Cost-Effectiveness of Eplerenone Compared With Placebo in Patients With Myocardial Infarction Complicated by Left Ventricular Dysfunction and Heart Failure

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Background—In the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), aldosterone blockade with eplerenone decreased mortality in patients with left ventricular systolic dysfunction and heart failure after acute myocardial infarction. The present study was performed to evaluate the cost-effectiveness of eplerenone compared with placebo in these patients.

Methods and Results—A total of 6632 patients with left ventricular systolic dysfunction and heart failure after acute myocardial infarction were randomized to eplerenone or placebo and followed up for a mean of 16 months. The coprimary end points were all-cause mortality and the composite of cardiovascular mortality/cardiovascular hospitalization. The evaluation of resource use included hospitalizations, outpatient services, and medications. Eplerenone was priced at the average wholesale price, $3.60 per day. Survival beyond the trial period was estimated from data from the Framingham Heart Study, the Saskatchewan Health database, and the Worcester Heart Attack Registry. The incremental cost-effectiveness of eplerenone in cost per life-year and quality-adjusted life-year gained compared with placebo was estimated. The number of life-years gained with eplerenone was 0.1014 based on Framingham (95% CI, 0.0306 to 0.1740), 0.0636 with Saskatchewan (95% CI, 0.0229 to 0.1038), and 0.1337 with Worcester (95% CI, 0.0438 to 0.2252) data. Cost was $1391 higher over the trial period in the eplerenone arm (95% CI, 656 to 2165) because of drug cost. The incremental cost-effectiveness ratio was $13 718 per life-year gained with Framingham (96.7% under $50 000 per life-year gained), $21 876 with Saskatchewan, and $10 402 with Worcester.

Conclusions—Eplerenone compared with placebo in the treatment of heart failure after acute myocardial infarction is effective in reducing mortality and is cost-effective in increasing years of life by commonly used criteria. **(*Circulation*. 2005;111:1106-1113.)**

Key Words: cost-benefit analysis ■ heart failure ■ myocardial infarction

One of the most serious and frequent consequences of acute myocardial infarction (AMI) is heart failure, which develops in ≈22% of men and 46% of women after an MI.[1] The presence of heart failure in patients with AMI is associated with a 55% greater risk of dying and 2.15-times-greater risk of death or recurrent AMI at 30 days.[2] Patients with AMI who present to the hospital with heart failure have longer hospital stays, higher readmission rates, and higher mortality rates during hospitalization and 6 months after discharge than those without heart failure.[3,4] With estimated direct and indirect health expenditures for heart failure nearing $26 billion annually,[1] cost-effective treatment strategies for this disease are needed.

Multiple therapeutic strategies have been used to prolong life and to decrease hospitalizations for heart failure, including diuretics, ACE inhibitors or angiotensin receptor blockers (ARBs), β-blockers, resynchronization therapy, implantable cardiac defibrillators, and heart transplantation. Additionally, nonselective aldosterone blockade has been shown to reduce mortality in patients with chronic, severe heart failure when used with ACE inhibitors, diuretics, and sometimes digoxin.[5] Recently, the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[6] demonstrated that selective aldosterone blockade with eplerenone significantly reduced mortality and morbidity in patients with left ventricular systolic dysfunction (LVSD) and heart failure after AMI who were receiving optimal medical therapies. This trial was the first to demonstrate incremental benefit of a therapeutic agent in addition to standard

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therapy (including an ACE inhibitor or ARB and a β-blocker) for improving outcomes in patients with heart failure after AMI.

Although its clinical efficacy is clear, the question remains as to whether the added benefit of eplerenone is worth the added cost. This study presents a cost-effectiveness analysis to define the value of the use of eplerenone compared with placebo in patients with heart failure after an AMI.

Methods

EPHESUS Trial Design

EPHESUS, a double-blind, multicenter, randomized, placebo-controlled trial, has previously been described in detail.[6] Briefly, 6632 patients were recruited from December 1999 to December 2001 at 671 centers in 37 countries. Patients were randomized to eplerenone or placebo from 3 to 14 days after AMI. Inclusion criteria included LVSD (documented ejection fraction ≤40%) and heart failure documented by pulmonary rales, venous congestion on chest x-ray, or the presence of a third heart sound. Patients with diabetes were required to have LVSD but were not required to have documentation of heart failure. Patients were randomized to eplerenone (25 mg/d) or placebo for 4 weeks, after which the dosage of eplerenone was increased to a maximum of 50 mg/d. Patients received standard optimal medical therapy, which could include ACE inhibitors or ARBs, diuretics, β-blockers, statin therapy, and coronary reperfusion. The 2 primary end points were time to death resulting from any cause and time to death caused by cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent AMI, stroke, or ventricular arrhythmia. The major secondary end points included death resulting from cardiovascular causes and death resulting from any cause or any hospitalization.

Economic Analysis and Costs

The economic analytic plan of EPHESUS was to compare the costs of the 2 treatment arms and, if the eplerenone arm was more costly and more effective, to perform an incremental cost-effectiveness analysis.[7] Although not all sources of costs could be accounted for, the overall perspective was societal. Costs included in the analysis were direct medical care costs for hospitalizations, outpatient procedures, and drugs.[8,9] No data were available from EPHESUS that could be used to calculate indirect costs resulting from lost productivity. All costs used 2001 as the base year, except the cost of eplerenone, which was not marketed until 2004. Costs and life expectancy differences were discounted 3% annually. The analysis used American unit costs but used resource use information and clinical outcomes for all 6632 patients. Cardiovascular healthcare resource use associated with the index and all follow-up hospitalizations, outpatient diagnostic tests and procedures, and medications were recorded prospectively.

Using a predefined algorithm designed by the investigators from case report form resource use, an investigator blinded to treatment group assigned the initial and subsequent hospitalizations for patients enrolled in EPHESUS to a diagnosis-related group (DRG) as used in the Medicare program in the United States. Costs for each DRG were estimated from average Medicare reimbursement rates obtained from the Medicare Part A data file,[10] and professional costs were calculated by percent share by DRG according to the method of Mitchell et al.[11] An investigator blinded to treatment group coded outpatient procedures by current procedural terminology and assigned a cost based on the Medicare fee schedule. All medications were assigned a cost based on Redbook average wholesale price (AWP).[12] Specifically, the AWP for eplerenone was $3.60. All medications were assumed to continue for the duration of time that each patient was followed up.

Utility was measured with the EQ-5D[13,14] in a subset from English-speaking countries of 1792 patients at baseline, 1530 patients at 6 months, and 1123 patients at 12 months. Quality-adjusted life-years (QALYs) were then calculated by multiplying survival by utility. For patients with a missing utility score, the average utility for all patients with available scores by treatment arm was used to estimate utility. Utility after 12 months was carried forward by use of the 12-month value. Because utility was measured in only a minority of patients, the primary analysis of cost-effectiveness remained cost per life-year gained, with cost per QALY gained as a sensitivity analysis.

Lifetime cost-effectiveness ratios in terms of cost per life-year gained and cost per QALY gained were predicted from in-trial estimates of incremental costs, event rates (death), and estimates of lost life expectancy associated with those in-trial deaths obtained from 3 sources: the Framingham Heart Study,[12,15] the Saskatchewan Health database,[16] and the Worcester Heart Attack Registry.[17,18] These 3 sources were used to estimate survival because no single source perfectly met these criteria. For the Saskatchewan and Worcester databases, data on 2543 and 1094 patients, respectively, with heart failure after an AMI were analyzed with fractional polynomials and piecewise regression to obtain death hazard functions over time.[19] These functions were adjusted according to patient characteristics through the use of separate Cox proportional-hazards models derived from the same data. For patients who died during the trial, life-years lost were obtained by subtracting the in-trial survival times from estimated age- and sex-specific life expectancy estimates.[12] Patients were considered to have 0 life-years lost if they survived during the trial period. Average life-years lost for each treatment group were calculated across all patients who died and survived in each arm of the trial. The difference in average life-years lost because of deaths (placebo minus eplerenone) yields an estimate of the life-years gained with eplerenone. Life-years and QALYs were discounted at 3% annually.[12] The additional healthcare costs attributed to life-years gained by treatment were estimated as a sensitivity analysis.[20] Costs beyond the trial period were estimated by calculating the costs during the trial by year, carrying forward the average cost in years 2 and 3 of the trial, and discounting by 3% annually. Bootstrap methods were used to estimate the fraction of the joint distribution of the cost and effectiveness differences lying in different regions of the cost-effectiveness plane.[21,22]

In addition to applying these methods to the overall population, we also performed these cost-effectiveness analyses for certain demographic subgroups defined by age, sex, diabetes, and prior AMI.

Results

There were no differences in the baseline characteristics of age, gender, prior AMI, diabetes, hypertension, prior history of heart failure, and ejection fraction (Table 1). There was a 15% relative decrease in death from any cause with eplerenone compared with placebo. There was a 13% relative decrease in the other primary end point of death or hospitalization for cardiovascular events and significant decreases in the secondary end points of death from any cause or any hospitalization, sudden death from cardiac causes, and the number of episodes of hospitalization for heart failure. The average follow-up was 16 months.

Healthcare resource use is presented in Table 2. No significant differences were found between eplerenone and placebo for initial or follow-up length of stay, repeated hospitalization, outpatient procedures, or emergency room visits, although point estimates for most favored the eplerenone arm.

Life-years and QALYs lost because of early mortality and gains with eplerenone compared with placebo, both in trial and with long-term extension from Framingham, Saskatchewan, and Worcester, are shown in Table 3. The average survival at 1 year in EPHESUS was 88.2% for the eplerenone group and 86.4% for the placebo group. For Saskatchewan

TABLE 1. Clinical Summary of EPHESUS

	Eplerenone (n=3319)	Placebo (n=3313)	*P*
Baseline characteristics			
Age (mean), y	64.2±11.3	64.7±11.7	0.14
Women, %	28.3	29.6	0.26
Prior MI, %	27.4	26.8	0.52
Diabetes, %	32.3	32.3	0.95
Hypertension, %	59.7	61.2	0.22
History of heart failure, %	14.2	15.2	0.24
Ejection fraction (mean), %	33.1±6.0	33.0±6.1	0.55
Primary end points, %			
Death (any cause)	14.4	16.7	0.008
Death or hospitalization for cardiovascular events	26.7	30.3	0.002
Secondary end points, %			
Death from any cause or any hospitalization	52.1	55.2	0.02
Death from cardiovascular causes	12.3	14.6	0.005

and Worcester, the average survival rates were 70.0% and 79.3%, respectively. Utility with eplerenone and placebo was 0.637 (n=881) and 0.638 (n=911) at baseline, 0.764 (n=759) and 0.763 (n=771) at 6 months, and 0.802 (n=558) and 0.779 (n=565) at 1 year, respectively (all P=NS). With the Framingham database, there were 0.5390 life-years and 0.3940 QALYs lost in the eplerenone arm and 0.6404 life-years and 0.4616 QALYs lost in the placebo arm. There was a significant gain in life-years with eplerenone compared with placebo in trial and based on each of the long-term projections from Framingham, Saskatchewan, and Worcester (Table 3). The gain in QALYs was systematically smaller than the gain in life-years because the utility score was <1.

Costs, the difference in costs, and the 95% CIs are displayed in Table 4. A positive number in the difference column means that treatment with eplerenone is more expensive than placebo; a negative number means that eplerenone treatment is less expensive. No significant differences in costs for the initial hospitalization, repeated hospitalizations, medications other than eplerenone, outpatient procedures, or emergency room visits were observed. The only significant difference found was the cost of the eplerenone at $1513.

TABLE 3. Life-Years and QALYs

	Eplerenone	Placebo	Gain With Eplerenone	95% CL for Gain With Eplerenone
Life-years observed				
In trial	1.33	1.30	0.0304	0.0026, 0.0567
Life-years lost				
Framingham	0.5390	0.6404	0.1014	0.0306, 0.1740
Saskatchewan	0.3103	0.3739	0.0636	0.0229, 0.1038
Worcester	0.6199	0.7536	0.1337	0.0438, 0.2252
QALYs lost				
Framingham	0.3940	0.4616	0.0676	0.0155, 0.1182
Saskatchewan	0.2253	0.2682	0.0429	0.0138, 0.0734
Worcester	0.4528	0.5435	0.0907	0.0231, 0.1580

There were small numerical differences in costs between the treatment groups, overall favoring eplerenone, and thus the increase in cost for the eplerenone arm was $1391 (95% CI, 656 to 2165). Cardiovascular hospitalizations were divided into 3 progressively broader categories: (1) heart failure hospitalizations, (2) narrowly defined cardiovascular hospitalizations using the definition from the clinical study (ie, hospitalizations for heart failure, AMI, ventricular arrhythmia, or stroke), and (3) all cardiovascular hospitalizations (ie, hospitalizations for progression of heart failure, AMI, ventricular arrhythmia, stroke, unstable angina, stable angina, peripheral vascular disease, hypotension, hypertension, atrial flutter/fibrillation, elective cardiovascular surgery, and other cardiovascular events) (Table 5). Overall, there were fewer heart failure hospitalizations and lower costs for heart failure hospitalizations with eplerenone compared with placebo. Similarly, for narrowly defined cardiovascular hospitalizations, there were fewer hospitalizations that were at a lower cost in the eplerenone arm. If all cardiovascular hospitalizations are considered together, there was a trend toward lower costs with eplerenone.

The incremental cost-effectiveness ratio (ICER) of eplerenone compared with placebo in the analysis with Framingham was $13 718 per life-year gained, with 96.7% of estimates falling below the threshold of $50 000 per life-year gained (Table 6). When the Saskatchewan estimates of life expectancy were used, the ICER was $21 876, with 93.8% of estimates under $50 000 per life-year gained. Based on

TABLE 2. Health Resource Use

	Eplerenone (n=3319)	Placebo (n=3313)	95% CL of Difference or *P*
Index hospital stay, days	14.3	14.5	95% CL=−0.5, 0.4
Rehospitalization length of stay, days	9.6	9.9	95% CL=−1.2, 0.5
Mean rehospitalizations per patient, n	0.91	0.96	*P*=0.47
Patients with ≥1 rehospitalization, %	49.0	49.7	*P*=0.54
Mean outpatient procedures per patient, n	1.69	1.70	*P*=0.34
Patients with ≥1 outpatient procedure, %	48.2	47.0	*P*=0.32
Mean ER visits per patient, n	0.30	0.34	*P*=0.10
Patients with ≥1 ER visit, %	18.7	19.7	*P*=0.32

TABLE 4. Cost

	Eplerenone, $	Placebo, $	Δ, $	95% CL of Δ, $
Initial hospitalization	6140	6164	−24	−46, 1
Rehospitalization	8027	8234	−207	−887, 504
Eplerenone	1513	0		
Medication (exclusive of eplerenone)	3346	3291	55	−67, 173
Outpatient procedures	566	532	34	−34, 105
Emergency room visits	43	47	−4	−10, 1
Total follow-up costs	13 494	12 104	1391	656, 2165

Worcester estimates of life expectancy, the ICER was $10 402 per life-year gained, with 98.8% of observations falling below the threshold of $50 000 per life-year gained. The ICERs were systematically higher when calculated in cost per QALY gained. The ICERs were also systematically higher if the costs after the trial period were included. The joint bootstrap distribution of the difference in efficacy in life-years and cost is displayed in Figure 1, with the Framingham estimates for lost life expectancy used. Almost all estimates are in quadrant 1 of the cost-effectiveness plane, meaning that there was greater efficacy at increased cost with eplerenone. The diagonal line from the origin represents $50 000 per life-year gained. Estimates below this line in quadrant 1 or 2 would be cost-effective, if $50 000 represents society's willingness-to-pay threshold.

The relationship between the threshold, or ceiling ratio, and the probability of eplerenone being cost-effective is shown in a cost-effectiveness acceptability curve in Figure 2. Life-years gained were used as the measure of efficacy, with results for Framingham, Saskatchewan, and Worcester presented. At a ceiling ratio of $20 000, eplerenone is cost-effective in >85% of estimates, whereas at a ceiling ratio of $50 000, eplerenone is cost-effective in >90% of estimates.

The differences in costs for subgroups are shown in Figure 3. The subgroups considered were age >65 or <65 years, gender, presence or absence of diabetes, and presence or absence of a prior AMI. The costs, inclusive of the eplerenone cost, tended to be higher in the eplerenone arm and were similarly higher across the subgroups. The ICERs for these subgroups all ranged from $10 000 to $21 000 per life-year saved except for patients with diabetes, for whom the point estimate was $42 160 per life-year saved (Figure 4).

TABLE 5. Costs of CHF Hospitalizations and CV Hospitalizations

	Eplerenone (n=3319)	Placebo (n=3313)	Δ (Eplerenone−Placebo)	95% CL*
CHF hospitalizations				
CHF hospitalizations, n	477	618	−141§	
Patients with ≥1 CHF hosp., n	345	391	−46‖	
Hospital costs, $	762.1	976.7	−214.6	−349.3, −77.5
Physician costs, $	215.3	275.9	−60.6	−101.0, −23.7
Total rehospitalization costs, $	977.4	1252.6	−275.2	−455.0, −111.3
Specified CV hospitalizations†				
CV hospitalizations, n	1194	1297	−103¶	
Patients with ≥1 CV hosp., n	791	795	−4#	
Hospital costs, $	1160.4	1344.6	−184.2	−327.1, −13.3
Physician costs, $	371.2	425.7	−54.5	−103.5, −7.7
Total rehospitalization costs, $	1531.6	1770.3	−238.8	−434.8, −24.6
All CV hospitalizations‡				
CV hospitalizations, n	2505	2650	−145**	
Patients with ≥1 CV hosp., n	1361	1368	−7††	
Hospital costs, $	5470.7	5658.8	−188.1	−704.0, 346.3
Physician costs, $	1679.1	1735.3	−56.2	−201.0, 100.4
Total rehospitalization costs, $	7149.8	7394.1	−244.3	−930.7, 450.4

CHF indicates congestive heart failure; CV, cardiovascular; and hosp., hospitalization.

*Using bootstrap.

†Including heart failure, MI, ventricular arrhythmia, or stroke.

‡Including progression of HF, MI, ventricular arrhythmia, stroke, unstable angina, stable angina, peripheral vascular disease, hypotension, hypertension, atrial flutter/fibrillation, elective surgery cardiovascular, and other cardiovascular events.

§P=0.002.

‖P=0.03.

¶P=0.6782.

#P=0.8757.

**P=0.5512.

††P=0.8132.

TABLE 6. Cost-Effectiveness

	Δ Cost, $	ΔEffectiveness	ICER, $	Dominant, %	Dominated, %	<50 000/LYG, %
No added costs resulting from life-years saved						
Life-years						
Framingham	1391	0.1014	13 718	0	0.30	96.7
Saskatchewan	1391	0.0636	21 876	0	0.02	93.8
Worcester	1391	0.1337	10 402	0.20	0.02	98.8
QALYs						
Framingham	1391	0.0676	20 579	0	0.54	92.5
Saskatchewan	1391	0.0429	32 405	0.20	0.04	81.8
Worcester	1391	0.0907	15 330	0.06	0.36	96.6
Costs resulting from life-years saved included						
Life-years						
Framingham	2136	0.1014	21 072	0	0.22	96.8
Saskatchewan	1929	0.0636	30 349	0	0.04	91.0
Worcester	2323	0.1337	17 374	0	0.26	97.8
QALYs						
Framingham	1992	0.0676	29 469	0	0.50	88.6
Saskatchewan	1858	0.0429	43 301	0	0.10	66.9
Worcester	2152	0.0907	23 724	0	0.50	94.5

LYG indicates life-years gained.

Discussion

This analysis revealed that eplerenone in the setting of heart failure after an acute MI is a life-saving medication that is cost-effective compared with placebo by the common benchmark ceiling ratio of $50 000 per life-year gained. This conclusion was robust throughout a range of projections using 3 different sources for estimates of lost life expectancy resulting from in-trial deaths in a patient population in which the majority received both β-blockers (75%) and ACE inhibitors or ARBs (87%).[6] Furthermore, the bootstrap analysis revealed that with each method of costing, >90% of simulations were below the $50 000 benchmark.

Previous reports from EPHESUS documented improved survival and fewer cardiovascular events in patients experiencing heart failure after an AMI who are treated with eplerenone compared with placebo.[6] The results from EPHESUS complement previous results from the Randomized ALdactone (spironolactone) Evaluation Study for congestive heart failure (RALES), which showed improved survival in patients with severe chronic heart failure who were treated with spironolactone and in whom recent MI was excluded.[5] EPHESUS is the first and only study to demonstrate the efficacy of aldosterone blockade for reducing mortality and morbidity in post-AMI patients with heart failure. It is important to note that eplerenone was effective in preventing

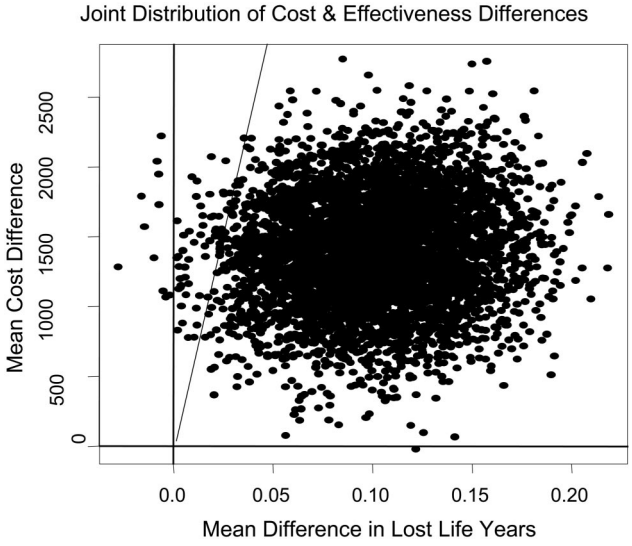

Figure 1. Scatterplot of joint distribution of cost and effectiveness differences in cost-effectiveness plane based on Medicare costs and Framingham life expectancy estimates.

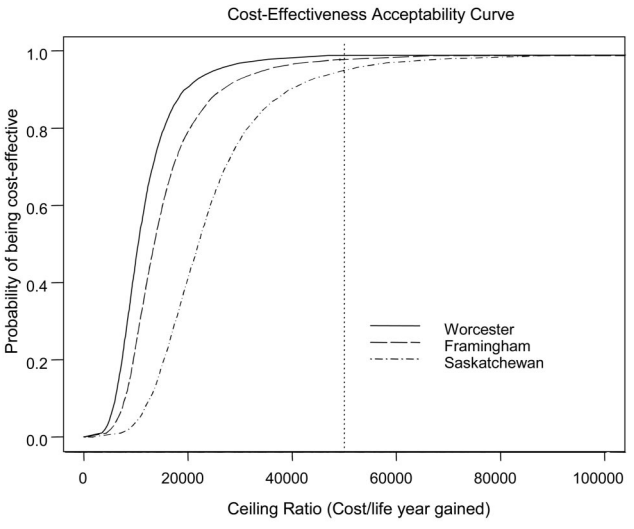

Figure 2. Cost-effectiveness acceptability curves based on Medicare costs and Framingham, Saskatchewan, and Worcester life expectancy estimates.

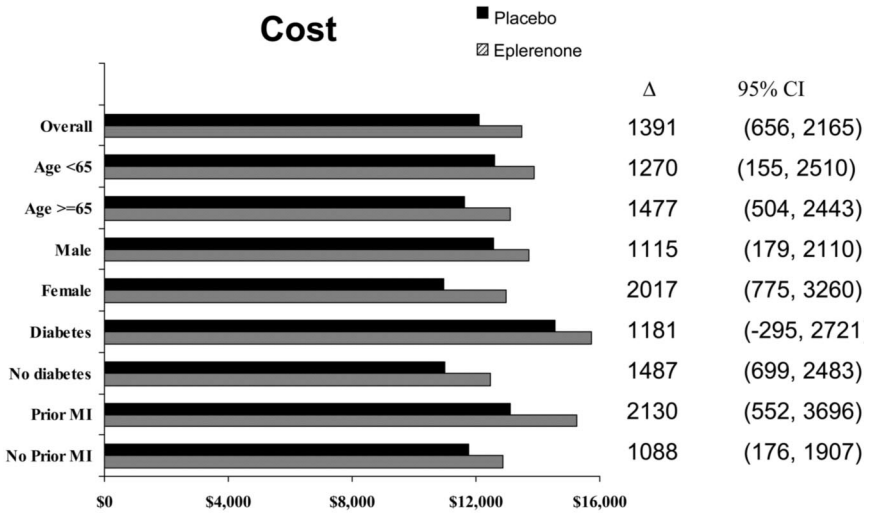

Figure 3. Total costs for subgroups defined according to age, gender, diabetes, prior MI, treatment based on Medicare costs, and Framingham survival estimates.

events in these patients who were already treated optimally with β-blockers and either ACE inhibitors or ARBs and that this is the only agent proven to add incremental benefit on mortality and morbidity above and beyond standard therapy in these patients;[6] β-blockers and ACE inhibitors have been shown to be clinically effective and cost-effective in the treatment of heart failure.[23] The present study reveals that compared with placebo, eplerenone is cost-effective in the treatment of post-MI heart failure in a population of patients already receiving standard therapy.

Study Limitations

The follow-up period in EPHESUS was of variable length (range, 0 to 33 months). Thus, cost-effectiveness was calculated for the average follow-up period of 16 months, with therapy with eplerenone for that period of time but not thereafter. This study does not and realistically cannot address the issue of how long eplerenone should be taken. The estimation of life expectancy assumes that the survival curves remain parallel after the trial period.

The in-trial results cannot give a full picture of the survival advantage of eplerenone. Thus, the estimation of survival was extended beyond the study period by using data from 3 separate sources. However, the degree to which the survival experience of patients from these observational studies yields accurate estimates of life expectancy for the EPHESUS population is uncertain. In both the Saskatchewan and Worcester databases, mortality within 1 year of MI was higher than in EPHESUS. This would mean a shorter projected life expectancy, rendering our results conservative. In

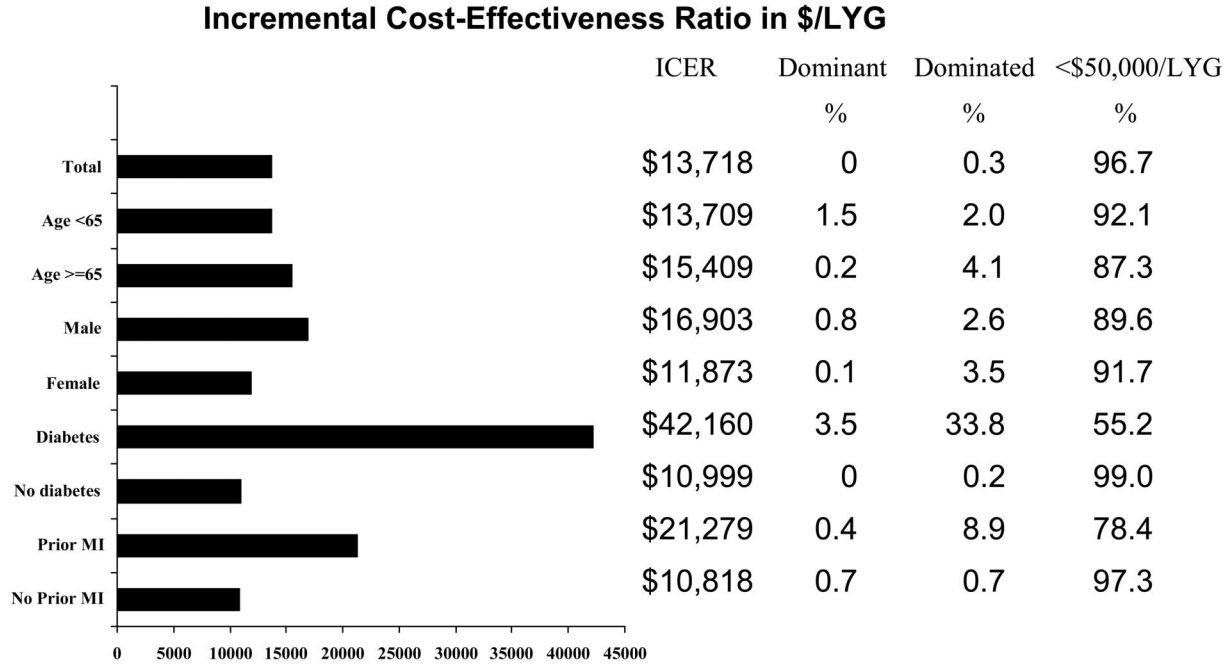

Figure 4. ICERs for subgroups defined according to age, gender, diabetes, and prior MI based on Medicare costs, and Framingham survival estimates. LYG indicates life-years gained.

addition, there was considerable variation between the estimates from these 3 sources, given variations in the populations. The Framingham Heart Study was used because it is a large, well-known, epidemiological database.[15] The Worcester and Saskatchewan databases also were chosen because they included patients similar to those in EPHESUS (ie, post-AMI heart failure patients), and both databases included long-term data.[16–18] Although the Worcester database had the greatest similarity to EPHESUS and the closest estimate of mortality hazard, the ICERs from these 3 databases were all in an acceptable range and provide a sensitivity analysis supporting the cost-effectiveness of eplerenone.

The costing methodology was based on Medicare payments for hospitalization, the Medicare fee schedule for procedures, and AWPs for medications. Eplerenone was priced at the AWP of $3.60 a day. The extent to which these costs reflect resource use from a societal point of view is somewhat uncertain because there is no single source for costs that unequivocally represents societal costs. Thus, Medicare payments may appropriately reflect costs for the Centers for Medicare and Medicaid Services but may not adequately represent resource consumption by hospitals and physicians because Medicare costs tend to be lower than managed care costs. Therefore, the present analysis may provide a conservative representation of the cost-effectiveness of eplerenone.

Costing beyond the trial period was based on projections of costs within the trial period. This approach, while reasonable, is not easily subject to empirical assessment.

Indirect costs were not included, especially those reflecting return to work. To the extent that eplerenone permits return to work by preventing hospitalizations or deaths, this would lower costs in the eplerenone arm, again rendering the results conservative.

Resource use and clinical outcomes were considered trial wide. Use of Medicare costing does not account for possible within-DRG differences in treatment practices and resource use across countries. With so many countries, it is not possible to adequately account for variation in DRGs across countries. Thus, the use of trial-wide data for costing in the United States may not perfectly reflect US resource utilization. In this respect, however, because the primary cause of the cost differential is the eplerenone cost, cost calculations using the unit resource use of other countries should have little effect on the results. The ability to generalize the EPHESUS data to the wider population of patients with post-AMI heart failure is also uncertain. Finally, EPHESUS cannot be used to compare the clinical outcomes or cost-effectiveness of eplerenone to spironolactone. In EPHESUS, eplerenone was compared with placebo; there is no direct comparison of eplerenone to spironolactone, making a comparison of the 2 aldosterone blockers speculative.

The ICER in the subgroup of diabetic patients was higher than in other subgroups analyzed but still under the standard benchmark of $50 000. Diabetics were the only patients in EPHESUS who did not necessarily have to manifest evidence of heart failure to be enrolled in the trial. Approximately one third of EPHESUS subjects were diabetic, and about one third of this diabetic subgroup did not have evidence of heart failure. It is difficult to draw firm conclusions about the higher, but still acceptable, ICER in the relatively small diabetic subgroup compared with the overall trial population.

Eplerenone compares well to other therapies in terms of cost-effectiveness. The ICER for eplerenone is slightly higher than the ICER for clopidogrel in acute coronary syndromes[24,25] but is similar to that of medications such as ACE inhibitors and β-blockers. The ICER for captopril therapy versus no captopril in post-AMI patients 50 to 80 years of age is $3700 to $10 400, depending on age,[26] whereas β-blocker treatment after AMI has an ICER ranging from $360 to $17 000, depending on patient status.[27] Note that in all studies of β-blockers and ACE inhibitors after AMI, the patients were not on an aldosterone blocker, and concomitant standard therapies were different. Higher ICERs have also been noted with life-saving interventions; an ICER of $40 000 was noted in a comparison of an implantable cardiac defibrillator with amiodarone in survivors of cardiac arrest.[28] With ICERs from $10 402 to $21 876 in cost per life-year gained, eplerenone compares well to other therapies in terms of cost-effectiveness and is below the $50 000 threshold used to determine whether society will consider the medication a good value.

Conclusions

The cost-effectiveness of eplerenone compares favorably to that of many other well-known and well-accepted therapies. Eplerenone is the only pharmacological agent proven to add incremental benefit on mortality and morbidity above and beyond standard therapy, including ACE inhibition and β-blockers, in patients with heart failure after AMI. Despite some limitations, EPHESUS provides strong support for both the efficacy and cost-effectiveness of eplerenone compared with placebo in patients with post-MI heart failure. Eplerenone therapy should be considered a cost-effective component of the current armamentarium to improve survival in patients with heart failure after AMI.

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