

Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

8-3-2021

Effect of alteplase use on outcomes in patients with atrial fibrillation: Analysis of the Initiation of Anticoagulation after Cardioembolic Stroke study

Shadi Yaghi

James Giles

Angela Liu

Salah Keyrouz

et al

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

ORIGINAL RESEARCH

Effect of Alteplase Use on Outcomes in Patients With Atrial Fibrillation: Analysis of the Initiation of Anticoagulation After Cardioembolic Stroke Study

Shadi Yaghi , MD*; Eva Mistry , MBBS*; Adam de Havenon , MD; Christopher R. Leon Guerrero, MD; Amre Nouh, MD; Ava L. Liberman , MD; James Giles , MD; Angela Liu, MD; Muhammad Nagy, MD; Ashutosh Kaushal, MD; Idrees Azher, MD; Brian Mac Grory , MD; Hiba Fakhri, BS; Kiersten Brown Espallat, RN; Syed Daniyal Asad , MD; Hemanth Pasupuleti, MD; Heather Martin, BS; Jose Tan, MD; Manivannan Veerasamy , MD; Charles Esenwa , MD; Natalie Cheng, MD; Khadean Moncrieffe , BS; Iman Moeini-Naghani, MD; Mithilesh Siddu, MD; Erica Scher, MPH; Tushar Trivedi , MD, MPH; Teddy Wu , MD; Muhib Khan, MD; Salah Keyrouz, MD; Karen Furie , MD; Nils Henninger , MD, PhD

BACKGROUND: Intravenous alteplase improves outcome after acute ischemic stroke without a benefit in 90-day mortality. There are limited data on whether alteplase is associated with reduced mortality in patients with atrial fibrillation (AF)-related ischemic stroke whose mortality rate is relatively high. We sought to determine the association of alteplase with hemorrhagic transformation and mortality in patients with AF.

METHODS AND RESULTS: We retrospectively analyzed consecutive patients with acute ischemic stroke between 2015 and 2018 diagnosed with AF included in the IAC (Initiation of Anticoagulation After Cardioembolic Stroke) study, which pooled data from stroke registries at 8 comprehensive stroke centers across the United States. For our primary analysis, we included patients who did not undergo mechanical thrombectomy (MT), and secondary analyses included patients who underwent MT. We used binary logistic regression to determine whether alteplase use was associated with risk of hemorrhagic transformation and 90-day mortality. There were 1889 patients (90.6%) who had 90-day follow-up data available for analyses and were included; 1367 patients (72.4%) did not receive MT, and 522 patients (27.6%) received MT. In our primary analyses we found that alteplase use was independently associated with an increased risk for hemorrhagic transformation (odds ratio [OR], 2.23; 95% CI, 1.57–3.17) but reduced risk of 90-day mortality (OR, 0.58; 95% CI, 0.39–0.87). Among patients undergoing MT, alteplase use was not associated with a significant reduction in 90-day mortality (OR, 0.68; 95% CI, 0.45–1.04).

CONCLUSIONS: Alteplase reduced 90-day mortality of patients with acute ischemic stroke with AF not undergoing MT. Further study is required to assess the efficacy of alteplase in patients with AF undergoing MT.

Key Words: alteplase ■ atrial fibrillation ■ mortality ■ stroke ■ thrombectomy

Intravenous alteplase improves outcomes in eligible patients with acute ischemic stroke, albeit with up to 6% risk of symptomatic intracranial hemorrhage in early trials¹ and lower rates with studies using real-world data.² Faster alteplase treatment is associated with better functional outcomes.³ Clinical trials show

Correspondence to: Shadi Yaghi, MD, FAHA, Department of Neurology, The Warren Alpert Medical School of Brown University, 593 Eddy Street, APC 5, Providence, RI 02903. E-mail: shadiyaghi@yahoo.com

†S. Yaghi and E. Mistry are co-first authors.

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.020945>

For Sources of Funding and Disclosures, see page 9.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Intravenous alteplase is associated with reduced mortality in patients with atrial fibrillation not receiving mechanical thrombectomy.

What Are the Clinical Implications?

- Prospective studies are needed to confirm our findings and to determine whether alteplase indications can be safely expanded to patients with atrial fibrillation on oral anticoagulant therapy.
- Future studies are also needed to establish whether intravenous thrombolysis before mechanical thrombectomy is beneficial in cardioembolic stroke.

Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
DIRECT-MT	Endovascular Thrombectomy With or Without Intravenous Alteplase in Acute Stroke
DOAC	direct oral anticoagulant
IAC	Initiation of Anticoagulation in Cardioembolic Stroke
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
SKIP	Randomized Study of EVT With Versus Without Intravenous Recombinant Tissue-Type Plasminogen Activator in Acute Stroke With ICA and M1 Occlusion

no benefit in 90-day mortality in patients treated with alteplase,⁴⁻⁶ likely because of limited efficacy in patients with increased stroke severity.⁵

Patients with atrial fibrillation (AF) are at high risk for ischemic stroke, and stroke caused by AF is associated with increased risk of hemorrhagic transformation, functional disability, and mortality.^{2,7-10} There are limited data on whether alteplase treatment improves mortality in patients with AF.

We sought to determine the association of alteplase treatment with the rate of hemorrhagic transformation and 90-day mortality in patients with AF-associated stroke.

METHODS

Institutional review board approval for the study was obtained from each of the study sites. Data from this study may be shared upon reasonable request to the corresponding author.

Study Sample

This is a multicenter retrospective study that analyzed data from the IAC (Initiation of Anticoagulation in Cardioembolic Stroke) study that included consecutive patients with nonvalvular AF hospitalized for acute ischemic stroke and treated at 8 comprehensive stroke centers in the United States for various periods across sites but between the years 2015 and 2018. The aim of the IAC study was to determine the optimal timing of initiation of anticoagulation in patients with acute cardioembolic stroke. Details of the study methodology have previously been described.¹¹⁻¹³ For this analysis, we included all patients in the IAC study except those who were lost to follow-up within 90 days. The index date was considered as the date stroke symptoms occurred or last known normal time.

Independent Variable (Predictor)

The primary predictor in this study was treatment with intravenous alteplase.

Dependent Variables (Outcomes)

The coprimary study outcomes were 90-day mortality and early hemorrhagic transformation defined as any hemorrhagic transformation on a brain imaging (computed tomography or magnetic resonance imaging) in the first 24 to 48 hours and before initiation of anticoagulation.¹³ Secondary outcomes were number of passes in mechanical thrombectomy (MT) and successful reperfusion as determined by the treating interventionalist defined as modified thrombolysis in cerebral infarction score $\geq 2B$.¹⁴

Covariates

The following covariates were collected as part of the IAC study and selected a priori based on biological evidence to provide information about cardiovascular risk as well as potential clinical and imaging factors associated with ischemic or hemorrhagic complications.

Baseline Demographics and Clinical Variables

Baseline demographics and clinical variables included age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of prior stroke or transient ischemic attack, active smoking, history of congestive heart failure, history of coronary artery

disease, admission National Institutes of Health Stroke Scale (NIHSS) score (abstracted from the medical record and performed by a certified provider), CHA₂DS₂-VASc score, and timing of initiating anticoagulation.

Home Medications

Home medications included aspirin and anticoagulation therapy (warfarin or direct anticoagulants).

Laboratory and Imaging Variables

Laboratory and imaging variables included serum glucose level on admission, infarct location (strictly posterior circulation involvement versus not), and largest ischemic infarct size calculated on magnetic resonance imaging largest ischemic stroke lesion volume determined on brain magnetic resonance imaging or computed tomography if magnetic resonance imaging was not obtained using the $ax \times bc/2$ method.¹⁵

Statistical Analysis

Given the known overwhelming benefit of MT as well as inherently different stroke characteristics between patients eligible versus not eligible for MT, we stratified our analyses based on whether patients received MT or not. For univariate comparisons we used χ^2 or Fisher exact test for categorical variables, as indicated, and t test or nonparametric (Mood's median test) tests for continuous variables, as indicated. We created unadjusted and adjusted binary logistic regression models

to determine associations between alteplase use and the study outcomes adjusted for age and admission NIHSS score. No imputations were made for missing data. We used SPSS version 25.0 (IBM, Armonk, NY) to perform the analysis, and a 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

Out of 2084 patients included in the IAC study, 195 were lost to follow-up at 90 days (Table S1), leaving 1889 patients for the analysis. The mean age was 77.2 ± 11.8 years, 51.8% were women, 32.0% had a history of stroke or transient ischemic attack, 35.6% were on anticoagulation before the ischemic stroke, 522 patients received MT, and 1367 patients did not receive MT. Figure 1 shows the flowchart of the study.

Patients Without Thrombectomy Treatment

Univariate Analyses in Patients Without Thrombectomy Treatment

Among patients not treated with MT, those who received intravenous alteplase were less likely to have hypertension (78.7% versus 84.2%, $P = 0.03$), diabetes mellitus (28.7% versus 37.4%, $P = 0.005$), a prior stroke or transient ischemic attack (27.0% versus 36.2%, $P = 0.003$), strictly posterior circulation infarcts (13.6% versus 21.4% $P < 0.001$), or be on anticoagulation at

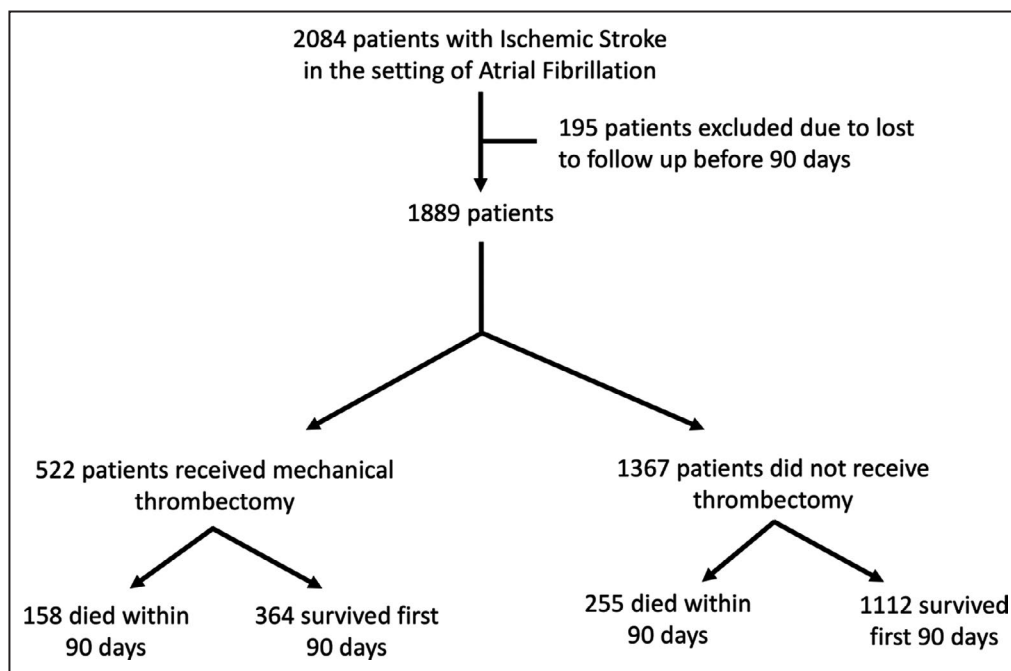


Figure 1. Study flowchart.

home (19.0% versus 41.9%, $P<0.001$). Conversely, patients treated with alteplase were more likely to be on aspirin at home (54.0% versus 45.5%, $P=0.011$) and have a higher initial median (interquartile range) NIHSS score (8 [4–15] versus 6 [2–14], $P=0.002$). Other baseline characteristics were not significantly different between the 2 groups (Table 1). The percentages of NIHSS score categories (≤ 5 , 6–10, 11–15, >15) are displayed in Figure 2.

Patients receiving intravenous alteplase were more likely to have hemorrhagic transformation (20.3% versus 10.2%, $P<0.001$) but did have a lower 90-day mortality rate (14.3% versus 19.8%, $P=0.029$) (Table 1).

Association Between Alteplase Treatment and Outcomes

In unadjusted analyses, intravenous alteplase use was associated with increased odds of hemorrhagic transformation (odds ratio [OR], 2.24; 95% CI, 1.59–3.16; $P<0.001$) but a reduced 90-day mortality (OR, 0.68; 95% CI, 0.47–0.96; $P=0.030$). These findings persisted in adjusted binary logistic regression showing that

intravenous alteplase use was associated with increased odds of hemorrhagic transformation (adjusted OR, 2.14; 95% CI, 1.49–3.07; $P<0.001$) but a reduced 90-day mortality (adjusted OR, 0.58; 95% CI, 0.39–0.87; $P=0.009$). The association between alteplase treatment and reduced mortality persisted when certain mortality predictors such as diabetes mellitus and prior stroke were included in the model (adjusted OR, 0.58; 95% CI 0.38–0.87; $P=0.009$). Furthermore, the association between alteplase treatment and increased odds of hemorrhagic transformation persisted when admission glucose level and anticoagulation use were included in the model (adjusted OR, 2.21; 95% CI, 1.49–3.07; $P<0.001$).

Patients With Thrombectomy Treatment Univariate Analyses

Among patients treated with MT, patients who received intravenous alteplase were older (78.6 ± 11.8 versus 76.4 ± 12.4 years, $P=0.043$), less likely to be on oral anticoagulation at home (15.7% versus 47.4%, $P<0.001$), and had higher low-density lipoprotein LDL level reported as median (interquartile range) (77 [59–99]

Table 1. Factors Among Patients Not Undergoing Mechanical Thrombectomy With Versus Without Alteplase

	Nonalteplase, n=1067	Alteplase, n=300	P value
Age, y, mean \pm SD	77.0 \pm 11.5	77.6 \pm 12.0	0.468
Sex, % men	49.0% (523/1067)	52.7% (158/300)	0.267
Hypertension, %	84.2% (898/1067)	78.7% (236/300)	0.030
Diabetes mellitus, %	37.4% (399/1066)	28.7% (86/300)	0.005
Hyperlipidemia, %	58.0% (618/1066)	53.7% (161/300)	0.187
Prior stroke or TIA, %	36.2% (386/1067)	27.0% (81/300)	0.003
Active smoking, %	13.4% (126/938)	10.7% (28/262)	0.256
Congestive heart failure, %	27.0% (286/1046)	25.8% (77/298)	0.657
Coronary artery disease, %	33.8% (358/1059)	31.7% (95/300)	0.532
Peripheral vascular disease, %	7.7% (80/1038)	4.8% (14/294)	0.093
CHA ₂ DS ₂ -VASc, median (IQR)	5 (4–6)	5 (3–6)	0.104
Aspirin, %	45.5% (482/1059)	54.0% (162/300)	0.011
Anticoagulation at home, %	41.9% (444/1059)	19.0% (57/300)	<0.001
NIHSS score, median (IQR)	6 (2–14)	8 (4–15)	0.002
Systolic blood pressure, mean \pm SD	152.8 \pm 29.1	150.2 \pm 28.4	0.164
Glucose, mg/dL, mean \pm SD	123 (103–153)	124 (103–149)	0.684
LDL, mg/dL, mean \pm SD	77 (59–104)	83 (60–110)	0.084
Posterior circulation, %	21.4% (208/971)	13.4% (37/277)	<0.001
Interval to start anticoagulation, median (IQR)	3 (1–7)	4 (2–10)	<0.001
Final infarct size \leq 10 mL, %	38.2% (361/944)	40.8% (106/260)	0.473
Outcomes			
Hemorrhagic transformation, %	10.2% (109/1067)	20.3% (61/300)	<0.001
Death within 90 d, %	20.0% (212/1067)	14.3% (43/300)	0.029

Interval to start anticoagulation is the interval from index event to initiation of anticoagulation. Anticoagulation is any therapeutic anticoagulation (eg, direct oral anticoagulant, warfarin, heparin, lovenox). Largest ischemic infarct size was calculated on MRI as the largest ischemic stroke lesion volume determined on brain MRI or computed tomography that shows the infarct if MRI was not obtained using the $a\times b\times c/2$ method. IQR indicates interquartile range; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

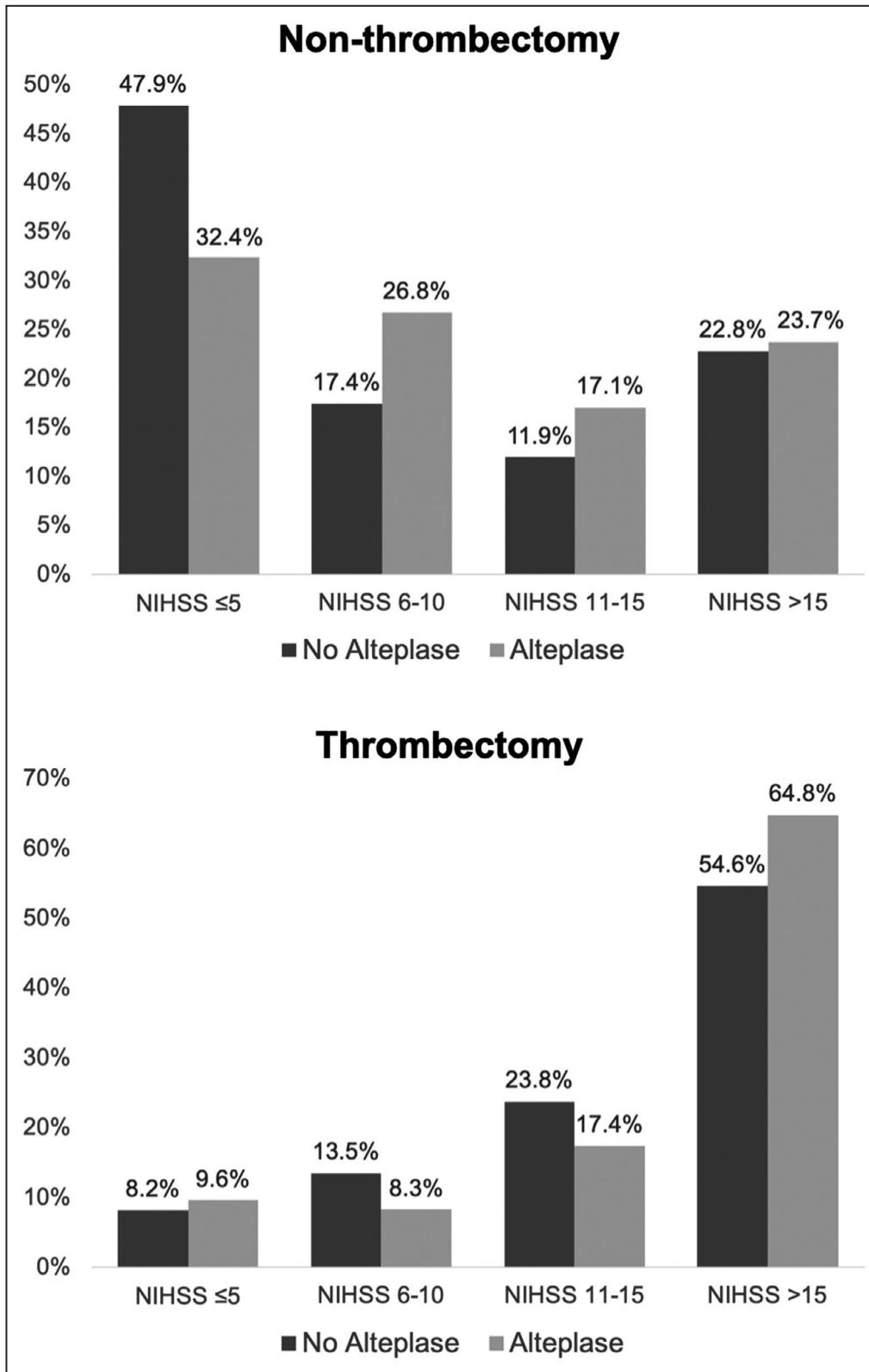


Figure 2. The percentage of patients (y axis) with the National Institutes of Health Stroke Scale (NIHSS) score categories (x axis) in patients with or without alteplase stratified by whether they received thrombectomy (lower part) or did not receive thrombectomy (upper part).

Downloaded from <http://ahajournals.org> by on September 9, 2021

versus 70 [52–93], $P=0.023$). Other baseline characteristics were not significantly different between the 2 groups (Table 2). The percentages of NIHSS score categories (≤ 5 , 6–10, 11–15, >15) are displayed in Figure 2.

Patients receiving intravenous alteplase tended to require fewer thrombectomy passes, though this was not statistically significant (median, 1; interquartile range, 1–2 versus median, 2; interquartile range, 1–2; $P=0.074$). There was no significant difference in the rate of successful recanalization (modified thrombolysis in cerebral infarction $\geq 2B$, 91.8% versus 92.3%, $P=0.729$), hemorrhagic transformation (29.7% versus 33.7%, $P=0.346$), and 90-day mortality (28.9% versus 31.4%, $P=0.566$) between patients treated with alteplase versus patients not treated with alteplase (Table 2).

Association Between Alteplase Treatment and Outcomes

In unadjusted analyses, intravenous alteplase treatment was not associated with a difference in the odds of

90-day mortality (OR, 0.89; 95% CI, 0.61–1.30; $P=0.537$) or hemorrhagic transformation (OR, 0.83; 95% CI, 0.57–1.20; $P=0.324$). In adjusted binary logistic regression models, intravenous alteplase treatment was associated with a nonsignificantly lower 90-day mortality (adjusted OR, 0.68; 95% CI, 0.45–1.04; $P=0.077$), but the odds of hemorrhagic transformation (adjusted OR, 0.82; 95% CI, 0.56–1.20; $P=0.312$) did not differ between the 2 groups. Results of the association between alteplase use and mortality remained unchanged when prior stroke and diabetes mellitus were included in the model (adjusted OR, 0.74; 95% CI, 0.48–1.13; $P=0.164$). Furthermore, results of the association between alteplase use and hemorrhagic transformation remained unchanged when admission glucose level and anticoagulation use were included in the model (adjusted OR, 0.72; 95% CI, 0.48–1.08; $P=0.108$).

Additional Analyses

Because warfarin treatment with international normalized ratio >1.7 and direct oral anticoagulant (DOAC)

Table 2. Factors Among Patients Undergoing Mechanical Thrombectomy With Versus Without Alteplase

	Nonalteplase (n=290)	Alteplase (n=232)	P value
Age, y, mean \pm SD	76.4 \pm 12.4	78.6 \pm 11.8	0.043
Sex, % women	43.4% (126/290)	44.8% (104/232)	0.790
Hypertension, %	81.9% (236/288)	80.2% (186/232)	0.652
Diabetes mellitus, %	27.9% (80/287)	23.8% (55/231)	0.315
Hyperlipidemia, %	54.2% (156/288)	45.7% (106/232)	0.064
Prior stroke or TIA, %	28.8% (83/288)	23.3% (54/232)	0.162
Active smoking, %	12.4% (31/250)	14.0% (29/207)	0.677
Congestive heart failure, %	23.9% (68/285)	24.9% (57/229)	0.836
Coronary artery disease, %	32.9% (95/289)	26.0% (60/231)	0.101
Peripheral vascular disease, %	7.3% (20/275)	4.2% (9/216)	0.178
CHA ₂ DS ₂ -VASc, median (IQR)	4 (3–6)	4 (3–6)	0.977
Aspirin, %	37.3% (107/287)	44.4% (103/230)	0.088
Anticoagulation at home, %	47.4% (136/287)	15.7% (36/230)	<0.001
NIHSS, median, IQR	17 (11–22)	18 (13–23)	0.140
Systolic blood pressure, mean \pm SD	145.7 \pm 27.9	145.9 \pm 26.4	0.920
Glucose, median (IQR)	125 (106–150)	119 (102–144)	0.156
LDL, median (IQR)	70 (52–93)	77 (59–99)	0.023
Posterior circulation, %	8.6% (22/257)	4.3% (9/207)	0.091
Interval to start anticoagulation, median (IQR)	7 (2–14)	7 (3.5–14)	0.202
Largest infarct size ≤ 20 mL, %	50.6% (125/247)	55.4% (112/202)	0.342
Outcomes			
No. of passes, median (IQR)	2 (1–2)	1 (1–2)	0.074
Successful recanalization, %	92.8% (244/263)	91.8% (191/208)	0.729
Hemorrhagic transformation, %	33.8% (98/290)	29.7% (69/232)	0.346
Death within 90 d, %	31.4% (91/290)	28.9% (67/232)	0.566

Interval to start anticoagulation is the interval from index event to initiation of anticoagulation. Anticoagulation is any therapeutic anticoagulation (eg, direct oral anticoagulant, warfarin, heparin, lovenox), and largest ischemic infarct size was calculated on MRI largest ischemic stroke lesion volume determined on brain MRI or computed tomography that shows the infarct if MRI was not obtained using the $a \times b \times c/2$ method. IQR indicates interquartile range; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

treatment within 48 hours before the index stroke represent contraindications for alteplase, we conducted additional analyses comparing mortality and hemorrhagic transformation rates in patients with AF on oral anticoagulant therapy with warfarin (n=349) or DOAC (n=327) who received alteplase versus those who did not.

As expected, patients on warfarin at home who did not receive alteplase had a significantly higher mean international normalized ratio level (1.7 ± 0.8 versus 1.4 ± 0.3 , $P < 0.001$). In models adjusted for age and NIHSS score, the mortality rate at 90 days was lower in those receiving intravenous alteplase as compared with those who did not receive alteplase (adjusted OR, 0.29; 95% CI, 0.13–0.67; $P = 0.004$). Nevertheless, patients who received intravenous alteplase were more likely to have hemorrhagic transformation as compared with patients who were not treated with alteplase (adjusted OR, 3.37; 95% CI, 1.77–6.43; $P < 0.001$).

In patients on DOAC treatment, adjusted models (adjusting for age and NIHSS score) showed that the mortality rate at 90 days (adjusted OR, 0.51; 95% CI, 0.12–2.13; $P = 0.357$) and hemorrhagic transformation (adjusted OR, 0.23; 95% CI, 0.03–1.79; $P = 0.159$) were not significantly different between groups.

Furthermore, to account for patient clustering by study site, we fit mixed-effects logistic regression models to our outcomes. The mixed-effects model estimates a separate intercept for each study site to account for between-hospital differences, such as case volume or proportion of cases treated with alteplase or MT as well as MT patient selection. In these analyses, our findings on associations between alteplase treatment and 90-day mortality were essentially the same in patients not treated with thrombectomy (adjusted OR, 0.58; 95% CI, 0.38–0.87; $P = 0.009$) and in patients treated with thrombectomy (adjusted OR, 0.68; 95% CI, 0.45–1.04; $P = 0.077$).

Moreover, we performed interaction analyses to determine whether the effect of alteplase on study outcomes was different in patients with versus without MT treatment. In these analyses, the effect of alteplase on mortality was not significantly different in patients with versus without MT treatment (P -interaction=0.616). On the other hand, the effect of alteplase on the odds of hemorrhagic transformation was more pronounced in patients with versus without MT treatment (P -interaction<0.001).

Finally, we performed matched analyses using propensity score matching (caliper set at 0.05, matched 1:1) for hemorrhagic transformation (matched for age, NIHSS score, glucose, and anticoagulation use) and mortality (matched for age, NIHSS score, history of diabetes mellitus, and prior stroke). In these analyses, alteplase treatment was associated with reduced mortality (OR, 0.48; 95% CI, 0.32–0.73) but increased

hemorrhagic transformation (OR, 1.71; 95% CI, 1.10–2.65) in patients not receiving MT (n=596 patients). On the other hand, alteplase was not associated with either mortality (OR, 1.08; 95% CI, 0.69–1.71) or hemorrhagic transformation (OR, 0.74; 95% CI, 0.48–1.15) in patients receiving MT (n=366 patients).

DISCUSSION

We found that intravenous alteplase treatment was associated with a reduced 90-day mortality in patients with acute ischemic stroke in the setting of AF who were not treated with MT. Among patients undergoing MT, there was a nonsignificantly lower number of passes and mortality in subjects that were treated with intravenous alteplase as compared with those who did not receive intravenous alteplase.

The decrease in mortality we observed in patients with AF who did not receive MT is consistent with prior studies encompassing all mechanisms of stroke.¹⁶ However, these findings are slightly different than other studies that showed no significant mortality benefit of intravenous alteplase in patients with acute ischemic stroke and AF.¹⁷ It should be noted, however, that these studies were done before MT became a standard of care for patients presenting with acute large-vessel occlusion stroke. Intravenous alteplase treatment (versus none) without MT has limited benefit in patients with proximal large-vessel occlusion,¹⁸ which may explain the negative findings in some of the aforementioned studies. Conversely, stroke systems of care have considerably improved over time, leading to faster and safer administration of intravenous alteplase,^{2,19} which may account for some of the observed improved efficacy of intravenous alteplase treatment in our study compared with the previous studies.^{20,21}

We found a nonsignificantly lower mortality with alteplase in patients with AF who received MT. This is consistent with the pivotal thrombectomy trials, which did not demonstrate an effect on mortality or outcome.^{22,23} This is also in line with recent studies showing no significant added benefit of alteplase use in patients with proximal occlusion undergoing MT^{24,25} and possibly related to the limited efficacy of alteplase in achieving successful reperfusion in patients with proximal large-artery occlusion. Nonetheless, our findings highlight the need to further study this issue, particularly because stroke patients with AF have worse clinical outcomes after MT compared patients without AF.²⁶

Mechanisms of Associations

There are several potential mechanisms by which intravenous alteplase treatment improved mortality in

patients with AF who were not selected for thrombectomy in our study. Arguably, the main mechanism related to thrombolysis of clots within smaller²⁷ and more distal^{28,29} vessels, which tend to respond favorably to alteplase. Unsurprisingly, there was increased risk of hemorrhagic transformation associated with intravenous alteplase use, which is likely multifactorial and related to induced coagulopathy, reperfusion injury, and disruption of the blood–brain barrier.^{2,30} Presumably, most of these hemorrhages were asymptomatic given the overall lower mortality rate associated with alteplase use in our study. Conversely, another explanation to our findings is that patients with extensive early signs of ischemia on initial brain imaging were not considered eligible for intravenous alteplase or thrombectomy, thus explaining the increased mortality in the nonalteplase group.

Prior large meta-analyses have shown that benefit of intravenous alteplase in patients undergoing thrombectomy extends to not only mortality but also improvement in functional outcome as well as increased procedural success rates without increase in symptomatic hemorrhage.^{31,32} Most recently, the SKIP (Randomized Study of EVT With Versus Without Intravenous Recombinant Tissue-Type Plasminogen Activator in Acute Stroke With ICA and M1 Occlusion) study³³ demonstrated a lack of noninferiority of foregoing intravenous alteplase treatment in favor of direct MT. Furthermore, the DIRECT-MT (Endovascular Thrombectomy With or Without Intravenous Alteplase in Acute Stroke) trial showed that endovascular therapy alone was noninferior to endovascular therapy plus alteplase in achieving improved functional independence at 90 days.²³ In this trial, however, patients treated with alteplase were more likely to achieve successful reperfusion.

Therapeutic Implications

The benefit of intravenous alteplase in acute stroke within 4.5 hours of onset is now well established, but up to 25% of eligible patients fail to receive alteplase treatment partially as a consequence of provider bias.³⁴ Our analysis suggests that patients with AF with acute ischemic stroke should receive intravenous alteplase when eligible, despite the slightly higher risk of a hemorrhagic conversion within this subgroup. In addition, a large number of acute ischemic stroke patients have a contraindication to alteplase, of which being anticoagulated is not uncommon.³⁵ In our analysis, premorbid anticoagulation for AF was more common in patients who did not receive intravenous alteplase, as would be expected. However, recent evidence suggests that the use of warfarin for stroke prevention in AF has become less frequent than the use of DOACs.³⁶ Although DOACs have a favorable safety

profile, one disadvantage is that rapid laboratory tests are not available to measure their therapeutic effect. As a result, patients with AF taking DOACs are not eligible to receive intravenous alteplase, unless they missed taking their medication within 24 to 48 hours of the index stroke. Although prethrombolysis DOAC reversal has been reported,^{37,38} rapid reversal of warfarin or DOACs for intravenous alteplase treatment is presently not recommended because of the risk of additional thrombosis created by their rapid reversal.³⁹ Because our analysis showed a mortality benefit for intravenous alteplase in patients with AF, it is appealing to further study the risk versus benefit of intravenous alteplase therapy in patients with AF on DOAC treatment.⁴⁰ A recent meta-analysis indicated that intravenous thrombolysis in select patients treated with DOAC did not to increase the risk of symptomatic intracerebral hemorrhage.⁴¹ Furthermore, in patients with AF with high risk of stroke, such as extensive atherosclerosis of the cerebrovasculature or CHA₂DS₂-VASc >5, one consideration would be left atrial appendage occlusion with subsequent antiplatelet therapy, which recent data suggest provides comparable efficacy compared with anticoagulation in stroke risk reduction.^{42,43} This will obviate the need for long-term anticoagulation and may potentially make these patients alteplase eligible if they were to have to an ischemic stroke.

Strengths and Limitations

Our study has several limitations including the retrospective and observational nature that may have introduced bias. Although we adjusted for potential confounders, we cannot rule out residual confounding. In addition, our findings may have been affected by contraindications to intravenous alteplase, which may have favored treatment of less-sick patients and those without large or already completed infarcts at presentation. However, this appears less likely, because in our study, patients treated with alteplase were older and had a higher initial NIHSS. Another limitation relates to the lack of data on several factors that have been associated with outcome after MT such as the time from symptom onset to treatment, perfusion imaging findings, ASPECTS (Alberta Stroke Program Early CT Score), collateral status, and location of where large-vessel occlusion is. Moreover, we used the $axb \times c/2$ method to calculate infarct volume, which has been validated but is not commonly used in patients with ischemic stroke. Furthermore, the lack of information on time to treatment in patients who received alteplase or MT, as well as possible heterogeneity in patient selection for thrombectomy across the study period, are additional limitations. These limitations, however, are unlikely to affect our findings, because the time to alteplase is only available for those

treated with alteplase and does not apply to untreated patients, and thrombectomy treatment was being used in all participating centers during the study duration. In addition, follow-up imaging was performed at the discretion of the provider and thus may have contributed to bias. Finally, the relatively high proportion of patients without a recorded 90-day modified Rankin Scale score precluded a more detailed analysis of the effect on functional disability.

Notable strengths of our study include its multi-center design and inclusion of a large cohort of patients that provided real-world contemporary data in the era of MT treatment. In addition, using validated methodology, we captured data on infarct volume, which was not included in prior studies, particularly in those studying the efficacy of alteplase in patients without thrombectomy.

CONCLUSIONS

Intravenous alteplase use was associated with reduced mortality in patients with acute ischemic stroke not undergoing MT. Larger prospective studies are needed to confirm our findings and to determine whether alteplase indication can be safely expanded to patients with AF on oral anticoagulant therapy, and future studies are needed to establish whether intravenous thrombolysis before MT is beneficial in cardioembolic stroke.

ARTICLE INFORMATION

Received January 18, 2021; accepted June 7, 2021.

Affiliations

Department of Neurology, Brown University, Providence, RI (S.Y., A.K., I.A., K.F.); Department of Neurology, Vanderbilt University, Nashville, TN (E.M., H.F., K.B.E.); Department of Neurology, University of Utah, Salt Lake City, UT (A.d.H.); Department of Neurology, George Washington University, Washington, DC (C.R.L.G., I.M., M.S.); Department of Neurology, Hartford Hospital, Hartford, CT (A.N., S.D.A.); Department of Neurology, Montefiore Medical Center, New York, NY (A.L.L., C.E., N.C., K.M.); Department of Neurology, Washington University, Saint Louis, MO (J.G., A.L., S.K.); Department of Neurology, Hackensack Medical Center, Hackensack, NJ (M.N.); Department of Neurology, Duke University, Durham, NC (B.M.G.); Department of Neurology, Spectrum Health, Grand Rapids, MI (H.P., H.M., J.T., M.V., M.K.); Department of Neurology, New York University, New York, NY (E.S., T.T.); Department of Neurology, Christchurch Hospital, Christchurch, New Zealand (T.W.); Department of Neurology (N.H.) and Department of Psychiatry, University of Massachusetts, Worcester, MA (N.H.).

Sources of Funding

Dr Henninger is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (K08NS091499). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr Liberman is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (K23NS107643). Dr Khan is supported by the National Institute of Neurological Disorders and Stroke (1r61ns117196-01).

Disclosures

None.

Supplementary Material

Table S1

REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demers BM, Hoh B, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. DOI: 10.1161/STR.000000000000158.
2. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e343–e361. DOI: 10.1161/STR.000000000000152.
3. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55:1649–1655. DOI: 10.1212/WNL.55.11.1649.
4. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329. DOI: 10.1056/NEJMoa0804656.
5. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
6. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379:2352–2363. DOI: 10.1016/S0140-6736(12)60768-5.
7. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV, Fornage M, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. DOI: 10.1161/STR.0000000000000046.
8. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack PME, et al. Stroke associated with atrial fibrillation—incidence and early outcomes in the north Dublin population stroke study. *Cerebrovasc Dis*. 2010;29:43–49. DOI: 10.1159/000255973.
9. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760–1764. DOI: 10.1161/01.STR.27.10.1760.
10. Henninger N, Goddeau RP Jr, Karmarkar A, Helenius J, McManus DD. Atrial fibrillation is associated with a worse 90-day outcome than other cardioembolic stroke subtypes. *Stroke*. 2016;47:1486–1492. DOI: 10.1161/STROKEAHA.116.012865.
11. Yaghi S, Trivedi T, Henninger N, Giles J, Liu A, Nagy M, Kaushal A, Azher I, Mac Grory B, Fakhri H, et al. Anticoagulation timing in cardioembolic stroke and recurrent event risk. *Ann Neurol*. 2020;88:807–816. DOI: 10.1002/ana.25844.
12. Yaghi S, Mistry E, Liberman AL, Giles J, Asad SD, Liu A, Nagy M, Kaushal A, Azher I, Mac Grory B, et al. Anticoagulation type and early recurrence in cardioembolic stroke: the IAC study. *Stroke*. 2020;51:2724–2732. DOI: 10.1161/STROKEAHA.120.028867.
13. Yaghi S, Henninger N, Scher E, Giles J, Liu A, Nagy M, Kaushal A, Azher I, Mac Grory B, Fakhri H, et al. Early ischaemic and haemorrhagic complications after atrial fibrillation-related ischaemic stroke: analysis of the IAC study. *J Neurol Neurosurg Psychiatry*. 2020;91:750–755. DOI: 10.1136/jnnp-2020-323041.
14. Sacks D, Baxter B, Campbell B, Carpenter JS, Cognard C, Dippel D, Eesa M, Fischer U, Hausegger K, Hirsch JA, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. *AJNR Am J Neuroradiol*. 2018;39:E61–E76. DOI: 10.3174/ajnr.A5638.
15. Sims JR, Gharai LR, Schaefer PW, Vangel M, Rosenthal ES, Lev MH, Schwamm LH. ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes. *Neurology*. 2009;72:2104–2110. DOI: 10.1212/WNL.0b013e3181aa5329.
16. Muruet W, Rudd A, Wolfe CDA, Douiri A. Long-term survival after intravenous thrombolysis for ischemic stroke: a propensity score-matched cohort with up to 10-year follow-up. *Stroke*. 2018;49:607–613. DOI: 10.1161/STROKEAHA.117.019889.

17. Saposnik G, Gladstone D, Raptis R, Zhou L, Hart RG. Atrial fibrillation in ischemic stroke: predicting response to thrombolysis and clinical outcomes. *Stroke*. 2013;44:99–104. DOI: 10.1161/STROKEAHA.112.676551.
18. Young-Saver DF, Gornbein J, Starkman S, Saver JL. Magnitude of benefit of combined endovascular thrombectomy and intravenous fibrinolysis in large vessel occlusion ischemic stroke. *Stroke*. 2019;50:2433–2440. DOI: 10.1161/STROKEAHA.118.023120.
19. Schwamm LH, Ali SF, Reeves MJ, Smith EE, Saver JL, Messe S, Bhatt DL, Grau-Sepulveda MV, Peterson ED, Fonarow GC. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at get with the guidelines-stroke hospitals. *Circ Cardiovasc Qual Outcomes*. 2013;6:543–549. DOI: 10.1161/CIRCOUTCOMES.111.000095.
20. Goyal M, Almekhlafi M, Dippel DW, Campbell BCV, Muir K, Demchuk AM, Bracad S, Davalos A, Guillemin F, Jovin TG, et al. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. *Stroke*. 2019;50:645–651. DOI: 10.1161/STROKEAHA.118.021840.
21. Agarwal S, Scher E, Lord A, Frontera J, Ishida K, Torres J, Rostanski S, Mistry E, Mac Grory B, Cutting S, et al. Redefined measure of early neurological improvement shows treatment benefit of alteplase over placebo. *Stroke*. 2020;51:1226–1230. DOI: 10.1161/STROKEAHA.119.027476.
22. McCarthy DJ, Diaz A, Sheinberg DL, Snelling B, Luther EM, Chen SH, Yavagal DR, Peterson EC, Starke RM. Long-term outcomes of mechanical thrombectomy for stroke: a meta-analysis. *ScientificWorldJournal*. 2019;2019:7403104. DOI: 10.1155/2019/7403104.
23. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, Peng YA, Han H, Wang J, Wang S, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382:1981–1993. DOI: 10.1056/NEJMoa2001123.
24. Zi W, Qiu Z, Li F, Sang H, Wu D, Luo W, Liu S, Yuan J, Song J, Shi Z, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA*. 2021;325:234–243. DOI: 10.1001/jama.2020.23523.
25. Suzuki K, Matsumaru Y, Takeuchi M, Morimoto M, Kanazawa R, Takayama Y, Kamiya Y, Shigeta K, Okubo S, Hayakawa M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA*. 2021;325:244–253. DOI: 10.1001/jama.2020.23522.
26. Munir MB, Alqahtani F, Beltagy A, Tarabishy A, Alkhouli M. Comparative outcomes of mechanical thrombectomy for acute ischemic stroke in patients with and without atrial fibrillation. *J Vasc Interv Radiol*. 2017;28:1604–1605. DOI: 10.1016/j.jvir.2017.06.024.
27. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingle R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42:1775–1777. DOI: 10.1161/STROKEAHA.110.609693.
28. Friedrich B, Gawlitza M, Schob S, Hobohm C, Raviolo M, Hoffmann KT, Lobsien D. Distance to thrombus in acute middle cerebral artery occlusion: a predictor of outcome after intravenous thrombolysis for acute ischemic stroke. *Stroke*. 2015;46:692–696. DOI: 10.1161/STROKEAHA.114.008454.
29. Gawlitza M, Friedrich B, Quaschling U, Schob S, Schaudinn A, Hobohm C, Hoffmann KT, Lobsien D. Distance to thrombus on MR angiography predicts outcome of middle cerebral artery occlusion treated with IV thrombolysis. *Neuroradiology*. 2015;57:991–997. DOI: 10.1007/s00234-015-1558-9.
30. Yaghi S, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke with thrombolysis with intravenous recombinant tissue plasminogen activator: a review of natural history and treatment. *JAMA Neurol*. 2014;71:1181–1185. DOI: 10.1001/jama-neurol.2014.1210.
31. Katsanos AH, Malhotra K, Goyal N, Arthur A, Schellinger PD, Köhrmann M, Krogias C, Turc G, Magoufis G, Leys D, et al. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol*. 2019;86:395–406. DOI: 10.1002/ana.25544.
32. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, Fusco MR. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke*. 2017;48:2450–2456. DOI: 10.1161/STROKEAHA.117.017320.
33. Suzuki K, Kimura K, Takeuchi M, Morimoto M, Kanazawa R, Kamiya Y, Shigeta K, Ishii N, Takayama Y, Koguchi Y, et al. The randomized study of endovascular therapy with versus without intravenous tissue plasminogen activator in acute stroke with ICA and M1 occlusion (SKIP study). *Int J Stroke*. 2019;14:752–755. DOI: 10.1177/1747493019840932.
34. Messé SR, Khatri P, Reeves MJ, Smith EE, Saver JL, Bhatt DL, Grau-Sepulveda MV, Cox M, Peterson ED, Fonarow GC, et al. Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry. *Neurology*. 2016;87:1565–1574. DOI: 10.1212/WNL.0000000000003198.
35. Kleindorfer D, Kissela B, Schneider A, Woo D, Khoury J, Miller R, Alwell K, Gebel J, Szafarski J, Pancioli A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke*. 2004;35:e27–e29. DOI: 10.1161/01.STR.0000109767.11426.17.
36. Katz DF, Maddox TM, Turakhia M, Gehi A, O'Brien EC, Lubitz SA, Turchin A, Doros G, Lei L, Varosy P, et al. Contemporary trends in oral anticoagulant prescription in atrial fibrillation patients at low to moderate risk of stroke after guideline-recommended change in use of the CHADS₂ to the CHA₂DS₂-VASc score for thromboembolic risk assessment: analysis from the National Cardiovascular Data Registry's outpatient practice innovation and clinical excellence atrial fibrillation registry. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003476. DOI: 10.1161/CIRCOUTCOMES.116.003476.
37. Barber PA, Wu TY, Ranta A. Stroke reperfusion therapy following dabigatran reversal with idarucizumab in a national cohort. *Neurology*. 2020;94:e1968–e1972. DOI: 10.1212/WNL.00000000000009155.
38. Beharry J, Waters MJ, Drew R, Fink JN, Wilson D, Campbell BCV, Parsons MW, Kleinig TJ, Wu TY. Dabigatran reversal before intravenous tenecteplase in acute ischemic stroke. *Stroke*. 2020;51:1616–1619. DOI: 10.1161/STROKEAHA.119.028327.
39. Frontera JA, Lewin JJ III, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EIB, Stiefel MF, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24:6–46. DOI: 10.1007/s12028-015-0222-x.
40. Hankey GJ, Norrving B, Hacke W, Steiner T. Management of acute stroke in patients taking novel oral anticoagulants. *Int J Stroke*. 2014;9:627–632. DOI: 10.1111/ijs.12295.
41. Shahjouei S, Tsvigoulis G, Goyal N, Sadighi A, Mowla A, Wang M, Seiffge DJ, Zand R. Safety of intravenous thrombolysis among patients taking direct oral anticoagulants: a systematic review and meta-analysis. *Stroke*. 2020;51:533–541. DOI: 10.1161/STROKEAHA.119.026426.
42. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protodopov AV, Betts T, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol*. 2019;12:e006841. DOI: 10.1161/CIRCEP.118.006841.
43. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, Poloczek M, Stasek J, Haman L, Branny M, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75:3122–3135. DOI: 10.1016/j.jacc.2020.04.067.

Supplemental Material

Table S1. Baseline characteristics of patients who were lost to follow up.

	Lost to follow up (n = 195)
Age (years, mean \pm SD)	77.3 \pm 11.6
Sex (% men)	43.6% (85)
Hypertension (%)	76.9% (150)
Diabetes (%)	26.2% (51)
Hyperlipidemia (%)	62.6% (122)
Prior stroke or TIA (%)	32.3% (63)
Active smoking (%)	12.2% (23/188)
Congestive heart failure (%)	25.6% (50)
Coronary artery disease (%)	24.6% (48)
Peripheral vascular disease (%)	5.8% (11/189)
CHA ₂ DS ₂ -Vasc, median (IQR)	5 (3-6)
NIHSS score, median (IQR)	6 (2-15)
Alteplase treatment	29.7% (58)
Mechanical thrombectomy	12.8% (25)