CREST, ACT 1 and Other Trials:

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The Cardiovascular Research Foundation

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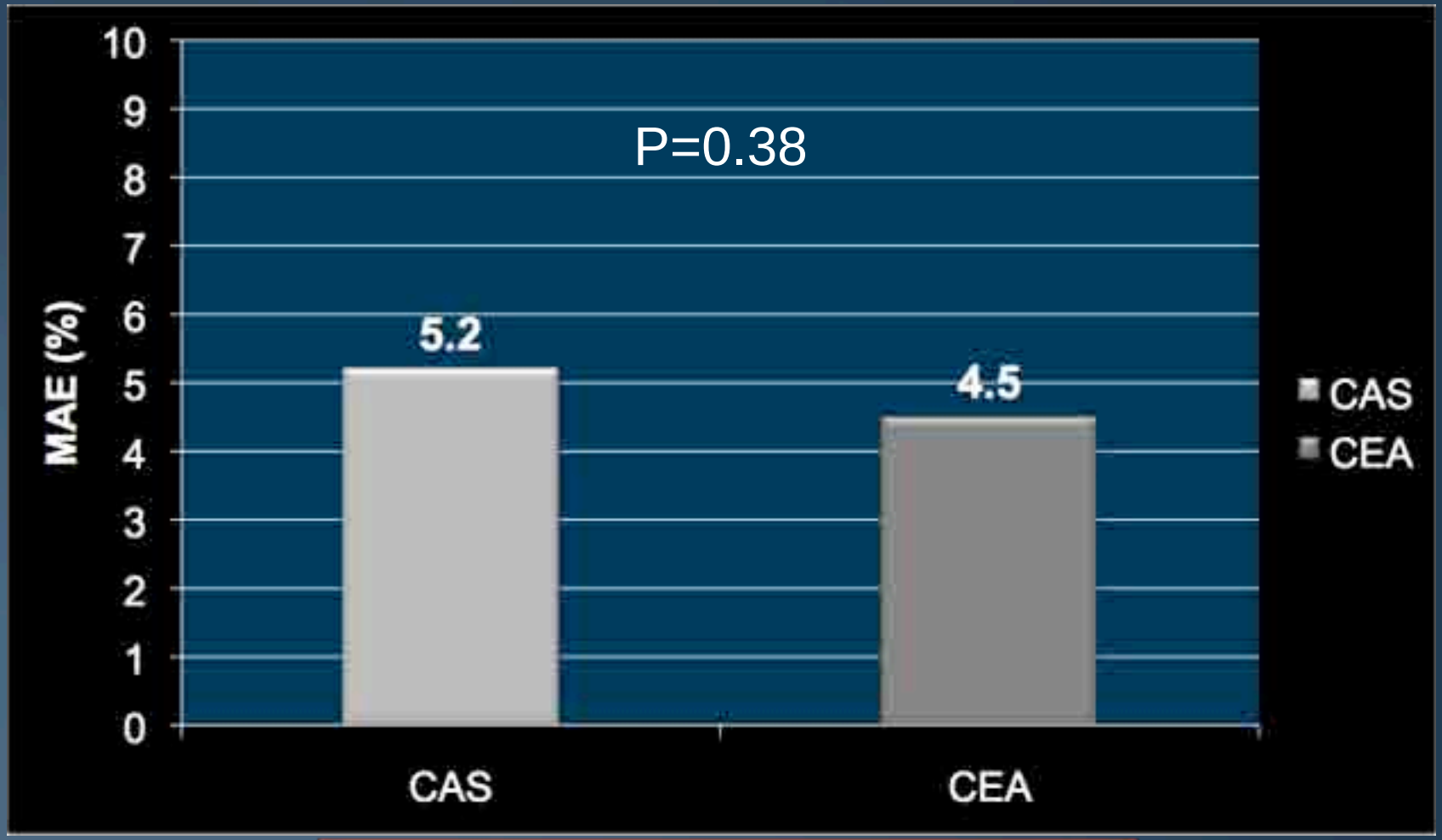
Overview

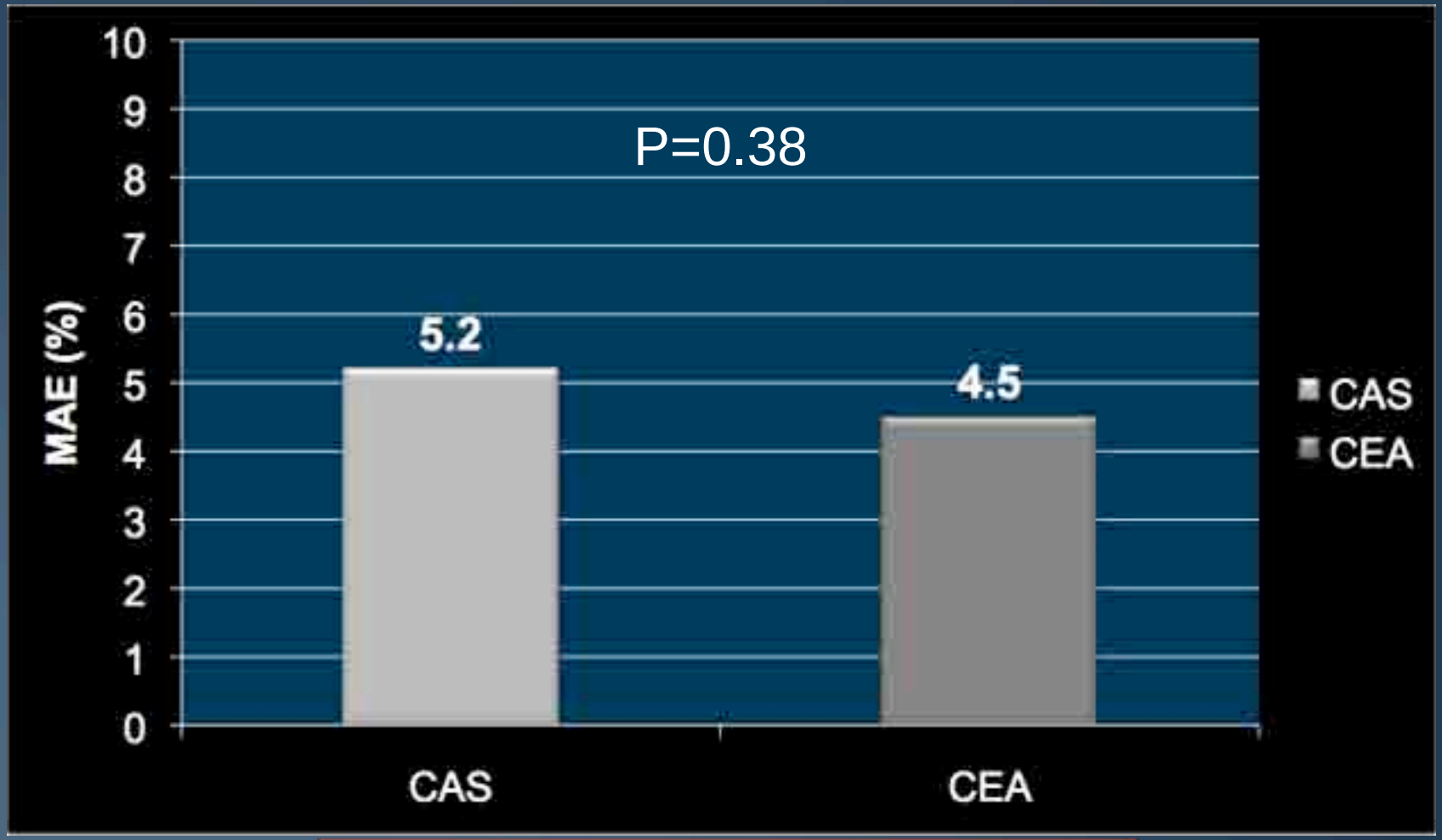
- Current state of carotid stenting in the US
  - Volumes
  - Outcomes
- Trials in active recruitment
  - ACST 2
  - SPACE 2
  - ACT I*
- Trials seeking funding
  - CREST 2

Medicare carotid procedural activity

Peri-procedural outcomes (D/S/MI)



HR 1.18 95% CI: 0.82-1.68



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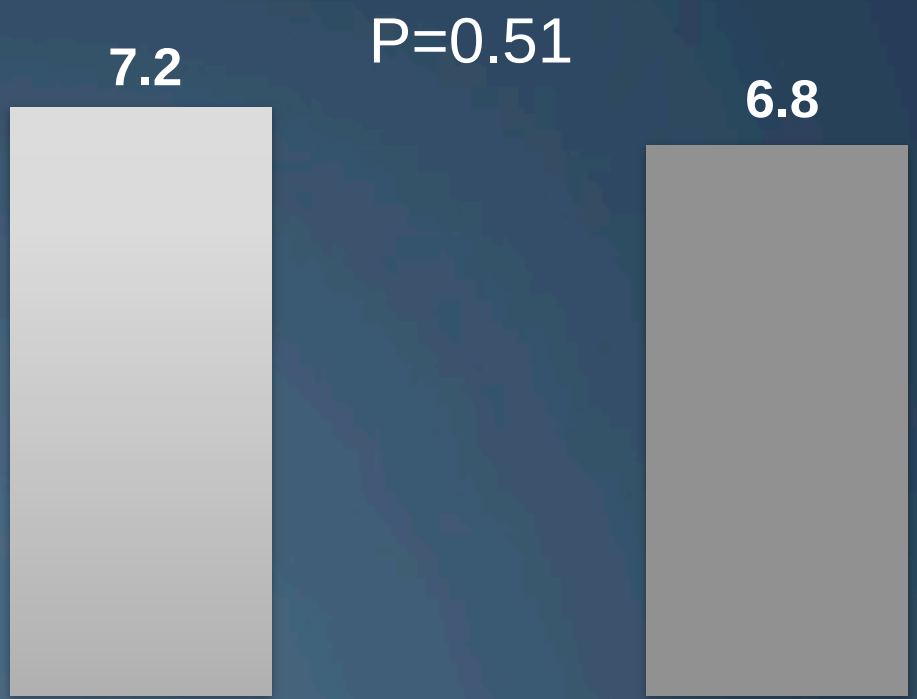
Primary endpoint ≤4 years (mean 2.5)



HR 1.11 95% CI: 0.81-1.51

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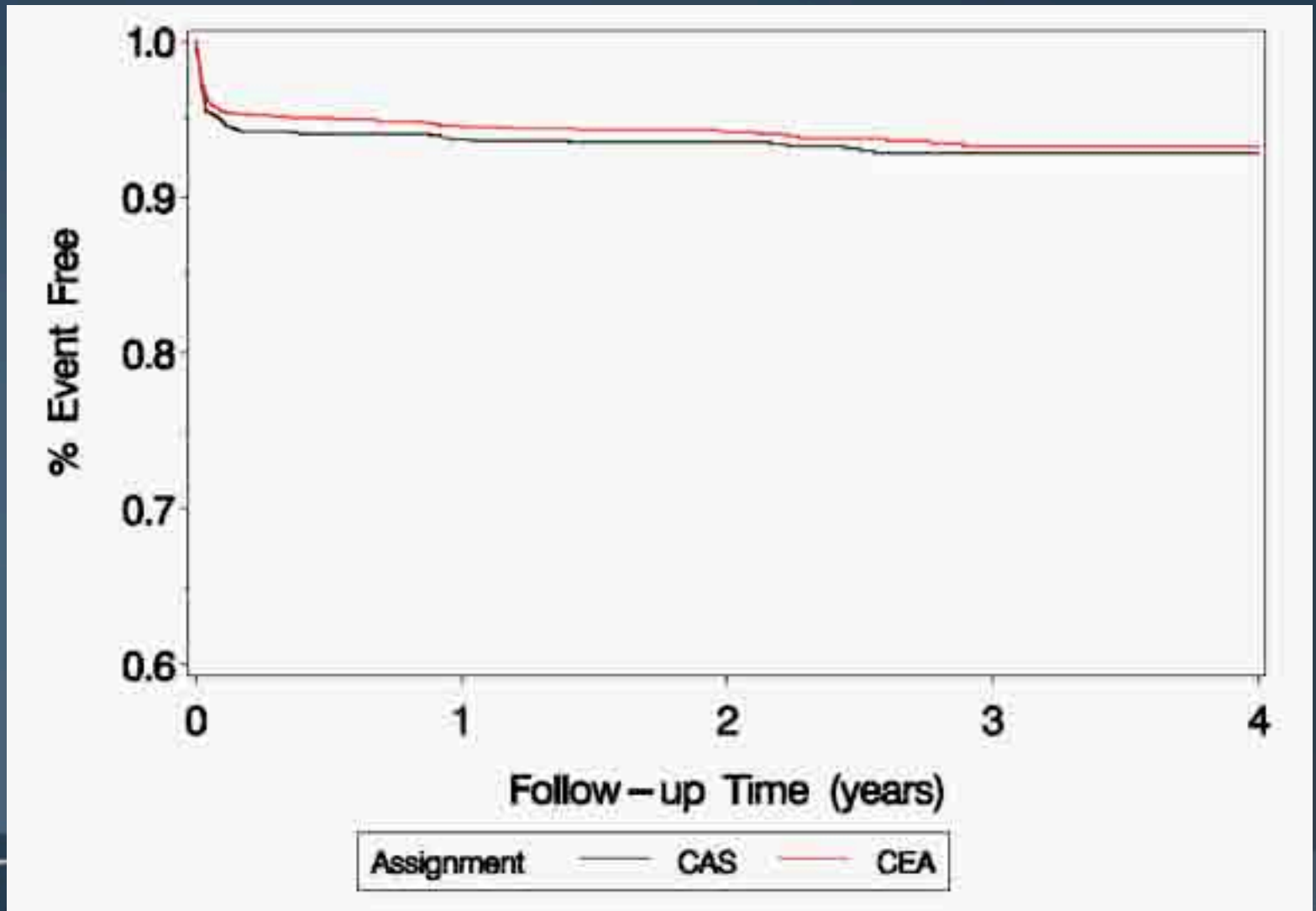
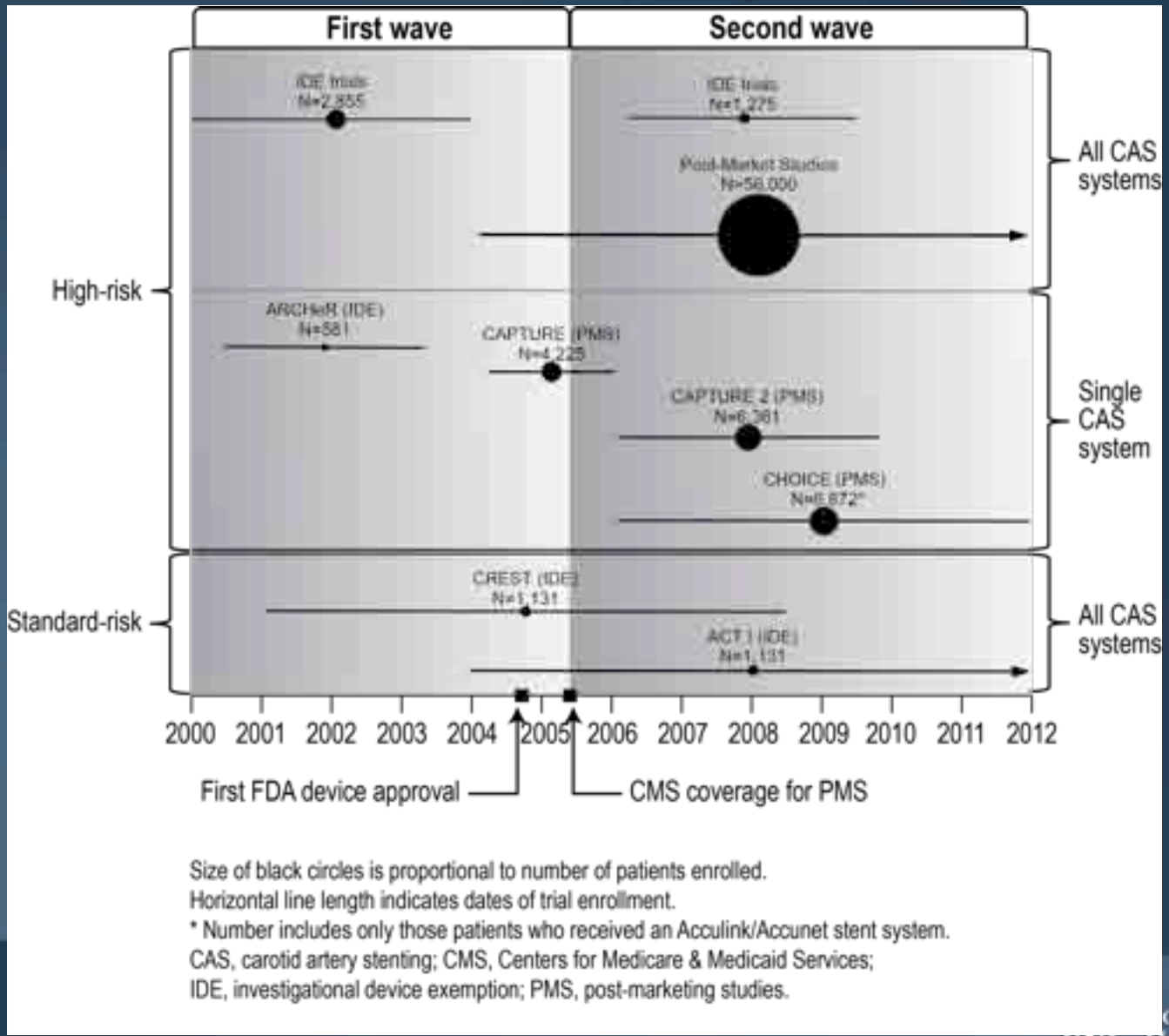
Stroke prevention efficacy between



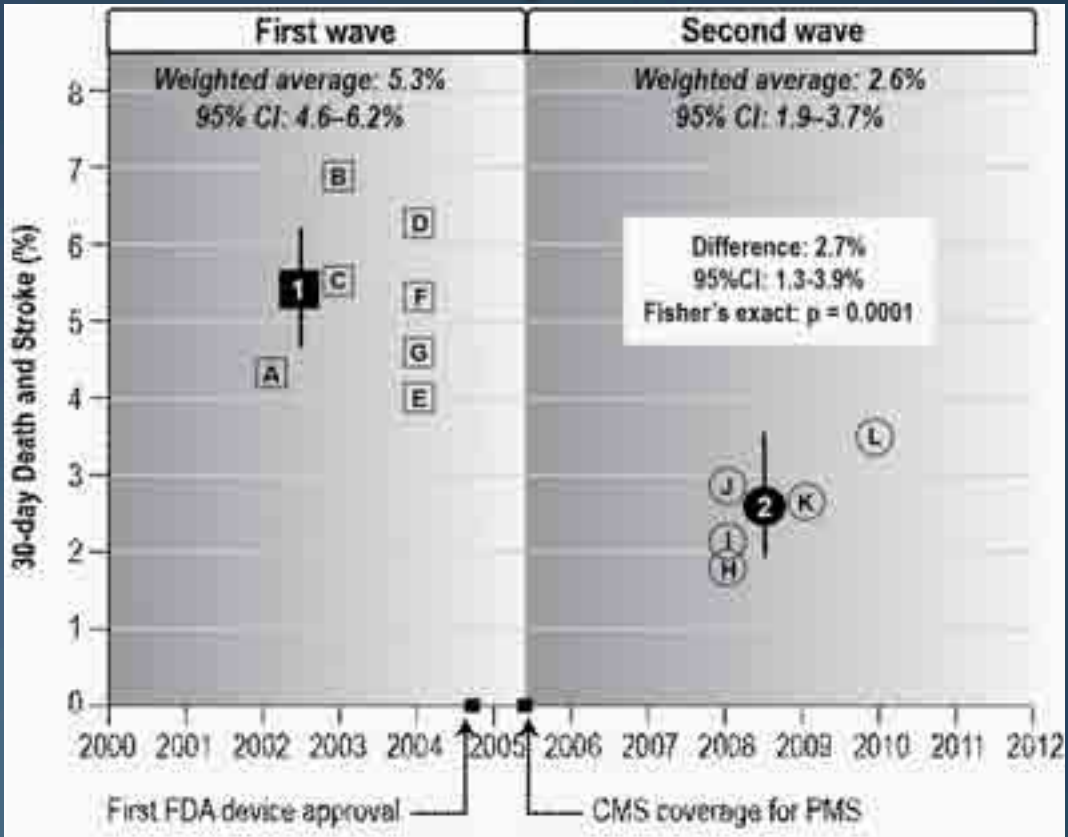
IDE Trial	N (CAS)	Year of FDA action	Stent System Approval/ EPD 510(k) Clearance	Postmarket Surveillance Study
ARCHeR	581	2004	Acculink PMA approval Accunet 510(k) clearance	CAPTURE (N=4,225) CAPTURE 2 (N=6,361) CHOICE (N=19,000)
SECURITY	305	2005	Xact PMA approval Emboshield 510(k) clearance	EXACT (N=2,145) CHOICE
SAPPHIRE	565	2006	Precise PMA approval Angioguard 510(k) clearance	CASES-PMS (N=1,493) SAPPHIRE WW (N=15,000)
CABERNET	488	2006	Nexstent PMA approval FilterWire Carotid 510(k) clearance	None
CREATE	419	2006 2007	Protégé Carotid PMA approval SpiderFX Carotid 510(k) clearance	CREATE PAS (N=3,500)
MAVErIC	449	2007	Exponent PMA approval GuardWire Carotid 510(k) clearance	None
PROTECT	320	2008	Emboshield NAV6 510(k) clearance	CHOICE
BEACH	480	2008	Wallstent Carotid PMA approval FilterWire EZ System clearance	CABANA (N=1,097)
EPIC	237	2008	Fibernet 510(k) clearance	None
EMBOLDEN	250	2009	GORE® Embolic Filter clearance	None
EMPIRE	245	2009	Gore Flow Reversal 510(k) clearance	FREEDOM (planned N=5,000)

FDA and CMS approvals (limited) lead to volume expansion



Size of black circles is proportional to number of patients enrolled.
Horizontal line length indicates dates of trial enrollment.
* Number includes only those patients who received an Acculink/Accunet stent system.
CAS, carotid artery stenting; CMS, Centers for Medicare & Medicaid Services;
IDE, investigational device exemption; PMS, post-marketing studies.

Volume expansion led to marked improvement in patient outcomes



First wave IDE studies	30-day D/S	Second wave IDE studies	30-day D/S
A. SAPPHIRE	4.2%	H. PROTECT	1.8%
B. ARCHeR	6.9%	I. EPIC	2.1%
C. BEACH	5.4%	J. EMPIRE	2.9%
D. SECURITY	6.2%	K. ARMOUR	2.7%
E. CABERNET	4.0%	L. EMBOLDEN	3.6%
F. CREATE	5.3%		
G. MAVERIC	4.6%		

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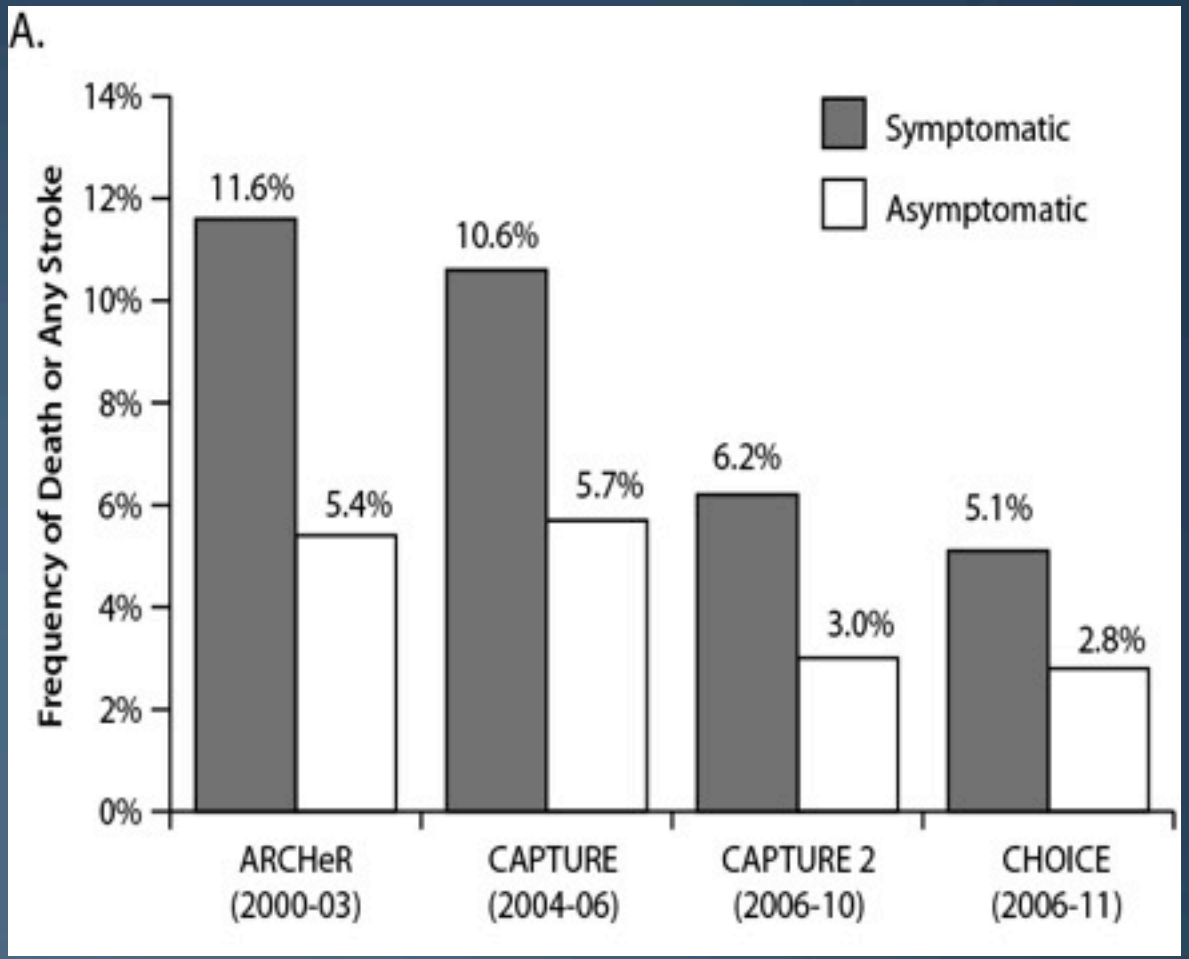

Applying the law of syllogism

$$\Big[(p \to q) \wedge (q \to r)\Big] \to (p \to r)$$

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- And
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Applying the law of syllogism

$$[(p \rightarrow q) \wedge (q \rightarrow r)] \rightarrow (p \rightarrow r)$$

- If
  - FDA and CMS approvals (limited) lead to volume expansion
- And
  - Volume expansion led to marked improvement in patient outcomes
- Then:
  - *FDA and CMS approvals (limited) led to marked improvement in patient outcomes*

So what is left to do?

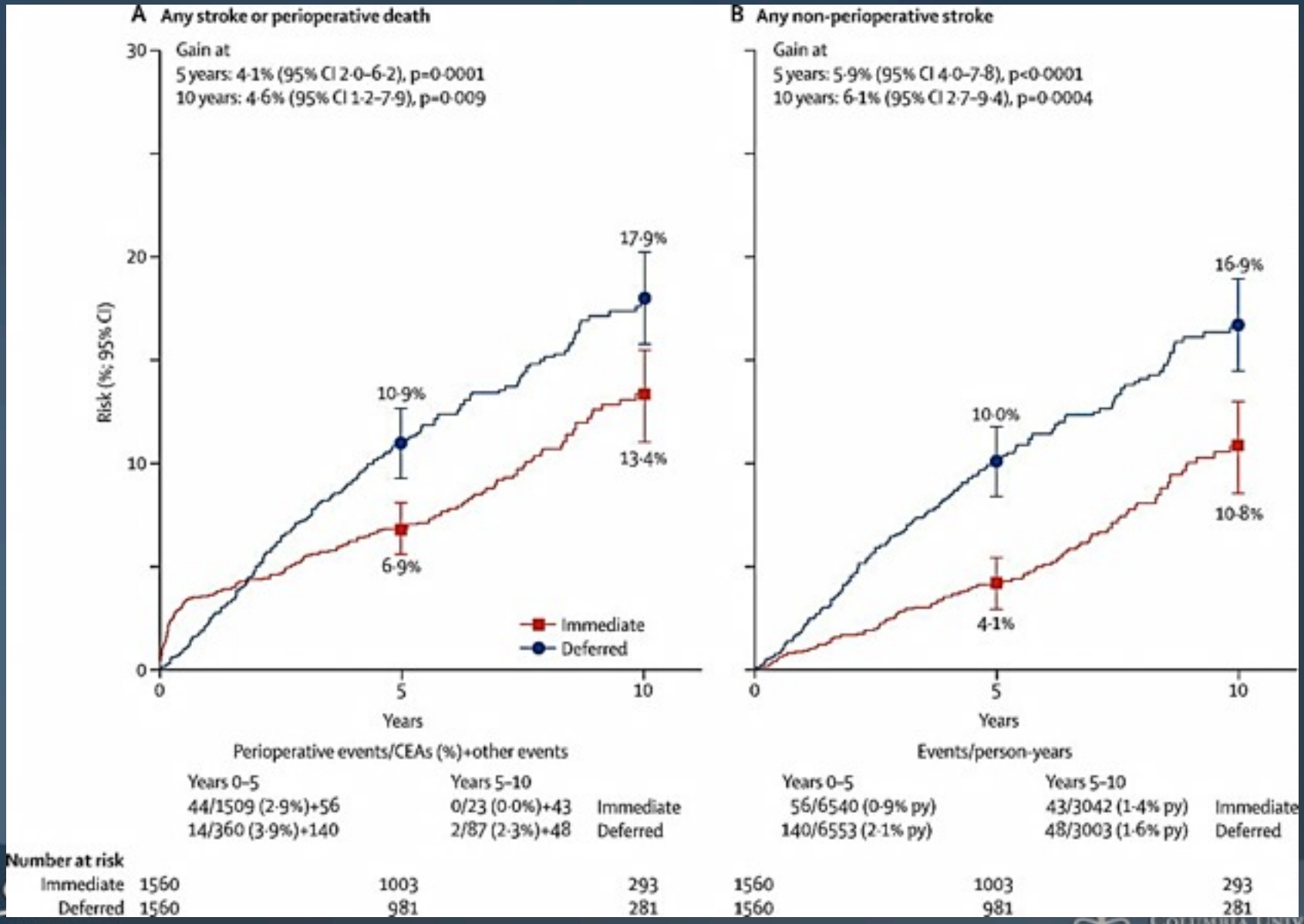
- Request of a CMS expansion of coverage in line with the available data and FDA approval
- Address the issue of asymptomatic carotid management
  - ACT I
  - ASCT 2
  - SPACE 2
  - CREST 2

Request for CMS coverage expansion

- Any effort will be based on several key guiding principles
  - Continued access to the technology for appropriate patients
    - Maintenance of the gains over the past decade
  - Quality oversight
    - Mandatory data collection through independent mechanisms (NCDR, SVS)
    - Independent accreditation (ACE, IAC)
    - Coverage with Evidence Development
  - Continued support for research in this area

Asymptomatic carotid disease

ACST: 10 year outcomes



The support for medical therapy without revascularization for severe asymptomatic carotid stenosis

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Anne L. Abbott

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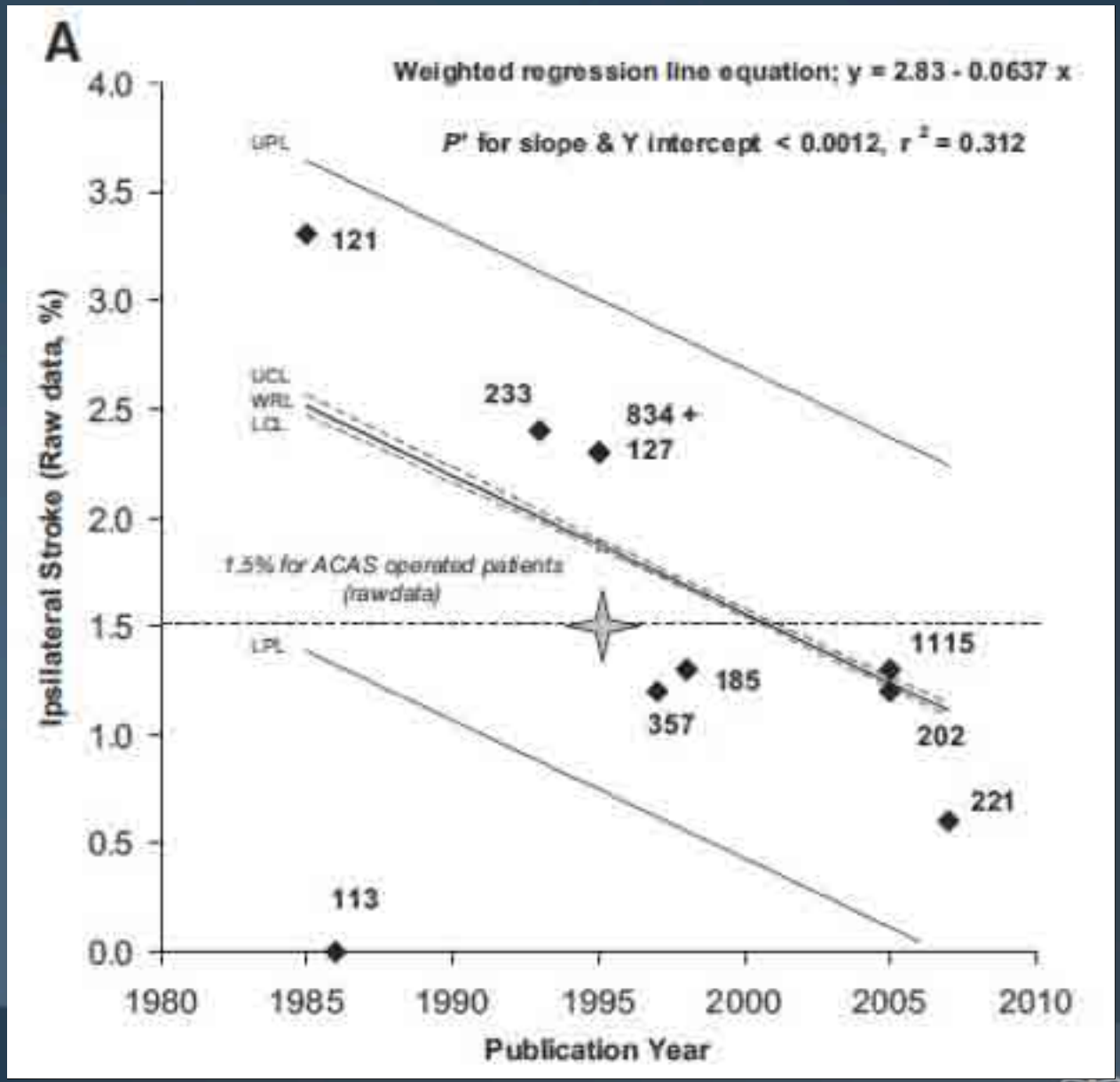
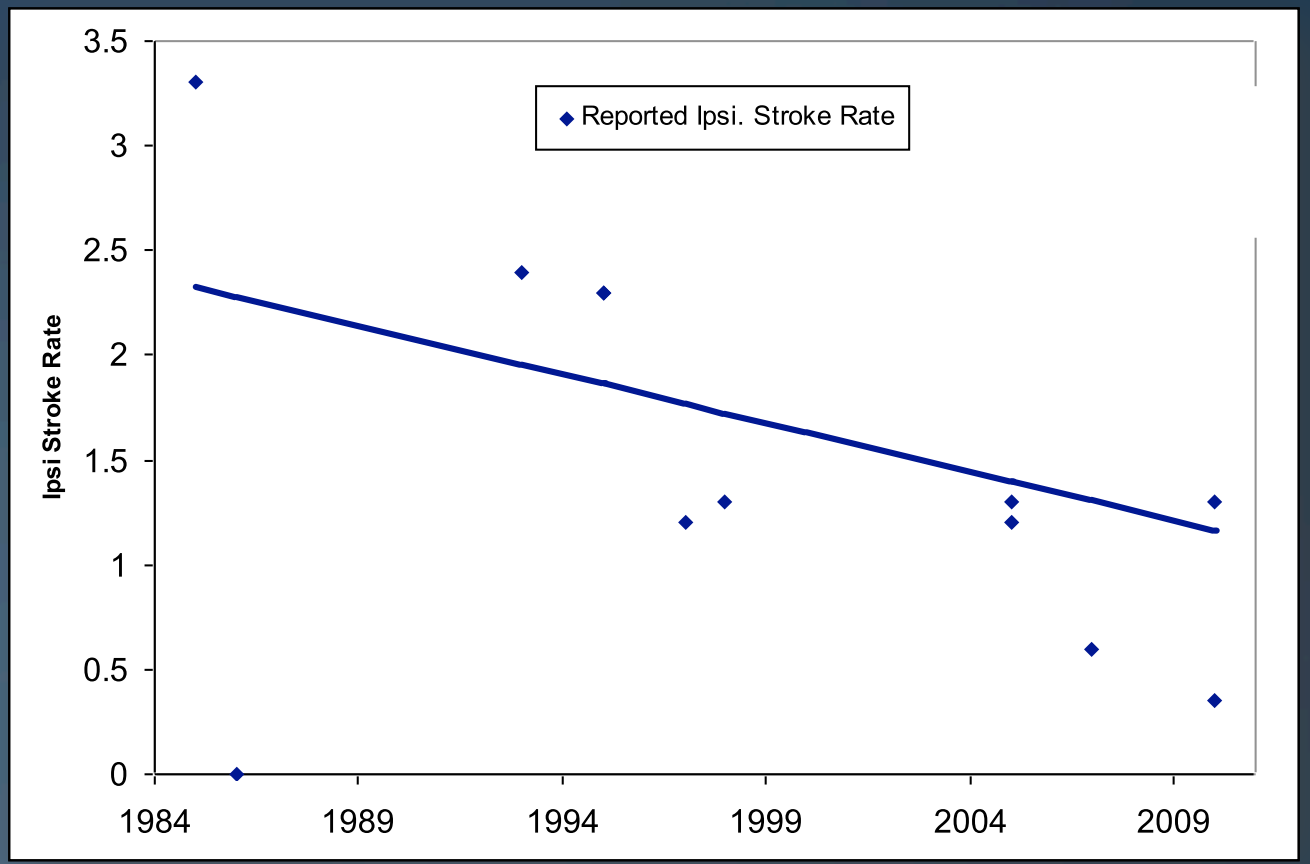
Trends in medical outcomes from Abbott analysis



Critical appraisal of Abbott analysis



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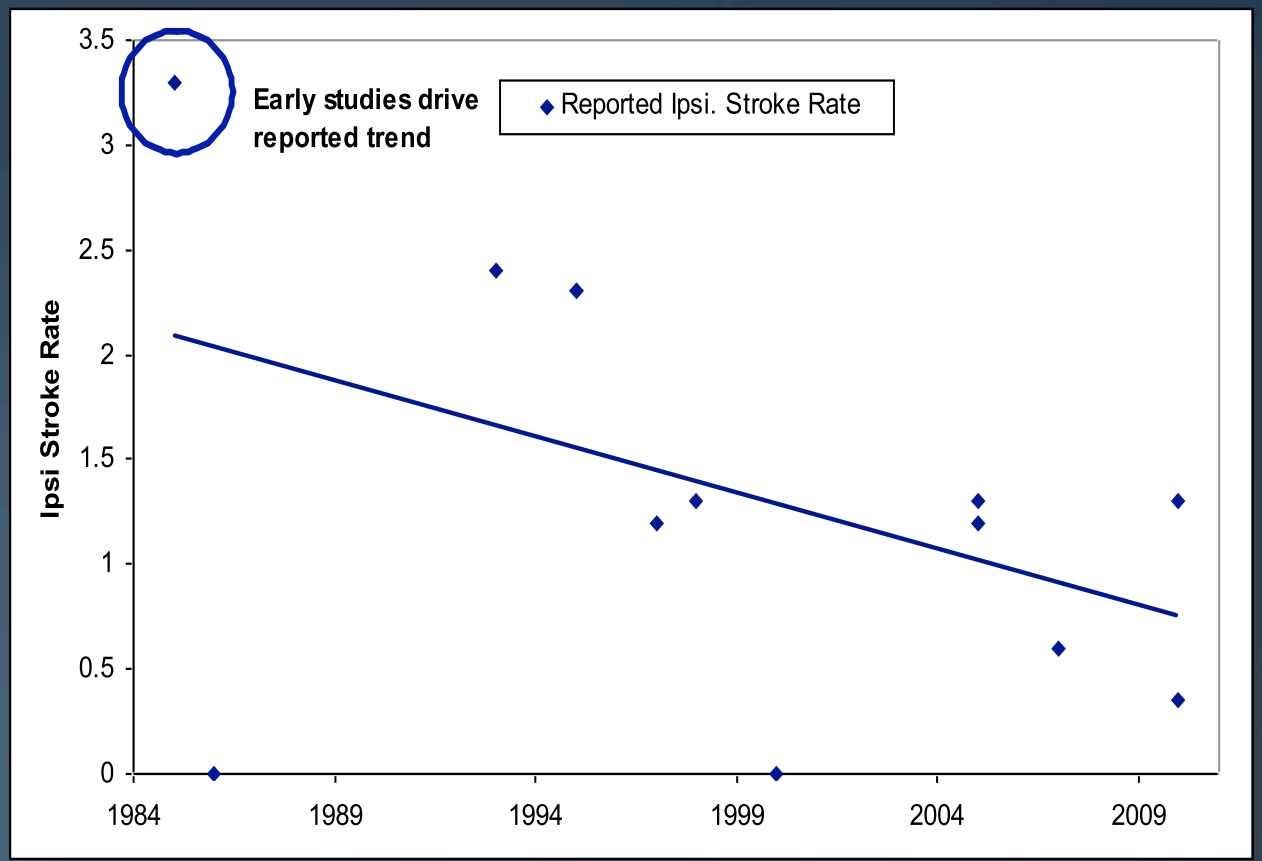

Trend sensitive to effects of early study with more complex patients

Critical appraisal of Abbott analysis

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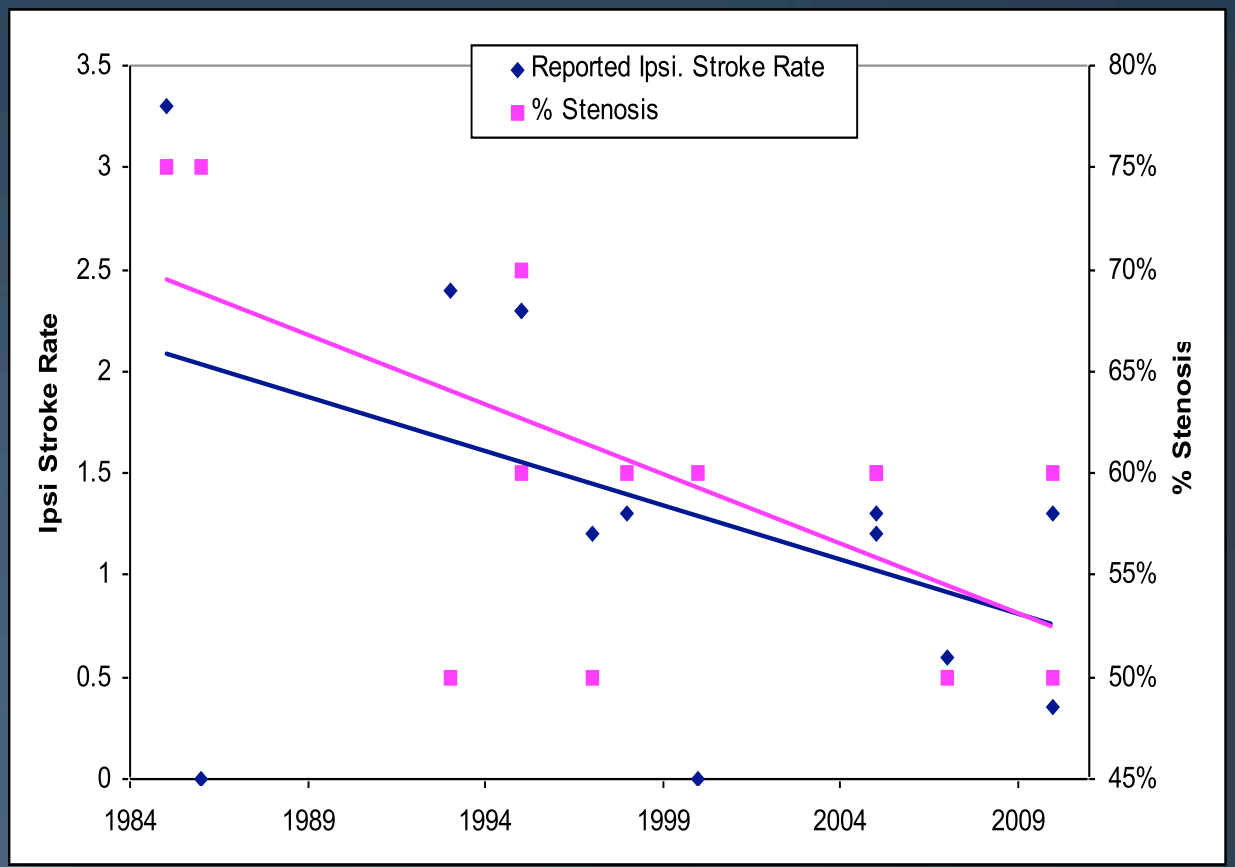

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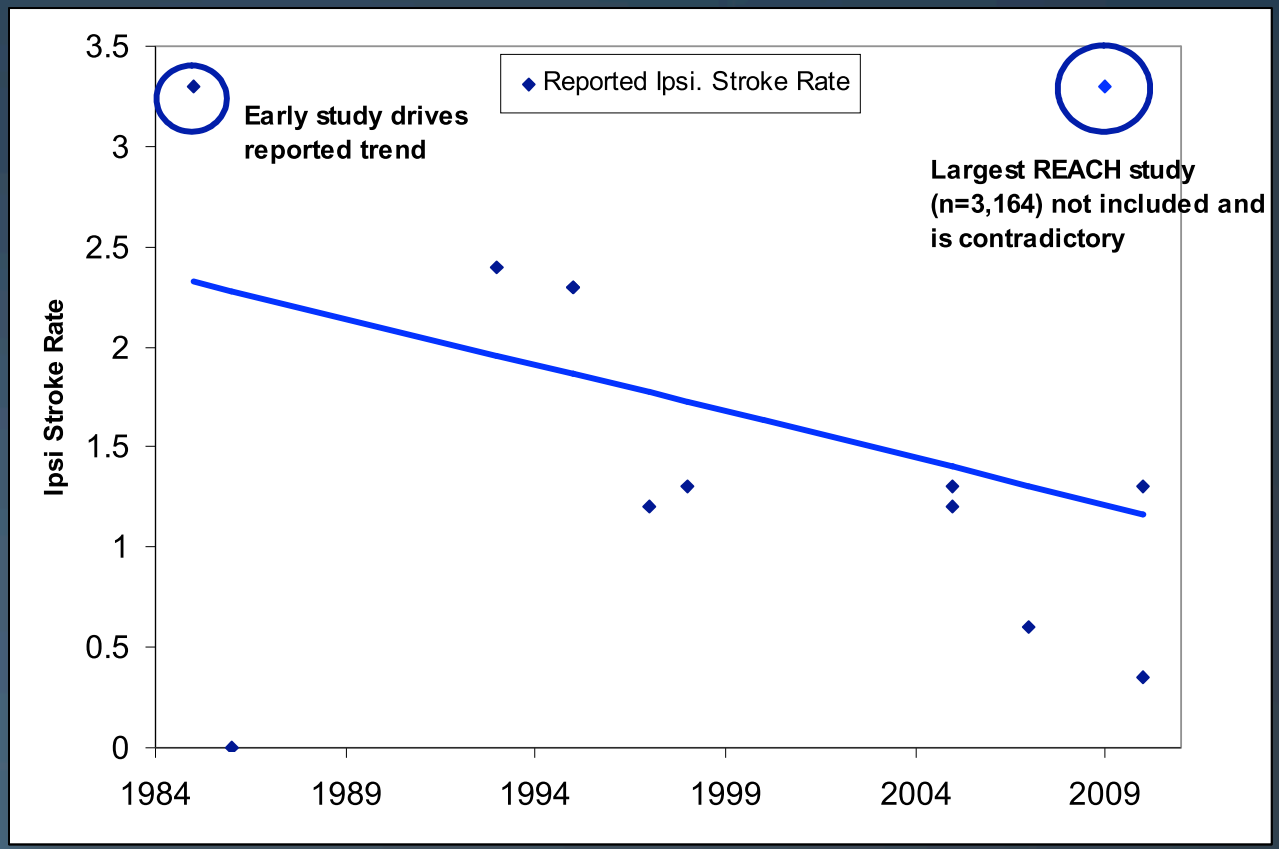

Largest and most recent REACH study (N = 3164) published after the systematic review contradicts the review findings

Critical appraisal of Abbott analysis

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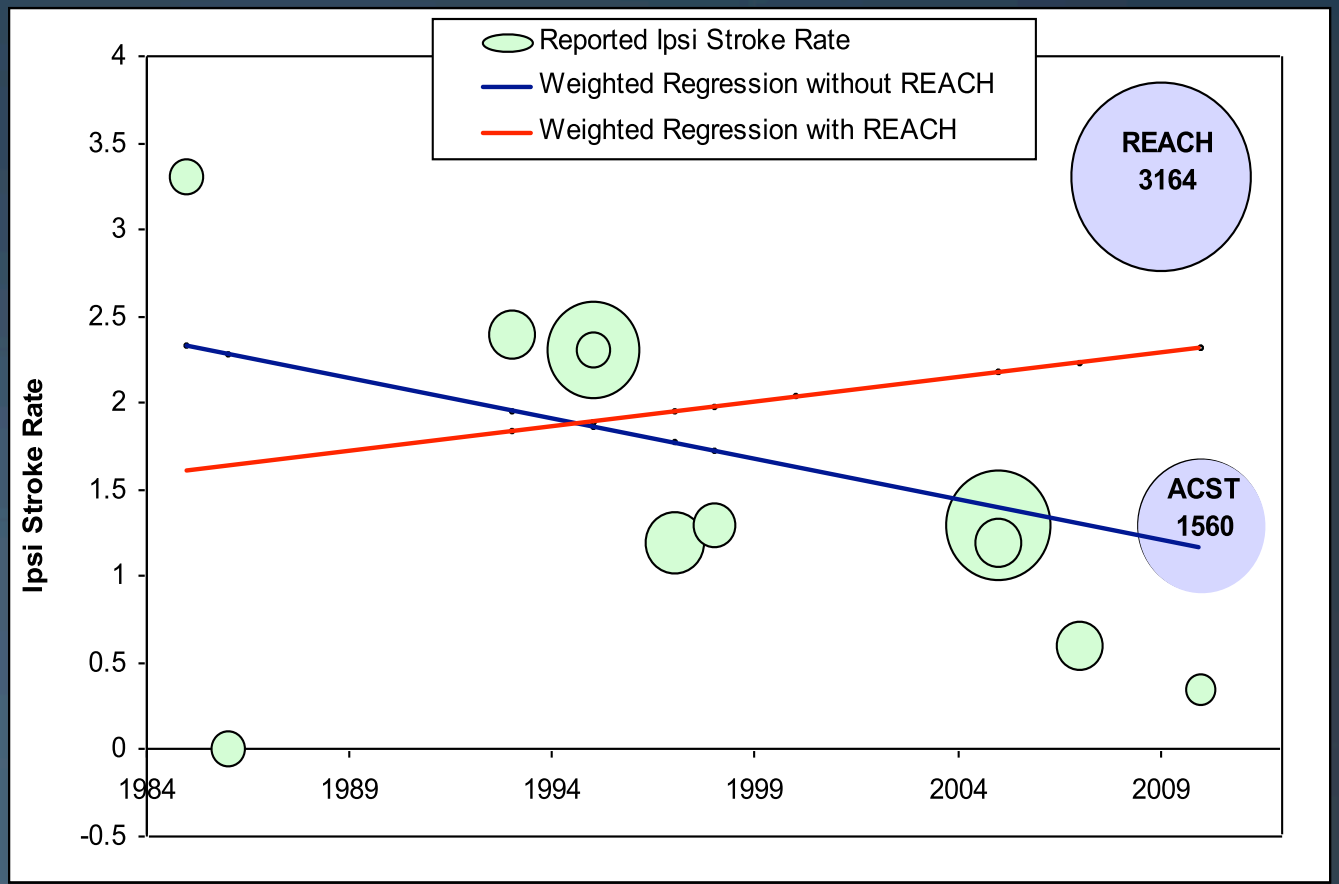


If the systematic review's analysis had adjusted for minimum % stenosis, or had included more recent studies (REACH and ACST) the trend in stroke rates would have been in the opposite direction (p = 0.55)

ACST: medical treatment

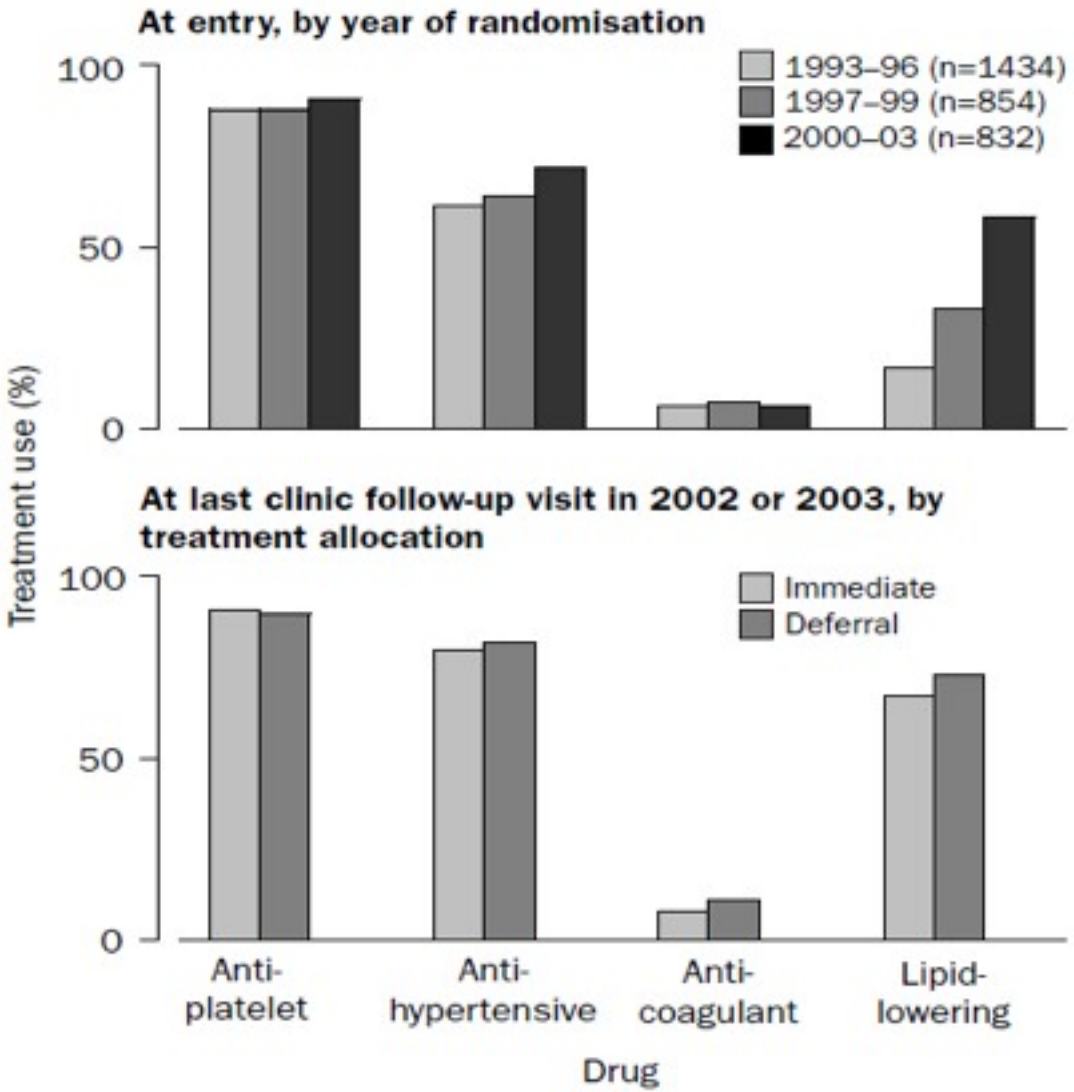
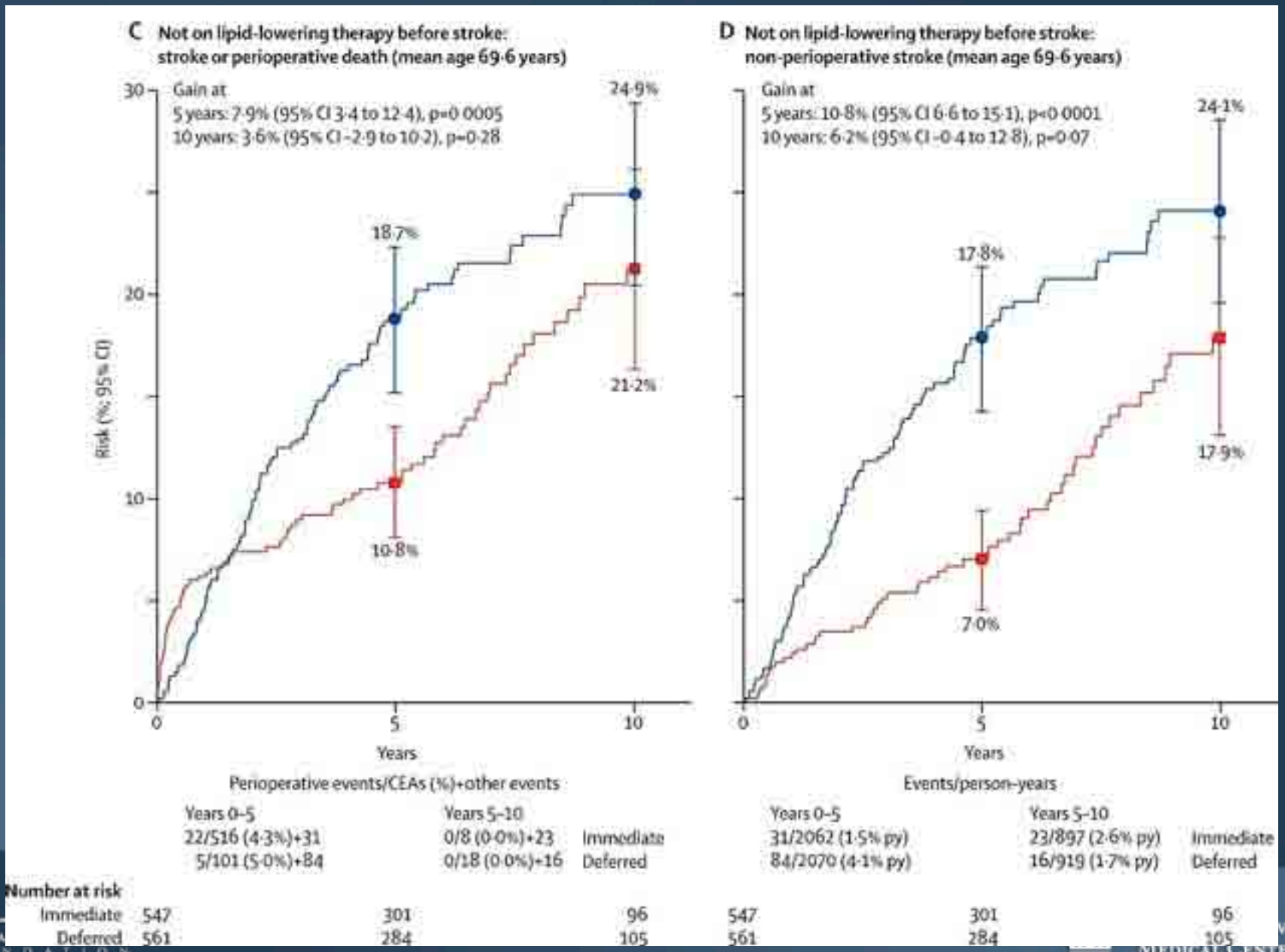
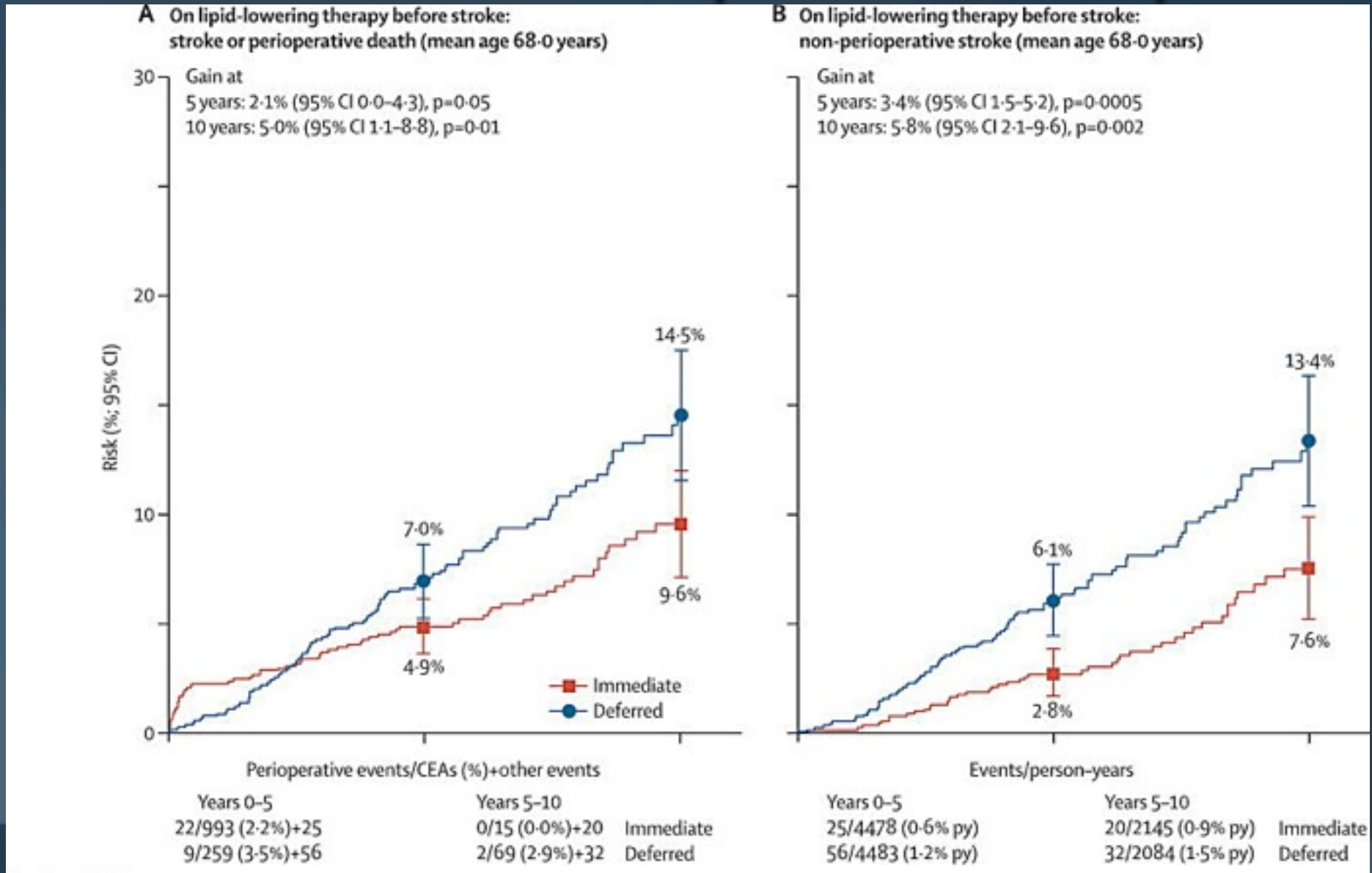


Figure 6: **Use of medical treatments**
At follow-up in 2002 or 2003, mean blood pressure was 148/79 in both groups.

ACST outcomes for patients not on lipid Rx



ACST outcomes for patients on lipid Rx



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Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence.

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Channing Laboratory, Boston, MA 02115.

Abstract

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Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gall-bladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this

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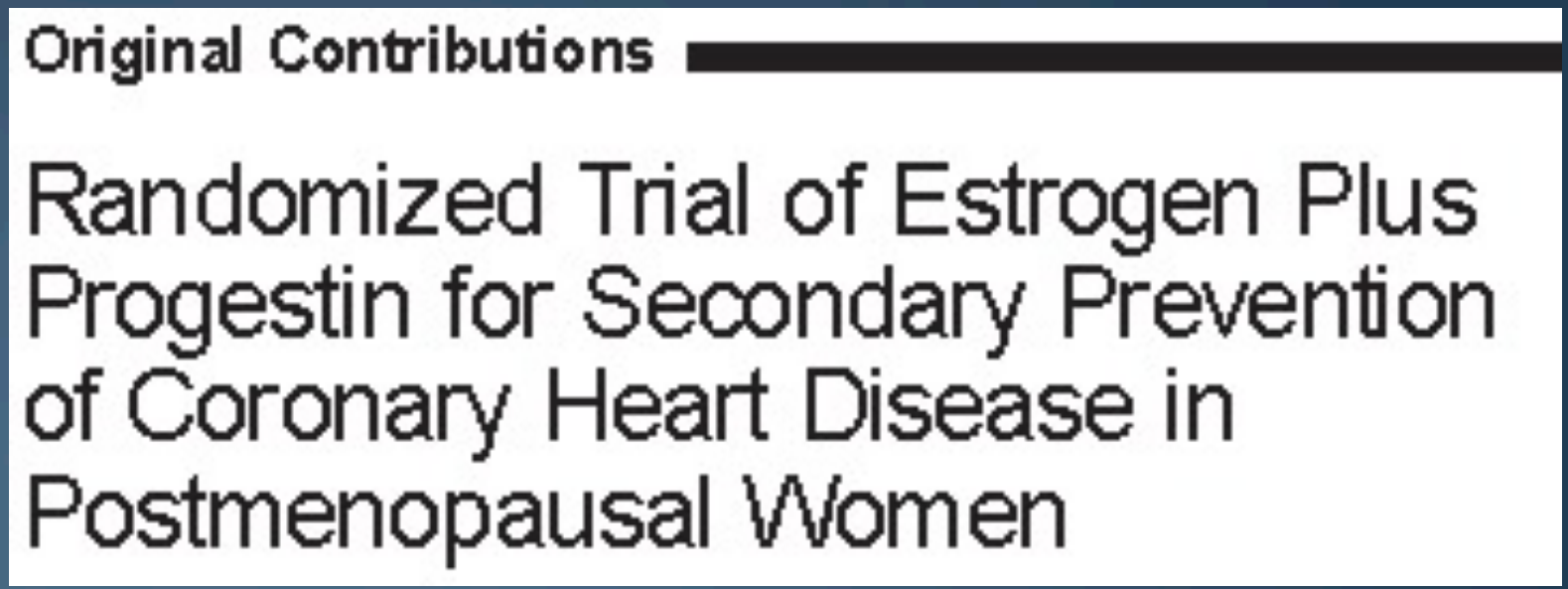
Original Contributions

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Best Medical Therapy in carotid artery disease: what's missing

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- Knowledge as to the correct "cocktail" of medication class, specific to carotid-related targets
  - What is "Best Medical Therapy"?
    - What BP med? What target BP?
    - Which lipid med? What target lipid levels? For LDL? For HDL?
    - How do we improve smoking cessation rates?

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- Measures and assurances of compliance and side effect issues
  - NHANES reports <25% patients achieve BP goal
- Randomized data showing equivalence or superiority to revascularization in *asymptomatic severe carotid stenosis*

Perspectives on CEA, CAS and Optimal Medical Therapy

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- All are improving
- The judicious and selective use of these therapies can result in overall improved patient outcomes:
  - Fewer strokes, fewer MI's
  - Less disability and less CV mortality
- CEA and CAS and medical therapy have complementary, not competitive roles in the patient requiring revascularization

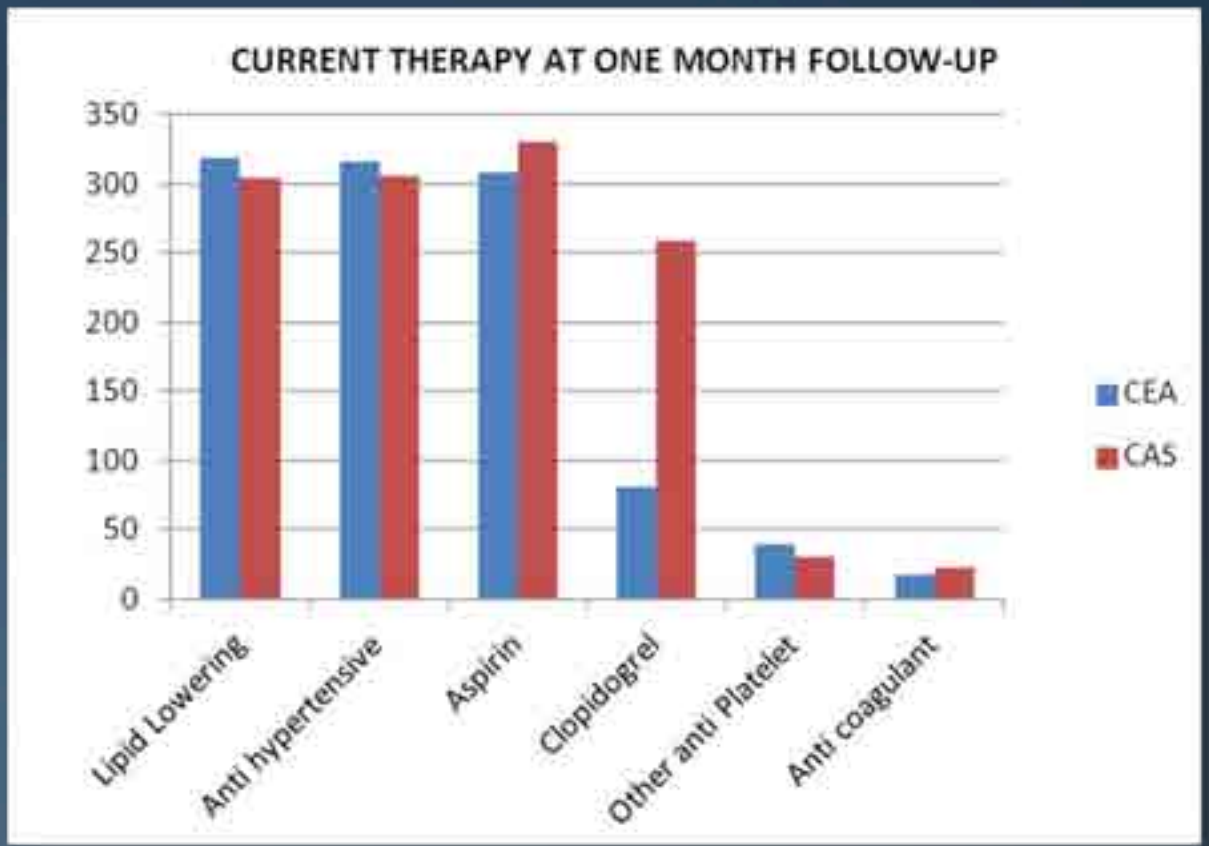
ACT I

- After completing randomization of 1450/1650 asymptomatic patients 3:1 CAS:CEA, the trial has been stopped
  - No safety concerns
- Significant and valuable data set with a primary endpoint of 1 year
- Opportunities to add to or combine with other data sets (CREST, etc.) for even more robust analysis

ACST 2

- Oxford/UK based multicenter/multinational effort
- 5000 patient trial randomizing asymptomatic patients 1:1 CEA:CAS
- Currently >1100 patients enrolled
- Early data are available on ~682 patients

ACST 2: interim blinded outcomes



ACST 2: interim blinded outcomes

Major events within 30 days (none were in people who did not have their allocated procedure)	Total (n=682)
1) Unrefuted stroke within 30 days, by severity of worst such stroke	
Fatal	2
Disabling	4
Non-disabling (excludes TIA)	14
Total	20
2) Unrefuted MI within 30 days, by outcome	
Fatal	1
Non-fatal	3
Total	4
3) Vascular event within 30 days that (eventually) caused death, or disabling stroke within 30 days	7 (1.0%)
4) Any unrefuted stroke, MI or related death within 30 days	24 (3.5%)
5) Death in 30 d probably unrelated to stroke, MI or procedure	1

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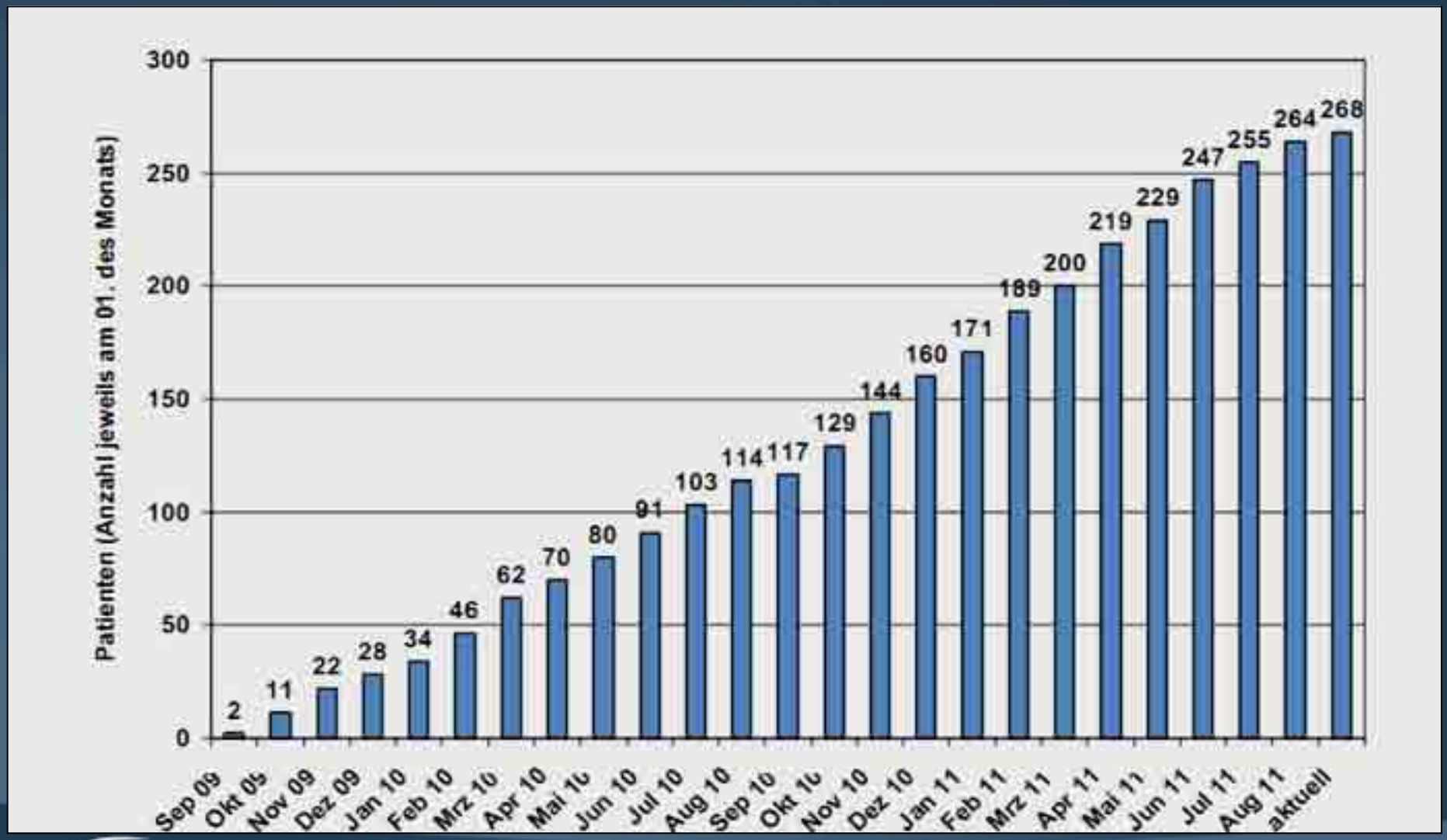
SPACE 2
Number of carotid procedures in Germany

SPACE 2

- Investigator-initiated prospective, randomized, multicenter trial
- Three arms: Optimal medical treatment (OMT)
  CEA + OMT
  CAS + OMT
- ~100 certified centers
- N=3,640 patients with a follow-up of five yrs. (duration 8-9 yrs.)
- Funding by the German Ministry for Education and Research (BMBF, about 4 Mio €)

SPACE 2


Patienten (Anzahl jeweils am 01. des Monats)
300
250
200
150
100
50
0
2
11
22
28
34
46
62
70
80
91
103
114
117
129
144
160
171
189
200
219
229
247
255
264
268
Sep 09
Okt 09
Nov 09
Dez 09
Jan 10
Feb 10
Mrz 10
Apr 10
Mai 10
Jun 10
Jul 10
Aug 10
Sep 10
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CREST 2

CREST 2: Primary Aim

- To assess if contemporary REVASCULARIZATION, either CAS or CEA, provides an incremental benefit of 1.2% annual risk reduction over contemporary medical therapy

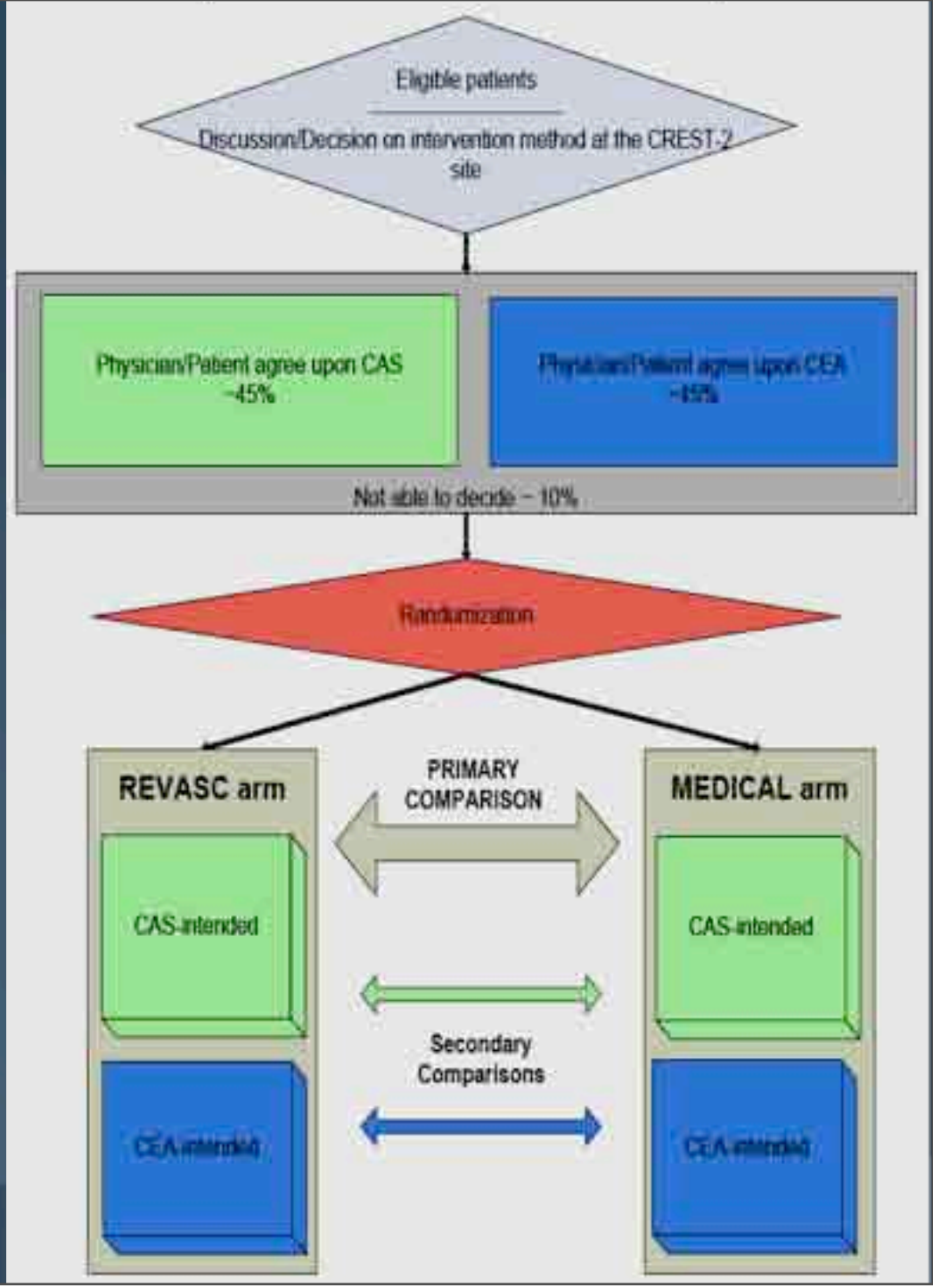
CREST 2: Primary outcome

- The primary outcome will be the classical composite of stroke or death within 30 days of enrollment or ipsilateral stroke up to 4-years thereafter.

CREST 2: Key design elements

- Sample size 950 participants at approximately 70 centers.
- Statistical power will be ~ 90% to detect a 4.8% treatment difference (1.2% per year)

After randomization, the CAS and CEA groups imbedded in the REVASC and MEDICAL arms will allow randomized-protected comparisons of CEA-intended and CAS-intended patients to the MEDICAL patients.



CARDIOVASCULAR RESEARCH FOUNDATION

…and “working groups” to study

- **Plaque** characteristics as predictors of risk– *BK Lal, MD, University of Maryland*
- **MRI**- treatment differences– *Michael Hill, MD, University of Calgary*
- **Cognitive**- treatment differences– *David Knopman, MD, Mayo Clinic and Ronald Lazar, PhD, Columbia*
- **QOL and costs**– *David Cohen, MD,* Saint Luke’s Mid America Heart and Vascular Institute
- **CMS and other databases** to enrich outcomes– *Judith Lichtman, PhD, Yale*
- **Hemodynamic changes -** by treatment and impact on outcomes– *Randy Marshall, MD, Columbia*

Initial NIH/NHLBI Review

- Moderate/major concerns:
  - The combined CEA and CAS arm:
    - ?whether CAS had established efficacy in reducing stroke and death in this population
    - Suggested a change in sample size that would allow independent assessment of each intervention vs. medical Rx
  - One-sided superiority for the primary hypothesis in a Phase III trial not adequately justified
  - Justification for the 4 year event rate in the medical group was limited, and would affect sample size significantly
  - SAMMPRIS intensive medical therapy is not “real world” and that compliance was not adequately addressed
    - Cognitive assessment was not included and should be, given adverse cognitive effects of statins

Summary

- The next wave of CAS testing will be dedicated less to CAS vs. CEA, and more to addressing the question as to the role of revascularization for patients on OMT
- Difficult trials to enroll, and will be several years before outcomes will be known