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Worse Stroke Outcome in Atrial Fibrillation Is Explained By More Severe Hypoperfusion, Infarct Growth And Hemorrhagic Transformation

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Abstract

Background—Atrial Fibrillation (AF) is associated with greater baseline neurological impairment and worse outcomes following ischemic stroke. Previous studies suggest that greater volumes of more severe baseline hypoperfusion in patients with history of AF may explain this association. We further investigated this association by comparing patients with and without AF on initial examination following stroke using pooled multimodal magnetic resonance imaging (MRI) and clinical data from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) studies.

Methods—EPITHET was a trial of 101 ischemic stroke patients randomized to IV tissue plasminogen activator (tPA) or placebo and DEFUSE was a prospective cohort of 74 ischemic stroke patients treated with IV tPA at 3–6 hours following symptom onset. Patients underwent multimodal MRI before treatment, at 3–5 days and 3 months after stroke in EPITHET; before treatment, 3–6 hours after treatment and 1 month after stroke in DEFUSE. Patients were assessed

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with the National institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) before treatment and at 3 months after stroke. Patients were categorized into definite AF (present on initial examination), probable AF (history but no AF on initial examination) and no AF. Perfusion data were reprocessed with automated MRI analysis software (RAPID, Stanford University, Stanford, CA., USA). Hypoperfusion volumes were defined using Time to maximum (Tmax) delays in 2-second increments from >4 to >8 seconds. Hemorrhagic transformation was classified according to the European Cooperative Acute Stroke Studies criteria.

Results—Of the 175 patients, 28 had definite AF, 30 probable AF, 111 no AF and 6 were excluded due to insufficient imaging data. At baseline, patients with definite AF had more severe hypoperfusion (median Tmax>8 seconds volume 48 vs. 29mL, p=0.02) compared to patients with no AF. At outcome, patients with definite AF had greater infarct growth (median volume 47 vs. 8mL, p=0.001), larger infarcts (median volume 75 vs. 23mL, p=0.001), more frequent parenchymal hematoma grade hemorrhagic transformation (30 vs. 10%, p=0.03), worse functional outcomes (median mRS score 4 vs. 3, p=0.03) and higher mortality (36 vs. 16%, p=0.03) compared to patients with no AF. Definite AF was independently associated with increased parenchymal hematoma [odds ratio (OR) = 6.05, 95% confidence interval (CI) 1.60–22.83) but not poor functional outcome (mRS 3–6, OR=0.99, 95%CI 0.35–2.80) or mortality (OR=2.54, 95%CI 0.86–7.49) 3 months following stroke, after adjusting for other baseline imbalances.

Conclusion—AF is associated with greater volumes of more severe baseline hypoperfusion, leading to higher infarct growth, more frequent severe hemorrhagic transformation and worse stroke outcomes.

Keywords

Atrial fibrillation; brain ischemia; cerebrovascular disease; magnetic resonance imaging; stroke outcome

Introduction

Atrial fibrillation (AF) is the most frequent persistent cardiac arrhythmia in clinical practice (1) and is associated with 10–30% of all ischemic strokes (2–4). AF is present in 1–2% of the general population and the prevalence increases with age, rising from 0.5% of the population aged ≤55 years to ≥7% in those aged ≥80 years (5, 6). Furthermore, the incidence of AF is increasing, even after adjusting for the effects of an aging population (6).

Ischemic stroke patients with history of AF have repeatedly been shown to have higher baseline stroke severity, leading to greater disability and mortality compared to those without a history of AF (2–4, 7). However, the pathophysiological mechanisms underlying the greater baseline stroke severity and worse outcomes in AF patients remain unclear, despite the potential implications for acute stroke therapy.

A recent analysis of 101 acute ischemic stroke patients enrolled in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) suggested this adverse effect of AF could be explained by greater volumes of more severe cerebral hypoperfusion, larger infarct size and more frequent severe hemorrhagic transformation (8). However, the comparison was based on a history and not the confirmation of AF during the acute phase of stroke. This study did

not detect a difference in infarct growth. Baseline antiplatelet and anticoagulant use were not taken into account. Furthermore, differing magnetic resonance imaging (MRI) analysis methods have been shown to produce highly heterogeneous findings (9). RAPID (Stanford University, Stanford, CA., USA), an automated MRI analysis software, has recently been validated to facilitate pooling and analysis of imaging data from different sites and trials by eliminating such heterogeneity (9). Hence, these preliminary findings need to be confirmed by comparing patients with and without AF during the acute phase of stroke using a larger comparable cohort and the more objective automated MRI analysis software.

We hypothesized that acute phase AF is associated with greater volumes of more severe cerebral hypoperfusion, leading to increased infarct growth, larger final infarct volume, more frequent severe hemorrhagic transformation and worse ischemic stroke outcomes. We tested our hypothesis by comparing pooled serial multimodal magnetic resonance imaging (MRI) and clinical data from the EPITHET and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study between patients with and without AF in the acute phase of stroke with standardization of perfusion data using RAPID.

Methods

EPITHET was a prospective, double blind, multicenter trial of 101 acute ischemic stroke patients randomized to IV tissue plasminogen activator (tPA) or placebo 3 to 6 hours after symptom onset. DEFUSE was a prospective open-label study of IV tPA in a cohort of 74 acute ischemic stroke patients 3 to 6 hours after symptom onset. Methodological details have been reported previously (9–11).

In brief, both studies enrolled patients aged ≥ 18 years with pre-stroke modified Rankin Scale (mRS) score ≤ 2, National Institutes of Health Stroke Scale (NIHSS) score > 4 in EPITHET and > 5 in DEFUSE, and no standard contraindications to tPA except for the extended treatment time window. A baseline non-contrast computed tomography (CT) scan was used to exclude patients with acute hemorrhage and major early ischemic change > 1/3 middle cerebral artery territory. Eligible patients then underwent acute MRI at 1.5 Tesla with diffusion weighted (DWI), perfusion weighted (PWI), T2-weighted sequences and time of flight or phase contrast magnetic resonance angiography, before receiving treatment.

In EPITHET clinical and imaging assessments were repeated between days 3 to 5 (subacute) and day 90 (outcome). In DEFUSE, these assessments were repeated between 3 to 6 hours (subacute) and at day 30 (imaging outcome) followed by a further clinical assessment at day 90 (clinical outcome). In both studies, treatment with tPA or randomization to tPA or placebo was carried out without the knowledge of the MRI results, which were analyzed centrally before unblinding. The institutional review boards at all participating centers approved both studies and informed consent was obtained from all the study participants.

In EPITHET, infarct volumes at all time points were calculated through manual outlining of regions of interest using Analyze (version 7, AnalyzeDirect Inc. Overland Park, KS., USA). In DEFUSE, these calculations were performed using a semi-automated thresholding method.

For this analysis, the original perfusion data were reprocessed using the RAPID (Stanford University, Stanford, CA., USA) automated MRI analysis software. The RAPID algorithm for calculating hypoperfusion (PWI) lesion volumes has been previously published (12). Regions of interest corresponding to the hypoperfusion lesion on time to maximum (Tmax) maps, generated automatically by RAPID, were reviewed by a stroke neurologist, who manually excluded artifact from the regions of interest when indicated. Hypoperfusion volumes were defined using Tmax delays in 2-second increments from > 4 to > 8 seconds. Although Tmax≥2s and Tmax>2s volumes were the primary measures of hypoperfusion in EPITHET and DEFUSE studies respectively, both have subsequently been found to include a substantial component of benign oligemia (13). Therefore, Tmax>6s PWI volume was chosen as the primary measure of hypoperfusion in this analysis and used to calculate the DWI/PWI mismatch volume, defined as the difference between the baseline DWI and PWI volumes.

Classification of the site of arterial obstruction into internal carotid, middle cerebral and posterior cerebral arteries and degree of obstruction into complete, partial and none for the pooled data was conducted jointly by two stroke neurologists (9). For this analysis, arterial obstruction was further dichotomized into any and no obstruction.

As the timing of reperfusion and recanalization assessment varied considerably between the two studies, recanalization was not included and reperfusion definitions and assessments that were used in the original analyses of the individual studies were adopted for the pooled analysis (9). For EPITHET, reperfusion was defined as a reduction in Tmax≥2s PWI lesion volume of >90% and >10mL between the baseline and day 3–5 MRI. In DEFUSE, reperfusion was defined as a reduction in Tmax>2 PWI lesion volume of >30% and >10mL between baseline and 3 to 6 hours follow-up MRI.

In previous EPITHET analyses, the method of last observation carried forward was utilized to compensate for missing final imaging data, as there was a significant difference in mortality between patients with and without history of AF (31 vs. 12%, p=0.04)(8, 11). However, the use of last observation carried forward for EPITHET patients in the pooled analysis would introduce significant heterogeneity. Therefore, the day 3 to 5 DWI lesion volume was adopted as the final infarct volume for all EPITHET patients in this analysis. DWI volume at this time point has been validated as a good correlate of final volume and functional outcome at 90days (14). The final infarct volume for all DEFUSE patients remained the day 30 T2 lesion volume.

Grading of both symptomatic and asymptomatic hemorrhagic transformation was done by consensus of three experienced stroke neurologists using the European Cooperative Acute Stroke Classification of hemorrhagic infarct or parenchymal hematoma (15). Symptomatic intracerebral hemorrhage was further defined according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)(16).

For this analysis, patients with AF on initial examination were categorized as definite AF. Patients without or not confirmed to be in AF on initial examination but had a history of AF

were categorized as probable AF. Patients without AF on history or on initial examination were categorized as no AF.

Comparisons between patients with definite, probable and no AF were performed for the following variables: baseline DWI and PWI volumes, DWI/PWI mismatch volume, arterial occlusion rates, reperfusion, final infarct volume, infarct growth, symptomatic and asymptomatic hemorrhagic transformation rates, NIHSS and mRS scores at 3 months.

Statistical analyses were performed using SPSS (version 20, SPSS Inc., Chicago, Ill., USA) and STATA (version 10, StataCorp, College Station, Tx., USA). The data were described as mean with standard deviation or median with interquartile range and analyzed using the unpaired t test with unequal variance or the Mann-Whitney U test depending on the underlying data distribution. Categorical and dichotomized variables were described as percentages and analyzed using Fisher's exact test. Unadjusted outcome effect sizes were estimated as differences in mean, median (Hodges-Lehmann nonparametric shift) or odds ratio (OR) with 95% confidence interval (CI) as appropriate.

Median regression modeling was applied to test the effect of source study (EPITHET and DEFUSE) on final infarct volume and infarct growth, adjusting for definite and probable AF as a combined term. Binary logistic regression modeling was applied to determine the effect of definite AF on mortality, poor functional outcomes (defined as mRS of 3–6) and occurrence of parenchymal hematoma grade hemorrhagic transformation within the first 3 months following stroke, adjusting for baseline imbalances in age (in yearly increments), tPA use, diabetes, prior antiplatelet use, systolic blood pressure, stroke severity (for each point on the NIHSS), DWI and PWI volumes as appropriate.

Results

Of the 175 patients in the pooled EPITHET-DEFUSE database, 169 were suitable for this analysis, of which 121 received IV tPA (72%), 58 had history of AF (34% overall, 42% in EPITHET, 23% in DEFUSE), 28 (16.6%) had definite AF and 30 (17.7%) had probable AF. The 6 excluded patients had poor or absent imaging data, including one patient who withdrew consent before baseline imaging.

At baseline, patients with definite AF had greater neurological impairment (median NIHSS 16 vs. 11, p=0.02) compared to patients with no AF (table 1). Otherwise, there was no significant difference in demographics, vascular risk factors, systolic blood pressure, glucose level, tPA treatment and antithrombotic use. Patients with definite AF also had greater baseline DWI volume (median 22.5 vs. 14.2mL, p=0.03) and hypoperfusion volumes at all measured severities (Tmax>4s to Tmax>8s) compared to patients with no AF (table 2).

In spite of a lack of difference in DWI/PWI mismatch volume, frequency of arterial occlusion, site of arterial occlusion or rate of reperfusion, patients with definite AF had higher infarct growth (median 47 vs. 8mL, median difference 24mL, 95% CI 8–30, p=0.007) and larger final infarct volume (median volume 75 vs. 23mL, median difference 41mL, 95% CI 13–73, p=0.001) compared to patients with no AF (table 3). Hemorrhagic transformation also occurred more frequently in patients with definite AF, (67 vs. 34%, OR=3.89, 95%CI

1.59–9.51, p=0.004), predominantly due to an increased rate of parenchymal hematomas (30 vs.10%, OR=3.75, 95%CI 1.33–10.56, p=0.03). This did not translate into a significant difference in the frequency of symptomatic hemorrhagic transformation, but the number of cases (7) was too small for meaningful analysis.

At 3 months, patients with definite AF had higher neurological impairment (median NIHSS 11.5 vs. 4, median difference 3, 95%CI 0–11, p=0.007), worse functional outcomes (median mRS 4 vs. 3, median difference 1, 95%CI 0–2, p=0.03) and greater mortality (36 vs. 16%, OR=3.04, 95% CI 1.20–7.70) compared to patients with no AF.

In contrast, there was no significant difference at baseline or at 3 months between patients with probable and no AF other than age (79 vs. 73 years, p=0.008). There was a baseline imbalance between patients with probable and definite AF in the proportion treated with IV tPA (83 vs. 54%, p=0.02) and patients with probable AF had less infarct growth (median volume 12 vs. 47mL, median difference 19, 95% CI 1–48, p=0.03), smaller final infarct volumes (median volume 43 vs. 75mL, median difference 34, 95% CI 4–81, p=0.02), a trend to lower neurological impairment (median NIHSS 6.5 vs. 11.5, median difference 0–14, p=0.08) and mortality (13 vs. 36%, OR=3.61, 95%CI 0.98–13.3, p=0.07). The trend for lower mortality persisted even after adjusting for differences in tPA use (OR=3.78, 95% CI 0.96–14.88, p=0.06). There was no difference in other baseline or outcome variables between patients with definite and probable AF.

In a median regression model with definite and probable AF, neither EPITHET nor DEFUSE was independently associated with differences in infarct growth (p=0.09) or outcome infarct volume (p=0.2). When binary logistic regression modeling was applied to the cohort of patients with definite and no AF, definite AF remained independently associated with the occurrence of parenchymal hematoma (OR=6.05, 95% CI 1.60–22.83, p=0.008) after adjusting for baseline differences in age, tPA use, history of diabetes, antiplatelet use, systolic blood pressure, neurologic impairment and stroke volume (table 4). This independent association was lost if just the Tmax>8s PWI volume was included in the model. Definite AF was not independently associated with the occurrence of mortality (OR=2.54, 95%CI 0.86–7.49, p=0.09) or poor functional outcome (OR=0.99, 95% CI 0.35–2.80, p=1.0) 3 months following stroke, after adjusting for baseline differences in age, tPA use, history of diabetes, neurologic impairment and stroke volume.

Discussion

The results of this first study comparing serial imaging and clinical data between patients with and without AF on initial examination 3–6 hours following ischemic stroke onset using automated and standardized perfusion data firmly establish the association between the presence of AF and greater volumes of more severe baseline hypoperfusion, leading to increased infarct growth, higher final infarct volume, more frequent severe hemorrhagic transformation and worse stroke outcomes.

Previous studies have shown that the collateral circulation quality is a major determinant of the cerebral hypoperfusion intensity (17–20). In particular, poor collateral grade has been

associated with larger areas of severe Tmax≥4s hypoperfusion and increased infarct growth (18). The similar rates of baseline internal carotid and middle cerebral artery occlusion between patients with definite and no AF also suggest that differences in clot size were not a major contributor to the differences in hypoperfusion volume and intensity in this study. Therefore the differences in the baseline hypoperfusion between patients with definite and no AF likely result from disparities in the quality of collateral circulation.

It has been postulated that patients with AF have less developed cerebral collateral circulation because the majority do not have concomitant carotid or intracranial large artery stenosis (17). Strokes due to intracranial large artery stenosis have previously been shown to have better collateral circulation compared to strokes due to extracranial large artery stenosis, cardioembolism and undetermined causes (19, 20). Cerebral blood flow in the hemisphere affected by atherothrombotic but not cardioembolic or lacunar strokes has also been found to increase within 40 months following stroke (21).

The quality of the collateral circulation has been shown to predict the outcome of patients with proximal intracranial vessel occlusion, particularly in those patients with imaging findings suggestive of significant ischemic penumbra (22). The risk the ischemic penumbra progressing to infarction has also been demonstrated to rise with increasing hypoperfusion severity (23). Measures to improve collateral circulation quality have therefore become a new focus of research in acute stroke treatment. Pilot studies have investigated the use of sphenopalatine ganglion stimulation and partial intra-aortic occlusion to improve cerebral perfusion following acute ischemic stroke. (24, 25). In addition, there is some evidence to suggest that AF-associated strokes may be more resistant to recanalization strategies (26, 27). Therefore, treatments that improve collateral circulation quality early following stroke could be of particular benefit in AF patients.

The association between AF and more frequent parenchymal hematoma may also be attributable to the greater volumes of more severe baseline hypoperfusion. One previous study suggested an independent association between the volume of severe Tmax>8s hypoperfusion and the frequency of hemorrhagic transformation (28). Similarly, the parameter termed ‘very low cerebral blood volume’ also reflects severe hypoperfusion due to poor collateral blood flow. This more intense ischemia has been postulated to damage blood vessel integrity, resulting in increased hemorrhagic transformation, especially with reperfusion (29).

AF is also associated with impaired cardiac output with inadequate compensation by cerebral autoregulation (30). The effect of cardiac output was actually excluded from the cerebral hypoperfusion volume calculations in this analysis because the deconvolution algorithm used one of the proximal cerebral artery signals as the arterial input function. The similar baseline systolic blood pressures between patients with and without AF in this study do not support a significant difference in cardiac output. However, no other imaging or clinical data were available in EPITHET or DEFUSE to further investigate the effect of global cerebral hypoperfusion due to reduced cardiac output on stroke outcome.

The retrospective nature of the analysis has also led to other limitations. The collateral circulation quality could not be rated directly because the magnetic resonance angiography from the source trials was performed using either time of flight or phase contrast techniques. Heterogeneity in the timing of the subacute imaging data between the source trials meant that some data such as recanalization could not be combined for analysis. Although statistical testing did not identify significant heterogeneity in the infarct growth and outcome infarct volume data between the two source trials, the use of day 3–5 EPITHET and 1 month DEFUSE data as final infarct volume to compensate for the higher mortality rate of AF patients may still have given more weight to the EPITHET data in the analysis. In addition, neither EPITHET or DEFUSE differentiated between paroxysmal and persistent AF, although this shouldn't affect the validity of the results as the main comparison was between patients with and without AF on initial examination. Furthermore, comparisons between small subgroups such as that between definite and probable AF would only have sufficient power to detect very large differences.

In conclusion, the presence of AF in ischemic stroke patients is associated with greater volumes of more severe hypoperfusion, most likely attributable to poorer collateral circulation quality. This leads to increased infarct growth, higher final infarct volume, more frequent severe hemorrhagic transformation and worse stroke outcomes. Strategies to improve collateral circulation quality may improve the stroke outcome in patients with AF, in addition to acute recanalization therapy

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Table 1

Baseline characteristics

	Definite AF N=28	No AF N=111	P value
Clinical characteristics			
Age, y, median (IQR)	76.5 (67.5–82)	73 (60–80)	0.09
tPA use %	54	73	0.07
Male gender %	61	52	0.5
Hypertension %	64	64	1.0
Diabetes %	21	26	0.8
Hyperlipidemia %	29	32	0.8
Current or past cigarette use %	43	40	0.8
History of IHD %	29	21	0.4
Previous stroke/TIA %	21	16	0.6
Baseline antiplatelet use %	50	39	0.3
Baseline anticoagulant use %	0	3	1.0
Baseline systolic BP, mmHg, median (IQR)	152 (140–160)	150 (135–164)	0.7
Baseline glucose, mmol/L, median (IQR)	6.95 (5.58–7.88)	6.79 (5.80–7.96)	0.9
Baseline NIHSS, median (IQR)	16 (10–20)	11 (8–17)	0.02
Imaging characteristics			
Acute DWI volume, mL, median (IQR, n)	22.5 (9.5–56.4)	14.2 (4.0–34.0)	0.03
Acute PWI (Tmax>6s) volume. mL, median (IQR, n)	83 (38–134, 25)	50 (18–113, 96)	0.01
Mismatch volume[1], mL, median (IQR, n)	49 (−3.7–79, 25)	15 (−1–64, 104)	0.3
Acute arterial occlusion, % (n)	70 (16/23)	69 (68/99)	1.0
ICA only	44 (7/16)	35 (24/68)	0.6
MCA only	56 (9/16)	60 (41/68)	0.8

AF, atrial fibrillation; IQR, interquartile range; tPA, tissue plasminogen activator; IHD, ischemic heart disease; TIA, transient ischemic attack; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; DWI, diffusion weighted Image; PWI, perfusion weighted Image; ICA, internal carotid artery; MCA, middle cerebral artery.

[1]Mismatch volume: acute PWI volume – acute DWI volume

Table 2

Baseline PWI volume with increasing hypoperfusion intensity

PWI Thresholds	Hypoperfusion Volume (mL)		Median difference (95% CI)	P value
	Definite AF N=25 Median (IQR)	No AF N=96 Median (IQR)		
Tmax>4sec	136 (64–194)	81 (34–160)	45 (10–87)	0.01
Tmax>6sec	83 (38–134)	50 (18–113)	33 (8–63)	0.01
Tmax>8sec	48 (24–115)	29 (8–70)	18 (3–38)	0.02

PWI, perfusion weighted image; IQR, interquartile range; CI, confidence interval

[1] p values not adjusted for multiple comparisons

Table 3

Outcome variables

	Definite AF N=28	No AF N=111	OR (95% CI) or Median difference (95% CI)	P value
Imaging outcomes				
Final infarct volume, mL, median (IQR, n)	75 (36–198, 24)	23 (8–73, 96)	41 (13–73)	0.001
Absolute growth[1], mL, median (IQR, n)	47 (12–99, 24)	8 (1–51, 96)	24 (7–47)	0.001
Reperfusion[2], %, (n)	30 (7/23)	39 (36/93)	0.69 (0.26–1.85)	0.6
Hemorrhagic transformation[3], % (n)	67 (18/27)	34 (37/109)	3.89 (1.59–9.51)	0.004
Hemorrhagic Infarct	37 (10/27)	24 (26/109)	1.88 (0.77–4.60)	0.2
Parenchymal Hematoma	30 (8/27)	10 (11/109)	3.75 (1.33–10.56)	0.03
SICH[4]	7 (2/28)	5 (5/111)	1.63 (0.30–8.88)	0.6
Clinical outcomes				
90 day NIHSS, median (IQR)	11.5 (4–42)	4 (1–13)	3 (0–11)	0.007
90 day mRS, median (IQR)	4 (2–6)	3 (1–4)	1 (0–2)	0.03
90 day mortality, %	36	16	3.04 (1.20–7.70)	0.03

AF, atrial fibrillation; CI, confidence interval; IQR, interquartile range; SICH, symptomatic intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

[1] Absolute growth = final infarct volume – acute diffusion weighted image volume

[2] Reperfusion defined as a reduction in Tmax≥2s perfusion weighted image volume of >90% and >10mL between the baseline and day 3–5 MRI for EPITHET and a reduction in Tmax>2 perfusion weighted image volume of >30% and >10mL between baseline and 3 to 6 hours follow-up MRI for DEFUSE

[3] Hemorrhagic transformation graded according to the European Cooperative Acute Stroke Study Classification

[4] SICH = significant clinical deterioration of ≥4 NIHSS points within 36h of treatment and grade 2 parenchymal hematoma on CT brain

Table 4

Multivariate analysis testing the effect of definite AF on 3 months mortality, poor functional outcome (mRS 3–6) and frequency of parenchymal hematoma grade hemorrhagic transformation

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Mortality		
Age[1]	1.04 (1.00–1.08)[a]	1.04 (0.99–1.08)
tPA use	1.46 (0.59–3.67)	2.04 (0.63–6.63)
Diabetes	1.96 (0.85–4.54)	1.87 (0.67–5.18)
Baseline NIHSS[2]	1.16 (1.08–1.26)[b]	1.15 (1.03–1.27)[b]
Baseline DWI volume[3]	1.01 (1.00–1.02)[a]	1.00 (0.99–1.01)
Definite AF	3.04 (1.20–7.70)[a]	2.54 (0.86–7.49)
Poor functional outcome (mRS 3–6)		
Age[1]	1.04 (1.02–107)[b]	1.05 (1.02–1.09)[b]
tPA use	0.87 (0.44–1.72)	0.66 (0.27–1.58)
Diabetes	1.73 (0.83–3.60)	2.07 (0.81–5.31)
Baseline NIHSS[2]	1.22 (1.13–1.31)[b]	1.17 (1.07–1.28)[b]
Baseline DWI volume[3]	1.02 (1.01–1.03)[b]	1.01 (0.99–1.02)
Definite AF	1.96 (0.82–4.72)	0.99 (0.35–2.80)
Parenchymal hematoma		
Age[1]	1.02 (0.98–1.05)	1.00 (0.95–1.05)
tPA use	2.38 (0.77–7.35)	16.40 (2.17–123.93)[a]
Diabetes	1.54 (0.61–3.89)	3.36 (0.98–11.54)
Prior antiplatelet use	1.88 (0.80–4.43)	0.74 (0.22–2.49)
Baseline systolic BP[4]	1.01 (0.98–1.03)	1.01 (0.98–1.05)
Baseline NIHSS[2]	1.11 (1.02–1.20)[a]	0.98 (0.87–1.10)
Baseline DWI volume[3]	1.01 (1.00–1.02)[b]	1.02 (1.00–1.03)[a]
Definite AF	3.75 (1.33–10.56)[a]	6.05 (1.60–22.83)[b]

OR, odds ratio; CI, confidence interval; tPA, tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion weighted image; AF, atrial fibrillation; BP, blood pressure.

[1] Per year;

[2] Per 1 point;

[3] Per mL;

[4] Per mmHg.

[a] P<0.05;

[b] P<0.01