Usefulness of ADAMTS13 to predict response to recanalization therapies in acute ischemic stroke

Alejandro Bustamante, MD, PhD, MingMing Ning, MD, PhD, Teresa García-Berrocso, PhD, Anna Penalba, BSc, Cristina Boada, BSc, Alba Simats, MSc, Jorge Pagola, MD, PhD, Marc Ribó, MD, PhD, Carlos Molina, MD, PhD, Eng Lo, MD, PhD, and Joan Montaner, MD, PhD

Correspondence

Dr. Montaner
joan.montaner@vhir.org

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Abstract

Objective

We aimed to analyze ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) in relation to arterial recanalization in patients treated with IV tissue plasminogen activator (tPA) and in relation to futile recanalization in patients treated with mechanical thrombectomy.

Methods

Acute ischemic stroke patients ($n = 108$) with documented arterial occlusions treated with IV-tPA were selected. ADAMTS13 activity was measured by ELISA in samples collected before treatment. Recanalization was assessed at 2 hours by transcranial Doppler. In 78 consecutive patients treated with endovascular thrombectomy, ADAMTS13 antigen was measured by ELISA and futile recanalization was defined as complete recanalization plus modified Rankin Scale score >2 at 3 months. Independent predictors of recanalization and futile recanalization were determined by logistic regression, adjusted by age, NIH Stroke Scale score, and time from stroke onset.

Results

Patients who achieved tPA-induced recanalization had higher baseline ADAMTS13 activity (78.1% [68%–88%] vs 70.1% [61%–79%], $p = 0.021$). In logistic regression analysis, ADAMTS13 activity $>75\%$ was an independent predictor of recanalization (odds ratio = 6.76 [1.52–30.02], $p = 0.012$), together with absence of early ischemic signs and Oxfordshire Community Stroke Project classification. Regarding endovascular therapies, a reduced ADAMTS13 concentration (<982 ng/mL) was an independent predictor of futile recanalization (odds ratio = 67.4 [1.4–3,282.1], $p = 0.034$), together with age and diabetes mellitus. The addition of ADAMTS13 to clinical predictors of tPA-induced recanalization and futile recanalization improved discrimination and reclassification (integrated discrimination improvement = 10.06% and 28.4%, net reclassification improvement = 61.0% and 107.4%, respectively).

Conclusions

A reduced ADAMTS13 was associated with poor response to recanalization therapies. If confirmed in future prospective studies, a panel of blood biomarkers including ADAMTS13 might be a useful tool to guide reperfusion therapies.

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[Page 535](#)

From the Neurovascular Research Laboratory (A.B., T.G.-B., A.P., C.B., A.S., J.M.), Institut de Recerca, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain; Clinical Proteomics Research Center and Cardio-Neurology Clinic (M.N., E.L.), Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and Stroke Unit (J.P., M.R., C.M.), Hospital Universitari Vall d'Hebron, Barcelona, Spain.

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Glossary

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **ASPECTS** = Alberta Stroke Program Early CT Score; **IDI** = integrated discrimination improvement; **NIHSS** = NIH Stroke Scale; **NRI** = net reclassification improvement; **OCSF** = Oxfordshire Community Stroke Project; **OR** = odds ratio; **POCI** = posterior circulation infarct; **TACI** = total anterior circulation infarct; **TICI** = thrombolysis in cerebral ischemia; **tPA** = tissue plasminogen activator; **vWF** = von Willebrand factor.

IV thrombolysis with IV tissue plasminogen activator (tPA) within the first 4.5 hours after stroke has been the only drug approved for acute stroke treatment for many years.^{1,2} The chance of recanalization depends on several factors, such as the localization of the culprit occlusion.^{3,4} Recently, phase III clinical trials have demonstrated a clear benefit of endovascular treatment as a bridging therapy on top of IV-tPA in patients with proximal intracranial occlusions.^{5–9} However, almost half of the patients treated with these procedures remained disabled several months after stroke, despite the achievement of complete recanalization.¹⁰ The mechanisms underlying this futile recanalization are not completely understood. In addition to penumbra viability, collateral status or resilience, it has been postulated that the increased permeability of the blood–brain barrier activates tissue factor, causing fibrin deposition and microvascular occlusion despite restoration of the main vessel's flow.¹¹

Currently, reperfusion therapies are indicated based on substantially definite parameters for IV-tPA or the presence of large vessel occlusion and preserved Alberta Stroke Program Early CT Score (ASPECTS) for mechanical thrombectomy. However, thrombolytic doses are not individualized but based on patient's weight, and there is a lack of specific definitive election criteria for endovascular devices. The use of blood biomarkers could be translated into a more personalized approach. Our group described some biomarkers from the coagulation and fibrinolytic pathways related with IV-tPA efficacy,^{12,13} but whether these biomarkers might predict response to endovascular therapies is so far unknown. A panel including several markers from different pathophysiologic pathways involved in response to reperfusion therapies, such as coagulation, fibrinolysis, inflammation, or blood–brain barrier disruption, might be more informative than an isolated biomarker.

ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is responsible for the cleavage and downregulation of the potent thrombogenic activity of ultralarge von Willebrand factor (vWF) multimers secreted from endothelium under circumstances of shear stress and hypoxia.^{14,15} An impaired ADAMTS13 activity is seen in thrombotic thrombocytopenic purpura, where accumulation of ultralarge vWF multimers leads to thrombotic events.¹⁶ In relation to arterial thrombotic diseases, ADAMTS13 activity has been found to be reduced in acute myocardial infarction.¹⁷ More recently, 2 studies have found significantly reduced

ADAMTS13 activity in the early phase after ischemic stroke when compared to healthy controls.^{18,19}

In the present study, we hypothesized that a prothrombotic or antifibrinolytic state, revealed by a low ADAMTS13, could be conditioning a poor response at the vessel level in patients treated with tPA. Moreover, in patients treated with endovascular therapies, a low ADAMTS13 might reflect a poor reperfusion of the recanalized penumbra in relation to microthrombotic processes. Therefore, we aimed to analyze ADAMTS13 in acute stroke patients in relation to vessel patency among those treated with IV-tPA. In an additional cohort of patients treated with endovascular thrombectomy, we aimed to analyze its relation with futile recanalization.

Methods

Patients

From March 2003 to September 2007, 392 acute ischemic stroke patients with documented arterial occlusions by transcranial Doppler, receiving IV-tPA in a standard dose of 0.9 mg/kg within the first 4.5 hours after symptoms onset, were recruited in the emergency room of Hospital Vall d'Hebron. During these years, endovascular procedures were not routinely performed in our center. For this part of the study, because of cost constrictions, we randomly selected 108 patients, not based on any characteristic other than availability of blood samples. This subgroup was compared to the remaining patients of the whole cohort regarding baseline variables.

From August 2012 to August 2015, 1,018 patients with suspected stroke within 6 hours after onset of symptoms were enrolled at the emergency department of Hospital Vall d'Hebron. From this cohort, a total of 78 patients with ischemic stroke were treated with endovascular thrombectomy, 17 of them according to the protocol of the REVASCAT randomized clinical trial.⁹ In both cohorts, a detailed history of vascular risk factors and current medication was obtained. Stroke severity was assessed with the NIH Stroke Scale (NIHSS). Stroke was also classified according to the Oxfordshire Community Stroke Project (OCSF) classification, as total (TACIs) or partial anterior circulation infarcts, or posterior circulation infarcts (POCIs). No patients with lacunar infarcts were included. All patients underwent CT scans at admission and at 24 to 48 hours. Early ischemic signs at admission CT scan were considered if one or more of the

following were present: hyperdense middle cerebral artery or basilar artery signs; sulcal, basal ganglia, or insular effacement; loss of cortical gray–white matter differentiation; mass effect and/or early hypodensities.

ADAMTS13 measurement

Peripheral blood was drawn at hospital admission before any treatment. Samples were centrifuged at 1,500g at 4°C for 15 minutes, and serum and plasma were blindly coded and stored at –80°C until analysis. In the first cohort, ADAMTS13 activity was measured in citrated plasma by ELISA (Kainos Laboratories, Tokyo, Japan) according to the manufacturer's instructions.²⁰ This kit captures ADAMTS13-cleaved products using a sandwich method with 2 antibodies. The anti-GST (anti-glutathione S-transferase) mouse monoclonal antibody immobilized onto the microplate reacts with vWF73 substrate. The sample is then applied to the microplate, and ADAMTS13 cleaves the vWF73 substrate. By applying the mouse monoclonal anti-N10 antibody, conjugated with horseradish peroxidase, the cleavage product is sandwiched. Because the amount of the cleavage products depends on ADAMTS13, the amounts of enzyme-labeled antibodies reflect ADAMTS13 activity. Results were expressed as percentage, being the 100% calculated in a pool of samples from healthy donors.

Given that ADAMTS13 activity can only be measured in citrated plasma, and such samples were not collected for the second cohort of patients receiving endovascular treatment, ADAMTS13 antigen was determined in these patients. It was measured in serum samples by ELISA (LXSAHM, Magnetic Luminex Screening Assay, Human Premixed Multi-Analyte Kit; R&D Systems, Minneapolis, MN) and expressed in nanograms per milliliter. All ADAMTS13 determinations were performed blinded to clinical data.

Outcomes

In the first cohort of patients treated with IV-tPA, a second transcranial Doppler was performed to detect recanalization of the occluded vessel 2 hours after IV-tPA bolus. Recanalization was defined by the thrombolysis in brain ischemia flow grading system.²¹

In the second cohort, recanalization was assessed at the end of the endovascular procedure, according to the thrombolysis in cerebral ischemia (TICI) classification, considering complete recanalization as a final TICI score of 2b–3.⁵ Futile recanalization was considered when complete recanalization was achieved but 3-month modified Rankin Scale score was ≥ 2 points.¹⁰ Futile recanalization at 24 hours was defined as complete recanalization without neurologic improvement at 24 hours (defined as decrease in the NIHSS score by ≥ 4 points).

Standard protocol approvals, registrations, and patient consents

Both study protocols (PR[AG]154/2004 and PR[AG]157/2011) were approved by the local ethics committee at

Hospital Universitari Vall d'Hebron, and all patients or relatives gave written informed consent.

Statistical analysis

Statistical analysis was performed using SPSS statistical package, version 17.0 (SPSS Inc., Chicago, IL). Intergroup differences were compared using χ^2 test for categorical variables. For continuous variables, depending on data distribution, Student *t* test or Mann-Whitney *U* test was used. Further analyses were performed in patients with baseline proximal occlusions, because in this subgroup, prediction of tPA response is more helpful in decision-making processes for further reperfusion therapies. However, the same analyses were repeated in the whole cohort. Logistic regression analyses were conducted by the forward-stepwise method. Recanalization at 2 hours was chosen as the dependent variable in the first cohort. In the second cohort, futile recanalization was considered as dependent variable, and only patients achieving complete recanalization at the end of the procedure were included in this analysis. All covariates associated with the endpoint in univariate analyses were included in the first steps of the logistic regression analyses, considering a threshold of $p < 0.1$. ADAMTS13 was analyzed after categorization by the cutoff with the better accuracy to predict the endpoint, calculated with receiver operating characteristic curves. The Youden index (sensitivity + specificity – 1) was used to calculate cutoffs.²² It was added to the model at the last step, by enter method. In addition, the final models were adjusted by age, NIHSS score, and time from stroke onset to therapy. Interactions between the marker and time from stroke onset to treatment were assessed. R^2 was calculated with the Cox and Snell method. Predictive models with and without ADAMTS13 were compared in terms of accuracy by comparing areas under the curve with the DeLong method,²³ and in terms of discrimination and reclassification, by the integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) indexes.²⁴

Results

IV-tPA cohort

No significant differences were found between the included and excluded patients of the whole cohort, except for a higher percentage of women in the ADAMTS13 group, slightly higher rates of TACIs and POCIs, and a lower proportion of patients with previous stroke (table e-1, [links.lww.com/WNL/A253](#)). Clinical and demographic data of the included stroke patients are summarized in table 1 (proximal occlusions) and table e-2. ADAMTS13 activity was not normally distributed (figure e-1, [links.lww.com/WNL/A252](#)). Patients who achieved recanalization ($n = 51$, 47.2%) showed higher baseline ADAMTS13 activity than those who did not recanalize (78.1% [68%–88%] vs 70.1% [61%–79%], $p = 0.021$) (figure 1). A cutoff point of ADAMTS13 activity of 75% had 59.1% sensitivity and 63.3% specificity for the prediction of 2-hour recanalization (figure e-2). In the selected group of 72

Table 1 Baseline characteristics of the first (IV-tPA) cohort and according to recanalization status, including only patients with proximal occlusions

	Total (n = 72)	Recanalization		p Value
		Yes (n = 33)	No (n = 39)	
Age, y	77 (63–85)	77.0 (63.0–86.5)	78.0 (64.0–84.0)	0.883
Sex, male	26 (36.1)	13 (39.4)	13 (33.3)	0.594
Arterial hypertension	45 (62.5)	20 (60.6)	38 (64.1)	0.651
Diabetes	17 (23.6)	7 (21.2)	10 (25.6)	0.615
Hyperlipidemia	18 (25.4)	9 (27.3)	9 (23.1)	0.729
Tobacco	7 (9.7)	3 (3.1)	4 (10.4)	0.781
Atrial fibrillation	31 (43.1)	17 (51.5)	14 (36.8)	0.214
Coronary disease	12 (16.7)	8 (24.2)	4 (10.5)	0.124
Previous stroke	5 (6.9)	1 (3)	4 (10.5)	0.363
Antiplatelets	21 (29.2)	10 (30.3)	11 (28.2)	0.901
SBP, mm Hg	147 (133–165)	140.5 (133.5–167)	150 (130–165)	0.860
DBP, mm Hg	80.0 ± 15.2	79.0 ± 15.9	80.7 ± 14.8	0.658
Glycemia, mg/dL	124 (96–146)	110.5 (93–135)	134 (103–161)	0.089 ^a
Baseline NIHSS score	19 (16–21)	17.5 (14.5–20)	19 (17–21)	0.035 ^b
Onset-to-tPA, min	176.2 ± 78.1	167.5 ± 60.4	184.4 ± 91.9	0.378
Early ischemic signs	11 (15.3)	1 (3)	10 (25.6)	0.007 ^b
TOAST classification				0.622
CE	42 (58.3)	21 (63.6)	21 (53.8)	
LAA	13 (18.1)	4 (12.1)	9 (23.1)	
UND	14 (19.4)	7 (21.2)	7 (17.9)	
UNC	3 (4.2)	1 (3)	2 (5.1)	
OCSF classification				0.032 ^b
PACI	5 (6.9)	4 (12.1)	1 (2.6)	
TACI	58 (80.6)	28 (84.8)	30 (76.9)	
POCI	9 (12.5)	1 (3)	8 (20.5)	
ADAMTS13 activity, %	72.8 (63.1–85.0)	75.8 (65.6–87.9)	70.1 (59.2–79.8)	0.050 ^b

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CE = cardioembolic; DBP = diastolic blood pressure; LAA = large artery atherothrombotic; NIHSS = NIH Stroke Scale; OCSF = Oxfordshire Community Stroke Project; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; SBP = systolic blood pressure; TACI = total anterior circulation infarct; TOAST = Trial of Org 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; UNC = uncommon (other determined causes of stroke); UND = undetermined.

Data for categorical variables are reported as n (%). For continuous variables, data are reported as mean ± SD (normally distributed variables) or as median (interquartile range) (nonnormally distributed variables).

^ap < 0.1.

^bp < 0.05.

patients with proximal occlusions, patients who achieved recanalization (n = 33, 45.8%) showed higher baseline ADAMTS13 activity than those who did not recanalize (75.8% [65.6%–85%] vs 70.1% [59.2%–85%], $p = 0.050$), and the selected cutoff of 75% activity had 68.8% sensitivity and 55.3% specificity for the prediction of 2-hour recanalization.

ADAMTS13 activity was not associated with long-term functional outcome (figure e-3).

Logistic regression analyses conducted in the subset of proximal occlusions confirmed ADAMTS13 activity >75% as an independent predictor of recanalization (odds ratio

Figure 1 ADAMTS13 according to the main outcomes after recanalization therapies

[OR] = 6.76 [1.52–30.02], $p = 0.012$), together with absence of early ischemic signs at baseline neuroimaging (OR = 14.42 [1.34–154.9], $p = 0.028$), OCSF classification (anterior vs posterior circulation infarcts, OR = 16.79 [1.01–179], $p = 0.049$), and baseline NIHSS score (OR = 0.85 [0.72–0.99], $p = 0.046$). No significant interaction between ADAMTS13 and time from stroke onset to treatment was noted. Of note, addition of ADAMTS13 to the clinical variables improved the discriminatory ability of the predictive model (IDI = 10.06% [2.5%–17.6%], $p = 0.009$), as well as reclassification (NRI = 61.0 [14.0–107.4], $p = 0.011$), but not accuracy. Logistic regression models and comparisons between predictive models are described in detail in table 2. Additional logistic regression analyses conducted in the entire cohort of 108 patient showed similar results for ADAMTS13, although clinical predictors were not further associated with recanalization (table e-3, links.lww.com/WNL/A253).

Endovascular cohort

Clinical and demographic data are summarized in table 3. Complete recanalization after endovascular thrombectomy was achieved in 59 cases (75.6%), and only these cases were included in further analyses. ADAMTS13 antigen was normally distributed (figure e-4, links.lww.com/WNL/A252). Although there were no significant differences in ADAMTS13 between patients with futile or successful recanalization, a cutoff point for ADAMTS13 of 982 ng/mL had 85.7% sensitivity and 42.3% specificity for the prediction of futile

recanalization; patients with ADAMTS13 <982 ng/mL had a higher incidence of futile recanalization (42.3% vs 14.3%; $p = 0.037$) (figures 1 and e-1). Similar results were found for futile recanalization at 24 hours (figure e-4). ADAMTS13 antigen levels were not correlated with long-term functional outcome (figure e-3). In logistic regression analysis, ADAMTS13 <982 ng/mL was an independent predictor of futile recanalization (OR = 67.4 [1.4–3,282.1], $p = 0.034$), together with age (OR = 1.17 [1.04–1.32], $p = 0.008$) and diabetes mellitus (OR = 125.6 [2.1–7,612.7], $p = 0.021$). No significant interaction between ADAMTS13 and time from stroke onset to sample collection, or with time to treatment, was noted. The addition of ADAMTS13 <982 ng/mL to the clinical model produced improved discrimination of futile recanalization (IDI = 23.3% [13.1%–33.3%], $p < 0.0001$), reclassification (NRI = 107.4 [56.8–157.9], $p < 0.0001$), and accuracy (area under the curve from 0.855 to 0.933, $p = 0.044$). Logistic regression models and comparisons between predictive models are described in detail in table 4.

Discussion

In the present study, we followed a candidate-by-function approach to test the value of ADAMTS13 in monitoring reperfusion therapies. Previous reports found that reduced ADAMTS13 activity could be a risk factor for vascular events

Table 2 Logistic regression analysis and additional predictive value of the model including ADAMTS13 activity for IV-tPA-induced recanalization at 2 hours in patients with proximal occlusions (n = 72)

	Recanalization	
	Clinical model	Clinical model + ADAMTS13
Logistic regression		
<i>R</i> ² (Cox & Snell)	0.247	0.332
OCSP classification (anterior vs posterior infarcts)	OR = 9.38 (0.71–123.5), <i>p</i> = 0.089	OR = 16.79 (1.01–179), <i>p</i> = 0.049
Early ischemic signs on CT (absence)	OR = 12.44 (1.28–120.7), <i>p</i> = 0.030	OR = 14.42 (1.34–154.9), <i>p</i> = 0.028
Age	OR = 1.004 (0.96–1.05), <i>p</i> = 0.868	OR = 1.03 (0.98–1.09), <i>p</i> = 0.259
Baseline NIHSS score	OR = 0.90 (0.77–1.04), <i>p</i> = 0.156	OR = 0.85 (0.72–0.99), <i>p</i> = 0.046
Time from onset to tPA	OR = 1.003 (0.99–1.01), <i>p</i> = 0.532	OR = 1.004 (0.99–1.01), <i>p</i> = 0.396
ADAMTS13 >75%	Ref.	OR = 6.76 (1.52–30.02), <i>p</i> = 0.012
ROC curve		
AUC	0.785 (0.671–0.899)	0.836 (0.733–0.938)
<i>p</i> Value	Ref.	0.266
IDI index, %		
IDI for recanalization	—	4.95
IDI for no recanalization	—	5.11
Total IDI	—	10.06 (2.5–17.6)
<i>p</i> Value	Ref.	0.009
NRI index		
Continuous NRI	—	61.0 (14.0–107.4)
<i>p</i> Value	Ref.	0.011

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (activity); AUC = area under the curve; IDI = integrated discrimination improvement; NIHSS = NIH Stroke Scale; NRI = net reclassification improvement; OCSP = Oxfordshire Community Stroke Project; OR = odds ratio; Ref. = reference; ROC = receiver operating characteristic; tPA = tissue plasminogen activator. The table represents the comparison between either predictive models, including or not including ADAMTS13 activity. For the logistic regression analysis, variables entered in step 1 (*p* < 0.1) were glycemia, OCSP classification, early ischemic signs on CT scan, and NIHSS score. The table shows only the variables entered in the final step. ORs and 95% confidence intervals are given for each of the variables.

such as myocardial infarction or stroke.^{25,26} Moreover, ADAMTS13 activity is decreased in acute stroke patients compared to healthy controls.^{18,19} The reasons for these results, however, are not completely understood, and it is unclear whether these reduced levels might act as a trigger for the acute event or are a consequence of the activation of thrombotic-fibrinolytic pathways. The present study confirms that reduced ADAMTS13 activity conditions IV-tPA efficacy, perhaps in relation to thrombus extension promotion.

Although recanalization of the occluded vessel is the only treatment that has shown efficacy in acute stroke, recanalization may fail to induce effective reperfusion. The restoration of vessel patency not translated into a clinical benefit is known as futile recanalization. Distal microthrombosis or extensive damage to the microvascular circulation, due to the no-reflow phenomenon, has been proposed to explain this dichotomy.²⁷ Clinical variables such

as advanced age, stroke severity,¹⁰ or the ASPECTS have been associated with futile recanalization.²⁸ In this study, we identified a biological marker to predict futile recanalization. A relative deficiency of ADAMTS13 might result not just in a lower chance of tPA-induced recanalization, but even with a worse reperfusion of the penumbra area when recanalization is mechanically achieved, perhaps in relation to incomplete clot dissolution and microemboli or microthrombosis. Based on our results, other explanations, such as the relation of ADAMTS13 with other predictors of futile recanalization (age, stroke severity, time after onset), are less plausible. In fact, none of these variables was correlated with ADAMTS13 with the exception of age, with different behavior in each cohort (tables e-4 and e-5, [links.ww.com/WNL/A253](https://www.ww.com/WNL/A253)).

In this study, together with ADAMTS13, we have found other independent predictors of resistance to recanalization, such as

Table 3 Demographic and clinical data for the second (endovascular) cohort and according to the presence of futile recanalization

	Total (n = 78)	Recanalization (n = 59)	Futile recanalization		p Value
			No (n = 27)	Yes (n = 32)	
Age, y	74.0 (60–81)	74.0 (59.5–81)	65.0 (48.5–75)	79.0 (71–83)	0.001 ^a
Sex, male	37 (47.4)	27 (54.2)	14 (51.9)	13 (40.6)	0.388
Tobacco	13 (16.7)	12 (20.3)	6 (22.2)	6 (18.8)	0.741
Hypertension	51 (65.4)	39 (66.1)	16 (59.3)	23 (71.9)	0.308
Diabetes	17 (21.8)	12 (20.3)	2 (7.4)	10 (31.3)	0.023 ^a
Dyslipidemia	43 (55.1)	31 (52.5)	12 (44.4)	19 (59.4)	0.253
Atrial fibrillation	26 (33.3)	22 (37.3)	8 (29.6)	14 (43.8)	0.264
Previous stroke	14 (17.9)	11 (18.6)	3 (11.1)	8 (25.0)	0.172
Antiplatelets	24 (30.8)	16 (27.1)	4 (14.8)	12 (37.5)	0.114
Glycemia	122.5 (108–150)	125 (108–153)	115 (101–133)	133.5 (111–163)	0.062 ^b
NIHSS score	18.0 (12–20)	18.0 (12.5–20)	16.0 (12–19)	18.0 (12.5–20.5)	0.202
Early ischemic signs	33 (43.4)	28 (47.5)	13 (48.1)	15 (46.9)	0.813
ASPECTS	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–10)	0.714
Previous IV-tPA	42 (53.8)	30 (50.8)	15 (55.6)	15 (46.9)	0.506
Onset-to-GP, min	215 (140–302)	207.5 (139–302)	195 (145–272)	235 (139–325)	0.608
TOAST classification					0.057 ^b
CE	42 (54.5)	33 (56.9)	11 (40.7)	22 (71.0)	
LAA	13 (16.9)	9 (15.5)	6 (22.2)	3 (9.7)	
UND	18 (23.4)	13 (22.4)	7 (25.9)	6 (19.4)	
UNC	4 (5.2)	3 (5.2)	3 (11.1)	—	
OCSF classification					0.162
TACI	63 (80.8)	47 (79.7)	20 (74.1)	27 (84.4)	
PACI	10 (12.8)	8 (13.6)	6 (22.2)	2 (6.3)	
POCI	5 (6.4)	4 (6.8)	1 (3.7)	3 (9.4)	
ADAMTS13, ng/mL	1,561.9 ± 628	1,452.2 ± 90.3	1,590.5 ± 121.8	1,340.5 ± 128.2	0.172

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ASPECTS = Alberta Stroke Program Early CT Score; CE = cardioembolic; GP = groin puncture; LAA = large artery atherothrombotic; NIHSS = NIH Stroke Scale; OCSF = Oxfordshire Community Stroke Project; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; TACI = total anterior circulation infarct; TOAST = Trial of Org 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; UNC = uncommon; UND = undetermined.

Data for categorical variables are reported as n (%). For continuous variables, data are reported as mean ± SD (normally distributed variables) or as median (interquartile range) (nonnormally distributed variables).

^a $p < 0.05$.

^b $p < 0.1$.

stroke severity, localization of the arterial occlusion, and the presence of early ischemic signs for those patients treated with IV-tPA, although these variables were only independent predictors in the subgroup of patients with proximal occlusions. These results are in line with previous literature. In fact, basilar occlusions are less prone to recanalize after IV-tPA,²⁹ and regarding early ischemic signs, the ASPECTS or the presence of a hyperdense middle cerebral artery has also been associated with a lower chance of tPA-induced

recanalization.^{30,31} All these conditions are usually associated with more severe strokes, which is also in line with our results. Regarding endovascular therapies, age and diabetes have been also described as predictors of futile recanalization.^{10,32} Although sensitivity and specificity of ADAMTS13 were not optimal in the present study, if our results are confirmed in future studies, a test predicting tPA response, integrating clinical and biological information, could be developed to be used at even the prehospital stage,

Table 4 Logistic regression analysis and additional predictive value of the model including ADAMTS13 activity for futile recanalization

	Futile recanalization	
	Clinical model	Clinical model + ADAMTS13
Logistic regression		
<i>R</i> ² (Cox & Snell)	0.166	0.480
Age	OR = 1.07 (1.01–1.12), <i>p</i> = 0.013	OR = 1.17 (1.04–1.32), <i>p</i> = 0.008
Diabetes	OR = 6.43 (1.08–38.1), <i>p</i> = 0.040	OR = 125.6 (2.1–7,612.7), <i>p</i> = 0.021
NIHSS score	OR = 1.02 (0.90–1.16), <i>p</i> = 0.764	OR = 0.99 (0.83–1.19), <i>p</i> = 0.911
Time to GP	OR = 1.002 (0.99–1.01), <i>p</i> = 0.363	OR = 1 (0.99–1.01), <i>p</i> = 0.844
ADAMTS13 <982 ng/mL	Ref.	OR = 67.4 (1.4–3,282.1), <i>p</i> = 0.034
ROC curve		
AUC	0.855 (0.743–0.966)	0.933 (0.858–1.000)
<i>p</i> Value	Ref.	0.0437
IDI index, %		
IDI for recanalization	—	11.9
IDI for no recanalization	—	11.4
Total IDI	—	23.3 (13.1–33.3)
<i>p</i> Value	Ref.	<0.0001
NRI index		
Continuous NRI	—	107.4 (56.8–157.9)
<i>p</i> Value	Ref.	<0.0001

Abbreviations: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (antigen); AUC = area under the curve; GP = groin puncture; IDI = integrated discrimination improvement; NIHSS = NIH Stroke Scale; NRI = net reclassification improvement; OR = odds ratio; Ref. = reference; ROC = receiver operating characteristic.

The table represents the comparison between either predictive model, including or not including ADAMTS13 antigen. For the logistic regression analysis, variables entered in step 1 (*p* < 0.1) were age, diabetes, glycemia, and TOAST classification. The model was further adjusted by NIHSS score and time from onset to GP. The table shows only the variables entered in the final step. ORs and 95% confidence intervals are given for each of the variables.

with the use of point-of-care technologies able to measure blood biomarkers in a few minutes.³³ The use of such measurement systems is essential in the present indication (management and decision-making of reperfusion therapies in acute stroke), given that the use of a biomarker should not delay treatment administration in any case. The inclusion of other biomarkers from different pathophysiologic pathways related with the response to reperfusion therapies might enhance sensitivity and specificity.

In the present study, ADAMTS13 was not associated with long-term clinical outcome. This fact is not surprising, because ADAMTS13 only partially explains outcome of reperfusion therapies, and the response to reperfusion therapies only explains long-term outcome in part. Many biomarkers in stroke have been repeatedly associated with long-term poor outcome.³⁴ However, none of them is yet used in clinical practice. As an explanation, translation of predicted outcomes such as disability or mortality into clinical decision-making is not easy. Perhaps a biomarker more directly linked to

a specific mechanism (response to reperfusion therapies) could be more easily translated. As an example, on presentation of an acute stroke patient, a low ADAMTS13 level might indicate the need for an emergent transfer to a comprehensive stroke center with availability of endovascular treatments, given the low chance of achieving recanalization with tPA. On the contrary, in a patient with high ADAMTS13 levels, perhaps IV-tPA should be prioritized. Regarding endovascular therapies, these results might be used to select suitable patients out of the currently recommended 6-hour time-window for endovascular therapies, if the biomarker(s) reflects a low chance for futile recanalization.

Our study has some limitations. First, patients in the first cohort were randomly selected. However, this subgroup was found to have only minor differences with the whole cohort, such as higher percentage of women and slightly different rates of TACIs, POCIs, and previous strokes (table e-1, [links.ww.com/WNL/A253](https://www.ww.com/WNL/A253)); therefore, we considered that the selected sample could be representative of the entire

population. Second, the sample size was small, and therefore, some results of the logistic regression analysis have wide 95% confidence intervals, which is less reliable. These large confidence intervals are present in the association between ADAMTS13 antigen and futile recanalization. Therefore, these data should be carefully interpreted. Altogether, our results confer a preliminary and hypothesis-generating nature to the present study, which will require further validation in larger, prospective studies. Third, the study was composed of 2 different cohorts for a better assessment of each type of reperfusion treatment. We thought that was the best way to explore the effect of ADAMTS13 in both tPA-induced recanalization (in patients enrolled before endovascular thrombectomy was performed routinely in our center) and mechanical thrombectomy. Third, the fact that ADAMTS13 activity was measured in the first cohort and ADAMTS13 antigen in the second remains a limitation. The activity assay has intrinsic limitations; it is performed in static conditions and has higher variability than the antigen assay. Protease activity of ADAMTS13 is not stable in various pathologic conditions, is not stable in vitro, and might be reduced after storage, although this effect was not found to be present in our samples (data not shown). Because the association between ADAMTS13 antigen and activity in the literature is controversial,^{35,36} future studies simultaneously comparing antigen and activity levels, or even vWF and other molecules involved in this pathway, should be conducted to demonstrate whether different biological information is given by each one of the measures in the acute stroke setting.

Author contributions

Alejandro Bustamante: data acquisition, analysis and interpretation of the data, drafting the manuscript. MingMing Ning: interpretation of the data, revising the manuscript for intellectual content. Teresa García-Berrococo: analysis and interpretation of the data, revising the manuscript for intellectual content. Anna Penalba: analysis and interpretation of the data, revising the manuscript for intellectual content. Cristina Boada: analysis and interpretation of the data, revising the manuscript for intellectual content. Alba Simats: interpretation of the data, revising the manuscript for intellectual content. Jorge Pagola: data acquisition, interpretation of the data, revising the manuscript for intellectual content. Marc Ribó: data acquisition, interpretation of the data, revising the manuscript for intellectual content. Carlos Molina: data acquisition, interpretation of the data, revising the manuscript for intellectual content. Eng Lo: interpretation of the data, revising the manuscript for intellectual content. Joan Montaner: design of the study, revising the manuscript for intellectual content, acquisition of funding.

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Disclosure

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Usefulness of ADAMTS13 to predict response to recanalization therapies in acute ischemic stroke

Alejandro Bustamante, MD, PhD, MingMing Ning, MD, PhD, Teresa García-Berrocso, PhD, Anna Penalba, Cristina Boada, Alba Simats, MSc, Jorge Pagola, MD, PhD, Marc Ribó, MD, PhD, Carlos Molina, MD, PhD, Eng Lo, MD, PhD, and Joan Montaner, MD, PhD

Correspondence

Dr. Montaner
joan.montaner@vhir.org

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Study question

Are levels of ADAMTS13 (i.e., A Disintegrin And Metalloproteinase with a Thrombospondin type-1 motif, member-13) related to responses to recanalization therapy in patients with acute ischemic stroke (AIS) treated with IV tissue plasminogen activator (IV-tPA) or mechanical thrombectomy (MT)?

Summary answer

Reduced ADAMTS13 is associated with poor responses to recanalization therapy.

What is known and what this paper adds

Reduced ADAMTS13 is a potential biomarker of a prothrombotic or antifibrinolytic state that would predict a poor response to recanalization therapies. This study provides evidence that ADAMTS13 activity is a prognostic biomarker for responses to recanalization therapies.

Participants and setting

The study randomly selected 108 patients from among 392 patients with AIS who received IV-tPA at the Hospital Vall d'Hebron in Barcelona between March 2003 and September 2007. In addition, the study included 78 patients treated with MT from August 2012 to August 2015.

Design, size, and duration

The study retrospectively analyzed ELISA-measured pretreatment ADAMTS13 levels, which are expressed as activity (percentages relative to physiologically normal levels) in the first cohort and antigen levels in ng/mL in the second cohort.

Primary outcomes

In the first cohort, primary outcome was recanalization, as defined by the Thrombolysis in Brain Ischemia flow grading system, measured 2 hours after the IV-tPA bolus. In the second cohort, primary outcome was futile recanalization, defined as poor functional outcome at 3 months after stroke (mRS > 2) despite achieving complete recanalization at the end of MT.

Main results and the role of chance

The median pretreatment ADAMTS13 activity was higher in the patients who recanalized ($n = 51$) than in those who did not (78.1% vs 70.1%; $p = 0.021$). In a subset of 72 patients with proximal occlusions, the median baseline pretreatment ADAMTS13 activity level was again higher in the patients who recanalized ($n = 33$) than in those who did not (75.8% vs 70.1%; $p = 0.050$). For this patient subgroup, the 75% cut-off predicted recanalization with 68.8% sensitivity and 55.3% specificity, and a logistic regression analysis confirmed that this cut-off independently predicted recanalization (odds ratio, 6.76; 95% CI, 1.52–30.02; $p = 0.012$). In the second

ADAMTS13 activity in stroke patients 2 hours after iv-tPA: not achieving recanalization versus achieving recanalization.

cohort, despite no significant differences on ADAMTS13 antigen between patients with futile or successful recanalization, a cut-off point of ADAMTS13 of 982 ng/mL had 85.7% sensitivity and 42.3% specificity for the prediction of futile recanalization. In logistic regression analysis, ADAMTS13 < 982 ng/mL was an independent predictor of futile recanalization (odds ratio, 67.4; 95% CI, 1.4–3282.1; $p = 0.034$).

Bias, confounding, and other reasons for caution

The sample was small and randomly selected. The activity assay had some intrinsic limitations, such as having higher variability than an antigen assay typically does.

Generalizability to other populations

The patient sample was representative of the population that it was selected from, which supports the generalizability of the results.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.