Brain Atrophy and the Risk of Futile Endovascular Reperfusion in Acute Ischemic Stroke

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Background and Purpose—We aimed to evaluate the impact of brain atrophy on long-term clinical outcome in patients with acute ischemic stroke treated with endovascular therapy, and more specifically, to test whether there are interactions between the degree of atrophy and infarct volume, and between atrophy and age, in determining the risk of futile reperfusion.

Methods—We studied consecutive patients with acute ischemic stroke with proximal anterior circulation intracranial arterial occlusions treated with endovascular therapy achieving successful arterial recanalization. Brain atrophy was evaluated on baseline computed tomography with the global cortical atrophy scale, and Evans index was calculated to assess subcortical atrophy. Infarct volume was assessed on control computed tomography at 24 hours using the formula for irregular volumes (A×B×C/2). Main outcome variable was futile recanalization, defined by functional dependence (modified Rankin Scale score >2) at 3 months. The predefined interactions of atrophy with age and infarct volume were studied in regression models.

Results—From 361 consecutive patients with anterior circulation acute ischemic stroke treated with endovascular therapy, 295 met all inclusion criteria. Futile reperfusion was observed in 144 out of 295 (48.8%) patients. Cortical atrophy affecting parieto-occipital and temporal regions was associated with futile recanalization. Total global cortical atrophy score and Evans index were independently associated with futile recanalization in an adjusted logistic regression. Multivariable adjusted regression models disclosed significant interactions between global cortical atrophy score and infarct volume (odds ratio, 1.003 [95%CI, 1.002–1.004], $P<0.001$) and between global cortical atrophy score and age (odds ratio, 1.001 [95% CI, 1.001–1.002], $P<0.001$) in determining the risk of futile reperfusion.

Conclusions—A higher degree of cortical and subcortical brain atrophy is associated with futile endovascular reperfusion in anterior circulation acute ischemic stroke. The impact of brain atrophy on insufficient clinical recovery after endovascular reperfusion appears to be independently amplified by age and by infarct volume. **(*Stroke*. 2020;51:15141521 DOI: 10.1161/STROKEAHA.119.028511.)**

Key Words: angiography ■ atrophy ■ brain ■ carotid arteries ■ outcome ■ reperfusion ■ stroke, acute

Stroke is a leading cause of death and disability worldwide.[1] Endovascular therapy (EVT) has emerged as the standard of care for large vessel occlusion acute ischemic stroke (AIS).[2–7] Unfortunately, regardless of the great advance that EVT provides in acute stroke care, up to 50% of patients with large vessel occlusion AIS do not show sufficient clinical improvement despite a technically successful recanalization through EVT.[8,9] Thus, futile recanalization is a major clinical problem for patients with AIS treated with EVT.

Different determinants of futile recanalization have been identified, including old age, hypertension, stroke severity, and the absence of collaterals.[8–12] Understanding the determinants and mechanisms underlying futile reperfusion may help identify new therapeutic targets and allow a more personalized patient selection for EVT.[13,14] In this regard, an important determinant may be brain reserve,[15] that is to say, the capacity of the brain to recover after AIS. In particular, brain atrophy may be a good indicator of brain reserve,[10] although its influence on

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functional recovery after EVT for AIS has been little studied.[16] Given the strong link between brain atrophy and brain's biological age, we hypothesized that its effect on the clinical response to EVT could be synergistically amplified by chronological age. Moreover, previous studies had shown that the maximum infarct volume tolerable to achieve a good clinical outcome after EVT diminishes progressively with age,[17] but whether this relationship is affected by the degree of brain atrophy remains unknown.

We aimed to evaluate the prognostic impact of brain atrophy on the risk of futile reperfusion in patients with AIS treated with EVT, and more specifically, to test whether there are interactions between the degree of atrophy and infarct volume, and between atrophy and age, in determining the risk of futile reperfusion after EVT.

Methods

Study Design and Patient Selection

We performed a retrospective long-term follow-up observational study, analyzing a prospectively collected brain reperfusion registry at our Regional Stroke Center (Hospital Clínico Universitario Valladolid, Castilla y León, Spain) from May 2015 to November 2018. All patients fulfilled criteria to receive mechanical thrombectomy therapy with or without previous use of intravenous thrombolysis with tPA (tissue-type plasminogen activator). At our Institution, there is no upper age limit to receive EVT, and we follow radiological selection criteria based on International Guidelines. Initial candidates had to fulfill the following additional criteria to enter this study: premorbid functional status defined by the modified Rankin Scale score ≤2, (2) intracranial large-artery occlusion affecting internal carotid artery or middle cerebral artery M1 segment, and (3) successful recanalization achieved with EVT, as defined by a modified Treatment in Cerebral Ischemia Scale score 2B, 2C, or 3. The degree of brain atrophy was not assessed before therapy and could not be used as a selection criterion to receive EVT. This study was approved by our Institutional Clinical Research Ethics Committee. Written informed consent was obtained from all patients or their relatives upon admission to the angio-suite, by which they gave allowance to enter their clinical and radiological information into our Reperfusion Registry and to use the data for scientific purposes, in accordance with the Spanish Personal Data Protection law. The database and the original sources of data, including computed tomography (CT) images, are at the disposal of all interested researchers upon reasonable request.

Clinical Data and Baseline Variables

All patients included were clinically managed according to our Institutional protocol, which is based on updated international guidelines. EVT was performed under continuous sedation whenever possible, leaving the indication of general anesthesia for clinical or technical reasons. The front-line endovascular strategy used was left at the discretion of the neuroradiologist in charge. After the procedure, the majority of our patients were admitted directly to our Stroke Unit, where they received subsequent neurological medical management, according to our Institutional protocol. Our Reperfusion Registry includes data pertaining to the following baseline variables: age, sex, premorbid functional status defined by the modified Rankin Scale, vascular risk factors (hypertension, diabetes mellitus, alcohol abuse, smoking), history of coronary disease and atrial fibrillation, pretreatment with anticoagulants, time window, and different time intervals. We collected the baseline clinical severity (National Institutes of Health Stroke Scale) and location of arterial occlusion. We obtained pretreatment previous use of tPA, type of anesthesia, and final TICI grade.

Neuroimaging Protocol

On admission, all patients underwent a noncontrast CT, CT angiography, and perfusion CT when indicated (>4.5 hours from onset or with baseline Alberta Stroke Program Early CT Score 5–7). CT was repeated 24 hours after EVT or earlier if neurological deterioration occurred. All CT imaging was performed using either a 64-slice GE Lightspeed scanner or a 32-slice Toshiba Aquilion, depending on availability. Pretreatment Alberta Stroke Program Early CT Score was assessed on the baseline noncontrast CT by the treating team and recorded in the Registry.

Assessment of Brain Atrophy, Leukoaraiosis, and Infarct Volume

We used the baseline noncontrast CT to assess brain atrophy and leukoaraiosis. Anonymized offline analysis of baseline CTs was performed by a neurologist with expertise in brain imaging (Dr Pedraza) who remained blind to all other clinical and imaging data. To evaluate the interobserver agreement, a random sample of 50 CTs was also analyzed by Dr Martínez-Pías.

Brain atrophy was evaluated using the global cortical atrophy (GCA) scale.[18] This scale systematically evaluates brain atrophy in 13 regions. First, cortical GCA assesses cortical sulci dilatation at frontal, parieto-occipital, and temporal areas. Second, ventricle GCA score is obtained evaluating ventricular dilatation of the frontal, parietal-occipital, temporal, and third ventricles in each hemisphere. For each evaluated region, a score from 0 to 3 is given. No cortical atrophy equals a GCA grade 0, mild atrophy (opening of sulci). a GCA grade 1, moderate atrophy (volume loss of gyri). a GCA grade 2, and severe atrophy knife blade atrophy, a GCA grade 3.[18] Total GCA score ranks from 0 (absence of atrophy) to 39 (maximal atrophy), subdivided into cortical GCA score (rank 0–18) and ventricular GCA (rank 0–21). To study the contribution of brain atrophy in different areas, atrophy scores obtained at frontal, parietal-occipital, temporal, and ventricular regions of both hemispheres were summed. Total score in each region was categorized in normal (absence), mild (scores 1–2), and moderate-severe.[3–6] Additionally, the Evans index was obtained measuring the ratio of the maximal width of the frontal horns to internal width of cranium. Both diameters were measured in the same CT slice.[19] Leukoaraiosis severity was assessed with Fazekas Scale.[20]

A control CT was performed in all patients at 24 hours and analyzed by the stroke team to assess the extent of hemorrhagic transformation and brain hypodensity volume as a proxy to infarct volume. Brain hypodensity volume was calculated using the formula for irregular volumes (A×B×C/2), where A is the hypodensity's largest diameter; B, the perpendicular diameter; and C, the coronal diameter. Hemorrhagic transformation was classified according to the radiological classification used in the ECASS study (European Cooperative Acute Stroke Study).[21] In patients showing hemorrhagic transformation, infarct volume was calculated, including the hemorrhage within the hypodensity limits.

Assessment of Futile Reperfusion

Main outcome variable was futile reperfusion, defined as the lack of functional independence at 3 months, despite successful arterial recanalization after EVT. Functional status was assessed 3 months after stroke with the modified Rankin Scale score, which was administered by certified stroke neurologists during a physical visit at our stroke outpatients clinic, whenever possible, or telephonically in the remaining cases. Futile recanalization was defined by a modified Rankin Scale score >2. For every patient, the person adjudicating Rankin Scale score was unaware of the scores obtained in brain atrophy scales.

Statistical Analysis

Statistical analyses were performed with SPSS statistical package (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY). Continuous variables are reported as mean±SD or as median±interquartile range. Categorical variables are reported as numbers and proportions. Statistical significance for intergroup differences was assessed by the χ^2 test for categorical variables, Mann Whitney *U* test, and Student *t* test for continuous variables. All continuous variables, except National Institutes of Health Stroke Scale score, noncontrast CT–Alberta Stroke Program Early CT Score, leukocyte, and platelet count, were normally distributed. The patient

sample was categorized into tertiles for global GCA, cortical GCA, ventricular GCA, and Evans index for some bivariate analyses. First, we attempted to identify baseline variables associated with the degree of brain atrophy, by analyzing the association between main baseline variables and the degree of GCA and Evans index, using crude and adjusted logistic regression models. Second, we studied the association between categories of brain atrophy at every assessed brain region and futile reperfusion. Then, we performed crude and adjusted logistic regression models to evaluate the prognostic impact of GCA and Evans index on long-term clinical outcome, using futile reperfusion as dependent variable, where GCA and Evan index were entered as a continuous variables into the model. And finally, we performed additional adjusted logistic regression models to test whether there were interactions between atrophy and 24 hour-brain hypodensity, and between atrophy and age, to determine long-term clinical outcome, entering the terms atrophy×brain hypodensity and atrophy×age as independent variables of the models, where brain atrophy was entered as a continuous variable. In every logistic regression model, adjustment was performed by all variables showing a $P<0.1$ on the respective bivariate analyses, and also by potential confounding baseline variables associated with a higher degree of atrophy in the first analysis. Results of logistic regression models are shown as odds ratios (ORs) and their correspondent 95% CI. Level of significance was defined as a $P<0.05$.

Results

Descriptive Analysis

During the study period, 361 consecutive patients with stroke with intracranial internal carotid artery or M1-middle cerebral artery occlusion who received thrombectomy were screened. In 302 patients, it was achieved modified Treatment in Cerebral Ischemia Scale 2b or 3 and 3-month follow-up was available in 295. Reasons for exclusion of the 59 remaining patients were: poor CT imaging quality to rate brain atrophy (n=2) and insufficient reperfusion grade after thrombectomy (n=57).

The distribution of baseline variables is shown in Table 1. One hundred thirty-eight (46%) were women, mean age was 71 years, 84 patients (28.47%) were older than 80 years, and median National Institutes of Health Stroke Scale score was

Table 1. Demographic and Baseline Variables in the Whole Study Sample and Across the Group of Patients With Good Clinical Outcome and Futile Recanalization

	Total (n=295)	Good Clinical Outcome (n=151)	Futile Recanalization (n=144)	*P* Value
Age, y, mean±SD	71.29±13.27	68.36±±13.172	74.37±±12.705	0.076
Sex (women), %	137 (46.4%)	66 (43.7%)	71 (49.3%)	0.335
Prior mRS 0, %	239 (81.3%)	130 (86.1%)	109 (76.2%)	0.059
Smoking, %	69 (23.4%)	47 (31.1%)	22 (15.3%)	0.001
Alcohol abuse, %	23 (7.8%)	15 (9.9%)	8 (5.6%)	0.161
Hypertension, %	187 (63.4%)	83 (55%)	104 (72.2%)	0.002
Diabetes mellitus, %	58 (19.7%)	21 (13.9%)	37 (25.7%)	0.011
Hypercholesterolemia, %	93 (31.5%)	49 (32.5%)	44 (30.6%)	0.726
Atrial fibrillation, %	74 (41.1%)	34 (37%)	40 (45.5%)	0.160
On anticoagulants, %	51 (17.3%)	19 (12.6%)	32 (22.2%)	0.029
Extended time window, %	133 (45.1%)	61 (33.1%)	72 (50%)	0.258
Time intervals, median (IQR), min				
Symptom onset to admission	177(70–285)	151 (60–255)	179 (70–286)	0.518
Door to groin	94 (77–115)	93 (76–110)	95(79–119)	0.616
Groin puncture to reperfusion	40 (25–63)	35(22–55)	45 (25–75)	0.813
Onset to reperfusion	350(263–572)	330 (211–62)	390 (291–592)	0.220
Baseline NIHSS, median (IQR)	18 (11–21)	13 (9–19)	19 (15–22)	<0.001
Baseline ASPECTS, median (IQR)	8 (7–10)	9 (8–10)	8 (7–9)	0.005
MCA M1 oclussion, %	252 (85.4%)	133 (88.1%)	119 (82.6%)	0.186
Cardioembolic origin	146 (49.5%)	74 (49%)	72 (50%)	0.970
TICI 3 final reperfusion, %	205(69.5%)	115 (76.2%)	90 (62.5%)	0.025
IV tPA before thrombectomy, %	114 (38.9%)	66 (43.7%)	48 (33.8%)	0.082
General anesthesia, %	101 (36.6%)	43 (31%)	58 (42.3%)	0.135
Symptomatic hemorrhagic transformation, %	23 (7.8%)	2 (8.7%)	21 (91.3%)	<0.001
Total GCA, median (IQR)	9 (5–14)	7 (4–13)	10 (7–16)	<0.001

Results are expressed as mean±SD, N (%), or median (IQRs), as appropriate. ASPECTS indicates Alberta Stroke Program Early CT Score; GCA, global cortical atrophy; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TICI, Treatment in Cerebral Ischemia Scale.

Table 2. Baseline Variables Associated With Atrophy in Each Region

Frontal Cortical Atrophy	Normal	Mild	Moderate-Severe	*P* Value
Smoking	17 (51.5%)	16 (17.8%)	37 (20.7%)	<0.001
Hypertension	13 (39.4%)	52 (57.8%)	127 (70.9%)	0.001
Cardioembolic origin	9 (27.3%)	41 (45.6%)	98 (54.7%)	0.004
Parieto-occipital cortical atrophy				
Smoking	44 (34.1%)	23 (14.7%)	3 (17.6%)	0.001
Hypertension	68(52.7%)	112(71.8%)	12 (70.6%)	0.003
Diabetes mellitus	18(14%)	35(22.4%)	6 (35.3%)	0.045
Hypercholesterolemia	32 (24.8%)	59 (37.8%)	4 (23.5%)	0.048
Temporal cortical atrophy				
Smoking	35 (42.2%)	27 (17.9%)	8 (11.8%)	<0.001
Hypertension	34 (41%)	110 (72.8%)	48 (67.6%)	<0.001
Diabetes mellitus	7 (8.4%)	30 (19.9%)	22 (32.4%)	0.001
Hypercholesterolemia	18 (21.7%)	57 (37.7%)	20 (29.4%)	0.037
Atrial fibrillation	10 (18.2%)	41 (46.6%)	23 (54.7%)	0.002
Cardioembolic origin	28 (33.7%)	80 (53%)	40 (58.8%)	0.043
Lateral ventricle frontal horn dilatation				
Smoking	58 (35.6 %)	9 (7.6%)	3 (14.3%)	<0.001
Hypertension	93(57.1%)	86(72.9%)	13 (61.9%)	0.024
Lateral ventricle parieto-occipital horn dilatation				
Smoking	60 (35.5%)	8 (8.1%)	2 (6.9%)	<0.001
Lateral ventricle temporal horn dilatation				
Smoking	62 (27.6%)	7 (10.4%)	1 (10%)	0.009
Diabetes mellitus	36 (16%)	19 (28.4%)	4 (40%)	0.021
Third ventricle				
Smoking	30 (44.1%)	24 (21.2%)	16 (13.2%)	<0.001
Hypertension	32(47.1%)	72(63.7%)	88 (72.7%)	0.002
Hypercholesterolemia	11 (16.2%)	40 (35.4%)	44 (36.4%)	0.009
Cardioembolic origin	24 (35.3%)	50 (49.6%)	68 (58.2%)	0.035

18. There were no patients diagnosed previously with dementia or cognitive impairment. Regarding EVT modality, 139 received treatment in an extended time window, and 115 received tPA before EVT. A TICI 3 score was obtained in 210 patients (70%), and general anesthesia was necessary for 105 (37%) patients.

Baseline variables associated with atrophy in each region are shown in Table 2. Hypertension was associated with more severe cortical atrophy and more dilated ventricles in most of the regions. However, smoking was associated with less cortical atrophy and less dilated ventricle in the majority of brain areas.

Brain Atrophy and Futile Recanalization

Third-month follow-up was available in 295 out of 302 patients. The remaining seven patients were transferred to remote hospitals and were lost to follow-up. Futile recanalization was observed in 144 (48.8%) patients. Baseline variables potentially associated with futile recanalization in bivariate analyses are shown in Tables 1 and 3. The Kappa value for GCA scale was moderate (κ=0.551). Regarding regional atrophy scores (Table 4), futile recanalization was significantly associated with higher atrophy scores in parieto-occipital regions (P=0.006), temporal regions (P<0.001), parieto-occipital ventricles (P=0.001), and temporal ventricles (P=0.004). With respect to scale scores, futile reperfusion was associated with higher scores in cortical GCA scale (P<0.001), ventricle GCA scale (P<0.001), total GCA scale (P<0.001), and Fazekas scale (P=0.016). The percentage of patients with good long-term clinical outcome was higher in the lower tertile of cortical GCA scale (P<0.001), ventricle GCA scale (P=0.005), and total GCA scale (P=0.002). The multivariate-adjusted logistic regression model is shown on Table 5; total GCA scale score (OR, 1.155 [95% CI, 1.085–1.229], P<0.001) and Evans index (OR, 0.001 [95% CI, 0–0.541], P=0.035) were found to be independent predictors of futile recanalization. To assess

Table 3. Bivariate Analysis of Radiological Variables Associated With Futile Recanalization

	Good Clinical Outcome (n=151)	Futile Recanalization (n=144)	*P* Value
Cortical GCA, median (IQR)	6 (3–8)	7 (4–9)	<0.001
Ventricle GCA, median (IQR)	2 (1–5)	4 (1–8)	<0.001
Total GCA, median (IQR)	7 (4–13)	10 (7–16)	<0.001
Fazekas scale, median (IQR)	2 (1–3)	2 (1–4)	0.016
Evans index, mean±SD	0.28±0.043	0.28±0.042	0.196
Cortical GCA, tertile 3, n (%)	39 (25.8%)	70 (48.6%)	<0.001
Ventricle GCA, tertile 3, n (%)	35 (23.2%)	57 (39.6%)	0.005
Total GCA, tertile 3, n (%)	38(25.2%)	56 (38.9%)	0.002
Evans index, tertile 3, n (%)	39 (25.8%)	47 (32.6%)	0.245

GCA indicates global cortical atrophy; and IQR, interquartile range.

the influence of symptomatic hemorrhagic transformation on these associations, a secondary analysis was performed, excluding the patients with symptomatic hemorrhagic transformation, which showed similar results.

Interaction Between Atrophy, Age and Infarct Volume

Multivariate-adjusted regression models disclosed significant interactions between GCA score and brain infarct volume (OR, 1.003 [95% CI, 1.002–1.004] $P<0.001$) and between GCA score and age (OR, 1.001 [95% CI, 1.001–1.002], $P<0.001$) in determining the risk of futile reperfusion. The Figure illustrates the interactions between brain hypodensity volume and GCA, and between GCA score and age, in determining the risk of futile reperfusion.

Discussion

In this observational study based on a prospective reperfusion registry, brain atrophy emerged as an independent predictor of futile cerebral reperfusion after EVT for anterior circulation AIS. Moreover, it was not only the global cerebral atrophy scale that was independently associated with a worse clinical outcome despite complete reperfusion but also cortical atrophy and subcortical atrophy were predictors of futile reperfusion independently of each other. In addition, significant interactions were found between global brain atrophy and age and between global brain atrophy and infarct volume to determine the risk of futile reperfusion. Taken together, these findings support the notion that brain atrophy plays a crucial role in determining the risk of futile reperfusion after EVT and that the impact of brain atrophy on the response to endovascular reperfusion is synergistically amplified by the patient's chronological age and by acute cerebral infarct volume.

Our main finding is in line with a recent study showing that brain atrophy was independently associated with a worse clinical outcome after EVT, although our study was focused specifically on futile reperfusion.[16] Moreover, in that study, global brain atrophy was automatically quantified using computer software, whereas, in our study, we used the GCA scale. This is a validated visual scale proposed by Pasquier et al[18] in 1996

Table 4. Bivariate Analysis of Cortical and Ventricle Region Associated With Futile Recanalization

	Good Clinical Outcome	Futile Recanalization	*P* Value
Frontal cortical GCA			
Normal	16 (10.6%)	16 (11.1%)	0.069
Mild	54 ((35.8%)	34 (23.6%)	0.069
Mod-severe	81 (53.6%)	94 (65.3%)	0.069
Parieto-occipital cortical GCA			
Normal	78 (51.7%)	50 (34.7%)	0.006
Mild	68 (45%)	82 (56.9%)	0.006
Mod-severe	5 (3.3%)	12 (8.3%)	0.006
Temporal cortical GCA			
Normal	53 (35.1%)	29 (20.1%)	<0.001
Mild	76 (50.3%)	69 (47.9%)	<0.001
Mod-severe	22 (14.6%)	46 (31.9%)	<0.001
Frontal ventricle GCA			
Normal	92 (60.9%)	67 (46.5%)	0.040
Mild	51 (33.8%)	64 (44.4%)	0.040
Mod-severe	8 (5.3%)	13 (9%)	0.040
Parieto-occipital ventricle GCA			
Normal	103 (68.2%)	69 (47.9%)	0.001
Mild	40 (26.5%)	54 (37.5%)	0.001
Mod-severe	8 (5.3%)	21 (14.6%)	0.001
Temporal ventricle GCA			
Normal	125 (82.8%)	96 (66.7%)	0.004
Mild	24 (15.9%)	40 (27.8%)	0.004
Mod-severe	2 (1.3%)	8 (5.6%)	0.004
Third ventricle			
Normal	40 (26.5%)	26 (18.1%)	0.036
Mild	61 (40.4%)	50 (34.7%)	0.036
Mod-severe	50 (33.1%)	68 (47.2%)	0.036

GCA indicates global cortical atrophy; and mod-severe, moderate-severe.

that allowed us to analyze the impact of brain atrophy affecting specific regions and also to study cortical versus subcortical components of brain atrophy. With this regard, temporal lobe and parietal-occipital lateral ventricles were the regions where atrophy seemed to have a greater impact on futile recanalization. In addition, the Evans index, an indicator of subcortical atrophy that can be rapidly calculated by performing simple measures on baseline CT, was also an independent predictor of futile reperfusion. Apart from this study and ours, the role of brain atrophy on the process of clinical recovery after endovascular reperfusion had deserved little attention. Regarding intravenous thrombolysis, brain atrophy was reported to be a predictor of poor outcome in patients with AIS treated with alteplase within the IST-3 (Third International Stroke Trial).[22]

Our results suggest that brain atrophy may be a reliable indicator of brain reserve, the expected capacity of the brain

Table 5. Multivariable Logistic Regression Adjusted for Baseline Variables

	Adjusted ORs for Futile Reperfusion		
	OR	95% CI	*P* Value
Baseline NIHSS score	1.145	1.089–1.204	<0.001
ASPECTS	0.758	1.002–4.418	0.002
mTICI 3	0.442	0.254–0.769	0.004
On anticoagulants	2.10	0.638–0.901	0.049
Total GCA scale score	1.155	1.085–1.229	<0.001
Evans index	0.001	0–0.541	0.035

ASPECTS indicates Alberta Stroke Program Early CT Score; GCA, global cortical atrophy; mTICI, modified Treatment in Cerebral Ischemia Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

to adapt and reorganize after an ischemic stroke. Brain reserve may be associated with age, comorbidities, the burden of leukoaraiosis and chronic ischemic lesions, and, importantly, with brain atrophy.[13] Therefore, assessment of brain atrophy on baseline CT scans could help us individualize patient selection for EVT in limit situations, especially in older patients with stroke. With this regard, there are contradictory results reported in the literature about the clinical benefit of mechanical thrombectomy in elderly patients with AIS. Age has been reported as a predictor of futile recanalization in some studies,[11] in which despite having similar rates of complete cerebral reperfusion than younger patients,[1,23,24] older patients have poorer functional outcomes, more medical complications, and higher intracranial hemorrhage risk and mortality rates.[25,26] In contrast, other studies clearly show that EVT is beneficial when compared with best medical therapy also in elderly patients.[27,28] These contradictory findings might be explained by the fact that it is not age alone that determines the likelihood of a good clinical recovery after endovascular reperfusion. Instead, the variability in clinical outcomes observed among older patients with stroke after EVT could be related to important individual differences in brain reserve,[15] which in turn could be estimated by assessing brain atrophy on CT images. Furthermore, age and atrophy interacted significantly to determine a poorer response to EVT, in the sense that older patients with higher GCA scores rarely achieved functional independence on the long term, despite complete cerebral reperfusion. And interestingly, a synergy was also observed between brain atrophy and 24 hour-infarct volume, meaning that with increasing brain atrophy, progressively smaller infarcts are able to produce dependence or mortality even after complete arterial recanalization.

The remaining predictors of futile recanalization found in our study, such as National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, TICI 2b versus C, and prior anticoagulant therapy, have been previously reported in the literature.[12,29] Interestingly, smoking was associated with a better clinical outcome, and this association likely reflects unknown confounders; for example, nonsmokers may be more likely to be ex-smokers due to comorbidities or being more motivated to cease smoking because of worse vascular disease. Regarding leukoaraiosis degree, higher scores in the Fazekas scale were associated with futile recanalization, but this association was not independent of the predictive factors encountered by the logistic regression model. This finding is opposed to what was reported in previous studies that identified leukoaraiosis as a predictor of futile reperfusion.[30,31] However, brain atrophy was not assessed in those studies, which suggests that the impact of atrophy on the response to EVT might be stronger than the effect of leukoaraiosis itself. Further research may be needed to evaluate whether a combination of brain atrophy, leukoaraiosis, and chronic ischemic lesions could function as a better indicator of brain reserve than any of these variables alone.

This study has limitations. First, given the retrospective design of the study, although based on a prospective registry, our results need to be confirmed in prospective studies. Second, we used the GCA scale, which was described to assess atrophy on brain magnetic resonance imaging. However, we think that it can be applied to CT images and, therefore, be used as a tool in the acute stroke setting, with a good interobserver agreement. In this context, an effect of ischemic edema, causing an underestimation of cortical atrophy in the affected hemispheres cannot be ruled out. Third, our workstation allowed us only to visualize axial sections of the brain, and it would have been ideal to complement axial with coronal views to optimize atrophy estimation in the temporal regions. Fourth, with a focus on the clinical decision-making process, it would have been ideal to test the interaction between atrophy and ischemic core volume on pretreatment CT perfusion instead of 24-hour hypodensity volume, but CT perfusion was only performed if indicated. Fifth, except Rankin Scale and vascular comorbidities, we did not assess other comorbidities that could be causing patient frailty and could be influencing the association between brain atrophy and futile reperfusion. Future studies are needed to address whether brain atrophy is a marker of frailty or comorbidity burden. And finally, given that patients with prior dependence were excluded from the study, the impact of more severe degrees of atrophy related to advanced neurodegenerative diseases could not be assessed.

In conclusion, a higher degree of cortical and subcortical brain atrophy emerged as a predictor of futile endovascular reperfusion in anterior circulation AIS. The impact of brain atrophy on insufficient clinical recovery after endovascular reperfusion appears to be independently amplified by age and by brain infarct volume. Further studies with large sample and prospective designs are needed to confirm the clinical

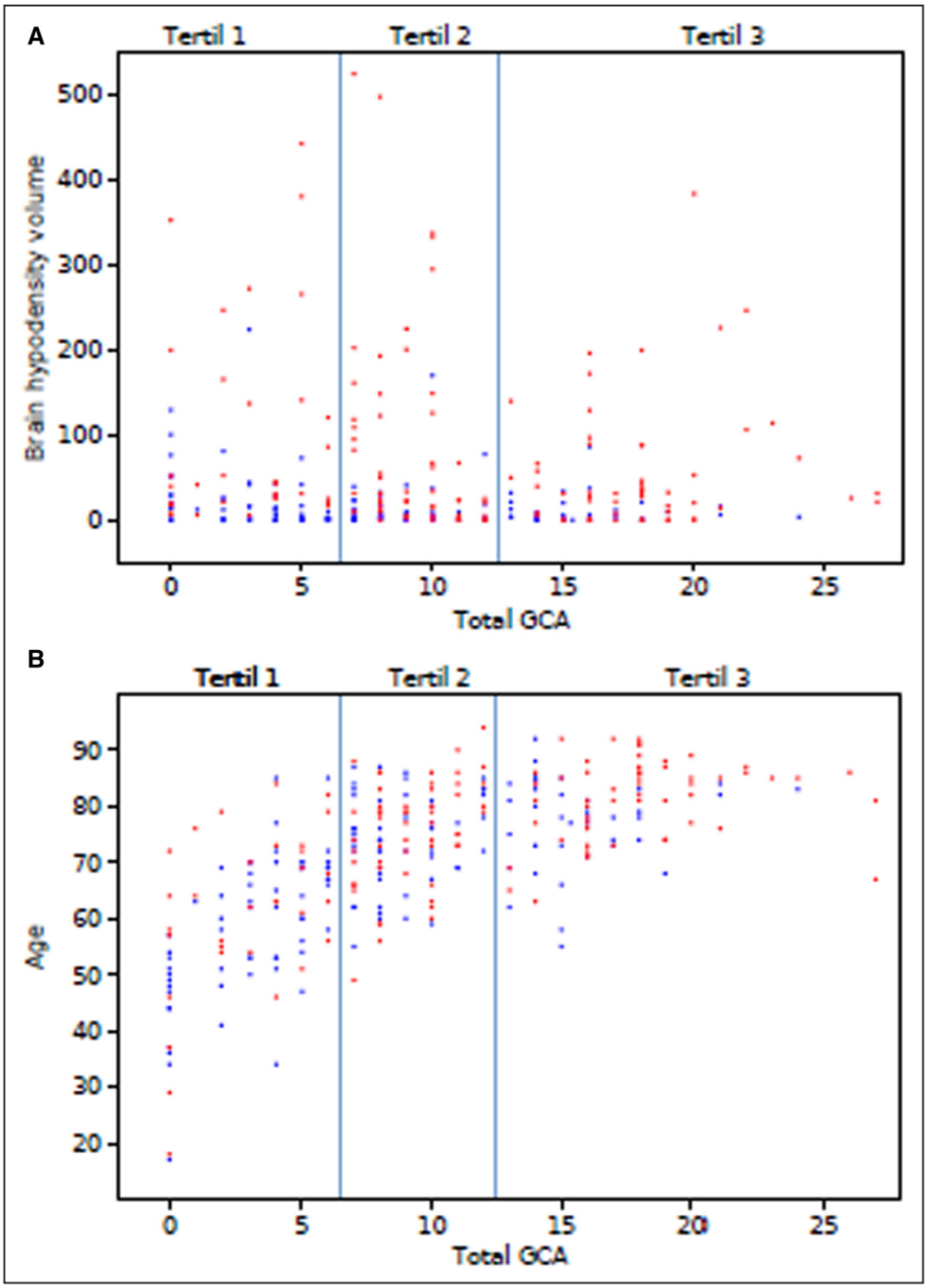

Figure. Interactions between brain hypodensity volume and global cerebral atrophy (GCA), and between GCA score and age. **A**, Red bubbles show futile recanalization, and blue bubbles indicate good clinical outcome. Patients with higher GCA scores included in tertile 2 and 3 tolerated progressively lower infarct volumes to achieve good clinical outcome. **B**, Red bubbles show futile recanalization, and blue bubbles indicate good clinical outcome. Age and GCA score interact significantly to determine the risk of futile reperfusion. Results of both interaction-term logistic regression models can be read on text.

applicability of brain atrophy assessment in the selection of patients with AIS for EVT.

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