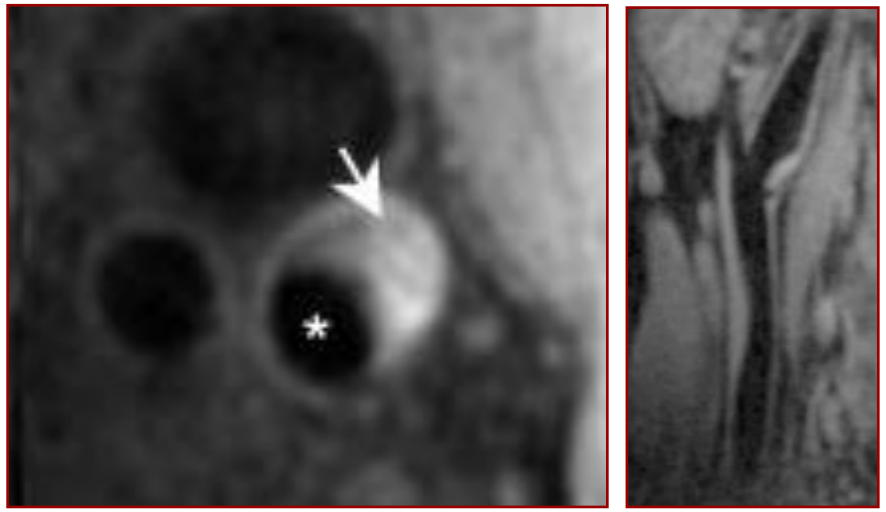
ECST-2

Resultaten, Implicaties en Toekomstige Ontwikkelingen



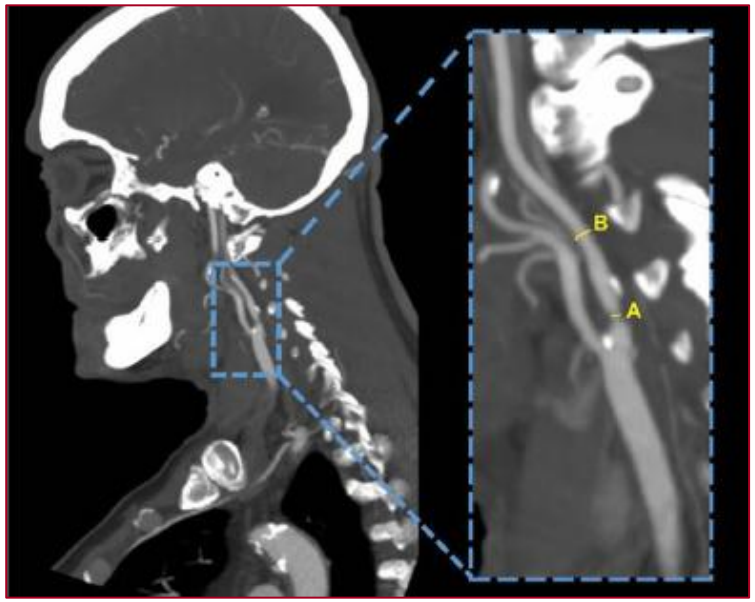
CVA/NAH Symposium 2025: Tijd voor samenwerken aan betere zorg, tijd voor actie!

Paul Nederkoorn, neuroloog, klinisch epidemioloog
p.j.nederkoorn@amsterdamumc.nl

Amsterdam UMC
Universitair Medische Centra

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Atherosclerotische stenose van de extracraniële arteria carotis



Atherosclerotische stenose van de extracraniële arteria carotis

- 15-20% van alle TIA- of beroerte-patiënten (stenose ≥50%)
- Prevalentie asymptomatische stenose: 3-4%
- Robust maar oud bewijs voor carotisendarteriëctomie (CEA)
- Optimale medische therapie is sterk verbeterd
- Rol van de ‘kwetsbare plaque’

Pathofysiologie

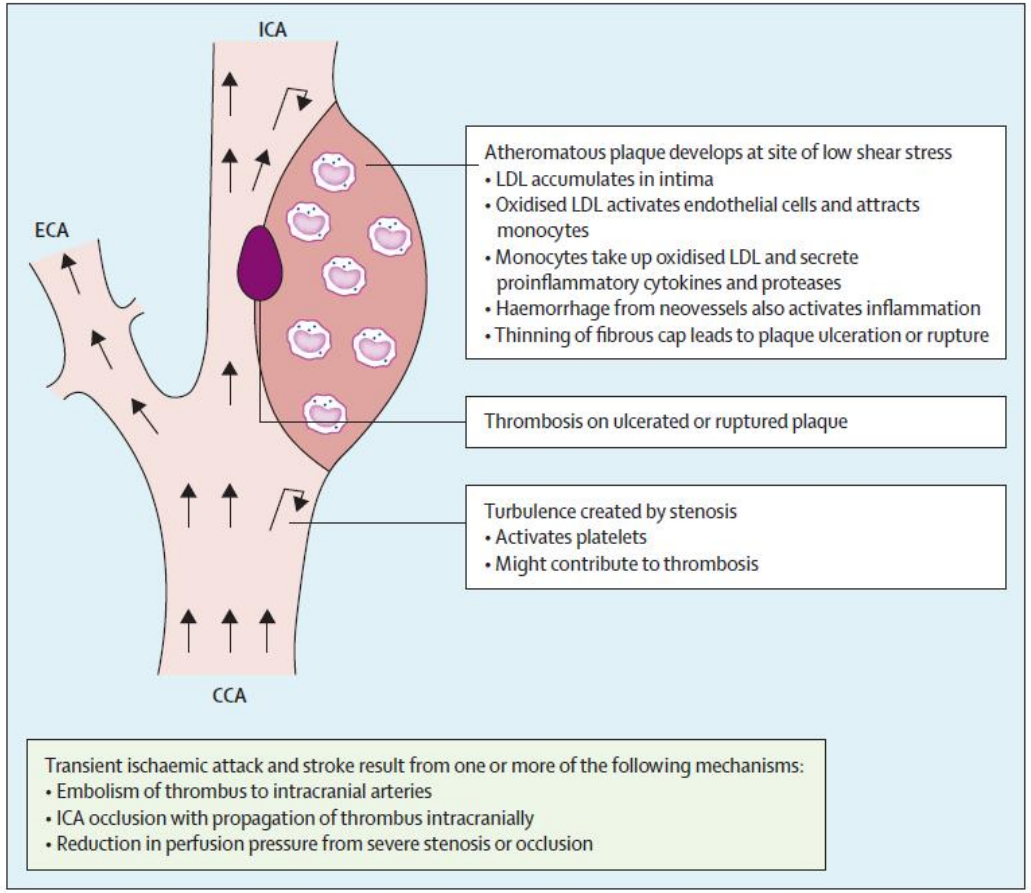
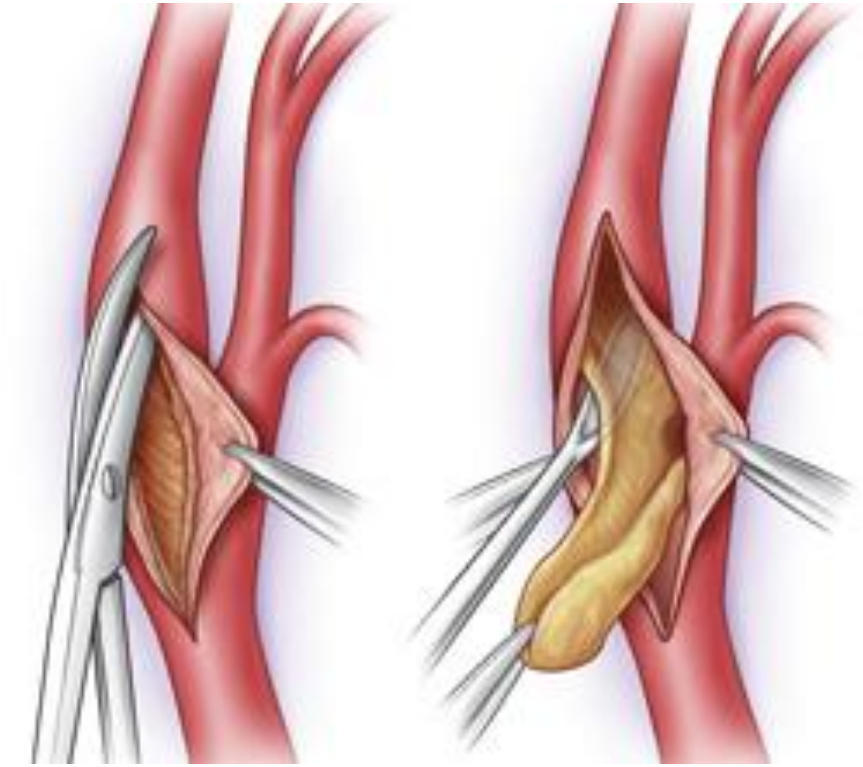


Figure 1: **Pathophysiology of stroke originating from carotid artery stenosis**
CCA=common carotid artery. ECA=external carotid artery. ICA=internal carotid artery.

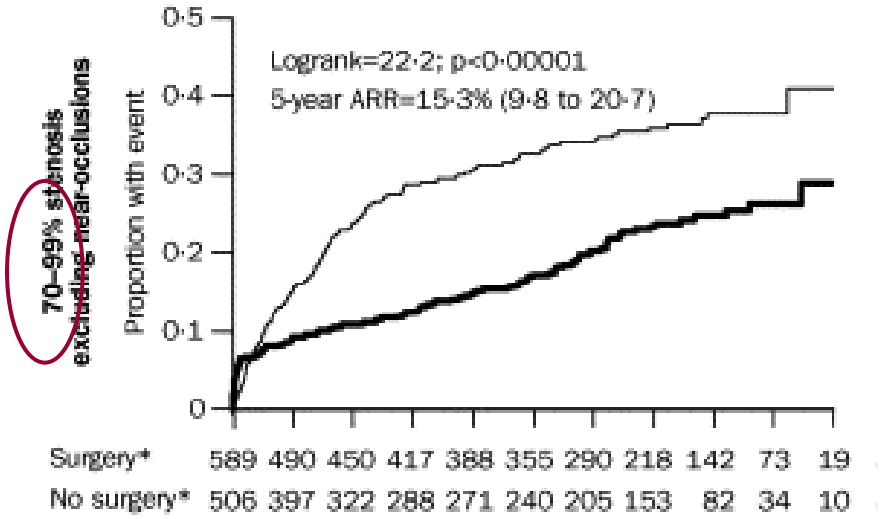
Bonati et.al., Lancet Neurology 2022

Carotisendarteriëctomie (CEA)

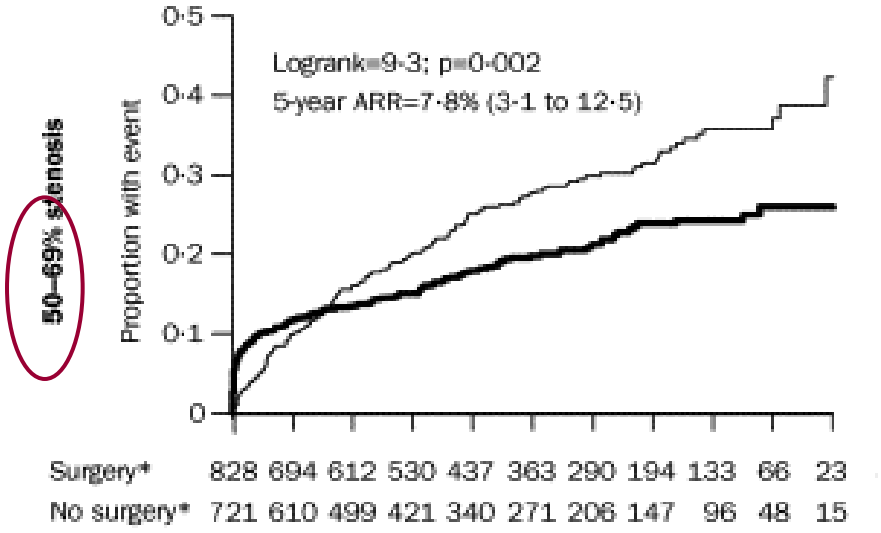


Eastcott et al. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. Lancet 1954.

Bewijs: robust maar oud..



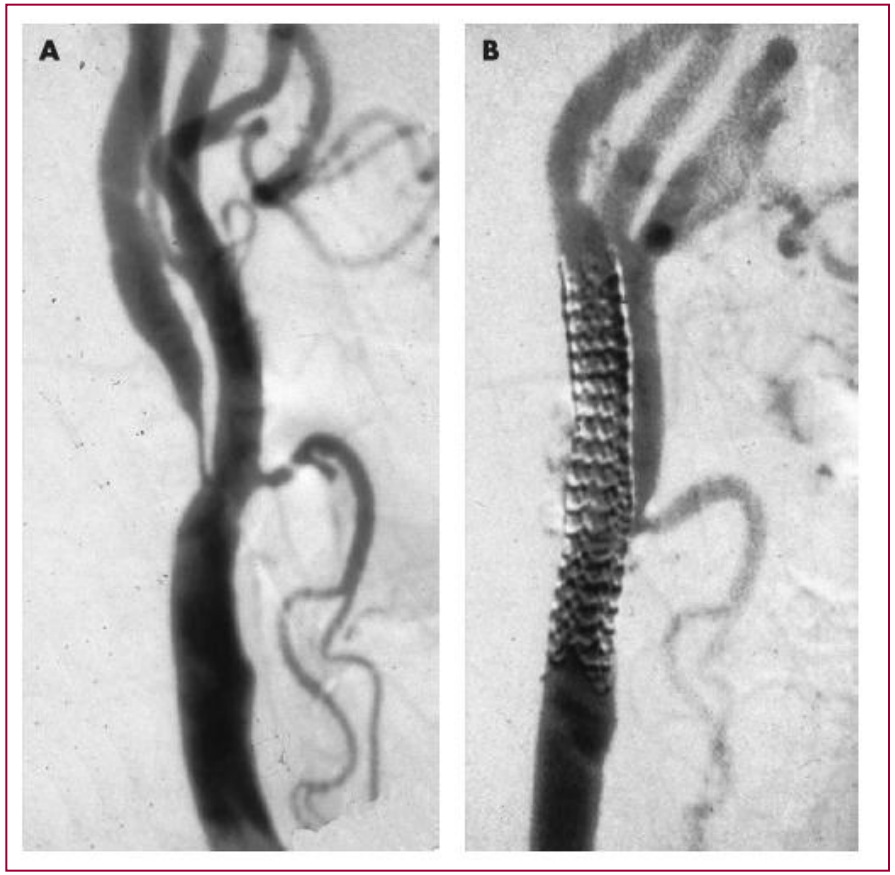
NNT = 6



NNT = >15

Rothwell et al, Lancet 2003

Stenten



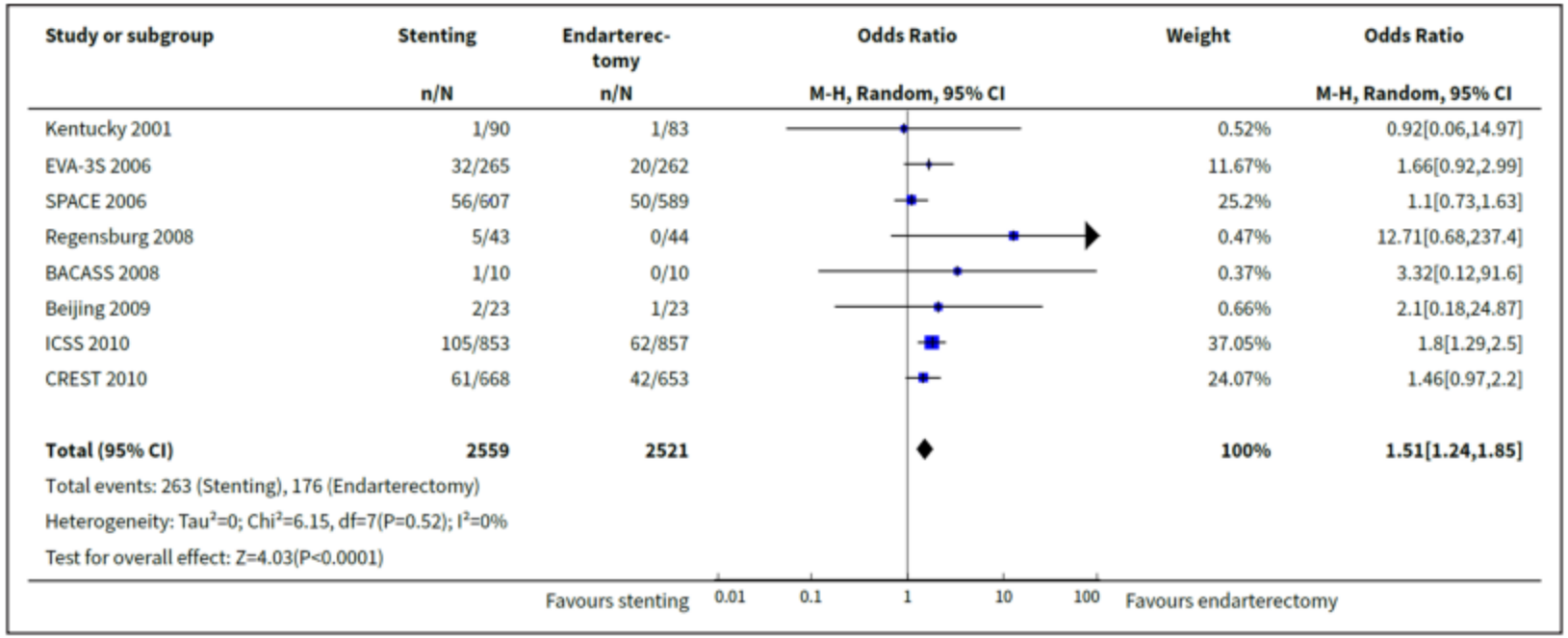
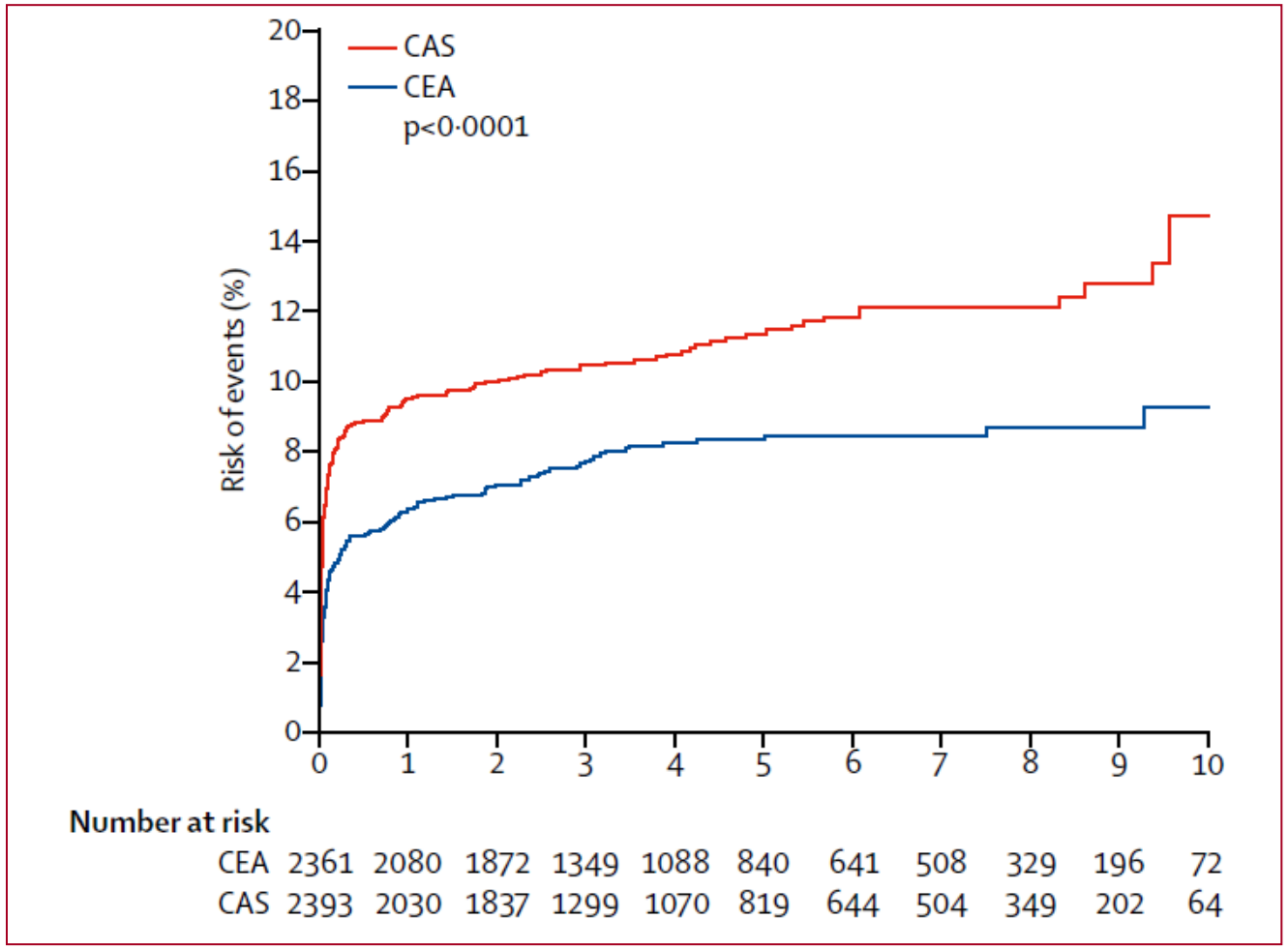


Figure. The combination of death or any stroke occurring between randomization and 30 d after treatment or ipsilateral stroke until the end of follow-up could be extracted from 8 trials.

Six trials[2–9] provided data on extensive follow-up periods of 4 years or longer. The primary combined outcome occurred significantly more often among participants randomized to stenting than among those allocated to endarterectomy.

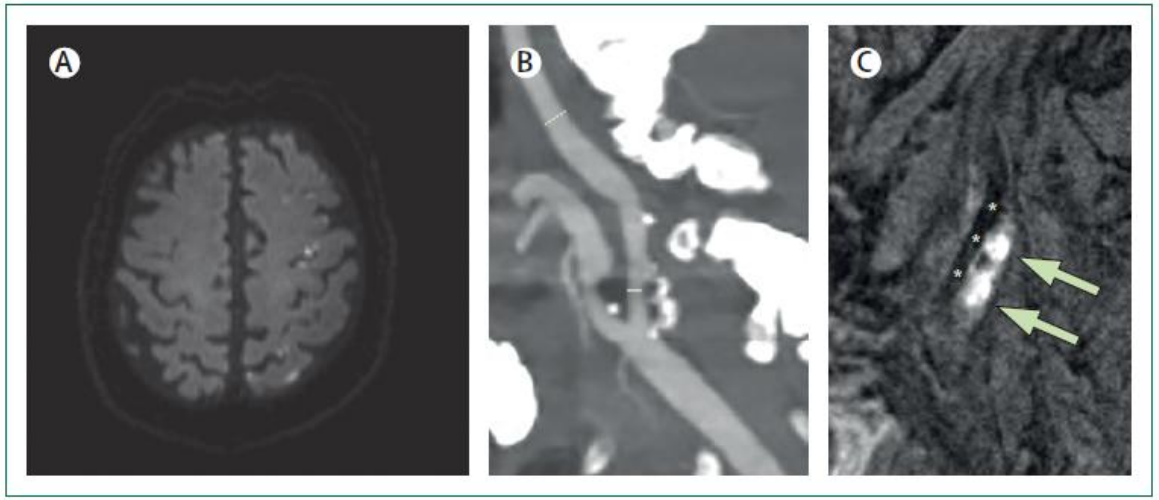
Müller et al, Cochrane 2020



Brott et al, Lancet Neurol 2019

Stenten

- Hoger risico tijdens procedure
- Langetermijneffect gelijkwaardig aan CEA
- Even effectief als CEA bij jongere patiënten

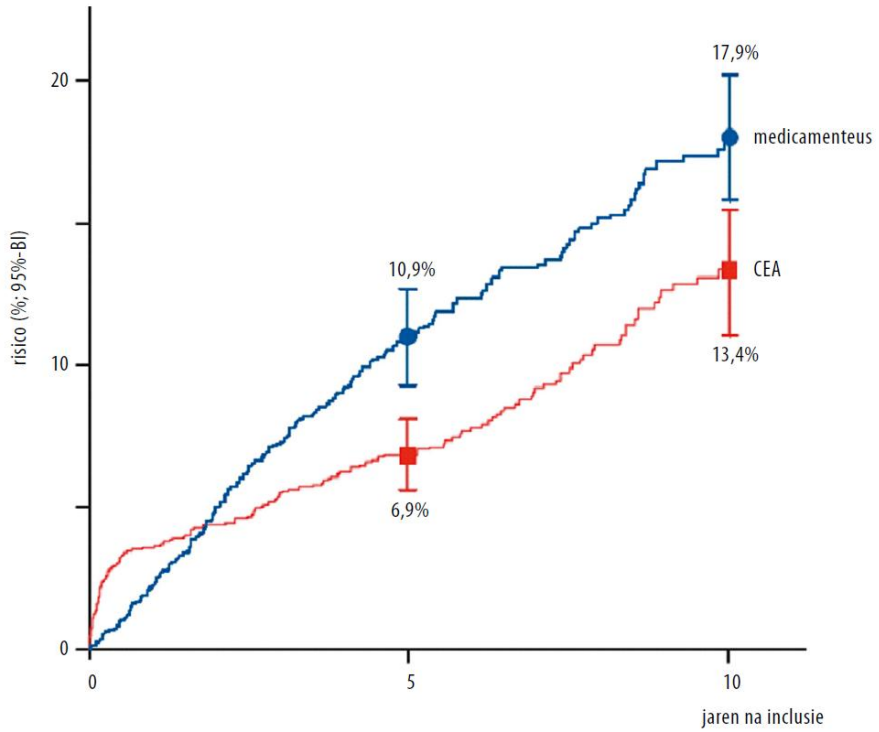


Asymptomatische carotisstenose

- Incidentie (>40 jaar): 3% bij vrouwen, 4% bij mannen (afhankelijk van etniciteit, stijgend met leeftijd)
- VS: 92% van alle CEA's bij asymptomatische patiënten
- Denemarken: 0%

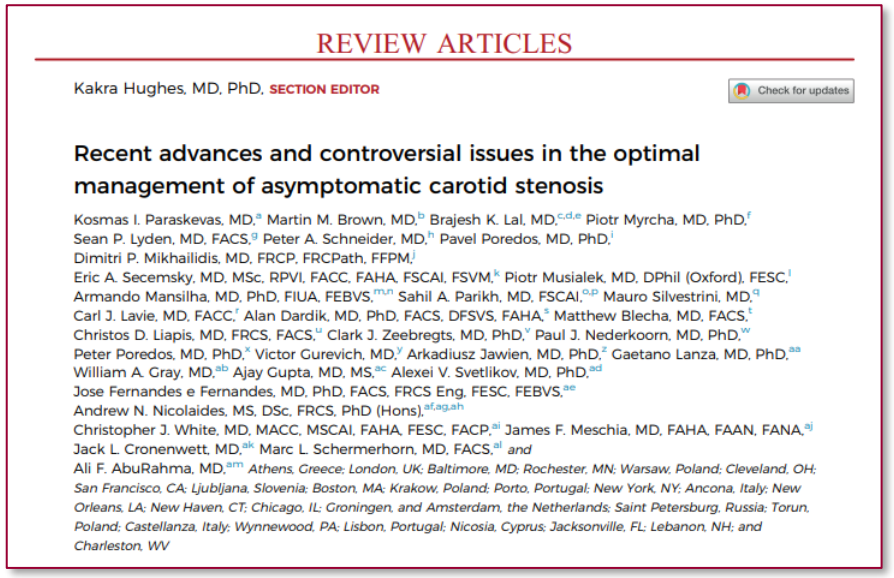


Asymptomatic Carotid Surgery Trial



- NNT 22
- Effect pas na 2 jaar
- Operatie risico 3%
- Vaak oude patiënten (‘competing risks’)
- Nog geen ‘OMT’

Lancet 2010
NTvG 2011



REVIEW ARTICLES

Kakra Hughes, MD, PhD, SECTION EDITOR

Check for updates

Recent advances and controversial issues in the optimal management of asymptomatic carotid stenosis

Kosmas I. Paraskevas, MD,[a] Martin M. Brown, MD,[b] Brajesh K. Lal, MD,[c,d,e] Piotr Myrcha, MD, PhD,[f] Sean P. Lyden, MD, FACS,[g] Peter A. Schneider, MD,[h] Pavel Poredos, MD, PhD,[i] Dimitri P. Mikhailidis, MD, FRCP, FRCPath, FFPM,[j] Eric A. Secemsky, MD, MSc, RPVI, FACC, FAHA, FSCAI, FSVM,[k] Piotr Musialek, MD, DPhil (Oxford), FESC,[l] Armando Mansilha, MD, PhD, FIUA, FEBVS,[m,n] Sahil A. Parikh, MD, FSCAI,[o,p] Mauro Silvestrini, MD,[q] Carl J. Lavie, MD, FACC,[r] Alan Dardik, MD, PhD, FACS, DFSVS, FAHA,[s] Matthew Blecha, MD, FACS,[t] Christos D. Liapis, MD, FRCS, FACS,[u] Clark J. Zeebregts, MD, PhD,[v] Paul J. Nederkoorn, MD, PhD,[w] Peter Poredos, MD, PhD,[x] Victor Gurevich, MD,[y] Arkadiusz Jawien, MD, PhD,[z] Gaetano Lanza, MD, PhD,[aa] William A. Gray, MD,[ab] Ajay Gupta, MD, MS,[ac] Alexei V. Svetlikov, MD, PhD,[ad] Jose Fernandes e Fernandes, MD, PhD, FACS, FRCS Eng, FESC, FEBVS,[ae] Andrew N. Nicolaides, MS, DSc, FRCS, PhD (Hons),[af,ag,ah] Christopher J. White, MD, MACC, MSCAI, FAHA, FESC, FACP,[ai] James F. Meschia, MD, FAHA, FAAN, FANA,[aj] Jack L. Cronenwett, MD,[ak] Marc L. Schermerhorn, MD, FACS,[al] *and* Ali F. AbuRahma, MD,[am] *Athens, Greece; London, UK; Baltimore, MD; Rochester, MN; Warsaw, Poland; Cleveland, OH; San Francisco, CA; Ljubljana, Slovenia; Boston, MA; Krakow, Poland; Porto, Portugal; New York, NY; Ancona, Italy; New Orleans, LA; New Haven, CT; Chicago, IL; Groningen, and Amsterdam, the Netherlands; Saint Petersburg, Russia; Torun, Poland; Castellanza, Italy; Wynnewood, PA; Lisbon, Portugal; Nicosia, Cyprus; Jacksonville, FL; Lebanon, NH; and Charleston, WV*

Optimale behandeling voor patiënten met asymptomatische carotisstenose bestaat uit:

✔ Beste medische behandeling (OMT) voor iedereen

✔ Profylactische revascularisatie (CEA, CAS, of TCAR) voor geselecteerde subgroepen

Rekening houdend met patiëntkenmerken, beeldvorming, sociale factoren en predictiemodellen

J Vasc Surg 2024

Huidige praktijk

Panel 4*: Indications for carotid endarterectomy and stenting

Symptomatic carotid stenosis

- Carotid endarterectomy
  - Recommended for severe stenosis (70–99%)
  - Suggested for moderate stenosis (50–69%)
  - Not recommended for minor stenosis (<50%)
  - Recommended within 14 days of the first ischaemic event
- Carotid artery stenting
  - Suggested as an alternative to endarterectomy in patients <70 years old
  - Not recommended in patients with severe atherosclerosis of the aortic arch or tortuosity of supra-aortic vessels

Asymptomatic carotid stenosis

- Carotid endarterectomy
  - Recommended for 60–99% stenosis in patients at increased stroke risk
- Carotid artery stenting
  - Not routinely recommended
  - Possible option in selected patients unsuitable for surgery, provided they benefit from revascularisation

*Recommendations for carotid endarterectomy and stenting, according to current guidelines.[5,87]

Bonati et.al., Lancet Neurology 2022

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

THE 2nd EUROPEAN

ECST-2

CAROTID SURGERY TRIAL










En alle ECST-2 investigators!

Locale onderzoekers van deelnemende centra

- Albert Schweitzer Hospital Dordrecht
- AMC/Flevo Amsterdam
- Ashford and St Peter’s Hospitals NHS Foundation Trust
- Bradford Teaching Hospitals NHS Trust
- Calderdale &Huddersfield NHS Foundation Trust
- Dalhousie University, Halifax
- East Kent Hospitals University NHS Foundation Trust
- Erasmus University Medical Centre, Rotterdam
- Frimley Park Hospital
- Hospices Civiles de Lyon
- Kantonsspital St. Gallen
- Leeds General Infirmary
- Maastricht University Medical Centre
- Manchester Royal Infirmary
- NHS Ayrshire and Arran
- Nottingham University Hospitals
- NSI-Lugano
- Pennine Acute Hospitals NHS Trust
- Radbound University Nijmegen Medical Centre
- Royal Devon and Exeter Hospital
- Sheffield Teaching Hospitals
- St George's Healthcare NHS Trust
- Stroke Centre, University Hospital Basel
- Universitätsklinikum Magdeburg
- Otto-von-Guericke-Universität
- University Hospital North Durham
- University Hospital South Manchester
- University of Leipzig
- University Medical Center Utrecht
- Verona University Hospital
- UCLH London

Achtergrond ECST-2

- Huidige richtlijnen voor CEA gebaseerd op oud bewijs (20-30 jaar geleden)*
- Medicamenteuze behandeling aanzienlijk verbeterd → risico op beroerte bijna gehalveerd
- Besluitvorming nu vooral gebaseerd op ernst van stenose en symptomen
- Ulceraties van plaque, patiëntkenmerken & comorbiditeit kunnen de afweging beïnvloeden

*NASCET, ECST, ACST, ACAS, pooled analyses

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Hypothese

- Patiënten met ≥50% carotisstenose **met een laag- tot matig risico op beroerte** profiteren niet van aanvullende revascularisatie wanneer zij optimale medicamenteuze therapie krijgen.

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

Methoden

- Multicenter, gerandomiseerde trial (open-label, blinded outcome)
- Randomisatie: OMT + revascularisatie vs OMT alleen
- Geschikte patiënten:
  - Atherosclerotische stenose ≥50%
  - Laag--middelmatig risico (5-jaars risico CAR-score <20%)
  - Symptomatisch & asymptomatisch

Protocol paper: Cheng et al, Trials 2022

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Carotid Artery Risk (CAR) score

- Voorspellingsscore om het 5-jaarsrisico op ipsilaterale beroerte te schatten
- Gegevens oorspronkelijk afkomstig uit ECST en NASCET
- Risico onder optimale medicamenteuze therapie (OMT) is sinds de studies sterk gedaald
- Score is opnieuw gekalibreerd voor het waarschijnlijke voordeel van OMT tot op heden
- Asymptomatische stenose = CAR ≤ 5%

- Sex
- Age
- Stenosis %
- Type of event
- Time since event
- DM
- MI
- PVD
- HT
- Ulcerated plaque

Rothwell et al, Stroke 2003, Cheng et al, Trials 2022

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Interventies

- Optimale Medicamenteuze Therapie (OMT)
  - Antihypertensiva
  - Cholesterolverlagers & dieet
  - Antistolling indien geïndiceerd
  - Vooraf vastgelegde doelen:

- Total cholesterol <4.0mmol/L
- LDL cholesterol <2.0mmol/L
- BP ≤ 135/85 mmHg (<80 years)
- BP ≤ 150/90 mmHg (≥80 years)

- OMT *plus* Revascularisatie
  - CEA
  - Stenten in geselecteerde patiënten
  - Aanbevolen binnen 2 weken (symptomatisch) / 4 weken (asymptomatisch)

Follow-up

- Follow-up bezoeken na 4–6 weken, 6 maanden en daarna jaarlijks: modified Rankin Score (mRS), klinische events
- Jaarlijkse duplex-echografie
- MRI van de hersenen bij baseline, na 2 jaar en na 5 jaar indien mogelijk
- MRI-plaque-beeldvorming bij baseline, in subgroep

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

Trial history

- Oorspronkelijk doel: 2000 patiënten
- Moeizame inclusie
- Nieuw trial design nodig na pilot
- Ander meer sensitief eindpunt

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

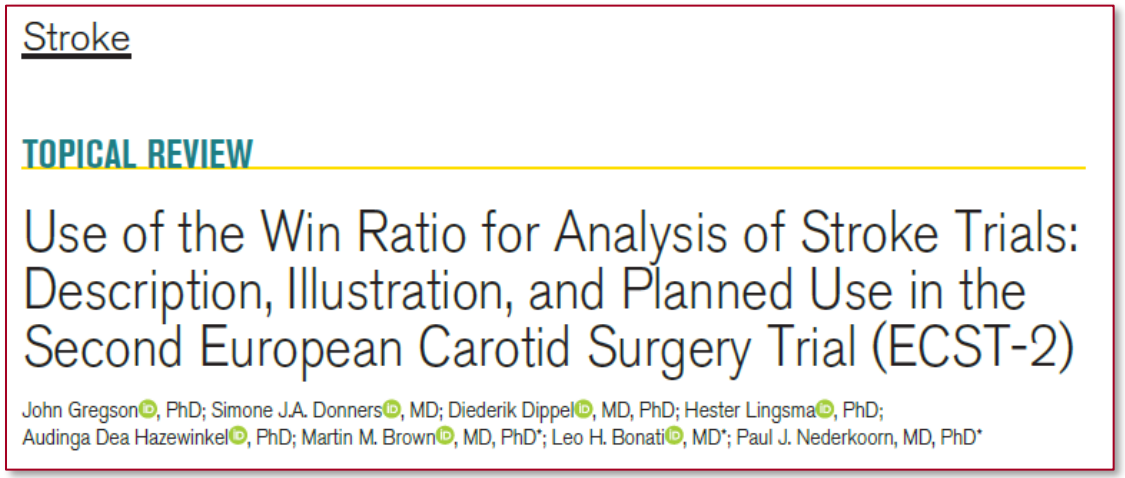
2-jaar interim resultaten

- Hiërarchisch primair eindpunt:
  1. time to peri-operative death, fatal stroke, fatal MI
  2. time to non-fatal stroke
  3. time to non-fatal MI; and
  4. new cerebral infarction on MRI (or CT) within 2 years of follow-up

- Analyse met de ‘win-ratio’

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

Win-ratio



I) time to peri-operative death, fatal stroke, or fatal myocardial infarction
II) time to non-fatal stroke
III) time to non-fatal myocardial infarction
IV) new cerebral infarction on imaging

Results ECST-2

- Eerste patiënt gerandomiseerd in maart 2012, laatste patiënt in oktober 2019.

- In totaal zijn 429 patiënten geïncludeerd in 30 centra in het Verenigd Koninkrijk, Zwitserland, Nederland, Frankrijk, Duitsland, Italië en Canada.

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

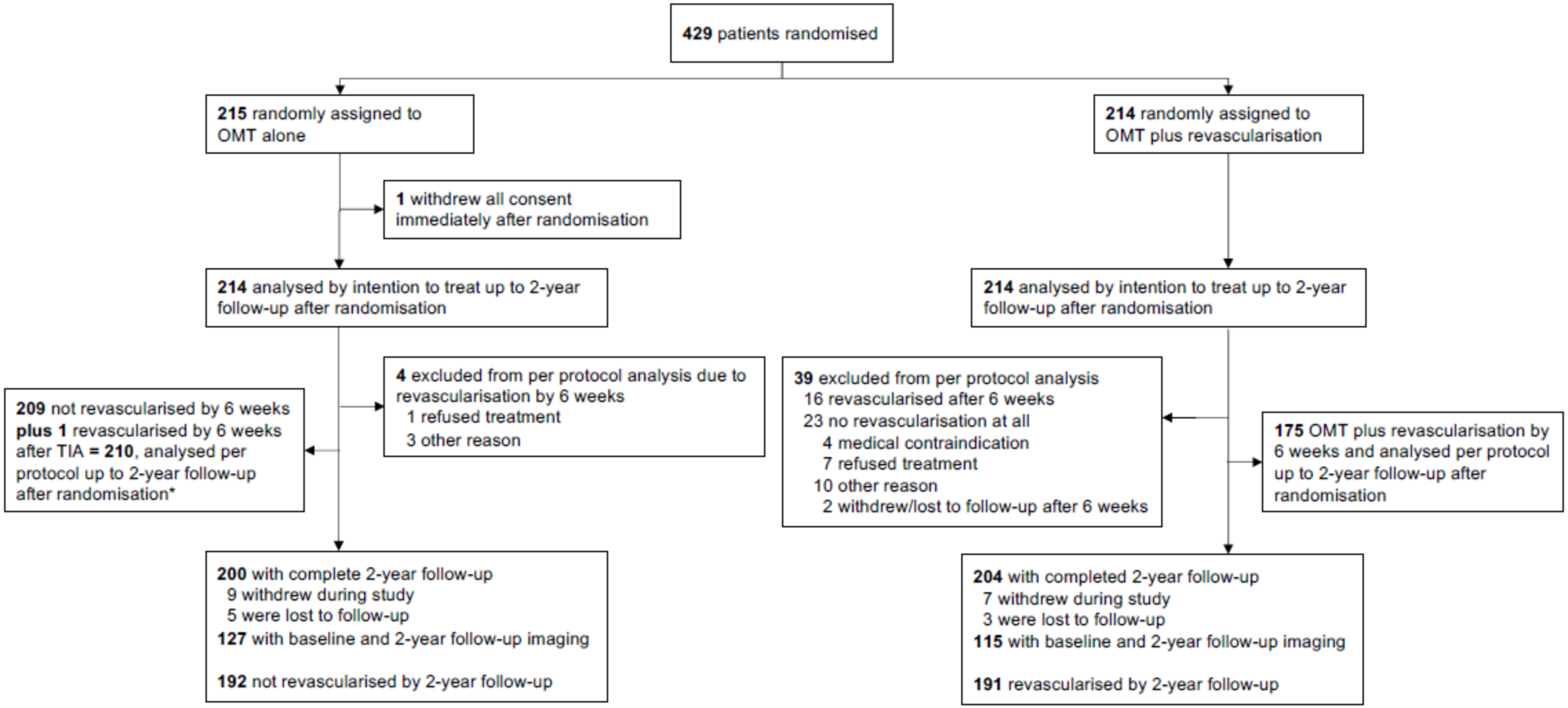


Figure 1. Trial profile

OMT=optimised medical therapy. TIA=transient ischaemic attack.*Patients allocated OMT alone who receive carotid revascularisation more than 6 weeks after randomisation were included in the per-protocol analysis but censored at the time of onset of the revascularisation procedure.

Baseline characteristics

		OMT	REVASC + OMT
N Patients		215	214
Symptomatic		86/215 (40.0%)	85/214 (39.7%)
Age (years)		72 (64 to 78), n=215	71 (65 to 77), n=214
Sex	Female	66/215 (30.7%)	67/214 (31.3%)
	Male	149/215 (69.3%)	147/214 (68.7%)
Smoking			
	Never Smoked	36/214 (16.8%)	44/214 (20.6%)
	Ex smoker	131/214 (61.2%)	132/214 (61.7%)
	Currently Smoking	47/214 (22.0%)	38/214 (17.8%)
Diabetes			
	No	151/215 (70.2%)	160/214 (74.8%)
	Yes - type I	2/215 (0.9%)	2/214 (0.9%)
	Yes - type II	62/215 (28.8%)	52/214 (24.3%)
Hypertension		163/215 (75.8%)	164/214 (76.6%)

Baseline characteristics

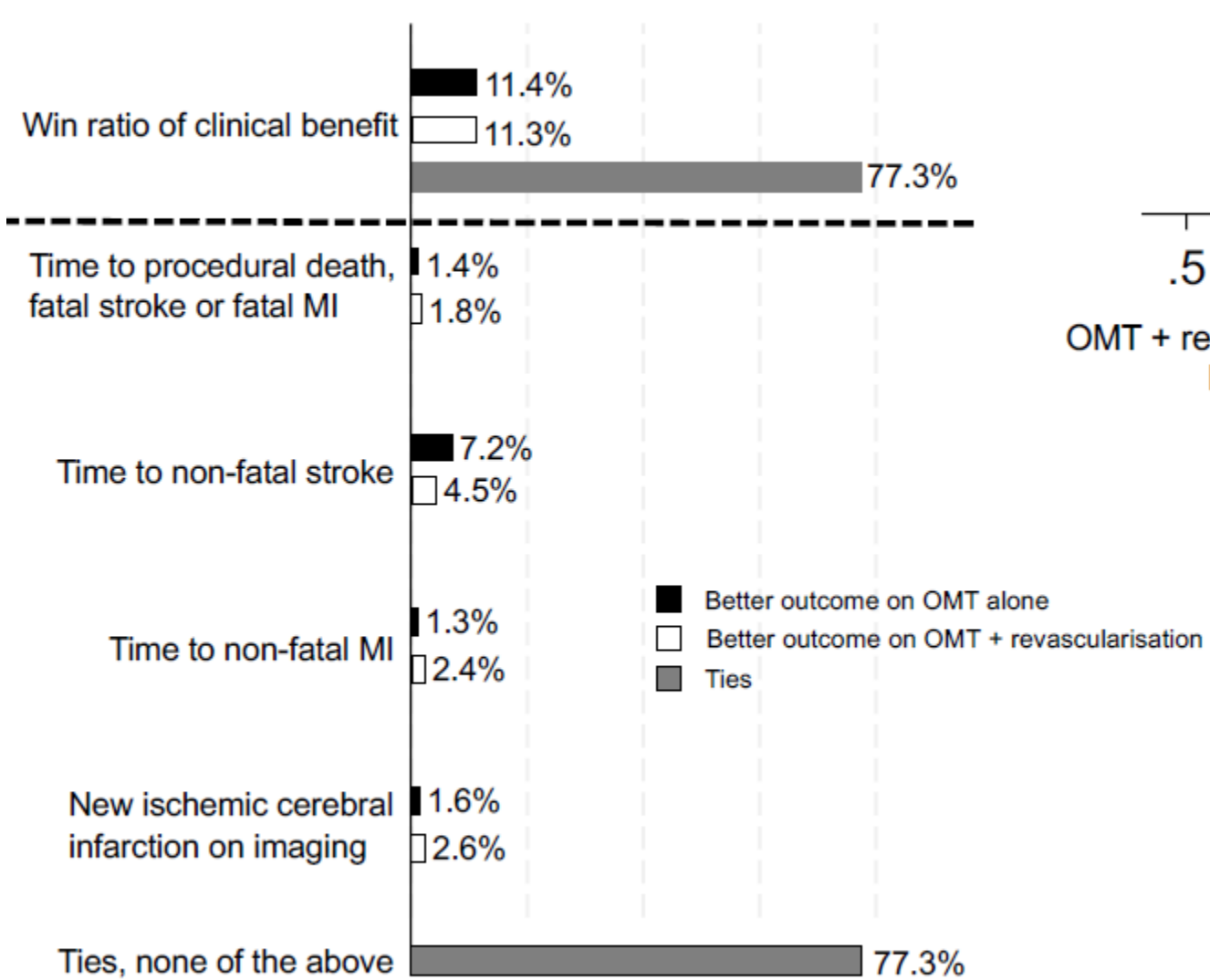
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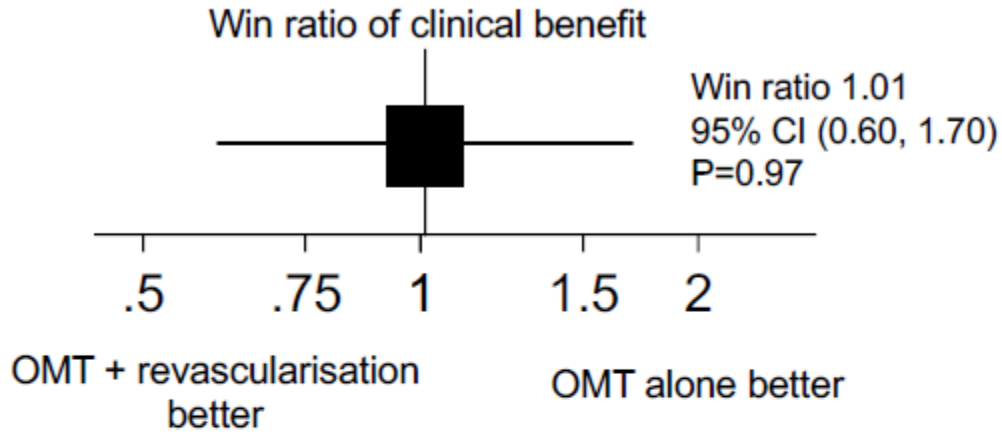
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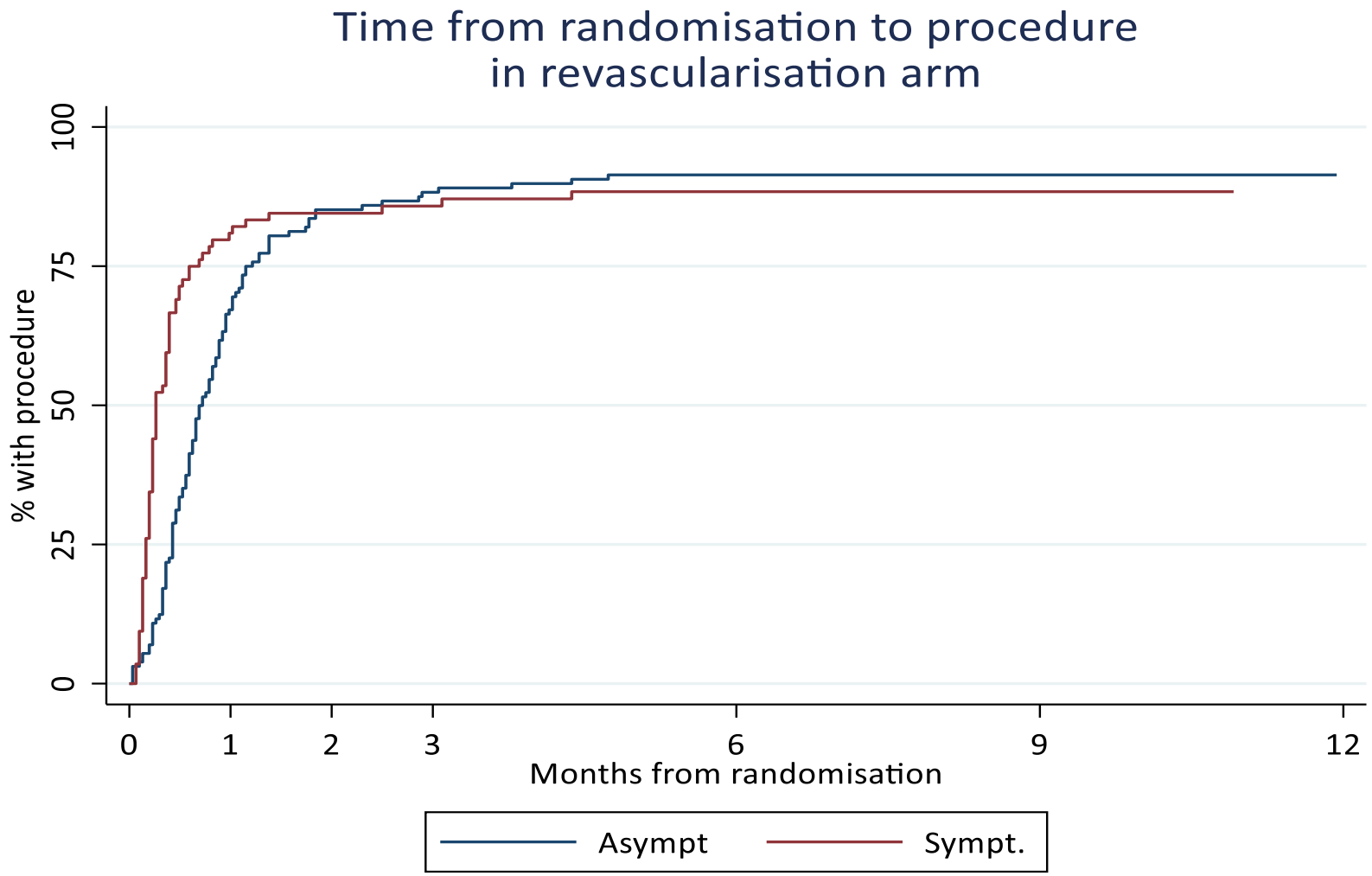
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Win ratio of clinical benefit
11.4%
11.3%
77.3%
Time to procedural death, fatal stroke or fatal MI
1.4%
1.8%
Time to non-fatal stroke
7.2%
4.5%
Time to non-fatal MI
1.3%
2.4%
New ischemic cerebral infarction on imaging
1.6%
2.6%
Ties, none of the above
77.3%
Better outcome on OMT alone
Better outcome on OMT + revascularisation
Ties


Win ratio of clinical benefit
Win ratio 1.01
95% CI (0.60, 1.70)
P=0.97
.5
.75
1
1.5
2
OMT + revascularisation better
OMT alone better


Time from randomisation to procedure
in revascularisation arm
% with procedure
0
25
50
75
100
0
1
2
3
6
9
12
Months from randomisation
Asympt
Sympt.

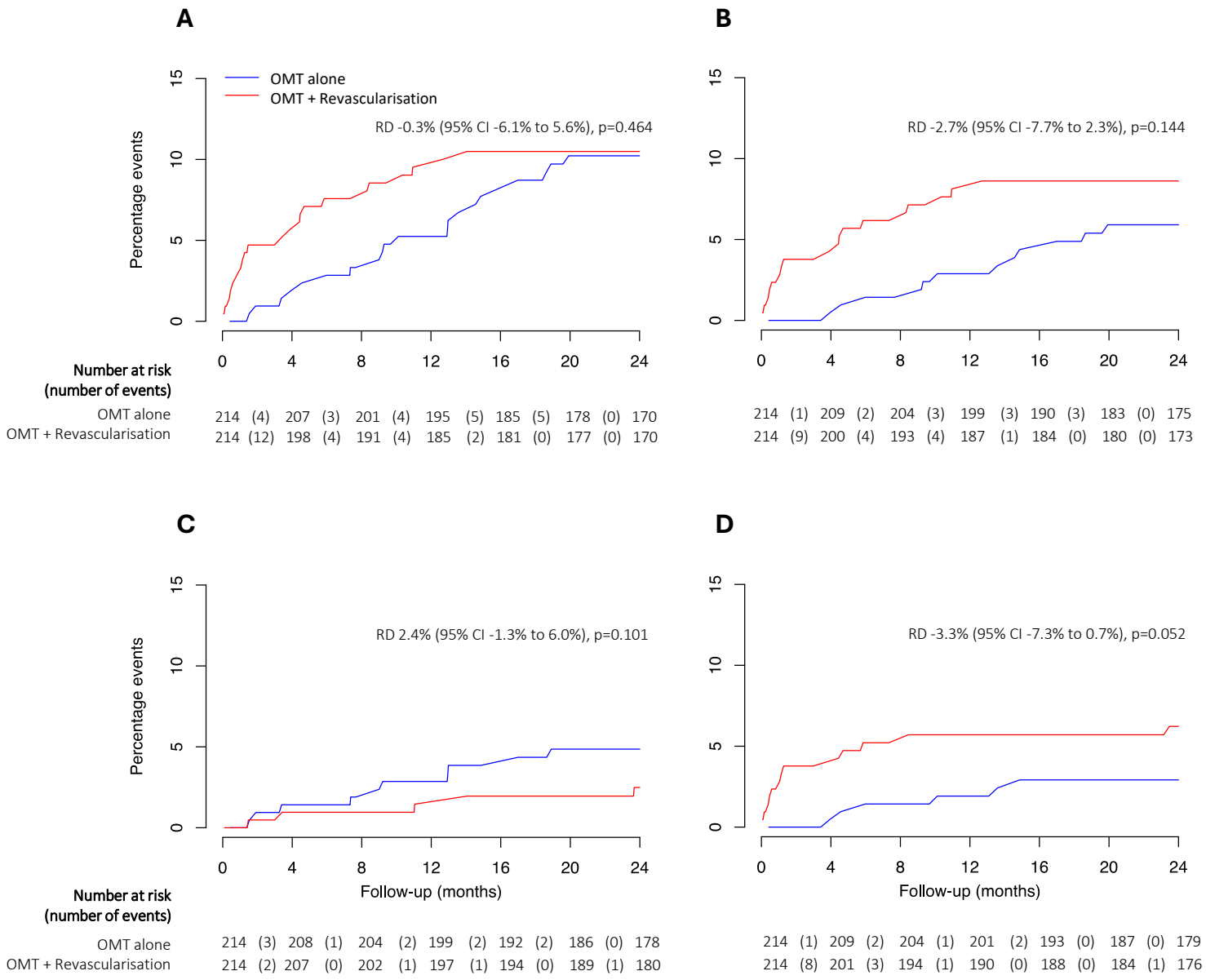


Figure 3. Kaplan-Meier estimates of 2-year cumulative incidence for major outcomes among patients randomly allocated to OMT (n=214) versus OMT plus revascularisation (n=214). A) composite of peri-procedural death, stroke or any myocardial infarction; B) stroke; C) myocardial infarction; D) ipsilateral stroke. The percentage of events (cumulative incidence) is shown plotted against months since randomisation. OMT=optimised medical therapy. RD=risk difference at 2 year follow-up.

Outcome	No. of events (%) at 2 years		Difference at 2 years (95% CI)	Hazard ratio (95% CI)	P-value
	OMT	Revasc + OMT			
Composite	21 (10.3%)	21 (10.0%)	0.3% (-5.5%, 6.1%)	0.96 (0.53, 1.76)	0.90
Procedural death	0 (0%)	1 (0.5%)	-	-	-
Stroke	12 (6.0%)	17 (8.1%)	-2.2% (-7.1%, 2.8%)	0.68 (0.32, 1.42)	0.30
Myocardial infarction	10 (4.9%)	5 (2.5%)	2.4% (-1.3%, 6.0%)	2.00 (0.68, 5.84)	0.21

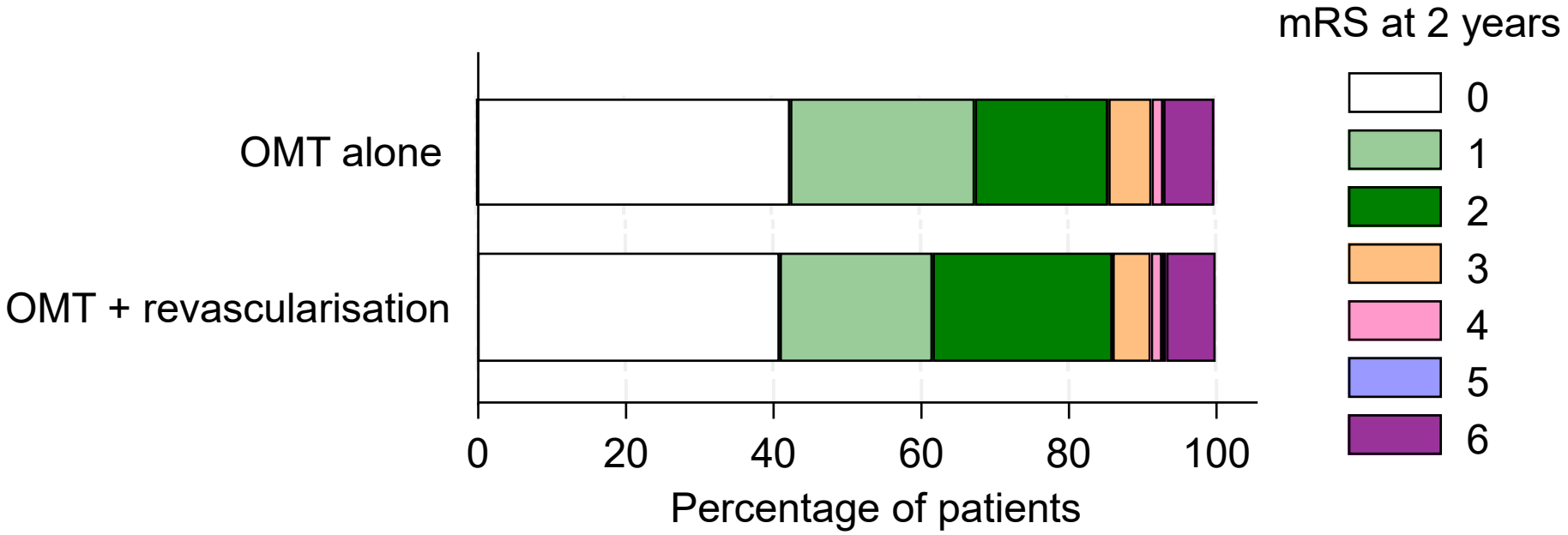
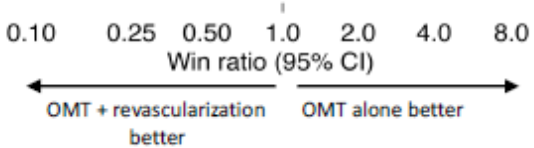


Figure 4: Functional ability measured by the modified Rankin Scale (mRS) at the end of 2 years of follow-up in the intention-to-treat population. Definition mRS scores according to the Rankin Focused Assessment: 0 no disability; 1 no significant disability; 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, 6 death.

	OMT alone (N)	OMT + revascula-risation (N)	OMT alone wins (%)	OMT + revascula-risation wins (%)	Win ratio (95% confidence interval)
All patients	214	214	11.4	11.2	1.01 (0.60 to 1.71)
Symptomatic					
No	129	129	9.4	13.7	0.68 (0.35 to 1.34)
Yes	85	85	14.6	7.9	1.85 (0.79 to 4.35)
Age					
< 70	88	91	7.0	10.8	0.64 (0.25 to 1.65)
≥ 70	126	123	14.8	11.7	1.27 (0.68 to 2.38)
Sex					
Female	66	67	16.6	6.8	2.45 (0.91 to 6.61)
Male	148	147	9.1	13.4	0.68 (0.36 to 1.27)
Risk group					
Asymptomatic, stenosis ≤ 69%	47	48	8.3	9.7	0.86 (0.25 to 2.92)
Asymptomatic, stenosis ≥ 70%	82	81	9.9	15.9	0.62 (0.28 to 1.39)
Symptomatic, CAR score <15%	35	35	11.3	0.0	NA
Symptomatic, CAR score 15-19%	50	50	16.6	13.1	1.27 (0.50 to 3.21)
Diabetes					
No	151	160	11.1	10.4	1.07 (0.58 to 1.99)
Yes	63	54	12.0	13.1	0.91 (0.35 to 2.39)
Hypertension					
No	52	50	6.0	8.0	0.75 (0.18 to 3.09)
Yes	162	164	13.2	12.3	1.08 (0.61 to 1.88)
Severity of stenosis					
≤ 69%	103	91	13.3	9.2	1.44 (0.66 to 3.12)
≥ 70%	111	123	10.0	13.2	0.76 (0.38 to 1.53)
Contralateral stenosis or occlusion					
≤ 50%	109	117	9.7	8.8	1.11 (0.50 to 2.46)
≥ 51%	71	59	14.8	13.4	1.10 (0.47 to 2.57)
Unknown	34	38	11.6	14.4	0.81 (0.24 to 2.67)
Centre					
Centres with ≤ 20 patients	89	87	8.2	12.9	0.64 (0.27 to 1.50)
Centres with ≥ 21 patients	127	252	17.9	13.3	1.34 (0.69 to 2.61)



Conclusies 2-jaar interim resultaten

- Er was geen bewijs voor voordeel van revascularisatie als aanvulling op optimale medicamenteuze therapie (OMT) voor symptomatische en asymptomatische patiënten met carotisstenose ≥50% met een laag of gemiddeld voorspeld beroerterisico in de eerste 2 jaar na de procedure.

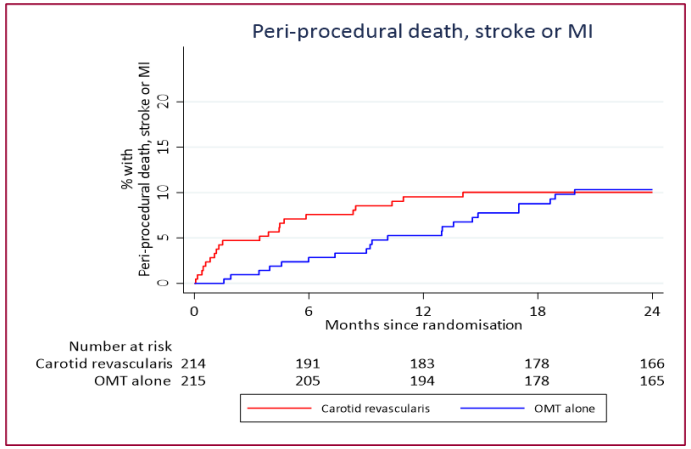
- De resultaten ondersteunen het behandelen van asymptomatische en laag- of gemiddeld risico symptomatische carotisstenose met alleen OMT, totdat meer gegevens beschikbaar komen uit langere follow-up.

- Zeer kosteneffectief.

THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL

Discussie

- Eerste studie met data gebaseerd op hedendaagse therapie
- Studie populatie te klein voor definitieve uitspraken
- 60% = asymptomatisch
- !! Nieuw predictive model met plaque imaging !!

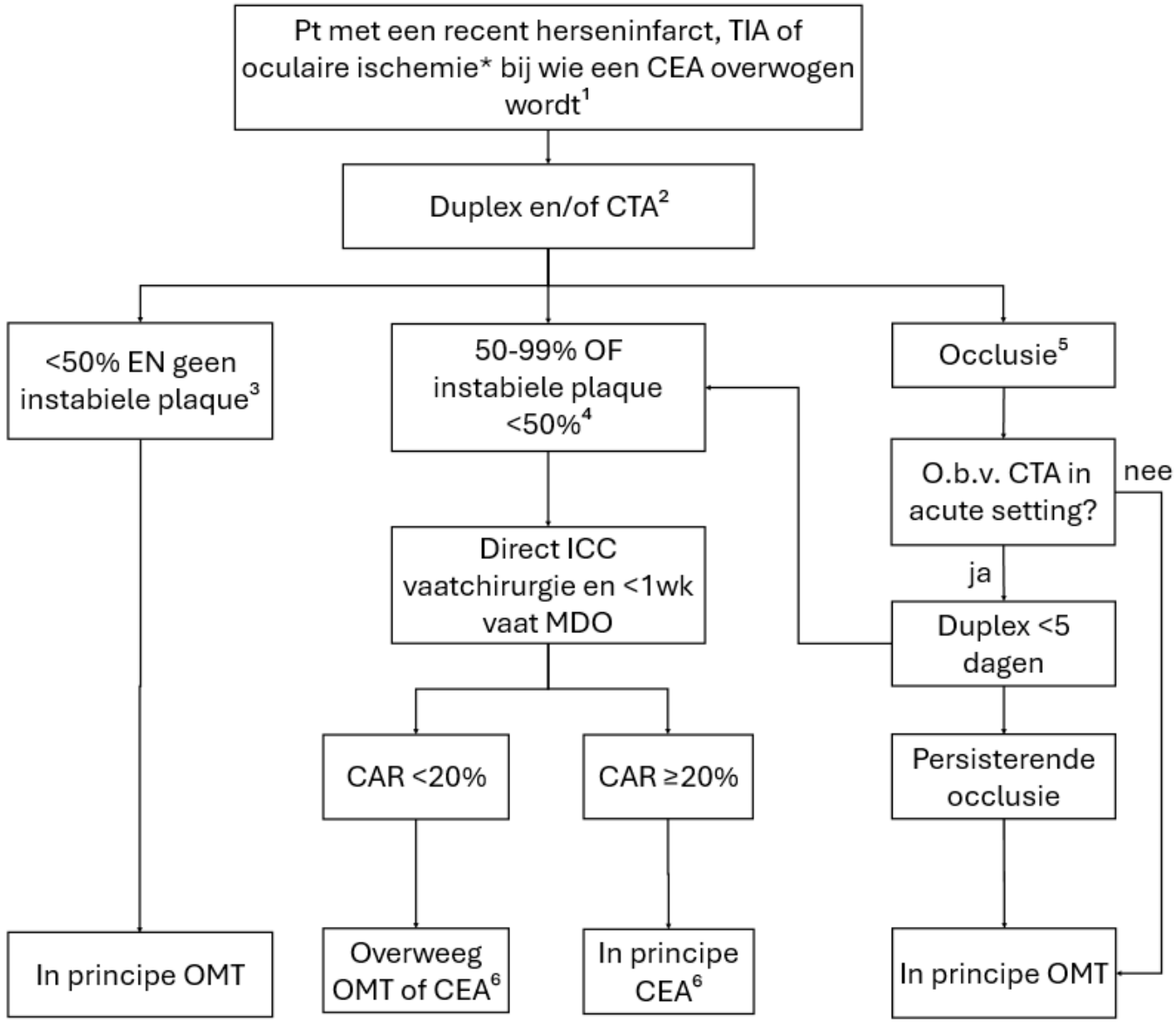


THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Clinical impact..

And future directions ?

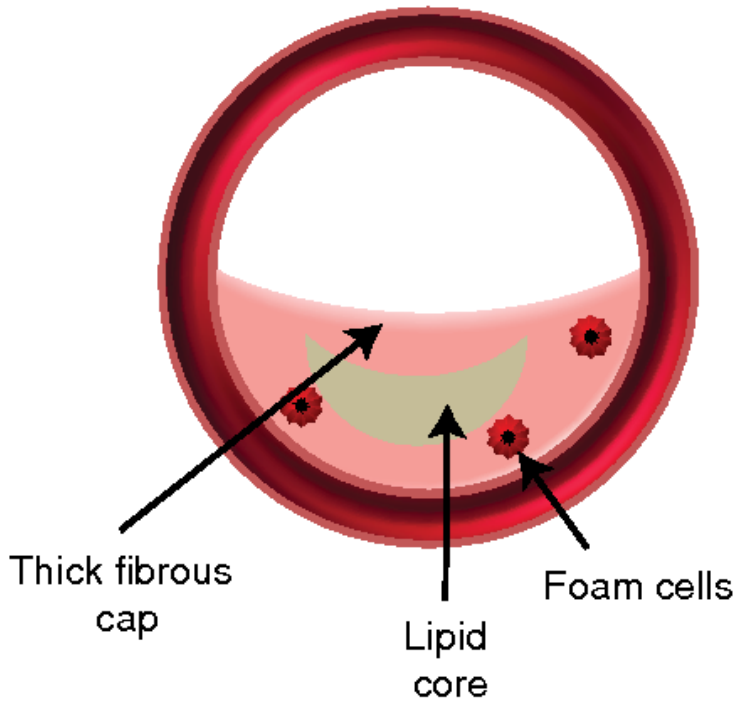
THE 2nd EUROPEAN
ECST-2
CAROTID SURGERY TRIAL


Pt met een recent herseninfarct, TIA of oculaire ischemie* bij wie een CEA overwogen wordt[1]
Duplex en/of CTA[2]
<50% EN geen instabiele plaque[3]
50-99% OF instabiele plaque <50%[4]
Occlusie[5]
O.b.v. CTA in acute setting?
nee
ja
Direct ICC vaatchirurgie en <1wk vaat MDO
Duplex <5 dagen
CAR <20%
CAR ≥20%
Persisterende occlusie
In principe OMT
Overweeg OMT of CEA[6]
In principe CEA[6]
In principe OMT

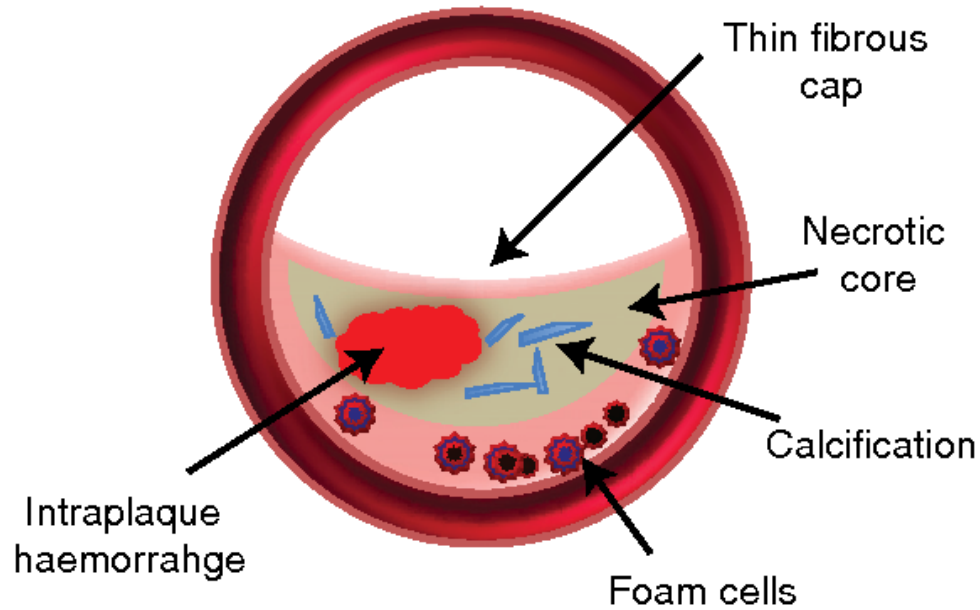
Toekomst

- Kosteneffectiviteitsanalyse
- Langetermijn follow-up (5 jaar)
- MRI plaque imaging sub-studie
  - Zeer sterke voorspeller voor recidief stroke
  - In ECST-2: relatie met behandelingseffect volgt
- Ontwerpen van nieuwe predictie regel inclusief MRI plaque imaging
  - Nieuwe RCT!

Stable plaque

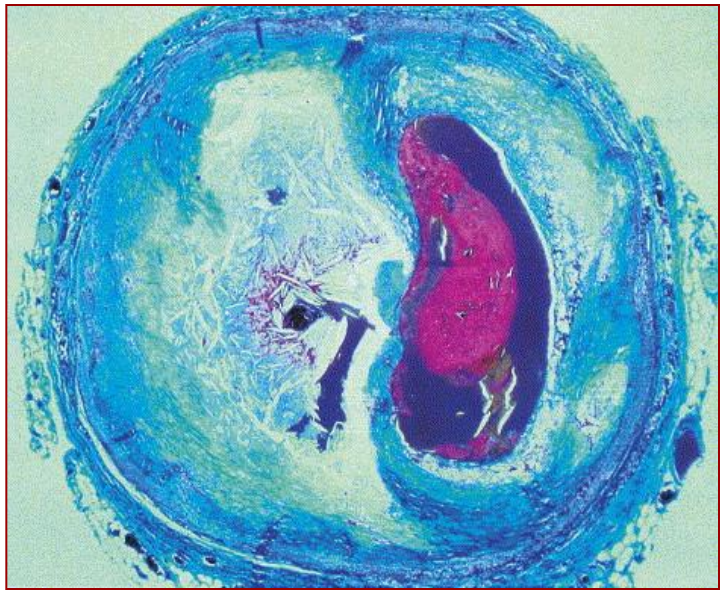


Vulnerable plaque



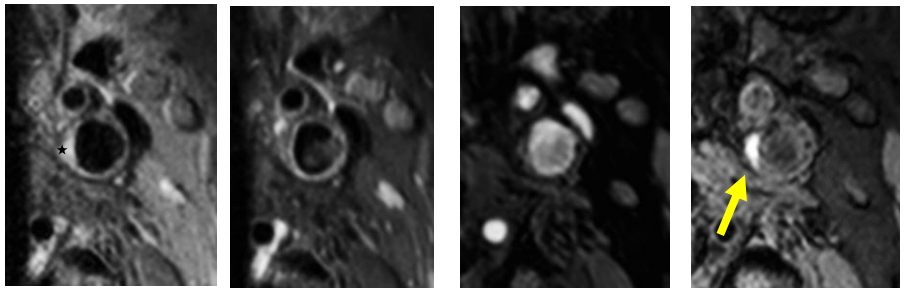
Vulnerable plaque

- ‘Stable plaques may narrow the arterial lumen and cause stable angina pectoris but are, otherwise, relatively harmless.’
- ‘Vulnerable plaques may rupture and thrombose, which is a potentially life-threatening event’



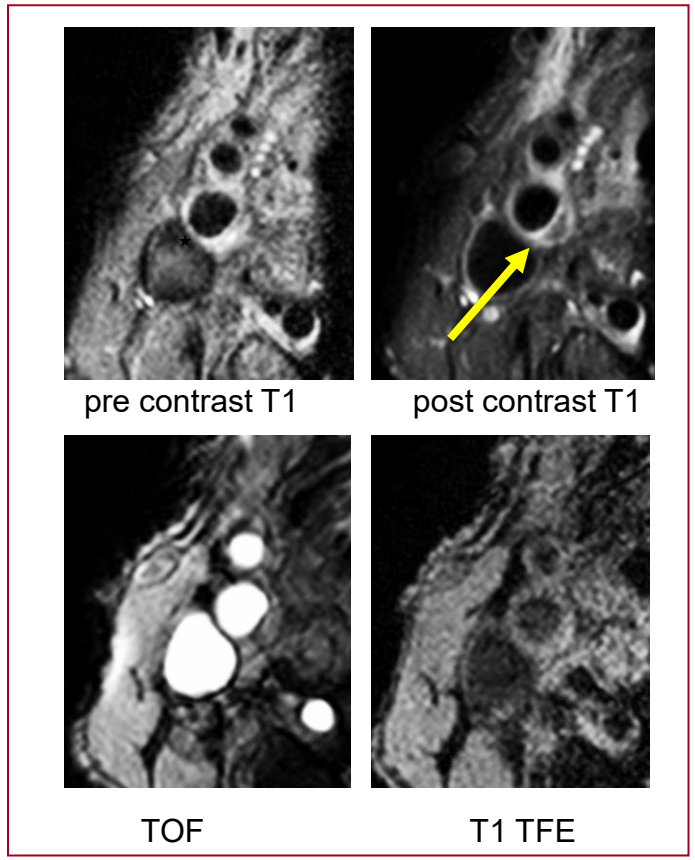
Falk et al, Circulation 1995

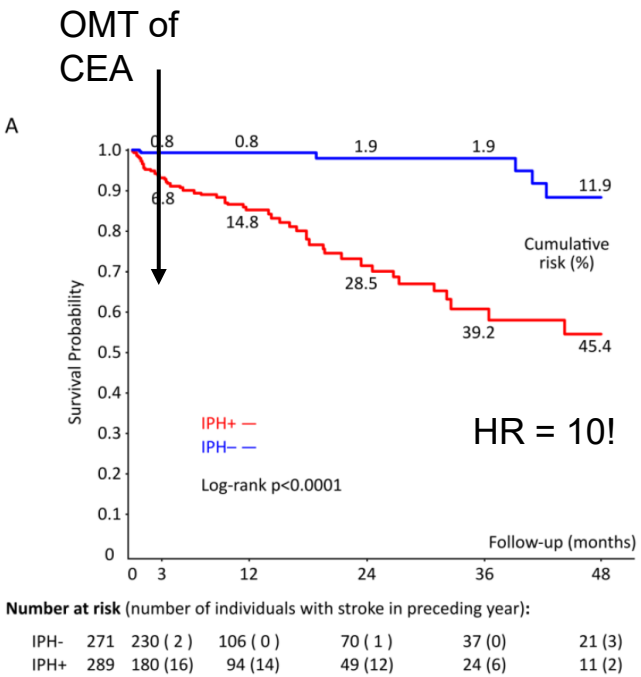
Intra-plaque haemorrhage

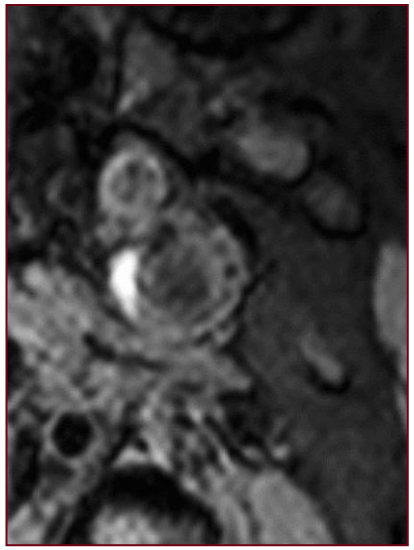


pre contrast T1 post contrast T1 TOF T1 TFE

Lipid rich necrotic core







Symptomatische patiënten, 30-79% stenose

PARISK, JACC 2021

Toekomst

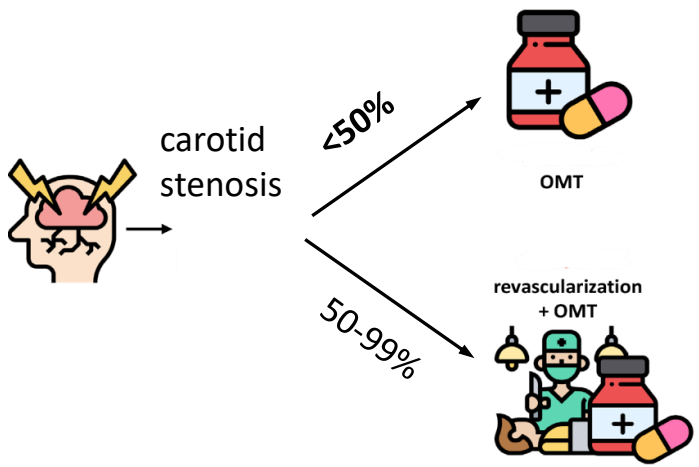
- Selectie van individuele hoog risico-patiënten op basis van een nieuwe voorspellingsregel, inclusief MRI-plaquebeeldvorming, die nog steeds zullen profiteren van CEA

- Nieuwe RCT?

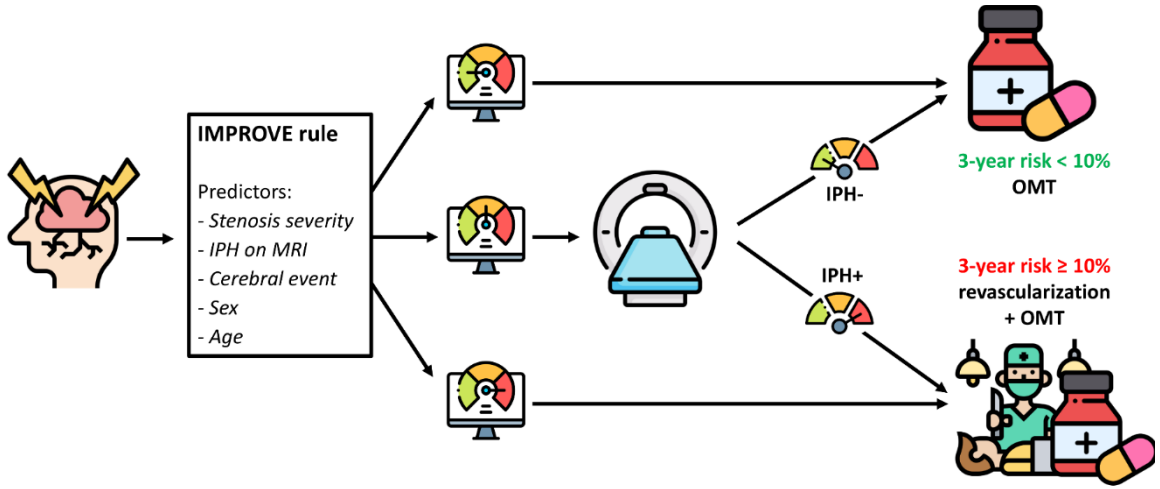
- IMPROVE

IMPROVE trial

CAU



IMPROVE decision rule



Acute fase





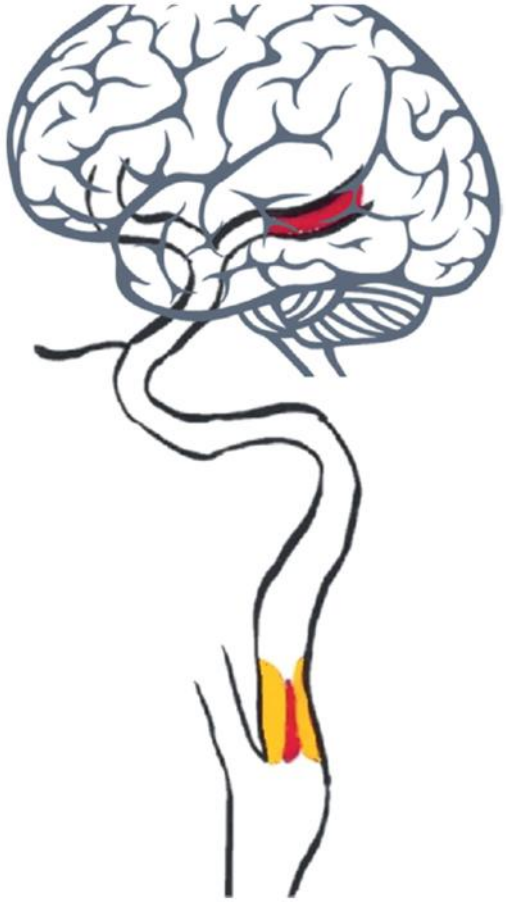


Figure 1. Diagram of tandem lesion with a large vessel occlusion and an ipsilateral carotid artery stenosis of atherosclerotic origin.

Van Elk et al, EJVES 2024

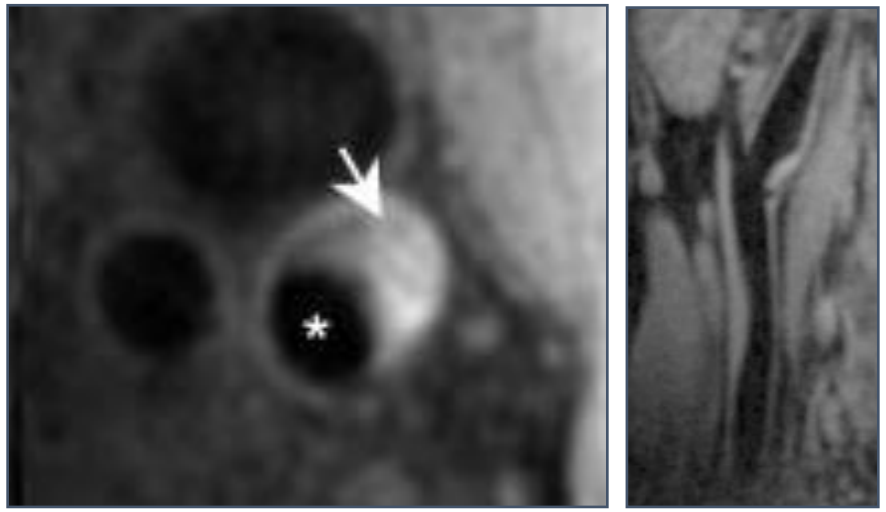


Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke (CASES) versus deferred treatment of carotid artery stenosis

Minder opereren, meer individualiseren

- Samenwerking!
- Richtlijnen
- Nieuwe studie

Dank u wel!



CVA/NAH Symposium 2025

Paul Nederkoorn, neuroloog, klinisch epidemioloog
p.j.nederkoorn@amsterdamumc.nl

Amsterdam UMC
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