J Surg Med. 2021;5(2):111-114.
DOI: 10.28982/josam.801301

Journal of Surgery and Medicine
e-ISSN=2602-2079

Outcomes of intravenous thrombolytic therapy in cardioembolic strokes

Mustafa Çetiner [1], Murat Seyit [2], Neslihan Eskut [3], Gönül Akdağ [1], Fatma Akkoyun Arıkan [1], Sibel Canbaz Kabay [1]

[1] Department Of Neurology, Kütahya Health Sciences University, Kütahya, Turkey
[2] Department Of Emergency Medicine, Pamukkale University, Denizli, Turkey
[3] Department Of Neurology, University Of Health Sciences, İzmir, Turkey

ORCID ID of the author(s)

MÇ: 0000-0002-4420-6452
MS: 0000-0002-8324-9471
NE: 0000-0003-1882-8992
GA: 0000-0002-0486-6026
FAA: 0000-0002-3543-6213
SCK: 0000-0003-4808-2191

Corresponding Author
Mustafa Çetiner
Kütahya Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Bölüm: Nöroloji AD, Bahçelievler mahallesi, Eryiğit sokak, No:24, Ladin sitesi. A - blok, K: 3, D-13. Kütahya, Türkiye
E-mail: drcetiner76@gmail.com

Ethics Committee Approval
The study was approved by the Dumlupinar University of Local Ethics Committee (Date: 14/11/2018, Decision no: 2018/14-8). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 February 19

Abstract

Background/Aim: It is controversial whether intravenous recombinant tissue plasminogen activator (IV r-tPA) treatment outcomes in cardioembolic strokes differ from other types of strokes. This study aims to investigate the clinical data of patients with cardioembolic and large-vessel atherosclerosis who received IV r-tPA treatment and compare and discuss the results according to the literature.

Methods: The data of the patients who were admitted within the first 4.5 hours following the onset of symptoms, diagnosed with acute ischemic stroke in the Neurology clinic of Kütahya Evliya Çelebi Training and Research Hospital and underwent IV r-tPA were evaluated in this retrospective cohort study. Demographic data, clinical and functional results of patients were compared between the two groups (cardioembolic and large vessel atherosclerosis).

Results: Eighty-five patients with ischemic stroke who received IV r-tPA treatment due to cardioembolism and large-vessel atherosclerosis were included in the study. There were 51 patients (60%) in the cardioembolic stroke group and 34 patients (40%) in the large vascular atherosclerotic group. There was no significant difference in terms of functional results between the groups (62.7% vs 44.1%; P=0.09). While symptomatic intracerebral hemorrhage was not detected in the large-vessel atherosclerosis group, it occurred in 3.9% of the cardioembolic stroke group.

Conclusion: This study proved that functional and clinical results are similar between cardioembolic and large-vessel atherosclerosis patients who were treated with IV r-tPA treatment. Regardless of the etiology, all suitable patients with acute ischemic stroke should be treated with thrombolytic therapy.

Keywords: Acute ischemic stroke, Cardioembolic stroke, Intravenous thrombolytic therapy

How to cite: Çetiner M, Seyit M, Eskut N, Akdağ G, Arıkan FA, Kabay SC. Outcomes of intravenous thrombolytic therapy in cardioembolic strokes. J Surg Med. 2021;5(2):111-114.

Introduction

Ischemic stroke is subdivided according to etiological causes and has different prognosis and mortality rates based on the mechanisms of its formation [1,2]. It has been reported that intravenous recombinant tissue plasminogen activator (IV r-tPA), the basis of intravenous thrombolytic therapy in acute ischemic stroke, improves functional results in all strokes [3,4]. However, the response to IV r-tPA treatment may vary depending on the size, content and the source of the clot. While thrombus formed under slow blood flow in the heart cavities is rich in fibrin, that formed under fast blood flow in atherosclerotic-stenotic lesions is rich in thrombocytes. Therefore, it is assumed that the response to fibrinolytic agents such as tissue-type plasminogen activator will be superior in heart-induced embolism [5]. Studies investigating functional results of intravenous thrombolysis in patients with cardioembolic stroke are contradictory in the literature. In the study of Molina et al. [6], early recanalization following thrombolysis was more frequent, faster, and higher in cardioembolic patients with middle cerebral artery infarction, and the improvement in the three-month period was better in non-cardioembolic strokes in the study of Rocha et al. [7]. On the other hand, in the study of Nam et al., the rate of full recanalization was lower in cardioembolic strokes, the rate of poor functional recovery in the third month was higher, and heart-borne embolism was an independent determinant for the poor functional result in the third month [8]. Similarly, in the study of Kimura et al., patients with atrial fibrillation (AF) who underwent IV thrombolysis in acute ischemic stroke had worse clinical results compared to the ones without AF [9].

On the other hand, in a study reported from our country, functional results were not different in the 3rd month after thrombolytic therapy in patients with acute middle cerebral infarction of different stroke types [10].

The aim of this study is to examine, compare and discuss the results of acute ischemic stroke patients undergoing IV thrombolytic therapy with cardioembolism and large vessel atherosclerosis according to TOAST classification.

Materials and methods

The data of the patients who were admitted to the emergency department within the first 4.5 hours following the onset of symptoms, diagnosed with acute ischemic stroke and underwent IV r-tPA at Kütahya Evliya Çelebi Training and Research Hospital Neurology Department between May 2014 and September 2018 were evaluated retrospectively. Thrombolytic treatment decision was made according to AHA / ASA 2013 [11] and 2016 [12] guidelines. All patients were given an intravenous bolus of 10% of the total dose of 0.9 mg / kg (maximum 90 mg) of r-tpA (alteplase®) and the rest was administered as hourly infusion. Ischemic stroke risk factors, demographic and clinical features, neurological examination findings, results of hemogram and biochemistry tests, and symptom needle (SN) time were recorded from patient files. The patients' evaluation was based on the etiological classification of Acute Stroke Treatment [13] (TOAST) in Trial of Stroke Org 10172. Eighty-five patients with cardioembolic and large vessel atherosclerosis were included in the study. The computed brain tomography images of the patients were examined before and during IV r-tPA, or intracranial bleeding. The presence of hemorrhagic infarction with more than 30% of the infarct area accompanied by neurological deterioration, intracranial hemorrhages causing an increase of more than 4 points in NIHSS or death were called symptomatic intracerebral hemorrhage (sICH), while those detected incidentally in control imaging were called asymptomatic intracerebral hemorrhage (aICH) [14]. Intracranial bleeding occurring within the first 36 hours of treatment was considered r-tPA complication. The pre-post-treatment neurological disabilities of the patients were evaluated with the national Health Institutes of Health Stroke Scale (NIHSS) scores and the 3rd month neurological disabilities, with modified Rankin Scale **(**mRS**)** scores.

Early neurological improvement (ENI) was defined as a NIHSS score of 0 to 1 24 hours following thrombolytic therapy or an improvement in the NIHSS score of ≥8 points (14). Having mRS ≤2 at 3 months was considered a good functional result, and mRS >2, a poor one [15].

The study was approved by the Dumlupinar University of Local Ethics Committee (Date: 14/11/2018, Decision no: 2018/14-8).

Statistical analysis

Statistical analyses were performed using SPSS 24.0 (IBM Corp.; Armonk, NY, USA) program. Normally distributed variables were presented as mean (standard deviation), and non-normally distributed variables were presented as median (minimum-maximum). In the comparison between the independent groups, t-test was used for the parametric data and Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by chi-square and Fisher's exact test. *P*-value <0.05 was considered statistically significant.

Results

Demographic and basic features of patients

The study included eighty-five patients with cardioembolic and large vessel atherosclerosis who were diagnosed with acute ischemic stroke and underwent IV-r tPA. Forty-eight were male (56.5%) and thirty-seven were female (43.5%) and their mean age was 70.32 (10.39) (range, 35-88) years.

Two groups were formed with fifty-one patients in the cardioembolic stroke (60%) group and thirty-four patients in the large vessel atherosclerosis (40%) group. Among vascular risk factors, smoking was more prevalent in the large vessel atherosclerosis group (P=0.03), while coronary artery disease (CAD) and atrial fibrillation (AF) were more common in the group with large vessel atherosclerosis (P<0.001). The two groups were similar in terms of age, gender, SN time, initial NIHSS score averages, glucose levels, systolic and diastolic blood pressure mean values. There was no significant difference in mean platelet volume (MPV) and platelet averages between the groups. Demographic and basic characteristics of the patients and the statistical comparison between them are presented in Table 1.

Table 1: Comparison of demographic and basic characteristics of patients with acute ischemic stroke receiving thrombolytic therapy

	Cardioembolism n=51 (%60)	Large vessel atherosclerosis n=34 (%40)	Total n=85	*P*-value
Age (year)	74 (35-88)	69.85 (9.97)	73 (35-88)	0.66
Gender, n (%)				
•Female	27 (52.9)	10 (29.4)	37 (43.5)	0.03*
Vascular risk factors,	n (%)	n (%)	n (%)	
•CAD+AF	40 (78.4)	7 (20.6)	47 (55.3)	<0.001*
•Hypertension	30 (58.8)	24 (70.6)	54 (63.5)	0.27
•Diabetes	19 (37.3)	15 (44.1)	34 (40)	0.52
•Hyperlipidemia	22 (43.1)	14 (41.2)	36 (42.4)	0.85
•Smoking	14 (27.5)	17 (50)	31 (36.5)	0.03*
SBP (mmHg)	146.76 (25.99)	152.35 (23.84)	149.00 (25.16)	0.31
DBP (mmHg)	80 (60-120)	82.50 (60-160)	80 (60-160)	0.91
Blood glucose level (mg/dL)	132 (78-347)	134.50 (93-345)	134 (78-347)	0.28
SN Duration (minute)	159.31 (54.90)	157.97 (53.55)	158.77 (60-270)	0.91
NIHSS (Before treatment)	14.76 (5.67)	12 (5-24)	13 (3-25)	0.17
MPV (fL)	9.14 (1.02)	9.12 (1.32)	9.13 (1.14)	0.95
Platelet (x10^3/mm^3)	243.37 (75.76)	238.02 (55.64)	241.23 (68.11)	0.72

* *P*<0.05, AF: Atrial fibrillation, DBP: Diastolic Blood Pressure, fL: Femtolitre, CAD: Coronary artery disease, Min.: Minimum, Max.: Maximum, NIHSS: The National Institutes of Health Stroke Scale score, MPV: Mean platelet volume, SD: Standard Deviation, SN: Symptom/needle, SBP: Systolic Blood Pressure.

Clinical and functional results

Clinically good functional results were obtained in forty-seven patients (55.3%) (mRS ≤2). Good functional results were obtained in 32 patients (62.7%) in the cardioembolic stroke group and in 15 patients (44.1%) in the atherothrombotic stroke group, the rates of which were similar (*P*=0.09).

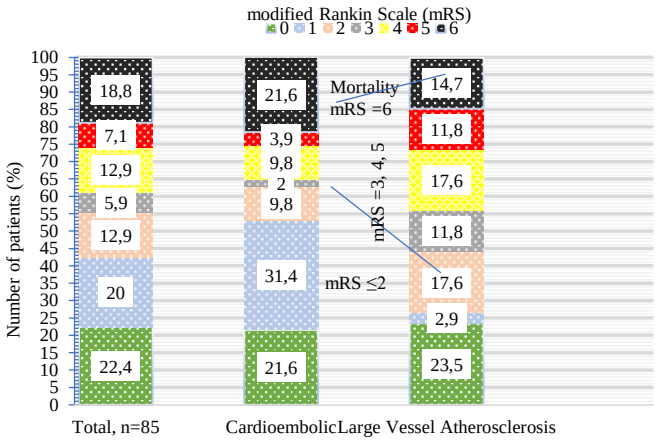
Early neurological improvement was detected in 26 (30.6%) patients. Among these, eighteen patients were (35.3%) in the cardioembolic stroke group and eight (23.5%) had large vessel atherosclerosis (*P*=0.88). Similarly, at the 24th hour after treatment, no significant difference was found between the mean scores of NIHSS (*P*=0.24). Asymptomatic intracerebral hemorrhage developed in 12 patients (14.1%). Although the cardioembolic group [10 patients (19.6%)] constituted the majority of asymptomatic bleeding, it was of no statistical significance (19.6% -5.9%, *P*=0.07). While symptomatic intracerebral hemorrhage was not observed in the atherothrombotic stroke group, symptomatic intracerebral bleeding was detected in 3 patients (5.9%) in the cardioembolic stroke group (*P*=0.27). Total mortality rate in this study was 18.8% (16 patients), and 21.6% (11 patients) of the patients who died were in the cardioembolic stroke group, while 14.7% (5 patients) had stroke due to large vessel atherosclerosis. There was no significant difference in mortality between the groups (*P*=0.42). Clinical and functional results of the patients are presented in Table 2 and mRS score distributions are given in Figure 1.

Table 2: Comparison of clinical and functional results in patients with cardioembolic and large-vessel atherosclerosis stroke

	Cardioembolic n=51, (%60)	Large vessel atherosclerosis n=34, (%40)	Total n=85	*P*-value
ENR, n (%)	18 (35.3)	8 (23.5)	26 (30.6)	0.24
NIHSS (24 hr after treatment)	10.09 (0-23)	8.5 (0-26)	8 (0-26)	0.88
aICH, n (%)	10 (19.6)	2 (5.9)	12 (14.1)	0.07
sICH, n (%)	3 (5.9)	-	3 (3.5)	0.27†
mRS (3rd month)≤2, n (%)	32 (62.7)	15 (44.1)	47 (55.3)	0.09
Mortality, n (%)	11 (21.6)	5 (14.7)	16 (18.8)	0.42

†: Fisher's Exact Test, aICH: Asymptomatic Intracerebral Hemorrhage, ENR: Early Neurological Recovery, Min: Minimum, Max: Maximum, mRS: Modified Ranking Scale, NIHSS: The National Institutes of Health Stroke Scale score, sICH: Symptomatic Intracerebral Hemorrhage.

Figure 1: Distribution of patients' mRS scores. There was no significant difference between mortality and functional outcomes (mRS ≤2) in stroke patients with cardioembolism and large vessel atherosclerosis (*P*>0.05).



Discussion

IV thrombolysis is the main treatment for acute ischemic stroke and effective in all stroke subtypes [3]. Different subtypes of ischemic stroke have different risk factors, clinical features, pathogenesis, and prognosis [16,17]. In earlier studies, it was investigated whether clinical results after thrombolysis differed from other stroke types in cardioembolic strokes, but contradictory results were obtained [7,18,19]. In this study, 3-month clinical and functional results were compared in patients with cardioembolic and large-vessel atherosclerosis following IV thrombolysis treatment, and no significant differences were observed.

Theoretically, cardioembolic thrombi are rich in fibrin and erythrocytes than atherosclerotic thrombi, which are more organized and richer in platelet. Thrombolytic treatment responses are expected to differ according to the structural composition of the thrombus, and thrombi of cardiac origin will be more prone to dissolution with intravenous alteplase. In this context, a study in which recanalization following IV thrombolysis was monitored with transcranial doppler showed that recanalization in patients with cardioembolic stroke was more frequent, faster and more complete than other stroke subtypes in patients with middle cerebral artery occlusion [6].

There are studies emphasizing that cardioembolic strokes are associated with poor results and high mortality [8,20]. In MRI-based studies of Schmitz et al. [19], earlier neurological recovery and better functional outcome (mRS: 0,1) were achieved following IV-tPA treatment in patients with cardioembolic stroke compared with stroke due to large vessel atherosclerosis. Similarly, in the study of Vaclavik et al. [14], compared to atherothrombotic strokes, the likelihood of symptomatic intracranial hemorrhage was low in cardioembolic strokes, and early neurological healing, increased 3-month good functional clinical outcome (mRS: 0,1), and indifferent mortality rates were observed. ENI is a strong determinant of positive functional results in 3 months in patients with acute ischemic stroke after thrombolytic therapy [21]. In the study of Fuentes et al., no significant difference was found between ENI and 3-month functional results in stroke subtypes, as in this study [22]. In accordance with the present study, no difference was found between the two groups in terms of ENI, 3-month good functional outcome, intracerebral hemorrhage and mortality.

Patients with cardioembolic stroke have a higher risk of hemorrhagic transformation [18,23,24]. Wang et al. [18] reported that this may decrease the benefit of thrombolytic therapy. In this study, symptomatic intracerebral hemorrhage was higher in patients with cardioembolic stroke after thrombolysis, and worse clinical results were obtained at 3 months follow-up compared to stroke patients with large vessel atherosclerosis. It has been reported that patients with AF have a higher risk and poor prognosis in terms of intracerebral bleeding following thrombolysis [25,26]. In this study, the rate of patients with AF and intracerebral bleeding rates were significantly higher in the cardioembolic stroke group. In a study investigating the frequency of hemorrhagic transformation in ischemic stroke and related factors, the size of AF and infarct area were independent risk factors, but no relationship was found between the 3rd month prognosis and hemorrhagic transformation [27]. In the report of Dang H et al., hemorrhagic transformation following the treatment was significantly higher in patients with AF undergoing IV thrombolysis, while no correlation was detected with prognosis [28]. Similarly, in a large-scale metanalysis study involving Chinese patients, Wen L., et al. stated that hemorrhagic transformation was significantly higher in patients with AF who underwent IV thrombolysis [29]. In our study, there was no significant difference between symptomatic and asymptomatic intracerebral bleeding rates and functional results between the two groups.

Limitations

The limitations of this study include its retrospective and single-center design, as only few patients with cardioembolic and atherothrombotic stroke were admitted. Therefore, etiologically, patients with cardioembolic stroke could not be compared with other stroke subtypes except for large vessel atherosclerotic strokes.

Conclusion

Thrombolytic therapy should be applied to all suitable acute ischemic stroke patients, regardless of the etiology. Sharing these results in terms of the spread of IV-r tPA in our country is valuable.

References

1. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Giralt-Steinhauer E, Jiménez-Conde J, Lopez-Cuiña M, et al. Relevance of stroke subtype in vascular risk prediction. Neurology. 2013;81:571-80.
2. Wei W, Li S, San F, Zhang S, Shen Q, Guo J, et al. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. Medicine (Baltimore). 2018:97:e0412.
3. The National Institute of Neurological Disorder and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-7.
4. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-51.
5. Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Brain infarction severity differs according to cardiac or arterial embolic source. Neurology. 1993;43:728-33.
6. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Sabín JA. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke. 2004;35:486-90.
7. Rocha S, Pires A, Gomes J, Rocha J, Sousa F, Pinho J, et al. Intravenous thrombolysis is more effective in ischemic cardioembolic strokes than in non-cardioembolic? Arq Neuro psiquiatr. 2011;69:905-9.
8. Nam HS, Lee KY, Kim YD, Choi HY, Cho HJ, Cha MJ, et al. Failure of complete recanalization is associated with poor outcome after cardioembolic stroke. Eur J Neurol. 2011;18:1171-8.
9. Kimura K, Iguchi Y, Shibazaki K, Iwanaga T, Yamashita S, Aoki J. IV t-PA therapy in acute stroke patients with atrial fibrillation. J Neurol Sci. 2009;276:6-8.
10. Güneş M. Relationship between blood pressure levels during thrombolytic therapy and functional outcomes in patients with middle cerebral artery infarction. J Surg Med. 2020;4:378-82.
11. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. 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. 2013;44:870-947.
12. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, E Fugate JE, Grotta JC, et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:581-641.
13. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
14. Vaclavik D, Vilionskis A, Jatuzis D, Karlinski MA, Gdovinova Z, Kõrv J, et al. Clinical outcome of cardioembolic stroke treated by intravenous thrombolysis. Acta Neurol Scand. 2018;137:347-55.
15. Mustanoja S, Meretoja A, Putaala J, Viitanen V, Curtze S, Atula S, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: Descriptive subtype analysis. Stroke. 2011;42:102–6.
16. Tan YF, Zhan LX, Chen XH, Guo JJ, Qin C , En Xu E. Risk Factors, Clinical Features and Prognosis for Subtypes of Ischemic Stroke in a Chinese Population. Curr Med Sci. 2018;38:296-303.
17. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062-8.
18. Wang XG, Zhang LQ, Liao XL, Pan YS, Shi YZ, Wang CJ, et al. Thrombolysis Implementation and Monitoring of acute ischemic Stroke in China (TIMS-China) Investigators. Unfavorable Outcome of Thrombolysis in Chinese Patients with Cardioembolic Stroke: a Prospective Cohort Study. CNS Neurosci Ther. 2015;21:657-61.
19. Schmitz ML, Simonsen CZ, Svendsen ML, Larsson H, Madsen MH, Mikkelsen IK, et al. Ischemic stroke subtype is associated with outcome in thrombolyzed patients. Acta Neurol Scand. 2017;135:176-82.
20. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus Histology Suggests Cardioembolic Cause in Cryptogenic Stroke. Stroke. 2016;47:1864-71.
21. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BPL, Wakerley B, et al. Early and continuous neurologic improvements after intravenous thrombolysis are strong predictors of favorable long-term outcomes in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22:e590-6.
22. Fuentes B, Martínez-Sánchez P, Alonso de Leciñana M, Egido J, Reig-Roselló G, Díaz-Otero F, et al. Madrid Stroke Network. Efficacy of intravenous thrombolysis according to stroke subtypes: the Madrid Stroke Network data. Eur J Neurol. 2012;19:1568-74.
23. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, et al. Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: Results of a prospective multicenter study. Stroke. 2008;39:2249–56.
24. Liu M, Pan Y, Zhou L, Wang Y. Predictors of post-thrombolysis symptomatic intracranial hemorrhage in Chinese patients with acute ischemic stroke. PLoSOne. 2017;12:e0184646.
25. Ge WQ, Chen J, Pan H, Chen F, Zhou CY. Analysis of Risk Factors Increased Hemorrhagic Transformation after Acute Ischemic Stroke.J Stroke Cerebrovasc Dis. 2018;27:3587-90.
26. Shon SH, Heo SH, Kim BJ, Choi HY, Kwon Y, Yi SH, et al. Predictors of Hemorrhage Volume after Intravenous Thrombolysis. J Stroke Cerebro vasc Dis. 2016;25:2543-8.
27. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol. 2014;261:905-12.
28. Dang H, Ge WQ, Zhou CF, Zhou CY. The Correlation between Atrial Fibrillation and Prognosis and Hemorrhagic Transformation. Eur Neurol. 2019;82:9-14.
29. Wen L, Zhang S, Wan K, Zhang H, Zhang X. Risk factors of haemorrhagic transformation for acute ischaemic stroke in Chinese patients receiving intravenous thrombolysis: A meta-analysis. Medicine (Baltimore). 2020;99:e18995.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.