MASSACHUSETTS GENERAL HOSPITAL
NEUROSCIENCE

Carotid Disease: Follow that Bruit

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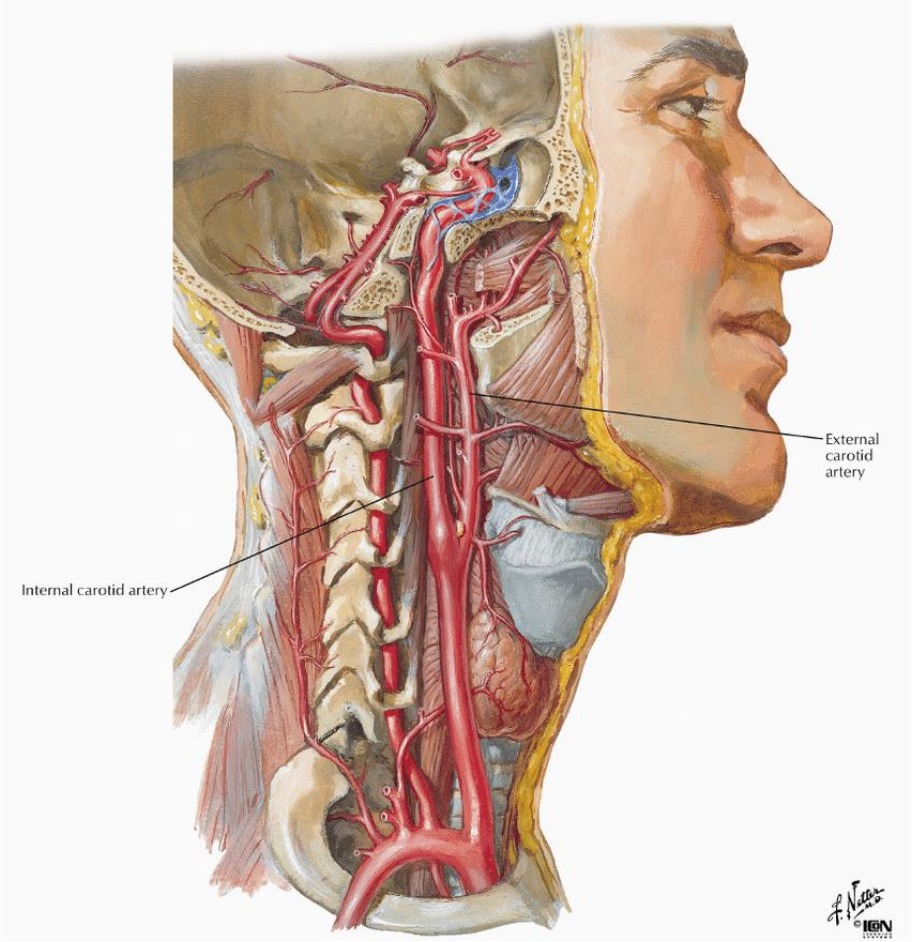
Disclosures

Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.

Internal Carotid Artery Stenosis

- Location
  - Extracranial
  - Intracranial
- Etiology
  - Atherosclerotic
  - Non-atherosclerotic
    - Dissection
    - FMD
    - radiation vasculopathy
    - Inflammatory
    - Moyamoya



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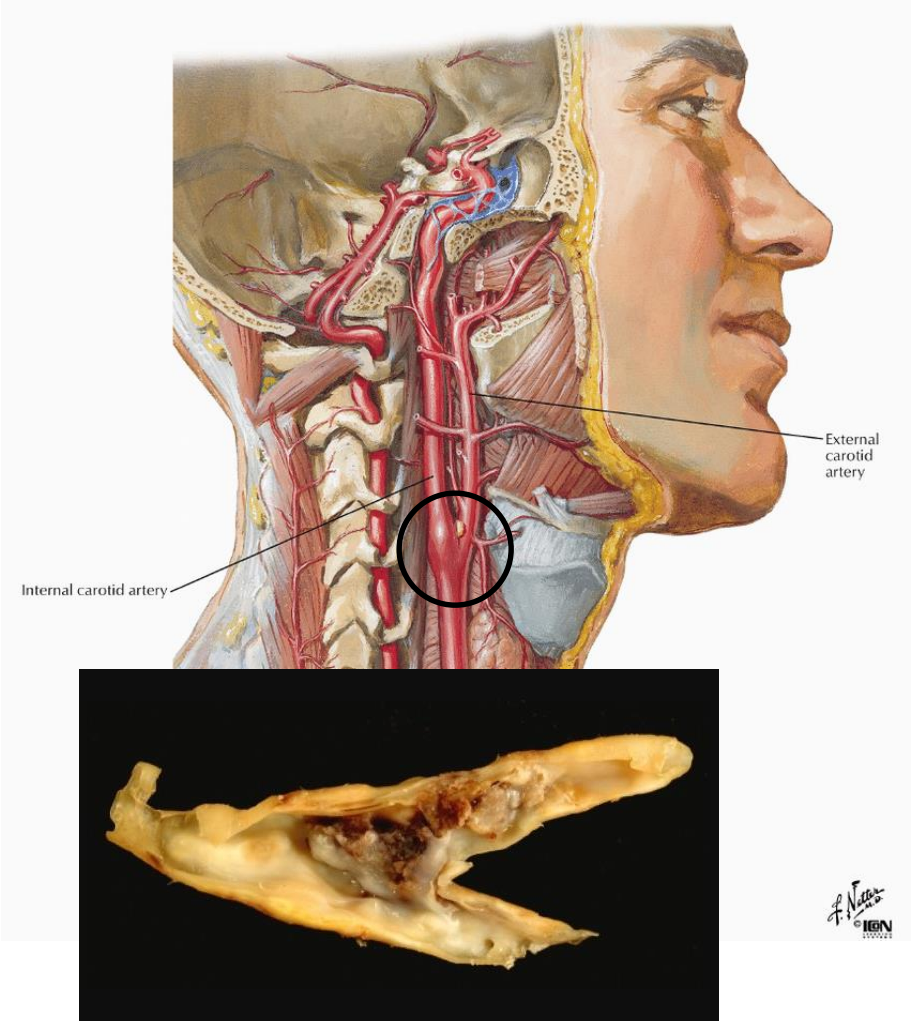


Carotid Stenosis

- Prevalence
  - > 50% stenosis: 7% women, 7-9% men
  - 75-100% stenosis: 1.1% women, 2.3% men
  - Risk factors:
    - Male sex
    - Hypertension
    - Diabetes
    - ↑ Cholesterol
    - Smoking
    - CAD, vascular disease
    - Alcohol use (men)

Table 3. Prevalence of asymptomatic >50% and >70% stenoses in the general population, stratified for gender and age.[a]

Age	Stenosis	Males	Females
<50 years	>50%	0.2%	0.0%
	>70%	0.1%	0.0%
50–59 years	>50%	0.7%	0.5%
	>70%	0.2%	0.1%
60–69 years	>50%	2.3%	2.0%
	>70%	0.8%	0.2%
70–79 years	>50%	6.0%	3.6%
	>70%	2.1%	1.0%
≥80 years	>50%	7.5%	5.0%
	>70%	3.1%	0.9%

Brott TG et al. Circulation 2011; Fine-Edelstein JS et al. Neurology 1994; O'Leary DH et al. Stroke 1992; Naylor, AR et al. Eur J Vasc Endovasc Surg 2018.

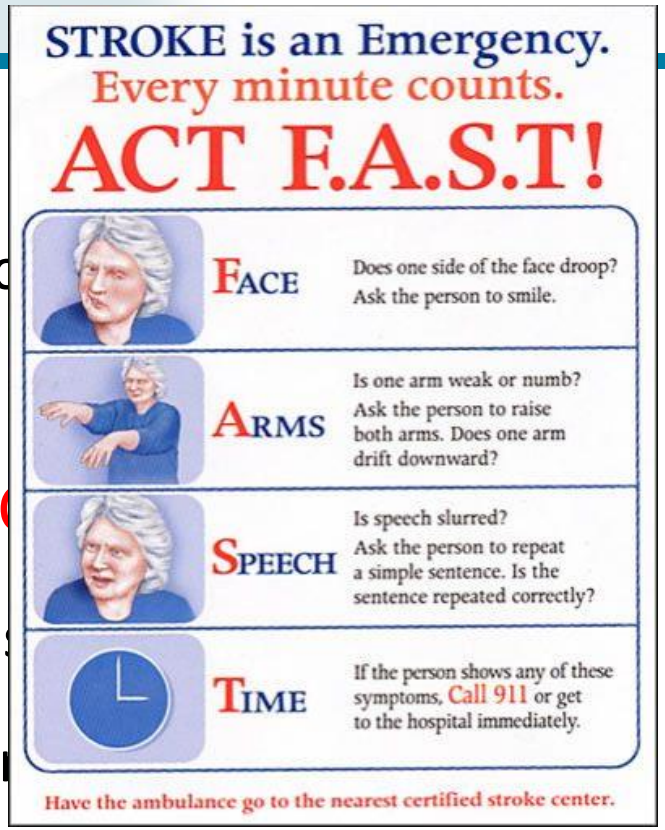
Carotid Stenosis

- Marker of systemic atherosclerosis
  - Aorta
  - Coronaries
  - Peripheral arterial disease
- Increased risk of vascular events/ vascular death with increasing degree of stenosis

Brott TG et al. Circulation. 2011; Rundek T et al. Neurology 2008

Stroke Risk and Carotid Disease

- Ischemic stroke risk
  - 15-20% ischemic strokes → > 50% c
    - 50% progression of stenosis
- ASYMPTOMATIC vs. SYMPTOMATI
  - Ipsilateral ocular ischemia (amauro
  - Ipsilateral hemispheric carotid arte
- Imaging: degree of stenosis, plaque characteristics
- Carotid bruit: sensitivity 46-77%; specificity 71-98%



Screening for Carotid Stenosis in Asymptomatic Patients

- USPTF
  - Routine screening for carotid stenosis is not recommended
  - Absence of data from primary prevention studies supporting reduction of stroke risk after surgical revascularization
  - Harm: risk of false positives, risk of unnecessary interventions (CTA, angiography, revascularization)

US Preventive Services Task Force; JAMA 2021

Selective Screening for Carotid Stenosis in Asymptomatic Patients

- May be considered in patients with cardiovascular disease
- Class IIb recommendations for consideration of carotid duplex US screening:
  - Symptomatic PAD, CAD, atherosclerotic aortic aneurysm
  - Asymptomatic patients without clinical atherosclerosis, who have $\geq$ 2 of: HTN, HLD, smoking, 1st degree relative with atherosclerosis at < 60y, family history of ischemic stroke

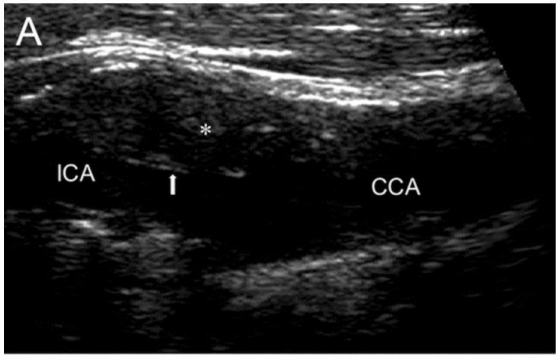
Brott T et al. Circulation 2011

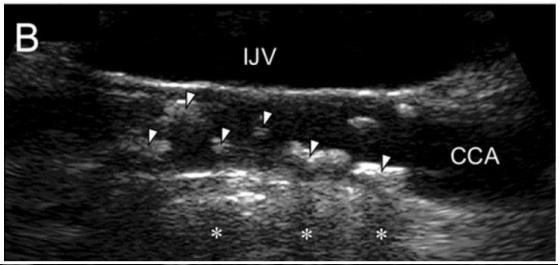
Radiological Evaluation

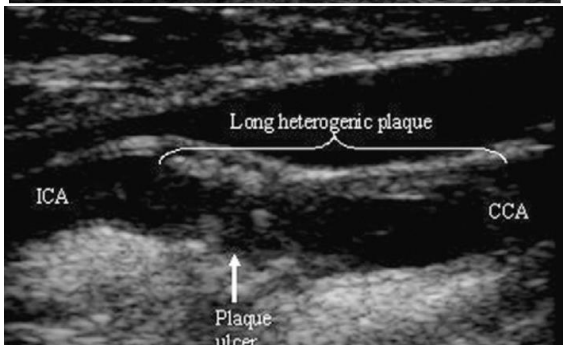
Carotid Imaging Methods					
	Duplex Sono	CTA	TOF MRA	MRA+Gd	DSA
ICA Stenosis	Good	Excellent	Good	Very Good	Excellent
Morphology	Very Good	Very Good	Fair	Excellent	Good
Evaluation of Proximal artery	Good	Good	Fair	Very Good	Excellent
Intracranial Visualization	None	Excellent	Good	Excellent	Excellent
Acceptance by surgeons	Fair	Excellent	Good	Very Good	Excellent
Risk Cost	None +	Low ++	None +++	Very Low ++++	Low-Moderate +++++

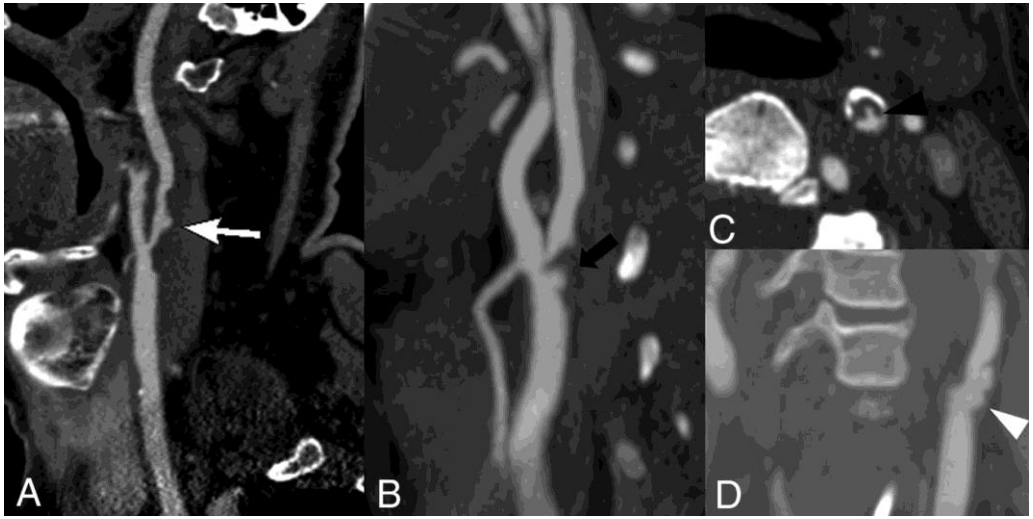
Nadallo LA. Medscape.com

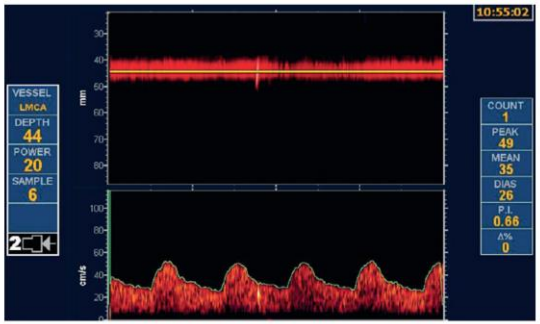
Carotid Artery Disease: Plaque Features as Predictors of Stroke Risk

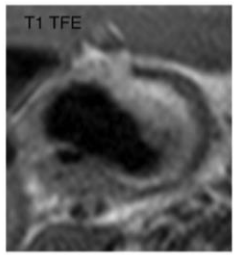


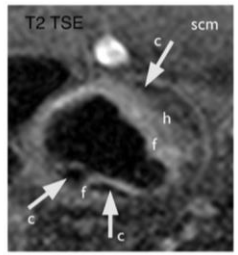


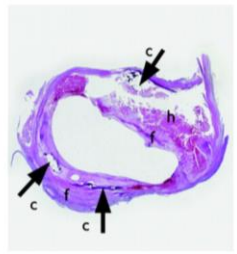












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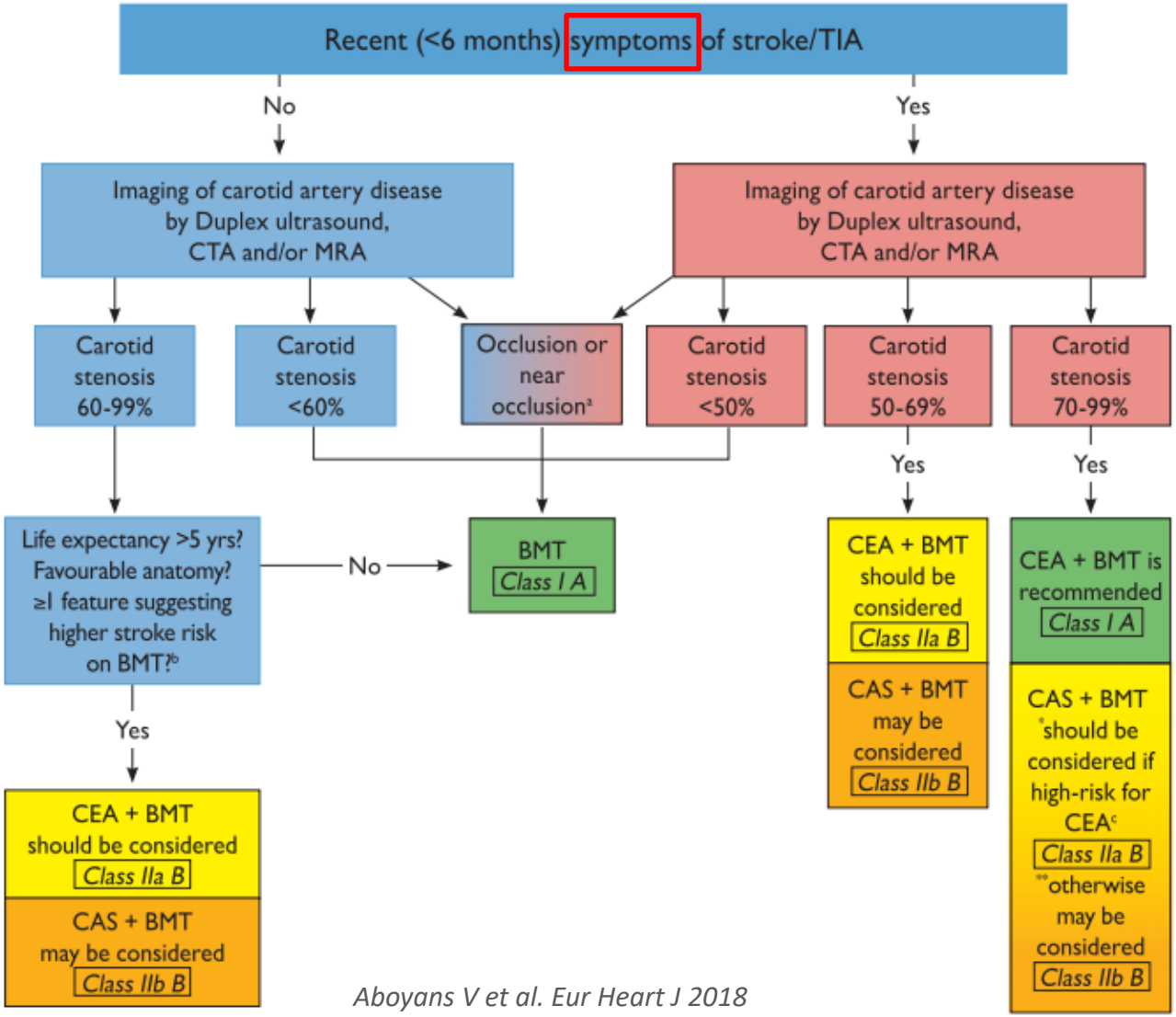
Kwee RM et al. Neurology 2008; Paraskevas KI et al. Stroke and Vasc Neurol 2018

Algorithm for Management of Carotid Stenosis



Aboyans V et al. Eur Heart J 2018

Medical Management: Lifestyle Interventions

- Smoking cessation
  - Smoking ↑plaque progression
- Heart healthy diet
- Exercise
  - Moderate-high levels → 25% RRR of ischemic stroke
- Weight loss
  - Overweight & obesity → 22% & 64% ↑ risk of ischemic stroke
- ETOH misuse avoidance

Herder M et al. Stroke 2012; Lee CD et al. Stroke 2003; Strazzullo P et al. Stroke 2010

Medical Management

- Blood pressure control
  - Target BP < 130/80 mmHg: diabetics & per new ACC/ AHA primary prevention guidelines & AHA secondary stroke prevention guidelines
  - ↓ plaque progression; ↑ plaque regression
- Glucose control:
  - Unclear benefit of aggressive glucose control in diabetics
  - Blood pressure control, antiplatelets and statins substantially reduce the risk of vascular events/ vascular death in diabetics

Sutton-Tyrrell K, Stroke 1994; Gaede P et al. NEJM 2008; Kleindorfer DO et al. Stroke 2021

Medical Management

- Antiplatelet therapy
  - Asymptomatic: Aspirin 75-325 mg daily → ↓cardiovascular events
  - Symptomatic: Early antiplatelet
    - Aspirin 75-325 mg daily
    - ASA + clopidogrel (21-30 days): reduces risk of early stroke/ TIA and embolization on TCD
    - Clopidogrel monotherapy
- Anticoagulation: no AHA recommendation
  - Used for bridging to revascularization in severe/critical symptomatic stenosis
- Lipid lowering
  - Asymptomatic:
    - Reduce long term risk of stroke/ death
    - Target: LDL < 70 mg/dL or ↓ LDL by 50%
  - Symptomatic:
    - Pre-operative statin ↓ 30d risk of death/ stroke; ↓ spontaneous embolization

Batchelder AJ et al. J Vasc Endovasc Surg 2015; Markus HS et al. Circulation 2005; Halliday A et al. Lancet 201; Kennedy J et at. Stroke 2005; Aboyans V et al. Eur Heart J 2018

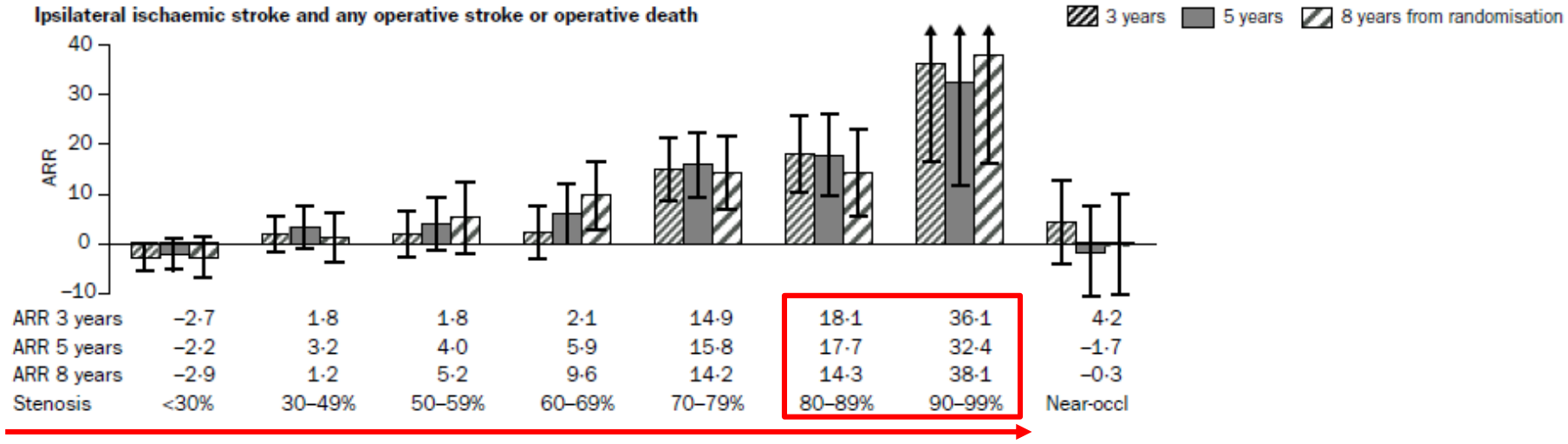
Symptomatic Carotid Stenosis

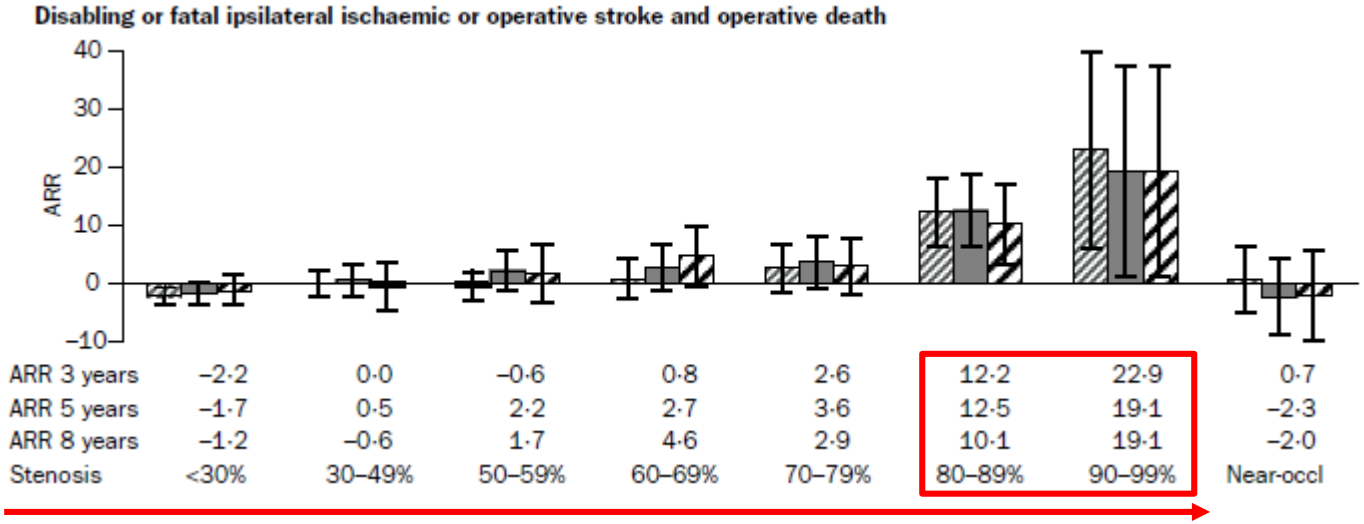
BMT vs. Carotid Endarterectomy

	NASCET	ECST
% Stenosis of ipsilateral carotid	30-99%	0-99%
Qualifying event	Hemispheric TIA, transient ocular ischemia, non-disabling ischemic stroke within 120 days	Hemispheric TIA, transient ocular ischemia, non-disabling ischemic stroke within past 6 months
Intervention	CEA vs. BMT	CEA vs. avoid surgery
Year	1988-1996	1981-1994
Follow-up	Mean= 5 years	Mean= 6.1 years
N	2926	3024
% Male	70%	72%
Age	< 80 y.o.: severe stenosis Any age: moderate stenosis	Any
BMT	Aspirin up to 1300 mg daily ± anti-HTN (up to 60%), lipid lowering (~ 14%), DM Rx	Antiplatelets (95%), anticoagulants (7%), lipid lowering (7%)

NASCET Collaborators NEJM 1991; Barnett H et al. NEJM 1998; ECST Collaborative Group Lancet 1998

CEA vs. BMT: Stenosis Severity



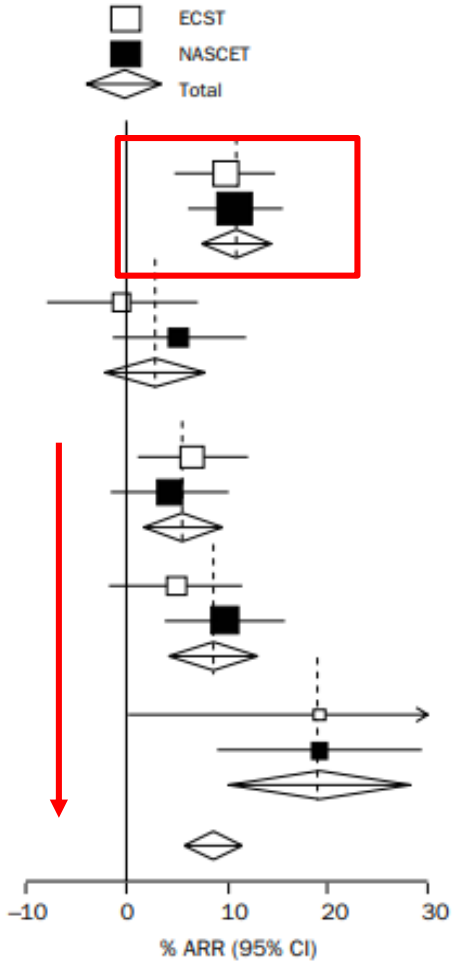


NNT to prevent 1 stroke at 5y by degree stenosis:
59-69% =13
70-99%= 6

Rothwell PM et al Lancet 2003

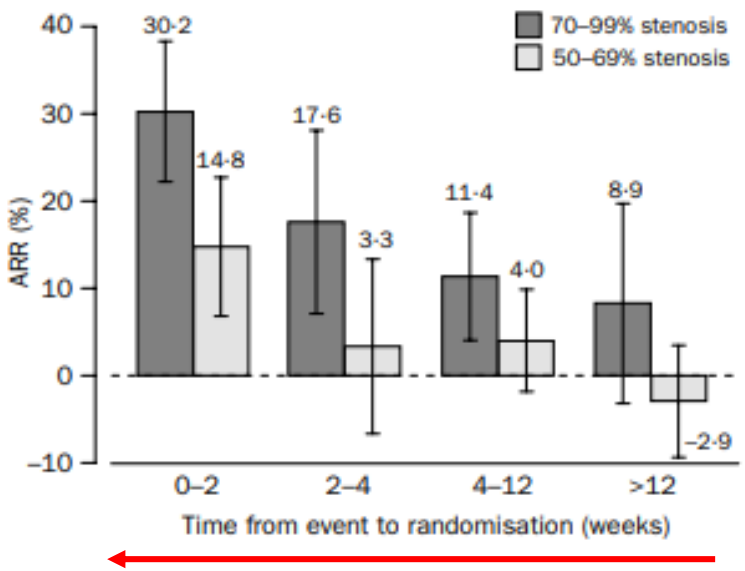
CEA vs. BMT: Age, Sex

Subgroup	Events / Patients: Surgical	Events / Patients: Medical	ARR (%)	95% CI
Sex				
Men	47/504	60/333	9·8	4·9–14·8
	65/509	124/540	10·7	5·9–15·5
	112/1013	184/873	11·0	7·6–14·4
Women	32/211	22/152	–0·4	–7·9–7·1
	31/250	38/219	5·2	–1·5–11·9
	63/461	60/371	2·8	–2·2–7·8
Age (years)				
<65	40/385	45/274	6·6	1·1–12·0
	46/346	48/276	4·3	–1·6–10·1
	86/731	93/550	5·6	1·6–9·6
65–74	33/283	28/180	4·8	–1·8–11·5
	41/318	81/362	9·7	3·8–15·7
	74/601	109/542	8·6	4·2–13·0
≥75 years	6/47	9/31	19·1	0·1–38·1
	9/95	33/121	19·2	8·9–29·5
	15/142	42/152	19·2	10·2–28·2
Total	175/1474	244/1244	8·5	5·6–11·3



Rothwell PM et al Lancet 2004

CEA vs. BMT: Timing of Intervention



CEA is recommended for symptomatic stenosis, surgical risk < 6%:
70-99% stenosis = Class I, level A
50-69% stenosis= Class I, level B

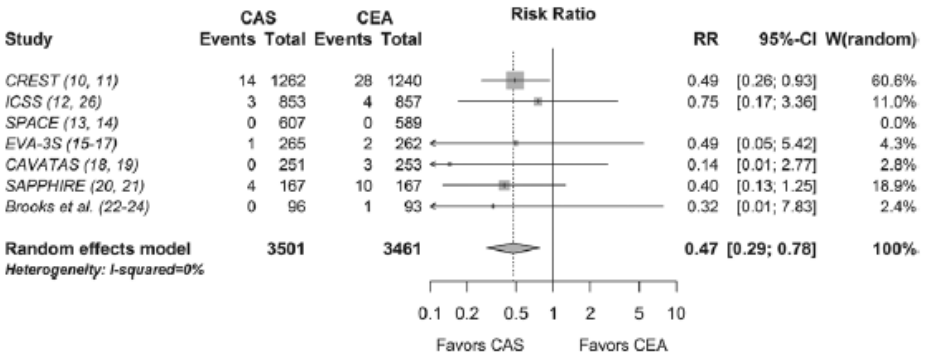
	Perioperative Stroke % Proportion (95% CI)	Perioperative Stroke and Death % Proportion (95% CI)
CEA procedures		
CEA within 0–15 d		
All patients	3.36 (2.57–4.25)	3.80 (2.99–4.71)
TIA subgroup of patients	1.64 (0.72–2.94)	1.86 (0.82–3.31)
Stroke subgroup of patients	4.99 (3.55–6.61)	4.94 (3.44–6.70)
Excluding administrative studies	3.28 (2.63–3.99)	3.57 (2.85–4.37)
Excluding thrombolysis studies	3.29 (2.48–4.22)	3.77 (2.91–4.74)
CEA within 0–7 d		
All patients	3.25 (2.12–4.61)	3.61 (2.60–4.78)
TIA subgroup of patients	1.51 (0.47–3.10)	1.87 (0.58–3.86)
Stroke subgroup of patients	5.31 (2.74–8.67)	5.55 (2.79–9.19)
CEA within 0–48 h		
All patients	5.26 (2.80–8.43)	5.75 (3.73–8.17)
TIA subgroup of patients	2.74 (0.45–6.87)	2.78 (0.40–7.20)
Stroke subgroup of patients	7.95 (4.58–12.15)	8.44 (4.96–12.74)

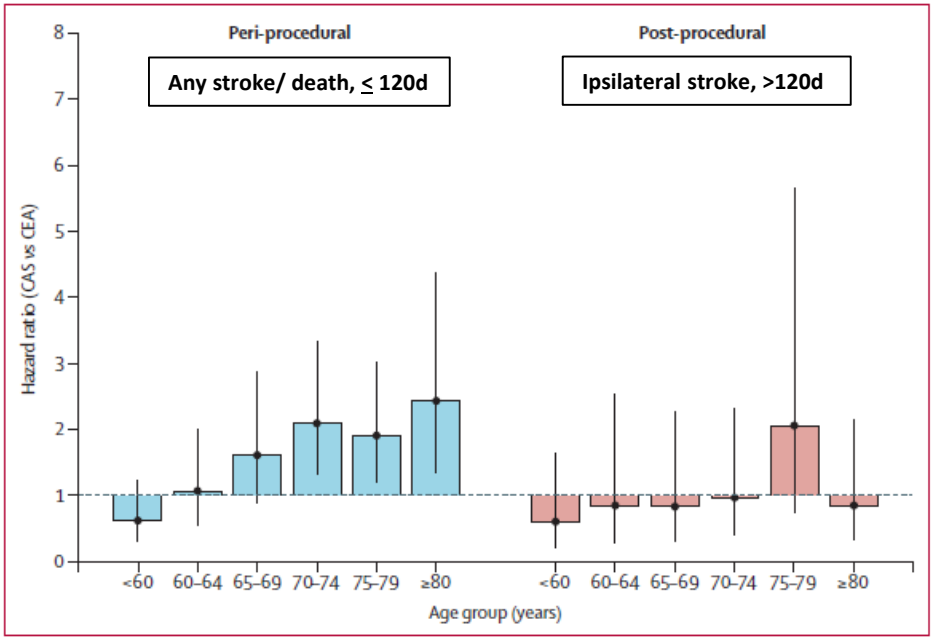
CEA within 15 days from stroke/transient ischemic attack can be performed with periprocedural stroke risk <3.5%.

Rothwell PM et al Lancet 2004; De Rango P et al. Stroke 2015

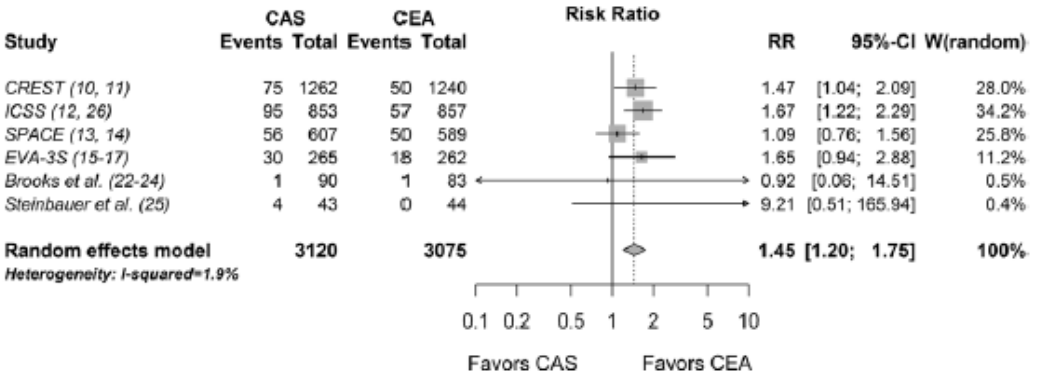
CEA vs. Carotid Stenting

Cumulative incidence of periprocedural myocardial infarction





Cumulative incidence of composite: long-term ipsilateral stroke, periprocedural stroke, death



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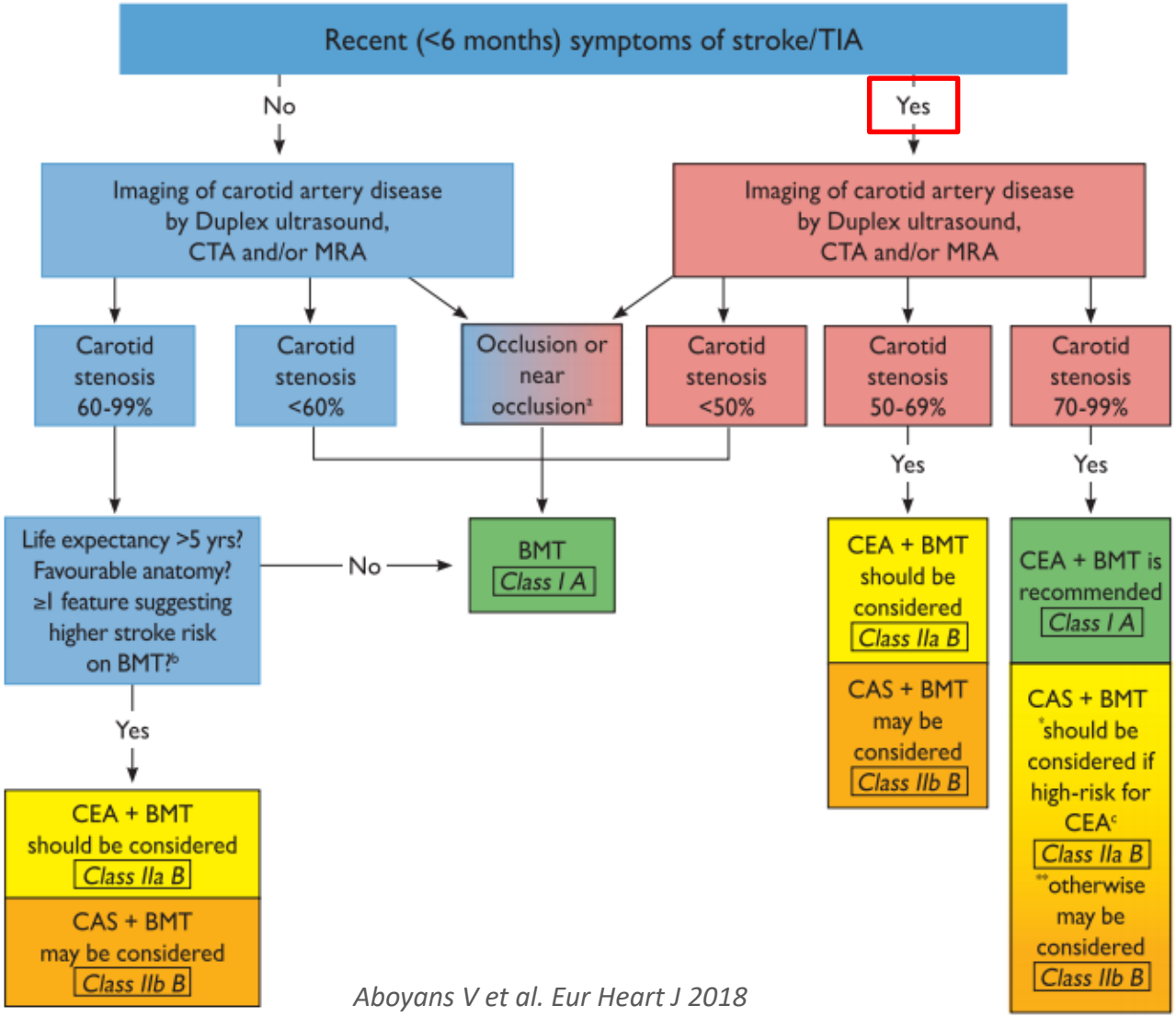
Vincent S et al. Circ Cardiovasc Qual Outcomes 2015; Howard G et al. Lancet 2016

Algorithm for Management of Carotid Stenosis



Aboyans V et al. Eur Heart J 2018

Asymptomatic Carotid Stenosis

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

Health and Hope for Patients at Risk for Stroke

MGH PI: Scott Silverman, MD

Stroke Risk: Asymptomatic Carotid Artery Disease

- 60-70% decline in annual stroke rates for medically treated pts
  - Before 2000: 2.3%/ year
  - 2000-2010: 1.13%/ year
- Similar 30% decline in rates of myocardial infarction

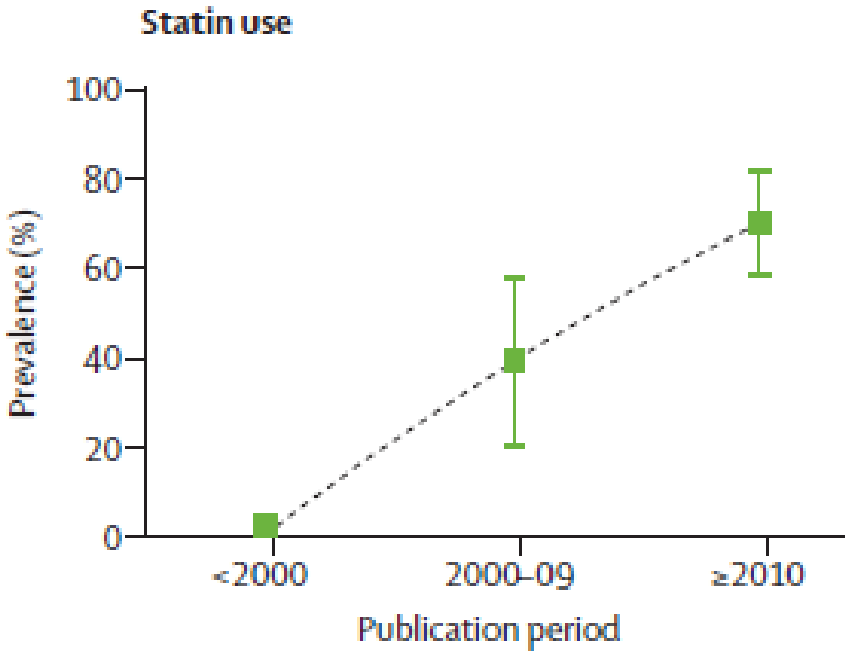
TRIAL	year published	study years	5 year rate of 'any' stroke	5 year rate of 'ipsilateral' stroke
ACAS	1995	1-5	17.5% (3.5%pa)	11.0% (2.2%pa)
ACST	2004	1-5	11.8% (2.4%pa)	5.3% (1.1%pa)
ACST	2010	6-10	7.2% (1.4% pa)	3.6% (0.7%pa)

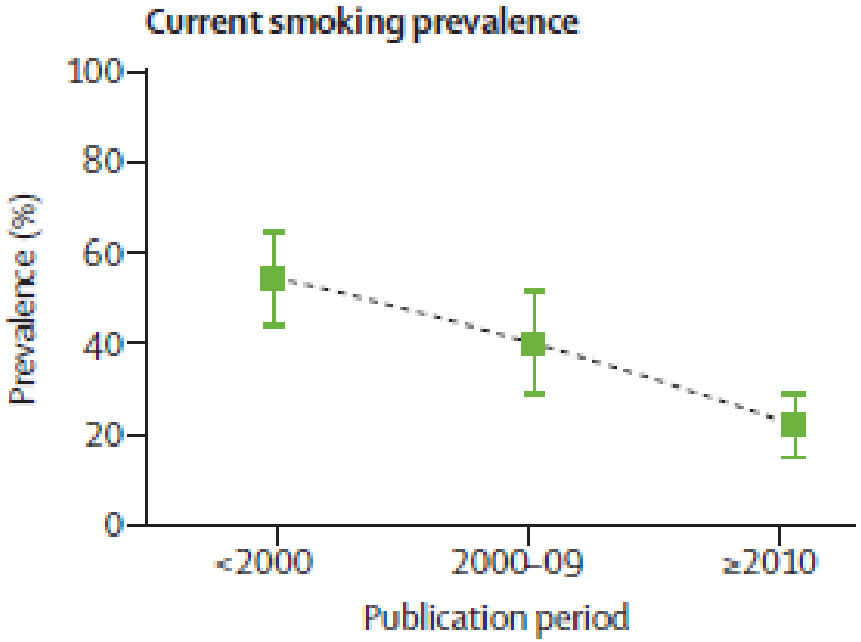
Naylor AR. The Surgeon 2015

Stroke Risk: Asymptomatic Carotid Artery Disease

Better risk factor management:

- BP control
- Statin use
- Antiplatelets
- Lifestyle modifications





Naylor AR. The Surgeon 2015; Howard DPJ et al. Lancet Neurol 2021

Stroke Risk in Asymptomatic Carotid Artery Disease: Plaque Features

Imaging/clinical parameter	OR/HR (95% CI); P value
Spontaneous embolisation on TCD	7.46 (2.24 to 24.89); P=0.001
Plaque echolucency (vs echogenic) on Duplex US	2.61 (1.47 to 4.63); P=0.001
Spontaneous embolisation on TCD+uniformly or predominantly echolucent plaque (70%–99% stenoses)	10.61 (2.98 to 37.82); P=0.0003
Stenosis progression (50%–99% stenoses)	1.92 (1.14 to 3.25); P=0.05
Stenosis progression (70%–99% stenoses)	4.7 (2.3 to 9.6)

Imaging/clinical parameter	OR/HR (95% CI); P value
Silent infarction on CT (60%–99% stenoses)	3.0 (1.46 to 6.29); P=0.002
Impaired cerebrovascular reserve (70%–99% stenoses)	6.14 (2.77 to 4.95); P<0.01
Juxtaluminal black area on computerised plaque analysis (<4 mm^2, 4–8 mm^2, 8–10 mm^2, >10 mm^2)	Trend P<0.001
Intraplaque haemorrhage on MRI	3.66 (2.77 to 4.95); P<0.01
Contralateral stroke/TIA	3.0 (1.9 to 4.73); P=0.0001

Paraskevas KI et al. Stroke and Vasc Neurol 2018

Stroke Risk: Stenosis Severity

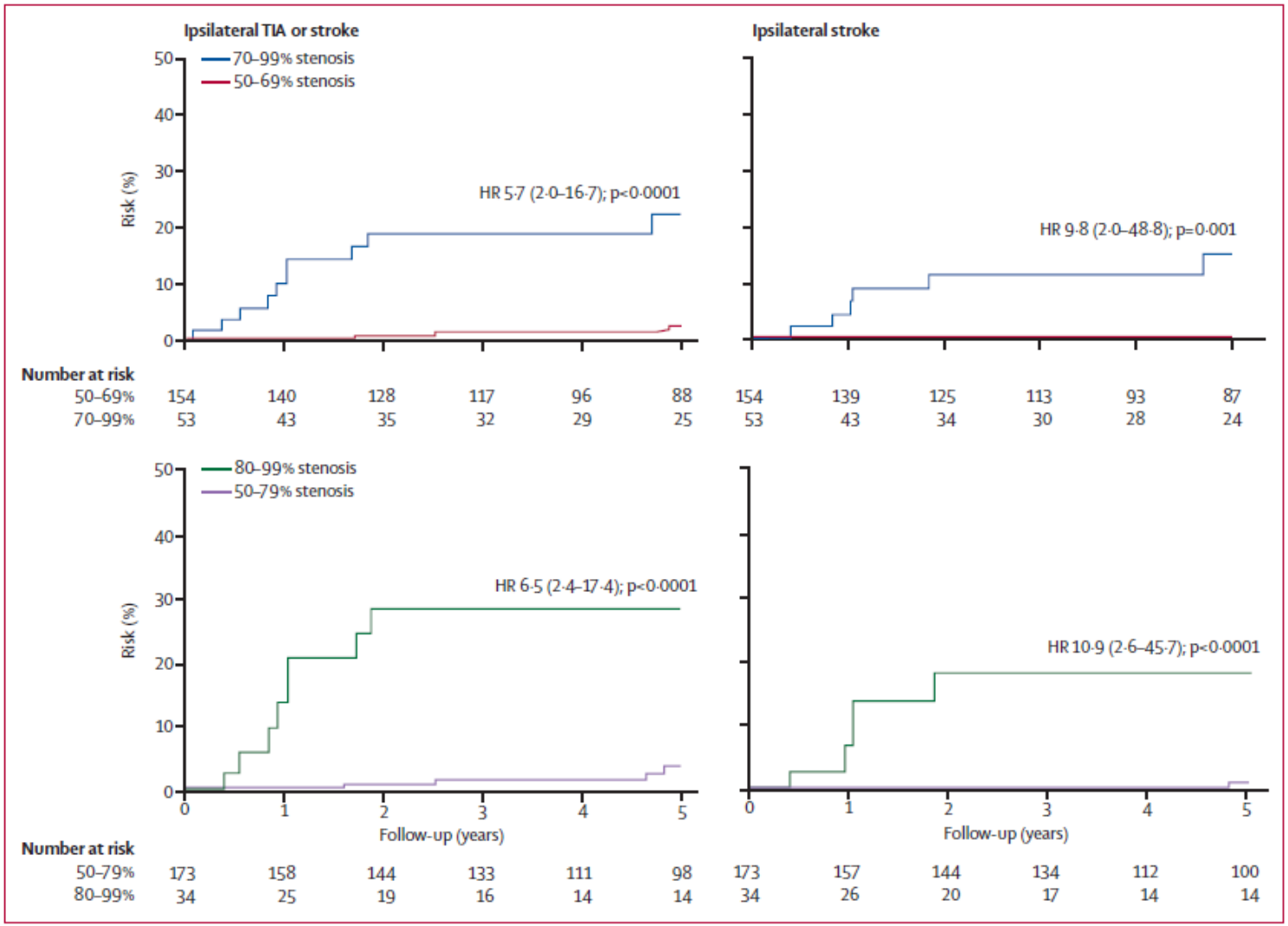


Figure 1: Risk of recurrent vascular events by degree of asymptomatic ipsilateral carotid stenosis in 207 patients with asymptomatic carotid stenosis in the Oxford Vascular Study

Howard DPJ et al. Lancet Neurol 2021

Revascularization Outcomes

	VACS	ACAS	ACST-1
% Stenosis	50-99%	60-99%	70-99%
Year	1983-1987	1987-1993	1993-2003
Years f/u	1991	1997	2008
N	5526	1662	3120
% Male	100%	66%	
Age	Any	40-79 y.o.	Any
BMT	Aspirin 325-650 mg, no statin, some anti-HTN	Aspirin 325 mg, risk factor counseling	Antiplatelet, statin (32%), anti-HTN

RCT	30-day death/stroke after CEA[a]	Ipsilateral stroke plus perioperative death/stroke		Any stroke plus perioperative death/stroke	
		CEA + BMT	BMT alone	CEA + BMT	BMT alone
VACS[75]	4.6%[a]	7.0% at 4 years	9.4% at 4 years	10.4% at 4 years	12.0% at 4 years
ACAS[13]	2.3%[a]	5.1% at 5 years	11% at 5 years	12.4% at 5 years	17.8% at 5 years
ACST-1[35]	2.8%	Not available	Not available	6.4% at 5 years	11.8% at 5 years

[a] Includes strokes occurring after diagnostic angiography as well.

Hobson RW et al. NEJM 1993; Walker MD et all. JAMA 1995; Halliay A et al. Lancet 2010; Naylor AR et al. Eur J Vasc Endovasc Surg 2018

Surgical Revascularization: Type of Intervention

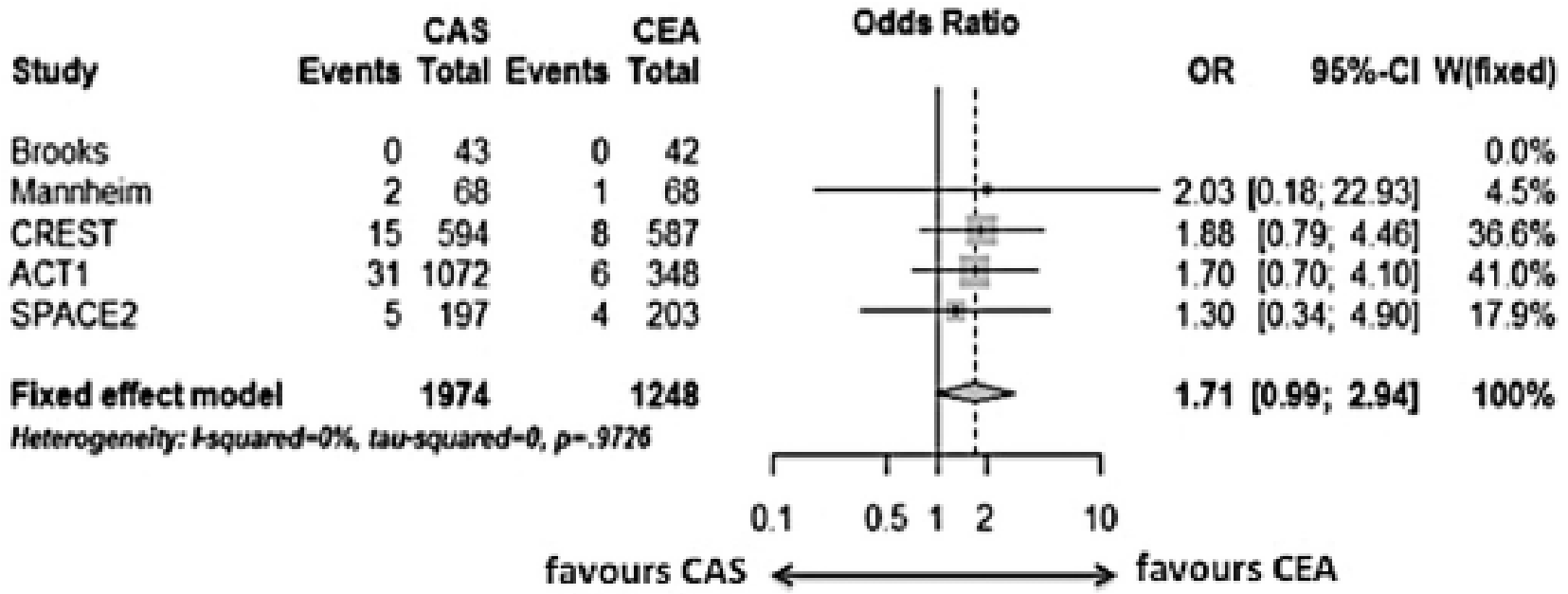
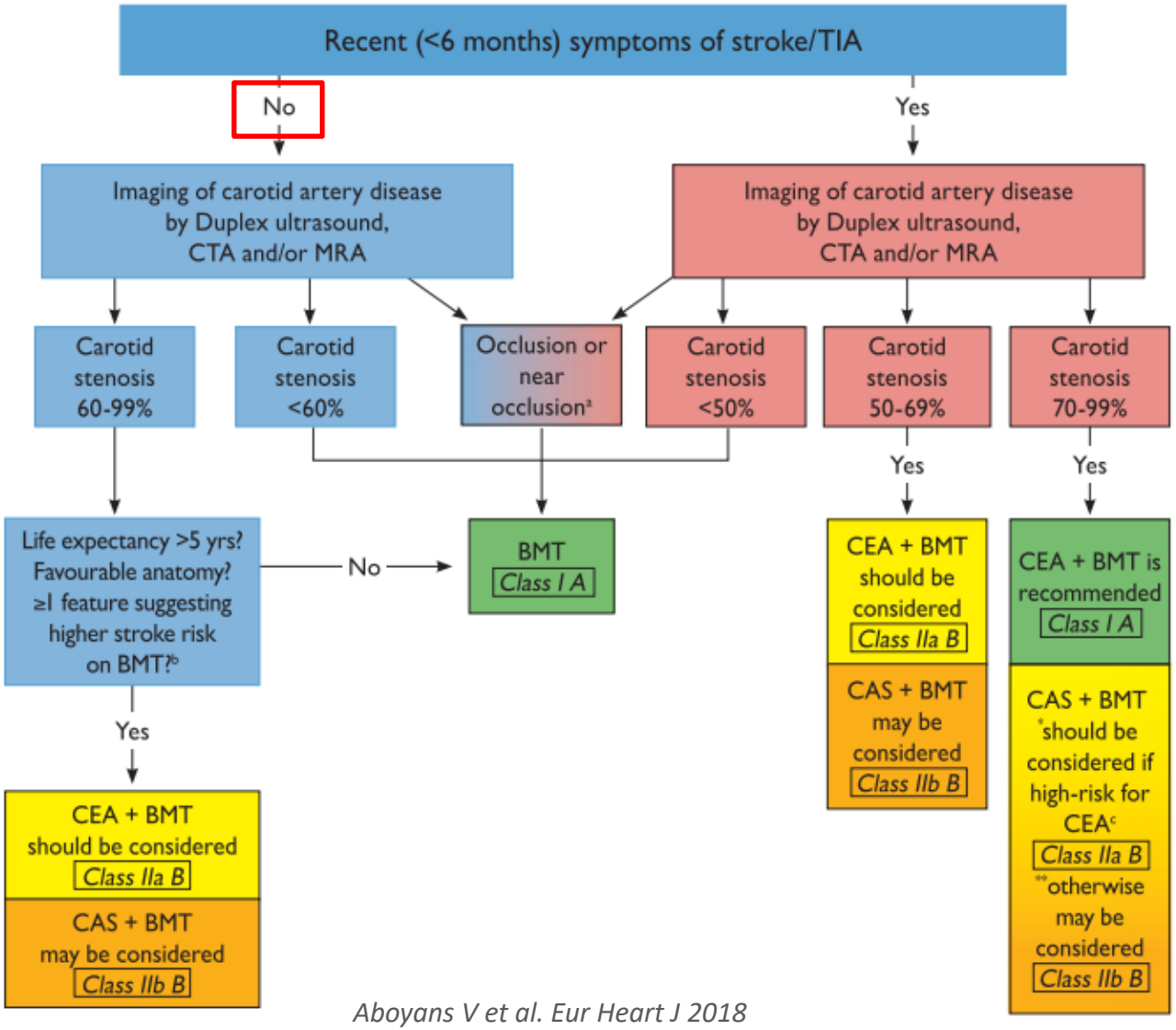


Figure 4. Forest Plot comparing 30-day death/stroke in four randomised trials comparing carotid endarterectomy and carotid artery stenting in asymptomatic patients.

Algorithm for Management of Carotid Stenosis



Aboyans V et al. Eur Heart J 2018

Conclusions

- Prevalence of carotid stenosis is low but carries a significant attributable risk for ischemic stroke.
- Screening for carotid stenosis is not recommended, although selective screening may be considered in specific circumstances.
- Stroke risk is significantly higher in patients with symptomatic disease as compared to asymptomatic disease.
- Revascularization, preferably carotid endarterectomy, should be offered for patients with symptomatic carotid stenosis.
- Risk of stroke in asymptomatic carotid stenosis has declined in the past decades due to increase in aggressive medical management.
- Revascularization should be considered for patients with asymptomatic carotid stenosis and high-risk features, especially when stenosis is 70-99%.