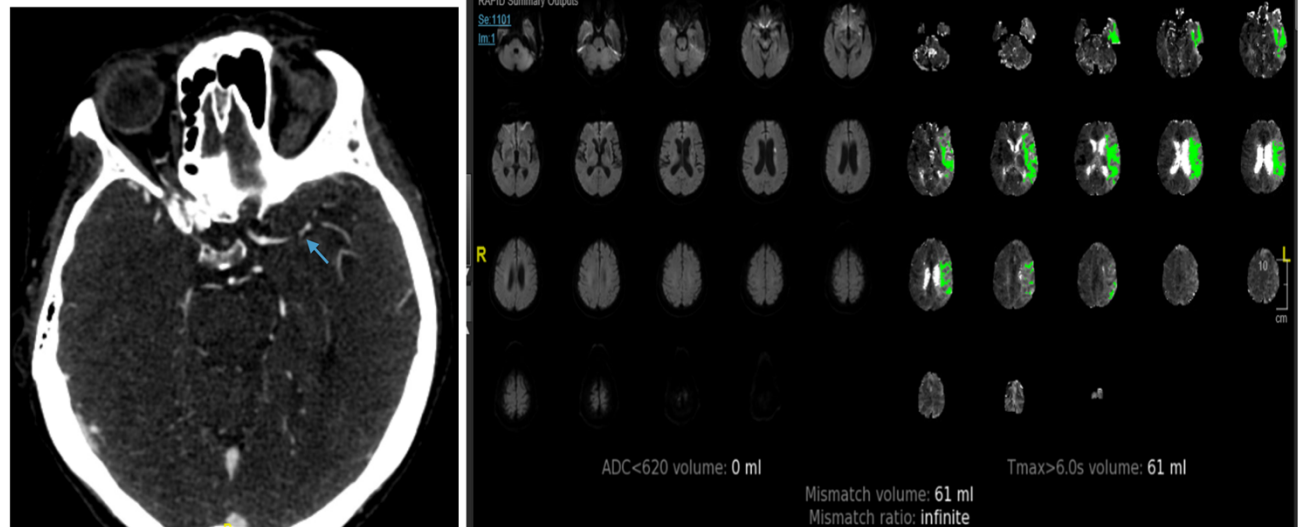


Perfusion Imaging and Early Neurological Deterioration in Symptomatic Intracranial Stenosis (PERFUSE-ICAS)

Shadi Yaghi, Sharon Yeatts, Pooja Khatri, Shyam Prabhakaran, David Liebeskind



SHADI YAGHI, MD

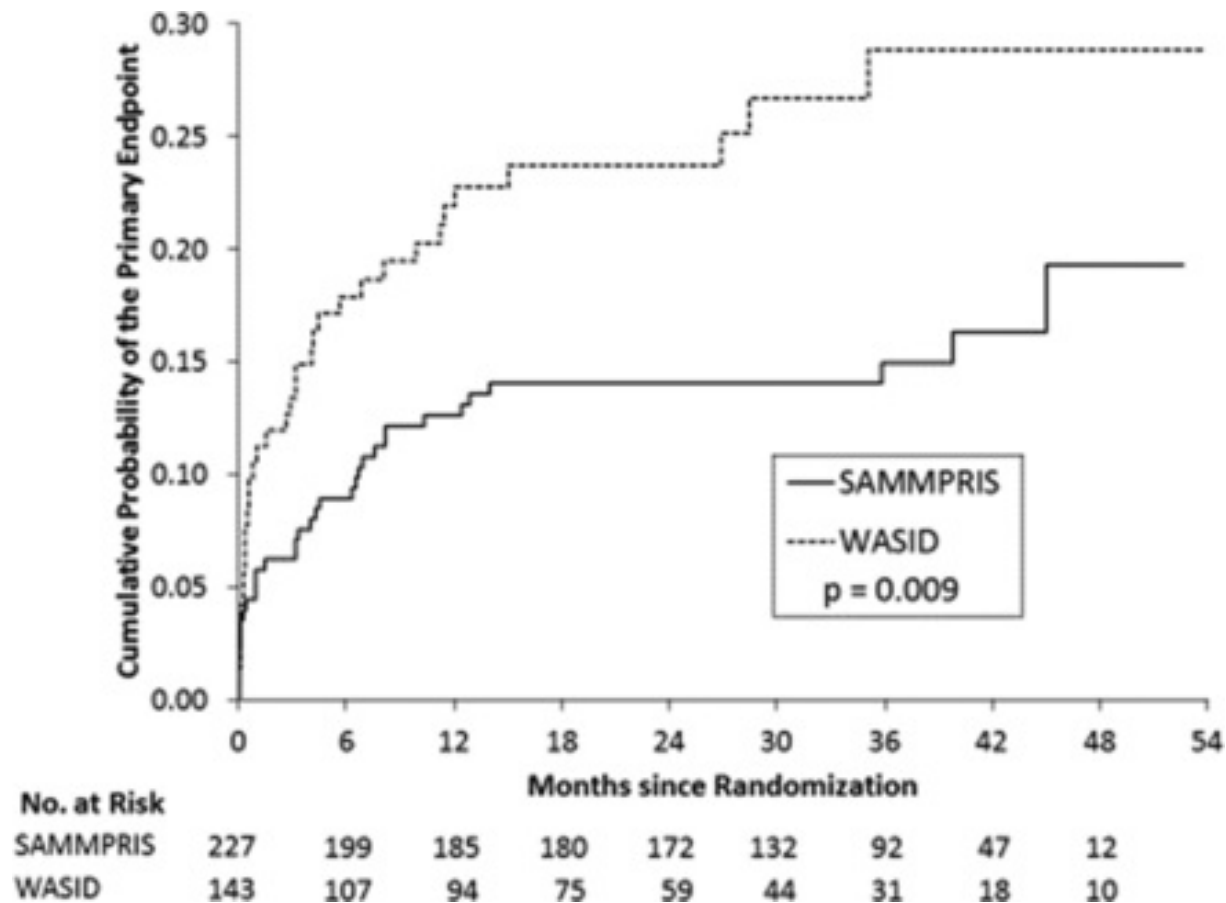
Director of Comprehensive Stroke Center, NYU Langone Brooklyn

Director of Stroke Research, NYU Langone Health

Intracranial Atherosclerosis

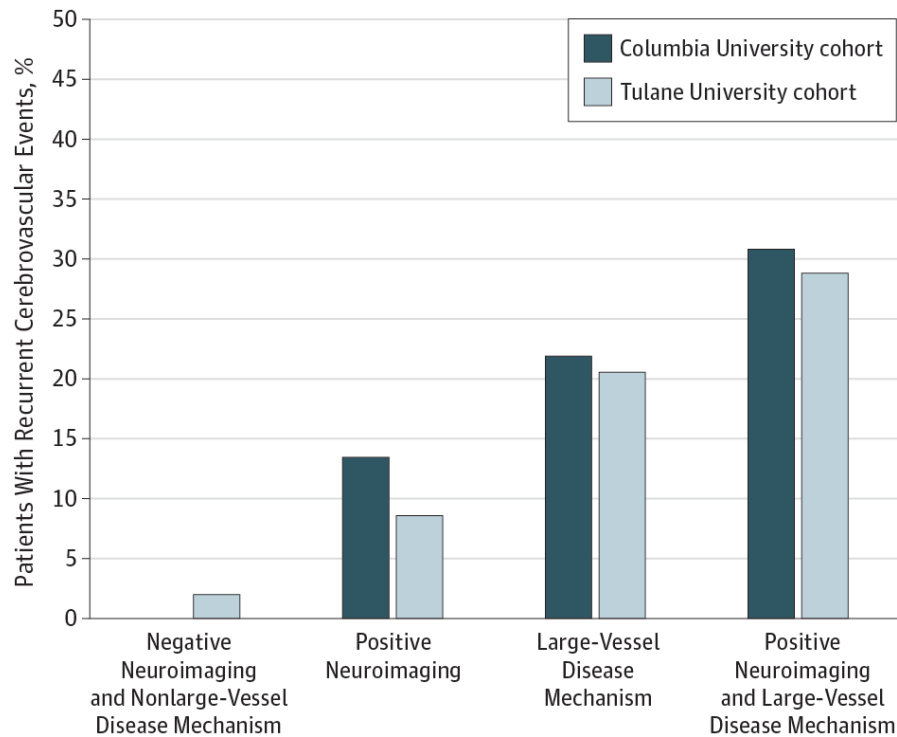
- Intracranial symptomatic large vessel atherosclerotic disease is a strong predictor of early recurrence (Yaghi et al, JAMA Neurology 2015)
- Treatment consists of aggressive medical management
 - Anti-thrombotics, high-intensity statin, other risk factor modification, and lifestyle modifications (exercise, smoking cessation, weight loss)
- Stenting trials: SAMMPRIS and VISSIT showed superiority of medical treatment

Medical treatment has significantly improved!

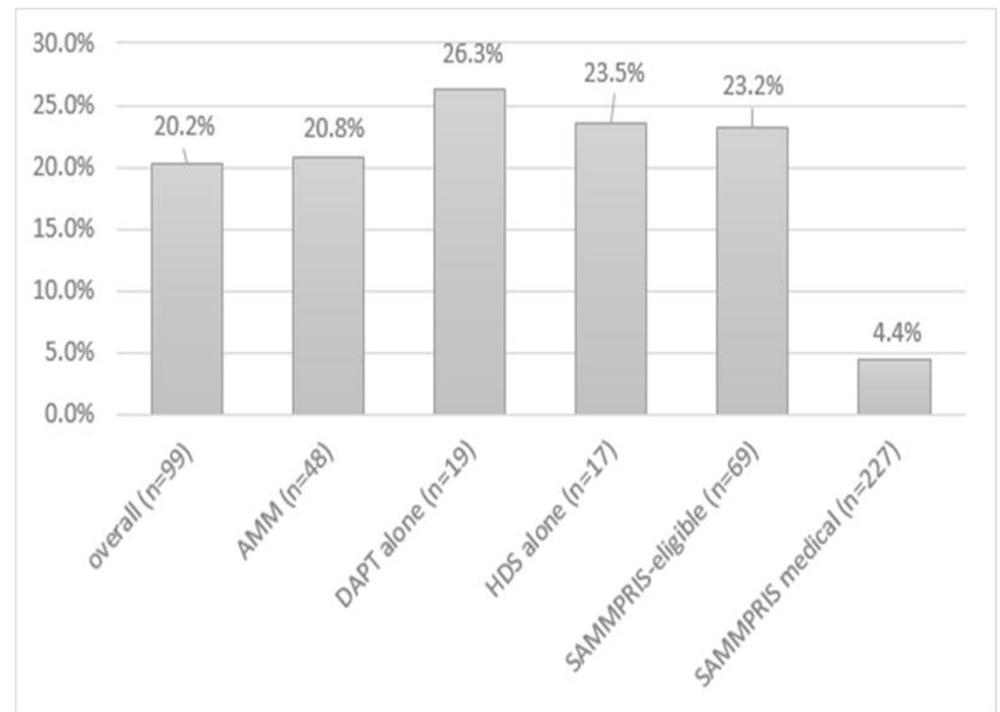


WASID vs. SAMMPRIS

But...the real world risk remains very high



Yaghi et al, JAMA Neurology 2015



Sangha et al, Stroke 2017

Potential reasons why patients fail medical treatment?

- 1- Medication non-compliance/poor risk factor control (Turan et al, Neurology 2017)
- 2- ? Plavix resistance (Wang et al, JAMA 2016)
- 3- Impaired distal perfusion (Yaghi et al, Stroke 2018)

The role of perfusion imaging in ICAS

- SAMMPRIS post hoc analyses
 - Increased risk of recurrence with:
 - T max delay on perfusion imaging
 - Liebeskind et al, ISC 2016
 - Anterior circulation borderzone infarcts
 - Wabintz et al, Stroke 2018

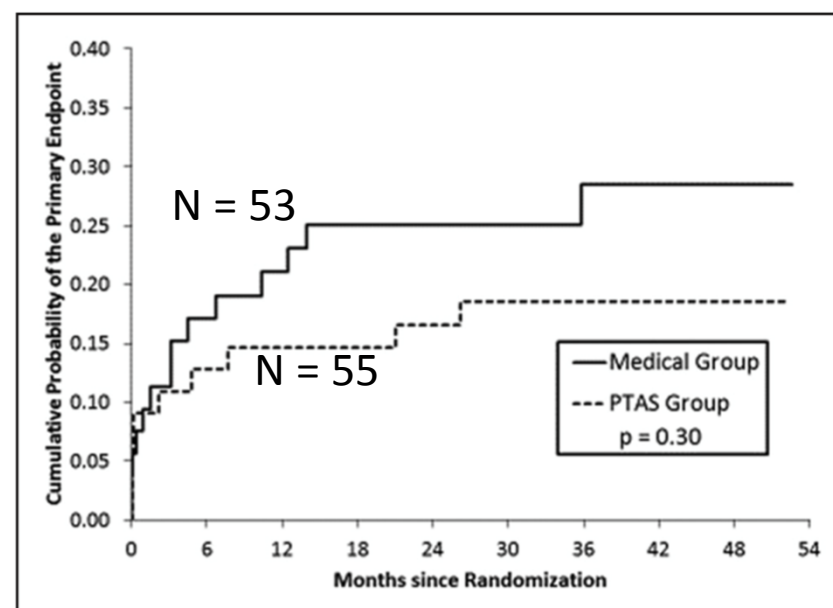
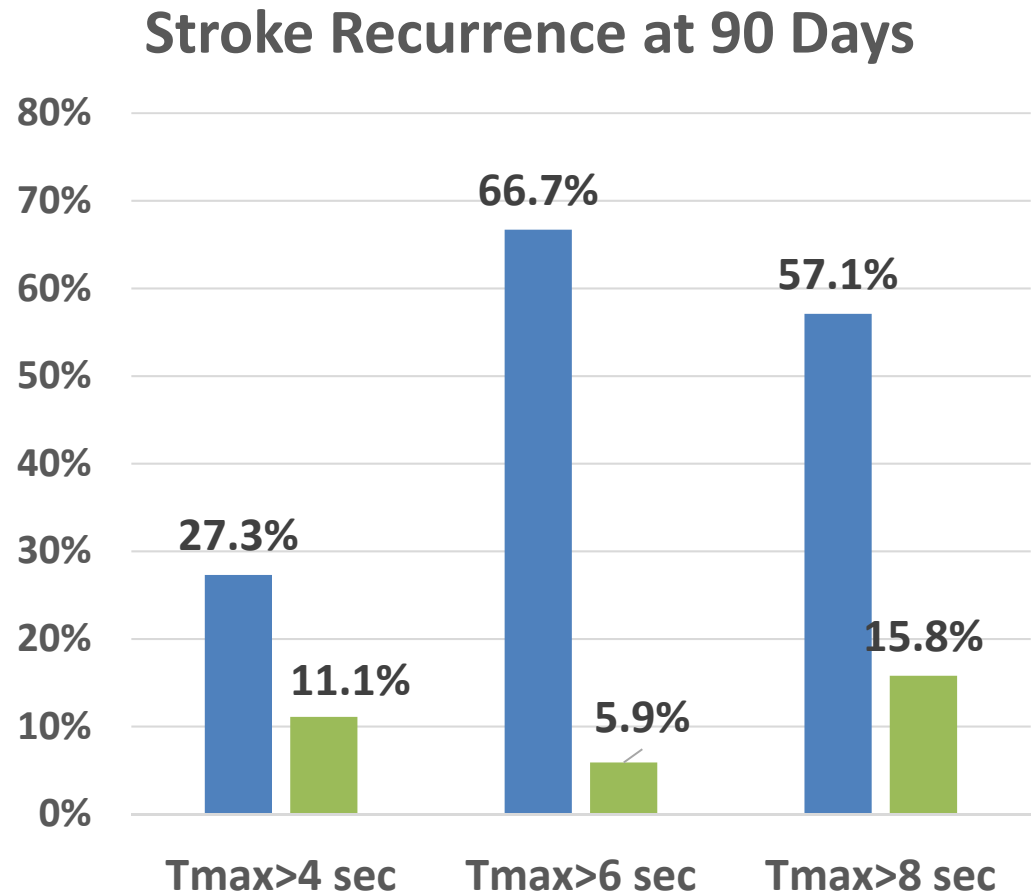


Figure 2. Kaplan-Meier curves showing the probability of a SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) primary end point in the medical and stenting arms in patients whose qualifying event for the trial was an anterior circulation borderzone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

Role of Perfusion in ICAS – pilot study

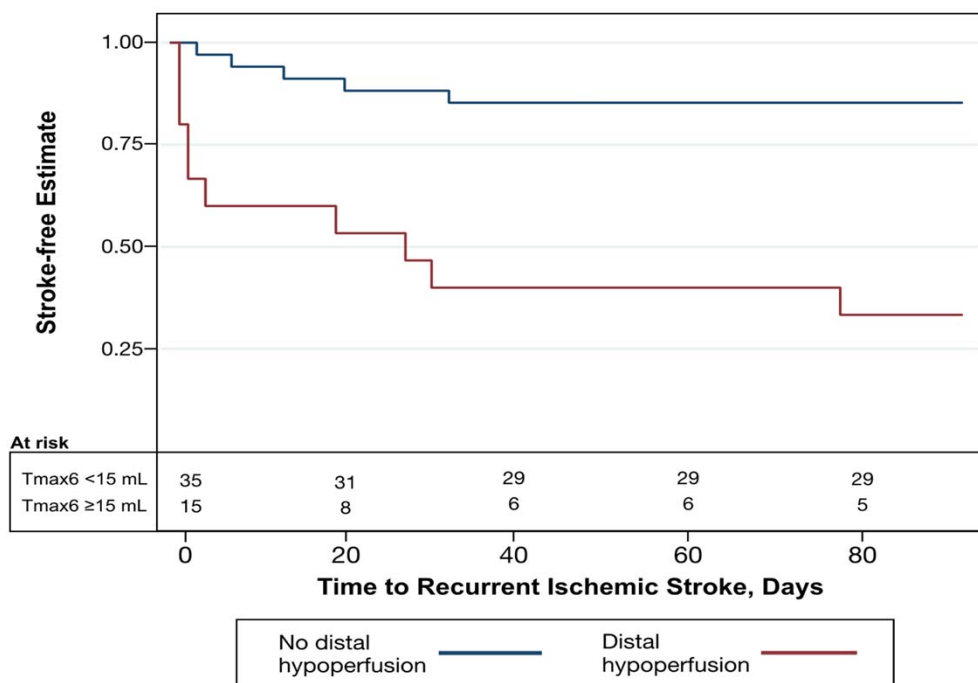
- 26 patients with proximal anterior circulation ICAS and PWI
- Threshold vs 90d stroke recurrence in Figure
 - T max >4 sec (p=0.35)
 - Tmax >6 sec (p<0.01)
 - Tmax >8 sec (p=0.05)
- Limitations
 - Small sample
 - single center
 - Retrospective study



Yaghi et al, Journal of Neuroimaging 2018

Role of Perfusion Imaging Cont'd

- Two center study
 - 50 patients with proximal anterior circulation ICAS; 15 (30%) with distal hypoperfusion (15 mL or more T max > 6 sec mismatch volume) (de Havenon et al)



Combined: HR 5.59 (95% CI 2.02-15.5, p=0.001).

Site 1: HR 9.76, 95% CI 1.19-80.0, p=0.03

Site 2: HR 5.15, 95% CI 1.14-23.2, p=0.03

Aim and Hypothesis

- Aim: To determine and validate the optimal mismatch profile on perfusion imaging that predicts 90-day recurrent stroke or death in patients with ICAS and medical management
- Hypothesis: The positive predictive value for recurrent stroke or death at 90 days associated with mismatch profile with penumbra defined by $T_{max} > 6$ sec delay is greater than that associated with $T_{max} > 4$ sec delay

Study design

- Prospective observational multicenter biomarker validation study
- Patients with symptomatic ICAS and $\geq 70\%$ luminal stenosis on brain CTA involving the intracranial ICA or M1 segment MCA
- Patients will undergo perfusion imaging (CT or MRI) with RAPID and will be treated with aggressive medical treatment*

*Medical management will include standard-of-care antithrombotic medications at the discretion of the treating physician (suggest using dual antiplatelet therapy for at least 21 days followed by single agent), high intensity statin therapy if tolerated or any additional lipid lowering agents, and aggressive risk factor modification.

Perfusion imaging

- Using the post-processing RAPID software, an unfavorable imaging profile on CT/MRI perfusion will be defined as:
 - Core infarct volume < 30 ml, mismatch ratio ≥ 1.8 and mismatch volume ≥ 15 ml
 - And different T max threshold delays (T max < 4 sec, T max 4-6 sec, T max > 6 sec) derived for each patient

Outcomes

- Primary outcome
 - Recurrent stroke* or death within 90 days
- Secondary outcome
 - 90-day mRS distribution
 - New infarct or infarct growth

Outcomes are determined by site PI and adjudicated by an independent committee

*Recurrent stroke: new or worsening neurological deficits attributable to a vascular etiology and lasting for more than 24 hours, or lasting less than 24 hours AND with imaging evidence of new infarct or hemorrhage or infarct extension

Inclusion criteria

- Signs and symptoms consistent with ischemic stroke
- <48 hours from last known normal
- 18-89 years
- Mild to moderate stroke severity (NIHSS 0-10)
- Pre-stroke mRS 0-2

Key Exclusion Criteria

- Plan for intraarterial treatment or intraarterial treatment within the last 90 days
 - Note: Patients receiving alteplase can be enrolled at 24 hours from alteplase infusion but would need repeat intracranial vascular imaging at the 24 hours from alteplase to ensure no change in the degree of luminal stenosis after alteplase treatment
- Atrial fibrillation or other major cardioembolic stroke mechanisms
 - Such as mechanical valve, ejection fraction less than 30%, myocardial infarction within 2 weeks, known cardiac thrombus, or endocarditis
- Unable to undergo contrast brain perfusion scan with either CT or MRI
- Current bleeding disorder
- Arterial hypercoagulable state (Antiphospholipid antibody syndrome, active cancer)

Neuroimaging inclusion/exclusion

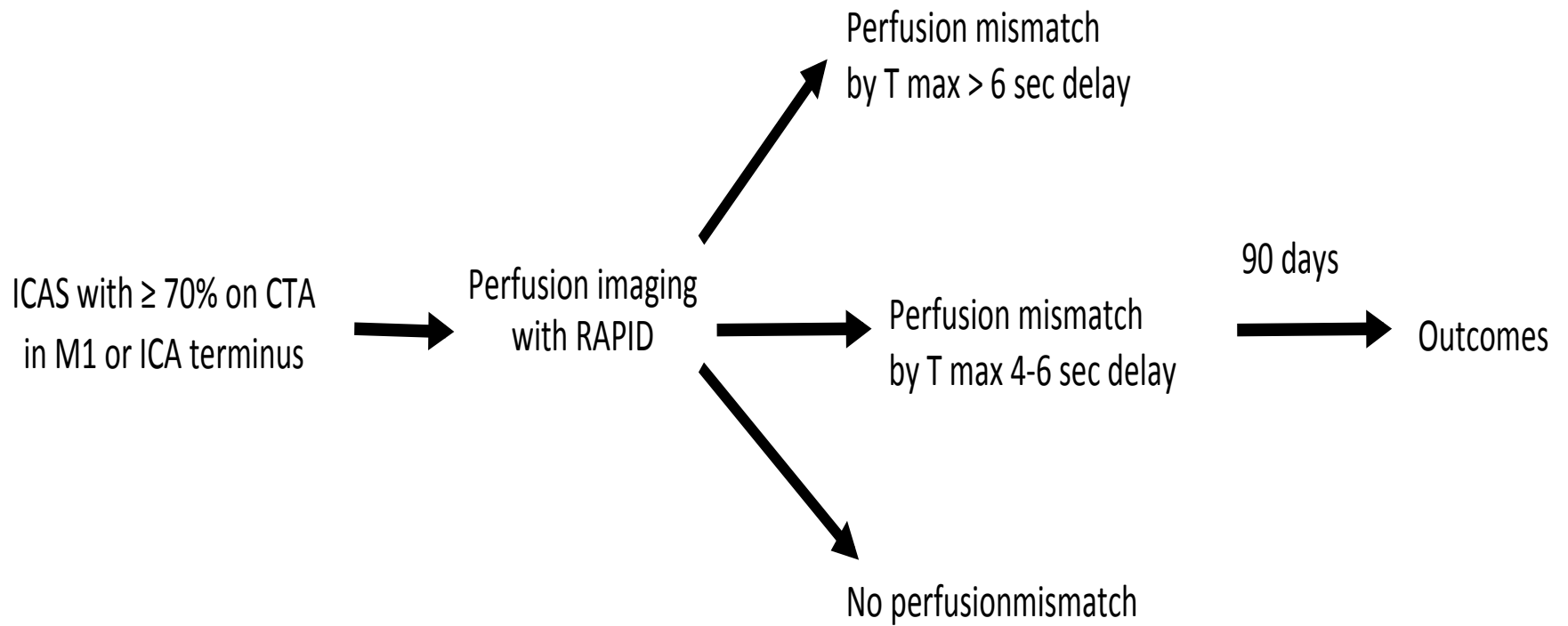
Inclusion:

- Intracranial ICA or M1 segment stenosis in relevant arterial distribution with $\geq 70\%$ luminal narrowing on CT angiogram using the WASID criteria

Exclusion:

- Evidence of brain tumor, intracranial hemorrhage, or vascular malformation
- Mass effect or midline shift
- Acute infarcts in other vascular territories suggesting a proximal cardio-aortic embolic source
- Suspicion for vasculitis, Moya-moya, or RCVS
- Cervical artery disease with $> 70\%$ stenosis proximal to the intracranial lesion
- Intracranial or extracranial dissection

Flow chart



Statistical Plan

- Patients divided into three categories: $T_{\max} < 4$ sec, $T_{\max} 4-6$ sec, and $T_{\max} > 6$ sec
- Assumptions based on preliminary data
 - Similar proportions of patients in the 3 categories
 - PPV of $T_{\max} > 6$ sec was 0.4
- A sample size of $n=240$ patients would test hypothesis with 80% power and level of significance 0.05.
- Increased to $n=300$ to allow for 10% LTFU and interim analysis

Go/no-GO criteria for a phase II study

- Rate of events in stenting arm of SAMMPRIS is 15% (10%-20%)
- If the confidence interval of the optimal biomarker lies entirely above 20%, this would be considered evidence that the biomarker identifies a group of patients who may benefit from reperfusion therapy
- With nearly 100 subjects with the optimally defined mismatch profile, a 95% confidence interval would be expected to exclude 20% for event rates of at least 29%

Thank you



