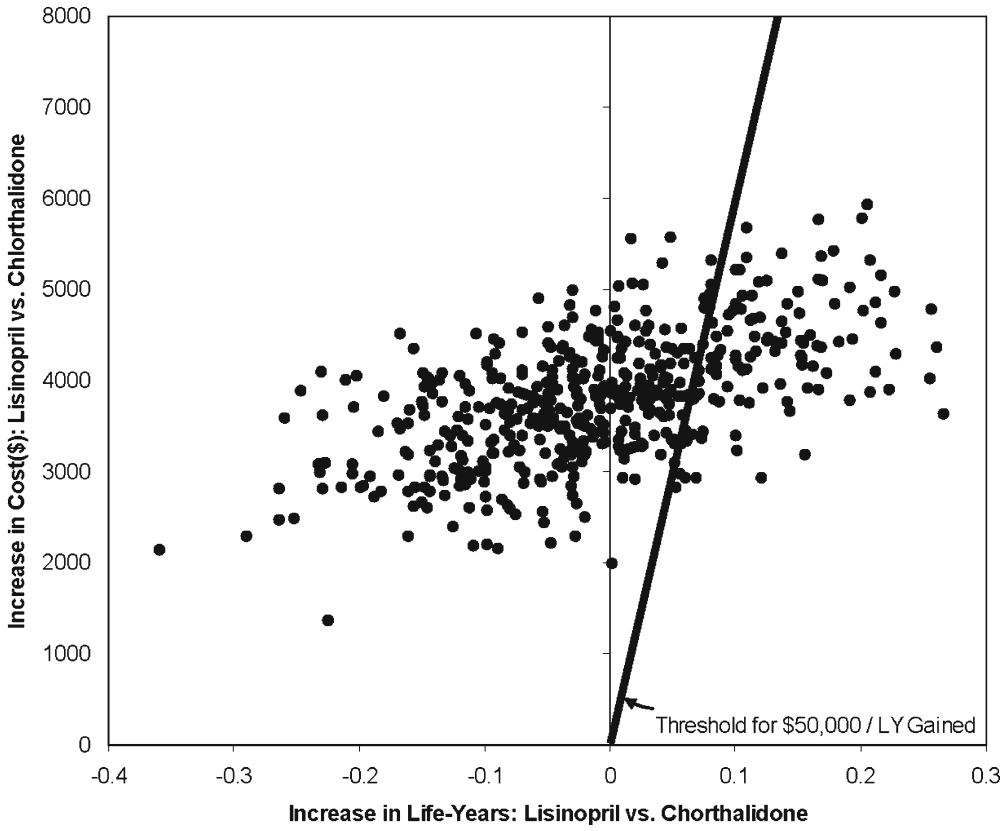

Figure 3. Incremental costs and outcomes for initial treatment with lisinopril versus chlorthalidone for 500 bootstrap samples. Lisinopril was more expensive in all (100%) samples, lisinopril had a better outcome in 45%, and the cost per LY gained was less than $50,000 in 18%. *Points to the right of the diagonal line* indicate samples where lisinopril was cost-effective at a threshold of $50,000 per LY gained.

the chlorthalidone group, and 4.47±0.63 years for the lisinopril group. Lifetime quality-adjusted days of life were slightly but not significantly greater with amlodipine (37 days, 95%CI= −10 to 95 days) and lisinopril (7 days, 95%CI=−47 to 58 days) compared with chlorthalidone.

Incremental Cost-effectiveness

Using the point estimates for differences in cost and survival, lisinopril was less effective and more expensive compared with chlorthalidone both during the trial (Table 3) and over the course of a lifetime (Table 4). With bootstrap resampling, the preferred initial treatment was amlodipine in 50% of lifetime samples, chlorthalidone in 40%, and lisinopril in 10%, assuming that a universal payer is willing to pay $50,000 per LY gained. Amlodipine increased longevity at a cost of $160,000 per LY gained during the trial and $48,400 during the patient's lifetime. When the analysis was limited to those with quality of life data, treatment with amlodipine cost $107,300 to gain a QALY during the trial and $41,700 during the patient's lifetime compared with chlorthalidone.

Sensitivity Analysis

The incremental cost-effectiveness was sensitive to the daily cost of drug therapy. Using online U.S. pharmacy prices ($1.87 for amlodipine, $0.14 for chlorthalidone, and $0.77 for lisinopril), the cost-effectiveness of amlodipine compared with chlorthalidone was $37,000 per LY gained. If amlodipine costs were reduced by 50% with chlorthalidone drug costs unchanged, then the incremental cost-effectiveness of initial treatment with amlodipine compared with chlorthalidone dropped to $58,100 during the first 6 years and to $22,500 over the patient's lifetime. Age-specific analyses indicated no drug preference.

The choice of initial treatment was also sensitive to a universal payer's threshold for cost-effectiveness (Fig. 4). If the threshold is $20,000 per QALY gained, chlorthalidone would be preferred in 74% of samples; by comparison, amlodipine would

Table 3. Six Year (In Trial) Costs and Outcomes for Different First-step Antihypertensive Treatments

Treatment	Cost	Incremental cost	LYs	Incremental LYs	Incremental cost-effectiveness $/LY
Chlorthalidone	11,447		5.200		
Lisinopril	13,671	$2,224	5.195	−0.005	Dominated†
Amlodipine*	13,966	$2,519	5.216	0.016	160,000

Costs and survival are discounted by 3% per year.
**Amlodipine compared with chlorthalidone because lisinopril is eliminated by dominance (chlorthalidone is more effective and less expensive).*
†Costs are greater and effectiveness is less than chlorthalidone.

Table 4. Projected Lifetime Costs and Outcomes for Different First-step Antihypertensive Treatments

Treatment	Cost	Incremental cost	LYs	Incremental LYs	Incremental cost-effectiveness $/LY
Chlorthalidone	$53,536		13.224		
Lisinopril	$57,236	$3,700	13.218	−0.006	Dominated†
Amlodipine*	$58,338	$4,802	13.323	0.099	$48,400

Costs and survival are discounted by 3% per year.
**Amlodipine is compared with chlorthalidone because lisinopril is eliminated by dominance (chlorthalidone is more effective and less expensive.).*
†*Costs are greater and effectiveness is less than chlorthalidone.*

be preferred in 63% of samples if the threshold were $100,000 per QALY gained.

If patients who developed diabetes incurred additional costs ($2,000 per year) and have an increased risk of death (relative risk=2.0) after the conclusion of the trial, the cost-effectiveness of amlodipine compared with chlorthalidone would be $40,200 per LY gained and $35,600 per QALY gained.

When the analysis was limited to nonblack patients, LYs were slightly greater with lisinopril (0.09) compared to initial treatment with chlorthalidone at a cost of $34,600 per LY gained. Amlodipine was dominated by lisinopril in the base-case for nonblack patients. With bootstrap resampling, lisinopril was preferred in 44%, chlorthalidone in 30%, and amlodipine in 25% of bootstrap samples.

For black patients, initial treatment with amlodipine dominated lisinopril and led to 0.14 greater LYs than treatment with chlorthalidone as a cost of $38,000 per LY gained. In bootstrap resampling limited to black patients, amlodipine was preferred in 59%, chlorthalidone in 45%, and lisinopril in 1% of samples.

DISCUSSION

This economic analysis of ALLHAT found, not surprisingly, that the first-step use of chlorthalidone was the least expensive treatment strategy. Differences in total costs among treatments were due primarily to the cost of the study medication and were robust over a wide range of assumptions.

Differences in total mortality tended to favor amlodipine (relative risk=0.96 for amlodipine versus chlorthalidone and 1.00 for lisinopril versus chlorthalidone) but were small and not significantly different.[1] Aside from the statistical issue, are the differences biologically plausible? Amlodipine was favored only for noncardiac mortality (p=.04), and for specific causes, the differences were largest for cancer (3.8 vs 4.3 per 100 over 6 year, p>.05) and violent causes of death (0.4 vs 0.6% over 6 year, p=.005).[1] We know of no clinical or preclinical studies that support the effects of calcium antagonists on these conditions.

These small, statistically insignificant differences nevertheless translated to a point estimate of a 37-day improvement in life expectancy for amlodipine compared with chlorthalidone and a 2-day decrease in life expectancy for lisinopril compared with chlorthalidone. To put these mean differences into perspective, breast cancer screening in women age 50–69 is thought to improve survival on average by 12 days per patient screened.[17]

Although the cost of therapy favored chlorthalidone treatment and our estimated differences in life expectancy among different therapies were small, the optimal initial treatment in terms of cost-effectiveness was unclear. Using a cost-effectiveness threshold of $50,000 per LY gained, amlodipine was optimal in a slight majority of samples (50%) with chlorthalidone optimal in 40% and lisinopril optimal in 10%. Thus, although initial treatment with amlodipine was clearly more expensive than treatment with chlorthalidone, we could not exclude a small mortality benefit that would make amlodipine treatment economically attractive. The uncertainty in the

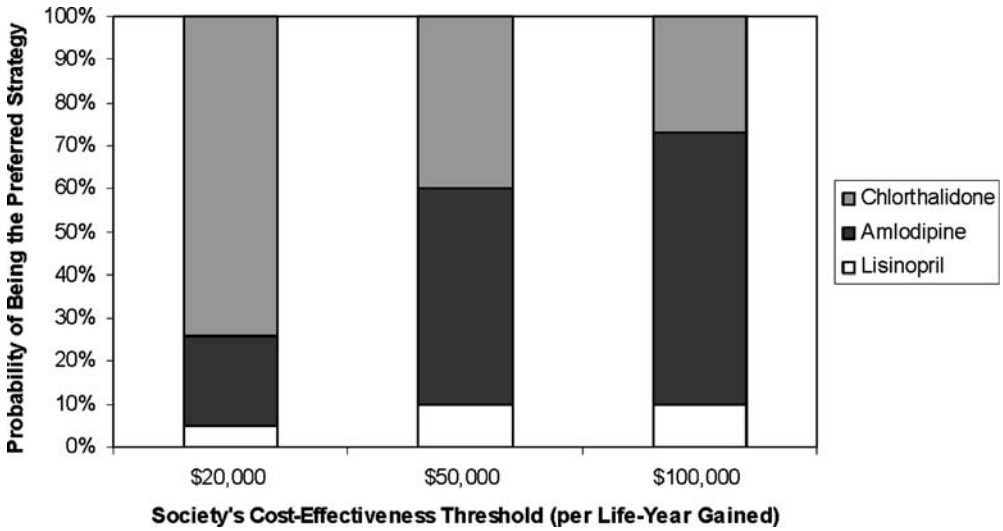

Figure 4. Impact of a universal payer's threshold for cost-effectiveness on the optimal first-step treatment for hypertension based on 100 bootstrap samples. There is substantial uncertainty in the appropriate first-step therapy with no treatment being preferred in over 90% of bootstrap samples.

optimal initial treatment was also observed when black and nonblack patients were examined separately. No treatment was favored in more than more than 60% of bootstrap samples. These data are consistent with an ALLHAT subgroup analysis that showed comparable medication benefits on total mortality for black and nonblack patients.[18]

Our study demonstrates the potential impact of small differences in outcome on the cost-effectiveness of pharmaceuticals. A 1-month gain in survival will be cost-effective at a threshold of $50,000 per LY gained even if lifetime costs are increased by $4,000. Most large randomized trials are powered to detect a moderate (often 5% or so) absolute difference in survival, so substantial uncertainty will remain regarding the optimal, cost-effective treatment when smaller, plausible, but statistically nonsignificant differences are found. We estimate that the ALLHAT would have to enroll at least 99,000 participants to have 80% power to demonstrate that amlodipine was not a cost-effective alternative to chlorthalidone at the $50,000 per LY gained threshold. Conversely, if a trial demonstrates that a new medication significantly improves survival, the medication will almost certainly be cost-effective in the tested population based on the usual, historical prices of new drugs for chronic diseases ($2–3 per day).

Our study found large potential savings from widespread initial treatment with a diuretic. There are at least 30 million patients treated for hypertension in the United States.[19] If initial treatment was chlorthalidone instead of lisinopril or amlodipine in 10% of these patients, costs would be reduced by over $6.4 billion during the first 6 years. Over the course of the patient's lifetime, costs would be reduced by $13.5 billion (10% of 30 million patients at $4,500 decrease in cost per patient with chlorthalidone). The population effect on survival is less certain, but it could result in 300,000 lost LYs based on the point estimate from ALLHAT.

We found only minimal differences in quality of life among the 3 treatment groups, and these differences did not reach statistical significance. These differences had a minor impact on our results given the similarity of our estimates of cost per LY gained with our estimates of cost per QALY gained. One of the limitations of our study was the use of an analog scale to estimate patients' preferences for their state of health. More sophisticated measures that ask patients to trade quality for length of life (time-tradeoff) or that incorporate risk (standard gamble) would have provided a more accurate estimate of patients' preferences,[20] but it is likely that any differences among treatment arms would remain small.

The differences in costs among study arms were due predominately to differences in the cost of the study drug. Although heart failure hospitalizations were more common for amlodipine than chlorthalidone,[1] the absolute differences were small and their associated cost was minor compared to the overall cost of care during the study. The costs of additional antihypertensive medications beyond the randomized first-line drug were similar for chlorthalidone and amlodipine but were greater for lisinopril. The cost of amlodipine relative to chlorthalidone is likely to decrease over time as generic amlodipine becomes available. For large purchasers such as the VA, the daily cost difference between amlodipine ($1.24 for 10 mg) and chlorthalidone ($0.03 for 50 mg) is already only $1.21 compared with the $2.28 daily price differential used in our baseline analysis. At these prices, amlodipine would be more cost-effective, but uncertainty about nonsignificant differences in outcomes would nevertheless cause persistent uncertainty in the cost-effectiveness ratio.

Our study has several limitations. One was the need to impute hospital data for patients who were not in Medicare or the VA system, although this limitation is unlikely to have affected our results substantially given the similarities in observed hospital costs for different study arms. The long-term effects of these medications on costs and health outcomes, such as diabetes induced by chlorthalidone, are unclear.[21] The inclusion of additional costs for the development of diabetes in sensitivity analysis increased the cost of the chlorthalidone arm slightly, but its costs still remained significantly less that the costs of either the amlodipine arm or the lisinopril arm. Finally, we had to estimate the cost of laboratory monitoring. However, these costs were small, and any inaccuracies in our estimates of the costs of laboratory testing are unlikely to affect our findings.

Summary

Substantial savings can be achieved by using chlorthalidone as the first drug for the treatment of hypertension. However, the nonsignificant mortality benefit with amlodipine, if real, could make it economically attractive compared with chlorthalidone. Our study demonstrates that small survival differences may have an important influence on the cost-effectiveness of pharmaceuticals, and even a large trial such as ALLHAT may be underpowered to determine the most cost-effective treatment.

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Conflict of Interest: *Dr. Davis has worked as a consultant for Takeda, Merck, and Glaxo Smith Kline. Dr. Furberg has received honoraria from Berlex and Wyeth and worked on a research grant funded by Glaxo Smith Kline. Dr. Nwachuku is presently employed by AstraZeneca. The other authors report no conflicts.*

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