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.[1, 2] 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[3-7], 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.[8] 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)[9]; 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[10, 11]; 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 $\geq$ 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).[12] 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.[13] 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.[14] 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.[15]

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**).[16] 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).[16] Average wholesale drug prices were obtained from the RED BOOK® on-line via Mircromedex®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.[17] Prior data indicate that patients with PA have worse quality of life scores when compared to patients with primary hypertension.[6, 18, 19]

Ranges of utility weights (i.e. measure of HRQoL) were calculated from longitudinal survey data.[18] 196 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.[6, 18, 19] 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[14]

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.[20] 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) .[21]

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).[22] 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.[23, 24] 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

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

Supplemental Table 2. Intervention model inputs and sources

Parameter	Value	Sensitivity analysis range	Source(s)
Epidemiology			
Prevalence of PA in resistant HTN	0.20	0.11-0.23	25-29
Proportion of unilateral PA	0.43	0.35-0.60	30-33
Prevalence of incidental adrenal nodules	0.05	0.01-0.09	34-43
Test characteristics			
Sensitivity of screening (ARR)	0.78	0.66-0.98	44-47
Specificity of screening testing (ARR)	0.83	0.63-0.99	44-47
Sensitivity of confirmatory testing (SIT)	0.83	0.55-0.90	48-51
Specificity of confirmatory testing (SIT)	0.75	0.75-1.00	48-51
Probability of contralateral nodule CT in APA	0.12	0.06-0.13	52-55
Probability of true positive CT in APA (sensitivity given APA)	0.59	0.49-0.62	52-55
Probability of bilateral CT abnormalities in APA	0.15	0.13-0.36	52-55
Probability of normal CT in APA	0.14	0.07-0.25	52-55
Probability of bilateral CT abnormalities in BAH (sensitivity given BAH)	0.41	0.19-0.46	52-55
Probability of normal CT in BAH	0.22	0.22-0.43	52-55
Probability of unilateral CT in BAH	0.36	0.33-0.38	52-55
Lateralizing AVS with BAH (false-positive given true bilateral disease)	0.02	0.02-0.20	53, 56, 57
Sensitivity of AVS for unilateral disease (true-positive given true unilateral disease)	0.93	0.80-0.93	52, 53, 57
Proportion of unsuccessful adrenal vein cannulation	0.18	0.04-0.37	52, 53, 55, 58
Procedural morbidity			
Morbidity from AVS (bleeding)	0.01	0.006-0.07	53, 57, 59
Morbidity from surgery	0.07	0.06-0.08	60
Mortality from adrenalectomy	0.01	0.00-0.01	60
Treatment effects (ΔmmHg)			
SBP change with death/no treatment	0.00	-	-
SBP change treatment of primary hypertensive patients with MRA	10.00	4-22	3, 5, 61-63
SBP change treatment PA with MRA	20.00	11-33	3, 5, 6, 64, 65
Incremental SBP change with PA	10.00	0-20	4, 6, 7, 57

adrenalectomy (over MRA)			
Costs			
Screening ARR (CPT 82088, 84244,84132)	$93	(0.5-1.5) × BCE	[16]
Confirmatory saline infusion testing (CPT 96365, 93666)	$141	(0.5-1.5) × BCE	[16]
Abdominal CT (CPT 74170)	$329	(0.5-1.5) × BCE	[16]
Adrenal venous sampling (CPT 75893, 36500)	$2,645	(0.5-1.5) × BCE	[16]
Adrenalectomy (surgery + anesthesia)* (CPT 60650, 00866)	$3,054	(0.5-1.5) × BCE	[16]
Hospitalization (DRG† 615)	$7,867	(0.5-1.5) × BCE	[16]
Hospitalization w/MCC (DRG 614)	$16,833	(0.5-1.5) × BCE	[16]
One year cost of spironolactone	$158	(0.5-1.5) × BCE	Mircromedex®2

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.[60] Reported imaging test characteristics were elicited from a recent meta-analysis and other reports which had confirmation of disease with surgical pathology.[52-54]

Supplemental Table 3. Disease progression inputs used in the CVD microsimulation model.

Parameter	Value	Source
From Disease Free State		
Non-CVD death	Age- and sex-specific table	[66]
CHD and stroke events	RF-based equations*	[23, 24]
% Cardiac Arrest	Age- and sex-specific table	[67]
% MI (males)	0.35	[68]
% MI (females)	0.20	[68]
Chronic mortality (i.e., post-1st year) multipliers(i.e., relative risks) for CVD health states		
Post-CHD, men <2 CHD events	1.6	[69]
Post-CHD, men ≥2 CHD events	3.4	[69]
Post-CHD, women <2 CHD events	2.1	[69]
Post-CHD, women ≥2 CHD events	2.5	[69]
Post-stroke	2.3	[70]
From Cardiac Arrest State		
Acute (within 1 year) death	0.954	[71]
MI event	0.064	Assumption: same as MI
From MI State		
Immediate death	0.15	[72]
Acute death (days 30-365)	Age- specific table	[67]
Acute CABG	0.082	[73]
Acute PTCA	0.300	[73]
% Procedure death	0.009	[74]
Acute 2nd MI (no PTCA)	0.060	[75]
Acute 2nd MI (after PTCA)	0.052	[76]
Repeat MI	0.064	[77]
From MI and CABG State		
Acute post-CABG death	0.027	[78]
Acute 2nd MI	0.051	[76]
Repeat MI	0.039	[77]
From Angina State		
Acute death	0.045	[75]
Acute cardiac arrest	0.006	[79]
Acute MI	0.035	[80]
Acute CABG	0.200	[81]
Acute PTCA	0.300	[81]
MI event	0.035	[80]

From Angina and CABG State		
Chronic (post 1st-year) death	0.018	[82]
MI event	0.021	[80]
From Stroke State		
Acute death	0.140	[83]
Repeat stroke event	0.040	[84]
MI event	0.022	[85]

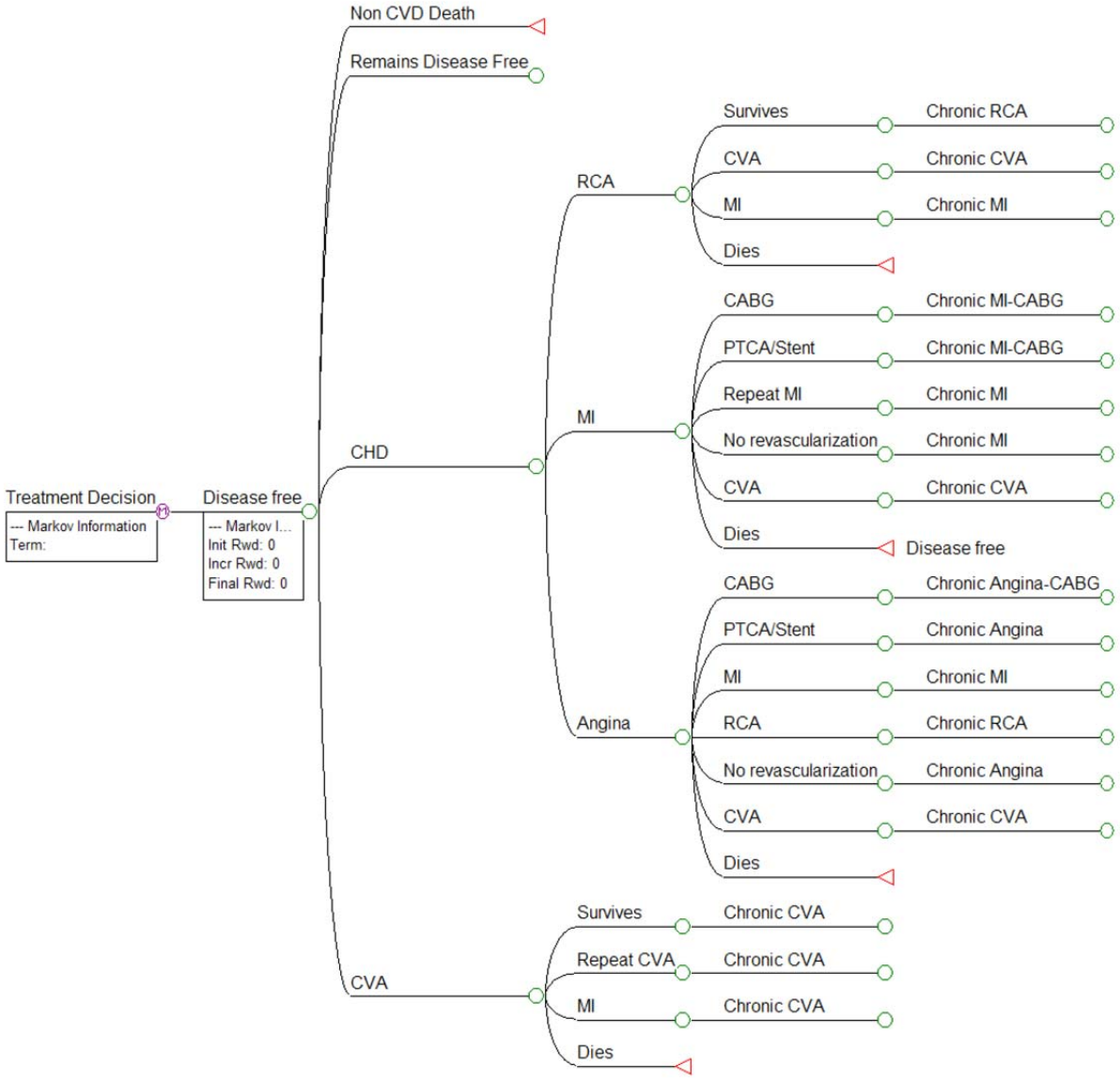
Supplemental Table 4. Surgical outcomes and mortality by disease and strategy.

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

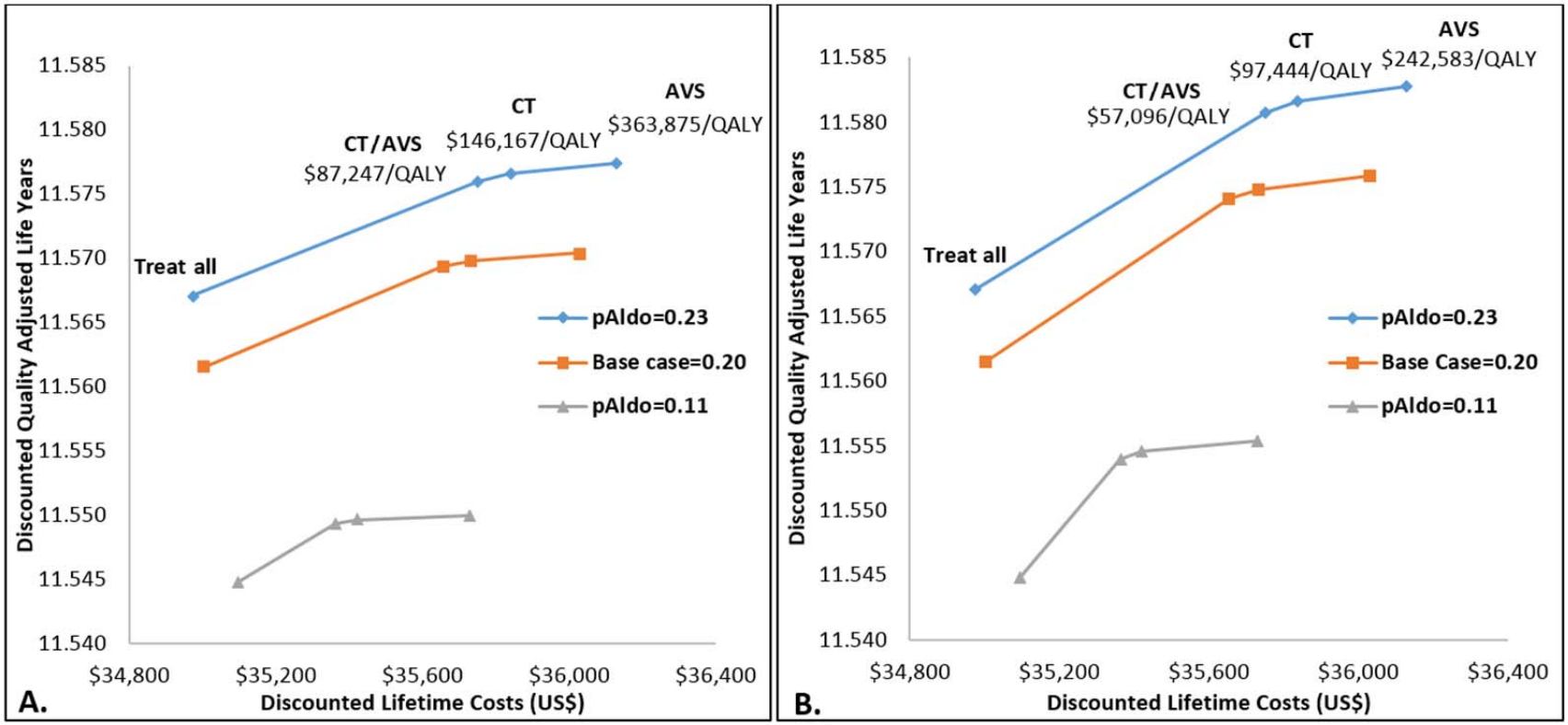
*Including wrong-sided surgery, adrenalectomy for bilateral adrenal hyperplasia, and adrenalectomy for primary hypertension.

Supplemental Figures

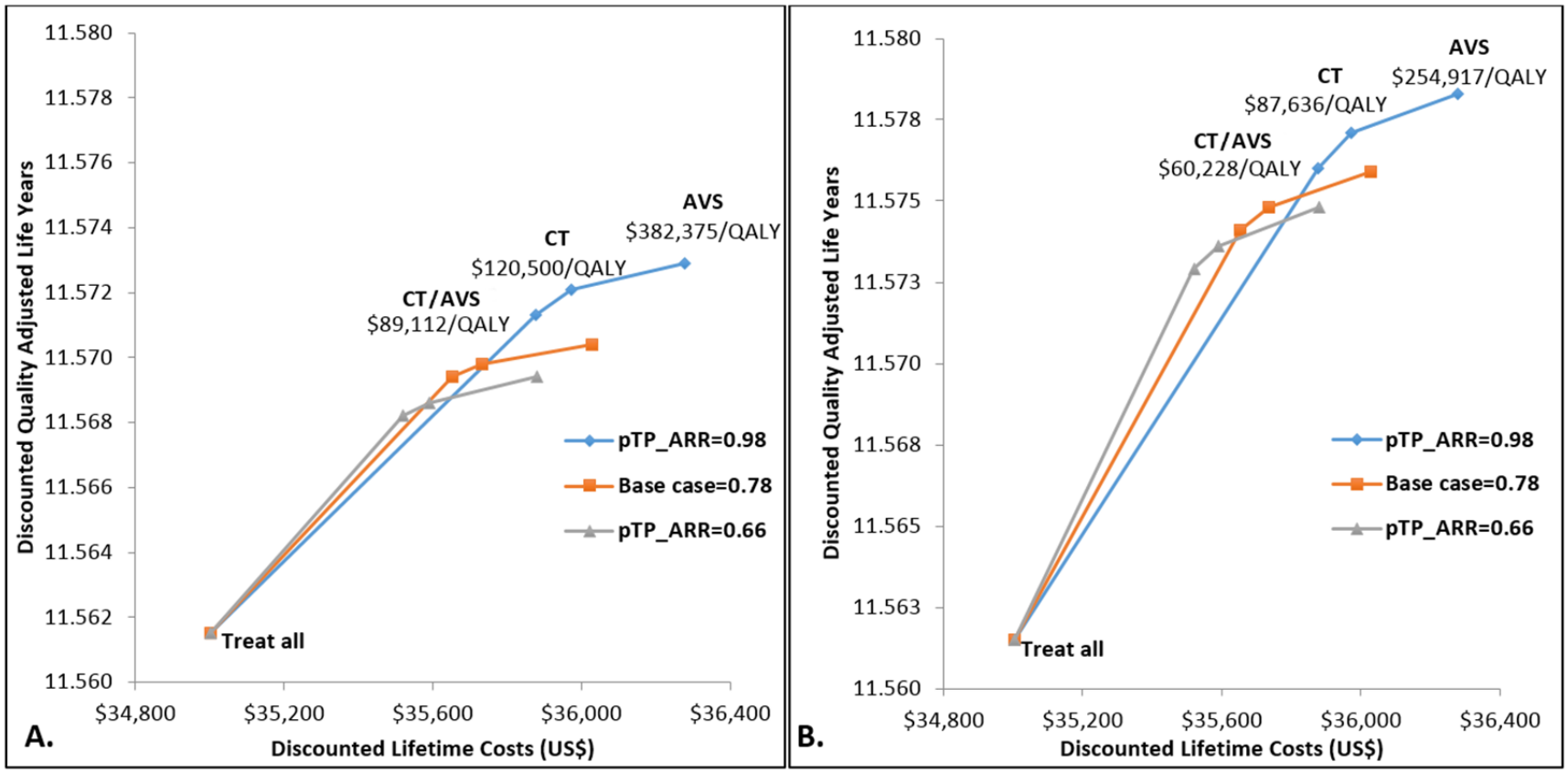
Supplemental Figure 1. Model schematic of the cardiovascular disease model.



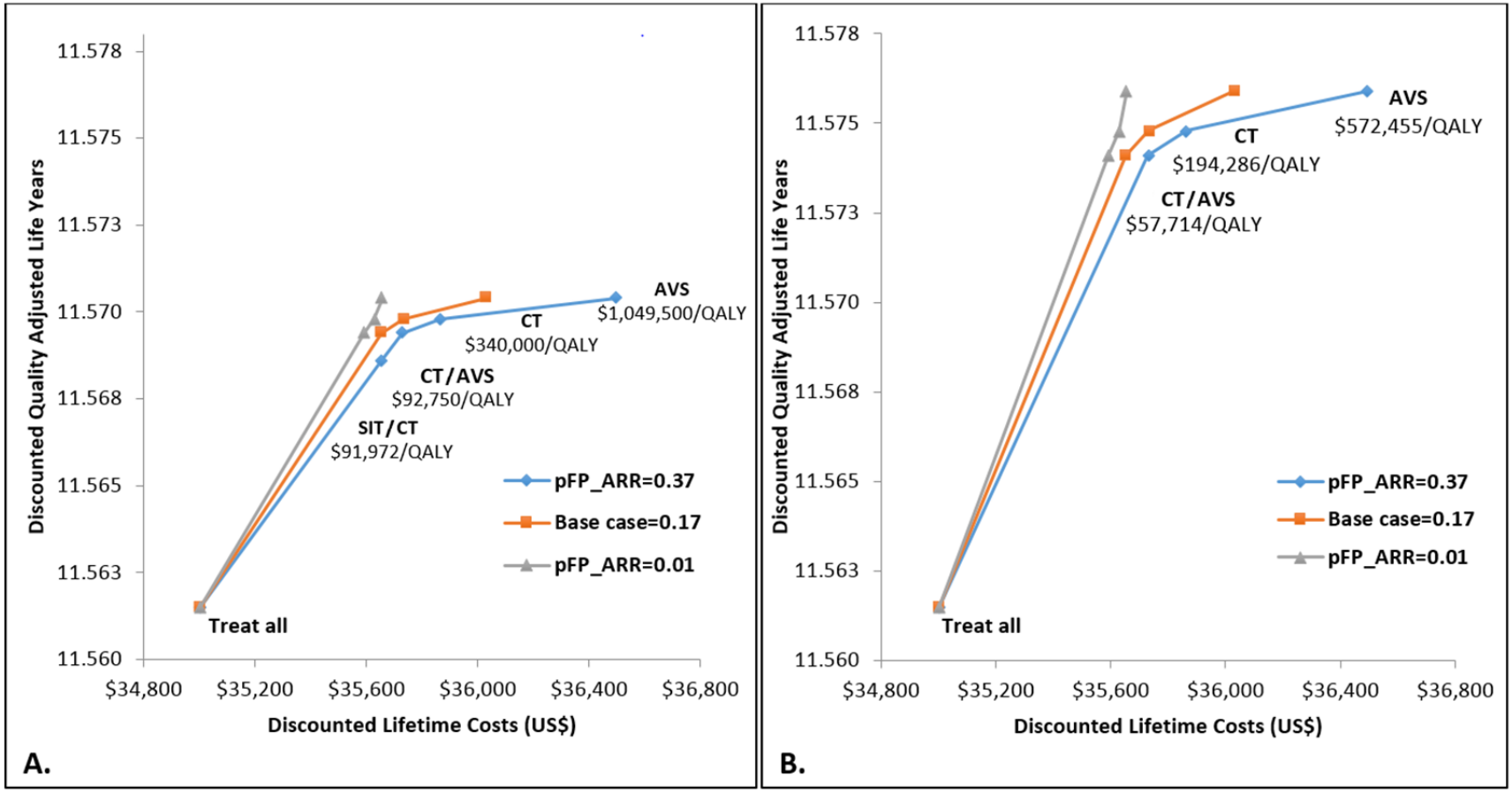
Supplemental Figure 2. Efficiency frontiers of a range of primary aldosteronism (PA) prevalence in the resistant hypertensive population for the: A) base-case analysis considering only effects of cardiovascular disease (CVD) on health related quality of life (HRQoL) and B) base-case analysis with differential 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.



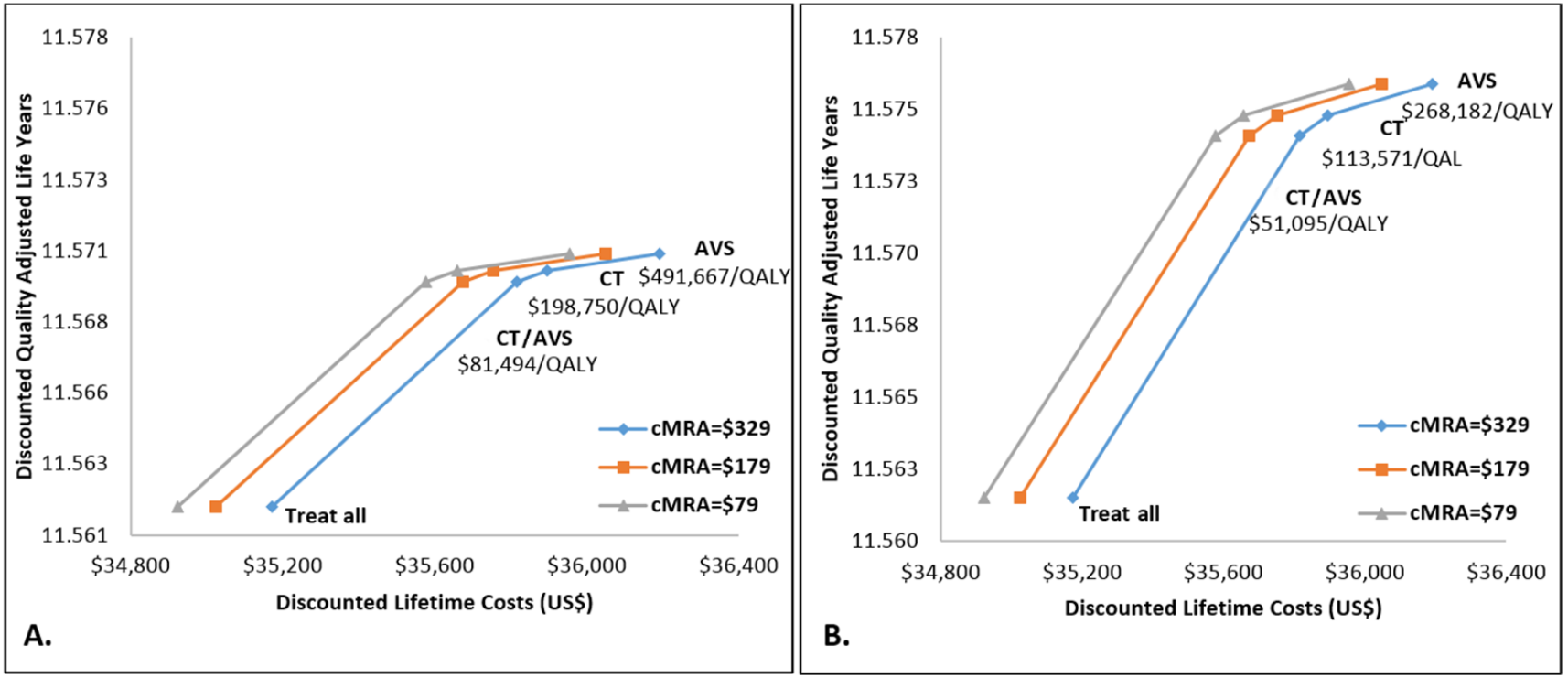
Supplemental Figure 3. Efficiency frontiers of a range of sensitivity (true-positive for PA) of screening with aldosterone to renin ratio (ARR): A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated 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.



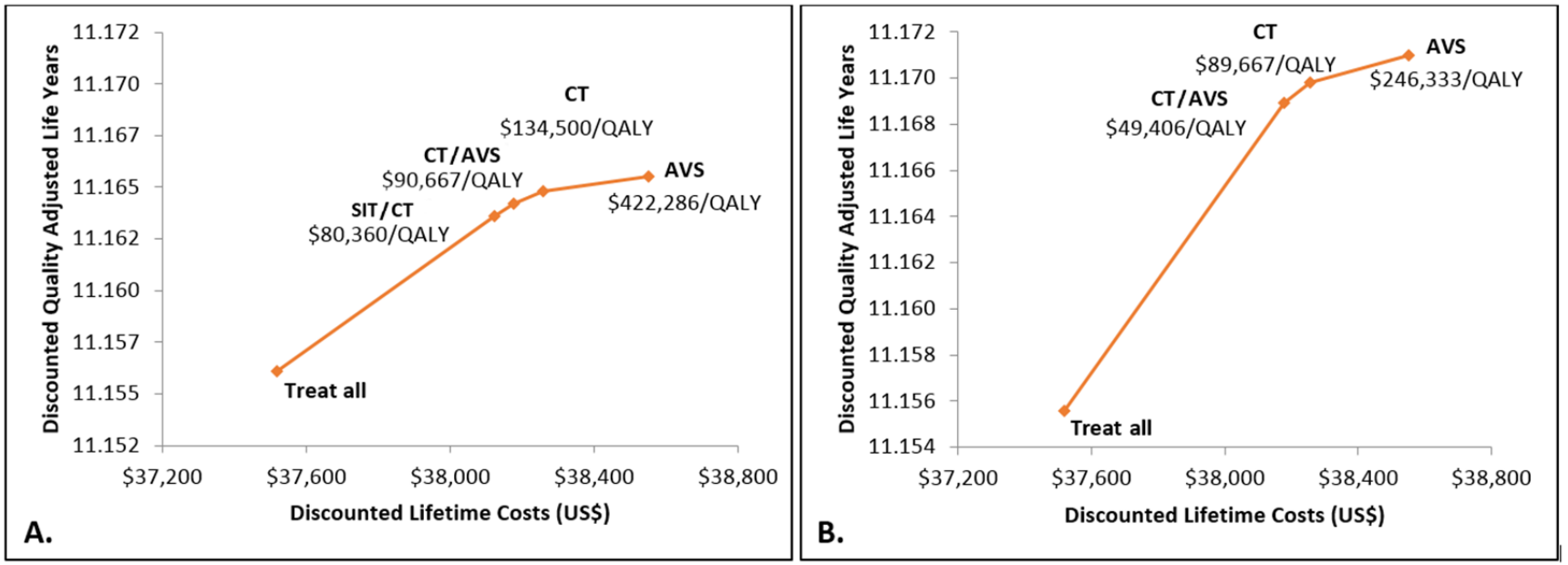
Supplemental Figure 4. Efficiency frontiers of a range of false positives (1- specificity) of screening with aldosterone to renin ratio (ARR): A) base-case analysis considering only effects of CVD on HRQoL, and B) base-case analysis with differential patient-reported HRQoL associated with untreated PA. 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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