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SPECIAL REPORT

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Special Report

Cost-Effectiveness of Impedance Cardiography Testing in Uncontrolled Hypertension

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To evaluate the short- and long-term cost-effectiveness of impedance cardiography (ICG) testing in uncontrolled hypertensives, we analyzed the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL) trial results that compared the blood pressure-lowering effects of standard vs ICG care. Short-term cost-effectiveness was evaluated as the incremental cost per incremental mm Hg reduced during the trial. Long-term cost-effectiveness was evaluated as incremental cost per quality-adjusted life-year gained over 10 years. ICG care short-term cost-effectiveness was \$20 per incremental mm Hg reduced for systolic blood pressure (vs standard care, \$36 per mm Hg reduced) and \$23 per incremental mm Hg reduced for diastolic blood pressure (vs standard care, \$79 per mm Hg reduced). In the long term, ICG resulted in a \$476 cost savings and 0.109 quality-adjusted life-years gained per patient (–\$4371 per quality-adjusted life-year gained, sensitivity analysis –\$8764 to \$13,163). The use of ICG testing to reduce blood pressure in uncontrolled hypertensive patients is cost-effective from both a short- and long-term perspective. ©2006 Le Jacq

Hypertension affects 65 million people in the United States¹ and significantly increases the risk of stroke, ischemic heart disease (IHD), heart failure, and renal disease.² Successful treatment of high blood pressure (BP) remains low, with only 31% of all hypertensives and 54% of those actively treated and taking medications achieving BP <140/90 mm Hg.³

Mean BP rises as a result of abnormal hemodynamics that include elevated systemic vascular resistance (SVR) and/or cardiac output (CO).⁴ While vasoconstriction is the dominant cause of high BP, there is wide variation in SVR and CO within patient groups.⁵ Antihypertensive agents lower BP by reducing SVR and/or CO but may affect patients differently depending on underlying hemodynamics.⁶ Hemodynamic parameters cannot be accurately assessed by physical examination,⁷ but non-invasive impedance cardiography (ICG) testing provides easy-to-acquire hemodynamic measurements.⁸ ICG-guided treatment was previously shown to

improve BP control in resistant hypertension treated by specialists.⁹ In the follow-up Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of BP Levels (CONTROL) trial,¹⁰ ICG testing resulted in even greater BP reduction and control rates in nonresistant hypertension treated by generalists.

The annual cost of treating hypertension in the United States is over \$63 billion, with \$23 billion attributed to direct patient care and \$24 billion to drugs costs.¹¹ Analysis of health care costs is not new,¹² but its importance has grown in recent years. Cost-effectiveness analysis is generally defined as a quantitative comparison of the economic costs and clinical benefits of medical therapies and technologies.¹³ To evaluate whether to accept or reject a new approach, an incremental cost-effectiveness ratio (ICER) is calculated, where the difference in cost (C) is compared with the difference in effectiveness (E):

$$\text{ICER} = \frac{C_{\text{incremental}}}{E_{\text{incremental}}}, \text{ where } C_{\text{incremental}} \text{ is } C_{\text{new}} - C_{\text{standard}} \text{ and } E_{\text{incremental}} \text{ is } E_{\text{new}} - E_{\text{standard}}.$$

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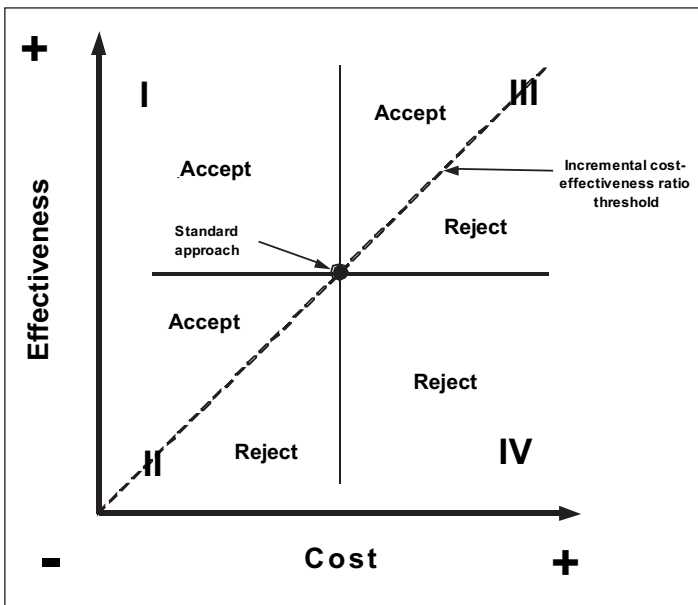


Figure 1. Cost and effectiveness of a new clinical approach can be evaluated vs a standard approach, resulting in 4 quadrants that help determine whether to accept or reject the new approach.

This calculation creates the 4 quadrants shown in Figure 1.^{14,15} New approaches should be accepted if they are less costly and more effective (quadrant I). If they are more costly and more effective (quadrant III), they should be evaluated vs a maximum willingness to pay¹⁶ (shown as the ICER threshold).

Since BP reduction is a commonly accepted surrogate end point, the incremental cost per mm Hg

reduced has been used to evaluate short-term pharmacologic cost-effectiveness.^{17,18} Long-term cost effectiveness is often evaluated as the cost per quality-adjusted life-year (QALY) gained.¹⁹ The cost per QALY gained allows evaluation of both quality and quantity of life simultaneously. The QALY takes into account that a year of life after stroke does not have the same quality as full health and that a year of life gained immediately is preferable to one in 20 years.

Based on the clinical results of the CONTROL trial, we sought to evaluate both the short- and long-term cost-effectiveness of ICG testing in uncontrolled hypertension (Figure 2).

Methods

CONTROL Trial Design. In the CONTROL trial, 164 patients from 11 primary care centers were evaluated. Patients aged 18–75 years (mean, 55 years) were eligible if they had a previous diagnosis of essential hypertension and were currently receiving 1–3 antihypertensive medications (mean, 1.7) with a systolic BP of 140–179 mm Hg (mean, 148 mm Hg) and/or diastolic BP of 90–109 mm Hg (mean, 88 mm Hg). Patients underwent a 2-week washout period during which all antihypertensive medications were discontinued. After the washout, eligible patients were randomized in a 3:2 ratio to a standard (n=95) or ICG (n=69) arm. After washout and over the next 3 months, each patient had a total

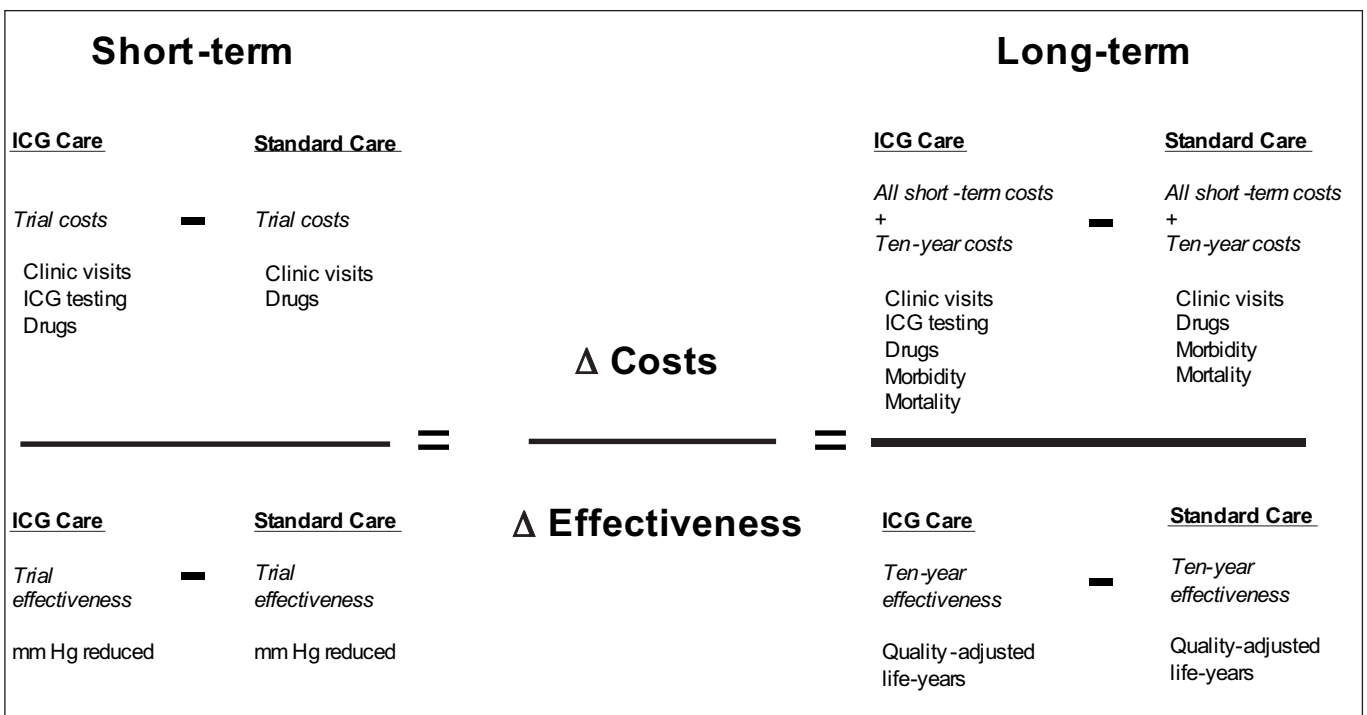


Figure 2. Calculation of short- and long-term cost-effectiveness ratios with impedance cardiography (ICG) to reduce blood pressure in uncontrolled hypertension.

of 4 office visits. Physician investigators prescribed medications consistent with published guidelines, usual practice patterns, and patient clinical characteristics. ICG data were collected in both arms of the study but available only in the ICG arm. In the ICG arm, treating physicians used the BioZ ICG monitor (CardioDynamics, San Diego, CA) to guide therapeutic decisions. If BP was high due to high SVR, investigators were encouraged to intensify vasodilating agents (ie, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or calcium channel blocker). If BP was high due to high CO, investigators were encouraged to intensify β -blocker use. If CO was low or normal, investigators were to consider reducing β -blocker use. Diuretic effectiveness was monitored by measuring the response in thoracic fluid content.

CONTROL Trial Results. Of those enrolled in the study, 54% were men, 78% were white, 47% had isolated systolic hypertension, 4% had type II diabetes mellitus, 4% had IHD, and 16% had hyperlipidemia. There were no differences between arms in the number of antihypertensive medications; patient demographics; or clinical, BP, or ICG variables at baseline or post-washout. Systolic BP reductions were 8 mm Hg greater in the ICG vs the standard arm (19 ± 17 mm Hg vs 11 ± 18 mm Hg; $P<.01$) and diastolic BP reductions were 7 mm Hg greater (12 ± 11 mm Hg vs 5 ± 12 mm Hg; $P<.001$). Final BP was lower in the ICG arm ($129/76\pm 14/11$ mm Hg vs $136/82\pm 15/10$ mm Hg; $P<.01$). Goal BP ($<140/90$ mm Hg) was achieved more frequently in the ICG arm (77% vs 57%; $P<.01$) as was more aggressive BP reduction ($<130/85$ mm Hg) (55% vs 27%; $P<.0001$). SVR index was lower at the final visit in the ICG arm (2523 ± 581 vs 2714 ± 619 dyne \cdot sec \cdot m 2 \cdot cm $^{-5}$; $P<.05$) and decreased more from baseline (-433 ± 660 vs -219 ± 667 dyne \cdot sec \cdot m 2 \cdot cm $^{-5}$; $P<.05$).

The ICG arm maintained superiority in 3 key subgroups: (1) patients who were older, (2) patients on thiazide diuretics, and (3) patients with isolated systolic hypertension. The final number of medications was not statistically different between the ICG and standard arms (2.1 vs 2.0; $P>.05$). The medication differences in the ICG arm included: (1) greater final angiotensin II receptor blocker use (47% vs 31%; $P<.05$), (2) lower final doses of thiazide diuretics (13.0 ± 2.6 mg/d vs 18.9 ± 8.3 mg/d; $P<.012$), (3) more vasodilating drug use when SVR was high (78% vs 67%; $P<.05$), (4) more avoidance of β -blockers or β -blocker dose reduction when CO was low or normal (85% vs 77%; $P<.05$),

and (5) fewer dose increases (3.0 ± 1.2 vs 3.6 ± 1.3 ; $P<.001$) and decreases (1.7 ± 1.0 vs 2.7 ± 1.3 ; $P<.001$) throughout the trial.

Short-Term Cost-Effectiveness. Short-Term Outcome Measures. The total cost per mm Hg reduced for systolic and diastolic BP was calculated by dividing the total cost in each arm by each arm's reduction in systolic and diastolic BP in mm Hg from baseline to final (ICG care, 19/12 mm Hg; standard care, 11/5 mm Hg). The incremental cost per incremental mm Hg reduced for the ICG arm was calculated by dividing the incremental cost in the ICG arm by the incremental systolic and diastolic BP reduction in the ICG arm during the trial (8 mm Hg systolic and 7 mm Hg diastolic).

Short-Term Costs. Costs in both arms included 4 office visits: 3 in which medications were prescribed and 1 for final BP measurement and clinical examination. ICG arm costs included the 3 ICG tests that were used to aid therapeutic decisions. Costs for office visits and ICG tests were taken from current procedural terminology (CPT) amounts in the 2006 Centers for Medicare & Medicaid Services (CMS) Fee Schedule.²⁰ Our base case used estimates of \$44 per ICG test (CPT 93701) and \$68 per clinic visit (average of CPT 99213 and CPT 99214). The CPT code amounts for office visits and ICG tests take into account all costs for the patient encounter, including physician and technician time, ICG device and disposable cost, overhead, and malpractice. Drug costs were estimated by taking the percentage of patients in each class of medication at the final CONTROL visit and the price²¹ of generic brands of drug within each class (except for angiotensin II receptor blockers and dihydropyridine calcium channel blockers, which were available only as commercial brands) at their median available dose (Table I).

Short-Term Sensitivity Analysis. Cost-sensitivity analysis was performed by calculating the hypothetical ICG test cost that would equate to a higher cost per mm Hg reduced for ICG than for standard care for both systolic and diastolic BP. Effectiveness sensitivity analysis was performed by calculating the minimum mm Hg reduced for both systolic and diastolic BP in which ICG would result in higher cost per mm Hg reduced.

Long-Term Cost-Effectiveness. Long-Term Outcome Measures. The incremental cost per QALY gained was calculated as the 10-year difference in costs

Table I. Estimated 3-Month and Annual Drug Costs* per Patient for Standard and Impedance Cardiography (ICG) Arms

DRUG CLASS	REFERENCE DRUG	DOSE PER DAY, MG	ANNUAL COST PER DRUG, \$	DRUG UTILIZATION, %	STANDARD ARM		ICG ARM		
					3-MONTH COST PER PATIENT, \$	ANNUALIZED COST PER PATIENT, \$	DRUG UTILIZATION, %	3-MONTH COST PER PATIENT, \$	ANNUALIZED COST PER PATIENT, \$
α-Blocker	Doxazosin mesylate	2	171.90	1.0	0.43	1.72	1.4	0.60	2.41
Angiotensin-converting enzyme inhibitor	Lisinopril	20	131.86	53.7	17.70	70.81	49.3	16.25	65.01
Angiotensin II receptor blocker	Valsartan	160	631.88	30.5	48.18	192.72	46.4	73.30	293.19
β-Blocker	Atenolol	50	33.98	19.0	1.61	6.46	8.7	0.74	2.96
Calcium channel blocker, dihydropyridine	Amlodipine	5	531.86	37.9	50.39	201.57	40.6	53.98	215.94
Calcium channel blocker, nondihydropyridine	Verapamil	240	34.60	6.3	0.54	2.18	10.1	0.87	3.49
Central-acting agent	Clonidine	0.2	48.78	0.0	0.00	0.00	1.4	0.17	0.68
Diuretic, thiazide	Hydrochlorothiazide	25	25.96	33.7	2.19	8.75	34.8	2.26	9.03
Diuretic, loop	Furosemide	20	23.60	1.1	0.06	0.26	9.0	0.53	2.12
Diuretic, potassium-sparing	Triamterene	50	131.86	6.3	2.08	8.31	4.3	1.42	5.67
Estimated cost, \$					123	493		150	601

*Estimates based on prices from www.drugstore.com.²¹

divided by the 10-year difference in QALYs between arms. The number of patients that would need to be treated with ICG to save 1 year of life was calculated by dividing 1 year by the incremental QALYs gained per patient with ICG.

Long-Term QALY and Cost Modeling. Cost-effectiveness analyses in hypertension often extrapolate the BP-lowering advantages at the end of a trial over a lifetime.^{22–24} We used a Markov model to extrapolate the 10-year effects of the incremental BP reduction achieved in the CONTROL trial into one of 4 states: (1) actively treated hypertension, (2) stroke event, (3) IHD event, and (4) other cardiovascular/vascular disease event (which included heart failure, hypertensive heart disease, aortic aneurysm, atherosclerosis, and sudden death). Each disease transition was assumed to occur at a single point after 5 years. We used a spreadsheet program (Excel 2003; Microsoft, Redmond, WA) to simulate clinical outcomes and costs for each transition state. Clinical outcomes were converted to expected quality and quantity of life through QALYs. Event-related costs and expected hypertension management costs were included. All QALYs and costs were discounted at a standard 3% annual rate.²⁵ The probability-adjusted

costs and QALYs for each arm were calculated by multiplying the QALY and cost for each transition state by its transition probability. All model inputs are shown in Table II.

Long-Term Absolute Risk. We used the 10-year stroke, IHD, and other cardiovascular disease mortality rate from a meta-analysis of 1 million subjects,²⁶ which showed linear reductions in mortality risk for both systolic and diastolic BP as low as 115/75 mm Hg. To estimate absolute 10-year mortality risk, we used the average mortality event rate for both men and women at the average final systolic BP achieved in the standard arm of the CONTROL trial, 136 mm Hg. The 10-year mortality risk was based on the average of the 50–59 and 60–69 years of age categories because, at the mean age of 55 years in the CONTROL trial, a patient would be subjected to 5 years of follow-up in both categories. We estimated the expected 10-year event rates by dividing the 10-year mortality rate by known event-survival rates.²⁷

Long-Term Risk Reduction. In the end of the CONTROL trial, the ICG arm achieved an incremental BP lowering of 8 mm Hg systolic and 7 mm Hg diastolic BP. In one pharmacologic trial of more

Table II. Long-Term Cost Utility Model Inputs

VARIABLE	SENSITIVITY ANALYSIS		
	BASE CASE ESTIMATE	ESTIMATE NOT FAVORING COST-EFFECTIVENESS OF ICG	ESTIMATE FAVORING COST-EFFECTIVENESS OF ICG
Trial morbidity and mortality	0		
Combined event and mortality rate, %			
Ten-year morbidity and mortality			
Event rate, %			
Stroke	15.0	11.3	18.8
Ischemic heart disease	30.0	22.5	37.5
Other cardiovascular	8.0	6.0	10.0
Mortality, %			
Stroke	4.5	3.4	5.6
Ischemic heart disease	9.0	6.8	11.3
Other cardiovascular	2.4	1.8	3.0
Event mortality rates, %			
Stroke	30.0	22.5	37.5
Ischemic heart disease (MI)	30.0	22.5	37.5
Other cardiovascular	30.0	22.5	37.5
Decrease in risk with BP advantage from ICG testing, %			
Stroke	20.0	15.0	25.0
Ischemic heart disease (MI)	7.0	5.3	8.8
Other cardiovascular	7.0	5.3	8.8
Utilities			
Stroke	0.60		
Ischemic heart disease (MI)	0.88		
Other cardiovascular	0.84		
Trial costs per patient, \$			
Total costs per standard-arm patient	394		
Total costs per ICG-arm patient	554		
Ten-year costs per patient, \$			
Event costs in year of occurrence			
Stroke, survive	22,112		
Stroke, die	34,961		
MI, survive	33,724		
MI, die	38,471		
Other cardiovascular, survive	5800		
Other cardiovascular, die	5800		
Annual event management costs			
Stroke, survive	4733		
MI, survive	2186		
Other cardiovascular, survive	2186		
Annual drug costs			
Standard care	493	616	370
ICG	601	751	450
Annual clinic visit costs for hypertension	136		
Annual ICG testing costs in ICG arm	44	89	22

ICG indicates impedance cardiography; MI, myocardial infarction.

than 15,000 patients, the BP-lowering advantage at 3 months was largely sustained at 66 months.²⁸ To equip our base model, we assumed only a 4-mm Hg sustained systolic BP advantage over the 10-year period, which assumed that 50% of the systolic and

100% of the diastolic BP advantage achieved with ICG would be lost for the full 10-year period. The meta-analysis reported that each 2-mm Hg systolic BP reduction over a 10-year period would result in 10% reduction in stroke mortality and 7% reduction

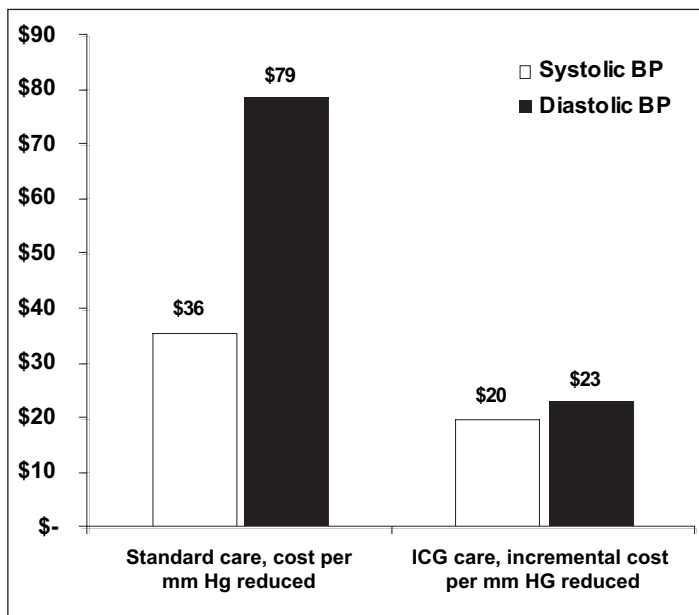


Figure 3. Standard-arm cost per mm Hg reduced vs impedance cardiography (ICG)-arm incremental cost per mm Hg reduced. BP indicates blood pressure.

in IHD or other cardiovascular disease mortality. We assumed that the combined 7% reduction in IHD or other cardiovascular disease was evenly distributed such that for each 2 mm Hg reduced, IHD mortality would be reduced by 3.5% and other cardiovascular disease would be reduced by 3.5%. Therefore, we estimated that a sustained 4-mm Hg systolic BP reduction would yield a 20% reduction in stroke mortality, 7% reduction in IHD mortality, and 7% reduction in other cardiovascular disease mortality. We assumed that the nonfatal stroke, IHD, and other cardiovascular event rates would be reduced similarly and that event-mortality rates would be the same for patients experiencing events in both arms.

Long-Term Utilities. QALYs were based on both quantity and quality of life for each disease state transition, in which each year of life is given a specific health index value. We used the following health index values: healthy 1.0, death 0.0, nonfatal stroke 0.60,²⁹ myocardial infarction 0.88,³⁰ and other cardiovascular events 0.84.³¹ Using the health index of 0.60 for nonfatal stroke as an example, 10 years of post-stroke life in stroke patients equates to 6 years of healthy life.

Long-Term Costs. Long-term costs included short-term costs and estimated costs for morbidity, mortality, hypertension management, hypertension drugs, and ICG tests (Table II). Morbidity and mortality

costs included the total diagnosis, treatment, and management costs during the event year for all events, as well as the subsequent annual cost of event-related management. Costs for stroke and myocardial infarction were based on a sample of CMS reimbursements.³² The costs of other cardiovascular events were based on the estimated CMS reimbursement for a hospital admission of heart failure. Annual costs for other cardiovascular events used the same cost as myocardial infarction. Clinic visit costs assumed 2 visits per patient per year in each arm. Although it is not clear whether additional ICG testing would be required to sustain the BP advantage in the ICG arm, we assumed that each ICG-arm patient would receive one additional ICG test per year. Annual drug costs for hypertension were estimated as described previously and were not modeled to reduce over time, although several branded drugs are expected to soon become generic.

Long-Term Sensitivity Analysis. Sensitivity analysis was performed for cost per QALY of ICG as a function of key inputs that were considered simultaneously favorable and unfavorable to ICG. Favorable estimates compared with the base case included a 25% higher event and mortality rate, risk reduction for the ICG arm based on a sustained 5-mm Hg lower systolic BP, 25% higher event-mortality rate, 25% decrease in annual drug costs for both arms, and only 50% of patients (vs 100%) receiving one additional ICG test per year. Unfavorable estimates compared with the base case included a 25% lower event and mortality rate, risk reduction for the ICG arm based on a sustained 3-mm Hg lower systolic BP, 25% lower event-mortality rate, 25% increase in annual drug costs for both arms, and 2 ICG tests per patient per year in the ICG arm.

Results

Short-Term Cost-Effectiveness. The 3-month total cost for the standard arm was \$394 (visits \$271, drugs \$123), equating to a \$36 cost per mm Hg reduced for systolic BP and a \$79 cost per mm Hg reduced for diastolic BP. The 3-month total cost for the ICG arm was \$554 (visits \$271, ICG tests \$133, drugs \$150), equating to a \$29 cost per mm Hg reduced for systolic BP and a \$46 cost per mm Hg reduced for diastolic BP. Figure 3 illustrates the short-term incremental cost per mm Hg reduced for ICG of \$20 for systolic BP and \$23 for diastolic BP, 44% lower for diastolic BP and 71% lower for systolic BP vs the standard arm cost per mm Hg

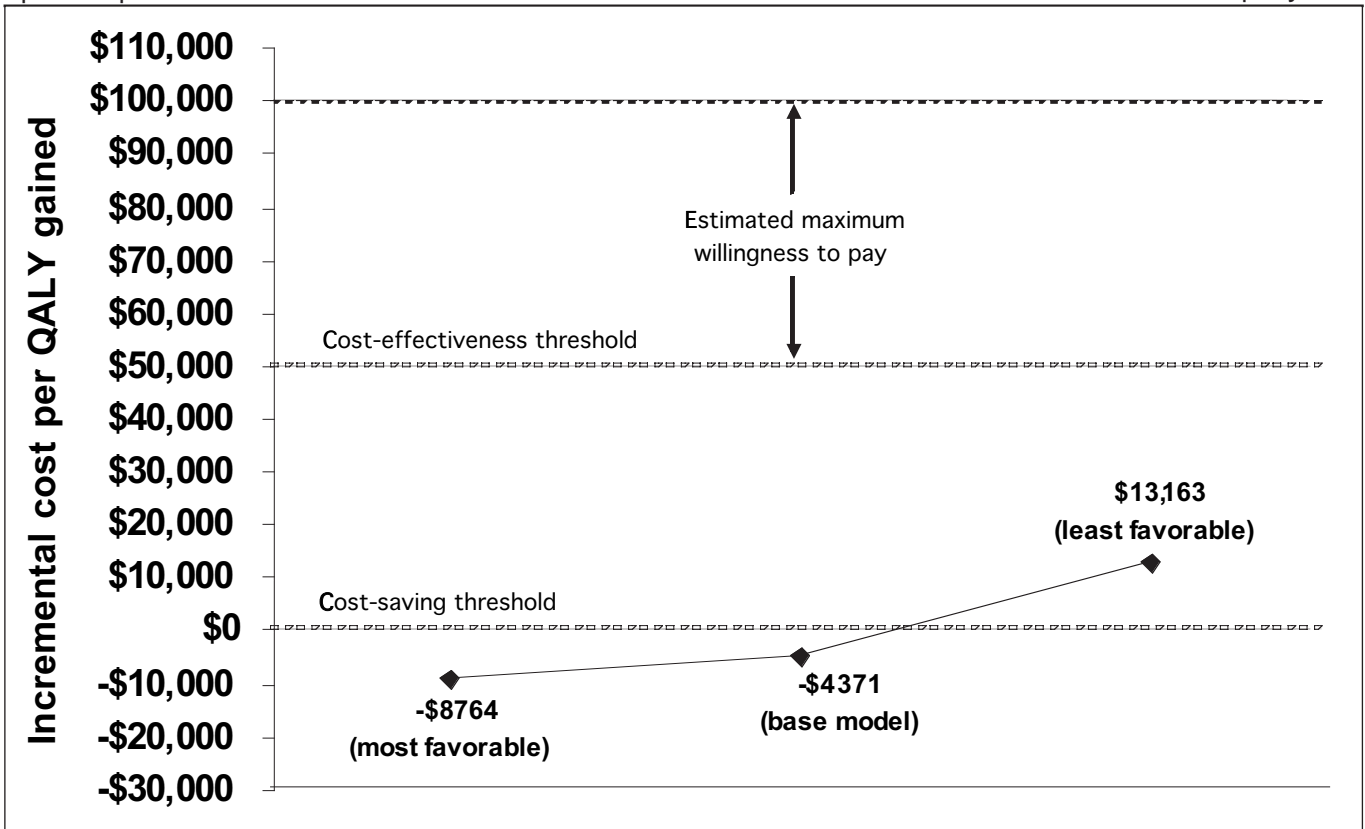


Figure 5. Incremental cost per quality-adjusted life-years (QALY) gained with impedance cardiography for base model and using most and least favorable inputs from Table II.

(8.241 ICG, 8.187 standard), equating to \$13,163 per QALY gained. Based on these QALYs, between 5.2 and 18.5 patients would need to be treated with ICG to save 1 year of life.

Discussion

New drugs are approved by the Food and Drug Administration (FDA) if they are safe and effective in randomized controlled trials and receive a large degree of clinical acceptance upon approval. In contrast, the FDA 510(k) marketing clearance for a new device or diagnostic test is not typically based on randomized controlled trial evidence, and clearance often marks only the beginning of the process of clinical acceptance. Fundamentally, the regulatory burden is much lower for a noninvasive test that provides information (upon which a clinician may or may not act) than for a drug, which directly causes benefit or harm. There is also a lower burden from an evidence-based perspective because the relationship between testing and clinical outcome is not as easily linked. Therefore, new tests are rarely held to the same randomized controlled trial standard as new therapies.³³ Instead, studies of reproducibility, accuracy, risk stratification, and/or effect on clinical decisions are generally the basis for clinical acceptance.³⁴ Because of the lack of

randomized trial results with most tests, evaluating their cost effectiveness is typically more difficult than with therapies.³⁵ However, one commercially available ICG device has accomplished something that most tests are not required to show—improvement in clinical end points in two randomized controlled trials. The CONTROL trial results are impressive, yielding BP reduction advantages seldom seen in pharmacologic trials of any duration (8/7 mm Hg).

New therapies and tests have increased patient longevity, while a more educated health care consumer has increased demand for the highest level of care possible, fueling the increase in health care costs in a resource-constrained environment. This has led some to advocate cost-effectiveness analysis to help guide health care policy decisions.³⁶ While CMS does not formally take cost into account when evaluating coverage,³⁷ cost-effectiveness is becoming increasingly important to health care policy decision makers. Even with the impressive clinical results from CONTROL, it is appropriate to evaluate ICG cost-effectiveness to help determine whether it should be more widely applied.

BP reduction by itself is an effective surrogate end point for long-term outcomes because it is equated with improved morbidity and mortality. However,

short-term cost-effectiveness analysis of new antihypertensive drugs is not common, perhaps because their benefits occur over longer periods. In our study, the incremental cost per incremental mm Hg of systolic and diastolic BP reduction resulting from ICG testing was 44% lower for systolic BP and 71% lower for diastolic BP vs the standard arm cost per mm Hg reduced. Therefore, ICG testing is cost-effective from a short-term perspective. This lower incremental cost is in striking contrast to typical clinical experience in which greater efforts must be expended to reduce BP after the initial reduction. In order for ICG to cost more per mm Hg reduced than the standard arm, either the cost of the ICG test would need to be 2–4 times greater than its current level or the incremental reduction in BP with ICG care would have to be <4.5 mm Hg systolic or 2 mm Hg diastolic. Both of these scenarios seem unlikely.

Some have advocated that new therapies or tests should be adopted only if the cost is under \$50,000 to \$100,000 per QALY gained.³⁸ Examples of cardiac devices approved by CMS and their estimated cost per QALY gained over a patient's lifetime include left ventricular assist devices (\$500,000 to \$1.4 million³⁹), implantable cardioverter-defibrillators (\$34,000 to \$70,200⁴⁰), and cardiac resynchronization therapy (\$79,800 to \$156,500⁴¹). Our base model actually showed that ICG lowered costs and increased QALYs, which is rare for new technologies. Even when the least-favorable estimates were more considered, use of ICG resulted in only a \$13,163 cost per QALY, still much lower than the other examples and the proposed thresholds. Therefore, ICG testing also appears to be cost-effective from a long-term perspective.

There are 30 million US adults older than 60 years with hypertension.³ Among these are 19 million in whom hypertension has been diagnosed and anti-hypertensive medications instituted. Approximately 8.5 million (44%) of these 19 million actively treated patients are still not controlled to BP <140/90 mm Hg and are thus at increased risk for cardiovascular events. Our study indicates that if implemented in this patient population, ICG would result in cost-effective utilization of short-term health care resources and, likely, long-term cost savings or a low cost per life-year gained. Our base model indicates that if used in all 8.5 million patients, ICG could increase lives by 927,000 years while saving as much as \$4 billion over a 10-year period. Using the worst-case scenario, ICG could increase lives by 459,000 years with a \$6 billion cost.

Ambulatory BP monitoring is an effective tool to diagnose white coat hypertension, and studies

have demonstrated that it is cost-effective for this purpose by preventing unnecessary treatment.⁴² Using serial ambulatory BP⁴³ or home BP monitoring^{44–46} as targets for clinic-based treatment, however, may not be as clinically or cost-effective as using them to identify white coat hypertension. In any case, we believe that the addition of serial ICG measurements to either ambulatory BP or home BP monitoring are complimentary because they serve different purposes. While ambulatory and home monitoring help identify whether to treat patients, ICG helps identify how to treat patients.

Cost-effectiveness studies are subject to even more limitations than clinical studies due to the number of assumptions required and the long-term extrapolation of shorter-term results. As such, our assumptions should be considered. In the short-term analysis, it was not possible to directly compare the costs of equivalent BP lowering in standard and ICG arms, as ICG-guided therapy resulted in a substantially greater BP reduction. It is likely that additional BP reduction in the standard arm would be more difficult and more expensive per mm Hg achieved, resulting in even greater cost-effectiveness for ICG. In the long-term analysis, we assumed that ICG's trial BP-lowering advantage of 8/7 mm Hg would be sustained as a 4-mm Hg lower systolic BP over a 10-year period (3 and 5 mm Hg in sensitivity analysis); the actual BP-lowering effects could be less than or greater than these levels. We assumed that there would be no sustained diastolic BP advantage with ICG over the full 10-year term; a small sustained decrease would be expected to further reduce event rates and improve ICG cost-effectiveness. We modeled sustained systolic BP reductions to result in lower event and mortality rates over a 10-year period; without a 10-year follow-up term, we cannot guarantee that these events would occur. We extrapolated the BP results of a smaller but sufficiently powered trial to the prognostic outcomes of pooled larger trials; it is unknown whether the scale is transferable. We did not model renal-related mortality or morbidity even though renal events cause a substantial risk for elevated BP; doing so would have increased event rates and improved long-term ICG cost-effectiveness. Our long-term analysis was based on 10 years when the average 55-year-old could be expected to survive 30 years or more. While 10 years was conservative, extending the modeling period to 30 years would have resulted in even better ICG cost-effectiveness. We also conducted more simplified long-term modeling than

is possible, with relatively basic assumptions for transition states, costs, and QALYs. While this was intentional, a more complex model may result in different cost per QALYs gained with ICG.

Conclusions

The use of ICG testing to reduce BP in uncontrolled

hypertensive patients is cost-effective from both a short- and long-term perspective. More widespread use of ICG in this population should be considered.

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