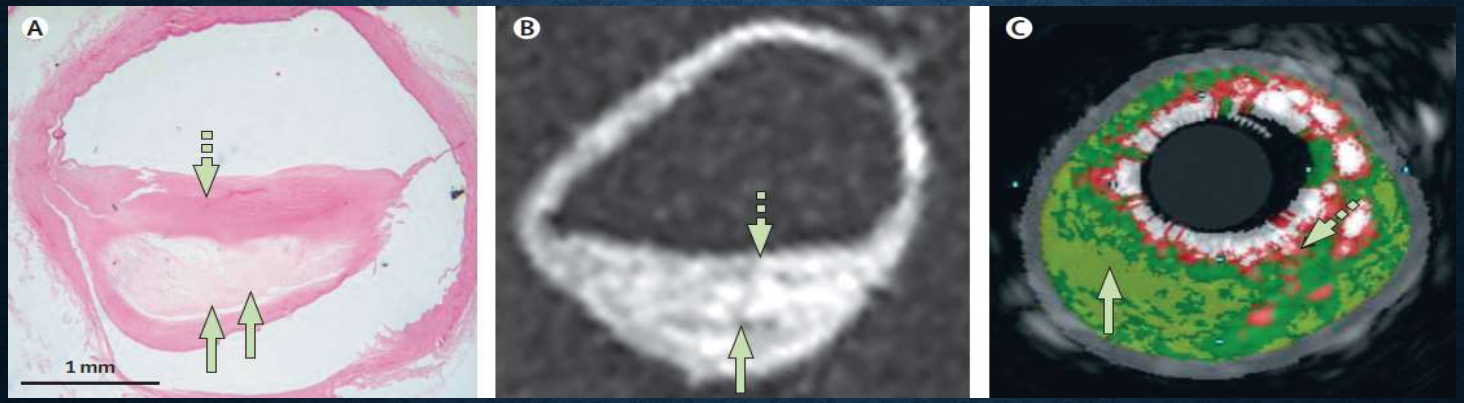
MEDICAL & SURGICAL TREATMENT OF INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

MARK D. JOHNSON, MD
DEPARTMENT OF NEUROLOGY
UT SOUTHWESTERN



Fibrous and Adipose component: Solid arrows

Fibrous Component: Dotted Arrow

White component is calcification and Red component is necrosis

A. H & E; B. 7T; C:. Intravascular Sonography

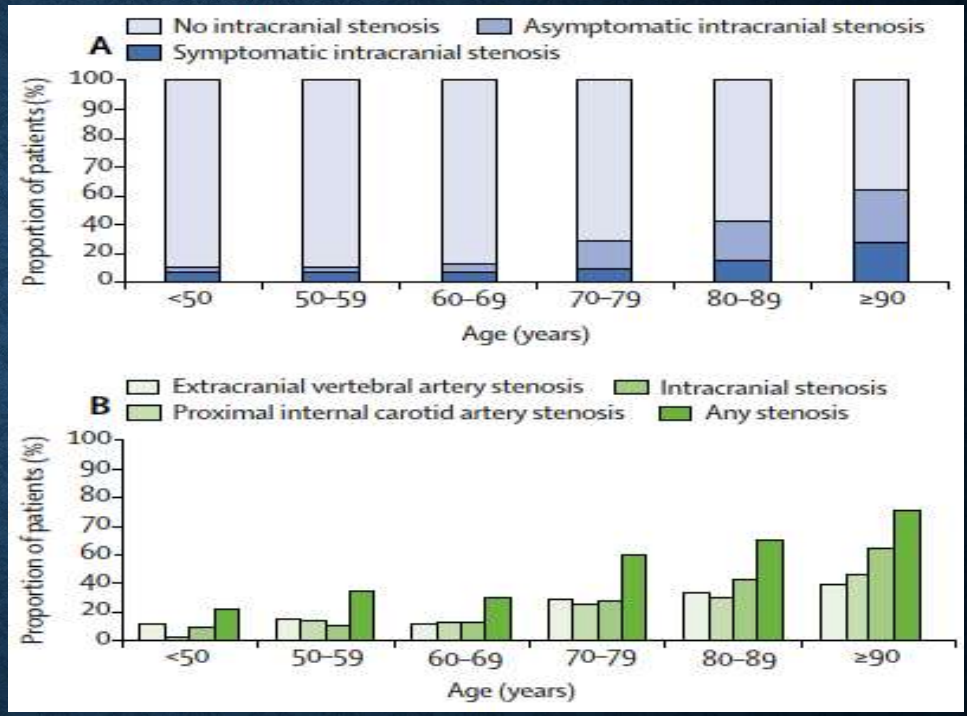
Lancet 2014:383: 984-98

DISCLOSURES

- I have participated in several of the clinical trials related to this lecture including WASID, SAMMPRIS, and MyRIAD as co-investigator or principal investigator in our institution.

ATHEROSCLEROTIC LARGE ARTERY INTRACRANIAL STENOSIS - EPIDEMIOLOGY

- Particularly prevalent in black, Asian, Hispanic, and Indian populations. Also in some Arabic countries.*
- High rate of vascular risk factors
  - 90% have multiple risk factors
  - 75% HTN, 50% DM, 65% CAD, 65% smokers, and 40% hypercholesterolemia
- Genetic factors undetermined –
  - 30-50% of strokes in Asian people (China, Japan, South Korea, India)
  - 5%-10% of strokes in white people
  - 11% in Hispanics
  - 11%-22% in Japanese (Nishimaru*; Brust*; Kieffer*)
- 50% present with TIAs
- Hypertension and diabetes are most important risk factors
- It is a marker of CAD in white patients
- In 2020 OxVASC population study the two year absolute risk for 70-99% vs 50-69% was 22.9% vs 4.8%.



- **Age-specific prevalence of intracranial and extracranial stenosis**

(A) 50–99% symptomatic, asymptomatic, and no intracranial stenosis.

(B) Proximal extracranial internal carotid artery stenosis, extracranial vertebral artery stenosis, 50–99% intracranial stenosis, and any stenosis (extracranial or intracranial)

Lancet Neu 2013; 12:1106-14*

RISK FACTORS

- Age
- Asian & Black Race
- Hypertension (In WASID SBP >140 mm Hg)
- Smoking
- Diabetes Mellitus
- Hyperlipidemia (In WASID TC > 200 mg/d)
- Metabolic Syndrome
- Sedentary Lifestyle
- Reduced adiponectin
- Increased lipoprotein-associated phospholipase A2
- Increased C-reactive protein, E-selectin, plasminogen activator inhibitor-1, and lipoprotein (a)
- Low serum vascular endothelial growth factor (associated with increased severity of disease)

- Stroke 2005; 36:92-97

- In the Trial of Cilostazol in Symptomatic Intracranial Stenosis 2 (TOSS-2) – a substudy – increased apolipoprotein B/A-I from baseline was associated with progression of stenosis on MRA
- In the WASID – patient with at least 70% stenosis had higher risk than 50%
- The presence of robust collateral in 70% or more reduced the above risk
- TCD (2004) micro embolic signals associated with higher risk of stroke Stroke 2004; 35: 2832-36
- GESICA (2006) patients who developed ischemic symptoms during change of position (supine to prone), or effort, or the introduction of or increase in dose of an antihypertensive agent, had subsequent rate of combined stroke and tia of 61% Neurology 2006; 66; 1187-91
- The risk of recurrent stroke also depended on how recently it occurred: 17 days risk was higher than between 18-90 days from the prior stroke
- VERITAS (2016) – in patients with symptomatic vertebrobasilar disease impaired distal flow is a strong predictor of recurrent events (HR 11.55 (95% CI, 1.88-71.00); P= 0.008) JAMA Neurol 2016; 73: 178-185
- Extracranial atherosclerotic disease is risk factor for Intracranial vessel disease Atherosclerosis 270 (2018) 218-223

LOCATION: ANATOMIC

- Basilar artery
- Internal Carotid Artery
- Middle Cerebral Artery
- Intracranial Vertebral Artery
- Posterior Cerebral Artery
- Anterior Cerebral Artery

PLAQUES

LANCET 2014:383: 984-98

- Ischemic events are associated to:
  - High-lipid content
  - Intraplaque Hemorrhage
  - Neovasculature
  - Macrophage and T lymphocyte infiltration
- Intracranial arteries might be more susceptible to inflammatory changes and plaque instability due to:
  - Reduced expression of inhibitors of inflammation
  - Prominent expression of proinflammatory proteasomes
  - Absence of external elastic lamina

MECHANISM OF ICAD*

- Hypoperfusion (impaired distal perfusion)→ watershed pattern – through a highly stenotic vessel
- Artery-to-artery embolism→ distal wedge shape infarct
- Perforator disease including plaque extension over small penetrating artery ostia (aka branch atheromatous disease)→ high resolution MRI may identify
- Combinations of the above (i.e Hypoperfusion prevents clearing of a distal embolus)

- Lancet Neu 2013; 12:1106-14*

PATHOPHYSIOLOGY

- Recurrent artery-Artery emboli is a common presentation but be aware that in the acute setting areas of narrowing may be related to embolic partially recanalized filling defects from a local or embolized thrombus which most frequently resolve on follow up images after a week.
- *58y/o with 5 spells over 2 months including headache, nausea, vomiting, gait unsteadiness, vertigo, tingling of the right are and leg, blurring of vision and diplopia*

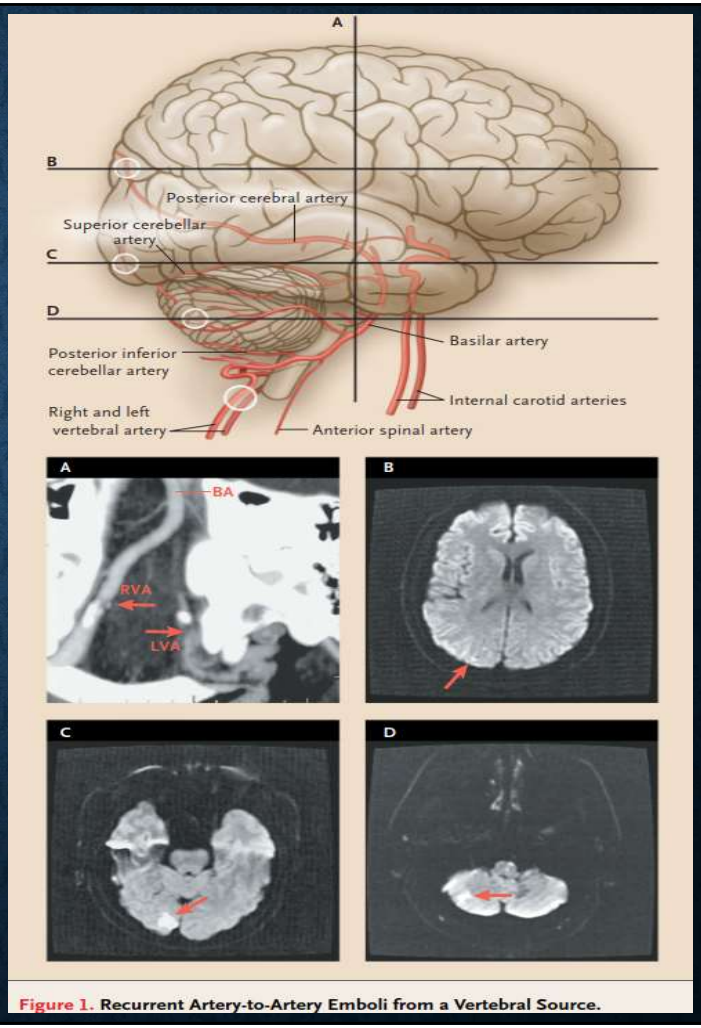
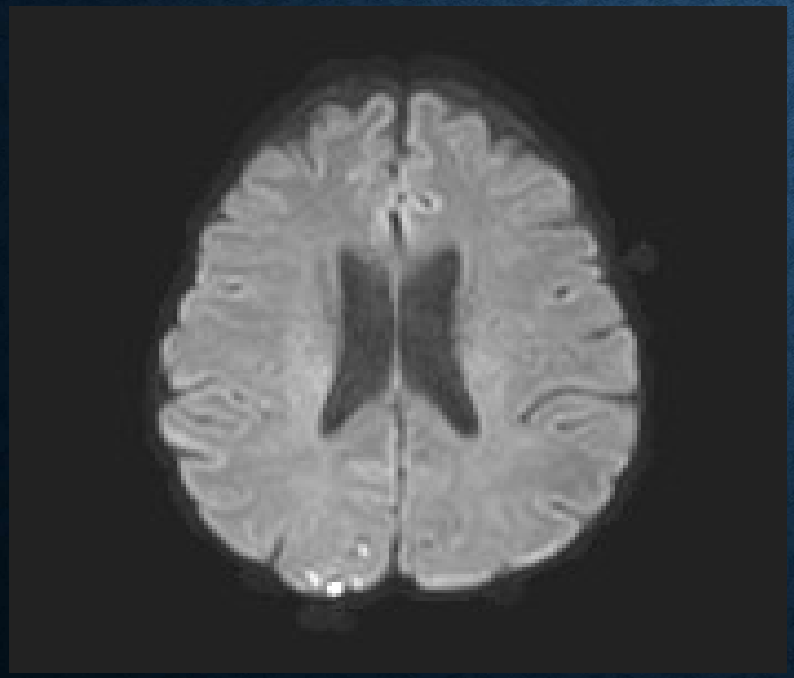


Figure 1. Recurrent Artery-to-Artery Emboli from a Vertebral Source.

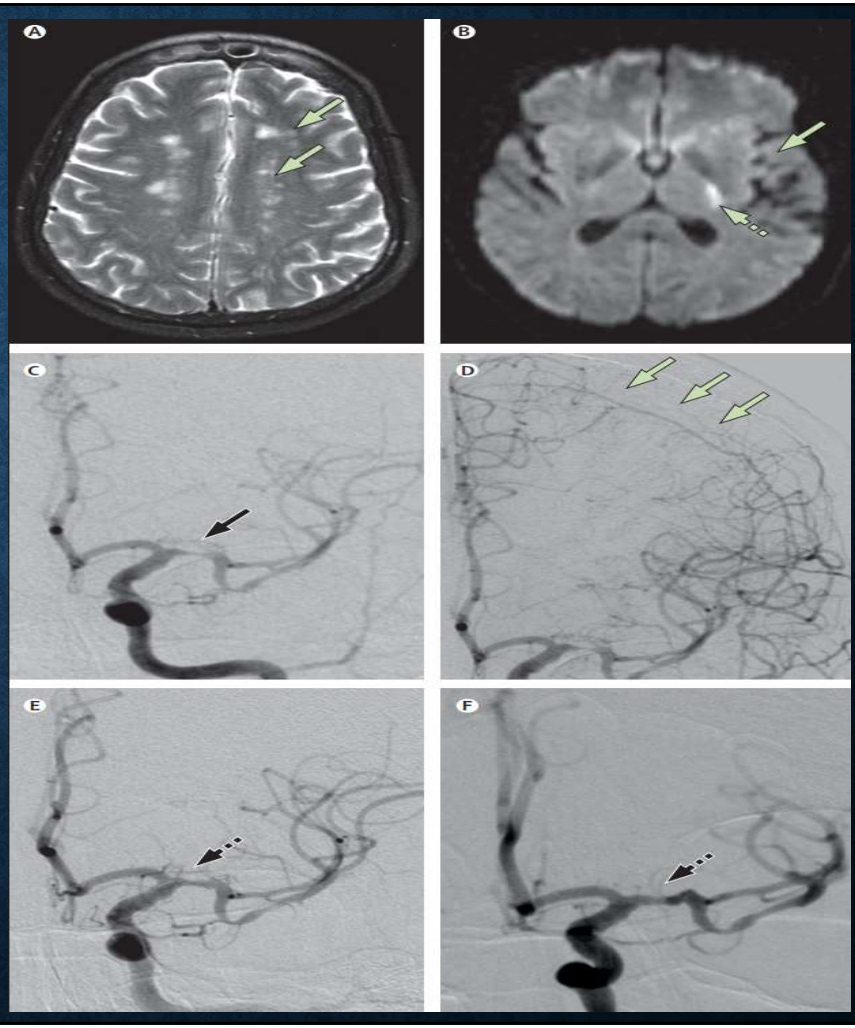
ARTERY-ARTERY EMBOLISM

70Y/O WITH VERTIGO AND LEFT MILD VISUAL FIELD DEFECT. SHE ALSO HAS HAD MARKED HYPERLIPIDEMIA AND INABILITY TO USE STATINS. OF NOTE IS THAT 2 YEARS PRIOR SHE HAD A PONTINE LACUNAR APPEARING ISCHEMIC STROKE WITHOUT CLEAR BASILAR ARTERY STENOSIS (? PLAQUE EXTENSION OVER SMALL VESSEL OSTIUM)



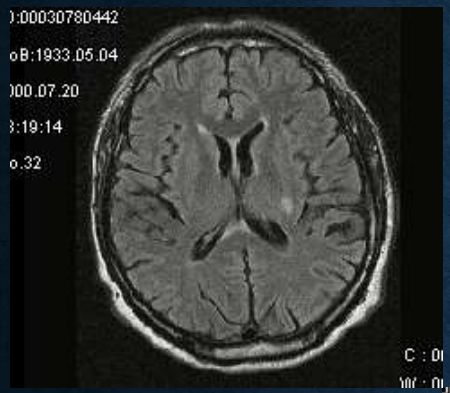
SUBCORTICAL LESIONS CAN BE PART OF LARGE VESSEL DISEASE

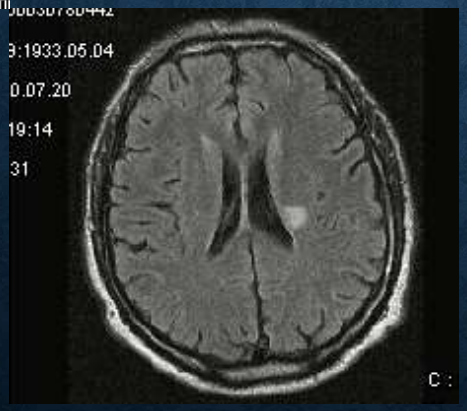
- While mechanisms are as previously discussed – patients can present with lacunar or subcortical infarctions
- Cognitive deficits to different degrees anterograde amnesia and executive functions are noted
- Infarcts have been described in anterior-medial thalamus, caudate nucleus and white matter zones important different cognitive measures
- *56y/o w right sided weakness TIAs*
- Lancet 2014; 383: 984-98



NON-STEREOTYPED L MCA TIAS

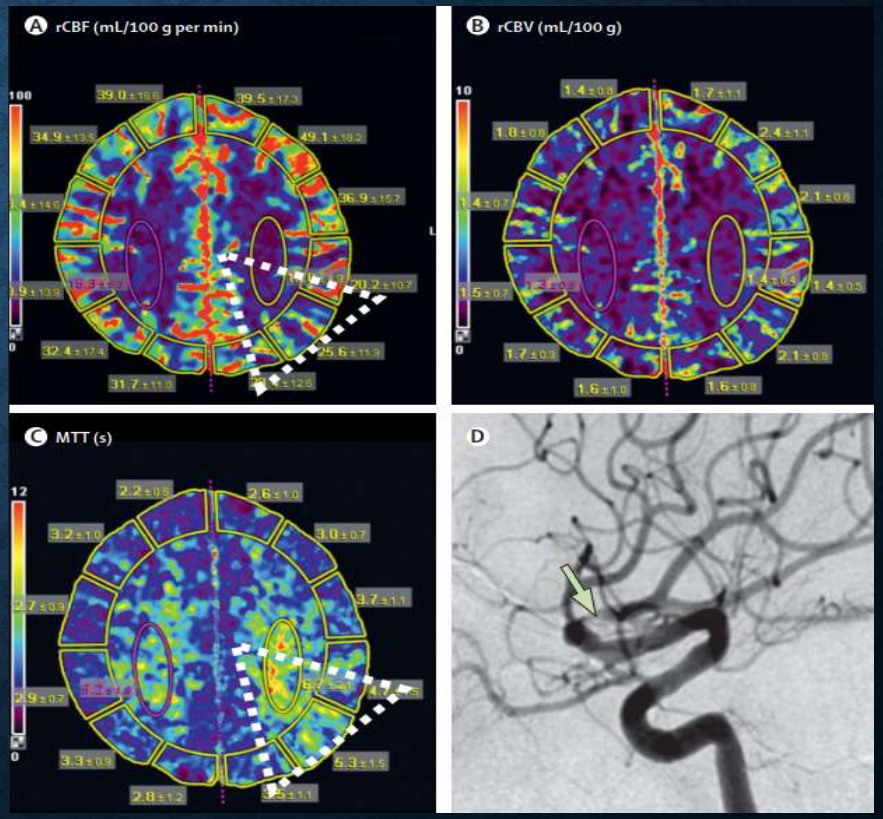
SENSORIMOTOR STROKE





HYPOPERFUSION EFFECTS

- In patients without infarcts cognitive deficits are attributable to white matter degeneration, hypoperfusion and hypometabolism
- 46y/o woman with left-sided hemispheric small ischemic stroke
  - A. low rCBF B. Preserved rCBV C. Delay in blood flow noted as increased MTT D. Catheter angio with left MCA high grade stenosis
- The hypoperfusion has been seen associated with loss of microstructural integrity
- Lancet 2014; 383:984-98



DIAGNOSTIC TESTING

- Transcranial Doppler (TCD)
- Magnetic Resonance Angiography (MRA)
  - Based on SONIA trial the two above had high negative predictive values (86-91%) but low positive predictive values (36-59%) – this suggest that these studies are useful screening test for exclusion of ICAS
- Computerized Tomography Angiography (CTA)
  - Other studies suggest CTA having higher sensitivity and specificity to detect 50% or higher ICAS but not for accurate measurement of degree of stenosis
- Conventional Cerebral Angiography
  - Currently gold standard for quantification of degree of stenosis
- High resolution MRI
- Lancet Neu 2013; 12:1106-14

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- 1955 – anticoagulation first reported treatment in ICAS
- 1995 – Retrospective study suggested warfarin better than aspirin
- 2005 - WASID showed no benefit of warfarin over aspirin; aspirin showed to be safer than warfarin (lower death and major hemorrhage)
  - Also patients with 70-99% stenosis, vertebrobasilar tx, and ones with recurrent stroke while on antithrombotic therapy were shown not to benefit with warfarin either.
- 2005 Cilostazol may decrease atherosclerosis progression
- 2007 FISS-tris no difference between nadroparin and ASA within 48 hrs stroke for 10 days. Also rate of stroke within 6 months was same Lancet Neurol 2007; 6;407-413
- 2011 SAMMPRIS – Med tx (& DAPT) better than angioplasty & stenting (70%)
- 2011 TOSS 2 -Cilostazol & ASA DAPT was noted equivalent to clopidogrel & ASA Stroke 2011; 34:2361-66
- 2012 CLAIR –study reduction in emboli via TCD for patients on DAPT Int J Stroke 2012

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- 2001 PROGRESS Trial – general better outcomes with ACE – Perindopril
- 2006 SPARCL -High dose atorvastatin better outcomes in ICAS –reduction of stroke or cardiovascular events
- 2006 ESPRIT subgroup analysis – ICAD patients had more hemorrhages Lancet 2006; 367; 6:115-24
- 2007 Post hoc analysis WASID - increased stroke/vasc events with SBP >140 mm Hg*
- 2009 Regression of Cerebral Artery stenosis study – rates of progression of cerebral white matter lesions, asymptomatic brain infarcts, all-cause mortality, and any clinical events were significantly lower in the simvastatin treated group Cerebrovasc Dis 2009; 28: 18-25
- 2011 SAMMPRIS risk factor control much lower risk than when compared to WASID patients with similar criteria as SAMMPRIS
- 2015 CHANCE secondary analysis study showed a trend toward fewer events with DAPT vs aspirin (HR, 0.79 (95% CI, 0.47-1.31) Neurology 2015;85:1154-1162
- Moderate or heavy intensity physical activity is associated with reduced risk of ischemic stroke (general)
- No DOAC studies yet done: individually or in combination to antiplatelet treatment
- Another question would be if to replace clopidogrel with ticagrelor, cilostazol or prasugrel

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- In WASID patients with HbA1c of 7 or greater had a higher rate of recurrent stroke (26% vs 15%, HR 1.7, 95% CI 0.8-3.6) – HgA1c goal to 7% with either insulin or pioglitazone is recommended
- In SOS-TIA study, early initiation (24 hrs) of antiplatelet, antihypertensive, and statin drugs, the incidence of recurrent vascular events (recurrent TIA, stroke, or myocardial infarction) was only 7% in 160 patients with intracranial narrowing or occlusion at 1 year Lancet 2007; 370:1432-42
- **Overall intense treatment is recommended systemically as well since**:
  - A third of deaths in patient with ICAD are attributed to CAD
  - A fifth of vascular events are attributed to coronary syndromes during 2y
  - In prior studies, 52% of patient with ICAD had evidence of silent MI by regional myocardial perfusion studies
  - 60% have asymptomatic moderate to severe CAD

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

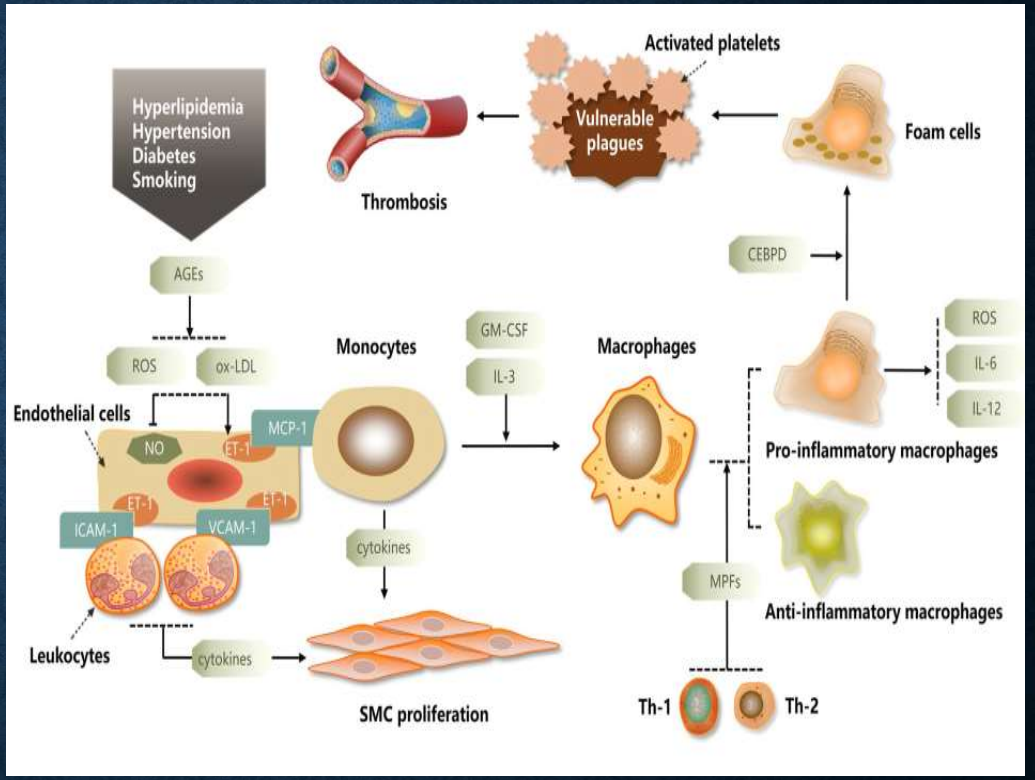
- Patients moderate stenosis (50-69%) or patients with Stroke/TIA >30 days have risk of 3-9% of stroke with usual management in WASID which would suggest that with intensive treatment the risk should be lower:
  - ASA
  - Intensive risk factor control:
    - SBP <140 mm Hg
    - LDL > 1.81 mmol/L (> 70 mg/dL)
- Patients with severe stenosis should follow SAMMPRIS protocol
  - DAPT; high potency statin LDL < 70; BP goal SBP < 140 (now <130) DM <130; HgA1C <7.0; Lifestyle Mod: Smoking cessation; aerobic exercise; mediterranean diet; weight loss BMI <25;
  - Post-Hoc analysis of SAMMPRIS showed that achieving **target physical activity was the most important factor with a 40% reduction in stroke recurrence** – Neurology 2017; 88:379-385
- Long term (>90 days) treatment with DAPT not recommended based on MATCH and CHARISMA trials (although the benefits in high risk patients of > 90 days tx could outweigh the risk of bleeding in selected cases but not proven)
- SAMMPRIS patients in intensive tx group had about 12.2% risk at 1 year (primary endpoint)

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- SPARCL trial (200) Atorvastatin vs placebo post stroke – within this study a trend toward secondary stroke prevention in patients with large artery athero was seen (Hr, 0.70 (95% CI – 0.49-1/02) but sample size was not large enough to answer the question Stroke 2009; 40: 1405-1409
- REDUCE-IT trial ***icosapent*** ethyl was associated with lower risk of ischemic events.
- Treat Stroke to Target (TST) – stroke and ASCVD – stopped early due to lack of funding but primary outcome was achieved include stroke reduction statistically significant
- PCSK9 inhibition – reduced stroke risk in patients with hyperlipidemia or atherosclerotic cardiovascular disease
- **Current and future areas of research**
  - External Counterpulsation – several sessions of intermittent compression of air-filled cuffs on the legs – associated with increases in intracranial cerebral blood flow velocities by TCD as well as greater improvement in neurologic deficits as compared with control Stroke 2012; 43:3007-11
  - High HDL cholesterol and low apolipoprotein B or A1 concentrations are associated with low rates of progression in severity of intracranial stenosis Stroke 2012; 43:1824-30

MEDICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- Current and future areas of research – treating the **inflammatory cascade**
  - CANTOS trial – Canakinumab lowered recurrent cardiovascular events compared to placebo but leg to higher rate of sepsis-related death so development was stopped
  - COLCOT trial – colchicine lowered risk of cardiovascular events and stroke in patients post MI



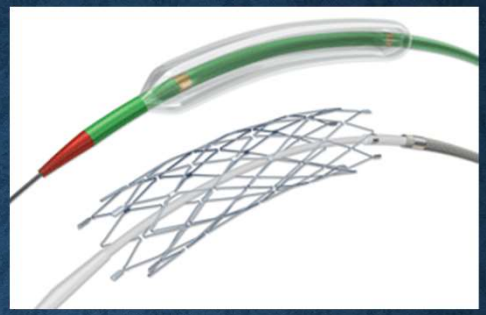
Molecular and cellular actions within the cerebral arteries in the progression of intracranial atherosclerosis

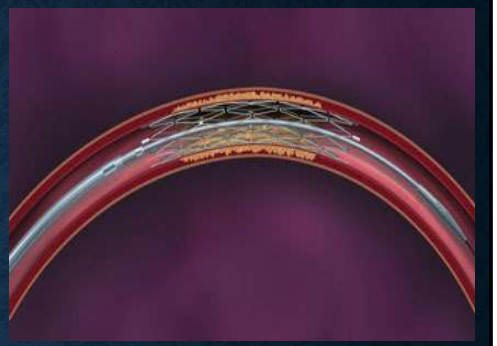
- J Neuro Res 2019; 97:1242-1252

ENDOVASCULAR/SURGICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- 1985 - EC/IC bypass trial – did not show benefit of bypass in patients with intracranial carotid or MCA stenosis or extracranial occlusion. In fact there were worse outcomes in the surgical arm.
- Late 1980s and early 1990s **angioplasty** single center studies with high variability in outcomes were published. This was related to high risk cases (acute or unstable) vs low risk (subacute/chronic). New techniques and **undersizing and slower balloon inflations** have shown better outcomes.
  - Angioplasty potential complications include issues with elastic recoil and residual stenosis post procedurally in up to 50% of cases. With these findings centers moved to **percutaneous angioplasty and stenting** (PTAS)

ENDOVASCULAR/SURGICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS





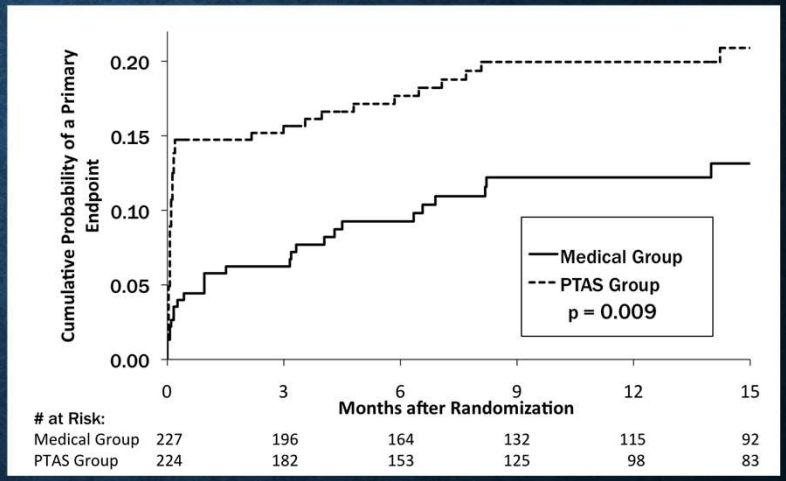
- =/- prior to 2004 - Initial studies with PTAS showed higher morbidity and mortality rates due to difficulty in navigation and trauma during balloon inflation and deployment of stents.
- 2004 - Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study using Guidant Neurolink system showed successful stent placement with 6% complication rate
- 2005 - FDA approved self-expanding Wingspan (self expanding nitinol) Stent (Stryker Neurov) for use under humanitarian device exception in medically refractory patients with TIA or stroke
- 2007-2008 – NIH & US wingspan registries showed PTAS with Wingspan stent could be done with high technical success rates and with a 30-day stroke rates of 6-9%
- Next generation angioplasty balloons, and self expanding and balloon expandable stents increase lumen diameter, improved regional CBF, and induce remodeling to reduce thrombogenicity in patients with ICAD

- Characteristics that are unfavorable for stenting:
  - Severe Deficit from stroke
  - Chronic total occlusion of the artery
  - A hemorrhagic stroke or stroke with mass effect within six weeks of the procedure
  - Contraindications or resistance to antiplatelet medications
- Characteristics that favor intracranial stenting include:
  - 70% stenosis or greater refractory to medical treatment
  - Minimum vessel diameter of 2.0 mm
  - Previous stroke or TIA with symptoms

SAMMPRIS

ENDOVASCULAR/SURGICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- 2008 SAMMPRIS trial began enrolment (publication 2011-2012) – high risk patients with 70-99% ICAS who had stroke or TIA within prior 30 days. It was stopped in April 2011 due to high risk of periprocedural stroke and death in the PTAS group. 30-day rate of stroke or death was 14.7% in the PTAS group and 5.8% in the medical group.
- Risk factors significantly associated with periprocedural ischemic events were
  - Non-smoking (possible because smoking increases the conversion of clopidogrel to its active metabolite)
  - Basilar artery stenosis
  - Diabetes
  - Older age
- Risk factors significant associated with periprocedural hemorrhages were:
  - High percentages of stenosis
  - Clopidogrel load associated with an high activated clotting time (ACT) above the target range*



Stenting & Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

SAMMPRIS

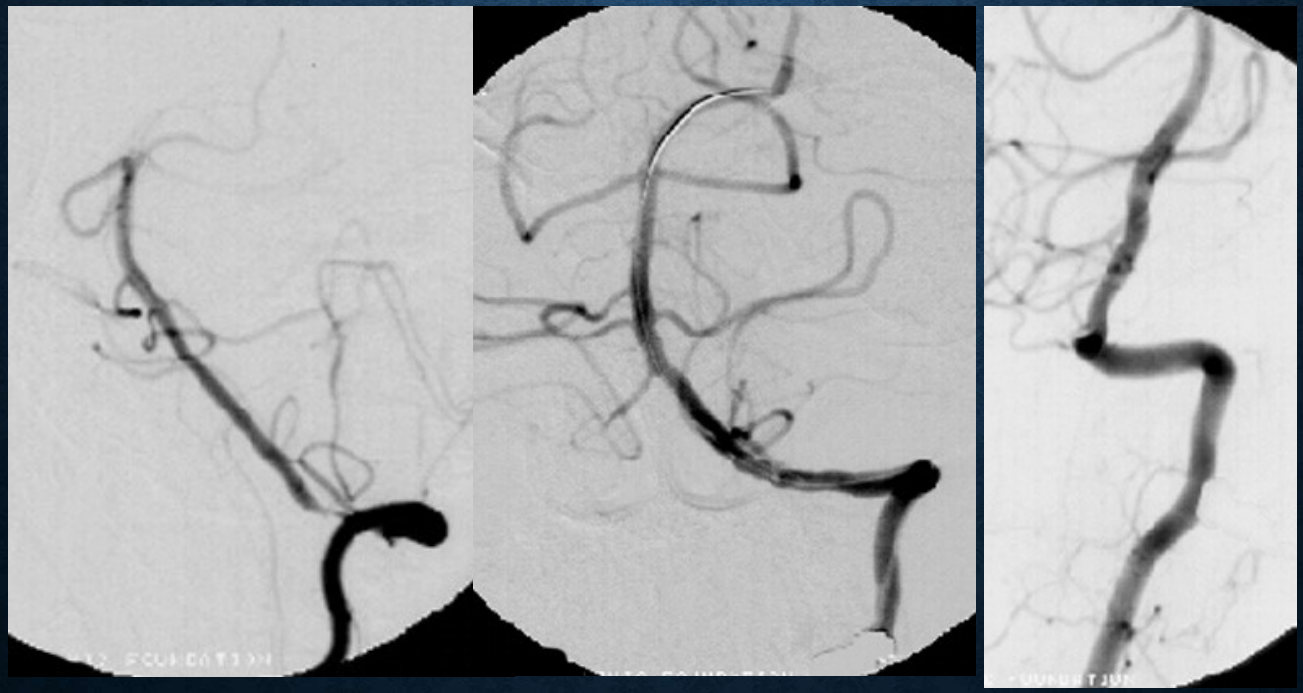
ENDOVASCULAR/SURGICAL TREATMENT INTRACRANIAL CEREBRAL ATHEROSCLEROSIS

- 2015 VISSIT (JAMA) Vitesse Intracranial Stent Study for Ischemic Stroke Therapy – increased 12-month risk of added stroke or TIA in the same territory, and increased 30-day risk of stroke or death (9.4 versus 24.1%, P=0.05).
- Current indication (since 2012) as per FDA for Wingspan stent is patients between 22-80 y/o who had >/+ 2 stroke despite medical treatment, had experience the most recent stroke >7 days before the planned treatment with Wingspan, had 70-99% stenosis due to ICAD, which was causal of the recurrent stroke, and had made good recovery from prior strokes with modified Ranking scale of </= or less before treatment
- WEAVE trial (2019) – post market registry in which there was a lower than expected (2.6%) periprocedural stroke, intracranial hemorrhage, or death rate, lower than the 4% periprocedural event rate set for the interim analysis.
- Some preliminary studies of angioplasty only are showing lower rates of complications and strokes

- Two Non-technical criticism of SAMMPRIS and VISSIT trials have been raised Lancet Neurol 2020; 19: 422-33
  - "The better than expected prognosis on medical treatment alone in these trials might reflect the exclusion of older patients from both, with a median age at recruitment of younger than 60 years, such that generalizability of the trial results to older patients is uncertain" (SAMMPRIS 30-80 y/o) (VISSIT 18-85 y/o)
  - "The particularly intensive medical treatment might have been responsible for the low stroke risks in the medical treatment-only groups compared with previous studies"

- Procedure description:
  - After induction of general anesthesia, a 6 French sheath is placed in the common femoral artery. After gaining vascular access, a heparin bolus and drip are started, and the activated clotting time (ACT) is maintained at two times the baseline.
- Procedure potential complications:
  - Dissection
  - Stroke
  - Vessel rupture

PTA/STENT AND 5 MO FOLLOW-UP



OTHER POTENTIAL INTERVENTIONS WITH COMPLETED AND FUTURE TRIALS

- MyRIAD – determine mechanisms of stroke in patients with ICAD by assessing antegrade flow through stenotic artery, distal tissue perfusion, and artery-to-artery embolism
  - QMRA – volumetric flow rate
  - PWI-MRI – distal tissue perfusion
  - BHI-TCD – vasomotor reactivity
  - TCD emboli monitoring – artery-to-artery embolism
- Angioplasty
- Encephaloduroarteriosynangiosis:
  - Donor arteries (STA & MMAs) are place close to the brain superficial arteries distal to the stenosis allowing a network collator to form
  - ERSIAS – prelim data showed safety with 9.6% death rate a 30 days or recurrent ischemic stroke in the same territory at 1 y
- Ischemic Preconditioning
- Pharmacological:
  - Direct Thrombin and Xa inhibitors vs antiplatelet agents (WASID showed patients with INR 2-3 had low IS/MI with few major hemorrhages

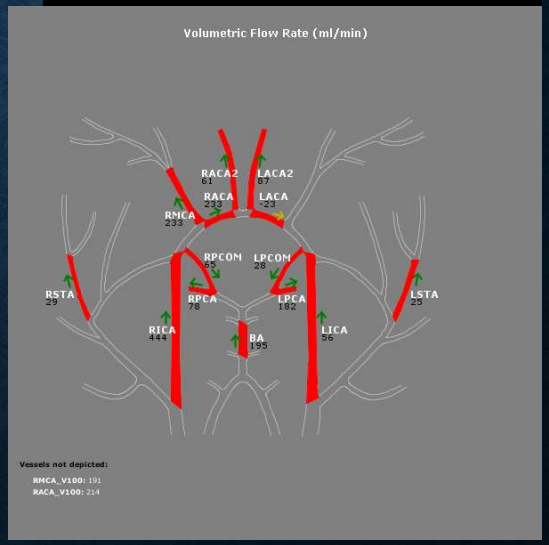
Trial	Location	Intervention	Outcome	Sample Size	Completion
International cooperative study of extracranial/ intracranial arterial anastomosis (EC/IC Bypass)	North America, Europe, Asia	STA-MCA bypass surgery vs medical management	Surgery resulted in more strokes and adverse events	1377	1985
Comparison of warfarin and aspirin for symptomatic intracranial atherosclerosis (WASID)	North America	Warfarin vs aspirin	Warfarin nonsuperior for stroke prevention and harmful	569	2005
Stenting vs aggressive medical management for intracranial atherosclerosis (SAMMPRIS)	United States	Stenting vs medical management	Stenting resulted in more strokes and death	451	2011
Stenting vs medical treatment in patients with symptomatic vertebral artery stenosis (VAST)	Holland	Stenting vs medical management	Stenting did not lower the risk of stroke and more adverse events	115	2015
Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis (VISSIT)	United States, China, Europe	Stenting vs medical management	Stenting resulted in more strokes and death	112	2015
Stenting for symptomatic vertebral artery stenosis: VIST	United Kingdom	Stenting vs medical management	Stenting did not lower the risk of stroke	182	2017
Surgical indirect revascularization for symptomatic intracranial arterial stenosis (ERSIAS)	United States	Single arm of EDAS surgery	EDAS had lower rate of recurrent stroke than historical controls	52	2018
Remote ischemic conditioning for avoiding recurrence of symptomatic intracranial atherosclerotic stenosis (sICAS)	China	Remote limb ischemic device vs sham	Pending; ischemic stroke	3000	2019
The effect of intensive statin in ischemic stroke with intracranialatherosclerotic plaques (INSIST-HRMRI)	China	Routine-dose vs high-dose statin	Pending; change in remodeling index, plaque burden, and composition	100	2021
PCSK9 inhibition in patients with symptomatic intracranial atherosclerosis (PINNACLE)	United States	PCSK9 inhibitor vs placebo	Pending; change in stenosis and plaque volume	40	2022

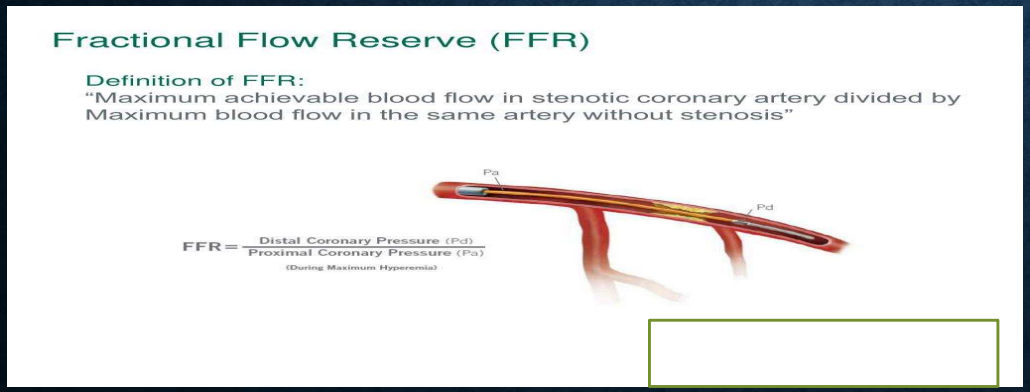
IDENTIFICATION OF HIGH-RISK SUBGROUP

- Cerebral hemodynamics, plaque components and morphology, and other factors may also determine the subsequent stroke risk, as well as different stroke mechanisms that may require different management methods.
- Changing shift of focus from anatomy (degree of stenosis) to functional assessment may be advocated.
- In hemodynamic assessment aside from the spencer criteria other factors like collaterals, hemodynamic impact, and other factors (fractional flow reserve) may need to be considered.

IDENTIFICATION OF HIGH-RISK SUBGROUP

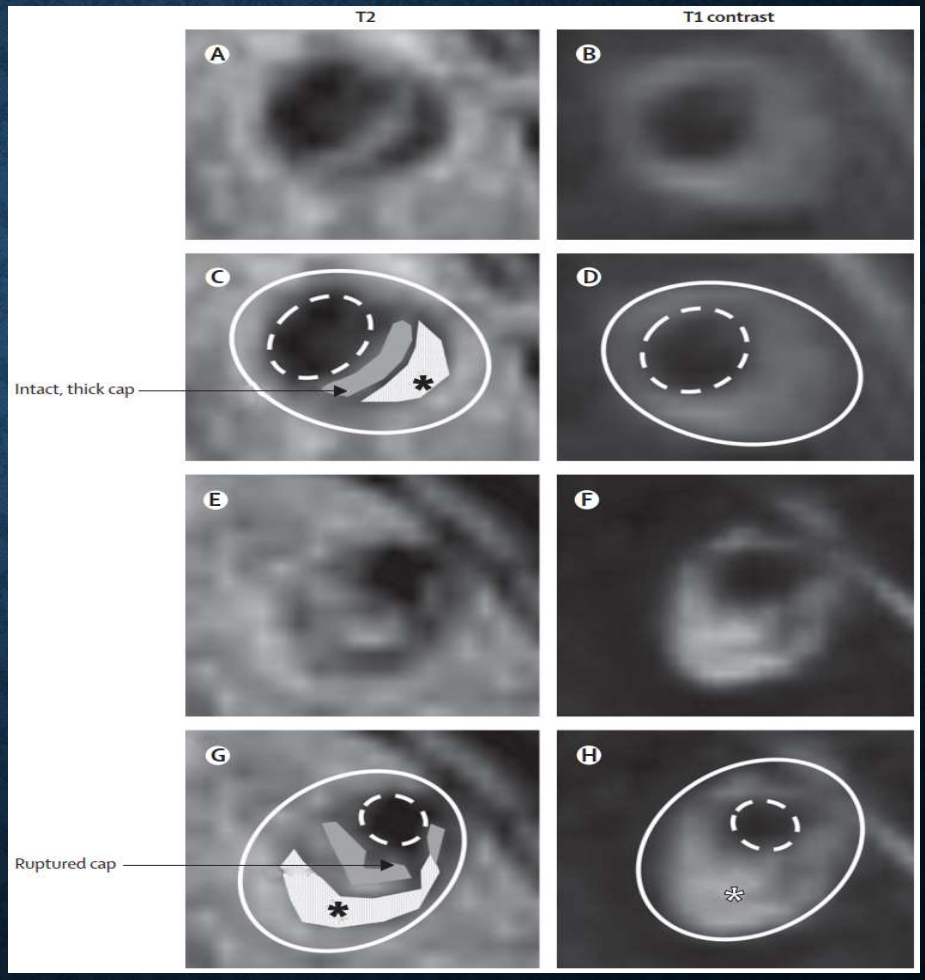
- Quantitative MRA
  - Combines Time-of-flight (TOF) and phase-contrast MRA techniques to derive vessel-specific volumetric flow rates
- Fractional Flow Reserve on MRA
  - Index that uses pressure gradient across a stenosis to identify lesions of hemodynamic significance (Distal-to-Prox ratio <0.9 TOF MRA



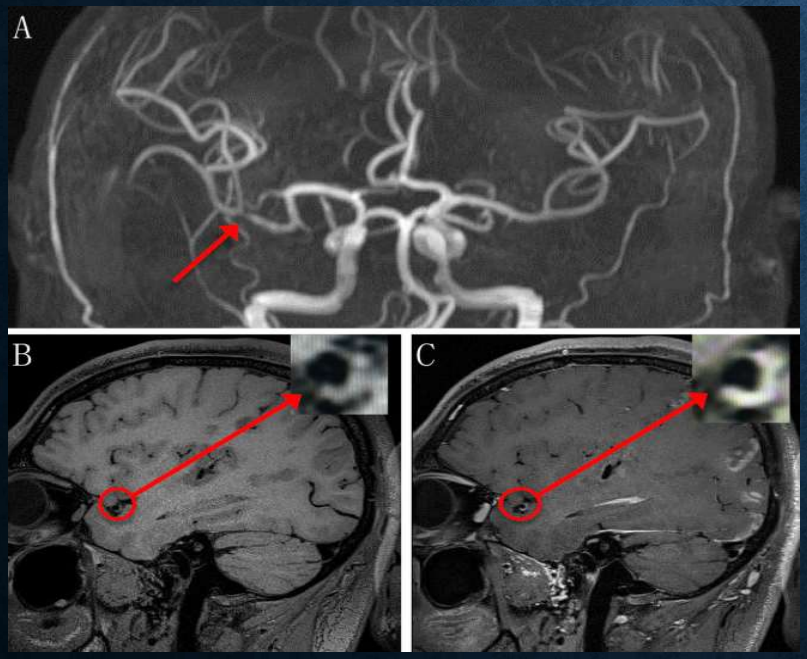


IDENTIFICATION OF HIGH-RISK SUBGROUP

- High Resolution MRI – usually uses 3T or higher to visualize the lumen and vessel wall which aids in the assessment of the underlying pathological abnormalities of the stenosis (atherosclerosis, inflammation or vasospasm). Identifying plaque formation data my help in secondary prevention strategies.
  - A-D: T2- weighted and T1 post-contrast images cross section VA plaque with thick, intact fibrous cap (grey) and lipid core (white with black asterisk)
  - As above (G and H) also VA reputed fibrous cap fibrous cap (grey) and lipid core(same) which enhances with contrast (white asterisk) also indicative of plaque rupture



IDENTIFICATION OF HIGH-RISK SUBGROUP



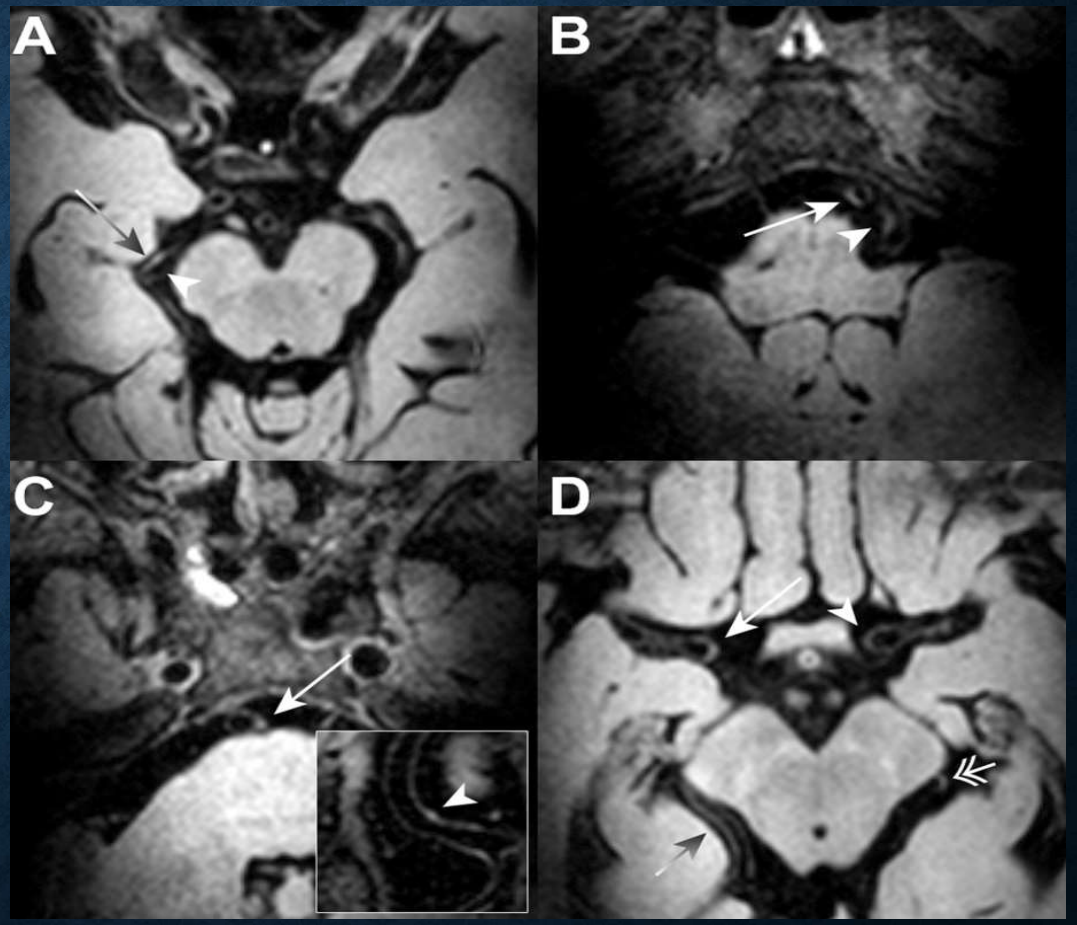
Representative TOF-MRA and HR-MRI images of ischemic stroke with stenosis

- A. 3-dimensional TOF-MRA image shows severe stenosis (arrow) at the proximal portion of the right MCA (M2 segment) in a 38-year-old male.
- Non-contrast (B) and contrast (C) image of T1-weighted HR-MRI shows the inward remodeling of plaque (cycle)
- Magnified image of plaque in inlet shows slightly hyperintense (B) and enhanced (C) signals of plaque

- Neurob Dis 124; 2019: 118-132

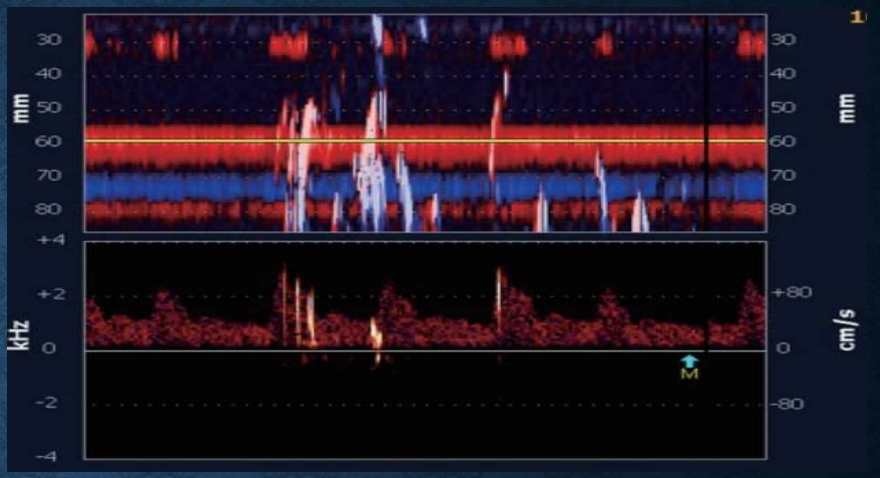
INTRACRANIAL VESSEL WALL LESIONS IN 7T MRI

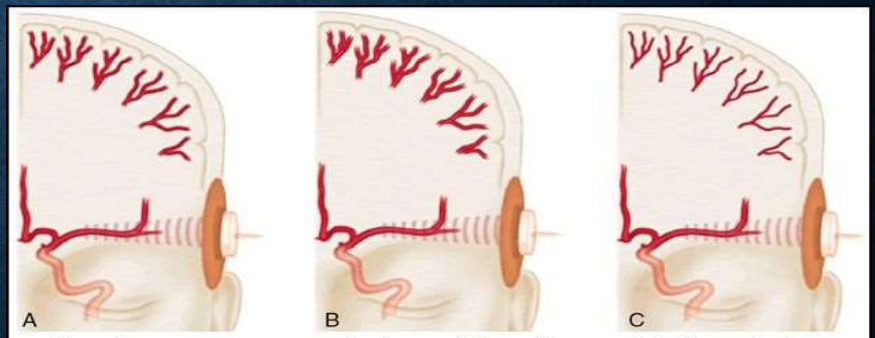
AJNR 2019 40 (12):2016-2022



IDENTIFICATION OF HIGH-RISK SUBGROUP

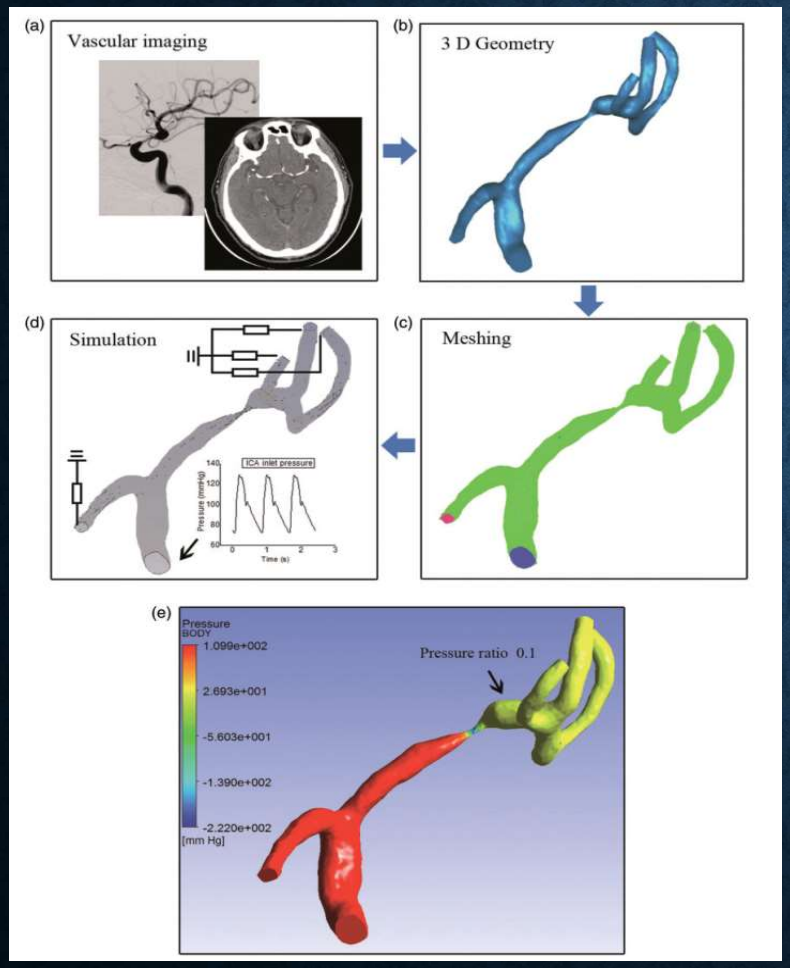
- TCD: Emboli Detection
- Vasomotor Reactivity





a. Normal vasomotor tone seen in the arterioles with normal middle cerebral artery (MCA) flow velocities during normocapnia.
b. After inhalation of 6% CO2 for three minutes vasodilation is seen in the arterioles, resistance to flow is lowered and velocitites in the MCA increase.
c. During hyperventilation the diameters of the arterioles decrease due to vasoconstriction, resistance to flow goes up and MCA velocities decrease.

- Reference:
- https://www.j-nn.org/upload//thumbnails/jnn-2019-00042f1.jpg
- https://neupsykey.com/wp-content/uploads/2017/02/image00961.jpeg



IDENTIFICATION OF HIGH-RISK SUBGROUP

- **Computational fluid dynamics (CFD) modeling in ICAD**
- (a) Cerebral vascular imaging for geometry extraction.
- (b) A three-dimensional vessel geometry generated.
- (c) Computation of mesh to generate millions of vertices and elements.
- (d) Boundary conditions and properties of blood flow are defined in the model for simulation cerebral blood flow.
- (e) An established CFD model used to depict the pressure field.

- International Journal of Stroke 2017, Vol 12(3) 236-245

TIMELINE OF ADVANCES AND TRIALS FOR ICAD

STROKE 2020; 51:E49-E53

GUIDELINES UNDER DEVELOPMENT BY AAN

PREVENTION OF STROKE IN PATIENTS WITH SYMPTOMATIC LARGE VESSEL INTRACRANIAL ATHEROSCLEROTIC DISEASE