BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

Evidence: Atherosclerotic Carotid Artery Disease

MEDCAC
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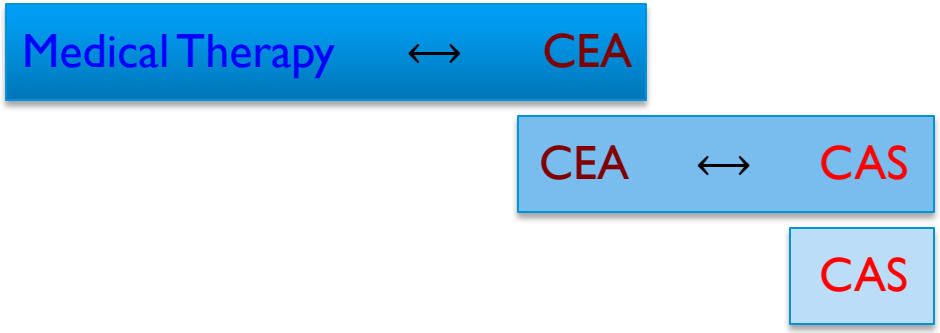
Which intervention—medical therapy, endarterectomy, angioplasty and stenting—is accompanied by greater expected net clinical benefit?

Outline

- Patients, interventions, comparators, outcomes
- Net health outcomes
- Evidence considerations
- Evidence



- Subgroups

THE ROLE OF THE CAROTID ARTERIES, IN THE CAUSATION OF VASCULAR LESIONS OF THE BRAIN, WITH REMARKS ON CERTAIN SPECIAL FEATURES OF THE SYMPTOMATOLOGY.[1]

By J. Ramsay Hunt, M.D.,

Associate Professor of Nervous Diseases, College of Physicians and Surgeons, Columbia University, New York.

The American Journal of the Medical Sciences, May 1914

RECONSTRUCTION OF INTERNAL CAROTID ARTERY

IN A PATIENT WITH INTERMITTENT ATTACKS OF HEMIPLEGIA

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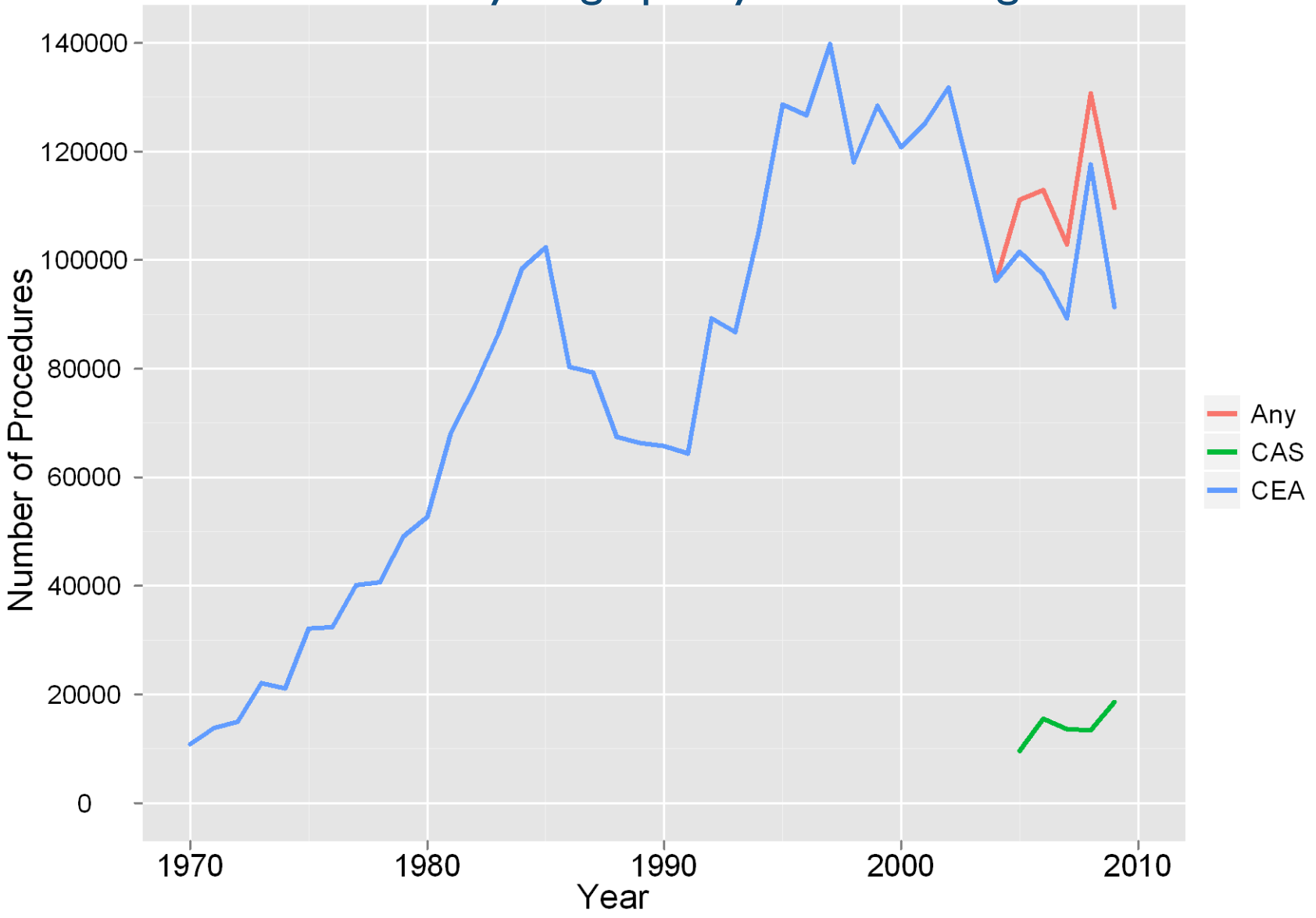
Carotid Endarterectomy, Angioplasty and Stenting U.S. 1970-2009



Source: National Hospital Discharge Survey

Patient Populations

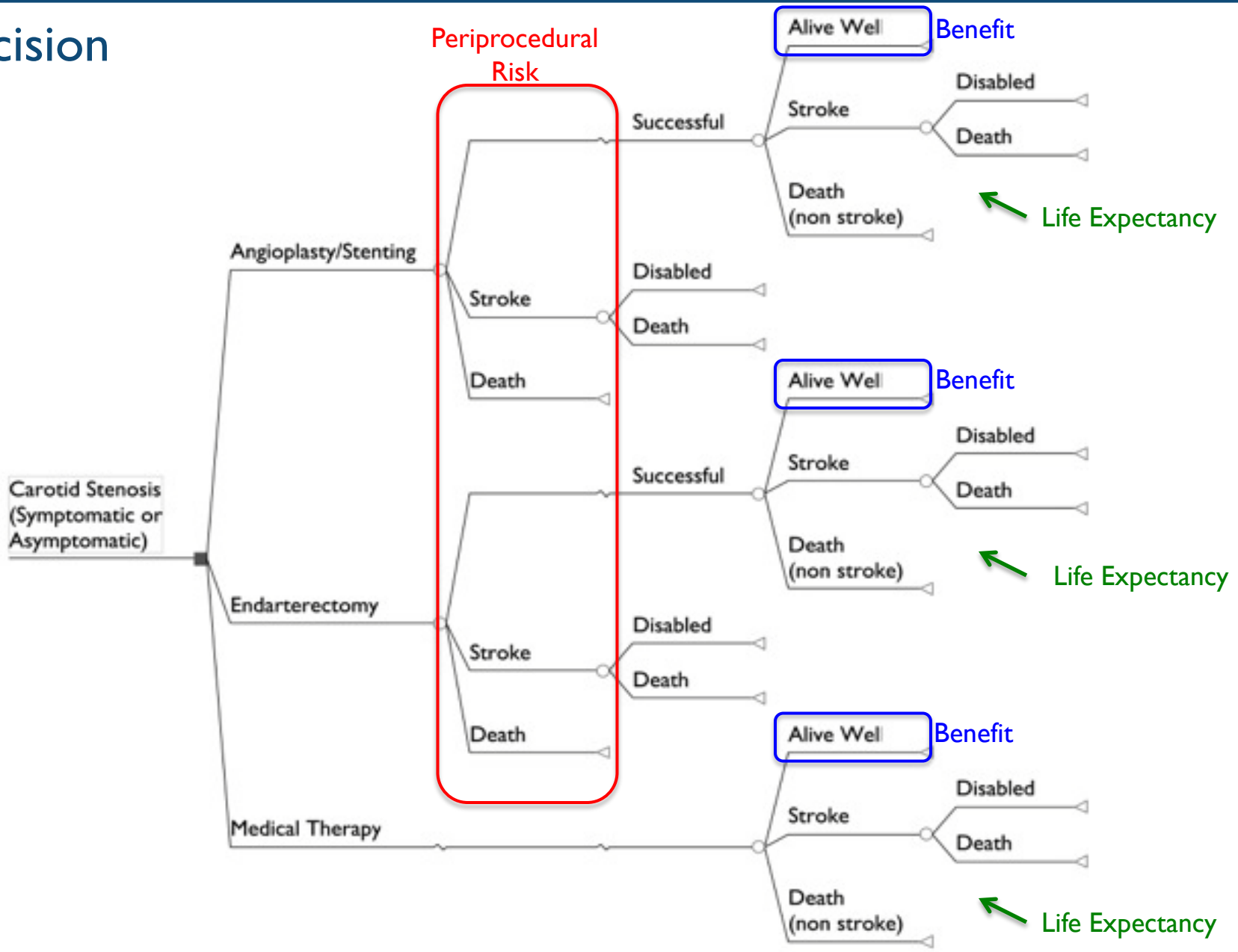
- Symptomatic
- Asymptomatic
- Surgical Risk
  - Standard/conventional surgical risk
  - High/increased surgical risk
- Subgroups
  - Age
  - (Sex)
  - (Recent symptoms)

Interventions, Comparators, and Outcomes

- Interventions/Comparators
  - Medical therapy
  - Endarterectomy
  - Angioplasty and stenting
- Outcomes
  - Periprocedural
    - Death
    - Stroke
    - *Myocardial infarction*
      - Clinical MI, no CHF EF < 0.40, utility 0.88*(stroke Rankin Score 2 utility ≈ 0.6†)
  - Long-term
    - Stroke (ipsilateral)
    - *Cranial nerve injury*
    - *Restenosis*

*Tsevat J, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993;13:161-5.
†Samsa GP, et al. Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: application to treatment of acute ischemic stroke. J Clin Epidemiol 1999;52:259-71.

Decision

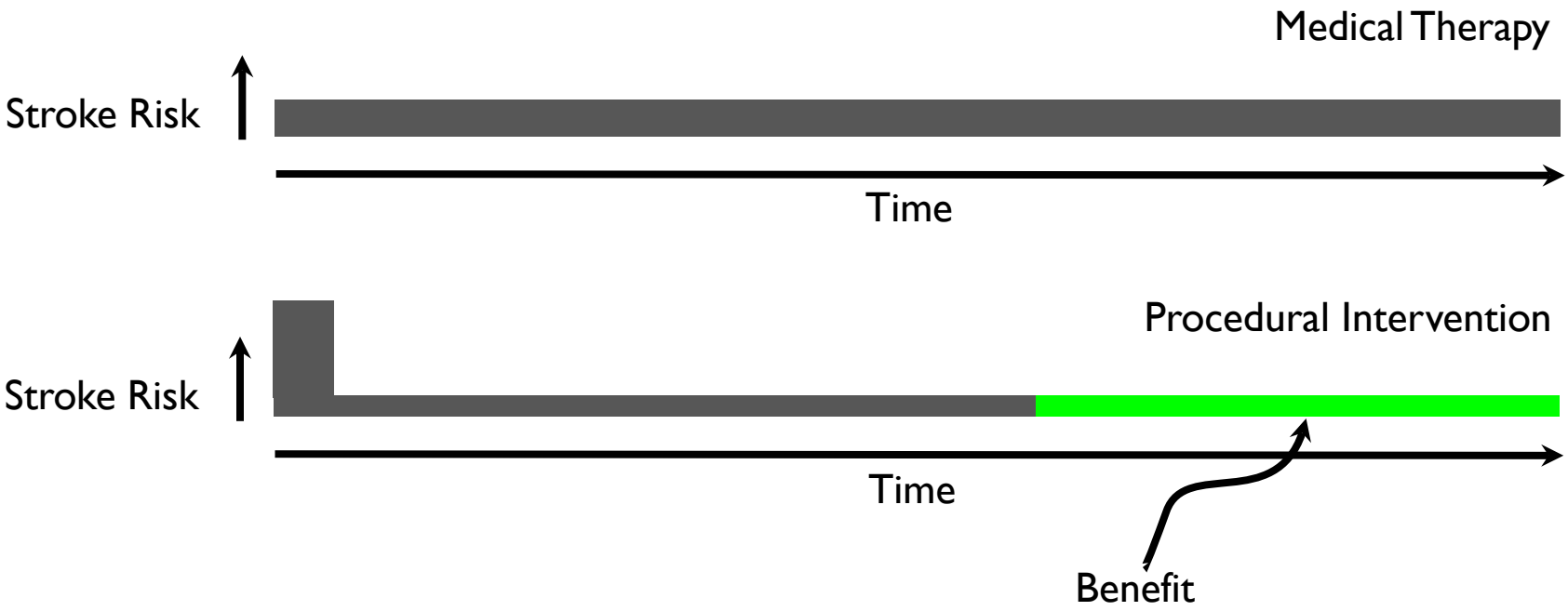


Determinants of Net Health Outcomes

- Procedure Risk
  - Periprocedural stroke/death rate
- Intervention Benefit
  - Decrease in stroke risk with intervention (medical therapy as referent)
- Life Expectancy
  - Patient must live long enough for any decrease in stroke risk to balance intervention risk

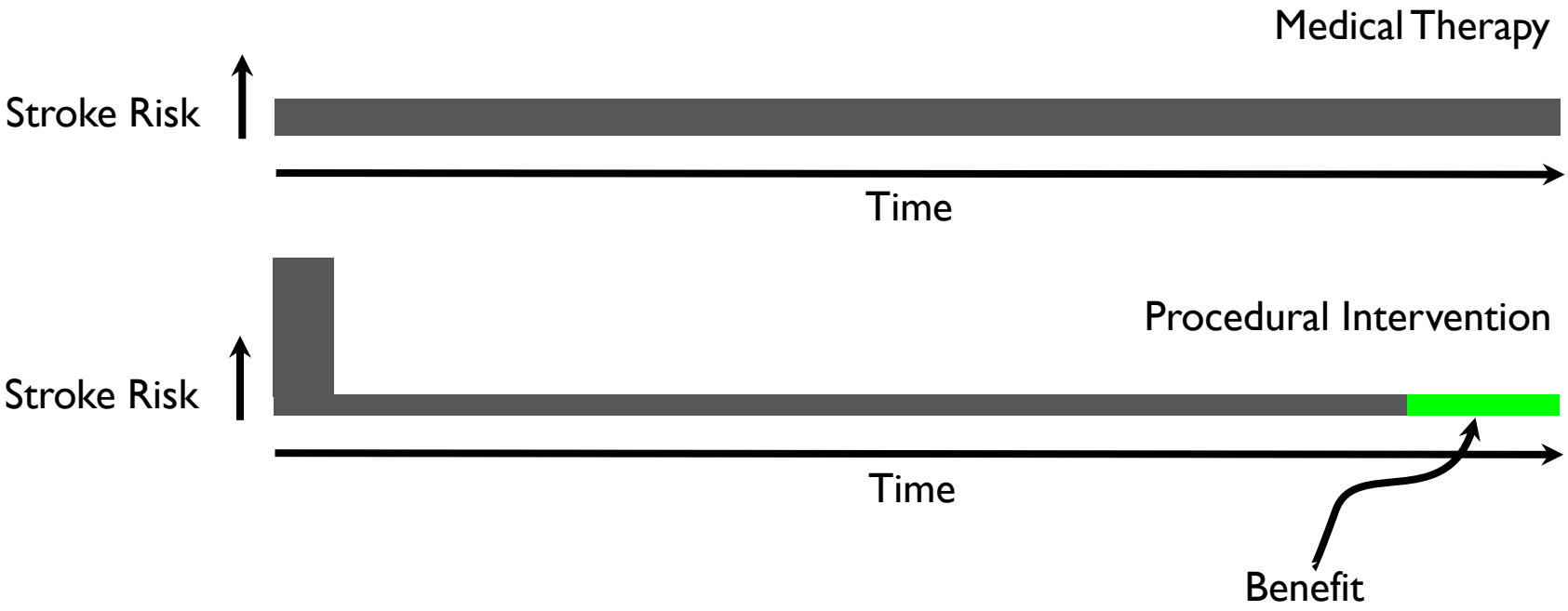
Determinants of Net Health Outcomes

Tradeoff with Expected Benefit



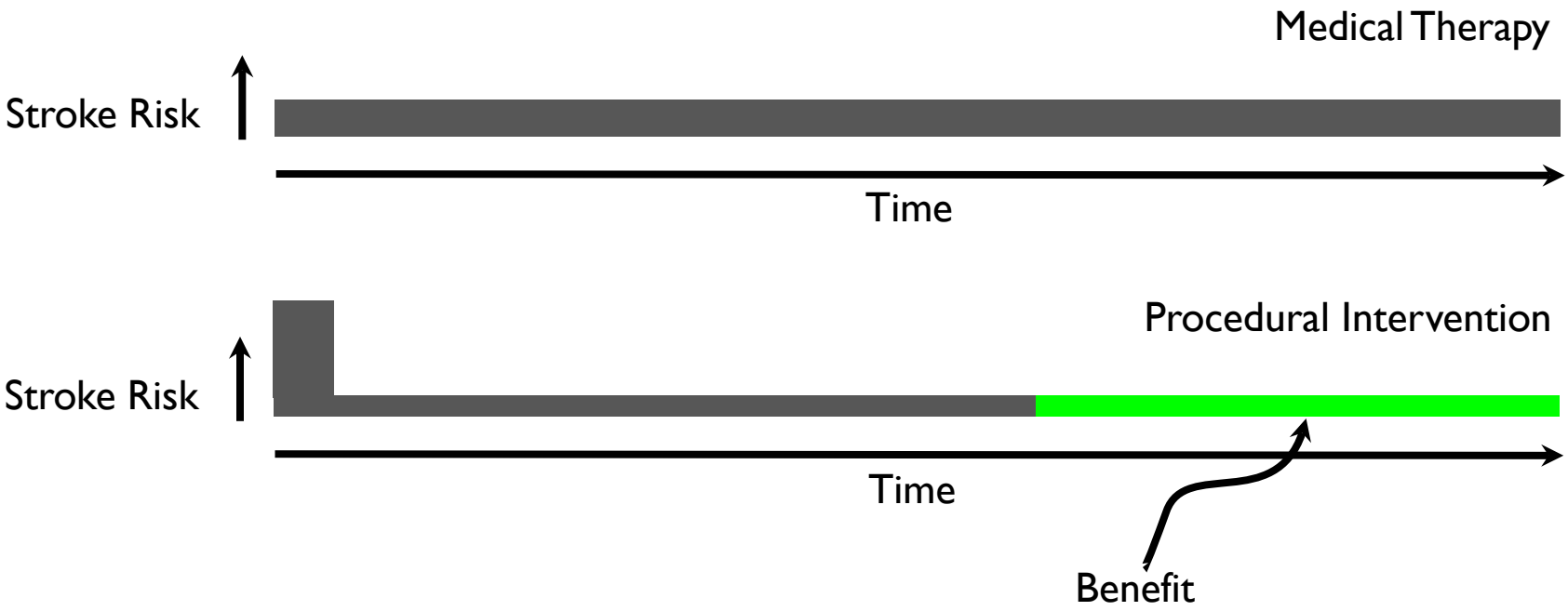
Determinants of Net Health Outcomes

Tradeoff with High Periprocedural Risk



Determinants of Net Health Outcomes

Tradeoff with Expected Benefit

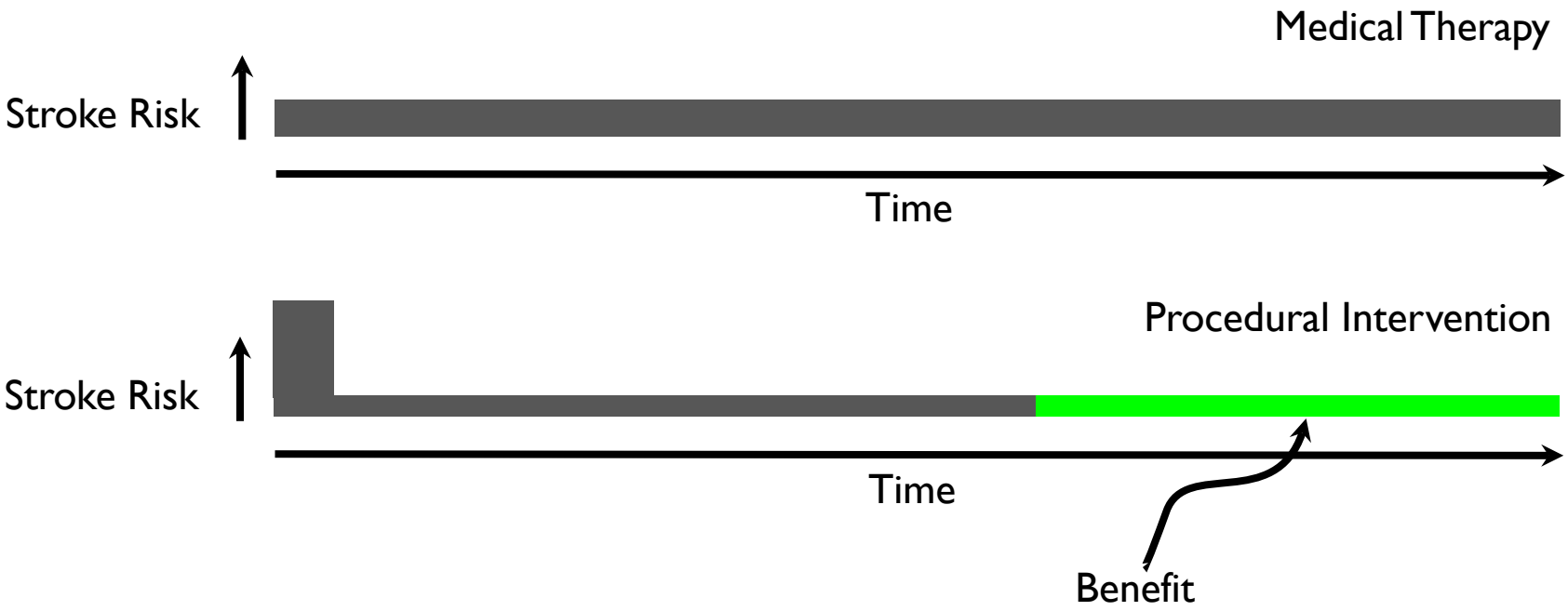


Determinants of Net Health Outcomes

Tradeoff with Improved Medical Care

Determinants of Net Health Outcomes

Tradeoff with Expected Benefit



Determinants of Net Health Outcomes

Tradeoff with Limited Life Expectancy

Interpreting Evidence

- "The Hidden Effect of Time"* and time-trend biases
  - Medical therapy improvements since pivotal CEA trials completed
  - Learning curves
- No direct evidence comparing CAS/CEA to contemporary medical therapy
- Noninferiority
  - Constancy over time *and* among participants—CEA ("standard") as used in the new trial must have the same magnitude of relative benefit compared to medical therapy as it had in the reference trials.
  - Inferential nature of noninferiority comparisons
- Disease natural histories
  - Symptomatic and asymptomatic patients
  - Life expectancy (increased risk/medical comorbidities)
    - "Payoff time" for procedural risk
- Endpoints

*Altman DG, Royston JP. The hidden effect of time. Stat Med 1988;7:629-37.

Constancy over time *and* among participants*

- "The circumstances under which the active control was found to be useful ought to be reasonably close to those of the planned trial."
- "Similarity of populations, concomitant therapy, and dosage are important."
- "…the studies that demonstrated benefit of the control against either placebo or no treatment must be sufficiently recent such that no important medical advances or other changes have occurred, and in populations similar to those planned for the new trial."

*Friedman LM, et al. Fundamentals of Clinical Trials. 4th Edition. Springer, New York, 2010.

Interpreting Evidence

Potential Clinical Contributors to Heterogeneity

- Surgical approaches
- Stents (7 approved by the FDA)
- Operator experience
  - Nallamothu BK, et al. Operator experience and carotid stenting outcomes in Medicare beneficiaries. JAMA 2011;306:1338-43.
    - Higher risk of 30-day mortality during first 11 procedures (OR 1.6, 95% CI: 1.1 to 2.2)
- Anesthetic
  - General
  - Local

Pivotal Carotid Endarterectomy Trials

TRIAL	Enrollment	Stenosis Severity	Absolute Risk Reduction Ipsilateral Stroke	Time to Reported Benefit	Peri-procedural Death/Stroke
Symptomatic					
NASCET	1988-1991	≥70%	17.0%	2 years	5.8%
ECST	1981-1994	≥70%	14.0%	3 years	7.5%
NASCET	1987-1996	50–69%	6.5%	5 years	6.7%
Asymptomatic					
ACAS	1988-1993	≥60%	5.9%	5 years	2.3%
ACST	1993-2003	≥60%	5.4%[a]	5 years	3.1%

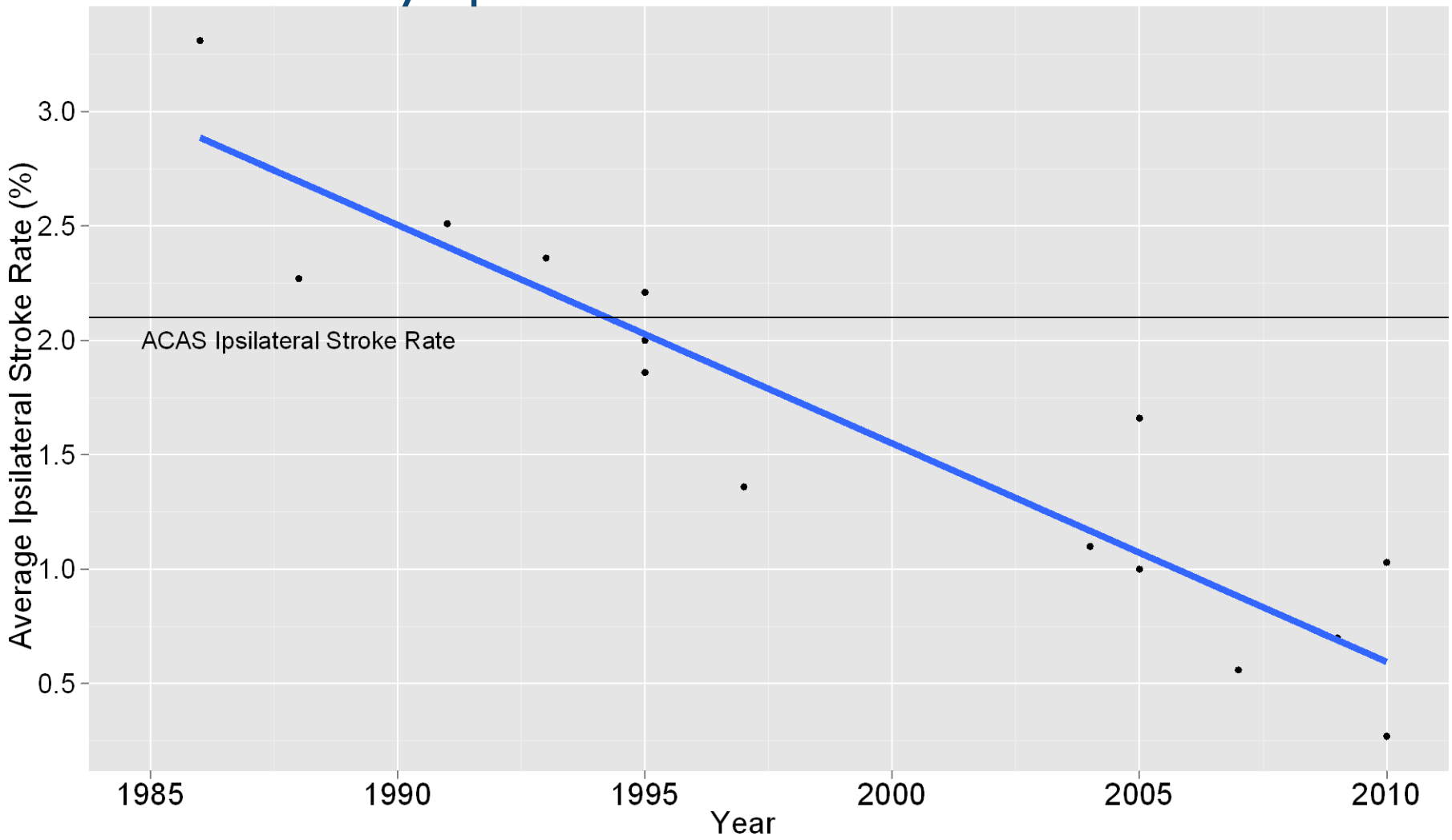
[a] All strokes

Average Annual Stroke Rates in Medically Treated Patients with Asymptomatic Carotid Stenosis

stenosis; ○,
ipsilateral stroke 60% to 99% stenosis; Δ, ipsilateral stroke 50% to 99% stenosis.

Naylor AR. What is the current status of invasive treatment of extracranial carotid artery disease? Stroke 2011; 42: 2080-5.

Average Annual Ipsilateral Stroke Rates in Medically Treated Patients with Asymptomatic Carotid Stenosis



Redrawn from Naylor AR. What is the current status of invasive treatment of extracranial carotid artery disease? Stroke 2011; 42: 2080-5.

CEA-CAS Trials

		Enrollment
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy	(2000-2002)
EVA-3S	Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis	(2000-2005)
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial	(2000-2008)
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy	(2001-2006)
ICSS	International Carotid Stenting Study	(2001-2008)

CEA-CAS Trials—Risk, Symptom, and Stenosis

	Surgical Risk (n)		Symptoms (Stenosis Severity)	
	Increased	Conventional	Symptomatic	Asymptomatic
SAPPHIRE	334		≥50%	≥80%
EVA-3S		527	≥60%	
SPACE		1183	≥50%	
ICSS		1713	>50%	
CREST		2502	≥50%	≥60%

CEA-CAS Trials—Primary Endpoints

Trial	Non Inferiority Margin	Primary Endpoint
SAPPHIRE	3.0%	Death, stroke, MI within 30 days or ipsilateral stroke 31 days to 1 year
EVA-3S	2.0%	Stroke or death within 30 days
SPACE	2.5%	Ipsilateral ischemic stroke or death within 30 days
ICSS	3.3%	Long-term fatal or disabling stroke in any territory
CREST	2.6%*	Death, stroke, MI within 30 days or ipsilateral stroke <4 years after randomization

* For FDA analyses events to 1-year

CEA-CAS Trials—Operator Experience

Trial	CEA	CAS
SAPPHIRE	Periprocedural death/stroke risk within AHA guidelines	Periprocedural death/stroke risk <6.0%
EVA-3S	25 CEAs in prior year	12 CAS, or 35 other stent procedures 5 carotid
SPACE	≥25 consecutive CEAs	≥25 consecutive successful procedures
ICSS	≥50 CEA (≥10/year)	≥50 stenting procedures; ≥10 carotid
CREST	Periprocedural death/stroke risk within AHA guidelines based on previous 50 or prior year (>50 procedures)	≥30 CAS or training and up to ≈20 reviewed procedures

CEA-CAS Trials—Embolic Protection

Trial	Embolic Protection Device Used	Note
SAPPHIRE	96%	
EVA-3S	92%	Recommended after initial 80 patients treated, 15 without EPDs.
SPACE	27%	No difference primary outcome with or without device (OR 1.09, 95% CI: 0.53 to 2.25)
ICSS	72%	
CREST	96%	

CEA-CAS Trials—Primary Outcomes

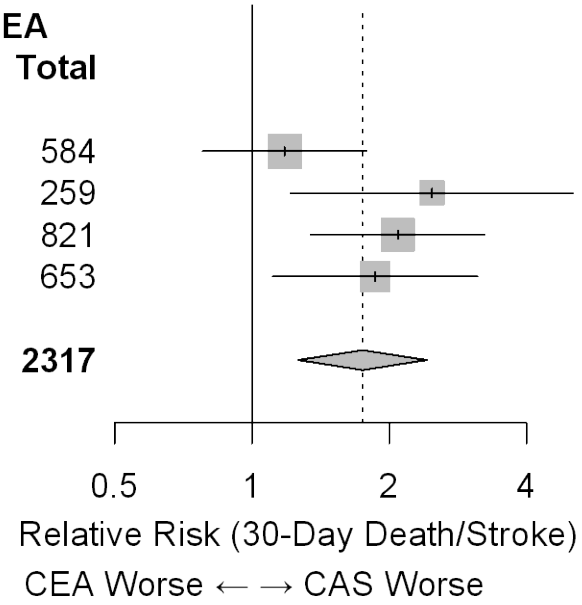
	CEA	CAS	RR (CAS vs. CEA)	95% CI	
SAPPHIRE	20.1%	12.2%	0.61*	(0.37 to 1.05)*	Death, stroke, MI ≤ 30 days or ipsilateral stroke 31 days to 1 year
EVA-3S	3.9%	9.6%	2.5	(1.2 to 5.1)	Stroke or death ≤ 30 days
SPACE	6.3%	6.8%	1.09	(0.69 to 1.72)	Ipsilateral ischemic stroke or death ≤ 30 days
ICSS	Not Yet Reported				Long-term fatal or disabling stroke in any territory
CREST	6.8%	7.2%	1.11	(0.81 to 1.51)	Death, stroke, MI ≤ 30 days or ipsilateral stroke <4 years after randomization

*Calculated

30-Day RR Death/Stroke
CEA-CAS Trials, Conventional Risk Symptomatic Patients

Study	CAS Events	CAS Total	CEA Events	CEA Total	RR	95% CI	W
SPACE	46	599	38	584	1.18	[0.78; 1.79]	31.0%
EVA3S	25	261	10	259	2.48	[1.22; 5.06]	15.6%
ICSS	59	828	28	821	2.09	[1.35; 3.24]	29.2%
CREST	40	668	21	653	1.86	[1.11; 3.12]	24.2%
Random effects model		**2356**		**2317**	**1.75**	**[1.26; 2.42]**	**100%**

Heterogeneity: I-squared=40.4%

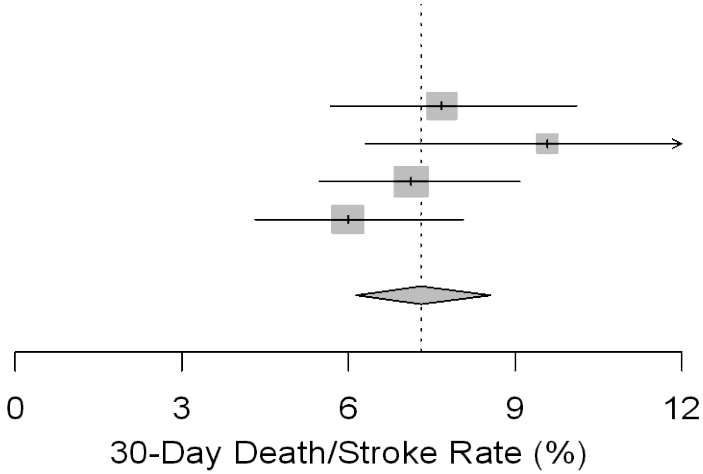


30-Day Death/Stroke Rates
CEA-CAS Trials, Conventional Risk Symptomatic Patients

CAS

Study	Events	Total	%	95% CI	W
SPACE	46	599	7.7	[5.7; 10.1]	25.9%
EVA3S	25	261	9.6	[6.3; 13.8]	13.0%
ICSS	59	828	7.1	[5.5; 9.1]	32.9%
CREST	40	668	6.0	[4.3; 8.1]	28.2%
Random effects model		**2356**	**7.3**	**[6.1; 8.6]**	**100%**

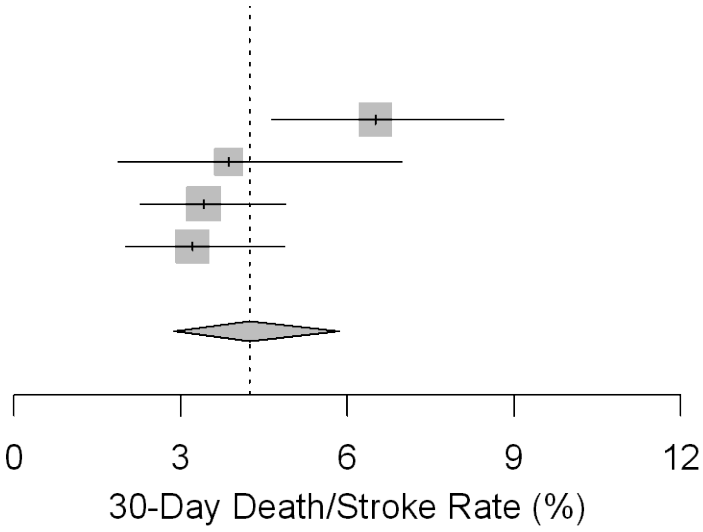
Heterogeneity: I-squared=22.2%



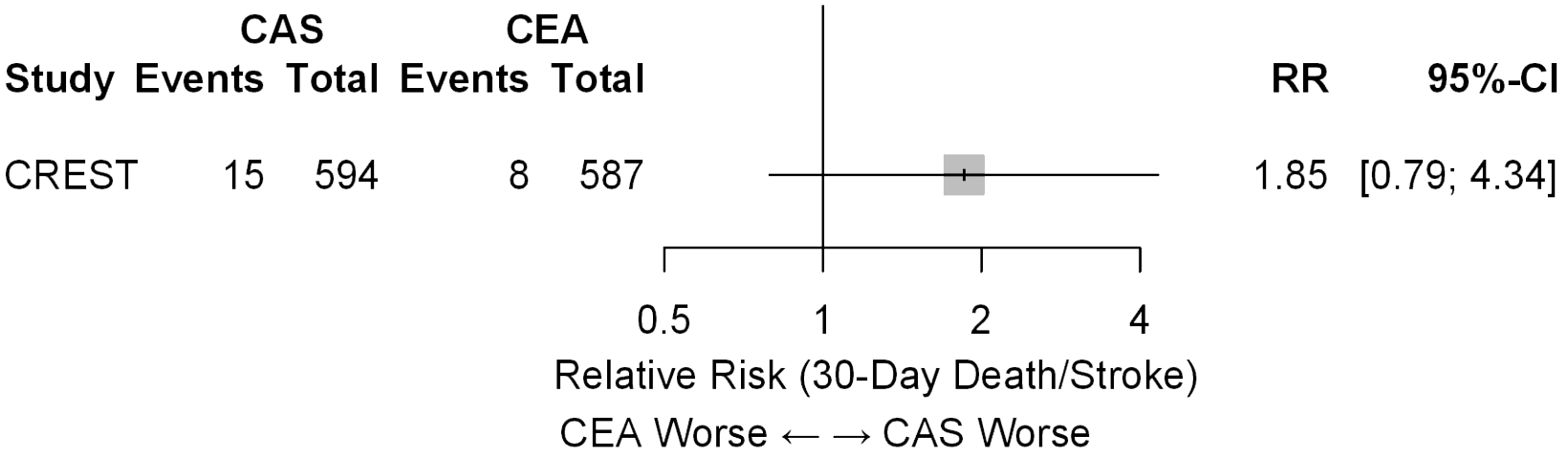
CEA

Study	Events	Total	%	95% CI	W
SPACE	38	584	6.5	[4.6; 8.8]	26.0%
EVA3S	10	259	3.9	[1.9; 7.0]	18.7%
ICSS	28	821	3.4	[2.3; 4.9]	28.5%
CREST	21	653	3.2	[2.0; 4.9]	26.8%
Random effects model		**2317**	**4.2**	**[2.9; 5.9]**	**100%**

Heterogeneity: I-squared=67.8%

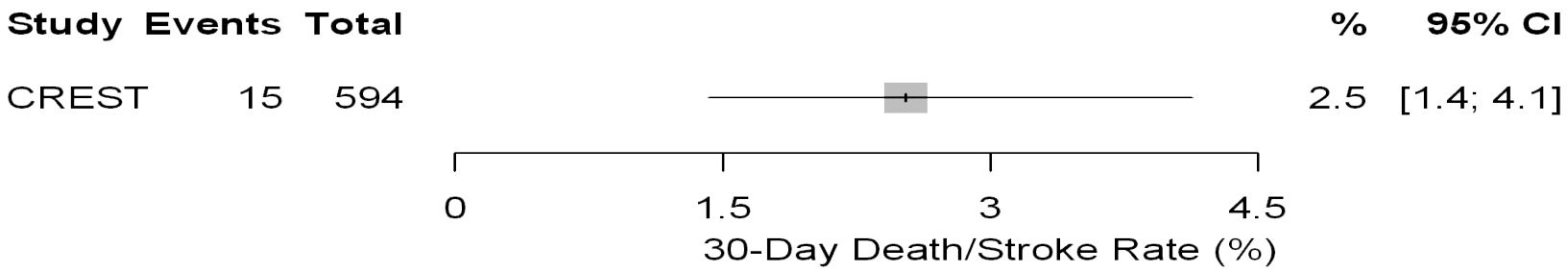


30-Day RR Death/Stroke
CREST, Conventional Risk Asymptomatic Patients

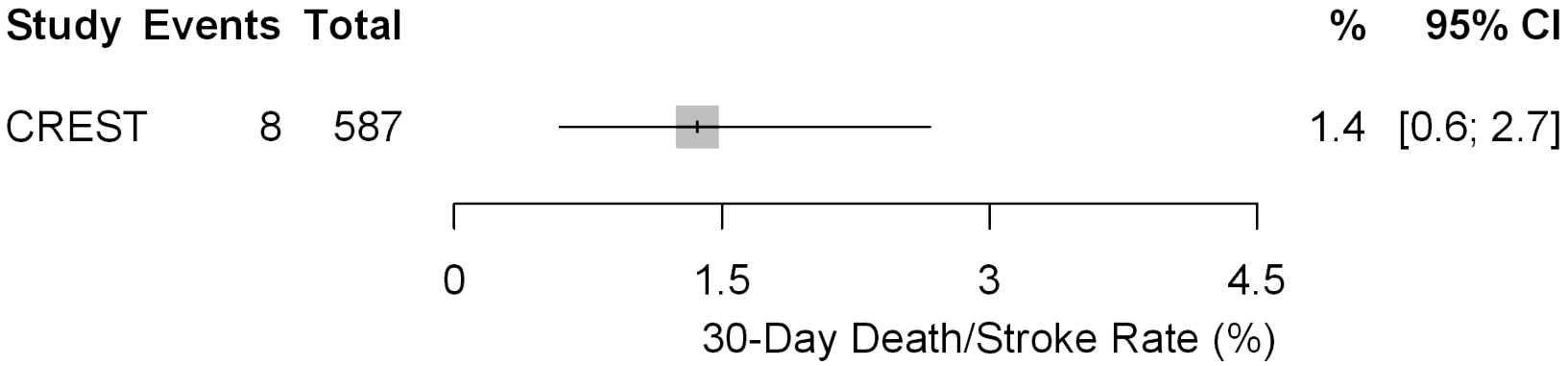


30-Day Death/Stroke Rates
CREST, Conventional Risk Asymptomatic Patients

CAS



CEA



Post-Procedural Ipsilateral Stroke

				Annual (≈)	
		CEA	CAS	CEA	CAS
Postprocedural Ipsilateral Stroke					
SPACE (Symptomatic)	2-year	1.9%	2.2%	1.0%	1.2%
EVA-3S (Symptomatic)	4-year	1.3%	2.0%	0.33%	0.51%
Periprocedural Stroke/Death or Postprocedural Ipsilateral Stroke					
CREST (Symptomatic)	4-year	6.4%	8.0%		
CREST (Asymptomatic)	4-year	2.7%	4.5%		

		CEA	Medical	CEA	Medical
Postprocedural Ipsilateral Stroke					
NASCET 70%-99%	2-year	3.2%	22.7%	1.6%	11.4%
NASCET 50%-69%	5-year	9.0%	22.2%	1.8%	4.4%

RR 30-Day Death, Stroke—SAPPHIRE

Symptomatic (n=96)	CAS % (95% CI)	CEA % (95% CI)
Death	0% (0 to 7.1)	6.5% (2.2 to 17.5)
Stroke	0% (0 to 7.1)	2.2% (0.1 to 11.3)
Asymptomatic (n=237)		
Death	1.7% (0.5 to 6.0)	0.8% (0.04 to 4.6)
Stroke	5.1% (2.4 to 10.7)	3.3% (1.3 to 8.2)

Registries—Approval, Postmarketing, & Independently Sponsored

- Some potential strengths
  - Can reflect real world experience
  - Size
  - Safety evaluation
  - Many data potentials, linkages….
- Some potential limitations
  - Might not reflect real world experience
  - Can lack standardized patient and outcome evaluation
  - Dissemination bias?
  - Observational, lacking control

Registries—Overview

- 18 multicenter prospective registries
  - Most standardized follow-up neurological exams
- 11 reported, calculable, or obtainable 30-day death/stroke rates
  - Approval (n=5) and postmarketing (n=6)
  - 13,783 asymptomatic patients
  - 3,353 symptomatic patients
- 30-day death/stroke rates
  - Symptomatic 7.4% (95% CI: 6.0 to 9.0; I^2=59%)
  - Asymptomatic 3.9% (95% CI: 3.3 to 4.4; I^2=57%)

Touzé E, et al. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. Stroke 2009;40:e683-93.

- Included registries and trials
- 30-day death/stroke rates
  - Symptomatic 7.3% (95% CI: 6.3 to 9.1), 42 studies, 4910 patients
  - Asymptomatic 3.3% (95% CI: 2.6 to 4.1), 23 studies, 8504 patients
- In combined symptomatic and asymptomatic patients found improvement in 30-day death/stroke over time

Postmarketing Registries—Real World?

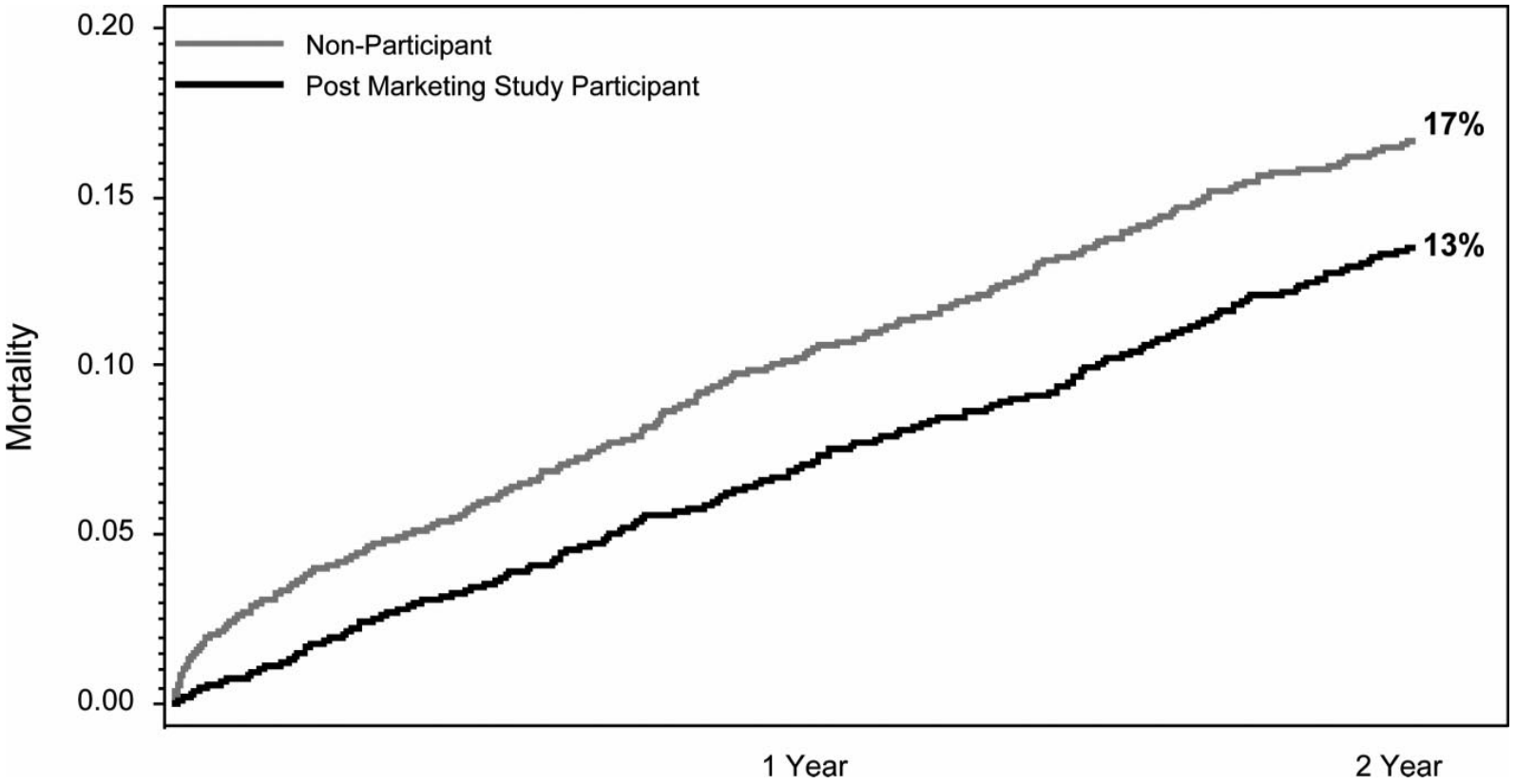
Table 2. In-Hospital Outcomes

Variable	Enrolled in PMS (n=3689)	Not Enrolled (n=3426)	*P*
Postprocedure NIH Stroke Scale	0.6±2.1	1.3±3.9	<0.001
Myocardial infarction, % (n)	0.4 (16)	0.6 (19)	0.47
New stroke, % (n)	1.7 (62)	2.7 (91)	0.005
Death, % (n)	0.3 (11)	1.4 (49)	<0.001
Combined death, stroke, or myocardial infarction, % (n)	2.3 (85)	4.1 (142)	<0.001

NIH indicates National Institute of Health; PMS, postmarketing surveillance.

Yeh RW, et al. Do postmarketing surveillance studies represent real-world populations? Circulation 2011;123:1384-90.

Postmarketing Registries—Real World?



Unadjusted cumulative all-cause mortality for postmarketing study participants (black) and nonparticipants (gray).

Yeh RW, et al. Do postmarketing surveillance studies represent real-world populations? Circulation 2011;123:1384-90.

Age

	Asymptomatic		Symptomatic			
30-Day Death/Stroke	<80	≥80	<80		≥80	
	CAS	CAS	CAS	CEA	CAS	CEA
EXACT/CAPTURE2	2.9%	4.4%	5.3%		10.5%	
CAPTURE		8.0%			17.1%	
			≤75		>75	
SPACE			5.9%	5.9%	11.0%	7.5%
120-Day Death/Stroke			<70		≥70	
EVA-3S; SPACE; ICSS			5.8%	5.7%	12.0%	5.9%

Summary

- Net health outcomes
- Noninferiority comparisons
  - Constancy
- Conventional risk patients
- Patients with comorbidities

Which intervention—medical therapy, endarterectomy, angioplasty and stenting—is accompanied by greater expected net clinical benefit?