


Intracranial Atherosclerosis: Mechanisms and Therapeutic Implications



BROWN


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Disclosures



- Medtronic (non-compensated)
- Steering committee member of DCC-Neuro COVID and Neuro-AF Study



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ICAD Journey

How it started? How it's going?

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- Use of acute vessel imaging in the ED to risk stratify ischemic stroke patients, particularly TIA and minor stroke




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Research

Original Investigation

Imaging Parameters and Recurrent Cerebrovascular Events in Patients With Minor Stroke or Transient Ischemic Attack

Shadi Yaghi, MD; Sara K. Rostanski, MD; Amelia K. Boehme, PhD; Sheryl Martin-Schild, MD; Alyana Samal, MPH; Brian Silver, MD; Christina A. Blum, MD; Mahesh V. Jayaraman, MD; Matthew S. Silet, MD; Muhib Khan, MD; Karen L. Furie, MD, MPH; Mitchell S. V. Elkind, MD, MS; Randolph S. Marshall, MD, MS; Joshua Z. Wiley, MD, MS

The Challenges of Stroke Prediction Scores

Deena M. Nasr, DO; Robert D. Brown Jr, MD, MPH

Transient ischemic attack (TIA) and stroke prediction scores have been a topic of both clinical and research interest for decades. The goal of these scores is to identify high-risk patients for both prognostic and clinical management purposes. There are several TIA and stroke prediction scores that aim to prognosticate re-

cluded both those with a TIA and those with a minor ischemic stroke. Neuroimaging findings, including presence of a cerebral infarction, could not be assessed in the multivariate model because only 1 patient with negative neuroimaging had an RCVE. Recurrent CVEs included recurrent strokes or TIAs and neurological deterioration. The latter was defined as any worsening of presenting neurological deficits or recurrence of

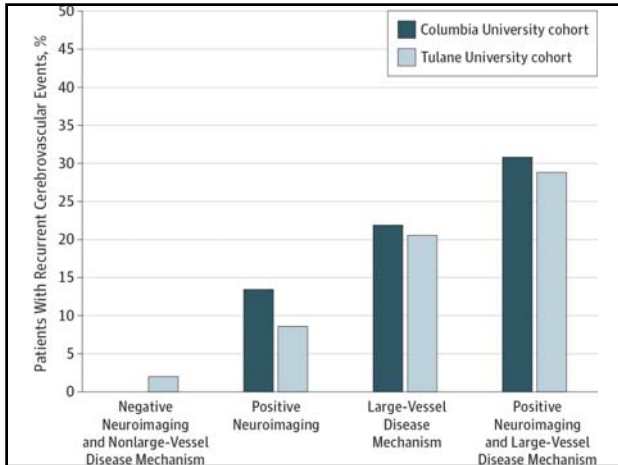
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Study Population and Design

- Hospitalized patients with suspected ischemic stroke (NIHSS 0-3) and TIA
- Two cohorts:
 - Derivation: Columbia University Medical Center
 - Validation: Tulane University Medical Center
- Aim to identify predictors of in-hospital deterioration in patients with minor stroke or TIA
- Hypotheses: large artery disease subtype is predictive, and ABCD2 score has limited value

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Take home messages

- 1- Brain imaging → improves diagnostic accuracy of minor stroke/TIA
- 2- Ischemic stroke and 50-99% carotid stenosis → urgent revascularization
- 3- Ischemic stroke in intracranial atherosclerosis has a high risk of early recurrence despite medical therapy

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Inspired by Dr. Furie...



AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

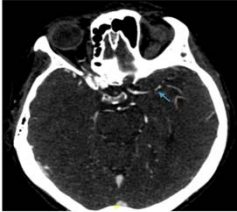
The American Association of Neurological Surgeons and Congress of Neurological Surgeons have reviewed this document and affirm its educational content.

Karen L. Furie, MD, MPH, FAHA, Chair; Scott E. Kasner, MD, MSCE, FAHA, Vice Chair; Robert J. Adams, MD, MS, FAHA; Gregory W. Albers, MD, Ross L. Bush, MD, MPH; Susan C. Fagan, PhD, FAHA; Anubhav L. Halperin, MD, FAHA; S. Catherine Johnson, MD, PhD; Bruce L. Klapper, MD, MS, FAHA; Walter N. Kerns, MD; Pamela H. Mitchell, PhD, CNRN, RN, FAAN, FAHA; Bruce Ovbiagele, MD, MS, FAHA; Yuh-Y. Palesch, PhD, RPh, F, SCSoc, MD, MS, FAHA, FAHA; Lee H. Schwamm, MD, FAHA; Sylvia W. Kasebuhl-Sandier, MD, PhD, FAHA; Tonya N. Tarran, MD, FAHA; Dorian Woodcock, MD, PhD, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

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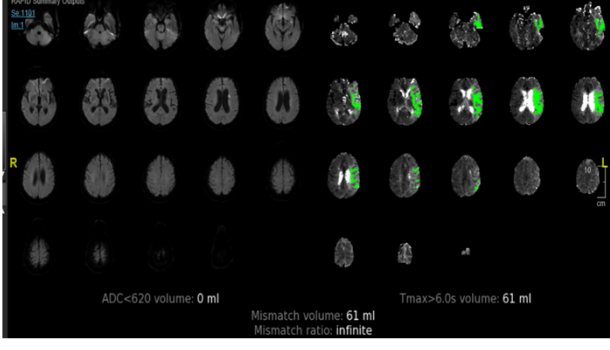
Case

- 75 YO woman with a history of HTN admitted for mild dysarthria
- Exam shows mild dysarthria and a right facial droop



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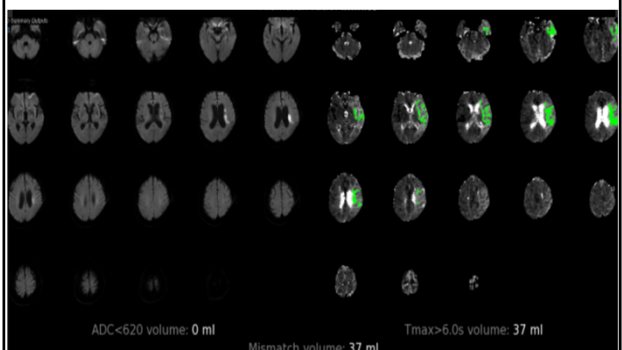
She was treated with DAPT and statin and Perfusion imaging showed:



ADC<620 volume: 0 ml
Mismatch volume: 61 ml
Mismatch ratio: infinite
Tmax>6.0s volume: 61 ml

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Neurological deterioration...



ADC<620 volume: 0 ml
Mismatch volume: 37 ml
Tmax>6.0s volume: 37 ml

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Follow up

- She was treated with intravenous phenylephrine and transitioned to oral midodrine and florinef, her exam stabilized.
- On 90-day follow-up: she had right sided weakness and vascular cognitive impairment and her mRS was 4.

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Intracranial Atherosclerosis

- Intracranial atherosclerosis accounts for nearly 10% of ischemic strokes in the United States and up to 50% of strokes in Asia (Wong et al, IJS 2006)
- Symptomatic large vessel atherosclerotic disease is a strong predictor of early recurrence (Yaghi et al, JAMA Neurology 2015)
- The SAMMPRIS study showed that the risk of recurrent events in patients with ICAS is nearly 12% at 1 year and 20% at 2 years from the initial event (Derdeyn et al, Lancet Neurology 2015)

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SECONDARY PREVENTION STRATEGIES



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Anticoagulation vs. antiplatelet

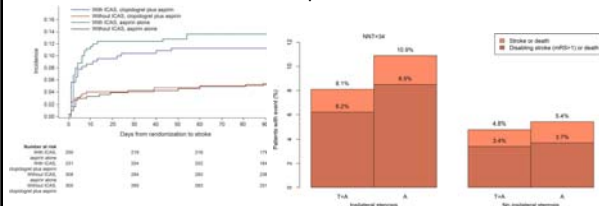
- WASID trial: warfarin vs. aspirin in patients with symptomatic ICAD: no difference between the two arms (HR 1.04 95% CI 0.73-1.48) (Chimmowitz et al, NEJM)
- NAVIGATE ESUS : Rivaroxaban no better than aspirin in ESUS + substenotic atherosclerosis (Ntaios et al)

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DAPT is more effective in patients with symptomatic stenosis

-CHANCE MRA sub-study:
608 patients ICAS
481 without ICAS

- Post-hoc analysis THALES:
Benefit of DAPT more pronounced in patients with ipsilateral stenosis



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Risk factor control effective...more so in ICAD

- High intensity statin → SPARCL (Ameranco et al, NEJM)
- No statin → predictor of recurrent stroke in SAMMPRIS (Waters et al, JAMA)
- Insulin sensitizers → IRIS trial (Yaghi et al, Circulation)
- BP out of control → predictor of recurrent MACE in SAMMPRIS (Turan et al, Neurology)
- Exercise → most effective strategy in SAMMPRIS (Turan et al, Neurology)

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Stenting

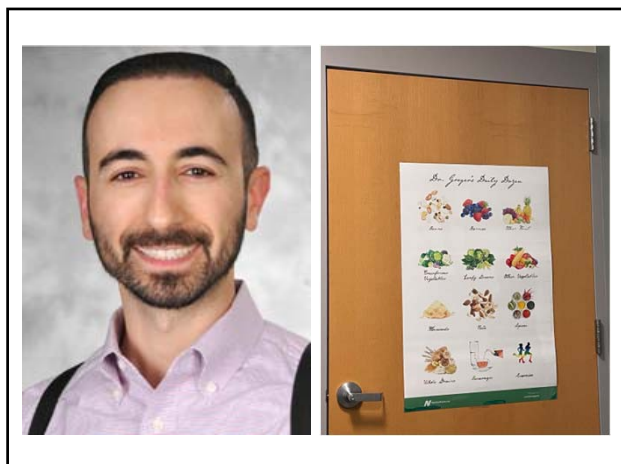
- **SAMMPRIS trial (Chimowitz et al, NEJM)**
- Randomized 451 patients with symptomatic ICAD to wingspan stent vs. medical treatment
- 30-day endpoint was 14.7% in the PTAS group and 5.8% in the medical-management group ($P=0.002$)
- **VISSIT trial (Zaidat et al, JAMA)**
- Randomized 112 patients with symptomatic ICAD to Vitesse stent vs. medical treatment
- 30-day end point occurred in more patients in the stent group 24.1% vs. the medical group 9.4% ($P = .05$)
- **CASSIS trial (Gao et al, JAMA)**
- Randomized 380 patients with symptomatic ICAD to Wingspan vs. medical treatment (excluded perforator infarct)
- 30-day end point occurred in more patients in the stent group 5.1% vs. the medical group 2.2% ($P > 0.1$)

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Standard of care?

- Dual antiplatelet therapy if safe
- High intensity statin therapy
- ? Early permissive hypertension
- Risk factor control

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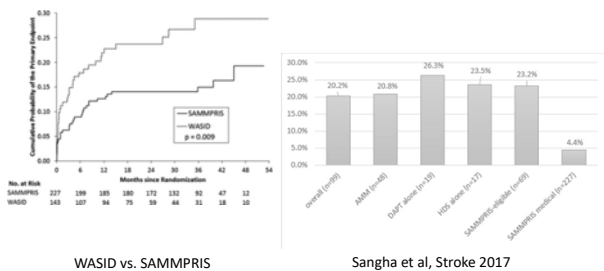
When to consider stenting?

- FDA on label criteria:
- age 22–80 years
- baseline mRS ≤ 3
- 70–99% stenosis
- 2 or more strokes on medical treatment
- time from last stroke to procedure of more than 7 days



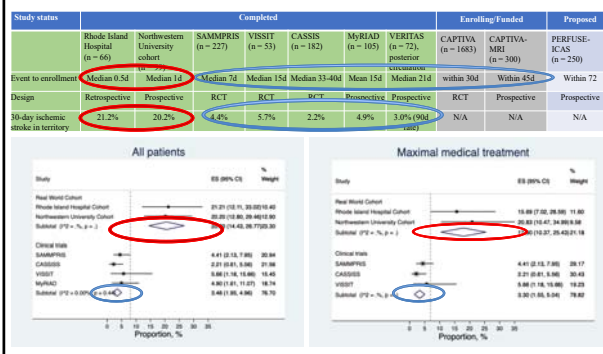
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Does medical treatment work for everyone?



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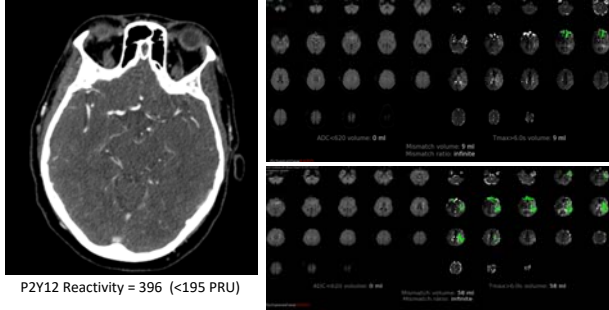
One reason is late enrollment in trials...



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Another reason why patients fail medical treatment?

Sub-optimal medical treatment



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Clopidogrel Resistance

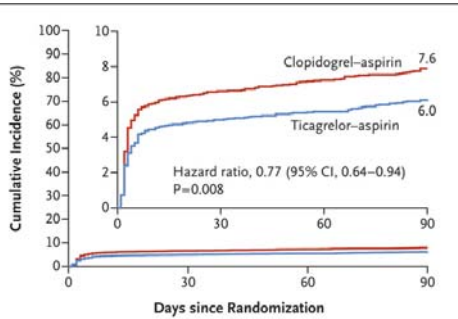
Table 3. Effect of Clopidogrel-Aspirin Compared With Aspirin on Clinical Outcome Stratified by CYP2C19 Loss-of-Function Carrier Status

Outcome	Carriers ^a				Noncarriers ^a				P Value for Interaction
	Total No. (%)	Aspirin (n = 872)	Clopidogrel-Aspirin (n = 854)	Hazard Ratio (95% CI)	Total No. (%)	Aspirin (n = 598)	Clopidogrel-Aspirin (n = 609)	Hazard Ratio (95% CI)	
Stroke	174 (10.1)	94 (10.8)	80 (9.4)	0.93 (0.69-1.26)	115 (9.5)	74 (12.4)	41 (6.7)	0.51 (0.35-0.75)	<.01
Composite event ^b	175 (10.1)	95 (10.9)	80 (9.4)	0.92 (0.68-1.24)	116 (9.6)	75 (12.5)	41 (6.7)	0.50 (0.34-0.74)	<.01
Ischemic stroke	171 (9.9)	93 (10.7)	78 (9.1)	0.85 (0.63-1.15)	113 (9.4)	74 (12.4)	39 (6.4)	0.51 (0.34-0.75)	<.01

Wang et al, JAMA 2016

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CHANCE-2 (6412 patients with loss of function of CYP2C19)



No. at Risk	0	30	60	90
Clopidogrel-aspirin	3207	2994	2973	2486
Ticagrelor-aspirin	3205	3046	3031	2554

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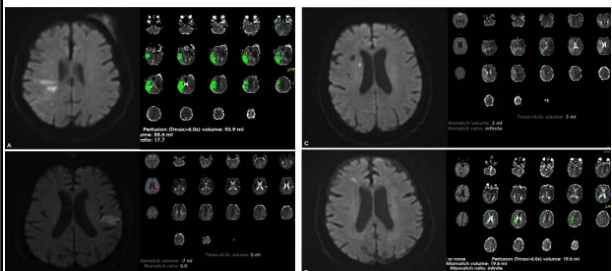
But...some patients have neurological deterioration despite standard medical treatment!!!



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Potential mechanisms

- Artery to Artery embolism
- Perforator disease
- Impaired perfusion



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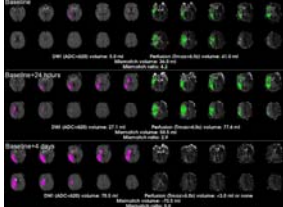
Hypothesis

- Patients with ICAD and impaired distal perfusion → likely to fail optimal medical treatment and may create a subgroup where reperfusion can be tested
- Patients with ICAD and preserved distal perfusion → endovascular treatment is not beneficial and leads to unnecessary adverse events

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Perfusion Imaging in Acute Stroke

- In acute LVO → perfusion mismatch predicts neurological deterioration in patients treated medically (Lansberg et al, Lancet Neurology)
- Reperfusion improves outcomes (DEFUSE-3 and DAWN trials)

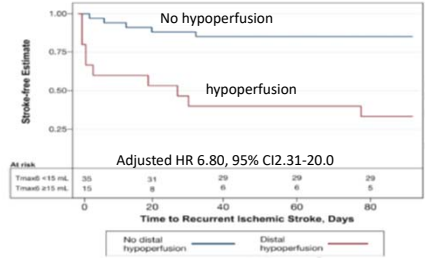


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Hypoperfusion Distal to Anterior Circulation Intracranial Atherosclerosis is Associated with Recurrent Stroke

Adam de Havenon, Pooja Khatri, Shyam Prabhakaran, Sharon D Yeatts, Cecilia Peterson, Daniel Sacchetti, Matthew Alexander, Shawna Cutting, Brian Mac Grory, Karen Furie, David S Liebeskind, Shadi Yaghi

From the Department of Neurology, University of Utah, Salt Lake City, UT (AD, CP, MA); Department of Neurology, University of Cincinnati, Cincinnati, OH (PK); Department of Neurology, University of Chicago, Chicago, IL (SP); Department of Neurology, Medical University of South Carolina, Charleston, SC (SD); Department of Neurology, Brown University, Providence, RI (PF, DS, BMG, SC, DSL); Department of Neurology, University of California Los Angeles, Los Angeles, CA (DSL); and Department of Neurology, New York University, New York, NY (SY).



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Perfusion and 30-day recurrence in SAMMPRIS

- SAMMPRIS post hoc analyses
 - 59 patients with perfusion imaging
 - T_{max} delay on perfusion imaging present in 66% of patients
 - T_{max} delay (vs. no delay) was associated with increased risk of 30-day stroke in the territory of the affected artery (p=0.015)

Liebeskind et al, Stroke 2015

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Perfusion and Recurrence in ICAD RIIH cohort (2019-2022)

- 44 patients with sICAD of M1 and ICA who underwent perfusion imaging, 11 patients with recurrence (25%) within 30 days
- Best medical management = DAPT + high intensity statin
- In univariate analyses, predictors of recurrence were lack of best medical management and hypoperfusion delay
- In Cox regression analyses, HPV > 5 mL at T_{max} > 6 sec and HPV > 13 mL at T_{max} > 4 sec were predictors of recurrence

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Another biomarker → Collaterals

- The collateral circulation is a compensatory mechanism for blood flow impairment across a stenosis:
 - In WASID, good collaterals was associated with lower risk of stroke in territory (Liebeskind et al)
 - In SAMMPRIS, impaired collateral flow was associated with increased recurrence risk (p = 0.016) (Wabnitz et al)
- Limitation of using collaterals: requires angiogram and core lab adjudication

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Borderzone Infarct Pattern

- SAMMPRIS post hoc analysis (101 anterior circ. patients)
 - increased recurrent stroke risk in patients with borderzone vs. non borderzone) infarcts (26.4% vs. 10.4%, p=0.05) (Wabnitz et al)

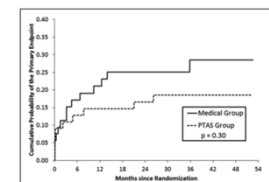
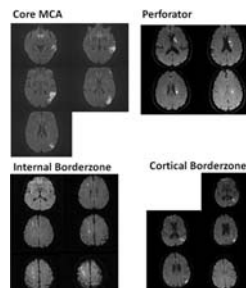
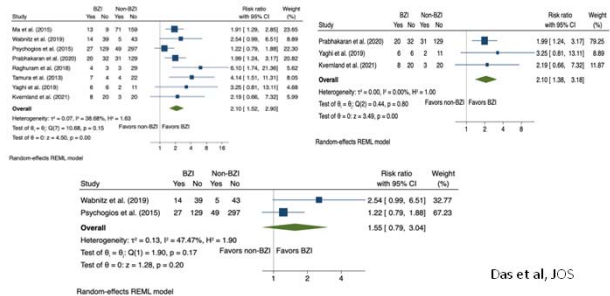


Figure 2. Kaplan-Meier curves showing the probability of a SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) primary end point in the medical and stenting arms in patients whose qualifying event for the trial was an anterior circulation borderzone infarct. PTAS indicates percutaneous transluminal angioplasty and stenting.

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Meta-analysis of studies showing an association between borderzone infarct and recurrence risk



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MyRIAD – Biomarkers

- Enrolled 105 patients with symptomatic 50-99% stenosis within 21 days
- Recurrent rate at 1 year was 8.6% and infarct recurrence 24.7% on 6 to 8 week f/u MRI
- Predictors were of infarct recurrence → younger age and number of DWI lesions
- In anterior circulation ICAS (64 patients), predictors were:
 - >5mL T max > 4 sec delay (33.3% vs. 14.3%, p=0.1)
 - Borderzone infarction (63.6% vs. 25.0%, p = 0.01)

Prabhakaran et al, Stroke 2021

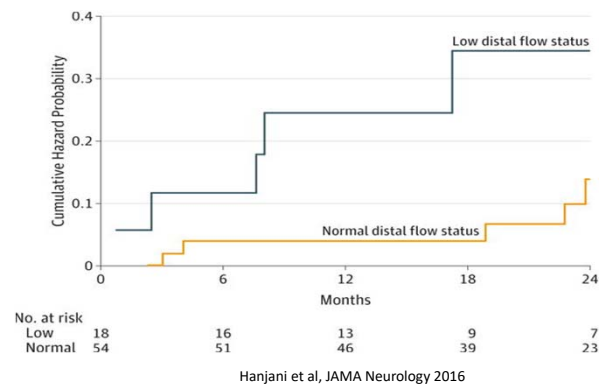
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Take-home messages from MyRIAD

- Low ischemic stroke rate (8.8% at 1 year):
 - median enrollment time of 2 weeks (most recurrent ischemic events occur early)
 - included patients with stenosis <70%, which are known to have lower recurrent stroke rates.
- New infarct on MRI was surprisingly very high (24.7% at 6-8 weeks)
- Only 1/5th had optimal risk factor control

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Blood Flow in Vertebrobasilar Disease (VERITAS)



Hanjani et al, JAMA Neurology 2016

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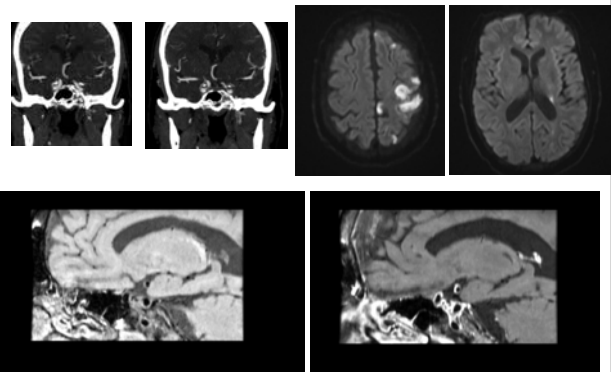
Other biomarkers → Vessel Wall Imaging

- Biomarkers
 - plaque enhancement
 - positive remodeling
 - T1 hyperintensity
 - surface irregularity
- Shown to be associated with symptomatic ICAS
- Studies investigating risk of recurrence mainly done in Asia with mixed results

Song et al, Stroke 2021

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63 YO with right hand numbness x7 days, then aphasia and right sided weakness; reports worsening headaches



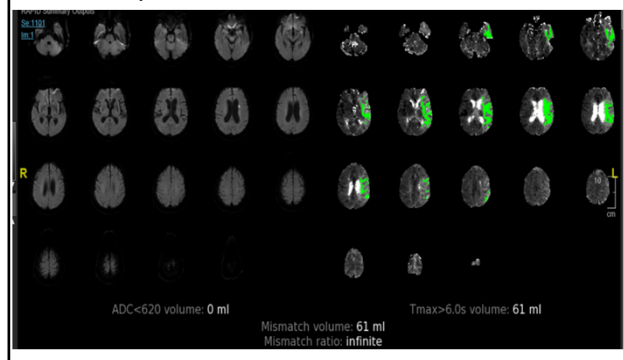
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In summary – who is at high risk?

- **Long term risk:**
 - No consistent predictors (SAMMPRIS, WASID, MyRIAD, and VERITAS): ? blood flow biomarkers, ? poor risk factor control/plaque becoming active
- **Early (90-day) risk:**
 - Biomarkers of impaired flow (perfusion delay and borderzone infarct) (Observational studies)
 - ? Lack of optimal medical treatment

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Back to patient → knowing that she will likely fail maximal medical treatment...



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Would she qualify for stenting?

- FDA on label criteria:
 - age 22–80 years (Yes)
 - baseline mRS ≤3 (Yes) → (No)
 - 70–99% stenosis (Yes)
 - **2 or more strokes on medical treatment (No)**
 - time from last stroke to procedure of more than 7 days (Yes)

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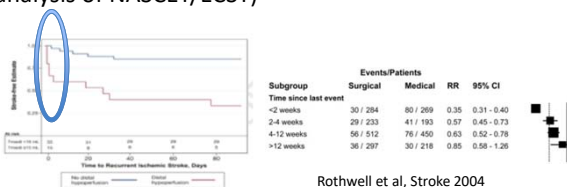
Can treatment for ICAD be improved based on biomarkers and risk of recurrence?

1. **Improve patient selection** (who is likely to benefit and to fail medical treatment)
2. **Reduce procedural complications**

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Improved patient selection

1. **Early selection:** where the risk of recurrent stroke on medical treatment is highest and thus an intervention will have the most impact
 - Carotid stenosis analogy: Benefit of surgery is highest when performed within 2 weeks (pooled analysis of NASCET/ECST)



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2. **High risk group:** Identify a group likely to fail medical treatment based on underlying mechanism (impaired perfusion/flow)
 - Prediction model using impaired perfusion/flow biomarkers
 - Mechanistically benefit from reperfusion

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Reduce procedural complications

- Angioplasty alone if possible
- Avoid clopidogrel in patients with resistance
- Increase operator experience
- Consider other devices with better safety profiles

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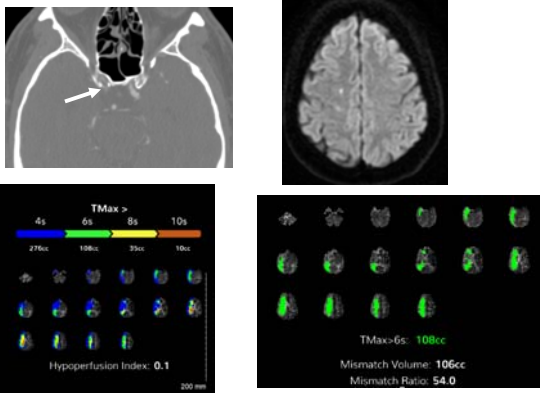
Lower risk with stenting post-SAMMPRIS

- The Wingspan Stent System Post Market Surveillance (WEAVE):
 - 2.6% with endovascular treatment in select patients with symptomatic ICAS
- China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSIS):
 - 30-day recurrent stroke or death rate of 5.1%

Alexander et al, Stroke 2019, Gao et al JAMA 2022

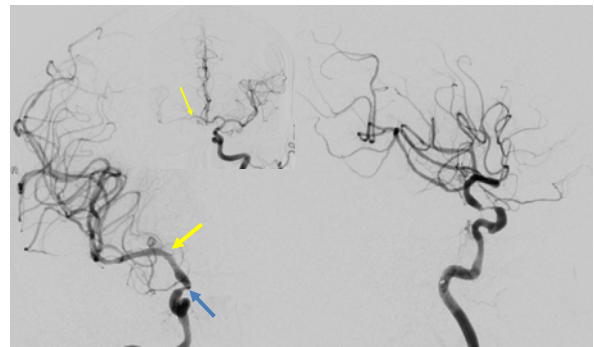
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Courtesy of Eytan Raz (Bellevue hospital)

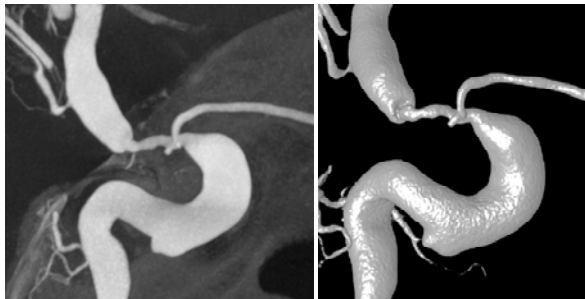


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High grade stenosis ICA at the supraclinoid segment

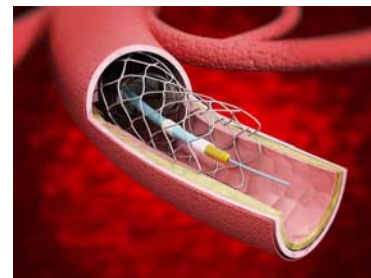


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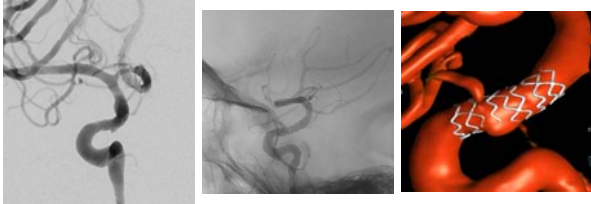
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Stent or not?



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Post intracranial stenting with off label balloon mounted stent Onyx Resolute 2.5 mm diameter by 8 mm length



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Are there any surgical options?

- EDASS surgery:
 - The ERSIAS study was an open label single arm study of 52 patients with severe symptomatic internal carotid artery or MCA stenosis and impaired distal perfusion
 - EDASS was relatively safe with a 9.6% rate of death at 30 days or recurrent ischemic stroke in the same territory at 1 year

Gonzales et al, IJ 2021

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Targeting potential mechanisms

- Artery to Artery embolism → optimizing medical treatment
- Perforator disease → optimizing medical treatment
- Impaired perfusion → optimizing medical treatment and clinical trials are needed to study reperfusion therapy

Yaghi et al, Stroke 2019

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Future Studies to Optimize Medical Treatment Regimens

- Further optimize medical treatment
 - CAPTIVA: low dose rivaroxaban plus aspirin vs. DAPT for 12 months
- Other areas of potential research
 - PCSK-9 inhibitors
 - Anti-inflammatory drugs

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Studies testing intervention/optimizing selection

PERFUSE-ICAS

VERITAS REFERESHED

ERSIAS

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Thank you



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