THE WARREN ALPERT Medical School
BROWN UNIVERSITY

Rhode Island STROKE SYMPOSIUM

Moyamoya Medical Management in Adults

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DISCLOSURE

- I have no relevant financial relationships to disclose
- My talk will not include any off -label discussion

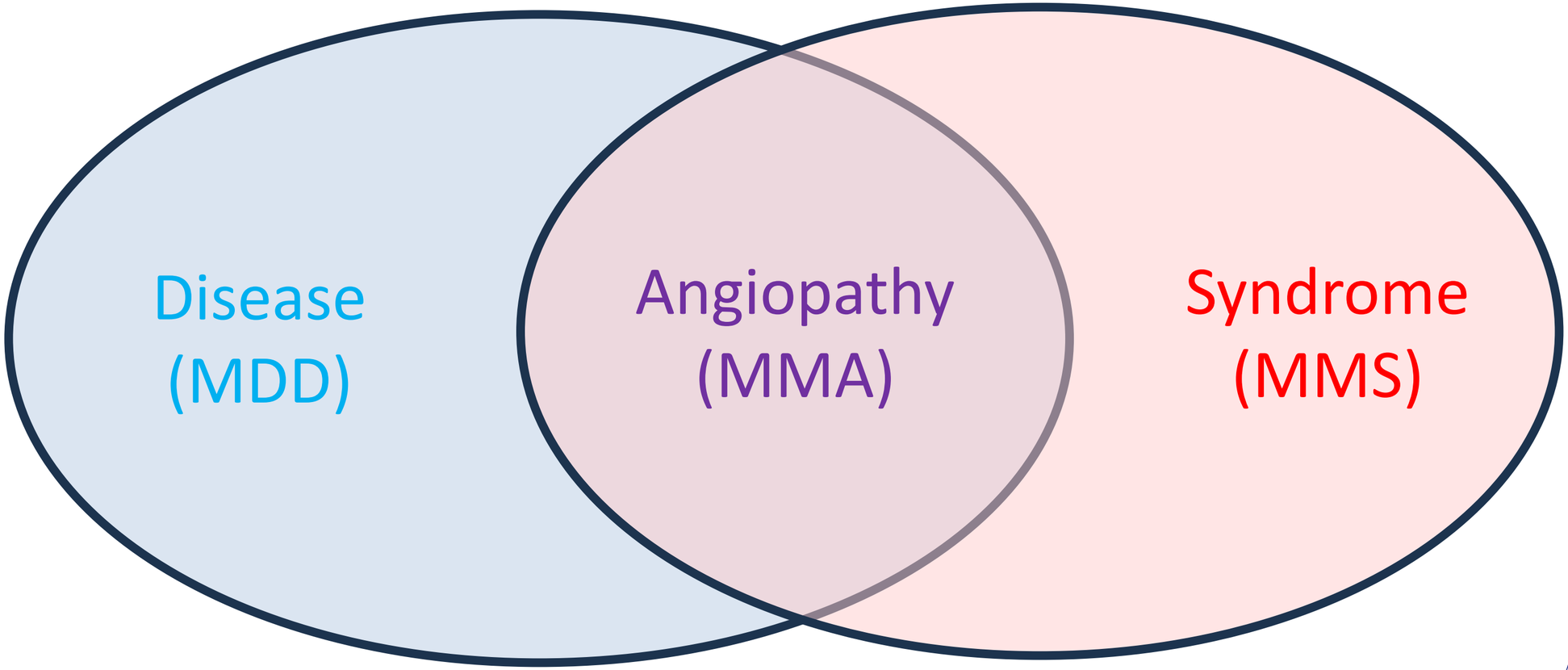
Outline

- Moyamoya
  - Disease (MMD), Syndrome (MMS), Angiopathy (MMA)
- Associated diseases in Moyamoya Syndrome
- Symptoms
- Imaging
- Ischemic events
- Hemorrhagic events
- Headache evaluation and management
- Risk factor management
- Summary

Moyamoya Disease (MMD)

- Cerebrovascular steno-occlusive condition
  - Unilateral or bilateral progressive stenosis of the terminal portion of the ICA, proximal MCA, ACA
  - Formation of abnormally dilated, fragile perforator network at base of brain
- Absence of other causes

Kuroda S 2008, Gonzalez NR 2023


Disease
(MDD)
Angiopathy
(MMA)
Syndrome
(MMS)

Moyamoya Syndrome (MMS) aka quasi-moyamoya – Associated Disorders

- Autoimmune disease (eg, SLE, APAS, PAN, Sjogren syndrome)
- Meningitis
- Brain tumors (eg, meningioma, hemangioblastoma, craniopharyngioma, glioma)
- Down syndrome
- Neurofibromatosis type 1
- Head Irradiation
- Variable inclusion:
  - Sickle cell disease, atherosclerosis, hyperthyroidism, head trauma

Gonzalez NR 2023

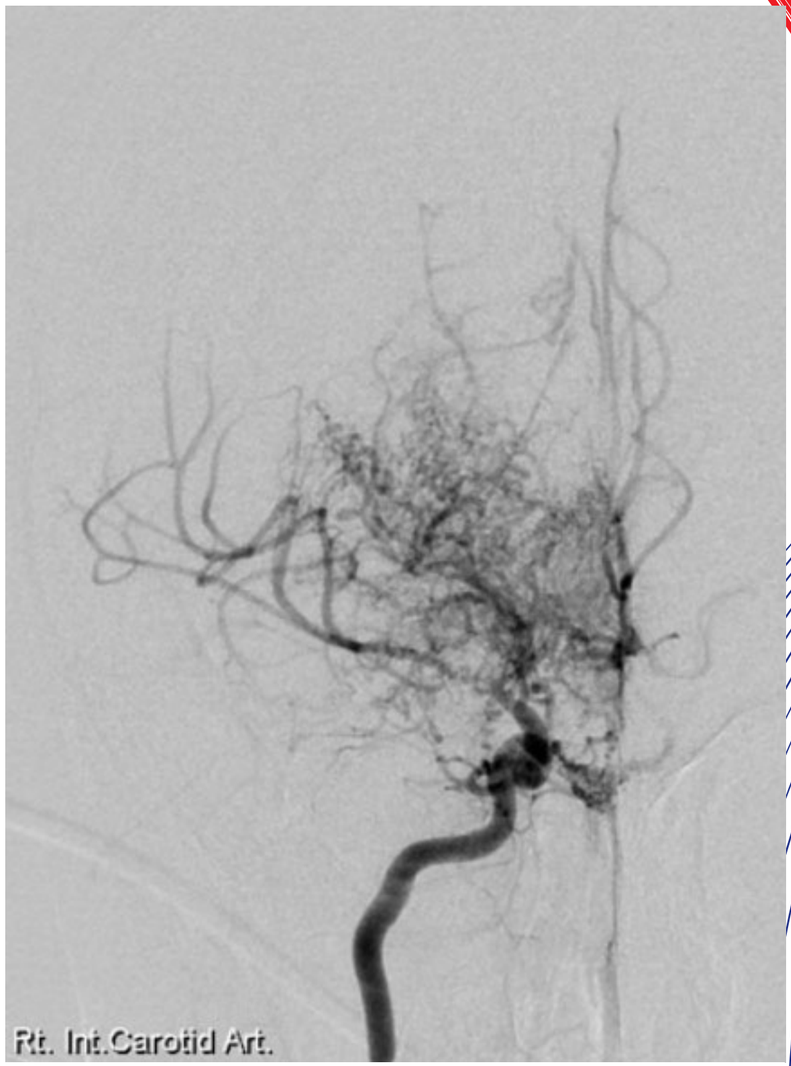
Symptoms

- Focal Neurological deficits
  - TIA, ischemic stroke, intracranial hemorrhage
  - Triggers: fever, dehydration, physical activity, hyperventilation, hypercoagulability, hypertension
- Seizures
- Headaches
- Neurocognitive impairment
- Secondary movement disorders

Gonzalez NR 2023

Moyamoya – Imaging

- Digital Subtraction Angiography (DSA)
  - Gold standard
  - Considerations
    - Invasive
    - Radiation and contrast exposure
- Patient-centered approach in imaging selection
  - Informative in monitoring disease progression
  - Ideally minimizes risk and exposure

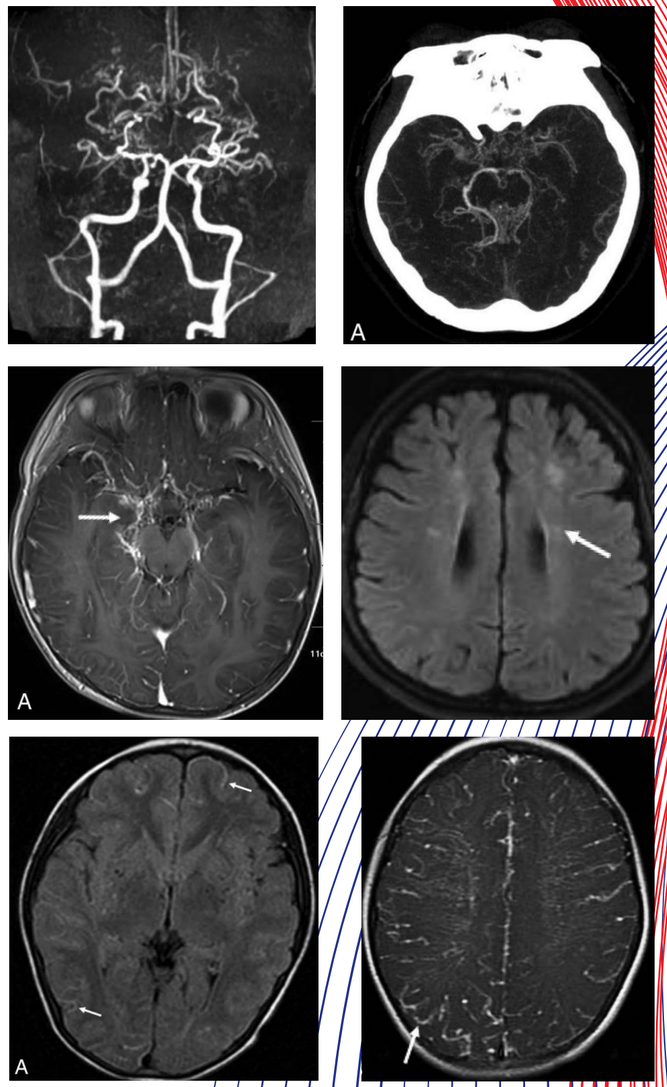


https://radiopaedia.org/articles/moyamoya-disease-1?lang=us

Li J 2019

Conventional Imaging

- MRA (3T) ≈ CTA
  - Sensitive to steno-occlusive disease terminal ICA, horizontal MCA
  - Can identify vascular networks in the BG and periventricular white matter
  - MRA advantages
    - Can be done without contrast
    - No radiation exposure
- MRI
  - Ivy sign, T1 and T2 weighted imaging
  - Infarct and hemorrhage identification



Lehman VT 2019, Li J 2019; Fujimura M 2022; Gonzalez NR 2023

Imaging – Hemodynamics and metabolism

- SPECT (radiation, $$, limited availability)
  - regional CBF and Cerebral vascular reserve (CVR)
- PET (radiation, $$, limited availability)
  - CBF, CBV, OEF, and cerebral metabolic rate of oxygen (CMRO2)
- Xe-CT (radiation, $$, limited availability)
  - CBF, CVR with vasodilator use
- CT perfusion (contrast, radiation)
  - CBF, CBV, MTT, and TTP, CVR with vasodilator use
- Quantitative DSA (contrast, radiation, invasive)
  - rTTP
- TCD (bone window limitations)
  - Blood flow volume in the ICA can be used as a correlate for CBF in the corresponding hemispheres

Li J 2019; Fujimura M 2022; Gonzalez NR 2023

MRI

TABLE 1. Key MRI techniques for evaluation of moyamoya disease

Technique	Utility
Cross-sectional MRI	
Volumetric techniques	Allow high-resolution imaging & multiplanar reformatting. Facilitate creation of 3D images & advanced image processing such as cortical thickness determination.
T2 FLAIR	Demonstrates the leptomeningeal "ivy sign" & medullary streaks. Allows assessment of regions of white matter T2 hyperintensity. Image appearance depends on technique (2D, 3D, recent Gd administration, synthetic MRI).
SWI	High sensitivity for most states of blood product, including chronic microbleeds. Can demonstrate prominent cortical & periventricular vasculature w/ increased deoxyhemoglobin & oxygen extraction.
Contrast-enhanced T1-weighted MRI	Demonstrates vascular enhancement corresponding to collateral arteries. Can demonstrate enhancing subacute infarcts.
DWI	High sensitivity for acute infarcts.
DTI & DKI	Allow assessment of anatomic connectivity btwn brain regions & can serve as an indicator of white matter integrity.
rsfMRI	Demonstrates the degree of functional connectivity btwn brain regions.
MRA	
3D-TOF	Delineates the lumen of major ICA & ECA branches w/o the need for intravenous contrast.
2D phase contrast	Allows assessment of direction of blood flow & approximation of flow velocity.
Time-resolved contrast enhanced	Can demonstrate arterial stenosis & progressive filling of collateral arteries.
Techniques to assess perfusion & CVR	
DSC	Can assess multiple perfusion parameters using a bolus of intravenous Gd. Interpretation can be quantitative or qualitative.
ASL	Facilitates assessment of CBF w/o the need for intravenous contrast. Interpretation can be quantitative or qualitative.
BOLD	Indirect representation of perfusion parameters w/o need of intravenous contrast. Interpretation is qualitative.
VWI	
A wide variety of techniques w/ high spatial resolution & suppression of signal from flowing blood	Differentiate btwn different causes of arterial stenosis. May serve as an indicator of MMD activity. Adjunct for assessment of the lumen.

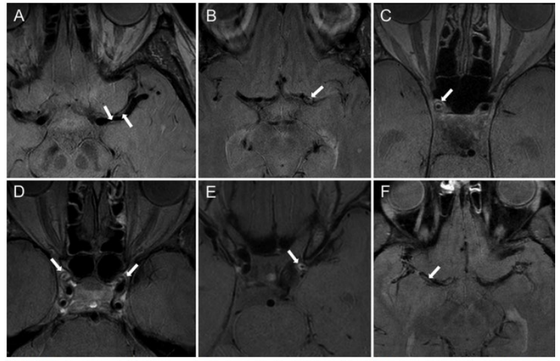


FIG. 6. VWI appearance of alternative causes of stenosis of the basal arteries with axial PD images demonstrating multiple distinct vessel wall features, although these vessel wall features can overlap in some cases. **A:** Eccentric plaques along the walls of the left M_1 segment (*arrows*) without negative remodeling are most consistent with atherosclerosis. **B:** In another case with focal short-segment stenosis, moderate associated vessel wall enhancement (*arrow*), and negative remodeling, the VWI findings are less specific; the favored diagnosis was atherosclerosis given the short segment involvement as seen on conventional angiography (not shown) and clinical presentation. Although atherosclerosis typically demonstrates normal vessel diameter or positive remodeling, it can occasionally demonstrate negative remodeling. **C:** Marked circumferential enhancement of the luminal surface of the right cavernous ICA wall (*arrow*) in a 75-year-old man with giant cell arteritis. **D:** Image obtained in a 66-year-old woman with primary angiitis of the CNS, demonstrating marked enhancement of the luminal border of the walls of both cavernous (*arrows*) and supraclinoid (not shown) ICAs with normal vessel diameter. **E:** Image obtained in a 46-year-old woman with a diagnosis of unilateral MMD, demonstrating marked circumferential vessel wall enhancement with negative remodeling (*arrow*). **F:** Dissection of the right M_1 segment demonstrating a thin linear flap (*arrow*) along the length of the vessel segment, separating the true lumen anteriorly from the dissected lumen posteriorly.

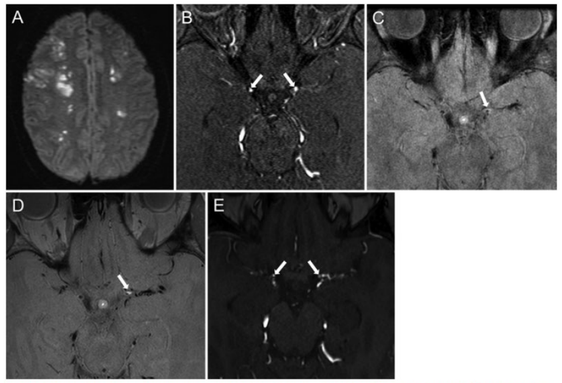


FIG. 7. A: A 31-year-old woman presented with bilateral border zone infarcts on DWI. **B:** Three-dimensional TOF MR angiogram obtained at presentation, demonstrating moderate stenosis of the bilateral distal supraclinoid ICAs and proximal M_1 segments (*arrows*). **C:** Axial PD VWI study with gadolinium, demonstrating mild to moderate circumferential vessel wall enhancement of the left supraclinoid segment (*arrow*) and no appreciable enhancement of the right ICA vessel wall. **D:** Axial PD VWI study with gadolinium obtained at the 8-month follow-up, demonstrating increased enhancement of the stenotic left segment (*arrow*). **E:** Axial 3D-TOF MR angiogram demonstrating progressive stenosis of both the nonenhancing right and enhancing left stenotic segments (*arrows*). This case demonstrates that infarcts and progressive stenosis can be associated with either enhancing or nonenhancing segments and that vessel wall enhancement can evolve over time.

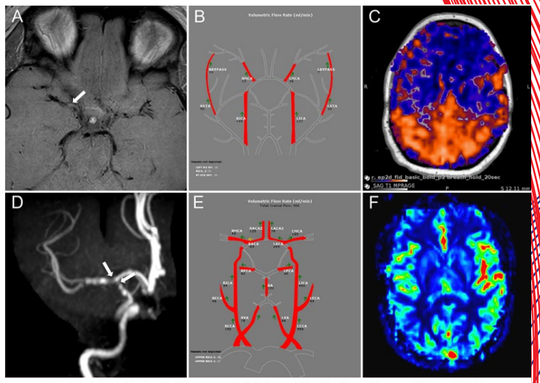


FIG. 4. Quantitative and direction blood flow assessment. **A–C:** Images obtained in a 40-year-old woman with bilateral MMD after a bilateral STA-MCA bypass. Axial PD VWI study with gadolinium, demonstrating marked stenosis or occlusion of the proximal right MCA (*arrow*) and marked stenosis of the proximal left MCA, better seen more inferiorly (A). Quantitative 2D phase-contrast image analysis segments (Nova software package) demonstrating anterograde flow within both bypasses (B). A 20-second breath-hold BOLD examination study, demonstrating decreased CVR throughout the anterior circulation bilaterally (*blue*) with preserved CVR posteriorly (C, *red*). **D–F:** Images obtained in a 48-year-old woman. Three-dimensional TOF MRA MIP study showing stenosis of the right supraclinoid ICA and proximal ICA stenosis (D, *arrows*). Quantitative 2D phase-contrast image analysis indicating reversal of flow within the right A, segment (*yellow arrow*), compatible with collateral flow to the right cerebral hemisphere via the circle of Willis (E). CBF image demonstrating normal to minimally diminished flow to the right cerebral hemisphere. CBV and MTT demonstrated similar findings (not shown), compatible with good collateral blood supply (F). BA = basilar artery; CCA = common carotid artery; L = left; PCA = posterior cerebral artery; R = right; VA = vertebral artery.

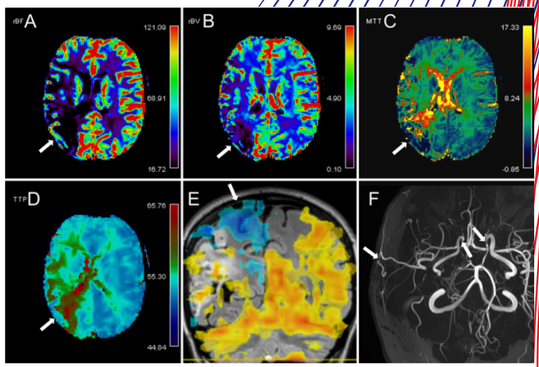


FIG. 5. Images obtained in an adult female with MMD and a history of right STA bypass. **A–D:** DSC perfusion with gadolinium permits evaluation of numerous parameters, including CBF (A), CBV (B), MTT (C), and TTP (D). There is decreased CBF and CBV (*arrows*) compatible with a large chronic infarct in the right cerebral parietal lobe. Some vascular perfusion persists with an elevated MTT and TTP (C and D, *arrows*), compatible with slow delayed flow within nonviable tissue. In the bilateral ACA territory, CBF and CBV are without substantial abnormality, compatible with adequate blood supply. DSC perfusion parameters in the left MCA and left posterior cerebral artery territories are also unremarkable. **E:** CVR was assessed with a 20-second breath-hold BOLD response superimposed on an axial 3D T2-weighted FLAIR image, demonstrating reduced CVR in the right ACA territory as a blue overlay (*arrow*), compatible with vascular steal. **F:** Three-dimensional TOF MIP image demonstrating focal stenosis of the bilateral distal supraclinoid ICAs. The STA bypass is also visualized with mild signal loss and narrowing near the level of the calvaria (*arrows*) but is otherwise patent.

Disease Progression

- Patients with progression, >50% will develop ischemic or hemorrhagic complications
  - Unilateral → bilateral progression ≈20%
  - Anterior → posterior progression ≈20%
- Posterior involvement
  - More severe presentation
  - Greater association w/ posterior hemorrhage and risk of recurrent hemorrhage

Kuroda S 2005; Hishikawa T 2014; Takahashi JC 2016; Funaki T, 2018

Ischemia and Hemorrhage

- Korean cohort
  - Ischemia
    - 5 yr - 17% stroke risk
    - 10 yr - 33% stroke risk
  - Hemorrhage
    - 5 yr - 15% risk
    - 10 yr - 40% risk
- Symptomatic patients in US
  - 5-year recurrent ischemic risk
    - 65% (unilateral)
    - 82% (bilateral)

Hallemeier CL 2006; Cho WS 2015, Gonzalez NR 2023

Ischemic stroke – IVT and EVT

- No RCT for acute ischemic stroke treatment (IVT, EVT, direct bypass)
- IVT may be considered per 2021 Japanese MMD guidelines
- Acute Ischemic Stroke meta summary, n = 10 (2295 records screened)
  - Median age 44.5 (IQR = 36-54)
  - 8 female, 2 male
  - 1 African-American, 2 Caucasian, one Hispanic, other 6 did not report race/ethnicity
  - Comorbities: HTN, HLD, prior stroke/TIA
  - Treatments: 6 IVT only, 2 IVT + EVT (1 w/ intracranial stent), 2 EVT only
  - Outcomes IVT and/or EVT
    - 7 of 10 w/ imaging (Improved imaging in 5, No ICH)
    - 9 of 10 w/ reported functional outcome, 9 showed improvement
    - Complications (1 emergent STA-MCA bypass, 1 persistent LICA thrombus and stenosis)
- Non-randomized studies: Direct bypass and EDAS w/ benefit in secondary ischemic stroke prevention

Koh MY 2022; Jeon JP 2018, Gonzalez NR 2015

Antiplatelet Therapy

- Antiplatelet monotherapy
  - Weak recommendation in patients with TIA or ischemic stroke per AHA/ASA 2021 guidelines
  - May consider use in medical management of ischemic MMD per Japanese guidelines
- Role of cilostazol? - no specific guideline recommendation for use
  - Phosphodiesterase 3 inhibitor w/ both antiplatelet and vasodilation effects and low bleeding risk

Gonzalez NR 2023

Table 4. Summary of Antithrombotic and Thrombolytic Use in Ischemic MMD

Oral antiplatelets	Guidelines recommendations				
	AHA/ASA 2021 Guideline Recommendation: In patients with MMD and a history of ischemic stroke or TIA, the use of antiplatelet therapy, typically aspirin monotherapy, for the prevention of ischemic stroke or TIA may be reasonable (Class of Recommendation: 2b [weak], Benefit ≥Risk; Level of evidence: C-LD [Limited Data]).[59] 2021 Japanese Guidelines for Management of MMD: Oral administration of antiplatelet agents may be considered as a medical treatment for ischemic MMD (Recommendation Grade: C, Level of Evidence: low).[3]				
Oral antiplatelets and vasodilator, cilostazol	Guidelines recommendations				
	No specific recommendation for cilostazol use in ischemic MMD from AHA/ASA or Japanese Guidelines.[3,59]				
	Selected studies				
	Study	Study type	MMD population	Outcome measures	Results
	Seo et al, 2021[62]	Retrospective, population-based, cohort study, comparing cilostazol vs other APD vs no APD.	Korean Health Insurance data on newly diagnosed MMD over 14 y with 14 y follow-up.	Survival.	Reduced mortality with: Cilostazol >other APD >no APD.
	Chiba et al, 2018[63] Ando et al, 2019[64] Kitakami et al, 2022[65]	Prospective observational studies comparing cilostazol vs clopidogrel.	Nonsurgical, symptomatic ischemic MMD without misery perfusion on PET.	CBF on PET. Cognition. Recurrence of ischemic events.	Improvement in CBF at 2 y: cilostazol >clopidogrel.[63] Improvement in cognition at 2 y: cilostazol >clopidogrel.[64] Overall APD (cilostazol or clopidogrel) led to low recurrence of ischemic events at 5 y.
Intravenous thrombolysis with rt-PA	Guidelines recommendations				
	2021 Japanese Guidelines for Management of MMD: Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) may be considered under careful evaluation of the risk of hemorrhagic complication in the hyperacute phase of cerebral ischemia in MMD (Recommendation Grade: C, Level of Evidence: low).[3]				

AHA/ASA indicates American Heart Association/American Stroke Association; APD, antiplatelet drug; CBF, cerebral blood flow; MMD, moyamoya disease; and PET, positron emission tomography.

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Intracranial hemorrhage

- Japan Adult Moyamoya Trial
- 50% adult-onset MMD experience ICH
- Multicenter RCT, 22 sites in Japan
  - n = 80 (42 bypass, 38 MM)
  - Originally projected 160 (slow enrollment)
  - Balanced anterior and posterior hemorrhage sites
- Treatment arms
  - Conservative medical care: HTN control, avoidance APD/OAC (unless recurrent TIA/stroke)
  - EC-IC direct bypass: both sides within 3 months of enrollment
- 5 yr outcomes
  - annual monitoring, imaging, measured bleeding time & coagulation time

Table 3. Baseline Characteristics of Patients

	Surgical Group (n=42)	Nonsurgical Group (n=38)	*P* Value
Mean age±SD, y	42.5±11.3	41.4±12.2	0.34
Female ratio	66.7%	73.7%	0.49
Hypertension (%)	7 (16.7)	9 (23.7)	0.43
Diabetes mellitus (%)	1 (2.4)	2 (5.3)	0.46
Hyperlipidemia (%)	2 (4.8)	2 (5.3)	0.65
Valvular heart disease (%)	0 (0.0)	0 (0.0)	
Atrial fibrillation (%)	0 (0.0)	0 (0.0)	
Moyamoya disease in relatives (%)	6 (14.3)	1 (2.6)	0.07
History of hemorrhagic stroke (%)	4 (9.5)	4 (10.5)	0.59
History of ischemic events (%)	12 (28.6)	10 (26.3)	0.82
Hemorrhagic types			
Intraparenchymal (ICH)	14	8	0.22
Extraparenchymal extension			
ICH+IVH	26	29	
SAH only	2	1	
Site of hemorrhage			
Anterior (type A)*	24	21	0.87
Posterior (type B)†	18	17	

ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.

*Hemorrhage attributed to rupture of the anterior collateral vessels (eg, caudate nucleus or putamen).

†Hemorrhage attributed to rupture of the posterior collateral vessels (eg, thalamus or trigone of the lateral ventricle).

Miyamoto S 2014

Table 4. Details of Outcomes and Cox Regression Analysis

	Surgical Group (n=42)		Nonsurgical Group (n=38)			
	n	Rate, %	n	Rate, %	Hazard Ratio (95% CI)	*P* Value
Primary end point	6	14.3	13	34.2	0.391 (0.148–1.029)	0.057
Recurrent bleeding	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052
Completed stroke	1	2.4	0	0.0	…	…
Crescendo TIA (bypass required)	0	0.0	1	2.6	…	…
Secondary end point (recurrent bleeding or related death/severe disability)	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052

CI indicates confidence interval; and TIA transient ischemic attack.

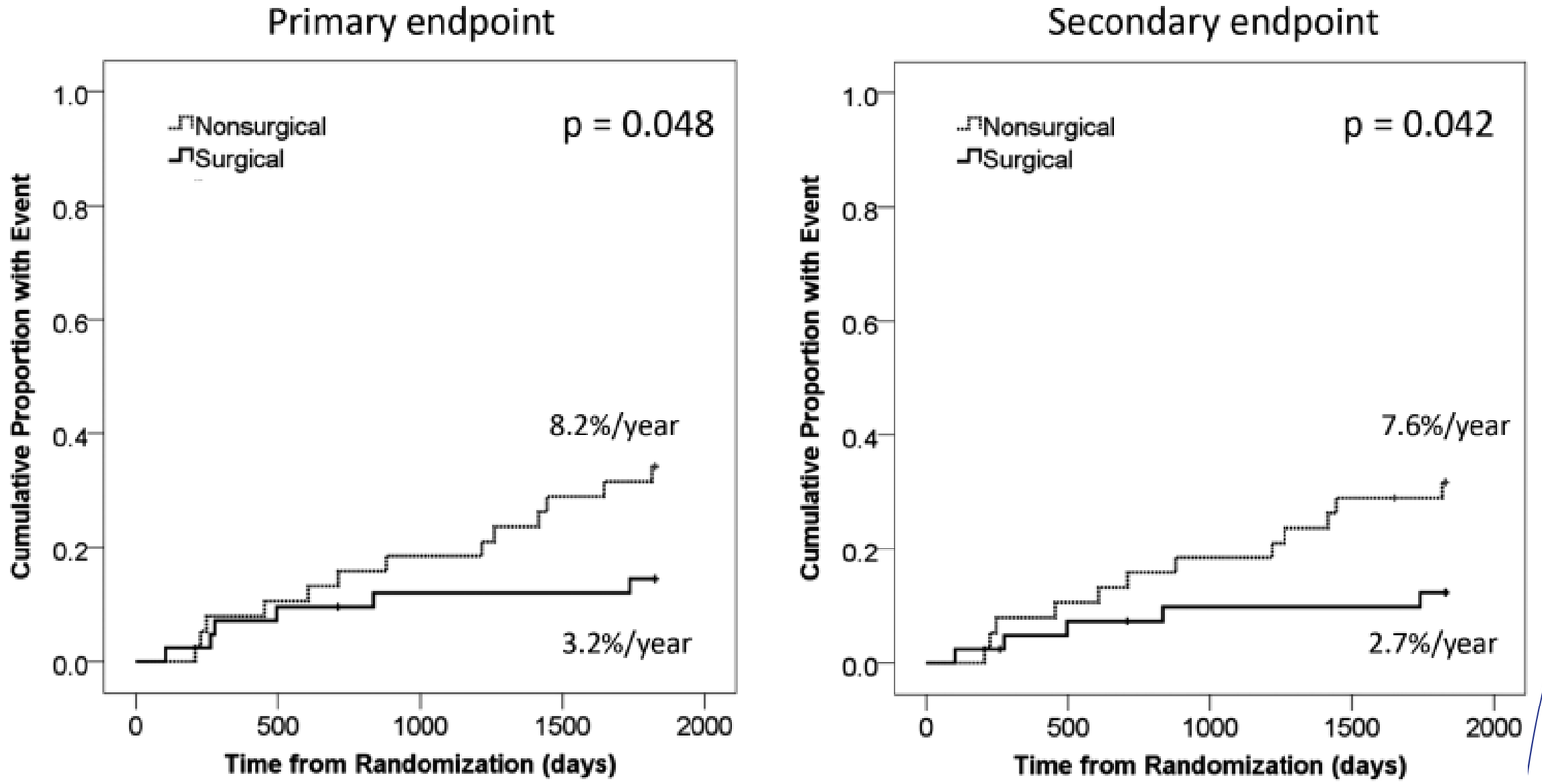

Figure 2. Kaplan–Meier cumulative curves for end points.

Miyamoto S 2014

Headache attributed to Moyamoya angiopathy

- Description:
  - Chronic recurrent headache, which may be migraine-like, caused by and associated with the other clinical features of Moyamoya angiopathy.
- Diagnostic criteria:
  A. Recurrent headache fulfilling criterion C
  B. Neuroimaging evidence of Moyamoya angiopathy (MMA)
  C. Evidence of causation demonstrated by both of the following:
     1. Headache has developed in close temporal relation to other symptoms and/or clinical signs and/or imaging evidence of MMA, or led to its discovery
     2. Either or both of the following:
        a. Headache has significantly worsened in parallel with other symptoms and/or clinical and/or radiological signs of worsening of MMA
        b. Headache has significantly improved after revascularisation surgery
  D. Not better accounted for by another ICHD-3 diagnosis.

Moyamoya Headache Pathophysiology

- Nociceptive activation
  - Arteries, venous sinuses, dura
  - Trigeminal nerve and branches
    - Intracranial ICA, proximal vessels of Circle of Willis, meningeal vessels (MMA), dura
  - High expression
    - Vascular endothelial growth factor
    - Angiopoietin-2 (pro-angiogenic cytokine)
  - Dilated leptomeningeal collaterals
    - Trans-dural/trans-cranial ECA anastomosis
    - Stimulation of dural perivascular nociceptors, trigeminovascular system, neuroinflammatory response
- Microvascular ischemia/hypoperfusion and cortical spreading depression
  - Consider role of surgical revascularization
- Vascular endothelial damage
  - Collagen exposure – platelet activation
  - Possible role of antiplatelets for prevention

Chiang CC 2022

Moyamoya Headache

- Often accompanied by other neurological symptoms
  - paresis, seizures, dysarthria, ptosis, and unilateral RLS
- Rule out hemorrhage w/ new or worsening headache
  - 2% de novo hemorrhage annual risk, higher if choroidal collaterals
- Headache (20-76.4%)
  - Migraine with aura (>50%)
  - Migraine without aura
  - Tension-type
  - Hemiplegic migraine
  - Cluster
- Surgical Revascularization
  - Many improve, but some worsen
  - Some will develop new onset post-surgical headache

Chiang CC 2022; Gonzalez 2023

Moyamoya Headache

AVOID

- Medications that limit vasodilation / cerebral autoregulation
  - CGRP therapies
- Vasoconstrictors
  - Triptans, ergots
- BP lowering
  - Beta-blockers, calcium channel blockers

CONSIDER

- Prophylaxis
  - Topiramate
  - Sodium valproate
  - Antidepressants, TCAs
  - Gabapentin
  - Tizanidine
  - Memantine
  - Consider antiplatelets (ischemic dz)
- Abortive
  - Acetaminophen
  - Antiemetics
  - Dopamine antagonists

Chiang CC 2022; Gonzalez NR 2023

Risk factor management

- Genetic testing
  - Unclear benefit in non-East Asian populations, likely autosomal dominant with incomplete penetrance
  - Family history (Korean cohort)
    - Most beneficial if affected: twin >> sibling >> mother >> father
- Identification and treatment of underlying disease process in MMS
- Treatment of
  - Hypertension, avoiding hypotension
  - Dyslipidemia
  - High BMI
  - Hypercoagulable states

Noh HJ 2015; HiranoY 2020; Ge P 2020; Gonzalez NR 2023

Summary

- Clarify MMD vs MMS
  - Identify underlying disease processes for MMS as a therapeutic target
- Symptomatic or worsening
  - Evaluate for hemorrhage/infarction
  - Early involvement of neurosurgical team for collaborative approach
  - Symptom treatments should minimize potential harm
- Patient-centered imaging selection to monitor progression
- Acute IVT and EVT may be considered with careful patient selection
- Future directions
  - Development of disease models (basic/translational)
  - Collaborations to enhance high-quality registries, standardize terminology and diagnostic criteria
  - Development of standardized imaging protocols to monitor disease progression and outcomes
  - Development of RCTs

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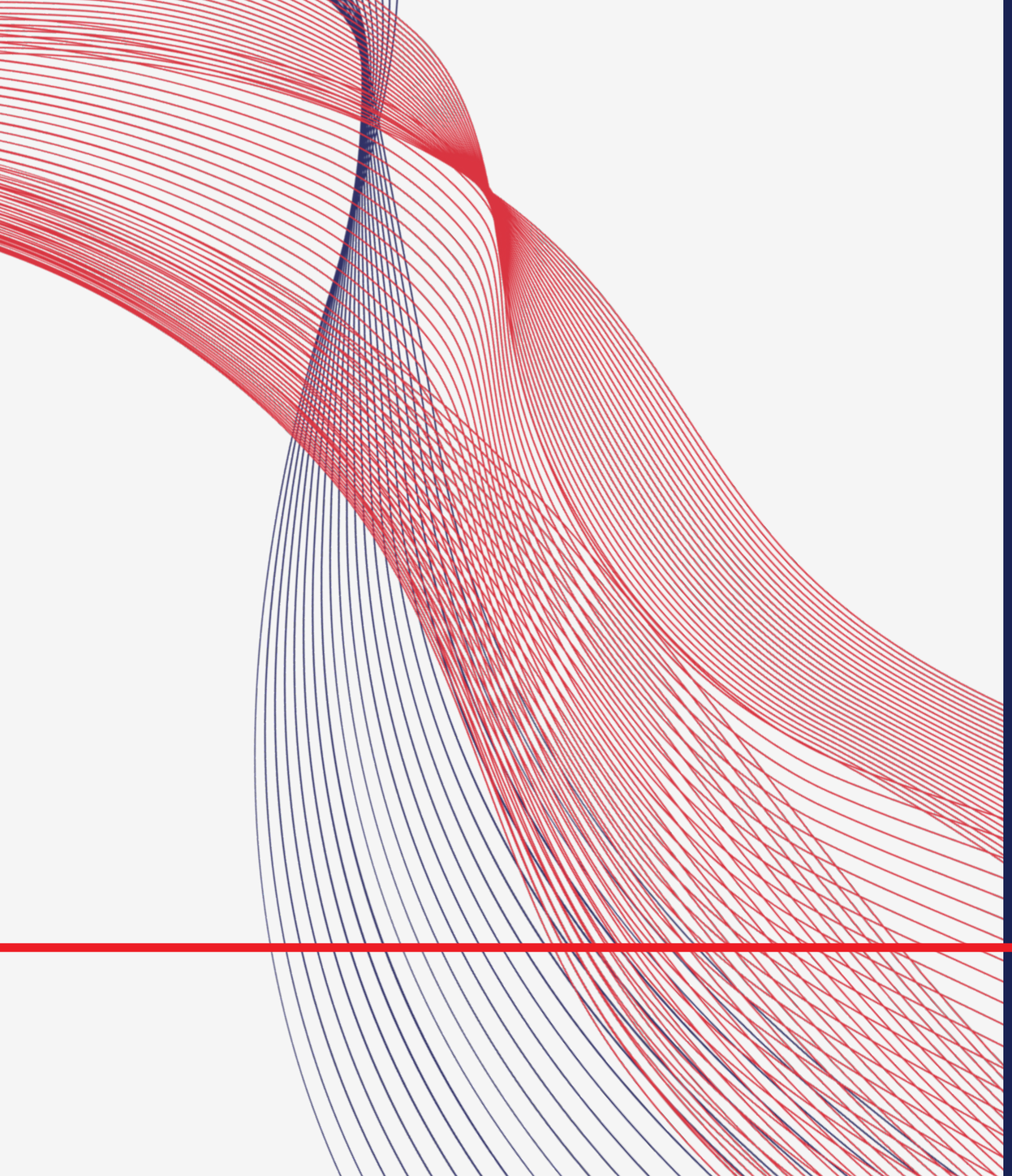

Thank you