Cost-Effectiveness of Screening for Primary Aldosteronism and Subtype Diagnosis in the Resistant Hypertensive Patients

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Background—Primary aldosteronism (PA) is a common and underdiagnosed disease with significant morbidity potentially cured by surgery. We aim to assess if the long-term cardiovascular benefits of identifying and treating surgically correctable PA outweigh the upfront increased costs in patients at the time patients are diagnosed with resistant hypertension (RH). Methods and Results—A decision-analytic model compares aggregate costs and systolic blood pressure changes of 6 recommended or implemented diagnostic strategies for PA in a simulated population of at-risk RH patients. We also evaluate a 7th “treat all” strategy wherein all patients with RH are treated with a mineralocorticoid-receptor antagonist without further testing at RH diagnosis. Changes in systolic blood pressure are subsequently converted into gains in quality-adjusted life years (QALYs) by applying National Health and Nutrition Examination Survey data on concomitant risk factors to an existing cardiovascular disease simulation model. QALYs and lifetime costs were then used to calculate incremental cost-effectiveness ratios for the competing strategies. The incremental cost-effectiveness ratio for the strategy of computerized tomography (CT) followed by adrenal venous sampling (AVS) was $82 000/QALY compared with treat all. Incremental cost-effectiveness ratios for CT alone and AVS alone were $200 000/QALY and $492 000/QALY; the other strategies were more costly and less effective. Integrating differential patient-reported health-related quality of life adjustments for patients with PA, and incremental cost-effectiveness ratios for screening patients with CT followed by AVS, CT alone, and AVS alone were $52 000/QALY, $114 000/QALY, and $269 000/QALY gained. Conclusions—CT scanning followed by AVS was a cost-effective strategy to screen for PA among patients with RH. (Circ Cardiovasc Qual Outcomes. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.115.002002.)

Key Words: blood pressure ■ cost-effectiveness ■ hyperaldosteronism ■ hypertension ■ mineralocorticoids

Hypertension (Table I in the Data Supplement) affects 76 million Americans and is the leading cause of heart disease, stroke, and death.1 Prevalence of resistant hypertension (RH) is estimated between 12% and 30% of the hypertensive population.2,4 The Joint National Committee suggests referral to a hypertension specialist in this subset of patients, although practice recommendations for the screening and diagnosis of secondary causes of hypertension vary.2,5,6

Primary aldosteronism (PA) is the most common cause of secondary hypertension and is characterized by autonomous, inappropriately elevated plasma aldosterone, stemming from an aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). Because hypertension—frequently the only sign of PA—is so common, the diagnosis of PA is often overlooked.5 The prevalence of PA in the hypertensive population is estimated to be 10% in recent studies, with nearly half being unilateral (ie, surgically correctable) disease.5,8 Patients with PA make up 17% to 23% of patients with RH and have worse outcomes.9–12 In comparison with primary hypertensive patients matched for blood pressure, patients with both subtypes of PA have 4 times the risk of stroke, 7 times the risk of nonfatal heart attack, and 7 to 12 times the risk of atrial fibrillation.11,13 Moreover, patients with PA have worse psychosocial and quality of life scores when compared with matched patients with primary hypertension.14–16

Adrenalectomy for APA (ie, unilateral PA) is effective and is shown to reverse cardiovascular and renal complications.13,15–19 However, there are costs and different levels of efficiency associated with the various screening strategies used to determine who is most likely to benefit from surgical
WHAT IS KNOWN

- Primary hyperaldosteronism is the most common cause of secondary hypertension and makes up ≈20% of the resistant hypertensive population.
- Patients with primary hyperaldosteronism have worse cardiovascular outcomes compared with matched patients with primary hypertension.
- Adrenalectomy is an effective treatment for primary hyperaldosteronism in ≈50% of patients.

WHAT THE STUDY ADDS

- At an accepted willingness-to-pay threshold, screening for primary hyperaldosteronism in the resistant hypertensive population is cost-effective in comparison with medical treatment alone.
- Computerized tomography followed by confirmatory adrenal venous sampling is the optimal screening strategy for identifying patients with surgically correctable (ie, unilateral) adrenal disease.

intervention. Furthermore, even small changes in blood pressure have been shown to have significant downstream effects on cardiovascular events. Treatment with mineralocorticoid-receptor antagonists (MRAs) also yields significant improvements in blood pressure and regression of left ventricular hypertrophy in all PA subtypes.

We hypothesize that it is cost-effective to screen the resistant hypertensive population for PA, which is known to have a high proportion of patients with PA. Specifically, we postulate that the improvements in blood pressure and consequent reductions in downstream cardiovascular events, in addition to improvements in quality of life resulting from appropriate treatment of patients with PA, outweigh the upfront cost to establishing a PA diagnosis and initiating disease-specific medical treatment or surgery when appropriate. In this analysis, we use a decision-analytic approach to compare recommended strategies and strategies commonly used in practice for PA screening and identification of patients with surgically correctable disease in the RH population versus treating all patients with MRAs.

Methods

Model Structure

A decision-analytic model (Figure 1) was used to compare the aggregate intervention costs and effectiveness associated with 6 screening strategies that are both diagnostic (ie, to distinguish primary hyperaldosteronism from primary hypertension) and help with lateralization (ie, to distinguish surgically correctable APA from BAH in those with positive blood tests) in a simulated cohort of patients with RH. As a clearly superior strategy has not been proven, we chose to perform a comprehensive analysis including many recommended strategies and commonly used algorithms in practice.

We considered 6 screening strategies (Table 1) to identify those patients with unilateral, surgically correctable hyperaldosteronism (ie, APA). All of these strategies begin with an aldosterone to renin ratio (ARR); patients with a negative ARR are started on a MRA. After a positive ARR, patients received one of the following testing options: (1) Confirmatory saline-infusion test (SIT), abdominal computerized tomography (CT), and adrenal venous sampling (AVS) (strategy SIT/CT/AVS), (2) CT and AVS (CT/AVS), (3) SIT and AVS (SIT/AVS), (4) AVS only, (5) SIT and CT (SIT/CT), or (6) CT only. A seventh strategy included upfront treatment with an MRA in all RH patients without further testing. Spironolactone was chosen as the base-case MRA as it is the least costly yet still effective medication against which to compare potential surgical strategies. We aimed to assess the consequences of immediate action at RH diagnosis as it has been shown that length of time with PA is correlated with failure of cure. Therefore, a strategy of medical trial followed by surgery was not considered.

On the basis of the best available published evidence (Table 2 and Table II in the Data Supplement), we assumed that patients with surgically treated APA would obtain an additional 10 mm Hg reduction in systolic blood pressure (SBP) compared with PA patients treated with MRA. In strategy MRA only, all patients with RH were treated upfront with MRA without ARR screening as it has been shown that primary hypertensive patients also respond, albeit to a lesser extent, to MRA therapy. All patients in all other strategies who had a negative ARR, negative CT (ie, no nodules found in either adrenal), or who underwent unsuccessful surgery (ie, those with BAH or primary hyperaldosteronism undergoing surgery) were given MRA therapy with resultant decreases in blood pressure at varying levels predicted by the true underlying RH cause (ie, patients with primary hypertension would have a reduction in SBP of 10 mm Hg, and those with PA would have a reduction of 20 mm Hg).

For the intervention decision tree, the clinical starting point was a patient with RH. For the primary analysis, we made several important assumptions: (1) patients were all considered surgical candidates; (2) patients diagnosed with unilateral APA (appropriately or inappropriately) all underwent laparoscopic adrenalectomy; (3) false-positive rates (ie, falsely determined to be PA) of CT results for RH patients with primary hypertension were reflective of prevalence of incidental adrenal nodules in the population; (4) if abdominal CT indicated an abnormality on both sides, patients either proceeded to AVS and surgery if AVS lateralized to 1 adrenal gland (strategies SIT/CT/AVS and CT/AVS), or in CT-only strategies (strategies SIT/CT and CT only) patients were treated with MRA; and (5) if CT did not show abnormalities in either adrenal gland, in CT only strategies (strategies SIT/CT and CT only) patients were treated with MRA.

TreeAge Pro 2014 (TreeAge Software, Williamstown, MA) was used to construct and analyze the intervention model. The change in SBP, change in the number of antihypertensive medications after treatment (estimates obtained from the literature), and differential projected annual costs of antihypertensive regimens were calculated for each strategy in the immediate intervention model.

Costs

The analysis was performed from a healthcare system perspective. Best available cost and probability estimates were extracted from the literature (Table 2 and Table II in the Data Supplement). The costs of screening, surgery, complications, and medications were included in the analysis, but nonhealthcare-related costs to the patient were not.

Quality-Adjusted Life Years and Lifetime Costs

Changes in SBP and cost of antihypertensive medications per strategy from the decision tree model were subsequently converted into gains in quality-adjusted life years (QALYs) and changes in lifetime cardiovascular disease (CVD) costs using a previously developed and validated CVD model, which is able to evaluate the long-term cardiovascular, costs, events, and mortality for each change in blood pressure reduction. The reductions in blood pressure and costs associated with each intervention strategy were applied to a National Health and Nutrition Examination Survey (NHANES) population with additional risk factor data to project CVD events.

From 40,790 patients available in the continuous NHANES database from 2005 to 2012, a cohort of 836 patients was selected according to the following criteria: (1) patients with SBP ≥160 mm Hg (presumed RH) and (2) patients with available data on cardiovascular risk factors required to assess 10-year Framingham risk score. These patients were sampled with replacement to create the simulation.
cohort (100,000 patients) and entered into the CVD Markov model (Figure I in the Data Supplement) with microsimulation to assess comparative discounted lifetime costs and QALYs (ie, incremental cost-effectiveness ratios, ICERs). Briefly, each year, patients had a probability of developing CVD (ie, coronary heart disease, stroke, or CVD-related death) based on Framingham risk function and a probability of death from other causes based on age and sex-based life tables (Table III in the Data Supplement). Differential annual costs of antihypertensive regimens for the years after the initial intervention were calculated for each strategy and factored into the CVD model (details are available in Methods section and Table II in the Data Supplement).

In the base case analysis, we consider only CVD effects on health-related quality-of-life (HRQoL). Utility weights for baseline primary hypertensive patients and downstream health states within the CVD model were based on a broad national sample of community-based, patient-reported EQ-5D utility scores associated with chronic diseases. We also performed an alternative analysis that incorporated a possible utility reduction owing to untreated PA. Prior data suggest that patients with PA have worse quality of life scores when compared with patients with primary hypertension. We derived estimates of utility weights (ie, measure of HRQoL) from longitudinal survey data using the Short Form-12v1 in a cohort of patients before and after treatment with adrenalectomy or MRA. Data were catalogued and translated into interval scale utilities (0 = dead to 1 = perfect health) using the QualityMetric health state score system, SF6D, for integration of a change of utility into the CVD model. The study was approved by the institutional review board and subjects gave informed consent. For the purposes of this study, median differences after treatment between surgically treated PA patients were used to adjust the base utility for each intervention strategy for the CVD model.

QALYs and lifetime CVD costs from the simulation model and per-patient diagnostic and treatment costs from the decision tree model were then used to calculate ICERS (cost per QALY) for the 7 competing strategies. Future costs and QALYs were discounted at 3% per annum. A willingness-to-pay (WTP) threshold of $US 150,000/QALY gained was used as a benchmark for cost-effectiveness, following the American College of Cardiology/American Heart Association position paper on integration of cost-effective data into clinical practice.

Sensitivity Analysis
We performed univariate sensitivity analyses on all variables to assess effects of varying key model parameters on our results (Table 2 and Figures II–VI in the Data Supplement). Given recommendations for utilization of CT for surgical planning and to assess for potential malignancy, we also tested the additional cost of the CT (with all patients still undergoing AVS regardless of the CT results) in the AVS-only strategies (SIT/AVS and AVS only). Probabilistic sensitivity analysis was performed to assess the effects of parameter estimate uncertainty.

Results
Costs and outcomes by strategy are shown in Table 3. Of the strategies evaluated, proceeding directly to AVS only yielded...
the greatest SBP reduction (12.49 mm Hg) and cost. Treating all patients with MRA was the least costly—given no further testing or surgery—but with the lowest SBP reduction. Using preliminary patient-reported survey data to measure the effects of treatment on HRQoL in patients with PA, we found a greater improvement with surgery when compared with MRA. A median utility decrement of 0.054 (IQR, 0.0–0.079) was found for those with PA treated medically versus surgically. Moreover, the strategies that resulted in more patients with true surgically correctable PA being treated with surgery...
also had a greater increase in quality of life (ie, AVS only strategy).

The 836 patients from the NHANES database had a mean age of 67.6 years, were 58.0% female, and had an initial mean SBP of 175 mm Hg. After entering intervention costs and changes in SBP into the CVD model, we found that none of the strategies with confirmatory SIT were cost-effective (ie, all were dominated). CT/AVS, CT only, and AVS only strategies all resulted in gains in life expectancy compared with treating all patients with MRA (ie, on the efficiency frontier) at an increased cost. At US WTP threshold of $150,000/QALY and without adjustments in HRQoL for patients with surgically untreated PA, CT/AVS strategy is the cost-effective choice with an ICER of $82,000/QALY (Figure 2). After integrating conservative HRQoL reductions for PA patients treated with MRAs alone, CT only strategy (with an ICER of $114,000/QALY) would be the cost-effective choice at this WTP threshold (Figure 3).

The proportion of patients undergoing surgery by underlying disease is shown in Table IV in the Data Supplement. Using the CT/AVS strategy, the preferred strategy at the WTP threshold of $150,000/QALY, 50% of patients with true unilateral PA are treated appropriately with adrenalectomy with a surgical mortality of <0.1%. At the same time, potentially ineffective surgery would occur in 0.1% of patients (ie, patients with BAH or primary hypertension). Surgical mortality in BAH and primary hypertension patients undergoing surgery nears zero.

**Sensitivity Analysis**

The same 4 strategies remain on the efficiency frontier over a wide-range of sensitivity analyses (Table 2), specifically through a wide range of prevalence of PA in the RH population (Figure II in the Data Supplement), prevalence of adrenal incidentalomas, and testing characteristics of screening ARR (Figures III and IV in the Data Supplement). When the prevalence of unilateral PA (APA) increased above 50%, strategy CT/AVS fell off the efficiency frontier. There was no effect on results for sensitivity of screening ARR and confirmatory testing. When the sensitivity and specificity of CT or AVS were diminished or costs of the tests changed significantly, competing strategies became more desirable. However, within reported ranges, our results were consistent. The efficiency frontier remained the same with the additional cost of the CT for surgical planning. Some patients require higher doses of MRA to attain improvement in blood pressure. No significant changes in the efficiency frontier were seen with increasing the cost of this medication (Figure V in the Data Supplement).

Efficient strategies are dependent on treatment effect, with the key parameters being the SBP change with MRA in Table 3.

<p>| Table 3. Aggregate Intervention Costs, Average Change From Baseline in Systolic Blood Pressure, Average Number of Antihypertensive Medications, and Health-Related Quality of Life Measurement Per Strategy* |</p>
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cause</th>
<th>Intervention Cost ($)</th>
<th>ΔSBP</th>
<th>ΔMED</th>
<th>ΔQALYs*</th>
<th>Discounted Cost ($)</th>
<th>Discounted QALYs†</th>
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<tr>
<td>SIT/CT/AVS</td>
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<td>1064</td>
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<td>−1.04</td>
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<td>AVS only</td>
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<td>11,5615</td>
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ΔSBP and ΔMED per strategy from the decision tree model were converted into aggregate lifetime discounted costs and QALYs using the cardiovascular disease model. ΔMED indicates average number of antihypertensive medications; ΔQALY, health-related quality of life measurement; ΔSBP, average change from baseline in systolic blood pressure; AVS, adrenal venous sampling; CT, computerized tomography; MRA, mineralocorticoid-receptor antagonist; QALY, quality-adjusted life year; PA, primary aldosteronism; PH, primary hypertension; and SIT, saline-infusion test.

*The utility gain attributable to surgical correction of PA was used only in an alternative analysis, not in the base case.
†Future costs and QALYs were discounted at 3% per annum.
patients with PA, and the incremental effect of surgery versus MRA in patients with PA, illustrated in Figure 4. However, even with a small incremental SBP effect between PA patients treated with surgery and medication, screening strategies to identify appropriate patients for surgery remained on the efficiency frontier (Figure 5). In the base-case analysis, with a 6 mm Hg change in SBP with surgery over MRA, CT/A VS is cost-effective. With including utility adjustments for untreated PA, at a 2 mm Hg improvement, CT/A VS is cost-effective.

In most reports, the average age at diagnosis is younger in patients with PA than with primary hypertension. Although patients entering the model did not have a diagnosis of PA as the cause of RH (by design), we tested our hypothesis that screening for PA at a younger age may increase the benefit of screening by performing a subgroup analysis in patients <50 years old from our NHANES cohort. We found the same strategies were cost-effective with substantial improvements in the ICERs (Figure 6). Very few patients with RH are younger than 40 years old (average age in our cohort was 67), and therefore, we chose not to test stratifying patients for surgery following a unilateral CT findings by age as recommended by the Endocrine Practice guidelines.

Finally, to test our assumption that NHANES patients in our sample had RH (versus inadequate treatment or poor patient adherence to antihypertensive regimen), we performed a subgroup analysis on patients who confirmed having a current prescription of antihypertensive medications on the NHANES questionnaire (Figure VI in the Data Supplement). We found that the same strategies were cost-effective in this subgroup analysis.

The results of the probabilistic sensitivity analysis are shown as a cost-effectiveness acceptability curve (Figure 7). This graph shows the proportion of the random samplings of parameter distributions resulting in the greatest net health benefit (vertical axis) at increasing WTP thresholds (horizontal axis). At a WTP threshold of $150,000/QALY, a strategy involving screening and subtype diagnosis of PA was cost-effective in 87% of simulations.

Discussion

Based on this analysis, our results support our hypothesis that screening for PA and surgically treating those with appropriate indications in all patients with RH (versus the MRA only strategy) are cost-effective. This result was consistent in the base-case and exhaustive sensitivity analyses. Which of the remaining intervention strategies is preferred depends on the WTP threshold. Before integrating the effects of untreated PA on health-related quality of life, the intervention strategy CT/A VS was the only cost-effective management strategy with an ICER of $28,636/life year saved. Although it may be counterintuitive that CT/A VS would be more cost-effective than CT alone, this can be explained by the costs incurred from downstream medical and CVD-event related costs from removing the wrong adrenal gland (ie, false-positive CT) and failing to remove a functional adenoma in cases with bilateral CT abnormalities in the CT-only strategy. This highlights the value of AVS in helping to lateralize lesions preoperatively. Finally, our study found that the differential effect of treatment on SBP (ie, medical versus surgical in patients with PA) had the greatest impact on the ICERs. A definitive controlled trial directly comparing the impact of medical management with surgery would be needed to clarify the magnitude of benefit that would be expected with adrenalectomy relative to treatment with MRA. Despite this variation, we found that with only small incremental differences in SBP in patients with PA undergoing surgery versus medical therapy (ie, 6 mm Hg in the base case and 2 mm Hg when additional quality of life decrements for those with PA were taken into account),
screening for surgically correctable PA was cost-effective, as small changes in blood pressure have been shown to have significant downstream effects on cardiovascular events.\textsuperscript{20,21} When a modest reduction in utility associated with untreated PA was incorporated into the model, there were notable decreases in the ICERs for all screening strategies. At a threshold of $150,000/QALY, CT only becomes the preferred strategy, with an ICER of $114,000/QALY. We postulate that an early improvement in quality of life may be derived from several factors including taking fewer medications and associated side-effects, decreased financial burden and fewer office visits. Downstream effects of health-related quality of life may be attributable to lower blood pressure resulting in fewer interventions and cardiovascular events. Psychometric survey data show that patients with PA have increased anxiety, depression, and SF36 domains compared with the general population and primary hypertensive controls.\textsuperscript{14,16} Studies suggest that patients show greater improvements after adrenalectomy compared with MRA at 6 months post treatment.\textsuperscript{16} In addition, patients can experience debilitating side effects from MRAs including gynecomastia and impotence. Although we do not currently have data on the differential effects of spironolactone versus eplerenone on HRQoL, we expect the potential improvement in HRQoL from fewer medication side effects to be offset by the incremental cost of eplerenone.

Our results show that the strategy with AVS alone after positive screening ARR resulted in the greatest reductions in SBP in the intervention model and greatest quality-adjusted life expectancy; however, this came at significant cost, leading to a high ICER. Use of AVS in all patients screening positive for PA is controversial. Proponents cite the need for AVS given the high false-negative and false-positive rates of CT for small aldosterone-secreting adrenal adenomas, whereas opponents cite technical difficulty, cost, and risk of adverse effects.\textsuperscript{31–36} The generalizability of published reports on the performance of AVS in tertiary care centers is open to question, given the lower success rates seen in the few published reports from nonacademic centers.\textsuperscript{13,32} Moreover, strategies with AVS remained on the efficiency frontier over a wide range of reported success rates of AVS. The addition of a CT for presurgical planning—commonly practiced—only adds a small incremental cost to this strategy and does not alter the effectiveness. Lastly, it is important to remember that although WTP thresholds are commonplace in Europe, they...
are contentious in the United States; values vary depending on the economy, location, relevant decision maker, values of the population, and the resources available. Estimated on current medical care spending in the United States, a range of $183,000/QALY to $264,000/QALY may be considered more reflective of current WTP.

Moreover, although guidelines recommend the use of confirmatory testing, we did not find any strategy that included SIT to be cost-effective. This is likely because of the fact the ARR as a screening test is fairly accurate and that the small incremental benefit from confirmatory testing does not outweigh the cost. It should be noted that we did not include the costs of SIT implementation (ie, 2 hours of staff observation for infusion) nor potential morbidity associated with changing or withholding hypertensive regimens or of salt-loading in this analysis. Inclusion of these additional costs would make strategies that include confirmatory testing even less cost-effective.

Our study has limitations, common to decision-analytic methods, which arise when using simplifying assumptions to model complex disease care pathways. First, we made the presumption that patients above a SBP threshold in the NHANES database had RH and not untreated hypertension. If our assumption was incorrect, then this would translate into a lower percentage of truly resistant patients and, therefore, a decreased proportion of patients with PA. We would expect that in a pure RH population our screening strategies would be even more cost-effective. Indeed, our subgroup analysis of NHANES patients self-reporting use of antihypertensives resulted in the same cost-effective strategies (Figure VI in the Data Supplement). Second, many retrospective studies may have misclassified patients at diagnosis by not properly identifying subtype (ie, by not performing AVS) or by leaving open to possibility that failure of adrenalectomy was from underlying primary hypertension (ie, because no postoperative ARR was performed). We expect that the majority of the misclassification is in failed identification of appropriate surgical candidates who would benefit most from diagnosis and treatment. For example, being younger or female is positively associated with hypertension cure after surgery for APA, but these patient characteristics were not taken under account in the base-case analysis.

Furthermore, given that patients with BAH do not undergo surgery, it is impossible to confirm the diagnosis of these patients, making specificity of tests challenging to determine. Finally, although medical and surgical treatment have been shown to have positive treatment effects, there are limited data on the comparative effect of treatment on blood pressure between the following 3 groups in controlled trials: (1) patients with primary hypertension receiving MRAs, (2) patients with PA receiving MRAs, and (3) patients with PA undergoing adrenalectomy. Rossi et al showed comparable efficacy of surgery and MRAs in lowering blood pressure in patients with PA. Other reports cite greater improvement in blood pressure between patients undergoing surgery compared with MRAs in patients with PA (Table II in the Data Supplement). However, more efficacy data are needed to strengthen the conclusions of this study. In a cost analysis of patients with PA (without comparison to MRA alone), Reimel et al found surgery to be significantly less expensive over a lifetime. It is important to note that while the incremental increased in life expectancy between strategies may be interpreted as small, it should be emphasized that this is an average result over a million simulated patients. Therefore, although many patients in this population (ie, 80% of whom have primary hypertension) have only a minimum benefit with these strategies, there is a smaller but substantial subset of patients...
(≈10% of the RH population with APA) who gain substantial health benefits.

Although we did include NHANES patients with a prior CVD event in this study, we chose not to enhance the relative risk of prior CVD events in the PA subpopulation. In a cross-sectional study, Milizie et al\textsuperscript{11} found that compared with matched controls, patients with PA were significantly more likely to have had a previous stroke or myocardial infarction. Catena et al\textsuperscript{10} confirmed the findings of higher pretreatment risk of CVD events and attenuation of this differential effect with treatment. We chose not to incorporate this into the model to isolate the benefit of screening and subsequent comparative improvement in SBP on outcomes. Our findings would be strengthened by integrating this differential history of CVD events given the significantly worse long-term outcomes in those with a prior CVD event. In practice, there is frequently a delay in diagnosing PA. Given that time with PA correlates with more CVD events and with failure of cure from surgery, early diagnosis of patients with PA—and in particular those with surgically correctable disease—is essential. Integration of this a priori differential risk of CVD between patients with PA and patients with primary hypertension is an important area for investigation.

In conclusion, our study addresses an increasingly important public health concern. Primary hyperaldosteronism is a common disease that is currently, grossly underdiagnosed and treated. Given a conservative estimate that 12.5% of the hypertensive population has RH, 20% of RH patients have PA, and half of patients with PA have unilateral disease, we estimate that 1 million hypertensive patients in the United States could be cured with surgery.\textsuperscript{3,4,9,12} At accepted WTP thresholds that 1 million hypertensive patients in the United States have RH, 20% of RH patients have PA, the common disease that is currently, grossly underdiagnosed and treated. Primary hyperaldosteronism is a tant public health concern. Primary hyperaldosteronism is a common disease that is currently, grossly underdiagnosed and treated.

SOURCES OF FUNDING

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DISCLOSURES

None.

REFERENCES


Cost-Effectiveness of Screening for Primary Aldosteronism and Subtype Diagnosis in the Resistant Hypertensive Patients
Carrie C. Lubitz, Konstantinos P. Economopoulos, Stephen Sy, Colden Johanson, Heike E. Kunzel, Martin Reincke, G. Scott Gazelle, Milton C. Weinstein and Thomas A. Gaziano

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SUPPLEMENTAL MATERIAL

Expanded Methods

Overview of the Model
The most frequently used abbreviations are listed in Supplemental Table 1. A decision-analytic model (Figure 1) was used to compare the aggregate intervention costs and effectiveness associated with six diagnostic and lateralization strategies in a simulated cohort of resistant hypertensive patients. Patients in strategies 1-6 underwent screening aldosterone to renin ratio (ARR) as per standard of care; patients in strategy 7 were treated with mineralocorticoid receptor antagonist (MRA) without ARR screen or other work-up. Following positive screening ARR (as defined by individual studies and tested with sensitivity analysis), patients underwent one of the following strategies to identify those patients with unilateral, surgically-correctable disease: 1) Confirmatory saline-infusion test (SIT), CT, and AVS (strategy SIT/CT/AVS), 2) CT and AVS (CT/AVS), 3) SIT and AVS (SIT/AVS), 4) AVS only, 5) SIT and CT (SIT/CT), and 6) CT only (Table 2). In strategies SIT/CT/AVS and CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan. In strategy MRA only, all patients were treated upfront with MRA (i.e. spironolactone) without further work-up or risk. Based on the best available published evidence (for references see Supplemental Table 2), we assumed that patients with surgically-treated PA would obtain an additional 10 mmHg reduction in SBP compared to PA patients treated with MRA.

The analysis was performed from a modified societal perspective. The costs of screening, surgery, complications, and medications were included in the analysis, but non-health care related costs to the patient (i.e. patient absence from work, cost for transportation) were not. Best available cost and probability estimates were extracted from the literature (Table 3 and Supplemental Table 2). TreeAge Pro 2014 (TreeAge Software, Williamstown, MA) was used to construct and analyze the model. The change in systolic blood pressure (SBP, mmHg), number of medications, and differential costs of anti-hypertensive regimens for the years following the initial intervention were calculated for each strategy in the immediate intervention model.

Changes in SBP were subsequently converted into gains in quality-adjusted life years (QALYs) using primary National Health and Nutrition Examination Survey (NHANES) data on concomitant risk factors and an existing cardiovascular disease simulation model to calculate incremental cost-effectiveness ratios (ICERs, cost per QALY) for the seven competing strategies. ICERs were assessed by ranking strategies (including the strategy of treating all patients with MRAs) in increasing order of cost and calculating the ratios of additional cost per additional QALY for successively more costly strategies. Strategies that cost more and had fewer life years/QALYs than another strategy (i.e. strongly dominated), or which were less effective but had a larger ICER (i.e., weakly dominated) were not considered further. A willingness-to-pay (WTP) threshold of $US 150,000/QALY gained was used as a benchmark for cost-effectiveness, following the ACC/AHA paper position paper on integration of cost-effective data into clinical practice. The undominated strategies comprise the “efficiency frontier”; among these, the one with the largest ICER below the WTP threshold would be the cost-effective choice.

For the intervention decision tree, we designated our base-case a patient with resistant hypertension (RH). For the primary analysis, we made a number of important assumptions: 1) patients were all considered surgical candidates (i.e. American Society of Anesthesiologists...
Physical Status Classification class I or II); 2) patients diagnosed with unilateral PA (APA) all underwent laparoscopic adrenalectomy per standard of care; 3) patients identified to have PA but who did not lateralize were given spironolactone at 25 mg daily; 4) false-positive rates (i.e. falsely determined to be PA) of CT results for RH patients with primary hypertension were reflective of prevalence of incidental adrenal nodules in the population; 5) if abdominal CT indicated an abnormality on both sides, patients either proceeded to AVS and surgery if AVS lateralized to one adrenal gland (strategies SIT/CT/AVS and CT/AVS), or in CT only strategies (strategies SIT/CT and CT only) patients were treated with MRA; 6) in strategies with CT, those cases with bilateral normal adrenal findings were treated with MRA, while strategies without CT all went to AVS following positive screening, and 7) if there was a failure of AVS – either with cannulation or from complication – patients did not undergo a repeat procedure and went on to get MRA.

Next, from 40,790 patients available in the continuous NHANES database from 2005-2012, a cohort of 836 patients was selected according to the following criteria: 1) patients with SBP ≥ 160 mmHg (presumed resistant hypertension) and 2) patients with available data on cardiovascular risk factors required to assess 10-year Framingham risk score (i.e. age, gender, SBP, total cholesterol, HDL cholesterol, smoking status). Out of 836 patients, 126 (15%) had a prior history of prior myocardial infarction or stroke. Patients with missing data for smoking status were assumed to be non-smokers. This assumption led to a 17% prevalence of smokers in the population, which is consistent with reported estimates in this population. These patients were sampled with replacement to create the simulation cohort (1,000,000 patients) and entered into an established cardiovascular disease Markov model with microsimulation (Supplemental Figure 1) to assess comparative lifetime costs and discounted QALYs based on the intervention costs and change in SBP of each strategy. A detailed description of the Cardiovascular Disease Policy Model (CVDPM) is provided below. Effects were measured in QALYs gained. Future costs and QALYs were discounted at 3% per annum according to recommendations of the Panel on Cost-Effectiveness in Health and Medicine.

Costs
Physician and facility costs were estimated from the Healthcare Common Procedure Coding System (HCPCS), Diagnosis Related Group (DRG), and/or Ambulatory Payment Classification (APC) as appropriate using Medicare national reimbursement data for 2013 for physician visits, imaging, laboratory tests, surgery, and hospitalization (Table 3). Medicare Schedule Part A, inpatient services, and Part B, outpatient services, were assessed separately. Anesthesiology fees were based on average anesthesia time (15 minute increments), 2013 HCPCS Anesthesia Base Units, and the 2013 national anesthesia conversion factor ($21.9243). Average wholesale drug prices were obtained from the RED BOOK® on-line via Micromedex®2 (Truven Health Analytics, Greenwood Village, Colorado). All costs are measured in 2013 U.S. dollars.

Sensitivity analyses
We performed univariate sensitivity analyses to assess effects of varying key model parameters upon our results. In particular, we varied prevalence of PA and incidentally identified adrenal nodules, the proportion of patients with APA (i.e. unilateral, surgically correctable disease), test performance characteristics (e.g. assessing various ARR threshold values for a “positive” screen), cost estimates, and the effect sizes based on underlying etiology and treatment (Table 3). Model inputs were tested over ranges reported in the literature when available and over a
wide-range (i.e. 0.5-1.5 * Base Case Estimate, BCE) when not available. While costs of
diagnostic studies are unlikely to vary greatly, we tested a hypothetical range to assess the effect
on incremental cost-effectiveness ratios. Moreover, while adjustments of medications and
potential for repeated tests due to mistiming of tests are difficult to quantify, we tested 0.5 – 1.5
* base-case cost range for key variables.

Probabilistic sensitivity analysis (PSA) was performed to assess the effects of parameter
estimate uncertainty. Distributions around base case estimates were as follows: β-distributions
for probabilities, γ-distributions for cost estimates, and normal distributions for effect measures.
Each of 1,000 random samples of parameter distributions was used to perform 1,000,000
simulated patients through the CVD model. Net Health Benefit was calculated [(Effectiveness-
Cost)/WTP] was compared between strategies for each sample.

Health-related quality of life

Health-related quality-of-life (HRQoL) adjustments were applied in two stages, first considering
only effects of CVD, and then also considering reductions in quality of life associated with
untreated PA. Utility weights for baseline primary hypertensive patients and downstream health
states within the CVD model were based on a broad national sample of community-based,
patient-reported EQ-5D utility scores associated with chronic diseases. Prior data indicate that
patients with PA have worse quality of life scores when compared to patients with primary
hypertension.

Ranges of utility weights (i.e. measure of HRQoL) were calculated from longitudinal
survey data. 1896 surveys were available from 65 patients. Short Form-12v1® responses were
available for a cohort of PA-confirmed patients before and after treatment with adrenalectomy
(n= 39) or MRA (n=12). The post-treatment data was collected on average 6 months following
either MRA initiation or surgery. Data were then catalogued and translated into interval scale
utilities (0 = dead to 1 = perfect health) using the QualityMetric health state score system,
SF6D®, for integration of a reasonable range in change of utility into the CVD model. For
the purposes of this study, changes in HRQoL (i.e. utility) were compared to the baseline of a
patient with resistant hypertension and the estimates are based on median changes post-treatment
for the surgical versus medically treated groups. Proportions of the cohort in each state (i.e. PA
patients treated with surgery, PA patients treated with MRA, primary hypertensive patients
treated with MRA, and dead) were calculated for each strategy. Median change [IQR] in utility
scores was used as the data were non-normal. Median change in PA patients treated with MRA
was 0 [-0.056, 0.017]; Median change PA treated with surgery 5.4 [0.000, 0.079]. In our second
set of analyses, these utility differences were integrated into the base value for each intervention
strategy for the CVD model (and discounted at 3% per annum for subsequent years).

Description of the Cardiovascular Disease Policy Model

The Cardiovascular Disease Policy Model (CVDPM), coded in C++, integrates information on
the associations between CVD risk factors and incidence, the prevalence of risk factors in the
population, the natural and treated history of disease, and the effects of CVD on survival, quality
of life, and medical care cost. The model is designed to be able to evaluate a wide range of
cardiovascular disease prevention and treatment policies. It is designed to produce results for
cost-effectiveness, comparative effectiveness, and projection analyses.
**Model Population**

The model is populated with a list of individuals with accompanying risk factor data. The CVD risk factors necessary to run the model are: sex, age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, and diabetes status. The model samples from the patient list, taking the initial set of patient risk factor characteristics for a drawn individual and simulating every subsequent year of the individual’s life using Monte Carlo micro-simulation techniques and common random numbers. Three main events occur each model cycle (one-year cycle length): 1) updating of the risk factors (e.g. an increase in systolic blood pressure); 2) potential transitions into a CVD health state; and 3) preventative interventions (i.e. screening and medication). Costs and health state utilities are also computed for each individual every year. After an individual’s remaining lifespan is simulated with the model, a new individual is selected and added to the model population. Model population characteristics based on weighted sampling (with replacement) of individuals from the fasting data samples of the 2005-2006, 2007-2008, and 2009-2010 waves of the nationally representative National Health and Nutrition Examination Surveys (NHANES).

**Risk factors**

Risk factors for all individuals update each model cycle. These updates were based on regressions from nine waves of cross-sectional NHANES data (data collected between 1973-2010). Specifically, systolic blood pressure, total and HDL cholesterol, and diabetes (statin-induced or otherwise) update as patients age in the model. All other individual characteristics, such as smoking and blood pressure treatment, do not change from baseline in the model.

**Transitions**

The health states in the CVDPM are: Disease Free (DF), Coronary Heart Disease (CHD) or Cerebrovascular Accident (CVA) events, and death. The CHD events we modeled are myocardial infarction (MI), angina, and resuscitated cardiac arrest (RCA). The MI and angina health states are further classified to with and without revascularization, either with percutaneous coronary intervention (PTCI) or coronary artery bypass graft (CABG). At any given point in time, a simulated individual can only be in one health state. We also classify disease states as acute or chronic, with the first year a patient is in a disease state considered acute, and every subsequent year a patient remains in the same disease state as chronic. A patient cannot return to the DF state after transitioning into a chronic CVD state. Supplemental Figure 1 shows the base structure of the model of how a DF individual can transition into other health states, and the appendix discusses in more detail all the possible transitions.

Individuals with no prior history of CVD enter into the model as DF, and those with prior history enter into the chronic state of that particular CVD event. The probability that a DF individual transitions into a CVA or CHD health state is derived from calibrated risk equations stemming from the Framingham Study, which factor in an individual’s risk factors, and are subsequently converted to an event probability for the model. Individual cans die from a non-CVD cause while in any health state, as well as a CVD-specific cause while in a CVD state. Individuals can also have repeat CVD events while in a CVD state. Transitions in the model are hierarchical, in which an individual faces the probability of the more severe events before less severe ones. For example, a DF individual would first face the probability of a non-CVD death, then a CVA event, and finally a CHD event. Likewise, an individual in the chronic MI state would first face the probability of a non-CVD death, then a chronic MI death, then a CVA event,
and finally a repeat MI event. If an individual has had multiple CVD events, the individual remains in the health state of the more severe event. Transition probabilities are either applied uniformly to all individuals or are age- and/or sex-specific. **Supplemental Table 4** lists the transition probabilities used in the CVDPM.
Supplemental Tables

**Supplemental Table 1.** Frequently used abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA</td>
<td>Aldosterone-producing adenoma</td>
</tr>
<tr>
<td>ARR</td>
<td>Aldosterone-renin ratio</td>
</tr>
<tr>
<td>AVS</td>
<td>Adrenal venous sampling</td>
</tr>
<tr>
<td>BAH</td>
<td>Bilateral adrenal hyperplasia (a.k.a. Bilateral idiopathic hyperplasia, idiopathic hyperaldosteronism)</td>
</tr>
<tr>
<td>BCE</td>
<td>Base case estimate</td>
</tr>
<tr>
<td>(S)BP</td>
<td>(Systolic) Blood pressure</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effective ratio</td>
</tr>
<tr>
<td>JNC</td>
<td>Joint National Committee</td>
</tr>
<tr>
<td>MRA</td>
<td>Mineralocorticoid-receptor antagonists</td>
</tr>
<tr>
<td>PA</td>
<td>Primary hyperaldosteronism</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RH</td>
<td>Resistant hypertension</td>
</tr>
<tr>
<td>SIT</td>
<td>Saline-infusion confirmatory testing</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
</tr>
</tbody>
</table>
Supplemental Table 2. Intervention model inputs and sources

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Sensitivity analysis range</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of PA in resistant HTN</td>
<td>0.20</td>
<td>0.11-0.23</td>
<td>25-29</td>
</tr>
<tr>
<td>Proportion of unilateral PA</td>
<td>0.43</td>
<td>0.35-0.60</td>
<td>30-33</td>
</tr>
<tr>
<td>Prevalence of incidental adrenal nodules</td>
<td>0.05</td>
<td>0.01-0.09</td>
<td>34-43</td>
</tr>
<tr>
<td><strong>Test characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity of screening (ARR)</td>
<td>0.78</td>
<td>0.66-0.98</td>
<td>44-47</td>
</tr>
<tr>
<td>Specificity of screening testing (ARR)</td>
<td>0.83</td>
<td>0.63-0.99</td>
<td>44-47</td>
</tr>
<tr>
<td>Sensitivity of confirmatory testing (SIT)</td>
<td>0.83</td>
<td>0.55-0.90</td>
<td>48-51</td>
</tr>
<tr>
<td>Specificity of confirmatory testing (SIT)</td>
<td>0.75</td>
<td>0.75-1.00</td>
<td>48-51</td>
</tr>
<tr>
<td>Probability of contralateral nodule CT in APA</td>
<td>0.12</td>
<td>0.06-0.13</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of true positive CT in APA (sensitivity given APA)</td>
<td>0.59</td>
<td>0.49-0.62</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of bilateral CT abnormalities in APA</td>
<td>0.15</td>
<td>0.13-0.36</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of normal CT in APA</td>
<td>0.14</td>
<td>0.07-0.25</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of bilateral CT abnormalities in BAH (sensitivity given BAH)</td>
<td>0.41</td>
<td>0.19-0.46</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of normal CT in BAH</td>
<td>0.22</td>
<td>0.22-0.43</td>
<td>52-55</td>
</tr>
<tr>
<td>Probability of unilateral CT in BAH</td>
<td>0.36</td>
<td>0.33-0.38</td>
<td>52-55</td>
</tr>
<tr>
<td>Lateralizing AVS with BAH (false-positive given true bilateral disease)</td>
<td>0.02</td>
<td>0.02-0.20</td>
<td>53, 56, 57</td>
</tr>
<tr>
<td>Sensitivity of AVS for unilateral disease (true-positive given true unilateral disease)</td>
<td>0.93</td>
<td>0.80-0.93</td>
<td>52, 53, 57</td>
</tr>
<tr>
<td>Proportion of unsuccessful adrenal vein cannulation</td>
<td>0.18</td>
<td>0.04-0.37</td>
<td>52, 53, 55, 58</td>
</tr>
<tr>
<td><strong>Procedural morbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity from AVS (bleeding)</td>
<td>0.01</td>
<td>0.006-0.07</td>
<td>53, 57, 59</td>
</tr>
<tr>
<td>Morbidity from surgery</td>
<td>0.07</td>
<td>0.06-0.08</td>
<td>60</td>
</tr>
<tr>
<td>Mortality from adrenalectomy</td>
<td>0.01</td>
<td>0.00-0.01</td>
<td>60</td>
</tr>
<tr>
<td><strong>Treatment effects (ΔmmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP change with death/no treatment</td>
<td>0.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SBP change treatment of primary hypertensive patients with MRA</td>
<td>10.00</td>
<td>4-22</td>
<td>3, 5, 61-63</td>
</tr>
<tr>
<td>SBP change treatment PA with MRA</td>
<td>20.00</td>
<td>11-33</td>
<td>3, 5, 6, 64, 65</td>
</tr>
<tr>
<td>Incremental SBP change with PA</td>
<td>10.00</td>
<td>0-20</td>
<td>4, 6, 7, 57</td>
</tr>
<tr>
<td>Procedure Description</td>
<td>Cost</td>
<td>BCE</td>
<td>Source</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Screening ARR (CPT 82088, 84244, 84132)</td>
<td>$93</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>Confirmatory saline infusion testing (CPT 96365, 93666)</td>
<td>$141</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal CT (CPT 74170)</td>
<td>$329</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>Adrenal venous sampling (CPT 75893, 36500)</td>
<td>$2,645</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
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<tr>
<td>Adrenalectomy (surgery + anesthesia)* (CPT 60650, 00866)</td>
<td>$3,054</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>Hospitalization (DRG† 615)</td>
<td>$7,867</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>Hospitalization w/MCC (DRG 614)</td>
<td>$16,833</td>
<td>(0.5-1.5) × BCE</td>
<td>16</td>
</tr>
<tr>
<td>One year cost of spironolactone</td>
<td>$158</td>
<td>(0.5-1.5) × BCE</td>
<td>Mircromedex®2</td>
</tr>
</tbody>
</table>

ARR – aldosterone to renin ratio; SIT – saline-infusion testing; APA – aldosterone producing adenoma; BAH – bilateral adrenal hyperplasia; MCC - major comorbidities or complications; SBP – systolic blood pressure; MRA: Mineralocorticoid-receptor antagonist; BCE – base-case estimate. *Cost of anesthesia was based on the product of average anesthesia time (15 minute increments), 2013 HCPCS Anesthesia Base Units, and the national anesthesia conversion factor. †DRG - Diagnosis-related group for adrenal procedures with and without major comorbidities or complications. Operative times of laparoscopic adrenalectomy, were based on the results of a meta-analysis comparing retroperitoneal versus transperitoneal laparoscopic techniques. Reported imaging test characteristics were elicited from a recent meta-analysis and other reports which had confirmation of disease with surgical pathology.
Supplemental Table 3. Disease progression inputs used in the CVD microsimulation model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From Disease Free State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CVD death</td>
<td>Age- and sex-specific table</td>
<td>66</td>
</tr>
<tr>
<td>CHD and stroke events</td>
<td>RF-based equations*</td>
<td>23, 24</td>
</tr>
<tr>
<td>% Cardiac Arrest</td>
<td>Age- and sex-specific table</td>
<td>67</td>
</tr>
<tr>
<td>% MI (males)</td>
<td>0.35</td>
<td>68</td>
</tr>
<tr>
<td>% MI (females)</td>
<td>0.20</td>
<td>68</td>
</tr>
<tr>
<td><strong>Chronic mortality (i.e., post-1st year) multipliers (i.e., relative risks) for CVD health states</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-CHD, men &lt;2 CHD events</td>
<td>1.6</td>
<td>69</td>
</tr>
<tr>
<td>Post-CHD, men ≥2 CHD events</td>
<td>3.4</td>
<td>69</td>
</tr>
<tr>
<td>Post-CHD, women &lt;2 CHD events</td>
<td>2.1</td>
<td>69</td>
</tr>
<tr>
<td>Post-CHD, women ≥2 CHD events</td>
<td>2.5</td>
<td>69</td>
</tr>
<tr>
<td>Post-stroke</td>
<td>2.3</td>
<td>70</td>
</tr>
<tr>
<td><strong>From Cardiac Arrest State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (within 1 year) death</td>
<td>0.954</td>
<td>71</td>
</tr>
<tr>
<td>MI event</td>
<td>0.064</td>
<td>Assumption: same as MI</td>
</tr>
<tr>
<td><strong>From MI State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate death</td>
<td>0.15</td>
<td>72</td>
</tr>
<tr>
<td>Acute death (days 30-365)</td>
<td>Age-specific table</td>
<td>67</td>
</tr>
<tr>
<td>Acute CABG</td>
<td>0.082</td>
<td>75</td>
</tr>
<tr>
<td>Acute PTCA</td>
<td>0.300</td>
<td>75</td>
</tr>
<tr>
<td>% Procedure death</td>
<td>0.009</td>
<td>74</td>
</tr>
<tr>
<td>Acute 2nd MI (no PTCA)</td>
<td>0.060</td>
<td>75</td>
</tr>
<tr>
<td>Acute 2nd MI (after PTCA)</td>
<td>0.052</td>
<td>76</td>
</tr>
<tr>
<td>Repeat MI</td>
<td>0.064</td>
<td>77</td>
</tr>
<tr>
<td><strong>From MI and CABG State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute post-CABG death</td>
<td>0.027</td>
<td>78</td>
</tr>
<tr>
<td>Acute 2nd MI</td>
<td>0.051</td>
<td>76</td>
</tr>
<tr>
<td>Repeat MI</td>
<td>0.039</td>
<td>77</td>
</tr>
<tr>
<td><strong>From Angina State</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute death</td>
<td>0.045</td>
<td>75</td>
</tr>
<tr>
<td>Acute cardiac arrest</td>
<td>0.006</td>
<td>79</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.035</td>
<td>80</td>
</tr>
<tr>
<td>Acute CABG</td>
<td>0.200</td>
<td>81</td>
</tr>
<tr>
<td>Acute PTCA</td>
<td>0.300</td>
<td>81</td>
</tr>
<tr>
<td>MI event</td>
<td>0.035</td>
<td>80</td>
</tr>
<tr>
<td>From Angina and CABG State</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Chronic (post 1st-year) death</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>MI event</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>From Stroke State</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>Acute death</td>
<td>0.140</td>
<td></td>
</tr>
<tr>
<td>Repeat stroke event</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>MI event</td>
<td>0.022</td>
<td></td>
</tr>
</tbody>
</table>
**Supplemental Table 4.** Surgical outcomes and mortality by disease and strategy.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Appropriate Surgical Therapy</th>
<th>Inappropriate Surgical Therapy*</th>
<th>Surgical Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - SIT/CT/AVS</td>
<td>0.420</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>2 - CT/AVS</td>
<td>0.506</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>3 - SIT/AVS</td>
<td>0.489</td>
<td>0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>4 - AVS only</td>
<td>0.589</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>5 - SIT/CT</td>
<td>0.457</td>
<td>0.035</td>
<td>0.007</td>
</tr>
<tr>
<td>6 - CT only</td>
<td>0.551</td>
<td>0.047</td>
<td>0.009</td>
</tr>
<tr>
<td>7 - MRA only</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Including wrong-sided surgery, adrenalectomy for bilateral adrenal hyperplasia, and adrenalectomy for primary hypertension.
Supplemental Figures

Supplemental Figure 1. Model schematic of the cardiovascular disease model.
Supplemental Figure 2. Efficiency frontiers of a range of primary aldosteronism (PA) prevalence in the resistant hypertensive population for the: A) base-case analysis considering only effects of cardiovascular disease (CVD) on health related quality of life (HRQoL) and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. Only non-dominated strategies shown. In strategy CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan. pAldo - prevalence of PA in the resistant hypertensive population.
Supplemental Figure 3. Efficiency frontiers of a range of sensitivity (true-positive for PA) of screening with aldosterone to renin ratio (ARR): A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. Only non-dominated strategies shown. In strategy CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan. pTP_ARR - sensitivity of screening with ARR.
**Supplemental Figure 4.** Efficiency frontiers of a range of false positives (1-specificity) of screening with aldosterone to renin ratio (ARR): A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. Only non-dominated strategies shown. In strategy CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan. pFP_ARR – false positives (1-specificity) of screening with ARR.
**Supplemental Figure 5.** Efficiency frontiers of various ranges of the cost of spironolactone: A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. Only non-dominated strategies shown. In strategy CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan. cMRA – cost of spironolactone.
Supplemental Figure 6. Efficiency frontiers including only patients who confirmed having a current prescription of antihypertensive medications: A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. Only non-dominated strategies shown. In strategy CT/AVS, all patients proceeded to AVS unless no abnormality is found on CT scan.
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