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### Title

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### Permalink

<https://escholarship.org/uc/item/1q78913w>

### Journal

Journal of Stroke and Cerebrovascular Diseases, 29(10)

### ISSN

1052-3057

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### Publication Date

2020-10-01

### DOI

10.1016/j.jstrokecerebrovasdis.2020.105051

Peer reviewed



# HHS Public Access

Author manuscript

*J Stroke Cerebrovasc Dis.* Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

*J Stroke Cerebrovasc Dis.* 2020 October ; 29(10): 105051. doi:10.1016/j.jstrokecerebrovasdis.2020.105051.

## Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD): Rationale and Design

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Declaration of conflicting interests

1. JG Romano reports no conflicts of interest.
2. I Campo-Bustillo reports no conflicts of interest.
3. DS Liebeskind reports no conflicts of interest.
4. S Prabhakaran reports no conflicts of interest.
5. A Nizam reports no conflicts of interest.
6. R Sangha reports no conflicts of interest.
7. E Feldmann reports no conflicts of interest.
8. S Koch reports no conflicts of interest.
9. T Rundek reports no conflicts of interest.
10. MI Chimowitz reports no conflicts of interest.
11. L Ostergren is an employee of VasSol, Inc.

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## Abstract

**Rationale:** Intracranial atherosclerotic disease (ICAD) is the most common cause of ischemic stroke with the highest rate of recurrence, despite aggressive medical management. Diverse mechanisms may be responsible for ICAD-related cerebral ischemia, with potential therapeutic implications. Here we present the rationale, design and methods of the Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD) study. The aim of MyRIAD is to determine the mechanisms of stroke in ICAD through physiologic imaging biomarkers that evaluate impaired antegrade flow, poor distal perfusion, abnormal vasoreactivity, artery to artery embolism, and their interaction.

**Methods and design:** This is a prospective observational study of patients with recently symptomatic (<21 days) ICAD with 50–99% stenosis treated medically and monitored for up to 1 year. An estimated 110 participants are recruited at 10 sites to identify the association between the presence of each mechanism of ischemia and recurrent stroke. The primary outcome is ischemic stroke in the territory of the symptomatic artery. Secondary outcomes include new cerebral infarction on MRI at 6–8 weeks and recurrent TIA in the territory of the symptomatic artery.

**Discussion:** MyRIAD is positioned to define the role of specific mechanisms of recurrent ischemia in patients with symptomatic ICAD. This knowledge will allow the development and implementation of effective and specific treatments for this condition.

## Keywords

stroke; intracranial arterial disease; research design; biomarkers

## Introduction and Rationale

Intracranial atherosclerotic disease (ICAD) is the most common cause of ischemic stroke worldwide, given its higher prevalence in Asians, Hispanics, and those of African descent.<sup>1</sup> Moreover, it has the highest risk of recurrence of any ischemic stroke subtype; even with modern aggressive medical management, the 1-year risk of recurrent stroke in high-grade recently symptomatic ICAD is 15%.<sup>2</sup> Diverse mechanisms of ischemia may be responsible for recurrent stroke in ICAD, but it is currently unknown if the risk of recurrence differs by ischemic mechanism, and if interventions that target these mechanisms reduce stroke recurrence.

The objective of this study is to determine the causes of stroke in ICAD by using imaging biomarkers for specific pathophysiological processes that underlie stroke recurrence, namely impaired antegrade flow, poor distal perfusion, abnormal vasoreactivity and artery-to-artery

embolism. Impaired antegrade flow across a stenotic vessel can be quantified through phase-contrast MRA (QMRA) by integrating flow velocity across a cross-sectional area of a vessel; low flow states are associated with a greater risk of stroke recurrence.<sup>3</sup> Distal tissue perfusion is influenced by both antegrade flow as well as collateral flow which can be evaluated by perfusion MRI (PWI); poor distal flow is associated with recurrence.<sup>4</sup> Risk of ischemia is also associated with poor vasomotor reactivity which results from exhausted collaterals and maximal vasodilation, which can be evaluated by transcranial Doppler with hypercapnic challenge calculated through breath holding index (TCD BHI).<sup>5</sup> Artery-to-artery embolism, detected by transcranial Doppler monitoring (TCD EDS), is common in the acute phase after ICAD-related stroke, and is associated with early recurrence.<sup>6</sup>

## Methods

### Design:

MyRIAD is a prospective multi-center observational study of patients with recently symptomatic ICAD.

### Participating sites:

Ten recruiting sites with the ability to perform QMRA, PWI, TCD BHI, and TCD EDS are included. Sites have accreditation by the Intersocietal Accreditation Commission ([intersocietal.org](https://www.intersocietal.org)) or meet its standards. Sonologists underwent a 1-day training session at the TCD core facility, and MR technicians had on-site QMRA training to assure harmonization of performance across the sites; after training each site submitted TCD VMR (6 vessels), EDS (3 vessels) and QMRA (2) studies on volunteers for quality review prior to initiation of recruitment. Sites agreed to institute intensive guideline-based medical management; their treatment practices were surveyed prior to study initiation confirming that they followed accepted intensive medical management as a first line of treatment in symptomatic ICAD.<sup>7</sup>

### Patient population and eligibility:

Eligible participants presented within 21 days of stroke or transient ischemic attack (TIA) caused by intracranial atherosclerosis. Stroke diagnosis included symptoms lasting >24 hours with imaging confirmation, and TIA required presence of DWI abnormality or 2 or more stereotypical and unequivocally ischemic events. We included ICAD of the intracranial carotid, middle cerebral M1 segment, intracranial vertebral or basilar artery, with stenosis of 50–99% diagnosed by catheter angiography, MR angiography or CT angiography, in the absence of a cardioembolic source or >50% proximal carotid or vertebral stenosis. The degree of stenosis was calculated by accepted criteria.<sup>8</sup> The eligibility vascular imaging obtained as part of standard of care was reviewed centrally. Disagreement between central and site interpretation of degree of stenosis resulted in feedback to the site, and repeated disagreement triggered further training. We included participants older than 50 years, or 30 to 49 years if they had 2 or more vascular risk factors or established atherosclerosis in another arterial bed. All participants were prescribed intensive medical management<sup>7</sup> without planned endovascular treatment.

Participants with a recurrent event between consent and baseline study imaging were re-evaluated for eligibility and symptomatic arterial patency. In case of a recurrent stroke or TIA in the territory of the stenotic artery with vessel patency, this became the new index event and imaging had to be completed within 21 days of the latest event. Consented participants who did not obtain study-specific baseline imaging were classified as screen failures.

### Study procedures:

Once participants provided informed consent, we collected baseline demographic information, vascular risk factors, information about the index event, baseline blood pressure, lipids and glycohemoglobin, and stroke prevention medications. MyRIAD-specific imaging studies, including QMRA, PWI, TCD BHI and TCD EDS, were performed within 21 days from the index event. The QMRA was remotely monitored to ensure that measurements were obtained at the appropriate angle and vessel location. At 6–8 weeks from the qualifying stroke or TIA, an MRI with FLAIR and DWI sequences was obtained. All imaging studies, including parenchymal and vascular imaging obtained at the index event and used for eligibility, studies obtained at endpoint events, and the study-specific biomarker imaging were sent to the respective cores (see below). We defined abnormal MyRIAD biomarker imaging states as follows: a >20% decrease in flow compared to age-adjusted controls on QMRA;<sup>9,10</sup> a >4 s TTP in a 10 cc volume on PWI; a TCD BHI <0.69;<sup>5</sup> and presence of any microembolic signal detected in the target vessel distal to the stenosis during 30 minutes on TCD EDS.<sup>6</sup> TCD EDS and TCD VMR required agreement between 2 independent experienced central readers; in case of disagreement a 3<sup>rd</sup> reader was engaged to make a decision. Clinical follow-up at 6–8 weeks, 3 months ± 15 days, 6 months ± 15 days and 12 months ± 21 days were conducted to detect the occurrence of recurrent ischemic events and compliance with stroke-prevention medication. Clinical and imaging data obtained at the time of recurrent cerebral ischemia was collected for endpoint adjudication. Study participation is completed at the time of the primary endpoint or after 12 months.

### Outcomes:

The primary outcome is ischemic stroke in the territory of the stenotic artery, based on clinical finding and imaging confirmation. The secondary outcomes are TIA in the territory of the stenotic artery, defined as transient neurological symptoms lasting <24 hours and clearly related to the stenotic artery, and new infarct detected on MRI at 6–8 weeks. This imaging window was selected as the highest risk of stroke recurrence in clinical trials occurred within 1 month of randomization, and 5–6 weeks after index event,<sup>2,12</sup> so the 6–8 week period was selected as optimal to capture new infarcts. Primary and secondary outcomes are centrally ascertained by 2 independent experienced vascular neurologists who evaluate medical records, baseline qualifying event-related imaging, 6–8 week study MRI, and clinically obtained imaging at the time of the primary endpoint; these ascertainers are blinded to the MyRIAD biomarker studies.

### Data capture and monitoring:

Study personnel at the recruiting sites and central readers at the core labs submitted data into electronic case report forms in iDataFax (version 2014.0.0, DF/Net Research, Seattle, WA).

Study-specific biomarker imaging interpretation was performed centrally at the respective cores; central readers were blinded to clinical and imaging endpoints. Ongoing data quality checks identified missing data and other data queries, which were forwarded to sites and cores for clarification and resolution.

**Sample size:**

Based on available data, we estimated a prevalence of 30% of abnormal imaging states, and a relative risk of 3.3 for the primary endpoint in the presence of an abnormal imaging biomarker. With 110 participants, assuming 10% lost to follow-up, we have 80% power at a 5% significance level to detect an association between the primary endpoint and impaired antegrade flow, poor distal perfusion, and abnormal vasoreactivity, and 60% power for artery-to-artery embolism.

**Statistical analysis:**

Planned analyses for the primary and secondary endpoints include Kaplan-Meier curve comparisons using log-rank tests to compare the abnormal and normal groups, defined by the imaging marker of primary interest measured at baseline. In addition, different cut points in the imaging biomarkers will be explored to identify predictors of clinical stroke and infarct recurrence. Recognizing the potential that various abnormal biomarkers are present in the same individual, we have prespecified analysis to test the interaction between microemboli and vasoreactivity, and between low antegrade flow and poor distal perfusion, as well as the effect of multiple abnormal biomarker states on outcomes. Baseline and recurrent infarct pattern will be used in prediction models.

**Organization, funding and registration:**

MyRIAD is an investigator-initiated study funded by the NIH/NINDS (R01 NS084288). VasSol Inc. (River Forest, IL) provided the NOVA software for QMRA at no cost. In addition to its 10 recruiting sites, MyRIAD has various core facilities: central coordinating and TCD core (U Miami), PWI and neuroimaging core (UCLA), QMRA core (U Chicago), eligibility and endpoint adjudication (Baystate) and statistical and data management core (Emory). It is registered in [ClinicalTrials.gov: NCT02121028](https://clinicaltrials.gov/ct2/show/study/NCT02121028). The institutional ethics review board at each participating institution approved MyRIAD.

**Discussion**

MyRIAD is designed to identify imaging biomarkers that correlate with specific mechanisms of ischemia ICAD. The negative endovascular intervention trials for symptomatic ICAD reinforce the importance of understanding the physiologic underpinnings of recurrent ischemic events.<sup>11,12</sup> In addition to identifying the specific mechanisms – and their interaction – associated with recurrent stroke, the study will also define the risk of early recurrent infarction on 6–8 week imaging. While this is not a clinical trial and treatment is not mandated by protocol, we expected that all participants would receive intensive medical management in accordance with practice trends in the US.<sup>13</sup> The strengths of MyRIAD include its multi-modal physiologic imaging and imaging in the subacute period to describe the accumulation of ischemic lesions in symptomatic ICAD. The

information derived from MyRIAD is critical to design future treatments for ICAD and permit the rational application of mechanism-specific secondary prevention measures.

## Grant Support:

NIH/NINDS (R01 NS084288)

## References

1. Gorelick PB, Wong KS, Bae H-J, et al. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke* 2008; 39:2396–2399. [PubMed: 18535283]
2. 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;383:333–341. [PubMed: 24168957]
3. Amin-Hanjani S, Pandey DK, Rose-Finnell L, et al. Effect of Hemodynamics on Stroke Risk in Symptomatic Atherosclerotic Vertebrobasilar Occlusive Disease. *JAMA Neurol*. 2016;73:178–185. [PubMed: 26720181]
4. Lan L, Leng X, Ip V, et al. Prolonged Perfusion Predicts Recurrent Ischemic Stroke but not Transient Ischemic Attack in Patients with Symptomatic Intracranial Stenosis. *Curr Neurovasc Res*. 2017;14:149–157. [PubMed: 28412909]
5. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283:2122–2127. [PubMed: 10791504]
6. Gao S, Wong KS, Hansberg T, et al. Microembolic signal predicts recurrent cerebral ischemic events in acute stroke patients with middle cerebral artery stenosis. *Stroke*. 2004;35:2832–2836. [PubMed: 15514175]
7. Turan TN, Lynn MJ, Nizam A, et al. Rationale, Design, and Implementation of Aggressive Risk Factor Management in the Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial. *Circ Cardiovasc Qual Outcomes*. 2012 9 1;5:e51–e60. [PubMed: 22991350]
8. Samuels OB, Joseph GJ, Lynn MJ, et al. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol*. 2000;21:643–646. [PubMed: 10782772]
9. Zhao M, Amin-Hanjani S, Ruland S, et al. Regional cerebral blood flow using quantitative MR angiography. *AJNR Am J Neuroradiol*. 2007;28:1470–1473. [PubMed: 17846193]
10. Amin-Hanjani S, Du X, Zhao M, et al. Use of quantitative magnetic resonance angiography to stratify stroke risk in symptomatic vertebrobasilar disease. *Stroke*. 2005; 36:1140–1145. [PubMed: 15890993]
11. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365:993–1003. [PubMed: 21899409]
12. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA*. 2015;313:1240–1248. [PubMed: 25803346]
13. Turan TN, Cotsonis G, Lynn MJ, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. *Cerebrovasc Dis*. 2014;37:203–211. [PubMed: 24557055]