The management of aldosterone-producing adrenal adenomas—does adrenalectomy increase costs?

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Background. Most experts agree that primary hyperaldosteronism (PHA) caused by an aldosterone-producing adenoma (APA) is best treated by adrenalectomy. From a public health standpoint, the cost of treatment must be considered. We sought to compare the current guideline-based (surgical) strategy with universal pharmacologic management to determine the optimal strategy from a cost perspective.

Methods. A decision analysis was performed using a Markov state transition model comparing the strategies for PHA treatment. Pharmacologic management for all patients with PHA was compared with a strategy of screening for and resecting an aldosterone-producing adenoma. Success rates were determined for treatment outcomes based on a literature review. Medicare reimbursement rates were calculated to estimate costs from a third-party payer perspective.

Results. Screening for and resecting APAs was the least costly strategy in this model. For a reference patient with 41 remaining years of life, the discounted expected cost of the surgical strategy was $27,821. The discounted expected cost of the medical strategy was $34,691. The cost of adrenalectomy would have to increase by 156% to $22,525 from $8,784 for universal pharmacologic therapy to be less costly. Screening for APA is more costly if fewer than 9.6% of PHA patients have resectable APA.

Conclusion. Resection of APAs was the least costly treatment strategy in this decision analysis model. (Surgery 2010;148:1178-85.)

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PRIMARY HYPERALDOSTERONISM (PHA) is characterized by the excessive unregulated secretion of aldosterone by the adrenal glands. There is strong evidence to suggest that PHA accounts for up to 10% of all cases of hypertension, and the financial burden of managing these patients might have greater societal significance than has been appreciated previously.1-3 As such, it is important that clinicians follow evidence-based guidelines to offer the optimal treatment to patients. In 2008, the Endocrine Society published clinical practice guidelines for the treatment of PHA.1 In most cases, PHA is caused by either bilateral adrenal hyperplasia or an aldosterone-producing adenoma (APA) of the adrenal gland. It is important to distinguish between these 2 causes because the treatment differs. To this end, patients undergo cross-sectional imaging of the adrenal glands looking for a tumor and selective venous sampling (SVS) to lateralize the process. The management algorithm calls for medical management of bilateral adrenal hyperplasia and laparoscopic adrenalectomy for unilateral APA. The resection of a unilateral APA is expected to lead to normalization of blood pressure (<140/90 mm Hg) in approximately 50% of patients, as well as the improvement in blood pressure and serum potassium in nearly all patients.1 Although it is evident that medical therapy for bilateral disease is ideal, recently, there has been some controversy over the optimal management of patients with APA. Some clinicians advocate forgoing operative resection even in cases of APA in favor of long-term therapy with oral mineralocorticoid-receptor antagonists for these patients, citing operative cost and potential surgical complications, among other factors.4,5 In this study, we sought to compare the costs of long-term medical management for all patients

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with PHA with the costs associated with following the Endocrine Society Clinical Practice Guidelines which recommend surgical resection for patients with PHA due to aldosteronoma.

MATERIALS AND METHODS

Case definition. The Reference Case recommendations outlined by the Panel on Cost-Effectiveness in Health and Medicine were followed during the construction of a decision-tree model that analyzed the 2 management alternatives for PHA. The reference case scenario was an otherwise healthy 40-year-old woman with PHA who was a candidate for laparoscopic adrenalectomy. The time horizon for the analysis was the patient’s remaining life expectancy. Actuarial Life Tables from the U.S. Department of Social Security were used as a reference for current life expectancy. A literature review was conducted to obtain estimates of the costs, health effects, and probabilities used in the model. Management and follow-up strategies were modeled based on the 2008 the Endocrine Society Clinical Practice Guidelines and expert opinion.

Decision model. Using TreeAge Pro 2009 Suite (Tree Age Software, Williamstown, MA), a Markov state transition model was constructed to compare 2 treatment strategies for APA. The first strategy was to follow the Endocrine Society’s Clinical Practice Guidelines and perform SVS on all surgical candidates with PHA and then perform adrenalectomy on those patients with APA, and to pharmacologically manage those patients with bilateral adrenal hyperplasia. The second strategy was to make no attempt to distinguish between bilateral hyperplasia and APA, forgo SVS, and treat all patients with PHA pharmacologically. For both strategies, the costs of lifelong follow-up and pharmacologic therapy were considered. We modeled 3 possible outcomes for operative treatment, with differing cost, and 2 possible outcomes for medical treatment, with differing cost, for a total of 5 possible outcome arms in a patient with PHA. The surgical outcomes were as follows:

1. Cure of hypertension
2. Improvement in hypertension
3. No improvement in hypertension.

The medical outcomes were as follows:

1. Successful medical management with spironolactone monotherapy;
2. Cross-over from spironolactone to eplerenone;
3. Successful medical management with mineralocorticoid receptor antagonist plus lisinopril.

A summary of the model is shown in Fig 1.

The success rates were estimated for each of the 5 treatment arms based on a review of the literature (Table I). The medical strategies were assumed to be successful in control of hypertension with aldosterone receptor-blocker monotherapy in 48% of cases. Successful control of hypertension was assumed to require an additional antihypertensive agent in 52% of patients. It was assumed that there would be a 1% annual cross-over from spironolactone to eplerenone because of side effects or suboptimal control. Surgical series published during the last 10 years, with a total of 439 patients, were reviewed for cure rates and other event probabilities. Based on this review, normalization of blood pressure was assumed to occur in 48.3% of patients after adrenalectomy. A 4.8% failure rate was also assumed. The remaining 46.9% were assumed to have improved blood pressure but still required a single antihypertensive. Because the literature supports a range of 33–67% for the proportion of PHA patients with APA (versus bilateral adrenal hyperplasia), the rate of unilateral disease was assigned a probability of 50% in this study. This assumption was then modeled in a 2-way sensitivity analysis to account for the wide variation in range. The drugs modeled were the aldosterone receptor antagonists spironolactone and eplerenone, and the angiotensin converting enzyme inhibitor lisinopril. Medication dosing and frequency were kept constant over all strategies.

Cost of treatment. To maintain a third-party payer perspective, Medicare charge and reimbursement data were used to estimate the costs for all health care components, which are reported in 2009 U.S. dollars in Table II. The costs outside the health care system, such as transportation and
lost-productivity costs, were not included in the analysis. Only those costs that differed between the treatment strategies were included. Consumer price index data from the US Bureau of Labor Statistics for health care over a 10-year period were used to compute an inflation rate of 0.041 for future health care costs.\textsuperscript{14} A discount rate of 0.03 was applied to all future costs.

The health care components involved in each treatment arm (physician visits, laboratory and radiologic evaluations, medications, and procedures) were identified, as were the corresponding current procedure terminology (CPT) or diagnosis related group (DRG) codes. The national average Medicare reimbursement rates were then used to estimate the costs for each CPT code.\textsuperscript{14} For hospital costs, a Medicare cost-to-charge ratio was calculated for listed DRGs and multiplied by the national median charge as listed in the Nationwide Inpatient Sample.\textsuperscript{14} The data to calculate anesthesia cost for a laparoscopic adrenal procedure was derived from Medicare and American Society of Anesthesiologists data.\textsuperscript{14} The operative time for this calculation was taken from a 2009 study examining operative characteristics of both laparoscopic transabdominal adrenalectomies and posterior retroperitoneal adrenalectomies.\textsuperscript{15} The medication costs were identified using 2009 average wholesale prices.\textsuperscript{16} The costs were then multiplied by the number of times they would occur within the first year of diagnosis, and then for each subsequent year of required treatment. Table II demonstrates costs of treatment components.

**Threshold analysis.** A threshold analysis was performed on each variable in the reference case to determine how the optimal strategy is affected by changing the value of a single variable across a wide range of possible values.

**Sensitivity analysis.** One-way and 2-way sensitivity analyses were performed to examine the impact of uncertainty of the model’s estimated costs, discount rates, inflation rates, and treatment arm probabilities.

**RESULTS**

**Discounted expected cost.** For a 40-year-old reference patient with 41 remaining years of life, the discounted expected cost of the guidelines strategy was $27,821. The discounted expected cost of the medical strategy was $34,691.

**Sensitivity analyses.** One-way sensitivity and threshold analyses: The model was found to be sensitive to

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<td>Probability of normotension after adrenalectomy</td>
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<td>Probability blood pressure improves but is not normalized after adrenalectomy</td>
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changes in the following variables: cost of adrenalectomy, cost of SVS, probability of surgical failure, probability of unilateral APA, life expectancy, inflation rate for health care, and discount rate.

The sensitivity and threshold analysis demonstrated that the cost of adrenalectomy would have to be $22,524.59 (a 2.5-fold increase over its current value of $8,784.41) for universal pharmacologic treatment to become the least costly strategy. These results are shown in Fig 2. The cost of SVS would have to be $9,040.87 (a 4.2-fold increase over its current cost of $2,171) for pharmacologic therapy to become the least costly strategy. The 1-way sensitivity analysis and threshold value is shown in Fig 3. If the health care inflation rate falls below 1% (a 75% drop from its current rate of 4.1%) and be maintained at or below that level, then universal pharmacologic management would be less costly. If more than 32% of patients fail to have an improvement in blood pressure after adrenalectomy (a 6.6-fold increase in surgical failure rate), then the pharmacologic therapy strategy would be less costly. This 1-way sensitivity analysis is shown in Fig 4. If the probability of unilateral APA were less than 9.6%, then universal pharmacologic management would be less costly. If a discount rate of 6% or higher is applied to future costs (current rate 3%), then the pharmacologic treatment strategy becomes less costly.

The conclusions of the reference case scenario were not sensitive to changes in the cost of drugs used, cost of yearly follow-up and monitoring, probability of surgical cure, probability of need for multidrug antihypertensive therapy, or the probability of needing to convert from spironolactone to eplerenone.

**Life expectancy.** Based on the variables used in the reference case scenario, the universal pharmacologic therapy strategy was the least costly treatment strategy for life expectancies of 1 year to 25.4 years. The Endocrine Society guideline strategy was optimal for life expectancies of 25.4–80 years.

**Two-way sensitivity analyses.** The life expectancy threshold was evaluated in 2-way sensitivity analysis against the annual cost of spironolactone, the probability of unilateral AHA, the probability of surgical cure, and the cost of annual monitoring.

The model assumed a daily spironolactone dose of 50 mg with an annual wholesale cost of $219. If the dose (and cost) of spironolactone is doubled in the reference case scenario, then the discounted expected cost of the guidelines strategy becomes $32,674, and the discounted expected cost of the medical strategy becomes $44,082. The
pharmacologic strategy becomes less costly for life expectancies of 19.5 years or less. If the cost of spironolactone is quadrupled (200-mg daily dose), then the pharmacologic strategy is less costly only for life expectancies of 12 years or less. The 2-way sensitivity analysis is shown graphically in Fig 5.

The model assumed a probability of 50% that PHA would be the result of a resectable unilateral APA. If that probability is set to 67%, the discounted expected cost of the guidelines strategy becomes $24,928 and the discounted expected cost of the pharmacologic strategy becomes $34,691. At life expectancies of 24.8 years or more, the guidelines strategy is less costly. If the probability of unilateral disease is set to 33%, then the discounted expected cost of the guidelines strategy becomes $30,714, and the discounted expected cost of the pharmacologic strategy remains $34,691. At life expectancies of 28.6 years or more, the guidelines strategy is less costly.

The model assumed a probability of surgical cure of APA (normotensive without medications) of 48%. Contemporary series report a cure rate of 35–80%. If the probability of surgical cure is set to 35%, then the discounted expected cost of the guidelines strategy becomes $30,714, and the discounted expected cost of the pharmacologic strategy remains $34,691. At life expectancies of 28.6 years or more, the guidelines strategy is less costly.

Our model also assumed that medical treatment of PHA would be successful with aldosterone-receptor monotherapy in 48% of patients. If a greater number of patients require multidrug...
therapy, then the costs for pharmacologic therapy would increase. If 80% of patients required multi-drug therapy in this model (spironolactone and lisinopril), then the discounted expected cost of the guidelines strategy becomes $28,630, and the discounted expected cost of the pharmacologic strategy becomes $35,555. At life expectancies of 26.3 years or more, the guidelines strategy is less costly.

DISCUSSION

This study demonstrates that the management strategy, as described previously and modeled after the Endocrine Society guidelines, is the dominant strategy from a cost perspective for a PHA patient who has a remaining life expectancy of 25.4 years or more. In other words, a treatment plan that screens PHA patients for APA and treats them selectively by adrenalectomy is the least costly treatment plan for a population of patients with PHA. The conclusions of the model were sensitive to changes in the cost of adrenalectomy, cost of SVS, probability of surgical failure, probability of unilateral APA, health care inflation rate, and discount rate.

A sensitivity analysis revealed that in this model the cost of adrenalectomy would have to increase by 2.5 fold to $22,524.59 for the current guideline-based monitoring strategy to cost more than universal pharmacologic management of PHA. Likewise, if the cost of SVS increased by 4.2 fold to $9,040.87, or if there was a 6.6-fold increase in the surgical failure rate to 32%, then universal pharmacologic therapy would be less costly.

Surprisingly, altering the probability of unilateral disease, probability of surgical cure, cost of annual follow-up, and cost of spironolactone did not substantially change the conclusions of the model in 1-way or 2-way sensitivity analyses. Increasing the cost of spironolactone had the most impact on the time horizon required for pharmacologic therapy to become more costly. Daily doses of spironolactone up to 200 mg have been found to be effective in PHA; therefore, the doses of 50, 100, and 200 mg were modeled in a 2-way sensitivity analysis. The results show that as the dose and cost of spironolactone increases, the threshold for remaining life expectancy falls from 25.4 to 12 years.

Our model also assumed that the medical treatment of PHA would be successful with aldosterone-receptor antagonist monotherapy in 48% of patients. Altering this probability in a 1-way sensitivity analysis had no impact on the conclusions.

Our analysis was done from a third-party payer perspective and, therefore, does not take into account the costs to society or the individual, such as costs from lost productivity, transportation, and lost

Fig 4. One-way sensitivity analysis on the probability that adrenalectomy fails to improve hypertension (surgical failure). In the reference case scenario, the pharmacologic treatment strategy was less costly if there was a 6.6-fold increase in the surgical failure rate from 4.8% to 32%.
ventricular mass and hypertrophy parameters.22

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life expectancy, one of the following unlikely sce-

strategy for patients with an approximately 40-year

tients with APA can be managed medically, to make

if these cardiovascular costs, complications, and

PHA would remain optimal from a cost perspective

cost of treating these cardiovascular events and com-

This model did not take into account the additional

income. Additionally, treatment effects were not

considered in this study; therefore, cost effectiveness

could not be evaluated. Patients with PHA have an

increased risk of cardiovascular disease and death

when compared with similar patients with non-PHA

hypertension. This holds true even when the degree

of blood pressure elevation is similar.17,18 Hyperaldo-

steronism has also been shown to affect adversely left

ventricular relative wall thickness and diastolic func-

tion, as well as caroid intimal-medial thickness.19-22

Patients with PHA have a higher rate of stroke

(12.9% vs 3.4% in those with essential hypertension),

myocardial infarction (4% vs 0.6%), and atrial fibril-

lation (7.3% vs 0.6%), and this increased risk is abro-

gated by appropriate treatment.17 Surgical treatment

normalizes plasma aldosterone and improves left

ventricular mass and hypertrophy parameters.22

This model did not take into account the additional

cost of treating these cardiovascular events and com-
plications. It is likely that the surgical treatment of

PHA would remain optimal from a cost perspective

if these cardiovascular costs, complications, and

other benefits were considered in the model.

Although it has been suggested that most pa-

tients with APA can be managed medically, to make

universal pharmacologic therapy the less costly

strategy for patients with an approximately 40-year

life expectancy, one of the following unlikely sce-
narios would need to occur: 1) the probability of

finding a unilateral APA would have to be less than

10%; 2) the cost of operative treatment would need

to more than double; 3) the cost of SVS would need

to more than quadruple; or 4) the surgical failure

rate would need to more than sextuple. The con-

clusions from the model were insensitive to changes

in the other cost and probability variables.

REFERENCES

1. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Man-
tero F, Stowasser M, et al. Case detection, diagnosis, and

treatment of patients with primary aldosteronism: an endo-

crine society clinical practice guideline. J Clin Endocrinol

Metab 2008;93:3266-81.

2. Plouin PF, Amar L, Chatellier G. Trends in the prevalence

of primary aldosteronism, aldosterone-producing adено-

mas, and surgically correctable aldosterone-dependent


et al. A prospective study of the prevalence of primary aldo-

steronism in 1,125 hypertensive patients. J Am Coll Cardiol

2006;48:2293-300.

4. Lim PO, Young WF, MacDonald TM. A review of the medical


5. Spence JD. Diagnosis of primary aldosteronism: for medical

management, not just surgery. J Hypertens 2009;27:204-5;

author reply 205.


York: Oxford University Press; 1996.

7. United States Department of Social Security SSo. Period life


8. Lim PO, Jung RT, MacDonald TM. Raised aldosterone to renin

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in the other cost and probability variables.

Fig 5. Two-way sensitivity analysis on the annual cost of

medical therapy and life expectancy. As the cost of spiro-

nolactone therapy increases, the treatment time required

for pharmacologic therapy to be more costly is reduced

from 25.4 years for a 50-mg daily dose ($219 annual

cost), to 12 years at a 200-mg daily dose ($876 annual

cost).

DISCUSSION

Dr Michael J. Demeure (Scottsdale, AZ): I will first ask you what your discount rate was, because, as you look at your costs, the deferred costs are in future dollars. So, did you subject the discount rate to your sensitivity analysis? And would you tell us how the cost of medical care was affected?

Dr BethAnn Reimel (New York, NY): Our discount rate was 3%, which is a fairly standard discount rate. We did subject it to a sensitivity analysis, and it had normal variation that would not affect the outcome of the model. Basically, you would have to have a doubling of our discount rate—it would have to rise to 6%—in order for it to change our model's outcome.

Dr Michael J. Demeure (Scottsdale, AZ): We know that the cost of health care is going up more than 6%. So, that is perhaps a cautionary number.

Dr BethAnn Reimel (New York, NY): It is a doubling of the discount rate, though, going from 3% to 6%, which would be a 100% increase. So, a 100% increase in the discount rate would be needed to alter the model's outcome.