CEA or CAS for asymptomatic carotid stenosis – which patients benefit most?

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Clinical/imaging characteristics with an increased carotid-related stroke risk – critical revision of the ESVS/ESC Guidelines 2017

Chairs: Gert de Borst, Holger Poppert

- Barbara Rantner Clinical variables with an increased late stroke risk
- David Spence Spontaneous embolisation on TCD and carotid plaque features
- Peter Ringleb Silent infarction and impaired cerebrovascular reactivity
- K Paraskevas Grade of carotid stenosis and stenosis progression
- Jonathan Nadjiri MRI features of unstable carotid plaques
- Jens Göttler Multi-modal MRI identifies carotid stenosis patients with reduced cerebral blood flow and oxidative metabolism
- Alison Halliday **Keynote Lecture:**
  CEA or CAS for asymptomatic carotid stenosis – which patients benefit most?

If we suppose that 'selective screening' is acceptable…

Recommendation 15	Class	Level	References
Routine population screening for asymptomatic carotid stenosis is not recommended	III	C	64
Recommendation 16			
Selective screening for asymptomatic carotid stenoses may be considered in patients with multiple vascular risk factors to optimise risk factor control and medical therapy to reduce late cardiovascular morbidity and mortality, rather than for identifying candidates for invasive carotid interventions	IIb	C	72,73

We need to know which patient (or lesion) characteristics may justify intervention

- Depends on expected risk, expected lifespan, medical treatments, lifestyle habits and patient preferences
- Not..on physician preferences and hospital reimbursements (!)
- It is likely that some countries do too many interventions and some too few
- We need reliable (although dated) evidence, to identify ‘high risk for stroke’ patients for intervention (see refs 84-94 in Guidelines)

2.2.2.5. Can a " high risk for stenosis" cohort be identified?

A **predictive model** was developed by Greco, based on a self-selected cohort of 2,885,257 patients who paid to have a carotid DUS via the Lifeline Screening company, where 66% were female and 20% were <55 years.[65]

Overall, 71,004 (2.4%) had a >50% ACS. Half the cohort were used to develop the scoring system, which identified increasing **age, smoking history, history of PAD, CAD, high BP, diabetes, abdominal aortic aneurysm (AAA), and high cholesterol** as independent predictors of a >50% ACS.

2017 Guidelines

Table 5. Clinical/imaging features associated with an increased risk of late stroke in patients with asymptomatic 50—99% stenoses treated medically.

Imaging/clinical parameter and stenosis severity Type of study	Annual rate of ipsilateral stroke	OR/HR (95% CI) p =
Silent infarction on CT[84] 60—99% stenoses Multicentre, observational	Yes = 3.6% No = 1.0%	3.0 (1.46—6.29) p = .002
Stenosis progression[85] 50—99% stenoses Multicentre, observational	Regression = 0.0% Unchanged = 1.1% Progression = 2.0%	1.92 (1.14—3.25) p = .05
Stenosis progression[86] 70—99% stenoses Multicentre, RCT	Regression No change Progression 1 stenosis grade Progression 2 stenosis grades	0.7 (0.4—1.3) Comparator 1.6 (1.1—2.4) 4.7 (2.3—9.6)

Table 5. Clinical/imaging features associated with an increased risk of late stroke in patients with asymptomatic 50—99% stenoses treated medically.

Imaging/clinical parameter and stenosis severity Type of study	Annual rate of ipsilateral stroke	OR/HR (95% CI) p =
Plaque lucency on Duplex US[91] 50—99% stenoses Meta-analysis	Predominantly echolucent 4.2% Predominantly echogenic 1.6%	OR 2.61 (95% CI 1.47—4.63) p = .001
Spontaneous embolisation on TCD[92] 50—99% stenoses Meta-analysis	Yes vs. no	OR 7.46 (95% CI 2.24—24.89) p = .001
Spontaneous embolisation plus uniformly or predominantly echolucent plaque[93] 70—99% stenoses Multicentre, observational	Yes = 8.9% No = 0.8%	OR 10.61 (95% CI 2.98—37.82) p = .0003
Contralateral TIA/stroke[94] 50—99% stenoses Multicentre, observational	Yes = 3.4% No = 1.2%	OR 3.0 (95% CI 1.9—4.73) p = .0001

Table 5. Clinical/imaging features associated with an increased risk of late stroke in patients with asymptomatic 50–99% stenoses treated medically.

Imaging/clinical parameter and stenosis severity Type of study	Annual rate of ipsilateral stroke	OR/HR (95% CI) $p =$
Plaque area on computerised plaque analysis[87] 70–99% Multicentre, observational	<40 mm^2 = 1.0% 40–80 mm^2 = 1.4% >80 mm^2 = 4.6%	HR 1.0 2.08 (95% CI 1.05–4.12) 5.81 (95% CI 2.67–12.67)
JBA on computerised plaque analysis[88] 50–99% stenoses Multicentre, observational	<4 mm^2 = 0.4% 4–8 mm^2 = 1.4% 8–10 mm^2 = 3.2% >10 mm^2 = 5.0%	Trend $p < .001$
Intra-plaque haemorrhage on MRI[89] 50–99% stenoses Meta-analysis	Yes vs. no	OR 3.66 (2.77–4.95) $p < .01$
Impaired CVR[90] 70–99% stenoses Meta-analysis	Yes vs. no	OR 6.14 (95% CI 1.27–29.5) $p = .02$

What do we mean by 'Most' benefit?

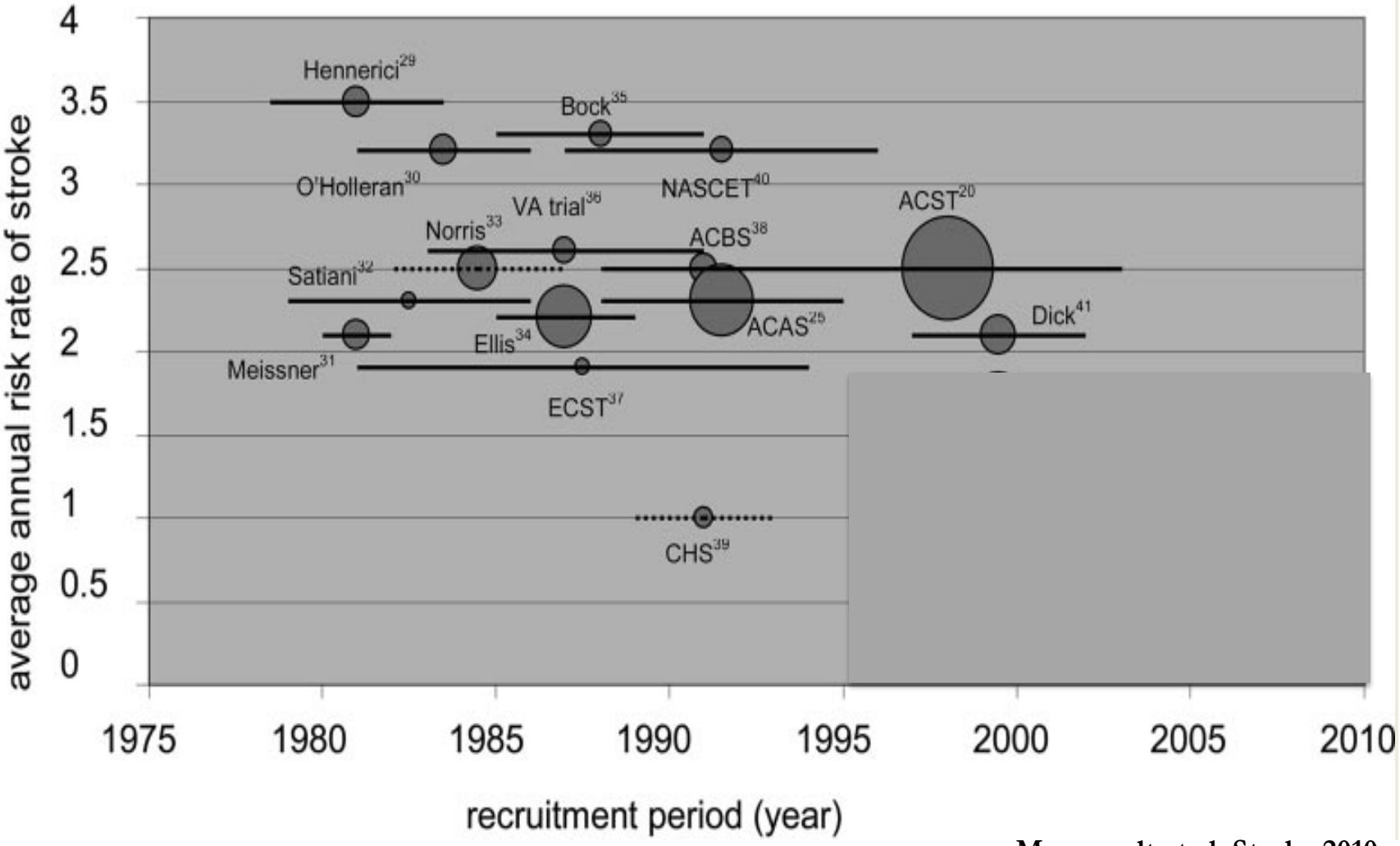
- Absolute Risk Reduction (ARR) - eg from 2% pa to 1.5%
- (or) Relative Risk Reduction (RRR) - odds ratios

However – for an individual patient, benefit is –

either stroke or MI are prevented
or time to index event is prolonged (by treatment)
or the event still happens…

On the other hand – populations may benefit, but the ARR or RRR depends on characteristics of that population….**trial** populations are different from **screened** populations

Stroke risk on Medical treatment for asymptomatic stenosis



Marquardt et al. Stroke 2010

Variable populations have variable stroke risks

- **ASED (Australia)**

200+ subjects ‘identified from referrals for carotid duplex (CD), usually requested because of carotid bruit, extracerebral vascular disease, or cerebrovascular symptoms’

- **CHS**

‘A community-based, prospective study of people aged ?65 years including 5888 subjects (attendance rate 57%)’

- **SMART**

Several thousand patients presenting with ‘a manifestation of arterial disease or vascular risk factor’

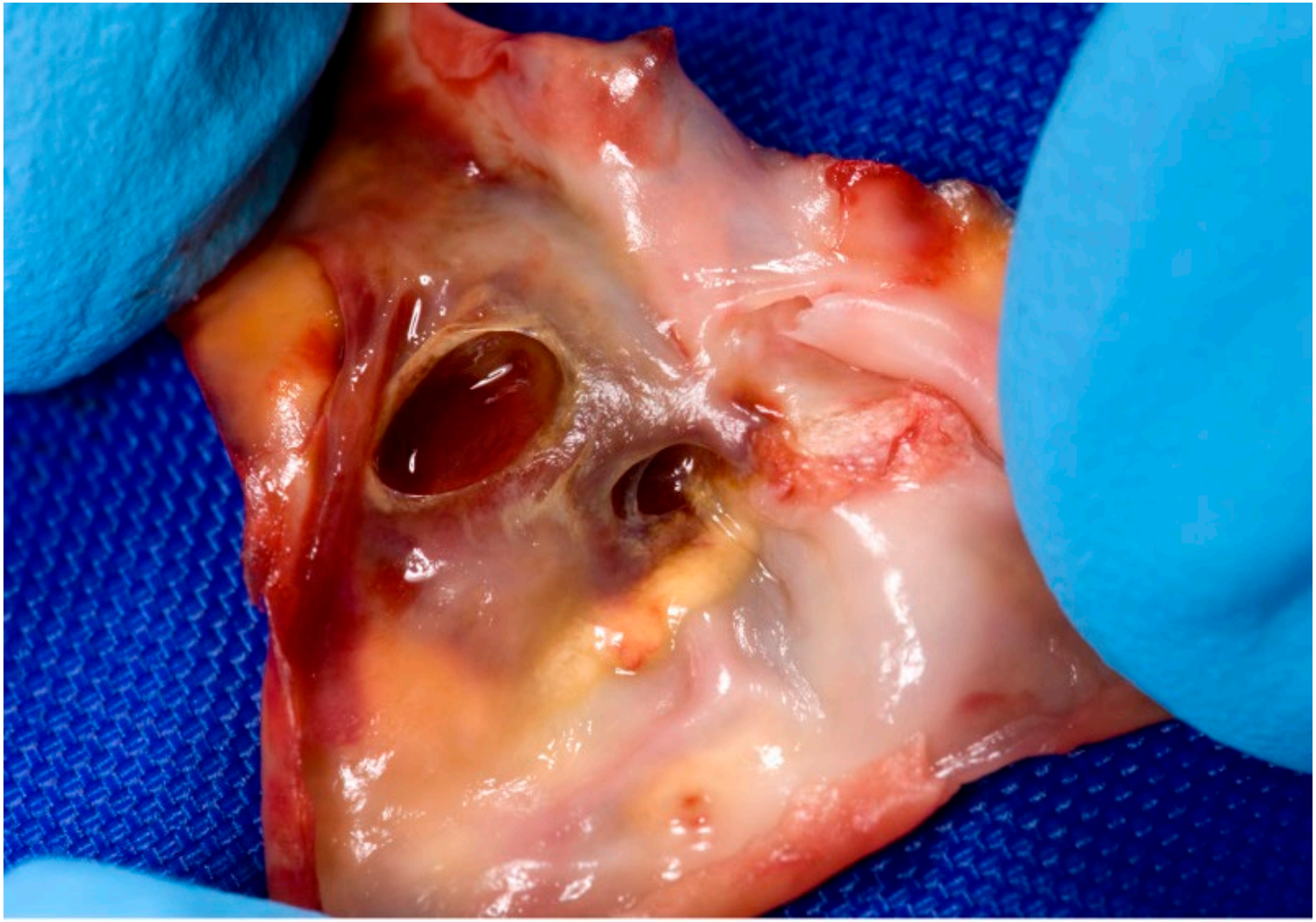
- **OXVASC**

‘vascular diseases (e.g. strokes, heart attacks) in patients registered with eight general practices in Oxfordshire’

Where can we find 'Most' benefit?….

- **Not** screened low-risk populations, benefit is low
- **'ideal' group** has high stroke risk (but also likely high risk MI risk and some – not easily modifiable - risk factors, such as age, smoking history, won't take statins etc..)
- **'maximise' benefit**, can specify a very particular (but small) group (eg those already having emboli) ……. **<u>or</u> find commoner circumstances -** more people with quite high risk , but.. procedural risk: benefit acceptable (eg predicted 10 year stroke risk 15-20%, procedural risk of 2%), perhaps those already referred with prior (usually contralateral) symptoms

‘asymptomatic’ patient (probably having emboli)



2.2.1. Optimal medical therapy - Risk factor control

In a pooled analysis of four population-based screening cohorts, **smoking** was associated with a significant **increase in the prevalence of a >50% ICA stenosis** (OR 2.3, 95% CI 1.8-2.8) **and of a >70% stenosis** (OR 3.0, 95% CI 2.1-4.4).[22]

About 5% of males aged >65 years who are current smokers have a >50% ICA stenosis on DUS screening[23] and smoking has been shown to **increase plaque progression**.[24] In a meta-analysis of 32 studies, smoking was associated with a significant **increase in late ischaemic stroke** (relative risk increase [RRI] 1.9, 95% CI 1.7-2.2).[25]

In a meta-analysis, moderate or high levels of **physical activity** were associated with a 25% relative risk reduction (RRR) in ischaemic stroke,[26] possibly via reductions in blood pressure (BP), body weight, and effects on other risk factors.

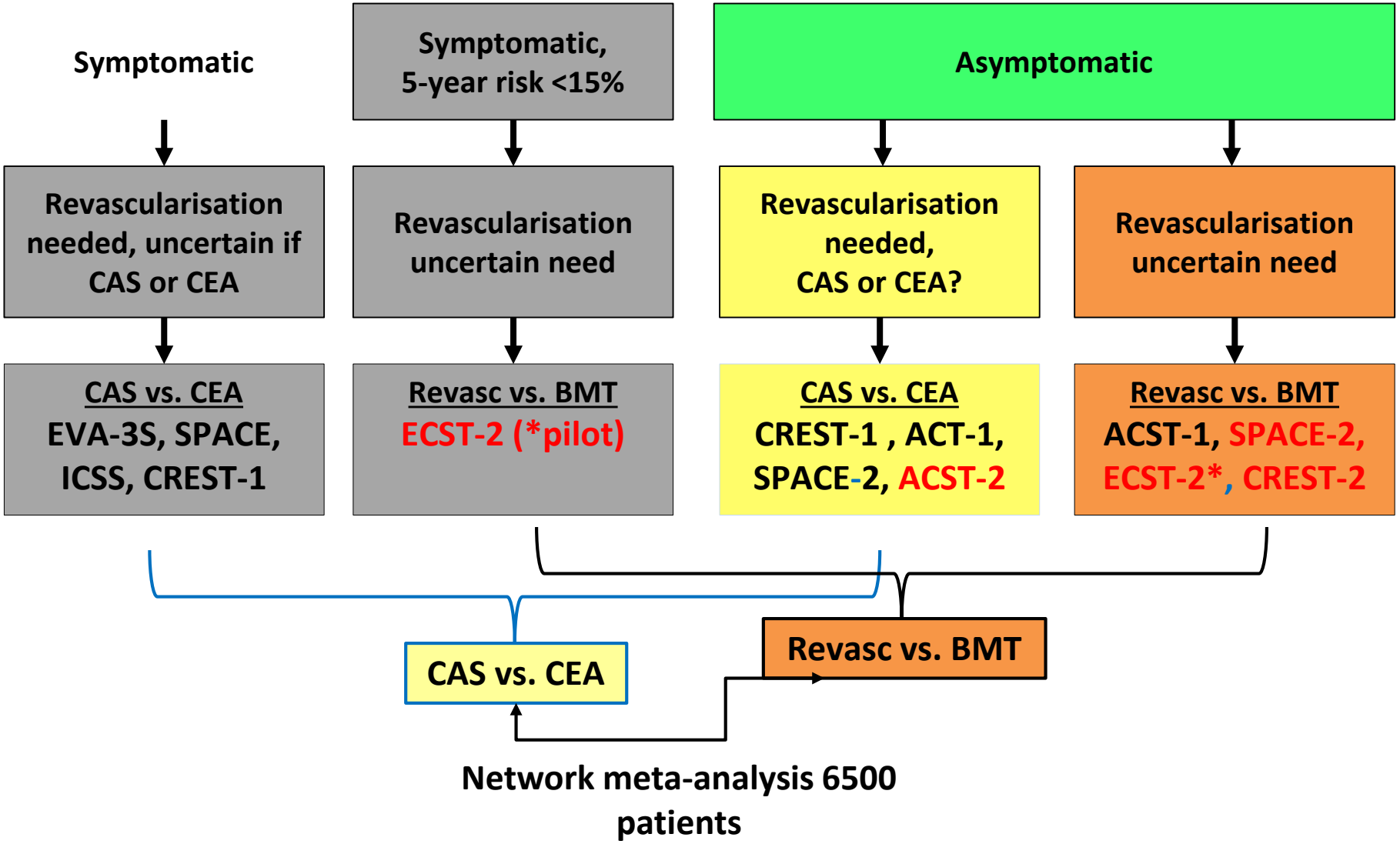
Finally, in a meta-analysis of 25 studies involving 2 million people, **obesity** was associated with a significant increase in stroke prevalence (RRI 1.64, 95% CI 1.36-1.99).[27]

2.2.1.3. Lipid-lowering therapy

In a post-hoc analysis of patients randomised within the Asymptomatic Carotid Surgery Trial (ACST-1) **on lipid lowering therapy**, **10-year risk of stroke/death was 13.4% in** best medical therapy **(BMT) patients and 7.6% after CEA.**

However, in patients **not taking statins**, the 10-**year stroke risk was 24.1% in BMT patients, versus 17.9% after CEA**, suggesting that statins reduced long-term stroke in patients with asymptomatic stenoses.[35]

Trials of CEA and CAS with long-term follow up



Which asymptomatic patients benefit most from carotid intervention?

AIM: to develop a simple clinical risk score to identify patients with **high risk** asymptomatic carotid stenosis

Using IPD from trials, in patients treated medically

Summative Risk Score

Risk Factors	Score
None	0
Diabetes only	1
Prior cerebral ischaemia* only	2
Both	3

**Prior contralateral symptoms or brain infarct on imaging*

Implications for patient with 'asymptomatic' disease

- **Statins work:** With CEA or without CEA, modern statin
  ~halves stroke risk

- **And CEA works:** With a statin or without a statin, successful CEA ~halves stroke risk

- Risk of stroke **~double with prior cerebral ischaemia**

- **Those with higher risk scores** should **derive greater absolute benefit** from CEA

Risk Model

Simple characteristics (diabetes, prior ischaemia)

can be used to **identify high stroke risk patients**

who might benefit most from CEA