What did we learn from the ACST-2 trial about carotid intervention in asymptomatic patients with severe stenosis?

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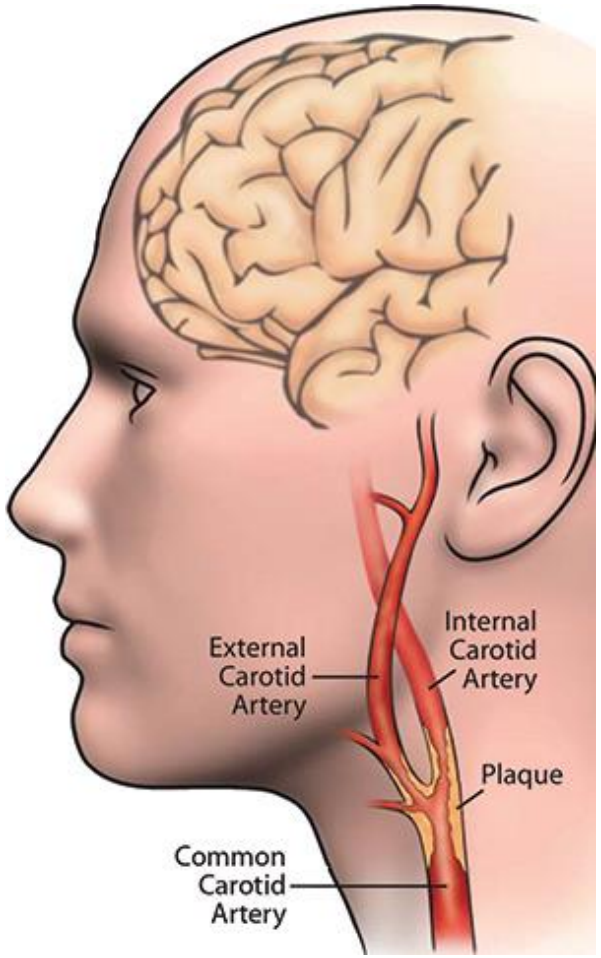
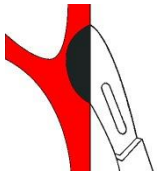
Background ~ 15% ischaemic strokes caused by carotid disease



UK ~15,000 strokes/year from carotid disease

EU - increase in all strokes likely:
~600,000 in 2015 to >800,000 in 2035
Worldwide: 12.2m first strokes/year
>100m alive after stroke, many disabled

So, Worldwide there are over 1m strokes/year from carotid disease, half disabling or fatal (**ineligible** for secondary preventive carotid interventions)



ACST-1 trial (1993-2010)

3120 patients with severe stenosis eligible for CEA

randomized:

Immediate CEA versus control

(no CEA unless symptoms occur)

Individual patient data analysis of all 3 trials

Over 5,000 in ACST-1, ACAS and VACS Trials

	VACS	ACAS	ACST-1
Nos. of patients (Immediate vs Deferred)	444 (211 vs 233)	1662 (828 vs 834)	3120 (1560 vs 1560)
Period of randomisation	Apr 83 – Oct 87	Dec 87 – Dec 93	Apr 93 – Jul 03
Date of last follow-up	May 1991	Feb 1997	May 2008
Median (IQR) follow-up year	4.5 (2.5-6.0)	4.2 (2.9-5.0)	6.1 (3.9-9.1)

Almost all were on double drug therapy
(Double therapy is BP lowering + anti-thrombotic)

Many were on triple therapy, which also includes a statin

5226 patients in VA, ACAS and ACST-1

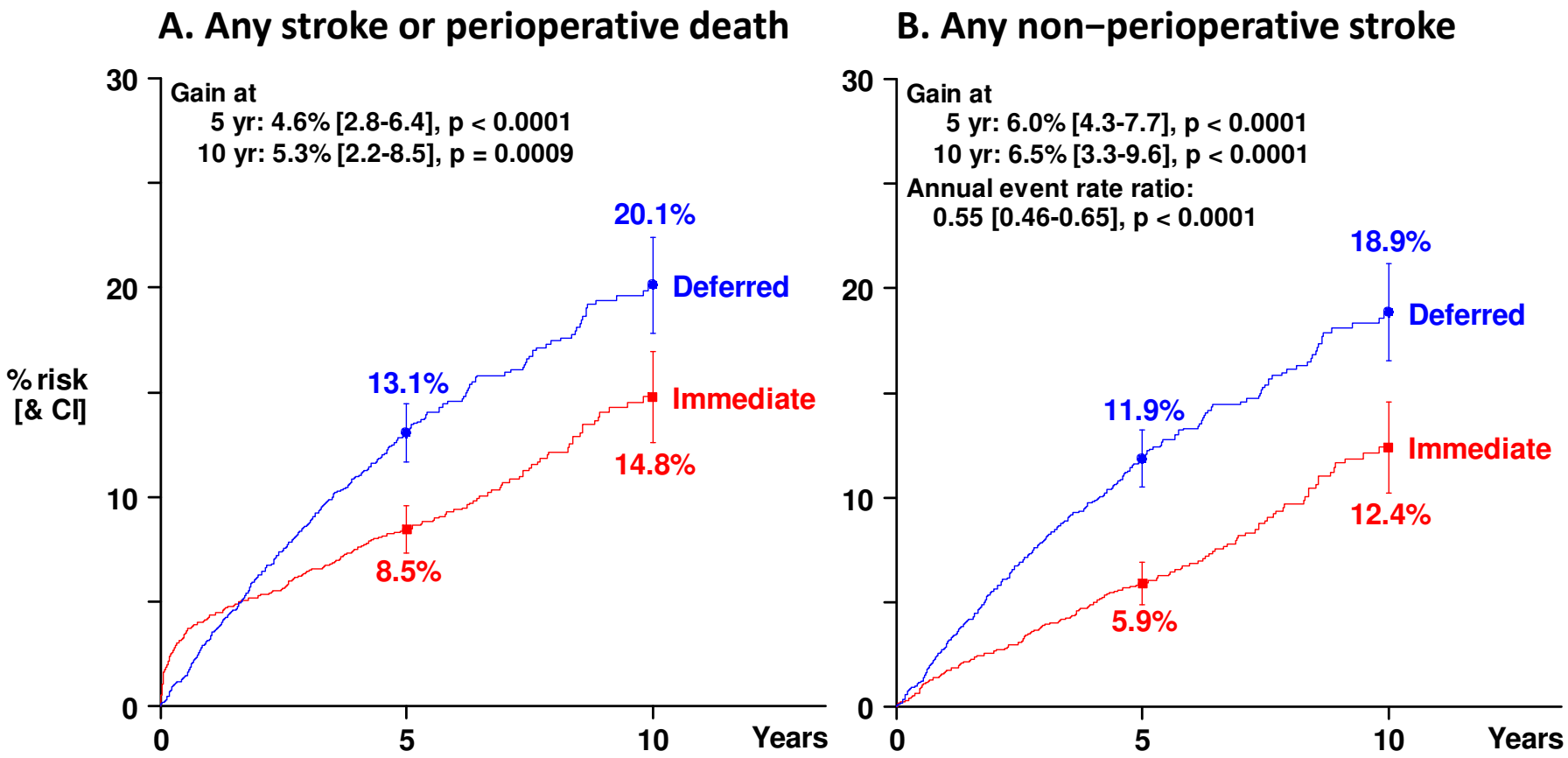
Medical therapy from 1983-2008

Table 1: Characteristics of randomised patients in VACS, ACAS and ACST-1 trials

Baseline characteristics	Veterans Affairs Cooperative Study (VACS)	Asymptomatic Carotid Atherosclerosis Study (ACAS)	Asymptomatic Carotid Surgery Trial (ACST-1)
Period of entry	1983-1987	1987-1993	1993-2003
Region	North America	North America	Mainly Europe
Number randomised	444	1662	3120
Median (IQR) follow-up year†	4.5 (2.5-6.0)	4.2 (2.9-5.0)	6.1 (3.9-9.1)
Age range, years	37-83	40-79	40-91
Mean age, years (SD)	64.5 (6.8)	66.7 (6.9)	68.1 (7.5)
Men %	100.0	65.8	65.5
Treated hypertension %	57.2	70.2	64.8
Mean blood pressure, mm Hg (SD)			
Systolic	142 (20)	145 (18)	153 (22)
Diastolic	75 (16)	78 (9)	83 (11)
Lipid lowering %‡	0.0	12.8	32.4
Mean cholesterol, mmol/L (SD)	No data	5.9 (1.1)	5.8 (1.2)
On antithrombotic therapy %	55.2	80.5	93.8
Diabetes %	27.7	23.3	19.9
Previous contralateral CEA %	20.5	19.4	24.0
Ipsilateral CT infarct %	No data	7.9	8.1
Contralateral occlusion %	0.0	9.3	8.8

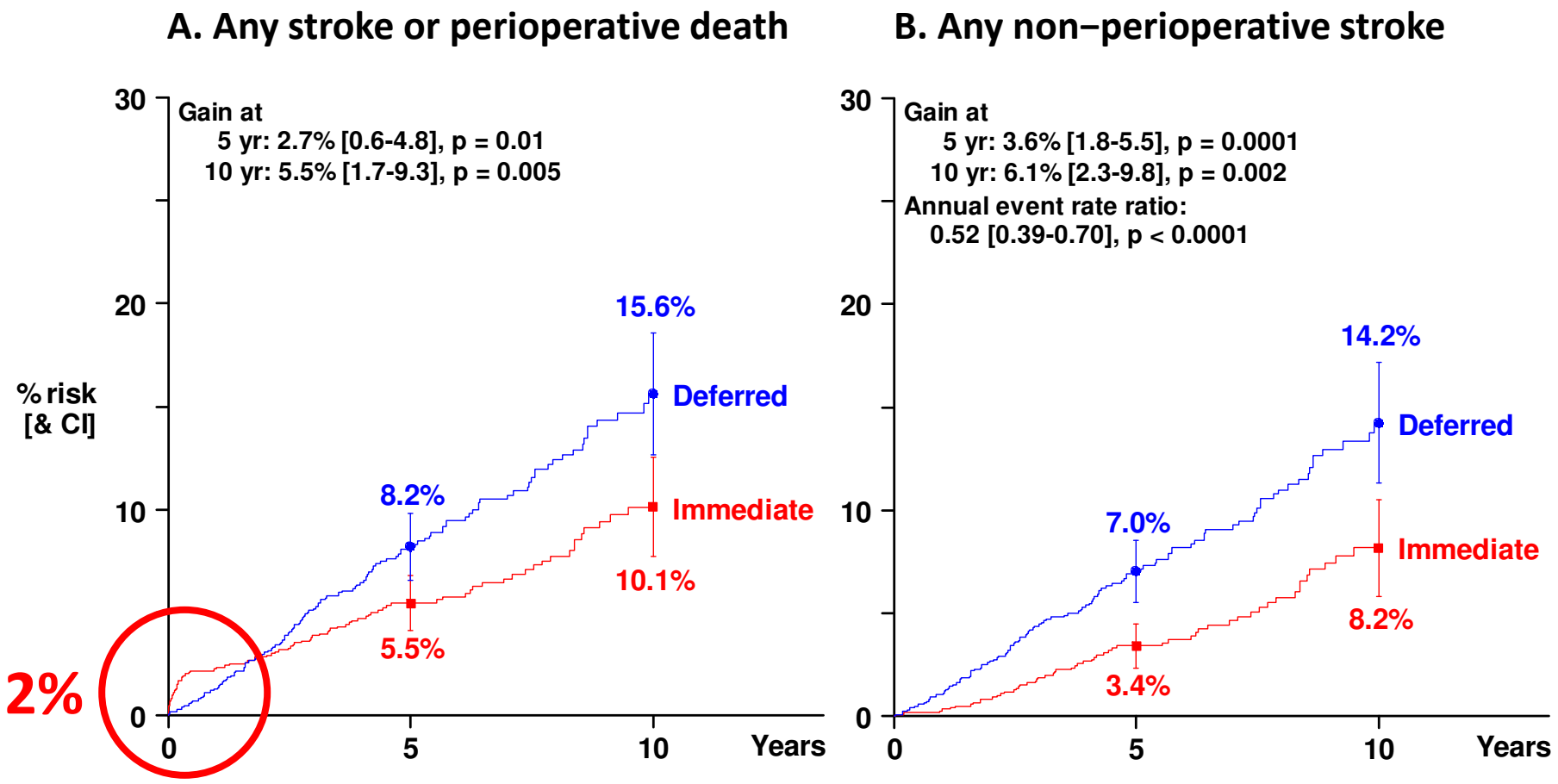
10-year risk of any stroke or perioperative death

All 3 trials, either with double or with triple drug therapy



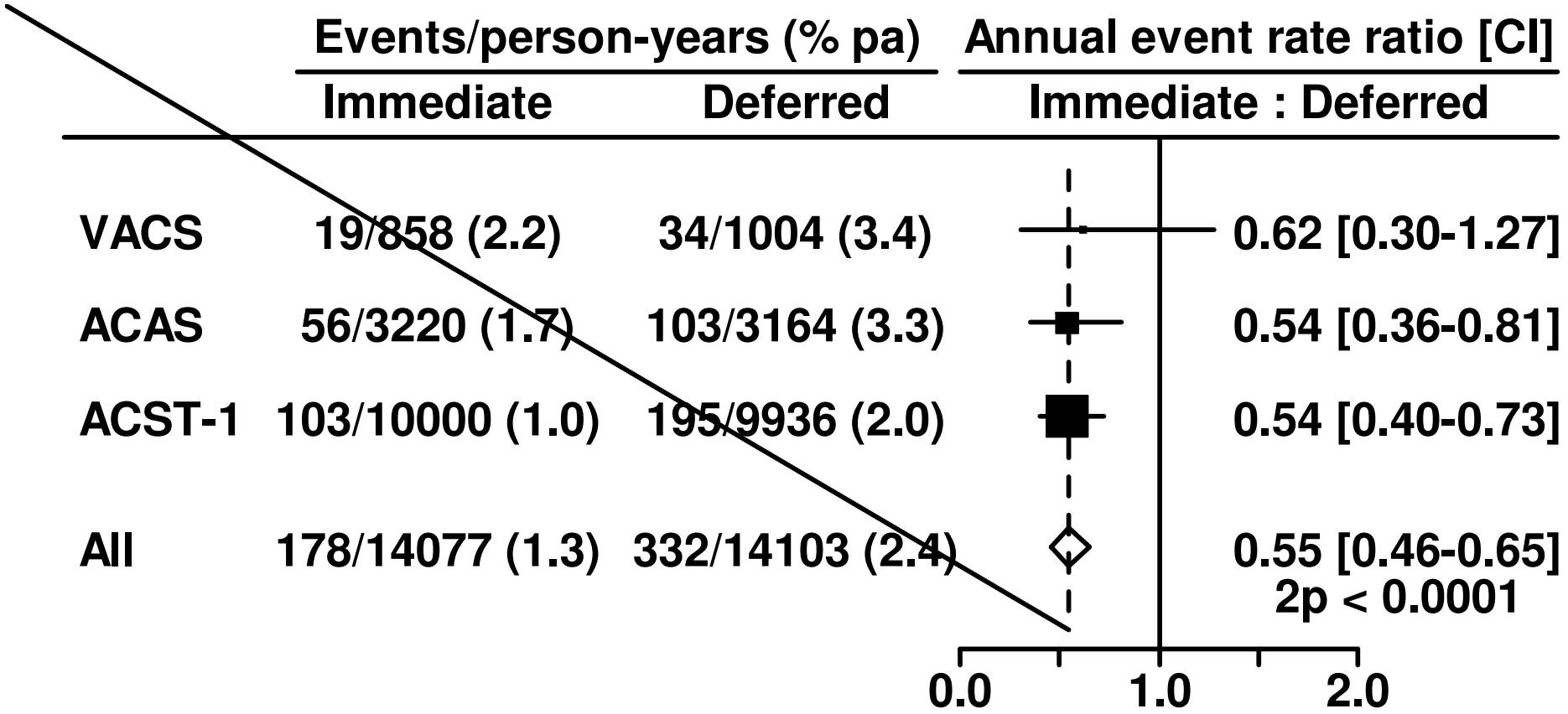
Asymptomatic Carotid surgery trials (ACST-1, ACAS, VA)

Only patients on triple therapy before event (Antithrombotic, blood pressure, statin)



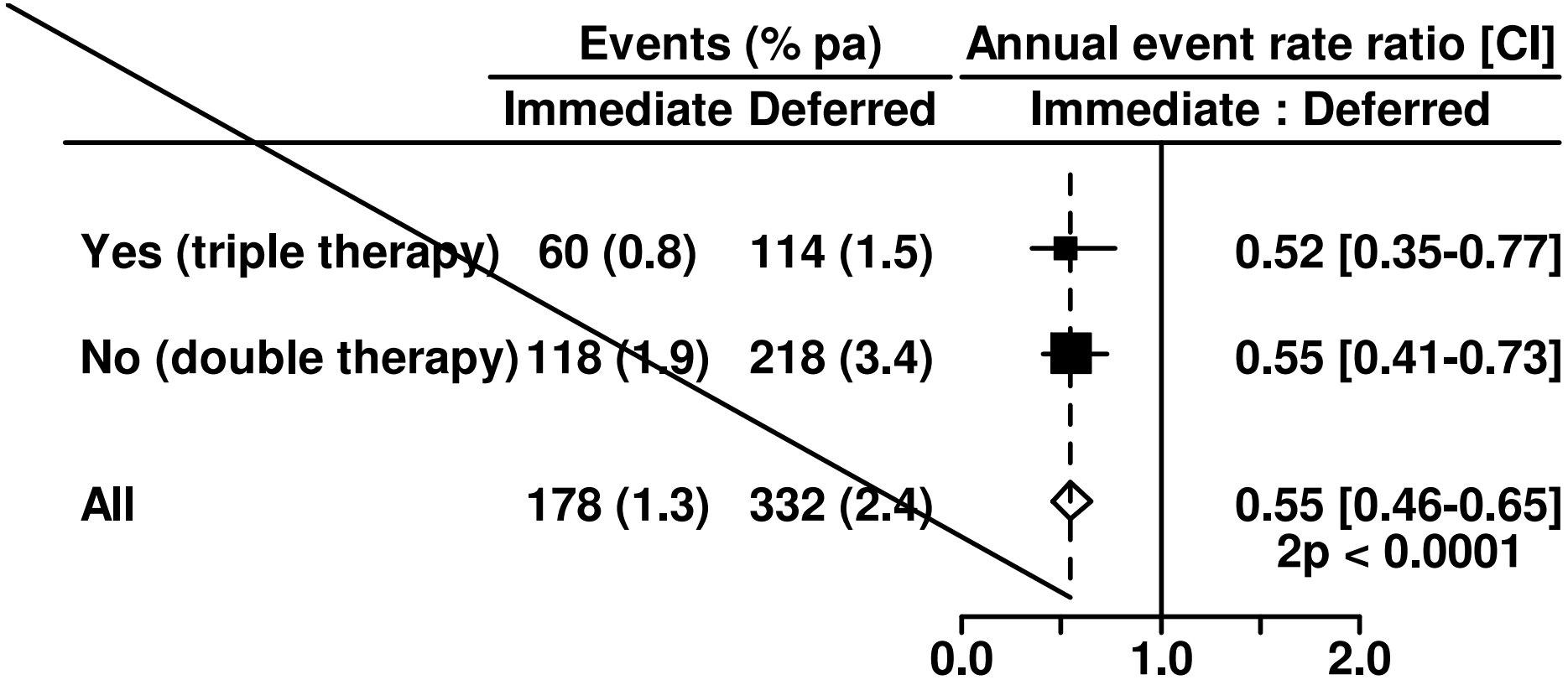
Non-perioperative stroke

Risks appear to have been halved by CEA in all three trials



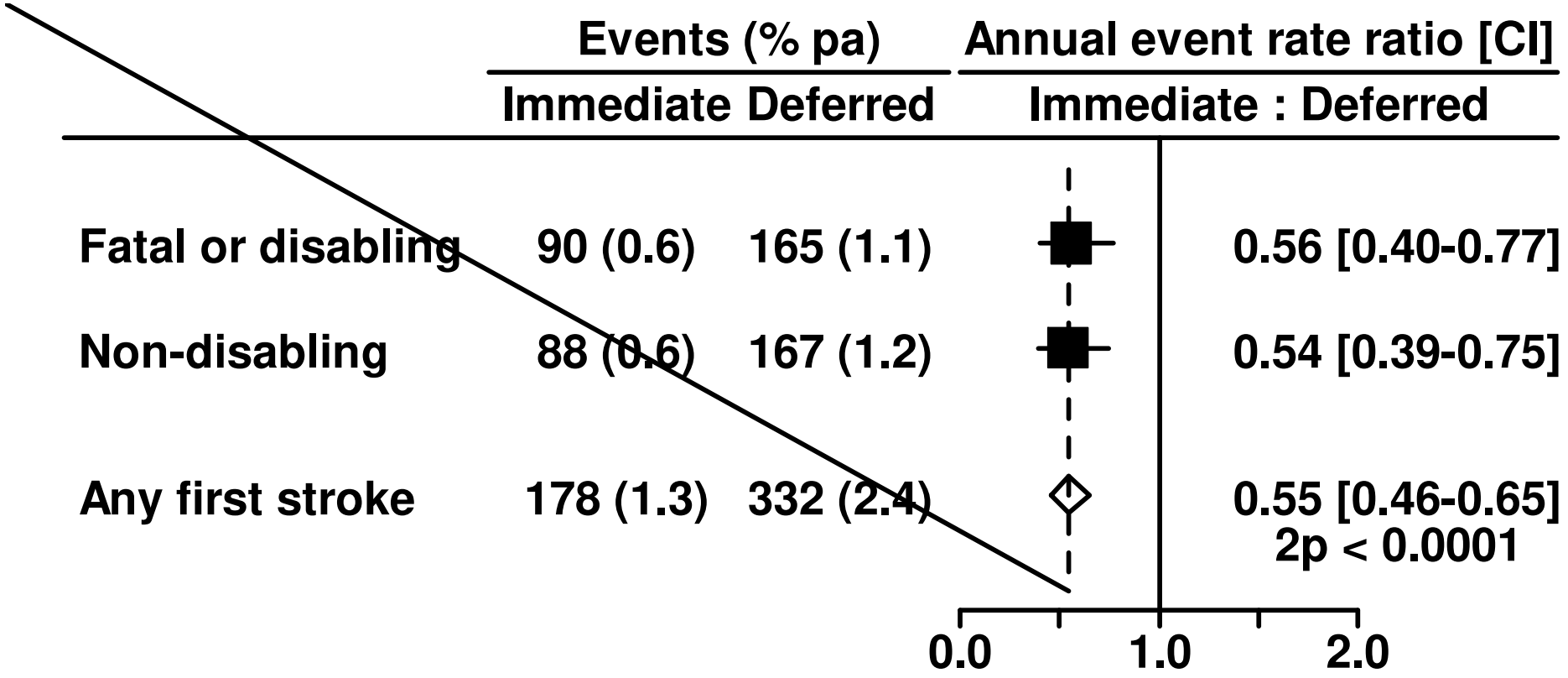
Non-perioperative stroke by lipid-lowering therapy before any stroke

CEA halves stroke rate whether or not statins are used (& statins halve stroke rates whether or not CEA is done)



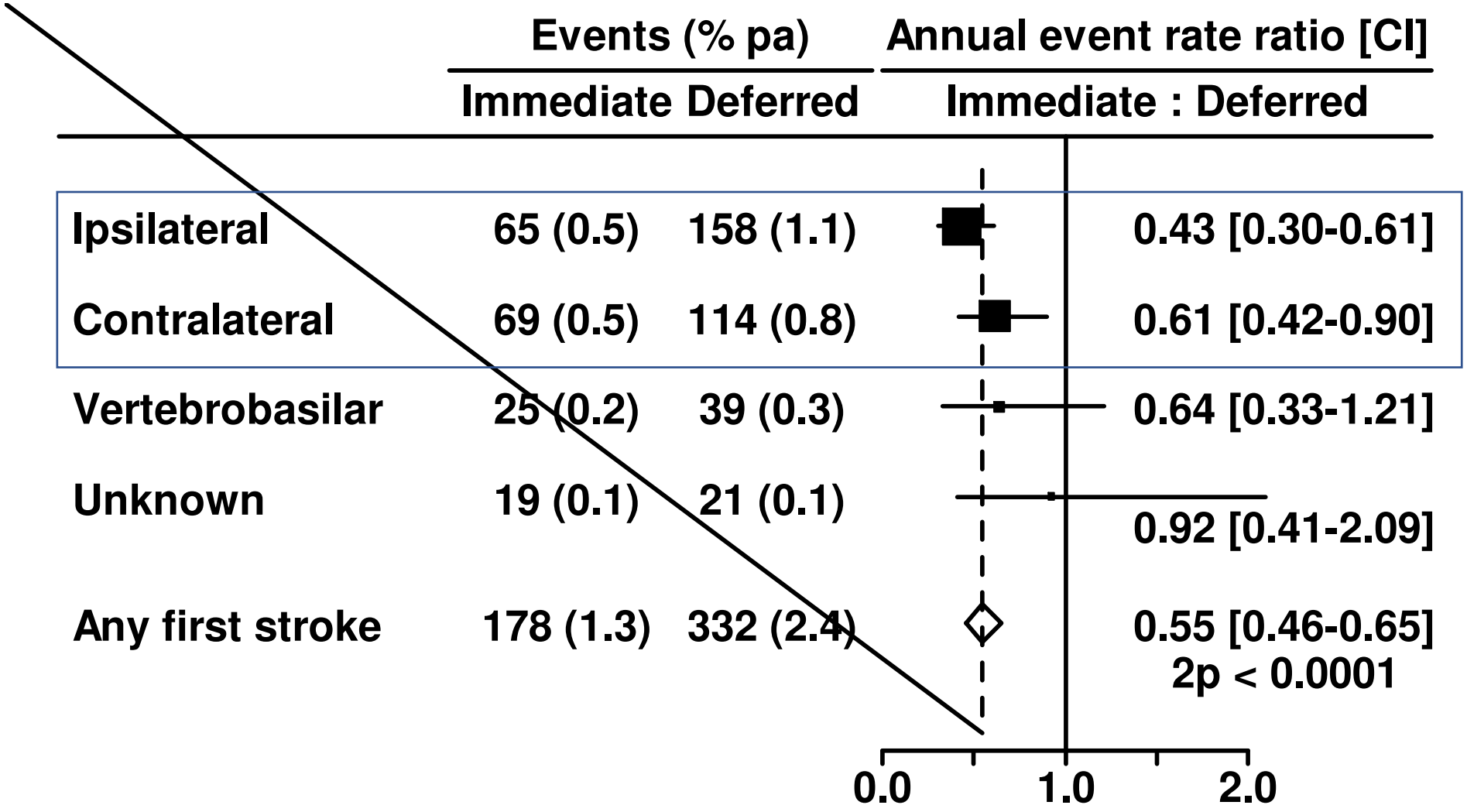
Non-perioperative stroke, by outcome

Fatal/disabling and non-disabling strokes are both halved



Non-perioperative stroke, by subtype

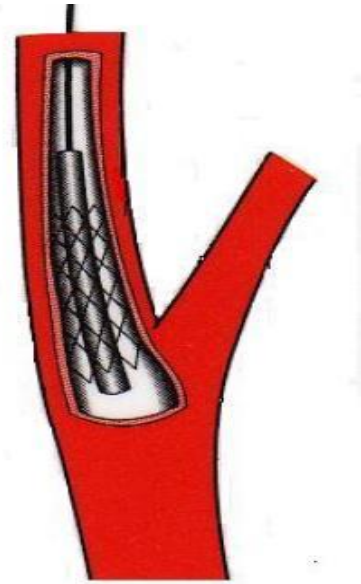
Ipsilateral and contralateral strokes are both reduced

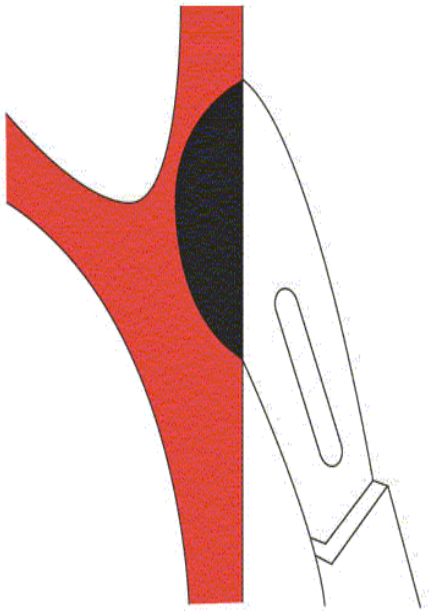


Conclusions from ACST-1 and the other major trials of CEA vs no CEA

For asymptomatic patients with severe stenosis, these three trials showed that, even if good medical treatment is given, CEA ~halves long-term stroke rate

ACST-2: trial of carotid artery stenting (CAS) versus carotid artery surgery (CEA: “endarterectomy”)





ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

Trials have shown CEA restores patency and ~halves later stroke rates, and that modern medical therapy also ~halves long-term stroke rates.

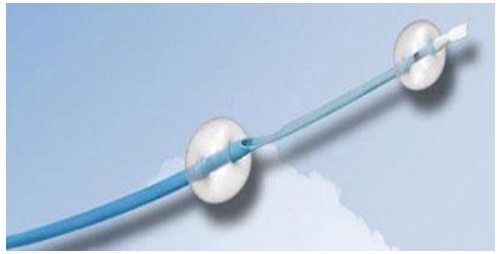
CAS can also restore patency, and in recent nationwide registry data CAS and CEA each has ~1% risk of causing disabling stroke or death.

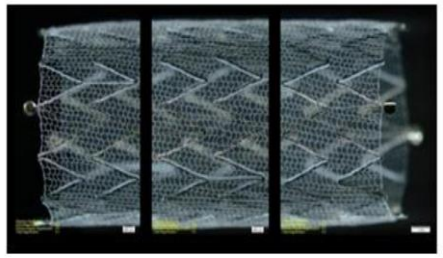
Recent Carotid Stenting therapy includes

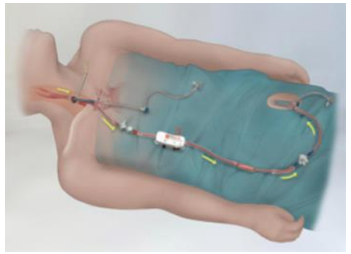
Statins and DAPT to lower peri-procedural risk and ..

- Newer stent designs
- Flow reversal (MOMA)
- Greater experience

which reduce risk further







2014-19 German mandatory nationwide registry of in-hospital* CAS/CEA risks in asymptomatic patients

	18,000 CAS	86,000 CEA
Disabling stroke or death:	0.7%	0.7%
Any stroke or death:	1.8%	1.4%

NB In-hospital stroke risks were not affected by gender or age.

* Median 4-5 days to discharge; 30-day risks would be higher.

Source: https://iqtig.org/qs-verfahren/qs-karotis

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

CAS vs CEA: why do we need randomised evidence?

Large, representative registries can assess procedural hazards, and determine reliably whether they depend on gender or age.

But, registries cannot reliably compare long-term non-procedural stroke rates; for this, *large-scale randomised evidence* is required.

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

- International trial; included 3625 patients from 130 hospitals (mostly European), each with an interventionist, a vascular surgeon, and a stroke doctor

- Collaborators used their normal procedures, with, for stenting, any CE-approved devices and double anti-platelet therapy.

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

- Severe carotid artery stenosis (≥60% on ultrasound), with no recent ipsilateral stroke or other symptoms from it

- Thought to need a carotid procedure (stenting or surgery), but substantially uncertain whether to prefer CAS or CEA

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

- Randomise 3625 patients to CAS vs CEA and follow for a mean of 5 person-years

- Give both groups good long-term medical treatment, usually with lipid-lowering, anti-thrombotic and anti-hypertensive therapy.

- Monitor long-term stroke rates, classifying outcome 6 months later (with disabling strokes having modified Rankin Score [mRS] 3-5).

ACST-2 and CAS therapy

Stent use

Closed cell	45%
Open cell	32%
Hybrid	13%
Membrane	10%

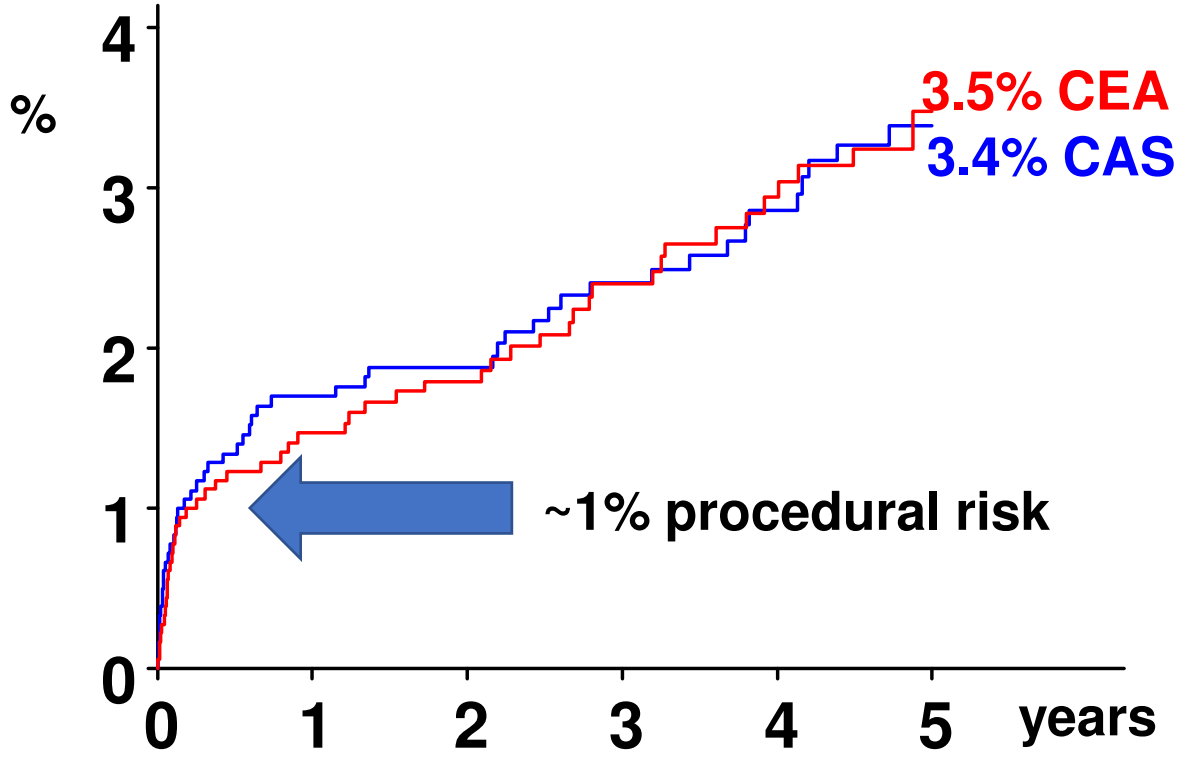
CPD use

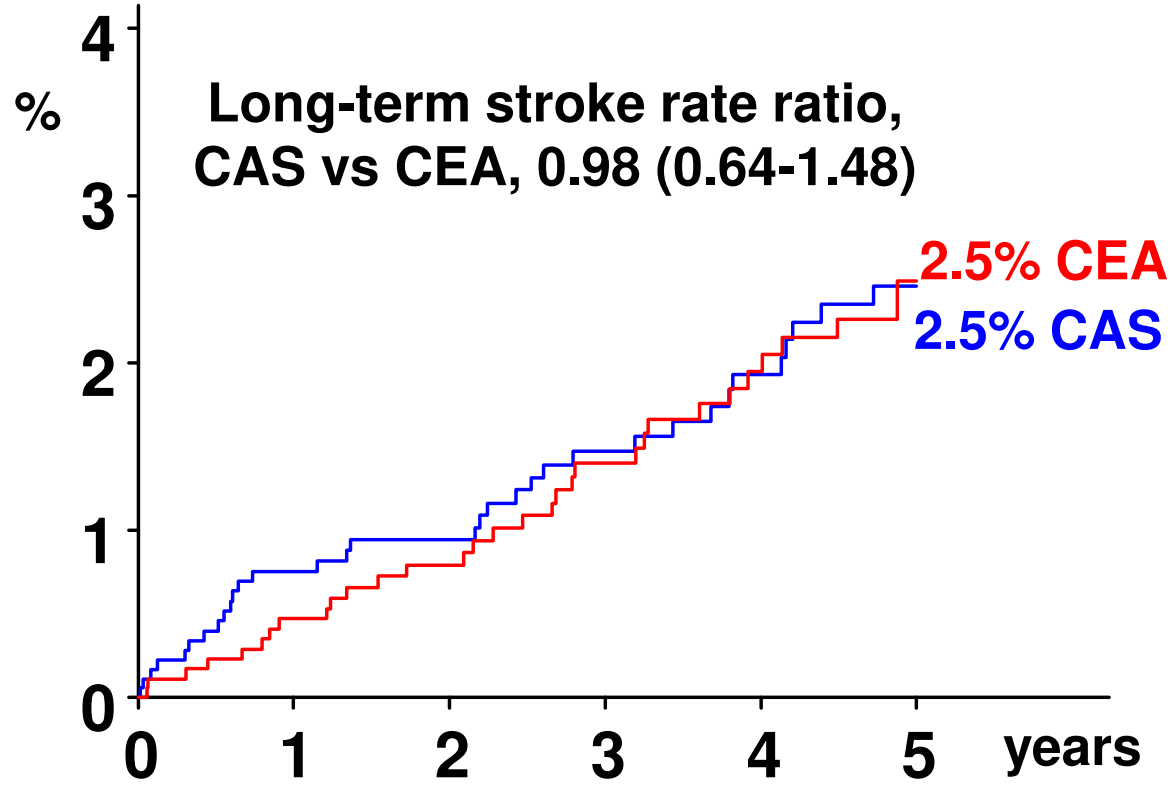
Filter	69%
Proximal occlusion	16%
Distal balloon	<1%
None	15%

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

5-year risk of procedural death, or of disabling or fatal stroke

Left: Including procedural risks, **Right:** Excluding procedural risks





ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

Severity of worst procedural event & worst non-procedural stroke

	Procedural (<30 days) stroke or death		Non-procedural stroke (with mean 5-year FU)	
	Allocated CAS n=1811	Allocated CEA n=1814	Allocated CAS n=1748*	Allocated CEA n=1767*
Disabling or fatal	15 (0.9%)†	18 (1.0%)†	44 (2.5%)	45 (2.5%)
Non-disabling	48 (2.7%)	29 (1.6%)	47 (2.7%)	34 (1.9%)

* Excludes the 63 CAS vs 47 CEA patients who had a procedural stroke or death

† Includes the 2 CAS vs 6 CEA procedural deaths not involving a stroke

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

Severity of worst procedural event, and worst non-procedural stroke

	Procedural (<30 days) stroke or death		Non-procedural stroke (with mean 5-year FU)	
	Allocated CAS n=1811	Allocated CEA n=1814	Allocated CAS n=1748	Allocated CEA n=1767
Disabling or fatal	15	18	44	45
Non-disabling:				
mRS score 2	9	9	9	5
mRS score 1	23	15	23	17
mRS score 0	16	5	15	12

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

Any procedural death or any stroke at any time, by severity

	Allocated CAS n=1811	Allocated CEA n=1814
mRS >1: Fatal, disabling, or unable to carry out some previously usual activities	77	77
mRS 0-1: Non-disabling, and still able to carry out all previously usual activities	77 (4.2%)	49 (2.7%)

ACST-2: carotid stenting (CAS) vs endarterectomy (CEA)

3625 patients with severe stenosis but no recent ipsilateral symptoms, half allocated CAS, half CEA; good compliance, and good medical therapy.

Summary of results

1% 30-day risk, in each group, of *procedural death or disabling stroke*;
2.5% 5-year risk, in each group, of *non-procedural disabling/fatal stroke*.

But, with stenting, there was a 1-2% excess risk of *non-disabling stroke* that left patients still able to carry out all their previously usual activities.

CAS vs CEA: ACST-2 results plus other evidence

Procedural strokes: An excess of non-disabling procedural strokes with CAS is consistent with large, recent, nationally representative registry data.

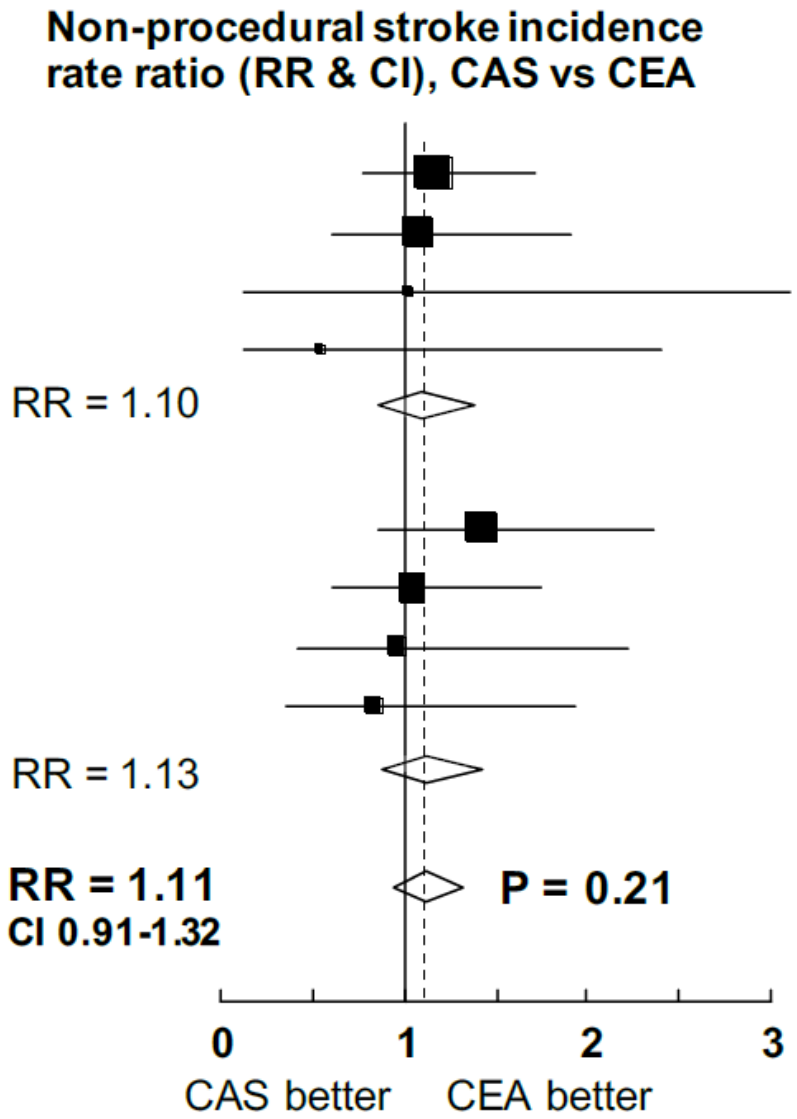
Non-procedural strokes: To compare the effects of CAS vs CEA, ACST-2 should be considered along with all other major trials.

8 major trials of CAS vs CEA, 4 in asymptomatic and 4 in symptomatic patients, have been reported. A formal meta-analysis can combine their findings.

Non-procedural stroke incidence in the 8 major trials of CAS vs CEA

Trial, and mean follow-up reported		Allocated CAS	Allocated CEA
a. No symptoms in past 6 months			
ACST-2	5 years	91 /1811	79 /1814
CREST	6 years	47 /594	43 /587
SPACE-2 ACT-1	each only 1 year		
Subtotal (a)		145 /3116	133 /3150
b. Symptoms in past 6 months			
ICSS	4 years	65 /842	47 /853
CREST	6 years	55 /661	52 /651
SPACE	2 years	20 /601	20 /584
EVA3S	7 years	19 /263	22 /259
Subtotal (b)		159 /2367	141 /2347
Total (a + b)		**304 /5483 5.6%**	**274 /5497 5.0%**

99% or 95% confidence interval (CI)



For the Total, RR is similar for ipsilateral strokes (131 vs 119) and for other strokes (173 vs 155)

Conclusions from the German national registry, ACST-2 and the other major trials of CAS vs CEA

Competent CAS and CEA involve ~1% procedural death or disabling stroke, then have similar effects on long-term rates of fatal or disabling stroke.

For asymptomatic patients with severe stenosis, previous trials showed that, even if good medical treatment is given, CEA ~halves long-term stroke rate.

If so, then in ACST-2, where 0.5%/year had a fatal or disabling stroke with either CAS or CEA, with neither procedure ~1% per year would have done so.

ACST-2 was published online in *The Lancet* on 29 Aug 2021 with immediate open access

The chief acknowledgements are to the patients who agreed to participate; the collaborating doctors at 130 hospitals in 33 countries who randomised them from 2008-20 and are continuing follow-up until 2026, and trial staff.

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