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Title

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Authors

Romano, Jose G
Prabhakaran, Shyam
Nizam, Azhar
et al.

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Jose G. Romano, MD,
University of Miami, Miami, FL, USA

Shyam Prabhakaran, MD, MS,
The University of Chicago, Chicago, IL, USA

Azhar Nizam, MS,
Emory University, Atlanta, GA, USA

Edward Feldmann, MD,
The University of Massachusetts Medical School-Baystate, Springfield, MA, USA

Rajbeer Sangha, MD,
University of Alabama at Birmingham, Birmingham, AL, USA

George Cotsonis, MS,
Emory University, Atlanta, GA, USA

Iszet Campo-Bustillo, MD, MPH,
University of Miami, Miami, FL, USA

Sebastian Koch, MD,
University of Miami, Miami, FL, USA

Tatjana Rundek, MD, PhD,
University of Miami, Miami, FL, USA

Marc I. Chimowitz, MD,

Corresponding author: Jose G. Romano, MD, 1120 NW 14th Street, Suite 1357, Miami FL 33136, Tel: 305-243-4453, jromano@med.miami.edu.
[a]See supplemental table

Medical University of South Carolina, Charleston, SC, USA

David S. Liebeskind, MD
University of California at Los Angeles, Los Angeles, CA, USA

MyRIAD Investigators[a]

Abstract

Background: Intracranial atherosclerotic disease (ICAD) is a common cause of ischemic stroke with a high risk of clinical stroke recurrence. Multiple mechanisms may underlie cerebral ischemia in this condition. The study's objective is to discern the mechanisms of recurrent ischemia in ICAD through imaging biomarkers of impaired antegrade flow, poor distal perfusion, abnormal vasoreactivity, and artery-to-artery embolism.

Methods: This prospective multicenter observational study enrolled patients with recent (21 days) ischemic stroke or transient ischemic attack (TIA) caused by ICAD with 50–99% stenosis treated medically. We obtained baseline quantitative MRA (QMRA), perfusion MRI (PWI), transcranial Doppler vasoreactivity (VMR), and emboli detection studies (EDS). The primary outcome was ischemic stroke in the territory of the stenotic artery within 1 year of follow-up; secondary outcomes were TIA at 1 year and new infarcts in the territory on MRI at 6–8 weeks.

Results: Amongst 102 of 105 participants with clinical follow-up (mean 253 ± 131 days), the primary outcome occurred in 8.8% (12.7/100 patient-years), while 5.9% (8.5/100 patient-years) had a TIA. A new infarct in the territory of the symptomatic artery was noted in 24.7% at 6–8 weeks. A low flow state on QMRA was noted in 25.5%, poor distal perfusion on PWI in 43.5%, impaired vasoreactivity on VMR in 67.5%, and microemboli on EDS in 39.0%. No significant association was identified between these imaging biomarkers and primary or secondary outcomes.

Conclusions: Despite intensive medical management in ICAD, there is a high risk of clinical cerebrovascular events at 1 year and an even higher risk of new imaging-evident infarcts in the subacute period after index stroke. Hemodynamic and plaque instability biomarkers did not identify a higher risk group. Further work is needed to identify mechanisms of ischemic stroke and infarct recurrence and their consequence on long-term physical and cognitive outcomes.

Trial Registration: ClinicalTrials.gov: NCT02121028.

Keywords

stroke; cerebral infarction; intracranial arterial disease; biomarkers

Introduction

Intracranial atherosclerotic disease (ICAD) accounts for about 8% of strokes in the US and up to 50% of strokes in China and Southeastern Asia;[1] as such, ICAD is probably the most common global cause of ischemic stroke. It also carries the highest risk of stroke recurrence, estimated at 12% at 1 year despite aggressive medical therapy.[2,3] The lack of benefit of stenting, a primary flow restoration strategy, in clinical trials completed to date[4,5] suggests that different mechanisms of ischemic injury may be responsible for stroke in patients with ICAD. We hypothesized that hemodynamic factors and plaque instability, assessed through

imaging biomarkers, would identify those at highest risk of stroke recurrence, that the occurrence of subclinical infarcts would be greater than clinical stroke events, and that the early period after the index event was particularly vulnerable.

The Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease (MyRIAD) Study is an investigator-initiated prospective observational study funded by the NIH/NINDS with the overall objective of discerning the mechanisms of ischemic stroke in ICAD through imaging biomarkers for specific pathophysiological processes that underlie stroke recurrence, namely impaired antegrade flow, poor distal perfusion, abnormal vasoreactivity and artery-to-artery embolism.[6]

Flow quantification of antegrade flow, evaluated by phase contrast MR angiography (QMRA)[7] is associated with increased risk of recurrent stroke in ICAD.[8] Distal tissue perfusion, assessed by perfusion MR imaging (PWI), identifies those with ICAD at risk for future cerebral ischemia.[9] Vasomotor reactivity (VMR) measures the response of arterioles to vasodilatory challenges. Transcranial Doppler with breath-holding (TCD BHI) has shown association with increased risk in large vessel stenosis.[10] Microemboli detected by transcranial Doppler (emboli detection study or TCD EDS), a marker of plaque instability[11] is also associated with greater risk of recurrent stroke in ICAD.[12]

Methods

The design of MyRIAD has been previously described.[6] Ten recruiting sites participated in MyRIAD; all patients signed informed consent, and the participating institutions' ethics committees approved the study. Eligible patients had a recent (21 days) ischemic stroke or a transient ischemic attack (TIA) caused by ICAD of the intracranial carotid artery, middle cerebral artery M1 segment, basilar artery, or vertebral artery V4 segment, with 50–99% stenosis, in the absence of proximal cervical arterial stenosis >50% or a cardioembolic source. Ischemic stroke required symptoms lasting >24 hours and imaging consistent with an ischemic event; TIA had symptoms lasting <24 hours and either diffusion weighted imaging (DWI) abnormality, or 2 or more stereotypical events with unequivocally ischemic symptoms. The degree of s tenosis was calculated by established methods[13] on digital substraction angiography (n=23), CT angiography (n=64) or MR angiography (n=10); a flow gap on MR angiography (n=8) was considered eligible. Vascular imaging for eligibility was reviewed centrally. Eligible patients were   30 years of age, but those of age 30–49 years had either established atherosclerosis in another vascular bed or 2 or more vascular risk factors. We excluded those with contraindications to MRI, MR contrast agents, including allergy, creatinine >1.5 or GFR <30 mL/min/1.73 m^2, and those with planned endovascular treatment for ICAD. All enrolled patients were treated with aggressive medical therapy based on the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial medical regimen.[14]

We recorded demographic and clinical characteristics, medications, laboratory tests at the time of the index event, and collected all eligibility brain parenchymal and vascular imaging. Consented patients who did not undergo baseline hemodynamic imaging were considered screen failures. Enrolled patients underwent initial study-related imaging including QMRA,

PWI, TCD VMR, and TCD EDS within 21 days of index stroke. A brain MRI with FLAIR and DWI/ADC sequences was obtained at 6–8 weeks. Clinical follow-up occurred at 6–8 weeks, 3 months ± 15 days, 6 months ± 15 days and 12 months ± 21 days to determine if an endpoint had occurred and to record treatment adherence.

The baseline study imaging was evaluated by central readers. Decreased antegrade flow in the stenotic vessel was considered when volumetric flow was 20% lower than the vessel and age specific normal values.[7,15] Abnormal tissue perfusion on PWI was defined by a time to peak (TTP) >4 sec involving 10 cc brain tissue volume. Low vasomotor reactivity was defined as a TCD BHI <0.69.[10] Any microembolic signal on TCD EDS during 30 minutes of monitoring was considered abnormal.[12]

The primary outcome was ischemic stroke in the territory of the stenotic artery, based on clinical finding of new focal symptoms lasting >24 hours with confirmatory imaging of new infarct in the territory. The secondary endpoints were: a) TIA in the territory of the stenotic artery; and b) new infarct detected on MRI at 6–8 weeks in the territory of the stenotic artery. A new infarct at 6–8 weeks was considered when new DWI/ADC or FLAIR sequence lesion developed compared to the baseline MRI; when a baseline MRI was not available (n=9), only new DWI/ADC lesions were counted. Primary and secondary outcomes were ascertained by 2 independent experienced vascular neurologists who reviewed clinical data and imaging studies, including that obtained at baseline, 6–8 weeks, and at the time of a clinical endpoint. In case of disagreement, they reviewed case to reach consensus.

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.[12,15,16,17] We calculated a sample size of 110 participants, assuming 10% lost to follow-up, to have 80% power (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.

Planned analyses for the primary and secondary endpoints included Kaplan-Meier curve comparisons using log-rank tests to compare the abnormal and normal groups, defined by the marker of primary interest measured at baseline. In addition, Fisher's Exact Tests or, where feasible, asymptotic chi-square tests were used to compare outcome risk differences in the abnormal and normal groups, and confidence intervals for risk differences were computed. Analyses were performed using SAS software, version 9.4 and R version 3.6.1. A significance level of 5% (confidence level of 95%) was used for inference-making; all inferences were two-sided.

Results

Between 04/2015 and 05/2019, 141 patients met eligibility criteria and 36 (25.5%) were screen failures; the main reasons for screen failure were the inability to complete study imaging in time (11), withdrawal of consent (11), and inability to complete MRI due to claustrophobia, movement, or metallic implant verification (6), ineligible after consent (2), endovascular procedure performed prior to study imaging (1). A total of 105 patients were

enrolled at 14.9 ± 8.8 (mean ± SD) days from the qualifying event. Baseline and qualifying event characteristics are included in Table 1. As noted, the cohort had a large burden of vascular risk factors, including a very high proportion with diabetes mellitus (54.3%). Overall, 73.7% had anterior circulation disease at index stroke or TIA. Most patients were enrolled after a stroke; these were relatively mild (NIHSS 2.4 ± 3.4 [mean ± SD], median 1.0 [IQR 0–3]) and amongst those with an available baseline eligibility MRI (n=96), the median infarct volume on DWI was 5 cc (n=71, IQR 5–10). The degree of stenosis was 78.6 ± 10.4% (mean ± SD; n=97) and 85.7% had stenosis in the 70–100% range. Flow gap was observed, and no stenosis measurement recorded, in 8 patients.

Treatment adherence is depicted in Figure 1. At the time of the qualifying event, 64% were on antithrombotic agents (51% on antiplatelet agents and 13% on an anticoagulant), 61% on antihypertensive agents, 45% on antilipidemic agents, and 57% of diabetic patients on antidiabetic treatment. Intensive medical treatment was instituted by the time of enrollment, which was highly sustained during the course of the study: stroke prevention medications were taken by over 80% at 6–8 weeks, and by over 75% at 3, 6 and 12 months. Lifestyle modification was modestly successful. Although 62% did not exercise regularly at baseline, 47–60% reported exercising regularly during follow-up. Active tobacco use was reported in 20% at baseline; there was an early reduction but 17% reported smoking at last follow-up.

Clinical follow-up beyond baseline was available in 102 patients. During follow up of 253 ± 131 days (mean ± SD), an ischemic stroke in the territory of the stenotic artery developed in 9 participants (8.8%, 12.7/100 patient-years), including 5 before the first 6–8 week follow-up visit, while 6 (5.9%, 8.5/100 patient-years) had a TIA attributed to the symptomatic artery. There were 2 deaths, one from pneumonia/sepsis 8 weeks after the qualifying event, and one from cardiac arrest at 37 weeks.

A study MRI at 6–8 weeks was available for 89 patients; the time from the qualifying event to imaging was 51.3 ± 16.6 days (mean ± SD). A new infarct in the territory of the target vessel was found in 24.7%. Amongst the 22 patients with new infarcts at 6–8 weeks, a DWI abnormality was noted in 14 while the rest had only new FLAIR lesions.

Overall, low flow state on QMRA was noted in 25.5%, poor distal perfusion on PWI in 43.5%, impaired vasoreactivity on TCD VMR with BHI in 67.5%, and presence of microemboli on TCD EDS in 39.0%. The association of MyRIAD imaging biomarkers with outcomes is illustrated in Table 2 and Figure 2 (A–D). At the predefined cut points, we did not identify a significant association between an abnormal imaging biomarker and recurrent stroke, TIA, or new infarcts at 6–8 weeks. We also performed pre-planned analysis for combination of abnormal biomarkers, including PWI with QMRA and TCD VMR with TCD EDS, as described in Table 2 and Figure 3, without a clear synergistic effect. Recurrent infarct was noted in 33% percent of 42 patients for whom two or more imaging biomarker abnormalities were noted, vs. 17% of 47 patients with one or fewer abnormalities (P=0.07).

Discussion

In a multi-center recently symptomatic ICAD cohort, we observed a high risk of recurrent cerebral ischemia. The rate of clinical stroke recurrence on contemporary medical therapy (12.7/100 patient-years) was similar to that reported by recent ICAD clinical trials: in the medical treatment arm of the SAMMPRIS trial, the 1-year rate of stroke or death within 30 days or recurrent stroke in the territory beyond 30 days was 12.2%,[3] while in the Vitesse Stent Ischemic Therapy (VISSIT) trial, the 1 year risk of stroke in the territory was 9.4%.[5] In MyRIAD, 5% of patients had a clinical stroke by 6–8 weeks, which is similar to recent clinical trials[4] and much lower than previous reports before intensive medical management was instituted.[18]

The risk of new imaging infarcts at 6–8 weeks (24.7%) was much higher that of clinical events. This risk of early infarct recurrence has not been well described before. In a small retrospective series of 25 patients with moderate to severe non-occlusive ICAD, 36% had a recurrent infarct within 1 week.[19] The impact of early small infarct recurrence is unknown. However, previous cerebral ischemia in ICAD is a risk factor for stroke recurrence,[20] and baseline infarct patterns such as subcortical location, multiple infarcts[21] and borderzone distribution[22] have been associated with greater risk of recurrence. There are also potential cognitive consequences to silent infarcts. In the Rotterdam study, baseline silent infarcts doubled the risk of developing dementia and the cognitive decline was greater in those with infarcts on follow up imaging.[23] The cause of dementia in this population is likely vascular: the presence of ICAD is associated with risk of dementia in population-based studies,[24,25] and ICAD is not associated with amyloid PET deposition,[26] indicating non-AD pathology of dementia in ICAD.

There was a high prevalence of imaging biomarker abnormalities. A low flow state on QMRA of 25.5% is very similar to that found in the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study.[8] However, since we applied different definitions to accommodate the anterior circulation in our study, it is difficult to compare the 2 studies directly. We also found a high prevalence of poor distal perfusion. Others have described similar finding; prolonged mean transit time on perfusion imaging was reported in 31% of patients with symptomatic ICAD.[9] Impaired vasoreactivity has been well described in ICAD with greater decrements at higher degrees of stenosis.[27] We found decreased VMR in two-thirds of patients, in line with other reports.[27] Although the 39% rate of microembolic signals in MyRIAD is in a similar range to previous reports,[12,28] the true incidence may be underestimated as we found a significant amount of turbulence, particularly in distal middle cerebral artery M1 segment stenosis, that precluded reliable identification of microembolic signals.

Based on the predefined definition of abnormal hemodynamic and plaque instability biomarkers, we were unable to define a particularly vulnerable subgroup of recently symptomatic ICAD at risk for recurrent clinical or subclinical events. It is possible that the study was underpowered as there was a directional indication, although not statistically significant, that the combination of abnormal biomarkers correlate with infarct recurrence. Other biomarkers of high risk such as vessel wall imaging and plaque load hold promise as

novel predictors to identify a particularly vulnerable group[29,30] though they remain investigational to date.

This study has limitations. First, we relied on non-invasive estimation of stenosis in most (n=82) patients, and it is possible that we included some patients with <50% stenosis; however, non-invasive techniques, particularly CTA, have excellent accuracy,[31] and we had independent adjudication for imaging eligibility. Second, treatment was not mandated or funded by the study, but sites indicated in a pre-study survey their intent to follow guidelines-based intensive medical management,[32] and we identified relatively good adherence to prescribed treatment, except for lifestyle changes. The suboptimal adherence to tobacco cessation and exercise are an opportunity to improve secondary prevention strategies in this population. There are also important strengths: the characterization of a high-risk ICAD cohort in the earlier period after an index event, a particularly vulnerable period for recurrence, than previous clinical trials;[2,4,5] and the determination of infarcts on MRI as a surrogate secondary outcome in the subacute timeline with independent adjudication.

Conclusions

In this contemporary cohort of recently symptomatic ICAD with intensive medical management, we confirmed the high risk of recurrent clinical stroke described in clinical trials, and found a much greater risk of early asymptomatic infarct recurrence which developed in nearly 1 in 4 individuals. We were unable to define a higher risk group based on abnormal hemodynamic and plaque instability imaging biomarkers. Novel technologies and biomarkers including plaque burden and genetic risk profile may help identify baseline characteristics of higher risk for early recurrence and aid in individualized management. [29,30,33,34] This study reinforces the need to develop better strategies to treat this highly prevalent and high-risk condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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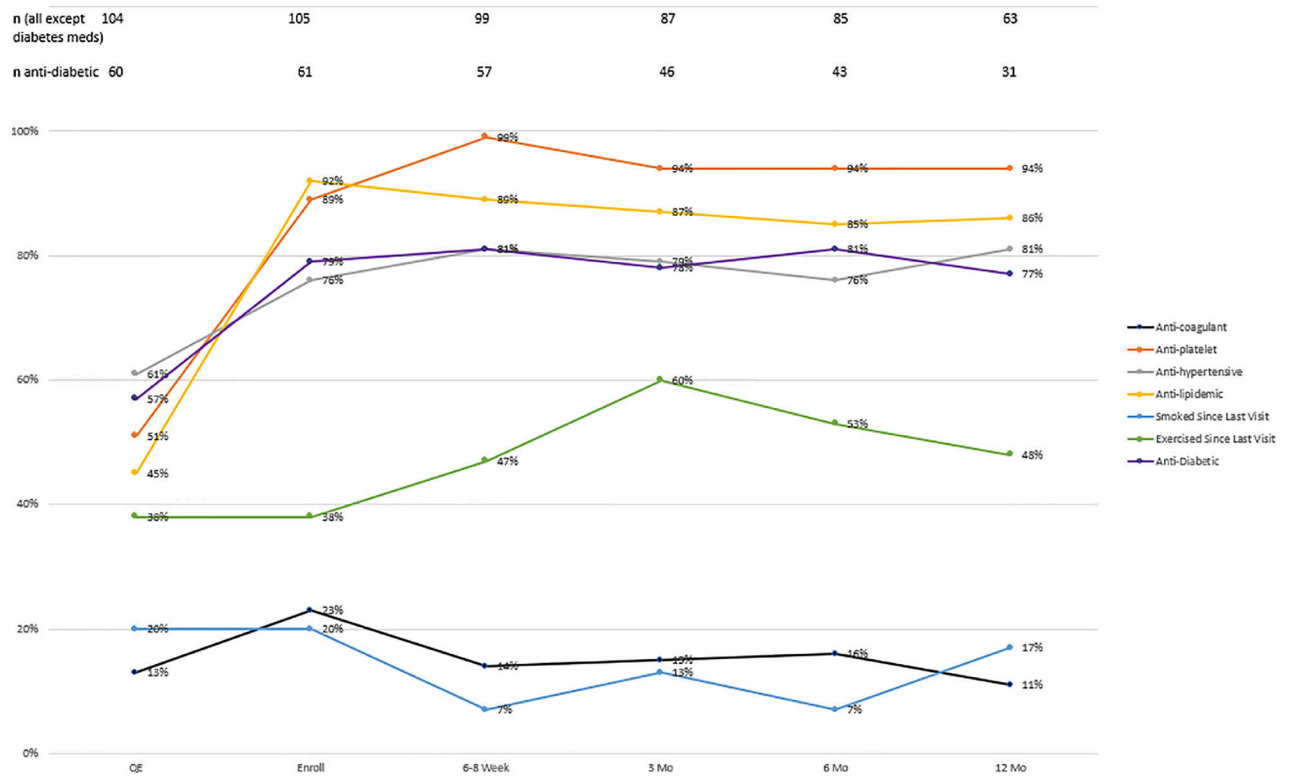
Figure 1.
Treatment adherence at baseline, enrollment and during follow-up visits.

Figure 2.
Kaplan-Meier curves for ischemic stroke in the territory showing the cumulative probability of stroke versus follow-up time, stratified by the presence/absence of baseline biomarker abnormality. Log-rank test p-values comparing the strata: 2A (PWI abnormality) p=0.77; 2B (QMRA abnormality) p=0.60; 2C (TCD VMR abnormality) p=0.79; 2D (TCD EDS abnormality) p=0.18.
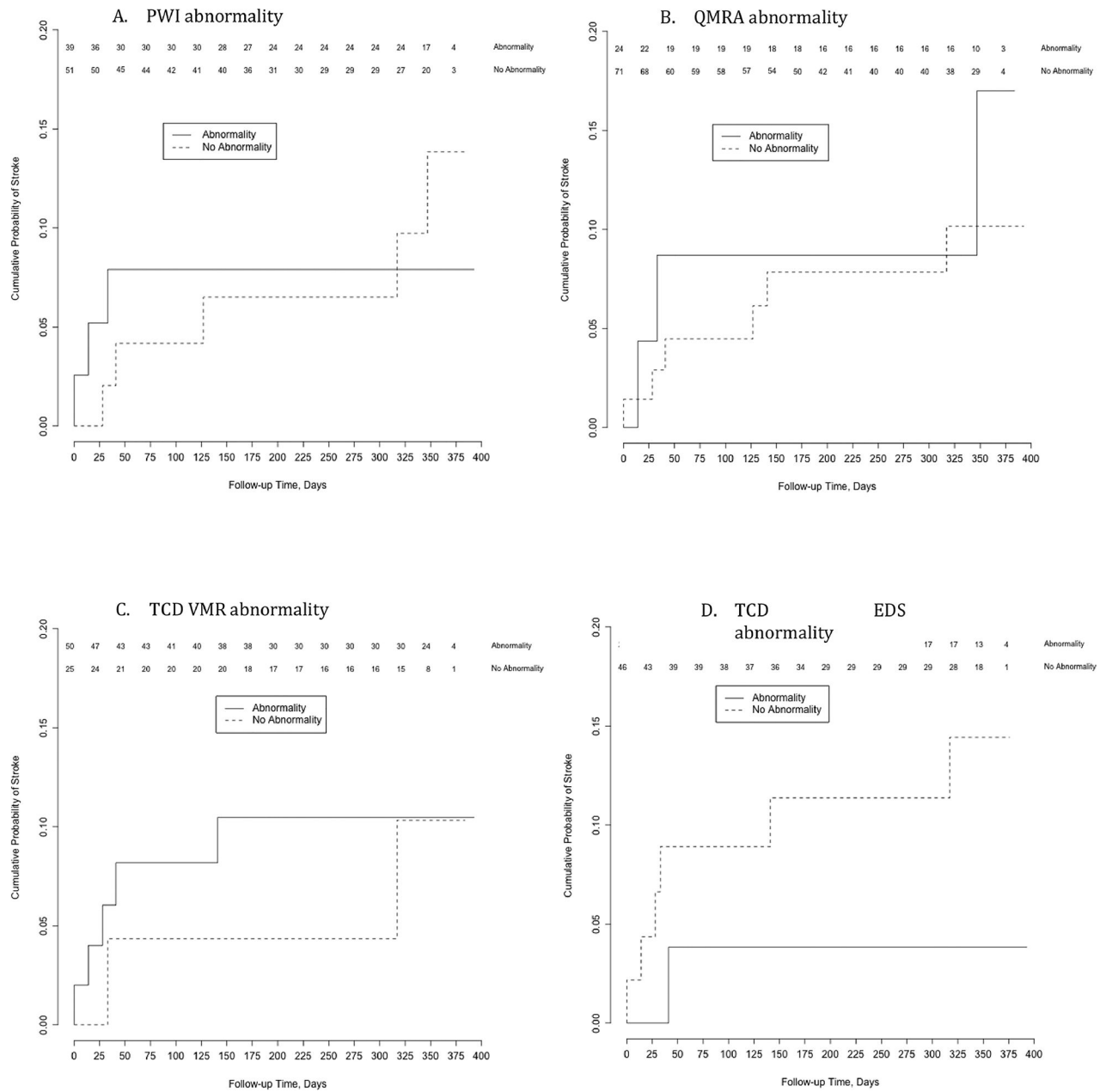
Figure 3.
Kaplan-Meier curves for ischemic stroke in the territory showing the cumulative probability of stroke versus follow-up time, stratified by the presence/absence of prespecified combination of baseline biomarker abnormalities. Log-rank test p-values comparing the strata: 3A (TCD VMR plus EDS abnormality) p=0.47; 3B (PWI plus QMRA abnormality) p=0.60.

Table 1.

Baseline and qualifying event characteristics.

Demographic characteristics	
Age (mean±SD)	63.7±11.8
Female sex	43%
Hispanic ethnicity	21%
Race White	56%
African American	37%
Asian	2%
Other	5%
Risk factors	
Hypertension	85.7%
Diabetes mellitus	54.3%
Hyperlipidemia	67.7%
Body mass index (mean±SD)	30.2±7.5
Tobacco current use	20%
Tobacco cessation <2 years	6.7%
No regular exercise	61.9%
Prior Stroke (>30 days)	20%
Prior TIA (>30 days)	11.4%
Coronary artery disease	18.1%
Baseline laboratory tests	
Cholesterol mg/dL (mean±SD)	182.4 ± 51
LDL mg/dL (mean±SD)	108.8 ± 43.9
HDL mg/dL (mean±SD)	41.3 ± 11.5
Triglycerides mg/dL (mean±SD)	166.6 ± 102.4
HbA1C % (mean±SD)	7.4 ± 2.3
Qualifying event	
Ischemic stroke	77.4%
TIA	22.6%
Symptomatic vessel	
Intracranial carotid artery	16.9%
Middle cerebral artery	55.8%
Vertebral artery	4.2%
Basilar artery	23.2%

Table 2.

Association between hemodynamic and plaque instability imaging biomarkers and outcomes.

Baseline Abnormality	Stroke		TIA		Infarct (6–8 week)	
	n (%)	p[*]	n (%)	p	n (%)	p
QMRA (VFR >20% lower)						
Yes	3/24 (13%)	0.7	2/24 (8%)	0.6	7/23 (30%)	0.4[†]
No	6/71 (8%)		3/71 (4%)		13/60 (22%)	
95% CI for Risk Difference[‡]	(−19%, 27%)		(−19%, 27%)		(−13%, 30%)	
PWI (Tmax >4 sec in >10 cc)						
Yes	3/39 (8%)	1.0	2/39 (5%)	1.0	9/35 (26%)	0.9[†]
No	5/51 (10%)		3/51 (6%)		11/45 (24%)	
95% CI for Risk Difference[‡]	(−23%, 19%)		(−21%, 20%)		(−18%, 20%)	
TCD VMR (BHI < 0.69)						
Yes	5/50 (10%)	1.0	3/50 (6%)	1.0	12/43 (28%)	0.7[†]
No	2/25 (8%)		1/25 (4%)		5/22 (23%)	
95% CI for Risk Difference[‡]	(−23%, 27%)		(−23%, 27%)		(−17%, 27%)	
TCD EDS (any microemboli)						
Yes	1/29 (3%)	0.2	3/29 (10%)	0.3	8/26 (31%)	0.7[†]
No	6/46 (13%)		1/46 (2%)		10/39 (26%)	
95% CI for Risk Difference[‡]	(−32%, 14%)		(−15%, 31%)		(−17%, 28%)	
Abnormal TCD VMR plus TCD EDS						
Yes	1/19 (5%)	0.7	2/19 (11%)	0.3	6/17 (35%)	0.5
No	6/57 (11%)		2/57 (4%)		12/49 (24%)	
95% CI for Risk Difference[‡]	(−31%, 21%)		(−20%, 33%)		(−17%, 38%)	
Abnormal PWI and QMRA						
Yes	2/16 (13%)	0.6	1/16 (6%)	1.0	5/15 (33%)	0.5
No	7/81 (9%)		4/81 (5%)		16/70 (23%)	
95% CI for Risk Difference[‡]	(−23%, 30%)		(−25%, 28%)		(−18%, 38%)	

[*]
p = p-value for test of differences, between the group that had the baseline abnormality and the group that did not have the baseline abnormality, in risk (i.e. in proportions having the event).

[†]Asymptotic chi-square test p-value. All other p-values are for Fisher's Exact test.

[‡]95% confidence interval for the risk difference (risk in group with the abnormality minus risk in group without the abnormality). Intervals were computed using exact methods where exact tests were performed, and using the Wald method where asymptotic chi-square tests were performed.