Neuro/Cardio CME

Minor Stroke Treatment
Lifestyle Impacts on Stroke Risk

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Disclosures

- I have nothing to disclose

College move-in day, September 2023

Outline

- Treatment of patients with minor stroke symptoms
- Emerging considerations for acute stroke treatment
- Lifestyle impact on stroke: exercise and alcohol consumption

Case 1

- 69 y/o woman with HTN, DM, HLD presents within an hour of symptom onset complaining of left sided tingling and numbness of face/arm/leg.
- On exam she has mild left facial droop, left-sided tingling and numbness, some left hand clumsiness and mild drift. Muscle groups are strong on testing. No neglect. NIHSS 3.
- CT/CTA negative

Case 2

- 52 y/o man with HTN presents within 2 hours of right sided visual loss. On exam he has a complete right homonymous hemianopsia and mild right facial droop.
- NIHSS = 3.
- CT negative. CTA negative

How would you treat these people? TPA/TNK? Aspirin? DAPT?

Minor Strokes

- How should patients with low stroke scale, non-disabling strokes be treated?

Data

- PRISMS Trial- 2018
- Randomized acute stroke patients with NIHSS < 6 to IV tpa or aspirin
- Outcome was reaching MRS of 0-1
- Stopped early after 313 patients
  - 78% of tPA patients and 81% of aspirin patients were at mRS of 0 or 1 at 90 days

Khatri P, Kleindorfer DO, Devlin T, et al. Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial. *JAMA*. 2018;320(2):156-166. doi:10.1001/jama.2018.8496

- ARAMIS Trial 2023
- Non-inferiority Trial of DAPT
- 760 patients with NIHSS < 6 randomized to tPA or DAPT with aspirin/clopidogrel
- Outcome was mRS 0-1
- 93% of DAPT and 91 % of TPA patients reached mRS of 0-1 at 90 days
- 1 bleed in DAPT and 3 in tpa
- DAPT is NON-inferior to tPA.

Chen HS, Cui Y, Zhou ZH, et al. Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke: The ARAMIS Randomized Clinical Trial. *JAMA*. 2023;329(24):2135-2144. doi:10.1001/jama.2023.7827

Minor, non-disabling stroke patients

- I am going to defer to DAPT unless patient with disabling symptoms like a visual field cut, aphasia, etc.

Case 1

- 69 y/o woman with HTN, DM, HLD presents within an hour of symptom onset complaining of left sided tingling and numbness of face/arm/leg.
- On exam she has mild left facial droop, left-sided tingling and numbness, some left hand clumsiness and mild drift. Muscle groups are strong on testing. No neglect. NIHSS 3.
- CT/CTA negative

I treated this patient with DAPT

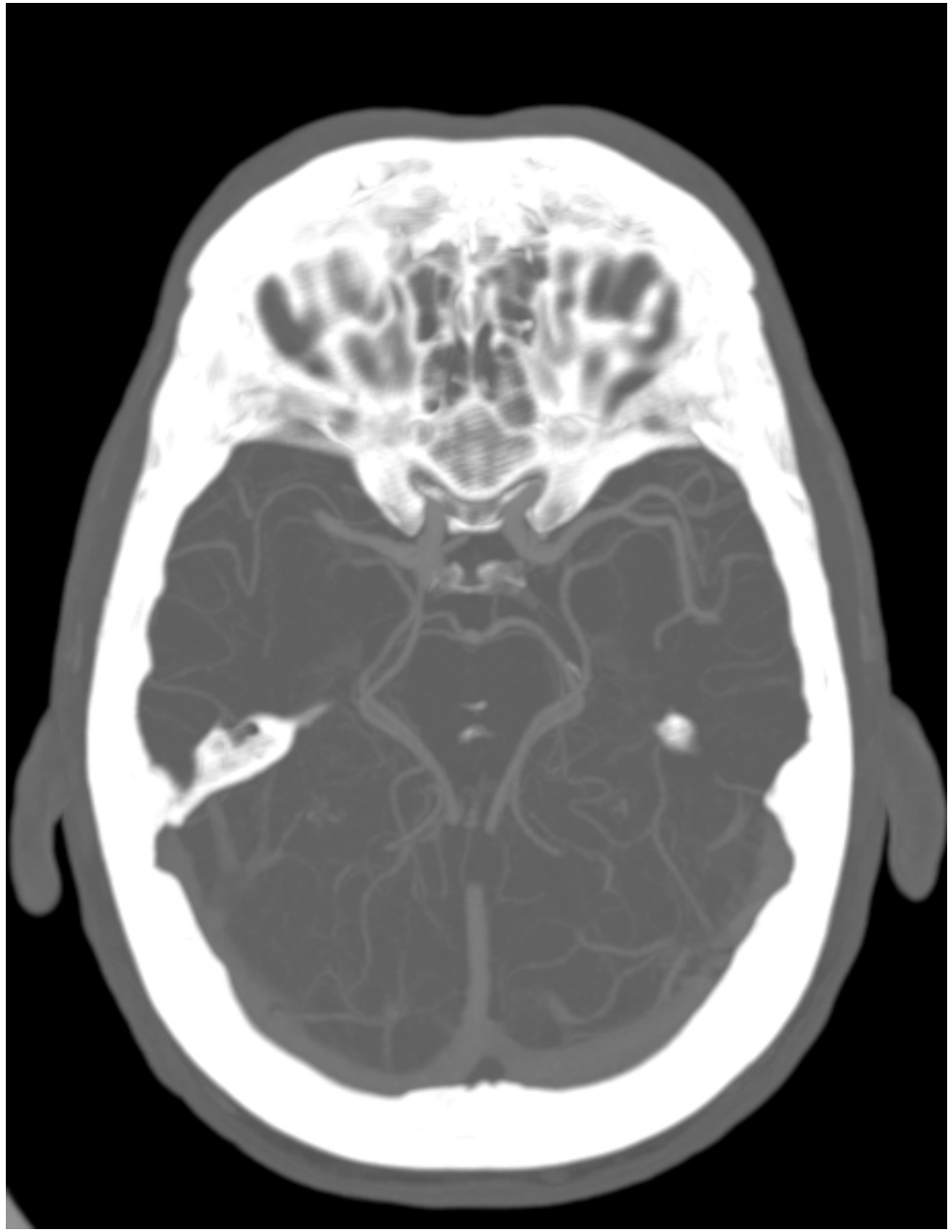
Case 2

- 52 y/o man with HTN presents within 2 hours of right sided visual loss. On exam he has a complete right homonymous hemianopsia and mild right facial droop.
- NIHSS = 3.
- CT negative. CTA negative

I gave this patient TNK

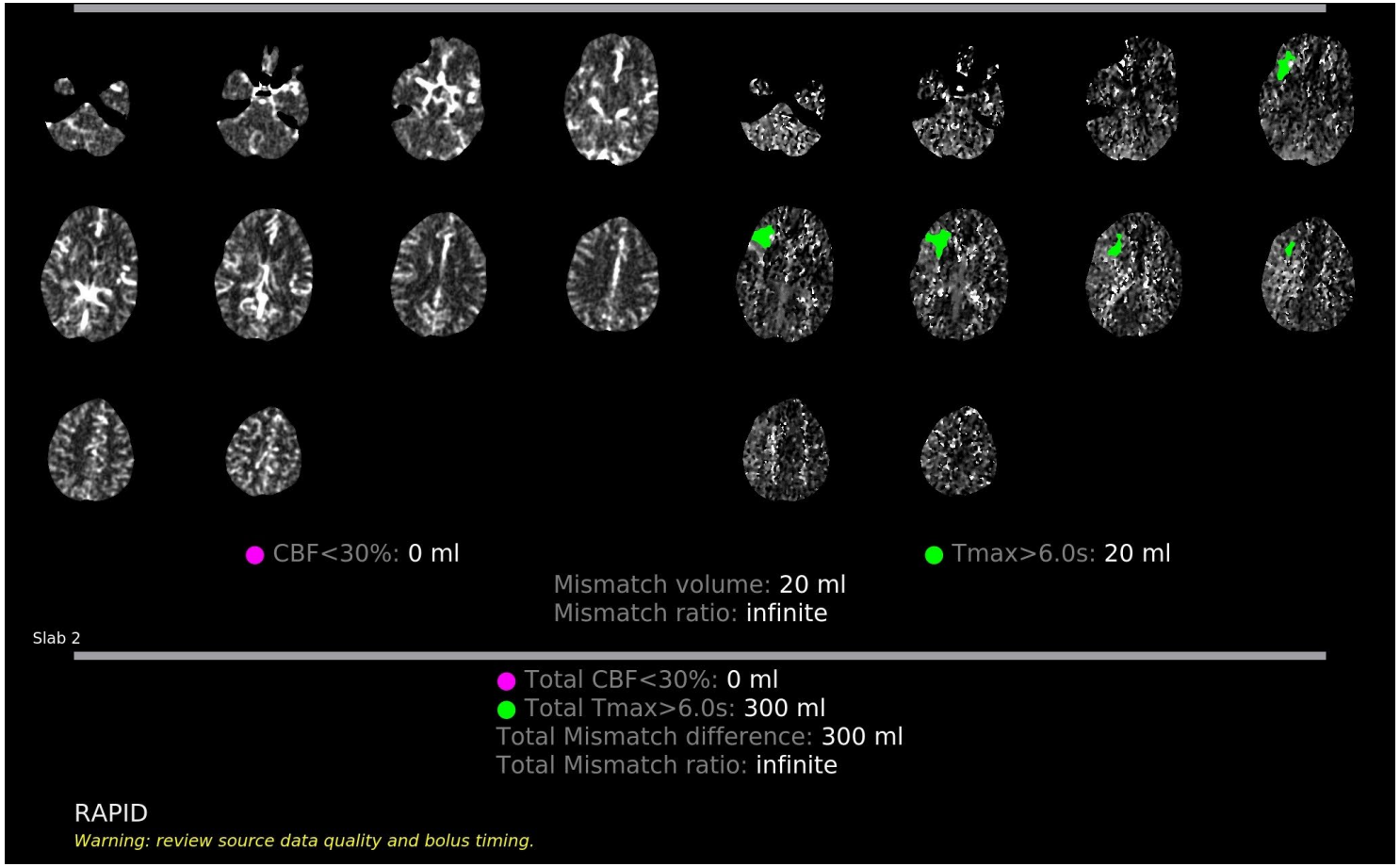
Case 3

- 53 y/o healthy man with known a-fib on apixaban. He ran out of his apixaban 3 days PTA.
- He came in with sudden onset of left arm weakness, slurred speech left facial droop to an outside hospital. NIHSS of 6. CT scan negative.
- He received TNK and was admitted there. His symptoms completely resolved. Later that evening his symptoms recurred with some left arm weakness and numbess but not as severe as the first time. CTA at outside hospital was then done.



Case

- He was transferred to our hospital then. Upon arrival he has mild facial droop, no dysarthria. Some pronator drift and abnormal sensation in the left hand. Leg is asymptomatic. NIHSS 3.
- CT Perfusion is done/


CBF<30%: 0 ml
Tmax>6.0s: 20 ml
Mismatch volume: 20 ml
Mismatch ratio: infinite
Slab 2
Total CBF<30%: 0 ml
Total Tmax>6.0s: 300 ml
Total Mismatch difference: 300 ml
Total Mismatch ratio: infinite
RAPID
Warning: review source data quality and bolus timing.

Case

- So, what is your next step? He is still within the 24 hour thrombectomy window.
- Do you go after the clot?
- Do you put him on heparin?
- Do you put him on antiplatelets?

What is the data

- Its scary to look at an M1 or proximal M2 clot and do nothing.
- 25% of LVO patients with a low stroke scale will deteriorate.
  - However, that means 75% do not.

Meta-analysis of 3 RCTs

- Looked at patients with LVOs (Distal ICA, M1, proximal M2)
- NIHSS < 7
- 236 patients
  - 139 received EVT, 50% had M1 occlusions and 15% ICA
  - 97 received medical therapy. 25% had M1 only 2% ICA
- Outcomes
  - EVT patients: 61% achieved mRS 0,1
  - MT patients: 63% achieved mRS 0,1
  - Mortality was the same
  - EVT patients had higher risk of early decline

Volny O, Zerna C, Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R, Kovar M, Sevcik P, Rohan V, Fiksa J, Cernik D, Jura R, Vaclavik D, Cimflova P, Puig J, Dowlatshahi D, Khaw AV, Fainardi E, Najm M, Demchuk AM, Menon BK, Mikulik R, Hill MD. Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. Neurology. 2020 Dec 15;95(24):e3364-e3372. doi: 10.1212/WNL.0000000000010955. Epub 2020 Sep 28. PMID: 32989100; PMCID: PMC7836655.

Case 3

- So, we put him in the ICU to monitor. At 24 hours post-TNK he received aspirin.
- The next day he was much better with face droop gone, no more drift just a little pronation. Still had some sensory loss in the left hand but coordination was much better.
- TCD showed good flow in the right MCA both proximally and distally indicating recanalization.
- Kept him one more day in the hospital.
- D/c on day 3 and back on his eliquis
- Sometimes its better to watch and wait

Case 4

- 63 year old with mild dementia, HTN, HLD has sudden onset of left sided weakness and neglect. Lives at home. Does all ADLs, still drives, cooks.
- Presents to the ED within 2 hours of symptoms onset
- Not on anticoagulants, no recent trauma or bleeding
- VS: BP 179/88 HR 92 afebrile
- Neuro exam: Right MCA syndrome with right gaze preference, left face droop, left hemiparesis and neglect.
- NIHSS 9-10

Case 4

- CTA shows distal M1 cutoff.
- CTP shows 9cc core and 88cc penumbra for whatever that is worth at 2 hours.
- How would you treat her?
  - TNK?
  - Thrombectomy?
  - TNK + thrombectomy?
  - DAPT?

Case 4

- Additional history:
  - She is receiving lecanemab for treatment of early Alzheimer's disease.

- Does that fact change your plan?

Lecanemab

- Anti-amyloid antibody for treatment of early Alzheimer’s disease
- FDA approved now for treatment
- A major side effect is amyloid-related imaging abnormalities
  - Microhemorrhages and SAH seen as hemosiderosis on MR imaging
  - Amyloid-related edema

12.6% of patients developed ARIA-E
17.3 developed ARIA-H
Patients homozygous for APO-E 4 Allele had the most risk for ARIA

~70% patients with ARIA was detected at 3 months and resolved within ~4 months of detection.

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

van Dyck CH, Swanson CJ, Aisen P, et al.
Lecanemab in Early Alzheimer's Disease.
N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948

Literature Case

- 65 y/o patient on lecanemab presented within 30 minutes of onset of aphasia and left gaze preference.
- She had received her last infusion of lecanemab 4 days prior.
- MRI 81 days prior on the study showed no microhemorrhages or edema
- Head CT showed distal left M2 occlusion
- BP was within tPA parameters (163/84) and she had no exclusions
- She was treated with IV tPA

Case

- 50 minutes into the infusion her BP spiked to 250/111 and the tPA was stopped and CT showed multifocal hemorrhages.
- She was treated with cryo and tranexamic acid
- She has severe, global aphasia and agitation and seizures and ended up intubated.
- MRI showed infarctions and multiple cortical and subcortical hemorrhages with surrounding edema.
- She subsequently went on Hospice care and died.

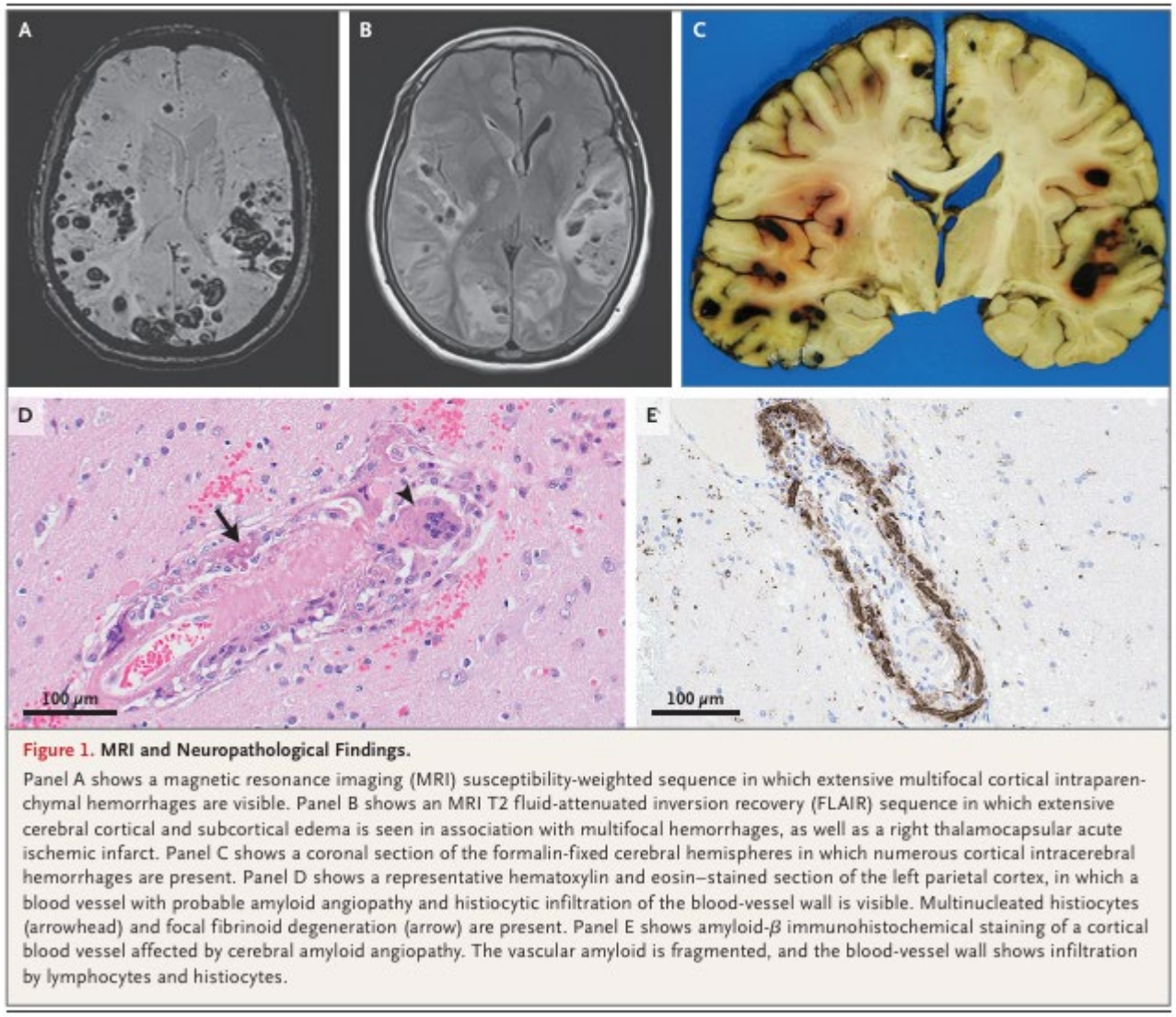


Figure 1. MRI and Neuropathological Findings.

Panel A shows a magnetic resonance imaging (MRI) susceptibility-weighted sequence in which extensive multifocal cortical intraparenchymal hemorrhages are visible. Panel B shows an MRI T2 fluid-attenuated inversion recovery (FLAIR) sequence in which extensive cerebral cortical and subcortical edema is seen in association with multifocal hemorrhages, as well as a right thalamocapsular acute ischemic infarct. Panel C shows a coronal section of the formalin-fixed cerebral hemispheres in which numerous cortical intracerebral hemorrhages are present. Panel D shows a representative hematoxylin and eosin–stained section of the left parietal cortex, in which a blood vessel with probable amyloid angiopathy and histiocytic infiltration of the blood-vessel wall is visible. Multinucleated histiocytes (arrowhead) and focal fibrinoid degeneration (arrow) are present. Panel E shows amyloid-β immunohistochemical staining of a cortical blood vessel affected by cerebral amyloid angiopathy. The vascular amyloid is fragmented, and the blood-vessel wall shows infiltration by lymphocytes and histiocytes.

Autopsy showed multiple hemorrhages, cerebral Amyloid angiopathy, diffuse histiocytic vasculitis With necrotizing vasculopathy involving amyloid Deposition within vessel walls but not outside of The vessels.

Reish NJ, Jamshidi P, Stamm B, et al. Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. *N Engl J Med*. 2023;388(5):478-479. doi:10.1056/NEJMc2215148

Appropriate Use Recommendations:

- Lecanemab may increase the risk of hemorrhage from concomitant administration of thrombolytics (intravenous or intra-arterial), and we recommend that patients on lecanemab not be treated with acute thrombolytics until safety evidence of their combined use is available.

- Cummings, J., Apostolova, L., Rabinovici, G.D. *et al.* Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* **10**, 362–377 (2023).

WFU Protocol

- For patients with dementia we are now asking about “IV treatments for Alzheimer’s disease.”
- We view lecanemab use as a contraindication to tPA/TNK therapy
  - If last dose was > 6 months ago, then would consider treatment for disabling stroke
  - With appropriate risk discussion with family

Exercise and Stroke

Mission Man Triathlon
July 2023
Team: The Loose Cannons
Ryan: Swim
Pat: Bike
Harris: Run
Podium Finish: 3rd place for The relays

Exercise and Stroke

- SAMMPRIS Trial (stenting vs medical management for severe intracranial stenosis)
- Medical Management was superior to stenting for reduction of recurrent stroke for intracranial stenosis
- The greatest benefit was from exercise and physical activity.

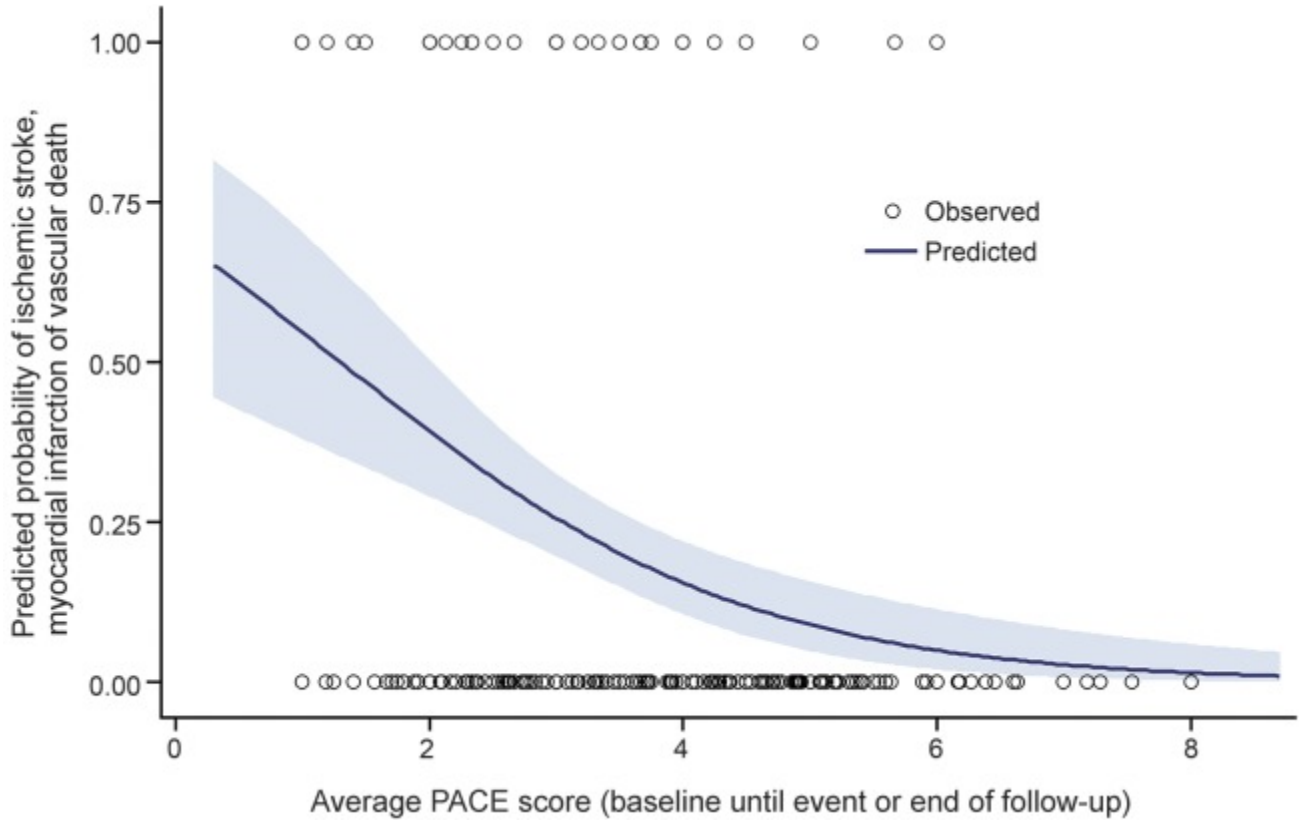
Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet*. 2014;383(9914):333-341. doi:10.1016/S0140-6736(13)62038-3

PACE Score for evaluating physical activity

1. I don’t do regular vigorous or moderate exercise now, and I don’t intend to start in the next 6 months.
2. I don’t do regular vigorous or moderate exercise now, but I have been thinking of starting in the next 6 months.
3. I’m trying to start doing vigorous or moderate exercise, but I don’t do it regularly.
4. I’m doing vigorous exercise less than 3 times per week (or) moderate exercise less than 5 times per week.
5. I’ve been doing 30 minutes a day of moderate exercise 5 or more days per week for the last 1-5 months.
6. I’ve been doing 30 minutes a day of moderate exercise 5 or more days per week for the last 6 months or more.
7. I’ve been doing vigorous exercise 3 or more days per week for the last 1-5 months.
8. I’ve been doing vigorous exercise 3 or more days per week for the last 6 months or more

Patients who achieved a PACE score of 4 had a 40% reduction in stroke, MI and vascular death over 3 year f/u

Turan TN, Nizam A, Lynn MJ, et al. Relationship between risk factor control and vascular events in the SAMMPRIS trial. *Neurology*. 2017;88(4):379-385. doi:10.1212/WNL.0000000000003534



Fitted logistic regression of combined endpoint (stroke, myocardial infarction, or vascular death) predicted by physical activity (Physician-based Assessment and Counseling for Exercise [PACE] score) averaged from baseline until the first event or end of follow-up Maximum follow-up was 3 years.
The blue shaded band represents 95% confidence intervals for the probability of the event. The markers represent the observed data.

Exercise

- 10-year cohort study showed that the high fitness group had a 68% reduction of risk of stroke and death compared to the low fitness group
- This effect remained after controlling for tobacco, alcohol, BMI, HTN DM
- Dose response: more is better

Prior PL, Suskin N. Exercise for stroke prevention. Stroke and Vascular Neurology 2018;3: e000155. doi:10.1136/ svn-2018-000155

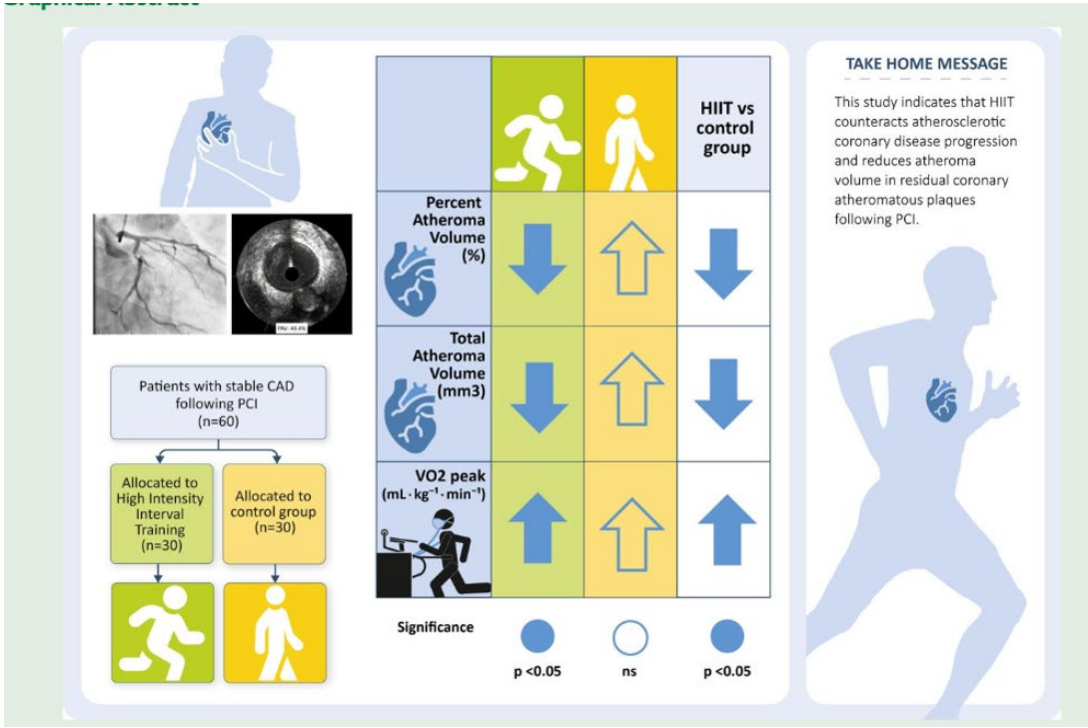
What does exercise do?

- Lipids
  - Increases HDL cholesterol on average 4-5%
  - This has a significant effect on the HDL: LDL ratio which is important to cardiovascular risk. The increased HDL may help promote plaque regression
  - Very aggressive aerobic exercise can increase HDL up to 13%
- BP
  - There is post-exercise hypotension of 2-12mmHg for several hours after an exercise session
  - On average, aerobic training reduces SBP and diastolic by 3mm but can range from 2-10mm Hg
  - A 1mm reduction in SBP = 6% reduction in stroke mortality
- Regular exercise lowers CRP

Cardoso Jr CG, Gomides RS, QueirozACC, Pinto LG, Lobo FS, T Tinucci,Mion Jr D, Forjaz CLM. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. Clinics. 2010;65(3):317-25

Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res*. 2015;117(2):207-219. doi:10.1161/CIRCRESAHA.117.305205

Vesterbekkmo EK, Aksetøy IA, Follestad T, et al. High-intensity interval training induces beneficial effects on coronary atheromatous plaques: a randomized trial. *Eur J Prev Cardiol*. 2023;30(5):384-392. doi:10.1093/eurjpc/zwac309



- 6 months HIIT caused a 1.4% reduction in plaque volume
- This is a similar effect to some of the statin trials on reduction of plaque burden

Iatan I, Guan M, Humphries KH, Yeoh E, Mancini GBJ. Atherosclerotic Coronary Plaque Regression and Risk of Adverse Cardiovascular Events: A Systematic Review and Updated Meta-Regression Analysis. *JAMA Cardiol*. 2023;8(10):937-945. doi:10.1001/jamacardio.2023.2731

- 1 % reduction in plaque burden results in a 20% reduction of major adverse cardiac events (MACE) [MI, stroke, mortality]

- Dawson LP, Lum M, Nerleker N, Nicholls SJ, Layland J. Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2022;79(1):66-82. doi:10.1016/j.jacc.2021.10.035
  - Generalize a trend towards a positive effect on plaque stabilization and regression with moderate to intense exercise.
  - This is cardiac data but you can probably generalize to stroke as well

What other data for exercise effect on stroke outcomes do we have?

- UK BioBank Study
- Factors associated with decreased stroke risk:
  - Walking for commute = 11% reduction
  - Strenuous exercise = 27% reduction
- Factors associated with increased stroke risk:
  - Commuting by car or train = 63% increased stroke risk
  - TV watching: 15% increased stroke risk

AHA guidelines for stroke

- Recommends 3-4 sessions/week of moderate to vigorou exercise of 40 minutes or more
  - Moderate intensity means you break a sweat and/or significar resting heart rate

- Dose response:
  - Any amount of exercise is better than none
  - Taiwanese study showed that just 15 minutes of exercise 3 times per week = 14% reduction in all cause mortality
- Being sedentary is not good.
- Get off the couch and walk. Better yet, run or cycle.

Alcohol and Stroke

Alcohol and Stroke

- Classic J-shaped curve
- Moderate alcohol use is associated with lower ischemic stroke incidence
  - A meta-analysis of 27 studies showed a relative risk of 0.9 for moderate drinkers compared to non-drinkers or heavy drinkers
  - Why is alcohol beneficial? It increases HDL cholesterol
- Any alcohol is bad for risk of intracranial hemorrhage and SAH with the risk rising linearly with increased consumption
- Newer data is showing that any alcohol is associated with increased all cause mortality
- Alcohol is bad for the heart.
  - Up to 1/3 of non-ischemic cardiomyopathies in the US may be related to alcohol!

So, what do you do to decrease your stroke risk?

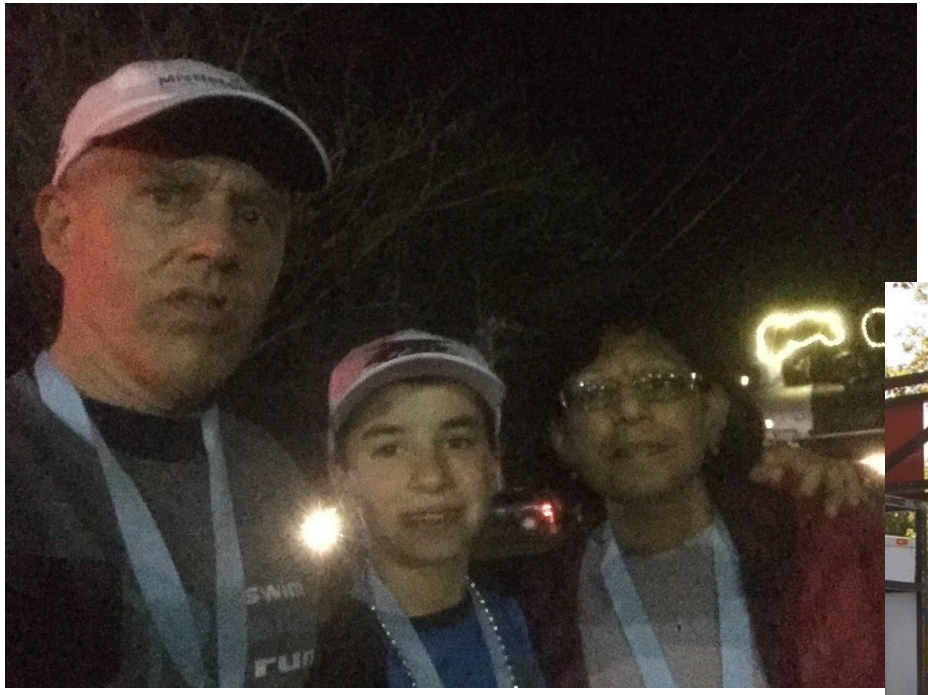
- How do you raise your HDL and lower your BP???

Get out and exercise

- HDL goes up
- BP goes down
- Stroke Risk goes down…

Hiking…

Running



Maybe a little skiing?

Cycling…

Then, you can do a little drinking…

Also, raises your HDL!

But, we're gonna drink responsibly and try not to worry too much about the negative effects!

Shots with cycling buddies!

Awesome with friends….

And, family....

Yes, he was legal
Here in Europe!

And Almost Family....

Questions?

Thanks for having me Ruth and Harper and Charlotte! ☺