DWMRI Lesions, Cranial Nerve Injury & Neuropsychometric Testing: Is It Time To Incorporate These Outcomes In Carotid Trials As Primary Endpoints?

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In Partnership with the ACC
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CARDIOVASCULAR RESEARCH FOUNDATION

Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization listed below.

Affiliation/Financial Relationship	Company
• Major Stock Shareholder/Equity	• Silk Road Medical

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Lecture Plan:

- Review choice of endpoints
- Compare relative incidence DWMRI lesions for various carotid interventional strategies
- Assess impact of baseline DWMRI lesions on stroke, dementia & mortality
- Analyze impact of baseline DWMRI lesions on subsequent intervention
- Report clinical relevance of neuropsychometry after carotid intervention
- Present incidence & impact of CNI after carotid interventions

Important Characteristics Of Study Primary Endpoints:

- **Well defined & reliable**
  - **Reliable evidence about whether the intervention provides clinically meaningful benefit (or harm)**
- **Sensitive to the effects of the intervention**
- **Readily measureable**
  - **Onerous testing leads to missing data points & substantial bias**

Fleming TR et al. Stat Med 2012;31:2973-2894

Important Characteristics Of Study Primary Endpoints; Surrogates:

- **Used as a substitute for a clinically meaningful endpoint**
  - **Changes induced by the intervention on a surrogate are expected to reflect changes in a clinically meaningful endpoint**
  - **"A correlate does not a surrogate make"**
- **Clinically meaningful:**
  - **A clinical event relevant to the patient**
  - **A direct measure of how the patient feels, functions or survives**

Important Characteristics Of Study Primary Endpoints; Composites:

- **Interpretable**
  - Composite endpoints impact negatively on interpretability
  - Dependent on whether each component part of the composite has similar clinical relevance

Relative Incidence DWMRI Lesions: CEA, Unprotected CAS & Filter - Protected Transfemoral CAS

ICSS Primary Analysis CEA Vs. CAS in 1713 symptomatic patients

ICSS Substudy: N = 231

New white lesions on DWI

62 of 124 (50%) transfemoral distal filter CAS

18 of 107 (17%) CEA

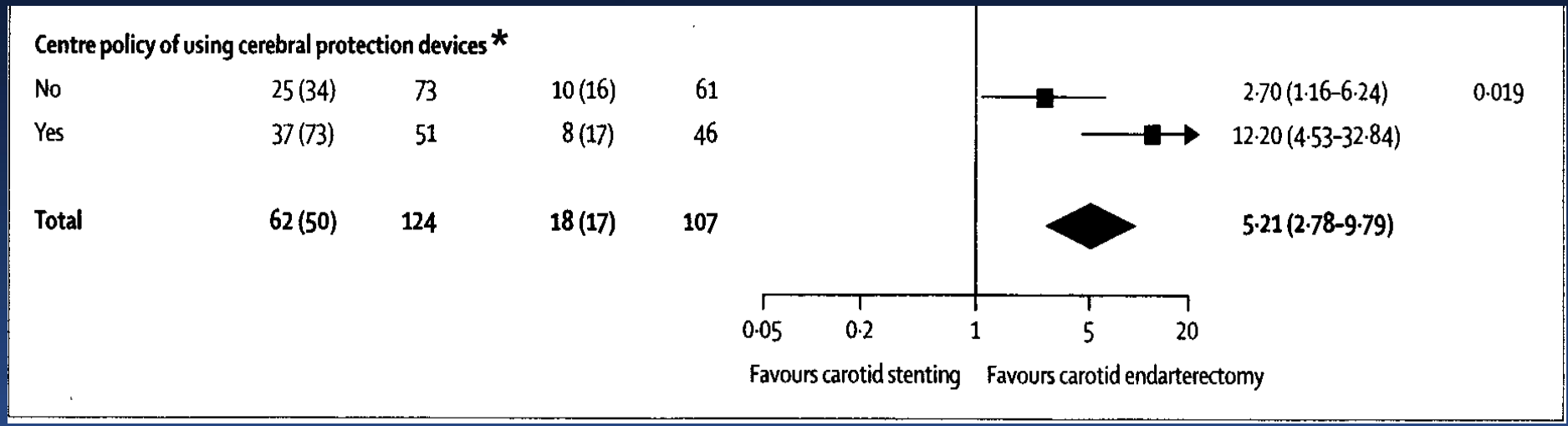
(OR 5.21, 2.78-9.79; p < 0.0001)

Lancet Neurol. 2010 Apr;9(4):353-62

ICSS Substudy: N = 231

2/7 centres performed unprotected CAS

5/7 centres performed filter-protected CAS



**Transfemoral Distal - Filter Type EPD*

ICSS Substudy: N = 231

Lesion Volumes:

Individual lesion volume significantly smaller

for CAS vs. CEA ($p < 0.001$)

Total lesion volume: Not significantly different ($p = 0.18$)

Hensicke G et al Stroke 2013;44: 80 -86

ICSS Substudy: N = 231

Recurrent stroke OR TIA (5 year cumulative)

CAS:

DWMRI +ve: 12/62

DWMRI -ve: 6/62

22.8% vs. 8.8% (p=0.04)
HR 2.85 (1.05-7.720)

" But the risk of stroke alone was not significantly increased "

Bonati L et al. European Stroke Congress May 2013

ICSS Substudy: N = 231

Recurrent stroke OR TIA (5 year cumulative)

CEA

DWI +VE

DWI – VE

} **“ No difference ”**

Influence of EPD Strategy On DWMRI Findings

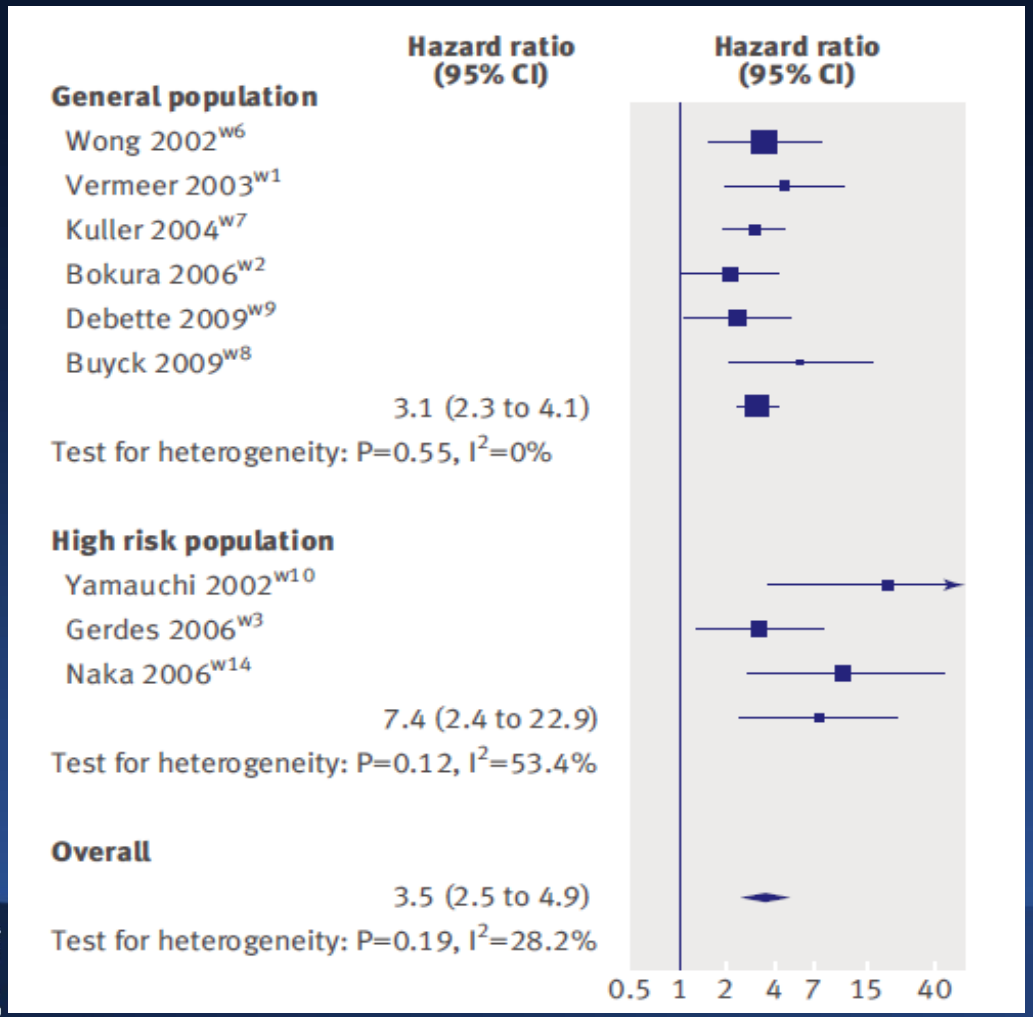
Study	Procedure	Embolic Protection	# subjects	% w/ New DWI Lesions
ICSS[1]	Transfemoral CAS	Distal filter (various)	51	73
ICSS[1]	CEA	Clamp, backbleed	107	17
PROFI[2]	Transfemoral CAS	Distal filter (Embosheild)	31	87
Leal[4]	Transfemoral	Distal Filter (FilterWire)	33	33
PROFI[2]	Transfemoral CAS	Proximal occlusion (MoMA)	31	45
PROOF[3]	Transcarotid CAS	High flow rate flow reversal	48	16.7
Leal[4]	Transcarotid CAS	Flow Reversal	31	12.9

1 Lancet Neurol. 2010 Apr;9(4):353-62
2. J Am Coll Cardiol. 2012;59:1383-1389
3. JVS 2011;54:1317-1323
4. JVS 2012 ;56:1585-1590

Baseline White Matter Changes Predict Stroke, Dementia & Mortality (Supporting Their Use as An Intermediate Marker In A Research Setting):

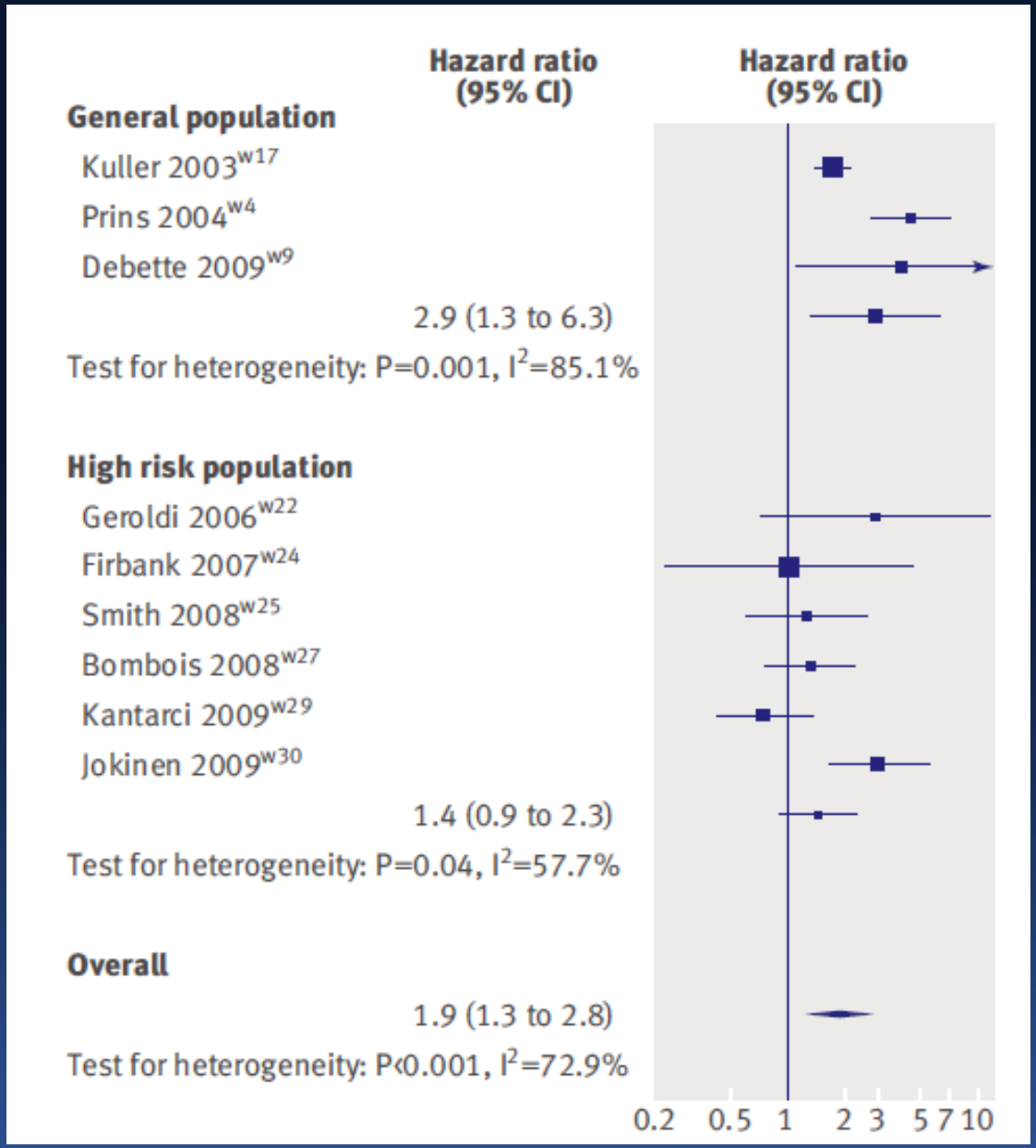
The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis

46 longitudinal studies; general population & hospital based

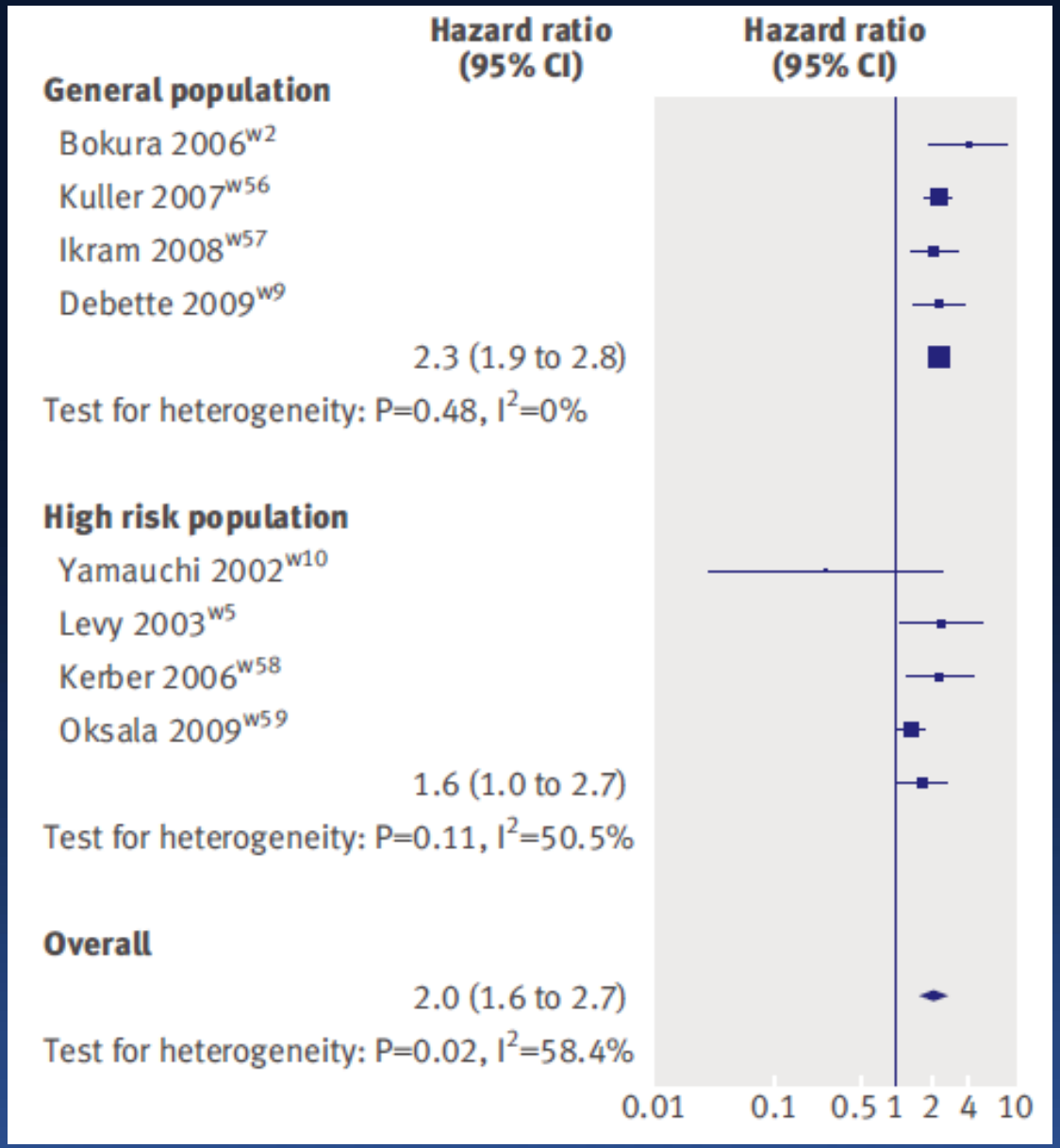


Association WM lesions & incident stroke

Debette S, Markus H. BMJ 2010; 341:c3666



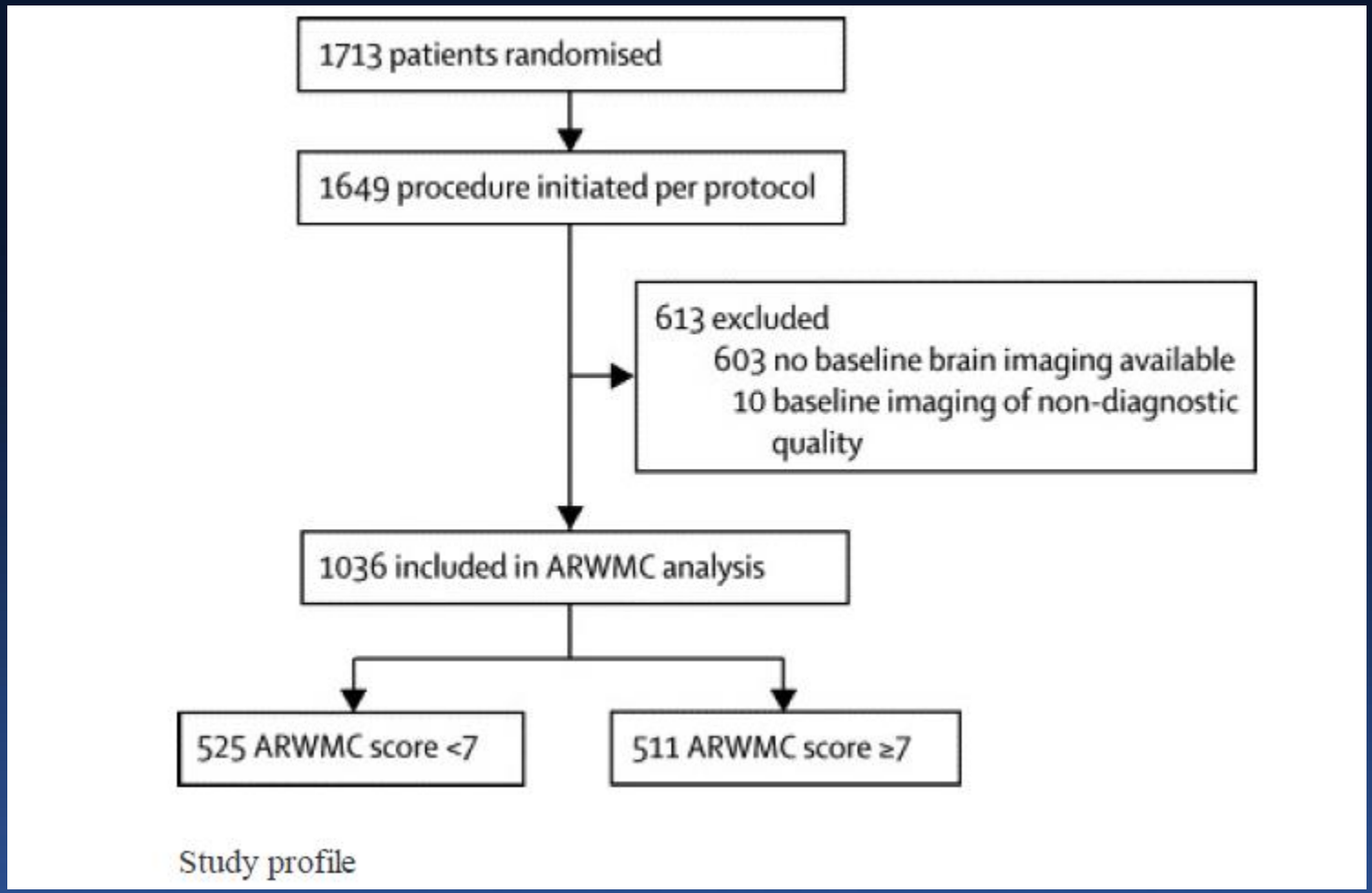
Association WM lesions & incident dementia



Association WM lesions & mortality

The Impact of Baseline White Matter Changes on Subsequent Intervention:

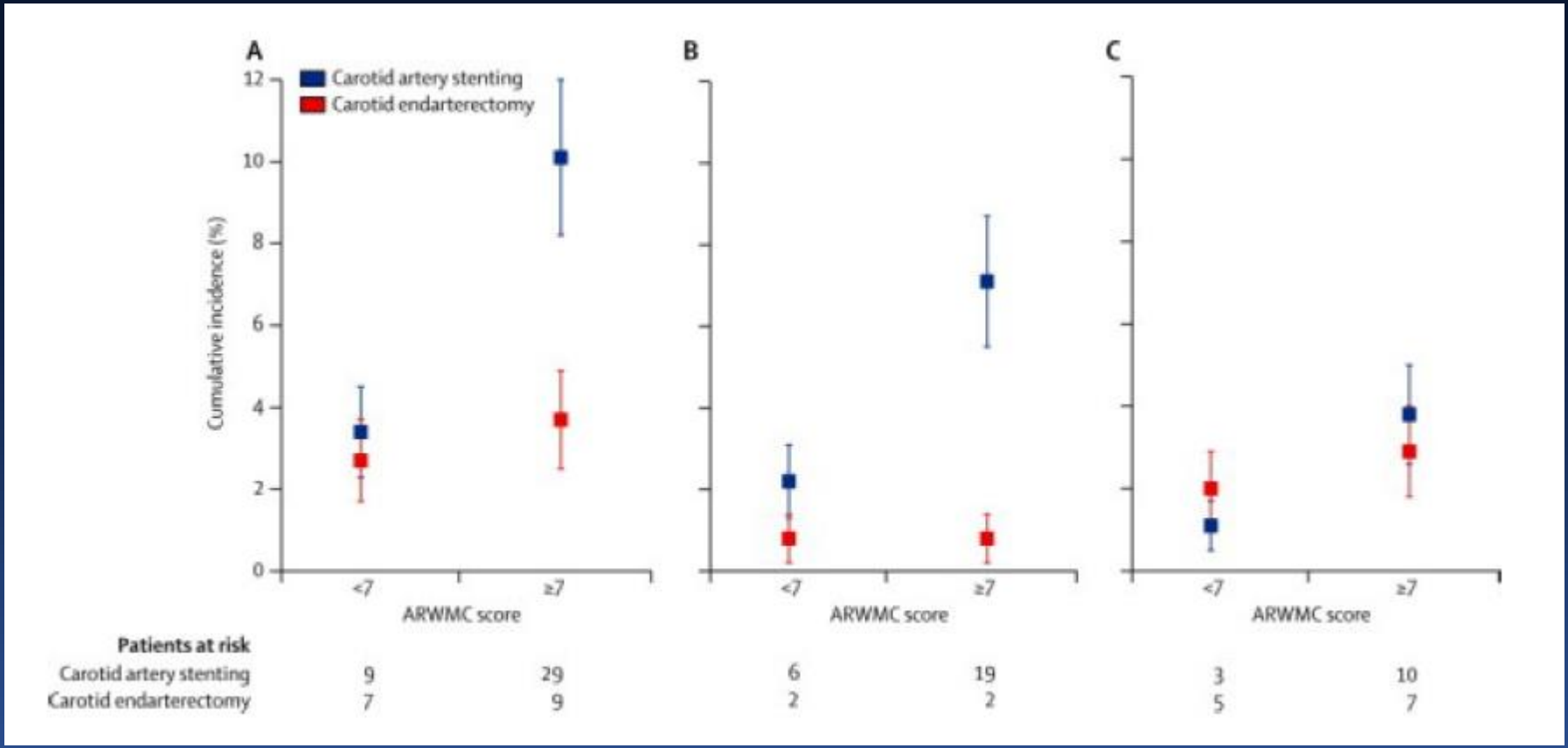
ICSS: Baseline Age-Related White Matter Changes



Study profile

Ederle J et al. Lancet Neurology 2013;12:866-872

ICSS: 30-day cumulative incidence of stroke by severity of white matter lesions



All stroke | Non-disabling | Fatal/disabling

Post Cardiac Surgery:

- Severe baseline white matter lesions (MRI) associated with a 3.9increase in the odds of delirium [95% CIs 1.2-12.3]
- Delirium associated with:
  - Increased long term mortality
  - Increased risk of stroke
  - Poor functional status
  - Increased hospital admissions
  - Substantial cognitive decline for one year post surgery

Brown CH. Current Opin Anesthesiology 2014;27:117-122

Clinical Relevance Of Neuropsychometric Testing After *Carotid Intervention*:

The Role of Carotid Artery Stenting and Carotid Endarterectomy in Cognitive Performance : A Systematic Review

N = 32 studies (25 CEA, 4 CAS)

“ No consistent findings…”

“ Assessment of cognition after carotid revascularisation is probably influenced by many confounding factors such as learning effect, type of test, type of patients, & control group ”

De Rango P et al. Stroke 2008;39:3116 - 3127

Cognition after carotid endarterectomy or stenting

A randomized comparison

An ICSS Sub-Study:

N = 177 patients recruited in two Dutch centres

N = 140 Cognitive Function Assessment at baseline

N = 120 Cognitive Function Assessment at 6/12

10 Domains including executive function

Altinbas A et al Neurology 2011;77:1084 - 1090

DWMRI & Cognitive Function:

New white lesions:

17 in 34 CAS (50%)

7 in 30 CEA (23%)

} RR 2.1; 95% CI 1.0 – 4.4, p = 0.041

Cognitive Function:

No significant difference

Incidence & Impact of Cranial Nerve Injury After Carotid Interventions:

Carotid Stenting Trialists' Collaboration:

	CAS (n=1679)	CEA (n=1645)	Risk ratio* (95% CI)	p value†	Risk difference* (95% CI)
Any stroke or death	130 (7·7%)	73 (4·4%)	1·74 (1·32 to 2·30)	0·0001	3·4 (1·8 to 5·0)
Disabling stroke or death	65 (3·9%)	43 (2·6%)	1·48 (1·01 to 2·15)	0·04	1·2 (0 to 2·4)
All-cause death	19 (1·1%)	10 (0·6%)	1·86 (0·87 to 4·00)	0·10	0·6 (–0·1 to 1·2)
Any stroke	125 (7·4%)	70 (4·3%)	1·74 (1·31 to 2·32)	0·0001	3·3 (1·7 to 4·9)
Stroke severity‡					
Fatal	12 (0·7%)	6 (0·4%)	1·97 (0·74 to 5·23)	0·16	0·4 (–0·1 to 0·8)
Disabling	47 (2·8%)	34 (2·1%)	1·35 (0·87 to 2·08)	0·18	0·6 (–0·4 to 1·6)
Non-disabling	66 (3·9%)	31 (1·9%)	2·09 (1·37 to 3·19)	0·0004	2·0 (0·8 to 3·2)
Stroke type§					
Ischaemic	118 (7·0%)	57 (3·5%)	2·02 (1·48 to 2·75)	<0·0001	3·7 (2·2 to 5·2)
Haemorrhagic	7 (0·4%)	12 (0·7%)	0·57 (0·23 to 1·45)	0·23	–0·3 (–0·8 to 0·1)
Unknown	0	1 (0·1%)	..	..	..
Stroke region§					
Ipsilateral carotid	113 (6·7%)	66 (4·0%)	1·67 (1·24 to 2·25)	0·0005	2·8 (1·3 to 4·3)
Contralateral carotid or vertebrobasilar	10 (0·6%)	4 (0·2%)	2·45 (0·77 to 7·81)	0·11	0·4 (–0·1 to 0·8)
Unknown	2 (0·1%)	0	..	..	..
Myocardial infarction	4 (0·2%)	7 (0·4%)	..	..	..
Non-fatal	1 (0·1%)	7 (0·4%)	..	..	..
Fatal	3 (0·2%)	0	..	..	..
Cranial nerve palsy¶	7 (0·4%)	99 (6·0%)	0·07 (0·03 to 0·15)	<0·0001	–5·6 (–6·7 to –4·4)
Severe haematoma‖	12 (0·7%)	32 (1·9%)	0·37 (0·19 to 0·71)	0·0016	..
Severe wound infection**	1 (0·1%)	4 (0·2%)	..	..	..

30-day outcomes (per protocol evaluation)

CREST

Patients with study procedure attempted/received	CAS N = 1,131	CEA N = 1,176	p-value
Procedure Related Cranial Nerve Injury	0.0%	5.3% (62/1176)	< 0.0001
* Unresolved at One Month	0.0%	3.6% (42/1176)	< 0.0001
* Unresolved at Six Months	0.0%	2.1% (25/1176)	< 0.0001

*80% motor – hypoglossal overrepresented

CREST: QoL

At One Month:

CAS patients had better outcomes:

- Physical function, pain, physical function component summary ($p < 0.01$)
- Less difficulty driving, eating, swallowing, neck pain & headache but more difficulty walking & leg pain ($p < 0.05$)

Health-Related Quality of Life After Carotid Stenting Versus Carotid Endarterectomy

Results From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial)

	Cranial Nerve Palsy	
SF-36 Subscale	Mean Difference* (95% CI)	p Value
Physical function	1.5 (−4.7 to 7.6)	0.643
Role–physical	3.9 (−6.7 to 14.6)	0.471
Vitality	4.6 (−0.5 to 9.7)	0.075
Pain index	−1.3 (−7.5 to 5.0)	0.692
General health	1.9 (−2.7 to 6.5)	0.429
Social function	3.2 (−3.0 to 9.4)	0.307
Role–emotional	0.8 (−9.1 to 10.6)	0.881
Mental health	3.0 (−1.1 to 7.1)	0.157
Physical component summary	0.1 (−2.4 to 2.6)	0.939
Mental component summary	1.4 (−1.0 to 3.7)	0.263

EDITORIAL

Just When We Thought We Knew All the Answers, Someone Changed the Questions!

(iii) are the majority of cranial nerve injuries after CEA 'benign' and short lived, and what proportion should be considered the equivalent of having suffered a stroke?

Naylor AR EJVES 2011;41:150-152

Lasting Impact of CNI:

Unclear;

- Effects variable - range from complete facial palsy or inability to swallow (feeding tube) to mild paraesthesia of the face (shaving) or tongue
- SF36 may be insensitive to degree of disability & HRQoL impairment

Conclusions:

- **Well defined & reliable** DWMRI CNI ~~NP~~
  - **Reliable evidence about whether the intervention provides clinically meaningful benefit (or harm)**
- **Sensitive to the effects of the intervention** DWMRI CNI ~~NP~~
- **Readily measureable** DWMRI ~~CNI*~~ ~~NP~~
  - **Onerous testing leads to missing data points & substantial bias**

***Longer term impact on QoL**

Conclusions:

- **Used as a substitute for a clinically meaningful endpoint** DWMRI CNI (procedural) NP
  - A clinical event relevant to the patient
  - A direct measure of how the patient feels, functions or survives

Conclusions:

- Rationale to include **DWMRI** as a surrogate marker OR co-primary endpoint in carotid trials, supported by traditional clinical outcomes
- Specific QoL tools required to fully assess the lasting impact of **CNI** & before CNI can be suggested as a co-primary endpoint but ought to be a secondary endpoint
- **NP** testing results in inconsistent findings in the world literature post carotid intervention & is onerous, requiring significant effort on the part of patient & researcher alike & should only be utilized as a surrogate alongside DWMRI endpoints *

***Dependent on absolute incidence of microembolic burden**

Scope of The Problem:

Table 1 Estimated Annual U.S. Patients With New Brain Lesions

Procedures	No. of Annual U.S. Patients	Incidence of New Brain Lesions, %	No. of Annual U.S. Patients With New Brain Lesions
Coronary angiography	1,072,000	11–17	118,000–182,000
Percutaneous coronary intervention	596,000	11–17	66,000–101,000
Coronary artery bypass graft	242,000	16–51	39,000–123,000
Surgical aortic valve replacement	90,000	38–47	34,000–42,000
Atrial fibrillation ablation	72,000	8–18	6,000–13,000
Transaortic valve implantation	10,000	68–91	7,000–9,000
Carotid endarterectomy	93,000	4–34	4,000–32,000
Carotid artery stenting	70,000	15–67	11,000–47,000
Cerebral angiography	300,000	11–20	33,000–60,000
Endovascular aneurysm	30,000	10–64	3,000–19,000
Total	2,600,000	13–24	321,000–628,000

Gress D. JACColl 2012;60:1614-1616