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Health Care Economics: Cost-effectiveness Alongside Clinical Trials

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Outline

- Patient-level CEA
- Estimating costs
- Estimating effectiveness
- Cost-effectiveness analysis
- Cost-effectiveness plane
- Sensitivity analyses
- CEA in an observational study

Cost-effectiveness

- Costs have become important factor in medical decision making.
- Therapy, treatment, device, etc. to improve health, quality of life, etc.
- Comes with a cost - usually higher than the previous standard of treatment.
- How much is an individual or society willing to pay for the improvement? **Willingness-to-pay (WTP)**

Cost-effectiveness patient-level data

- **Outcome** from study -
  Survival, life years gained, Quality-adjusted life years (QALYs)
- QALYs calculated by multiplying survival by utility, a measure of health status scaled from zero (death) to one (perfect health).
- **Cost** of treatment – Procedures, physician, medications, hospitalizations

Estimating patient-level costs

- UB-04
- System reimbursement schedules
- Diagnosis related group (DRG)
- Case Mix Group (CMG) – Canada
- Medicare – Medicaid data
- Medications – Redbook wholesale costs

What to cost?

- Primary events: CV death, MI, Stroke, etc.
- SAEs: bleeding, syncope, etc.
- Subsequent hospitalizations: heart failure, PVD, etc.
- Physician costs: separate from hospital costs
- Follow-up care: rehabilitation costs
- Medications: statins, diuretics, etc.
- Lost wages: but usually too difficult to estimate

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Clopidogrel for the Reduction of Events During Observation (CREDO) trial

Table 3: Top Ten Hospitalization Diagnostic Related Groups (DRGs) in CREDO

DRG	Description	Number of Hospitalizations Clopidogrel	Number of Hospitalizations Placebo	Hospitalization Cost (MEDSTAT)	Hospitalization Cost (Medicare)
116	OTH PERM CARD PACEMAK IMPL OR PTCA W CORONARY ARTERY STENT IMPLNT	882	883	$17,768.60	$11,515.94
112	PERCUTANEOUS CARDIOVASCULAR PROCEDURES	221	234	$10,687.98	$9,399.47
140	ANGINA PECTORIS	125	118	$4,136.23	$2,064.18
143	CHEST PAIN	102	109	$3,663.06	$2,008.86
107	CORONARY BYPASS W CARDIAC CATH	89	88	$41,764.23	$27,039.70
133	ATHEROSCLEROSIS W/O CC	12	21	$7,921.07	$2,439.87
127	HEART FAILURE & SHOCK	20	12	$7,207.79	$4,557.51
90	SIMPLE PNEUMONIA & PLEURISY AGE >17 W/O CC	8	12	$4,800.75	$2,516.23
106	CORONARY BYPASS W PTCA	7	12	$43,902.70	$37,259.59
122	CIRCULATORY DISORDERS W AMI W/O MAJOR COMP, DISCHARGED ALIVE	8	9	$11,047.59	$4,260.53

Table 2. Acute CVD Event Costs (Per Episode)

Costs (2018 USD) by age group	Mean	Standard Deviation	Minimum	Maximum	Distribution	Reference
Fatal CVD event						
45-64	$18,940	$5,175	$11,921	$32,205	Gamma	(4,5)
65-84	$17,473	$4,567	$11,518	$29,420	Gamma	
≥85	$11,970	$3,394	$7,620	$20,926	Gamma	
Myocardial infarction						
45-64	$22,542	$3,908	$14,353	$29,672	Gamma	(4,5)
65-84	$22,410	$4,176	$14,241	$30,612	Gamma	
≥85	$14,159	$3,822	$8,288	$23,270	Gamma	

4. (HCUP) NCaUP. Overview of the National (Nationwide) Inpatient Sample (NIS). Agency for Healthcare Research and Quality, 2019.
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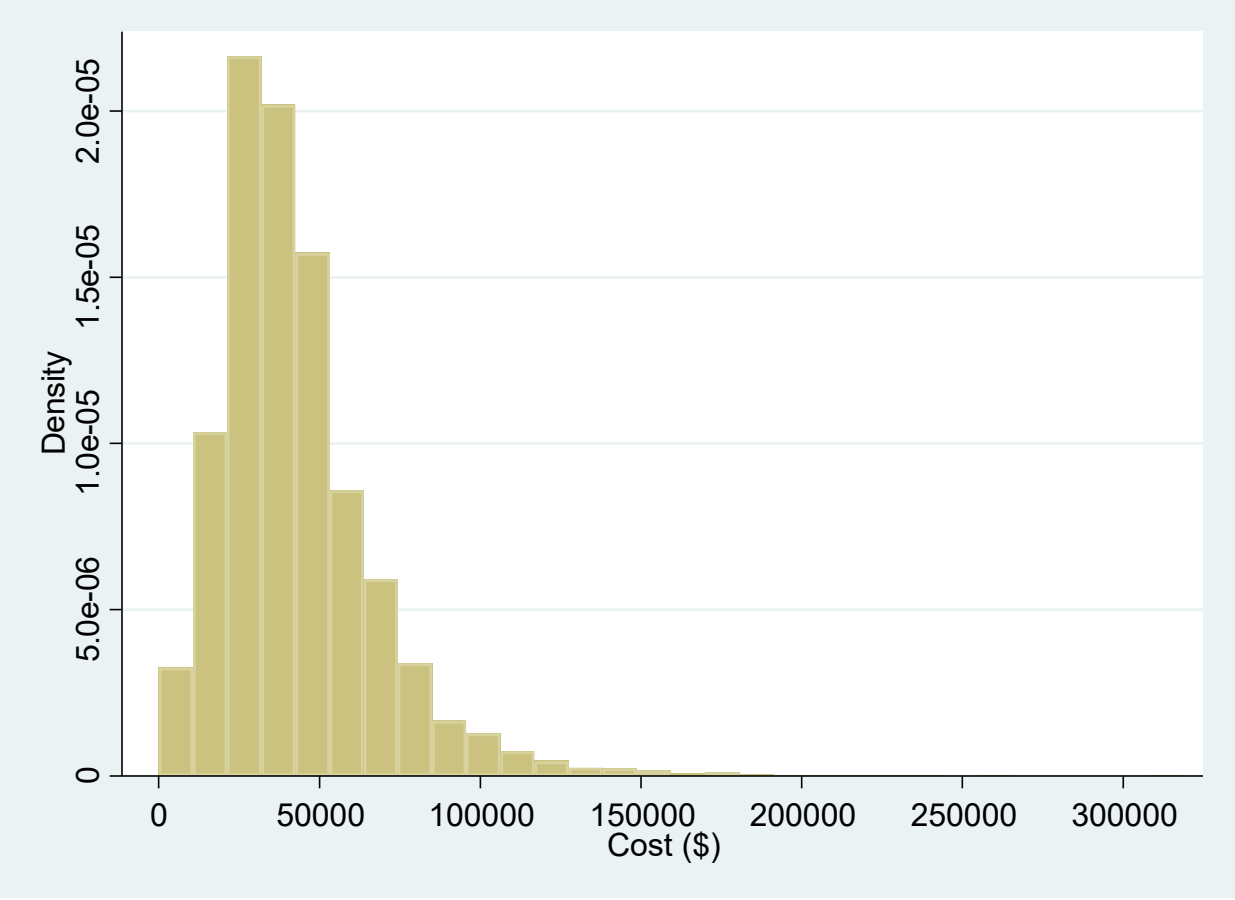

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Utilities

- Measure of patient quality of life.
- Scaled from 0 (death) to 1 (perfect health).
- Patient reported – obtained during the trial via published instruments (EQ-5D).
- Estimated from similar sample (age and sex) if not available in trial.

Supplemental Table 4. Cost-effectiveness analysis utility values.

Description	Value	Distribution	SD	Reference
Chronic Utility				
No history of CVD	1.0000	Beta	----	18,19
History of angina	0.9064	Beta	0.0223	18,19
History of MI	0.9648	Beta	0.0287	18,19
History of stroke	0.8835	Beta	0.0241	18,19
History of MI & stroke	0.8524	Beta	0.0359	18,19
Acute Disutility*				
Angina	-0.0078	Beta	0.0021	18,19
PCI	-0.0096	Beta	0.0028	18,19
CABG	-0.0192	Beta	0.0046	18,19
MI	-0.0079	Beta	0.0022	18,19
Stroke	-0.0113	Beta	0.0031	18,19

* Disutilities applied if patient experienced event or revascularization during the trial.
SD = standard deviation; CVD = cardiovascular disease; MI = myocardial infarction;
PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

Trial effectiveness

- Survival
- Life-years gained.
- Quality adjusted life years (QALYs) = utility x life years.
- 4.5 * .8835 = 3.98 (hx of stroke)
- 3.98 - .0113 = 3.97 (non-fatal stroke during trial)

Incremental cost-effectiveness

$$\textbf{Incremental Cost-Effectiveness Ratio (ICER)} = \frac{\mu\text{CostA} - \mu\text{CostB}}{\mu\text{EffA} - \mu\text{EffB}}$$

$$= \frac{\mu\Delta\ \text{C}}{\mu\Delta\ \text{E}}$$

What is cost-effective?

- US: ICER = $50,000
- Dates back to 1950's congressional hearing on cost of dialysis.
- Spend $50,000 for 1 QALY gained.
- Willingness-to-pay (wtp)?
- Depends on perspective: society, insurance company, etc.

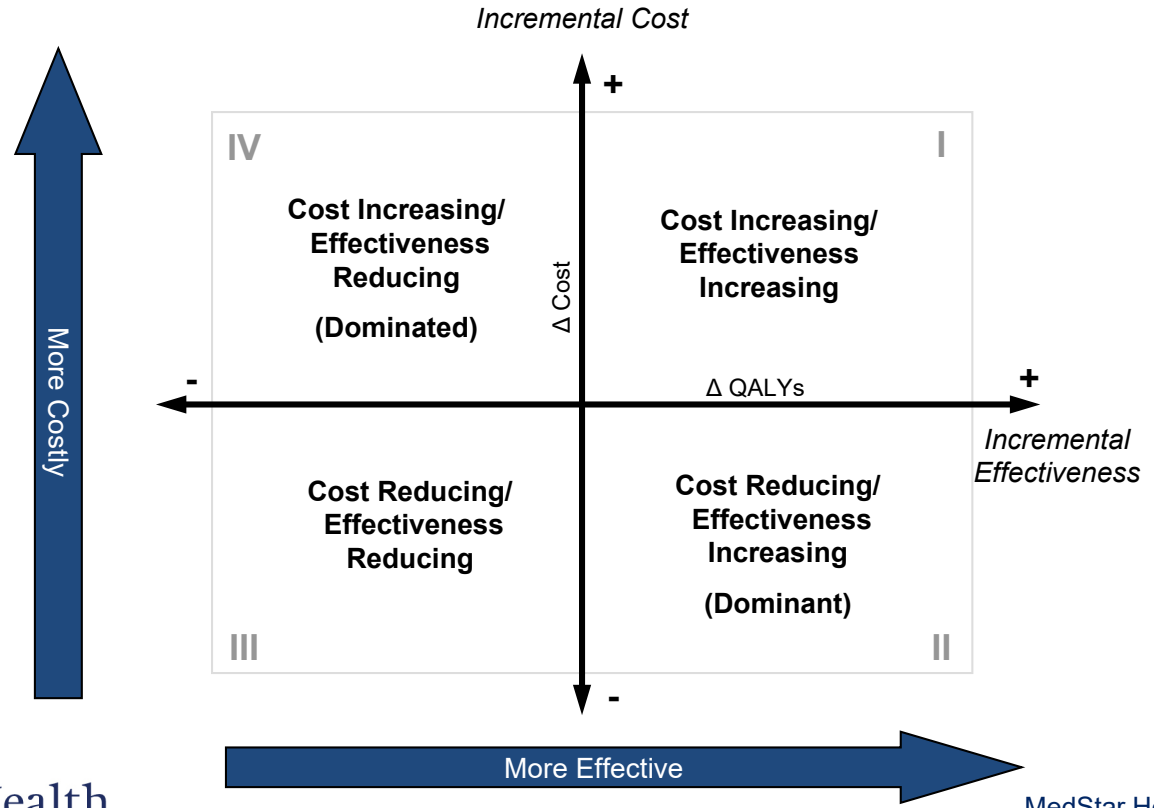
Statistical analysis of ICER

- ICERs with same sign may have different meaning
- Ratio of differences in means
- Need a sampling distribution for the ICER (e.g., normal, gamma, beta) to estimate variability (standard deviation)

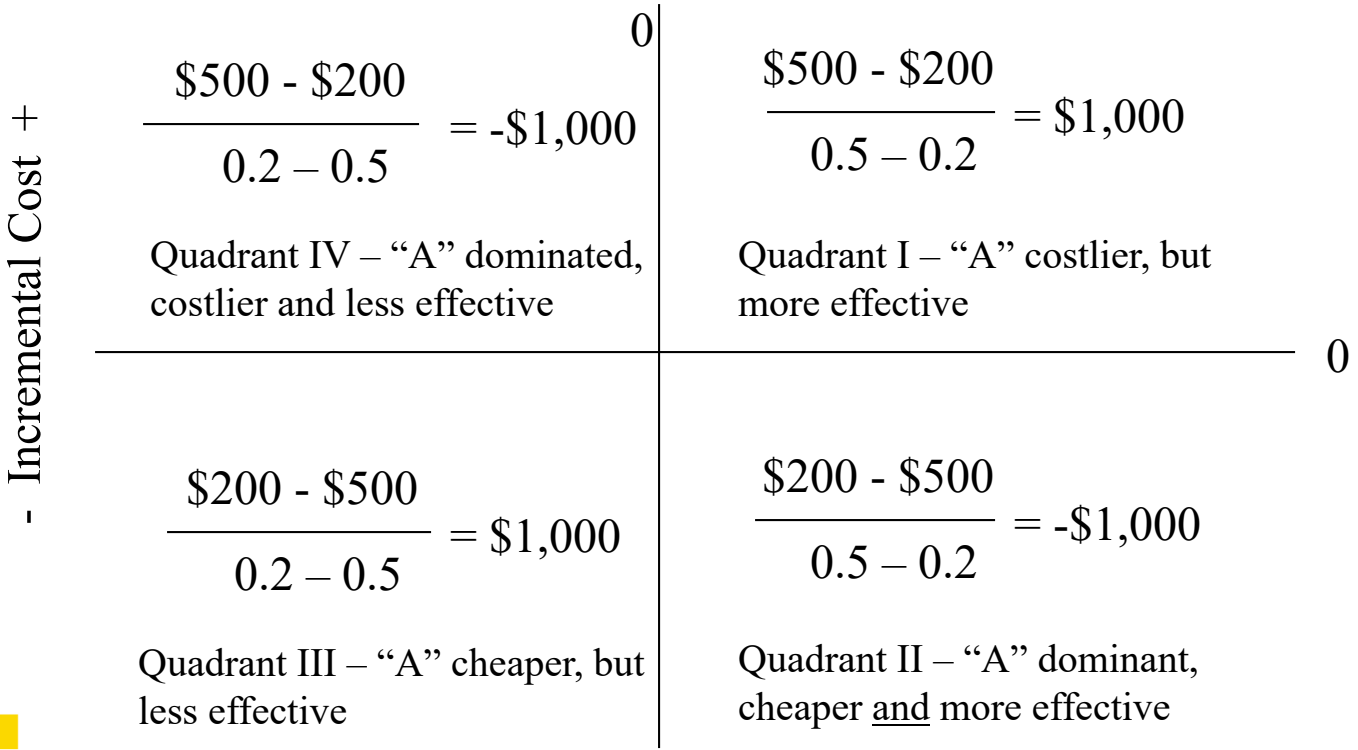
Bootstrap with replacement

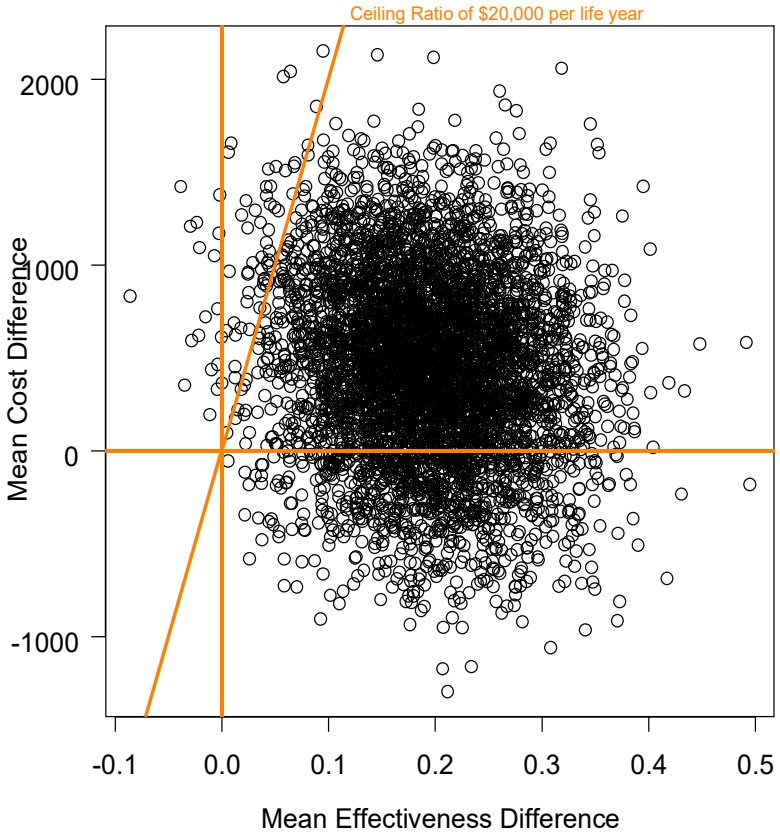
- Draw random samples from data
- Draw same number of random samples as number of patients or observations in data – calculate statistic of interest
- Replace each observation after it is drawn
- Repeat a large number of times (5000 – 10,000)
- Results in a distribution of the statistic of interest (ICER)

Cost-effectiveness plane



Cost-effectiveness plane





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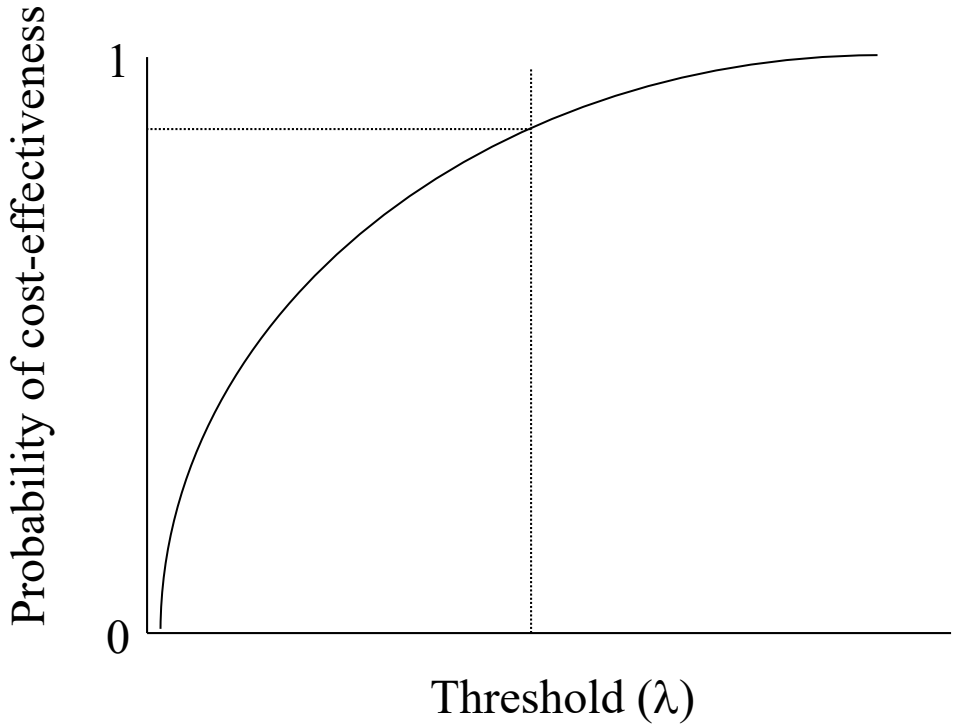
Cost-Effectiveness Acceptability Curve



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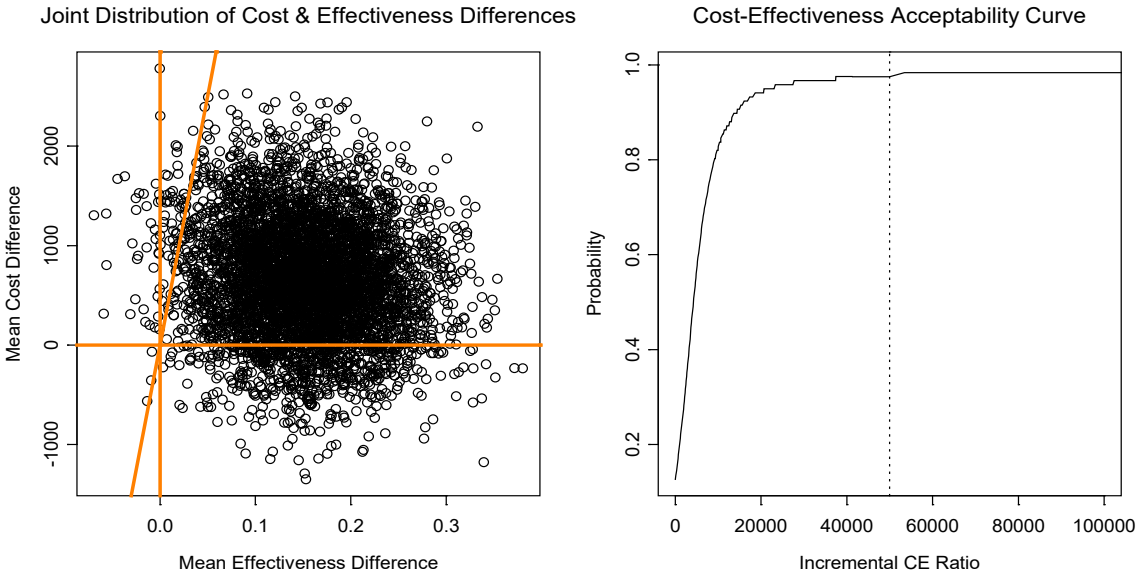
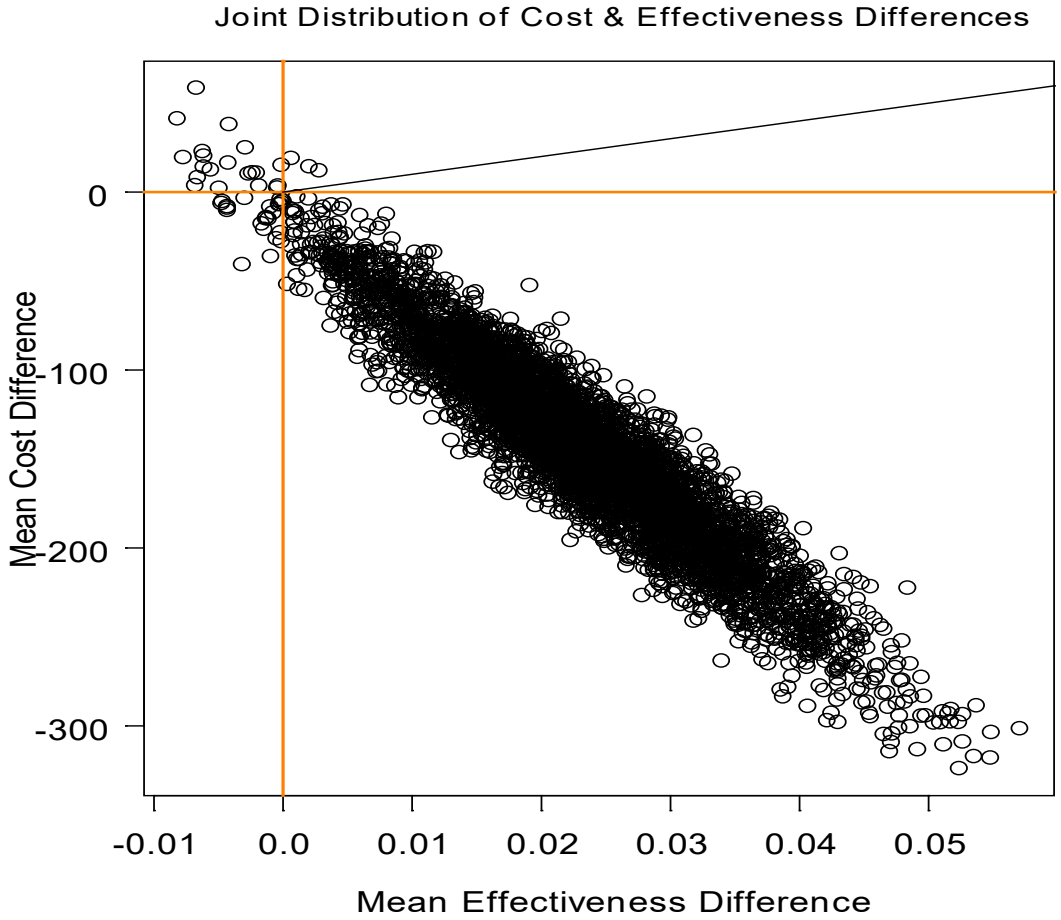
Long Term Cost Effectiveness (Cost per life year gained)
Framingham





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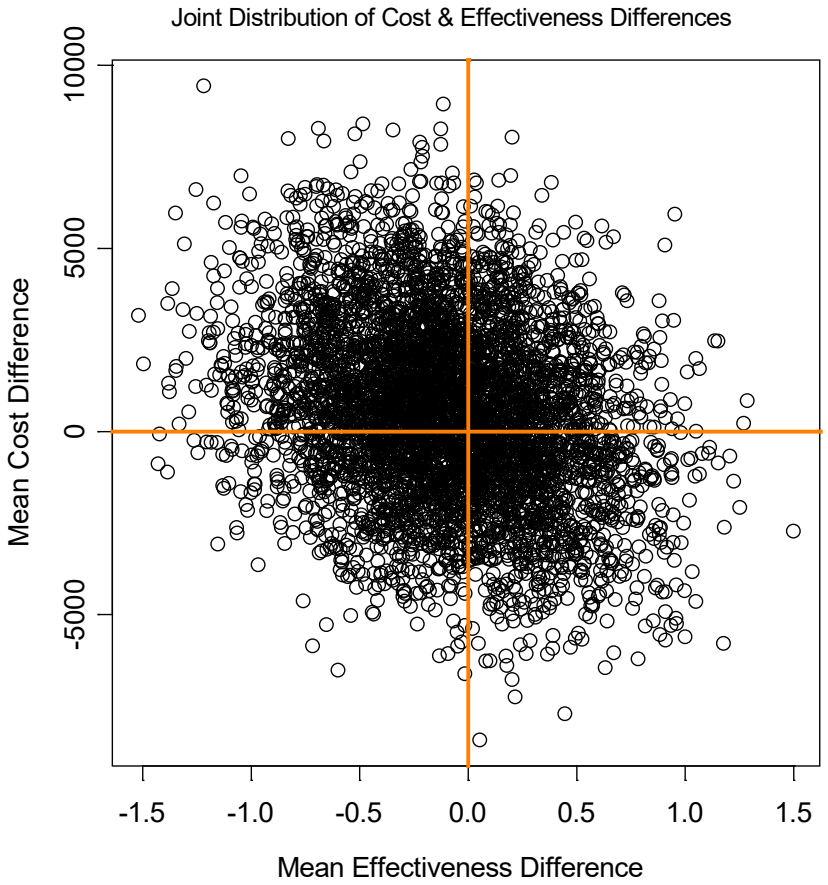

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CEA discounting

- Value of QALY diminishes over time.
- No discounting in first year.
- Second year (3%) = $(1/(1 + 0.03)^2)$
- Third year (3%) = $(1/(1 + 0.03)^3)$
- Etc.
- Discount both QALYs and costs.

Sensitivity Analyses

- Every source of data used in cost-effectiveness research is subject to error – cost and QALYs.
  - Demonstrate how error affected the accuracy and reliability of the cost-effectiveness.
  - Judge the robustness of conclusions
  - Determine whether results are insensitive to substantial but plausible variation in a parameter

Types of Sensitivity Analysis

- One-way (univariate) Sensitivity Analysis
- Two-way (bivariate) Sensitivity Analysis
- Multi-way Sensitivity Analysis
- **Probabilistic sensitivity analysis**
- **Scenario analyses** (e.g., what if treatment effect only lasts 1 year?)

What does a probabilistic sensitivity analysis do?

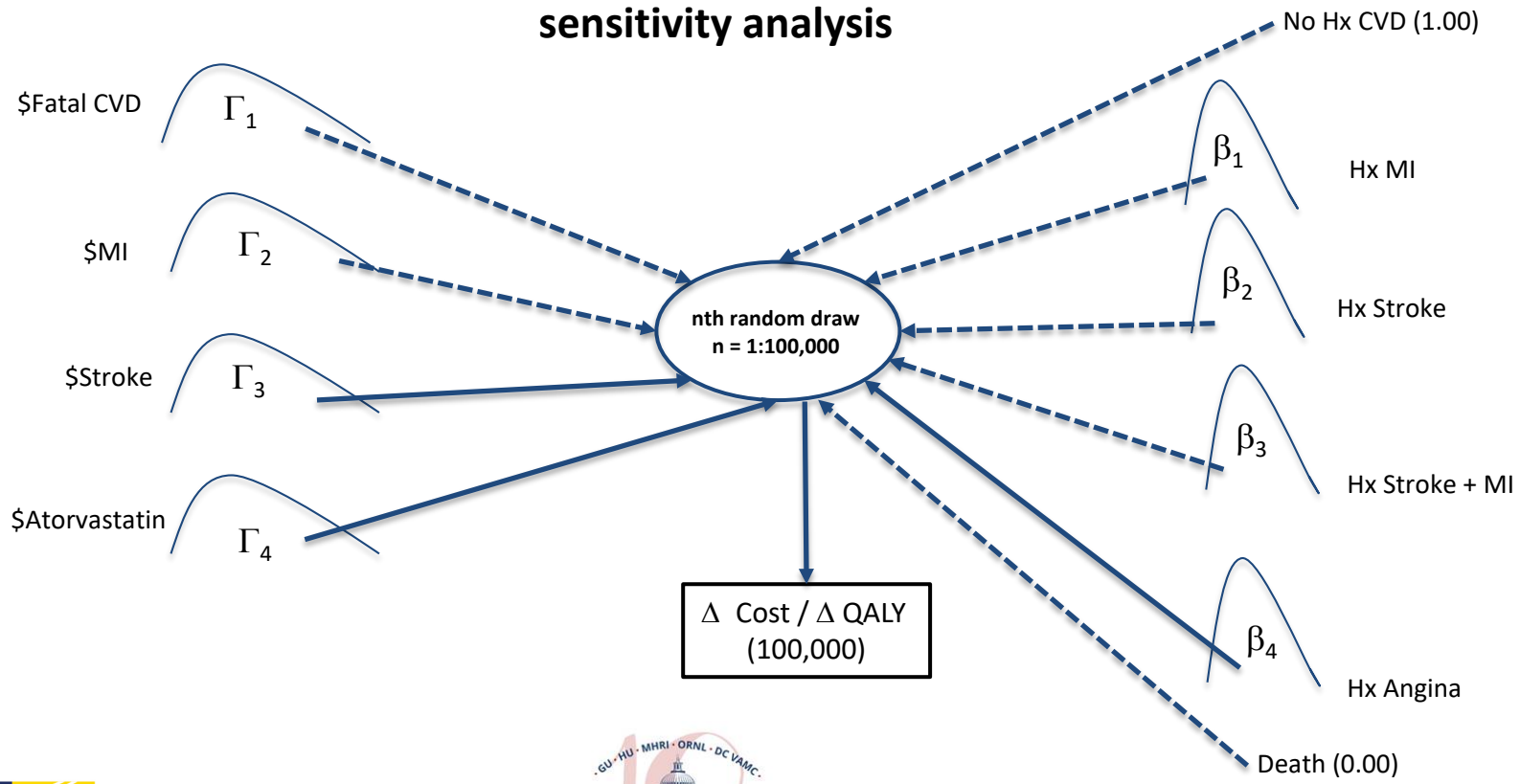
- Define a distribution of a parameter.
- Draw a random value from the distribution.
- Calculate the ICER with the value drawn.
- Repeat the process a large number of times.
- Report the mean & standard deviation of the distribution, or percentiles of the distribution, or what proportion of the results are below a threshold value (wtp) for the ICER.

Bayesian analysis

Characteristics of variables in the analysis of probabilistic sensitivity analysis: COURAGE

		Base Value	Range	Distribution
Effectiveness	CVD (Mortality)	0.0787	0.003, 0.20	Beta
	AMI (Prevalence)	0.1185	0.037, 0.30	Beta
	Stroke (Prevalence)	0.0257	0.016, 0.40	Beta
	QALF lost	0.8063	0.5, 2.6	Gamma
	Utility	0.91	0.50, 0.95	Beta
Cost	In-trial	$29805	$19,000, $45,230	Gamma
	Initial cost	$6,484	$4,220, $9,710	Gamma
	Revascularization Hospitalization	$9,660	$5,840, $10,760	Gamma
	Other cardiovascular Hospitalization	$9,671	$5,200, $14,620	Gamma
	Medication	$3,184	$1,900, $6,560	Log-normal
	Outpatient service	$6,509	$3,580, $11,670	Gamma
	Beyond trial period	$65,313	$45,590, $109,620	Normal

Probabilistic (Bayesian) sensitivity analysis



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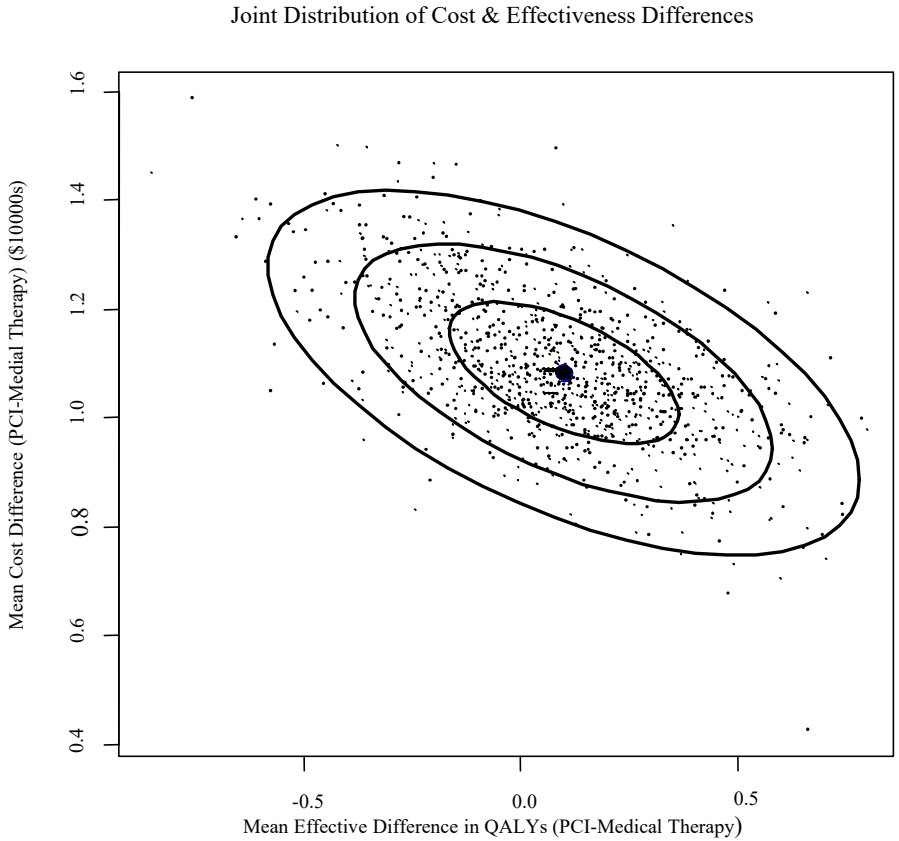
Probabilistic sensitivity analysis in COURAGE

- The probability assumptions of effectiveness were derived from American Heart Association statistics and the Cardiovascular Health Study.
- Monte Carlo simulation was performed to derive the differences in QALYs and mean cost between the two treatment groups (PCI + OMT vs. OMT alone).

Contour Plot



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Cost-effectiveness beyond the study period

- In-trial data used to project beyond the study period.
- **Time horizon:** 10 years; lifetime
- **Life expectancy** beyond trial period
- **Probability of events** beyond trial period
- **Discounting** (0%, 3%, 6%)

Cost-Effectiveness Analysis: Observational Studies

- Reduce selection bias
  - Matching
  - Weight adjusted
- The impact of unmeasured confounder

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ORIGINAL INVESTIGATIONS

Cost-Effectiveness of Revascularization Strategies

The ASCERT Study

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ABSTRACT

BACKGROUND ASCERT (American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies) was a large observational study designed to compare the long-term effectiveness of coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) to treat coronary artery disease (CAD) over 4 to 5 years.

OBJECTIVES This study examined the cost-effectiveness of CABG versus PCI for stable ischemic heart disease.

METHODS The Society of Thoracic Surgeons and American College of Cardiology Foundation databases were linked to the Centers for Medicare and Medicaid Services claims data. Costs for the index and observation period (2004 to 2008) hospitalizations were assessed by diagnosis-related group Medicare reimbursement rates; costs beyond the observation period were estimated from average Medicare participant per capita expenditure. Effectiveness was measured via

Characteristics of the Patients

Characteristic	Unadjusted Data		
	CABG (N=86,244)	PCI (N=103,549)	P Value
Age (yr)	73.1±5.6	74.7±6.5	<0.001
Male sex (%)	68.6	57.8	<0.001
History of heart failure (%)	11.5	10.2	<0.001
History of myocardial infarction (%)	25.3	24.6	<0.001
Diabetes (%)			
Any	38.6	34.4	<0.001
Requiring insulin	10.2	9.8	0.007
Hypertension (%)	84.8	83.4	<0.001
Renal failure (%)	6.1	6.2	0.57
Chronic lung disease (%)	20.7	18.9	<0.001
Cerebrovascular disease (%)	17.6	15.8	<0.001
Peripheral arterial disease (%)	17.9	15.3	<0.001
Body-mass index†	28.7±5.8	28.7±5.9	0.78
Smoking status (%)			
Former smoker	44.0	42.5	<0.001
Current smoker	12.9	11.6	<0.001
Angina (%)			
None	21.8	30.8	<0.001
Stable	49.6	22.6	<0.001
Unstable	28.6	46.6	<0.001
Ejection fraction (%)	52.9±12.2	55.5±11.4	<0.001
Three-vessel disease (%)	80.3	32.1	<0.001
Urgent status (%)	68.6	57.8	<0.001

† Plus–minus values are means ±SD.

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Results: IPW Adjusted and Matched Data

TABLE 1 Baseline Characteristics

	Unadjusted			Inverse Probability Weighted Adjusted			Matched Data		
	CABG (n = 86,244)	PCI (n = 103,549)	p Value	CABG (n = 86,244)	PCI (n = 103,549)	p Value	CABG (n = 43,084)	PCI (n = 43,084)	p Value
Age, yrs	73 ± 6	75 ± 7	<0.0001	74 ± 9	74 ± 8	0.49	74 ± 6	74 ± 6	0.62
Male	69	58	<0.0001	62	63	0.17	64	64	0.69
History of heart failure	12	10	<0.0001	11	11	0.07	11	11	0.31
History of MI	25	25	0.0001	25	25	0.51	24	24	0.89
Diabetes	39	34	<0.0001	36	36	0.97	37	37	0.63
Insulin-RDM	10.2	9.8	0.0069	9.7	9.9	0.35	10.1	10.0	0.66
Hypertension	85	83	<0.0001	84	84	0.58	84	84	0.37
Renal failure	6.1	6.2	0.57	6.1	6.1	0.80	6.2	6.2	0.84
Chronic lung disease	21	19	<0.0001	19	20	0.50	20	20	0.99
Cerebrovascular disease	18	16	<0.0001	17	17	0.86	17	17	0.93
Peripheral artery disease	18	15	<0.0001	16	16	0.97	16	17	0.45
BMI, kg/m^2	29 ± 6	29 ± 6	0.78	29 ± 9	29 ± 8	0.97	29 ± 6	29 ± 6	0.58
Former smoker	44	43	<0.0001	43	43	0.45	43	43	0.37
Current smoker	13	12	<0.0001	12	12	0.74	12	12	0.39
No angina	22	31	<0.0001	26	27	0.23	28	28	0.94
Stable angina	50	23	<0.0001	35	35	0.46	34	34	0.65
Unstable angina	28	47	<0.0001	39	38	0.066	38	38	0.71
Ejection fraction	53 ± 13	55 ± 13	<0.0001	54	54	0.58	54 ± 12	54 ± 13	0.43
Vessels diseased									
2	20	68	<0.0001	47	46	0.043	37	37	0.88
3	80	32		53	54		63	63	
Status urgent	35	36	<0.0001	36	35	0.051	36	36	0.43

Values are mean ± SD or %.

BMI = body mass index; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; RDM = requiring diabetes mellitus.

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Cost-effectiveness Analysis PSBB Adjusted

TABLE 2 Cost-Effectiveness Analysis: PSBB Adjusted

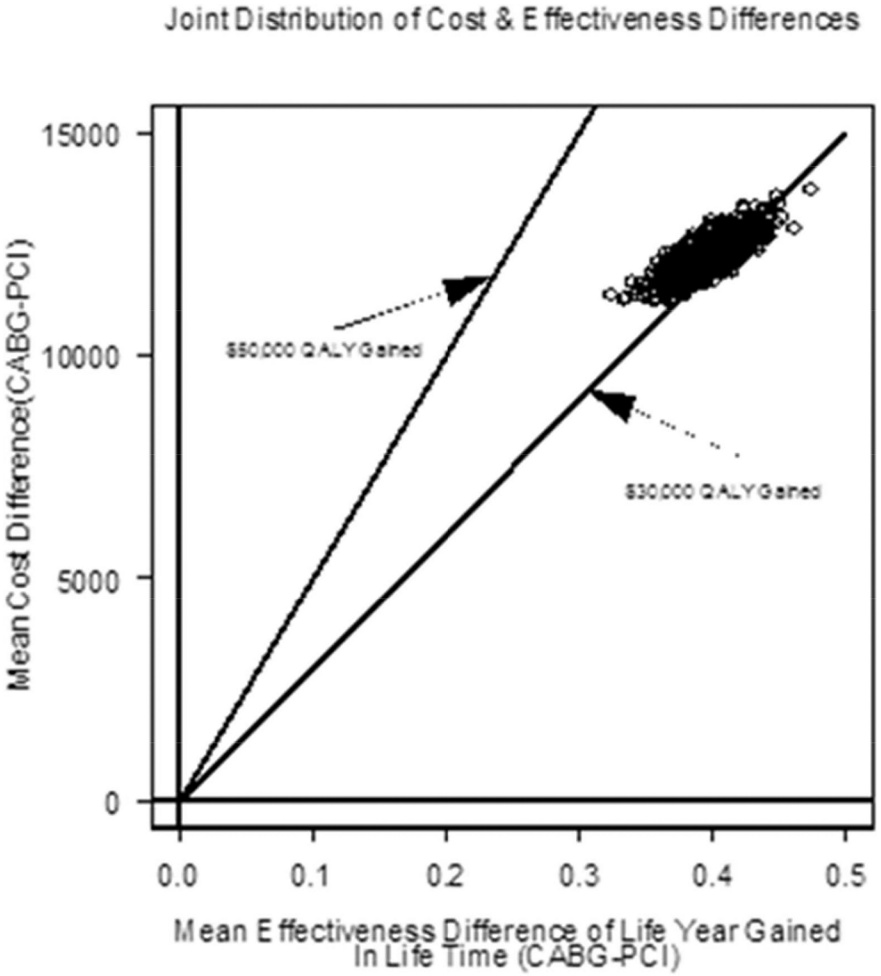
	Δ CABG-PCI	Life-Years or QALY Gained With CABG	ICER	% CABG Dominated	% CABG Dominant	% <$30,000/LYG	% <$50,000/LYG	% <$100,000/LYG
Life-years from 2004 through 2008	$8,323	0.1178	$70,647	0	0	0	0	99.0
Life-years from 2004 through 2008: 3% discount and PSBB adjusted	$8,088	0.3088	$26,192	0	0	70	97.0	100.0
Lifetime: 3% discount and PSBB adjusted	$11,575	0.3016	$38,379	0	0	3.0	91.0	99.0
Quality-adjusted lifetime: 3% and PSBB adjusted	$11,575	0.3801	$30,454	0	0	47.0	98.0	100.0

ICER = incremental cost-effectiveness ratio; LYG = life-years gained; PSBB = propensity score bin bootstrapping; QALY = quality-adjusted life-year(s); other abbreviations as in Table 1.

Cost-effectiveness Analysis: Matched Analytic Population

TABLE 3 Cost-Effectiveness Analysis: Matched Analytic Population

	Δ CABG-PCI	Life-Years or QALY Gained With CABG	ICER	% CABG Dominated	% CABG Dominant	% <$30,000/LYG	% <$50,000/LYG	% <$100,000/LYG
Life-years from 2004 through 2008	$8,079	0.2674	$30,217	0	0	45.0	100.0	100.0
Lifetime: 3% discount	$12,157	0.3172	$38,330	0	0	0	100.0	100.0
Quality-adjusted lifetime: 3% discount	$12,157	0.3947	$30,803	0	0	21.0	100.0	100.0



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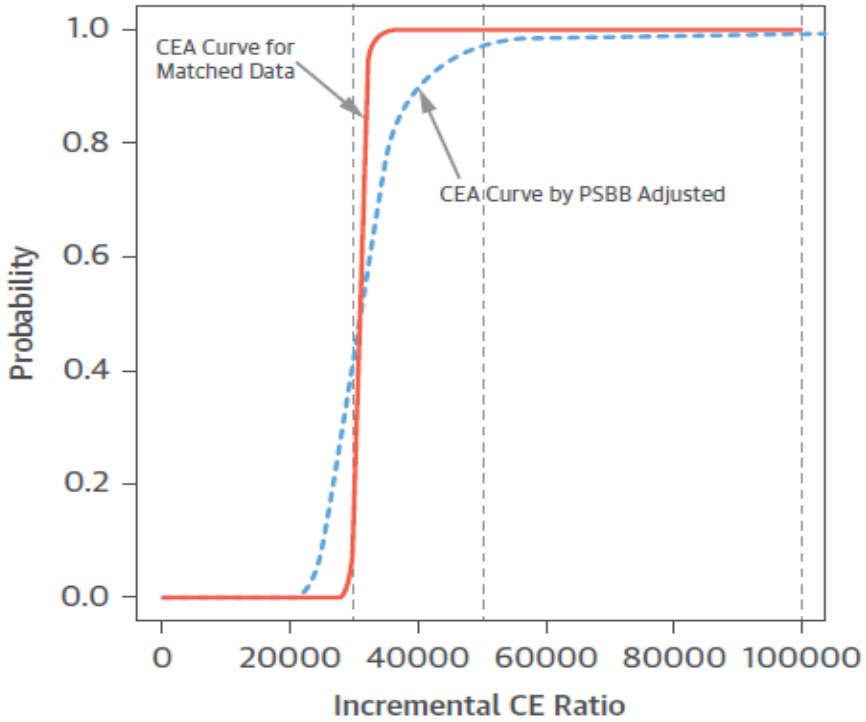
Cost-Effectiveness Acceptability Curve



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Conclusion

Over a period of 4 years or longer, patients undergoing CABG had better outcomes but at higher cost than those undergoing PCI. CABG will often be considered cost-effective at thresholds of $30,000 or $50,000/QALY.

CEA of multinational trials

- Enrollment from different countries (health care systems).
- Costs from a single country – otherwise CEA doesn't apply anywhere.
- Costs in US, Canada, UK, EU, Australia

Cost-effectiveness publications

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Thank you

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