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Early Recurrent Ischemic Stroke Complicating Intravenous Thrombolysis for Stroke

Incidence and Association With Atrial Fibrillation

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Background and Purpose—Mechanisms of early neurologic deterioration after treatment with intravenous, recombinant, tissue-type plasminogen activator (IV rt-PA) include symptomatic intracerebral hemorrhage (SICH) and early recurrent ischemic stroke. We observed a number of cases of acute deterioration due to recurrent ischemic events.

Methods—We undertook a single-center, retrospective analysis of consecutive acute stroke patients treated with IV rt-PA between January 2006 and December 2008 to define the incidence of early neurologic deterioration (≥4-point drop on the National Institutes of Health Stroke Scale within 72 hours) and its mechanism. Deterioration was attributed to SICH when associated with a PH1 or PH2 hemorrhage on postdeterioration computed tomography scans, to recurrent ischemic stroke when there was clinical and radiologic evidence of a new territorial infarction or new vessel occlusion, and otherwise to evolution of the incident stroke.

Results—Of 228 consecutive IV rt-PA–treated patients, 34 (15%) developed early neurologic deterioration, 18 (8%) secondary to incident strokes 10 (4.4%) due to SICH, and 6 (2.6%) due to early recurrent ischemic events, which were significantly associated with atrial fibrillation (present in 5 of 6 patients; 4 paroxysmal, 1 permanent). In 4 patients, sudden clinical deterioration developed during or shortly after IV rt-PA infusion, and in 2, deterioration developed 3 days later. All died 2 days to 2 weeks later. The single case without atrial fibrillation had a recurrent, contralateral, middle cerebral artery stroke during IV rt-PA infusion and multiple high-signal emboli detected by transcranial Doppler. Early recurrent ischemic stroke accounted for 5 of 12 (42%) cases of early neurologic deterioration in patients with atrial fibrillation.

Conclusion—In this single-center series, the incidence of early recurrent ischemic stroke after IV rt-PA was 2.6% and was associated with previous atrial fibrillation. **(*Stroke*. 2010;41:1990-1995.)**

Key Words: acute care ■ atrial fibrillation ■ embolism ■ thrombolysis

Early neurologic deterioration (END) after acute ischemic stroke is common and is associated with a poor outcome.[1] Whereas END has no standardized definition, a drop of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS) within the first 48 to 72 hours after acute stroke[1,2] has been commonly used. Mechanisms of deterioration include brain swelling after large infarction, and hemorrhagic transformation. Late deterioration has predominantly systemic causes.[3] When END occurs after intravenous (IV) thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), this usually raises the possibility of symptomatic intracranial hemorrhage (SICH), the most common safety concern of treatment. Randomized, controlled trials and registries have accordingly concentrated on the risk of SICH but offer only a limited description of alternative mechanisms of END. Arterial reocclusion accounts for some cases of END after thrombolysis, but the clinical scenario is more often deterioration after initial improvement rather than END alone.[4,5]

Embolic stroke shortly after systemic thrombolysis has been described in acute myocardial ischemia and prosthetic valve thrombosis and more recently in a few cases of acute ischemic stroke. We describe a series of cases wherein early recurrent ischemic stroke (ERIS), confirmed clinically and radiologically, occurred shortly after IV rt-PA, and compare the incidence and clinical associations with other causes of END.

Subjects and Methods

We reviewed the clinical and imaging data of all stroke patients treated with IV rt-PA for 3 years (January 2006 to December 2008) at a single center. All cases were registered with the Safe Implemen-

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Table 1. Basic Clinical Data for All Ischemic Stroke Patients Treated With IV rt-PA

	All Patients	Patients With AF	Patients Without AF
N/n (%)	228 (100%)	74 (32.4%)	154 (67.6%)
Age, mean±SD, y	69.5±13	76±10	66.4±13.4
Male, no. (%)	121 (53%)	30 (40%)	91 (59%)
Medical history, no. (%)			
Hypertension	151 (66%)	52 (70%)	99 (64%)
Diabetes mellitus	24 (10%)	12 (16.2%)	12 (7.8%)
Hyperlipidemia	48 (21%)	14 (19%)	34 (22%)
Cigarette smoking	56 (24.5%)	11 (15%)	45 (29%)
Previous TIA or stroke	45 (19.7%)	13 (17.5%)	32 (20.8%)
Aspirin use	105 (46%)	44 (59.5%)	61 (39.6%)
Other antiplatelet agent	22 (9.5%)	6 (8%)	16 (10%)
Anticoagulants	7 (3%)	5 (6.7%)	2 (1.3%)
Stroke characteristics			
NIHSS, median (IQR)	14 (8–20)	14 (8–19)	14.5 (7–20)
Time to treatment, mean±SD min	170±38	162.7±32	173.3±40
END due to	34 (15%)	12 (16.2%)	22 (14.3%)
Incident stroke	18 (8%)	4 (5.4%)	14 (9%)
SICH	10 (4.4%)	3 (4%)	7 (4.5%)
ERIS	6 (2.6%)	5 (6.8%)	1 (0.6%)

Data include those for patients with a history of AF, including paroxysmal AF, and those with no evidence of AF. TIA indicates transient ischemic attack; IQR, interquartile range. Other abbreviations are as defined in text.

Table 2. Basic Clinical Data for Acute Stroke Patients Who Developed END After Treatment With IV rt-PA

	Mode of END		
	Incident Stroke	SICH	ERIS
n (%)	18 (8%)	10 (4.4%)	6 (2.6%)
Age, mean±SD, y	69.5±13	70.7±7	72±7.5
Male, no. (%)	9 (50%)	5 (50%)	3 (50%)
Medical history			
Hypertension	11 (61%)	9 (90%)	3 (50%)
Diabetes mellitus	1 (5.5%)	3 (30%)	1 (16.6%)
Hyperlipidemia	3 (16.6%)	1 (10%)	1 (16.6%)
Cigarette smoking	5 (27.7%)	2 (20%)	3 (50%)
Previous TIA or stroke	5 (33.3%)	4 (40%)	3 (50%)
Premorbid AF	4 (22%)	3 (30%)	5 (83.3%)
Aspirin use	7 (39%)	6 (60%)	2 (33.3%)
Other antiplatelet agent	3 (16.6%)	2 (20%)	2 (33%)
Anticoagulants before stroke	0 (0%)	2 (20%)	0 (0%)
Stroke characteristics and outcome			
NIHSS, median (IQR)	15 (7, 21.25)	18 (10.25, 25.5)	13 (9.25, 18.25)
Onset to treatment time, mean±SD, min	162.5±26	186.7±16	176±25
3-month mortality, no. (%)	9 (50%)	9 (90%)	6 (100%)

TIA indicates transient ischemic attack; IQR, interquartile range. Other abbreviations are as defined in text.

tation of Thrombolysis register. Demographic and clinical data were extracted from the local Safe Implementation of Thrombolysis registry and hospital records.

Patients with ischemic stroke were treated with standard-dose IV alteplase according to the National Institute of Neurological Disorders and Stroke schedule and criteria,[6] with the exception that no age restriction was applied and that treatment was allowed up to 4.5 hours after onset, provided that there were no other contraindications in either situation. Routine pretreatment imaging was performed by noncontrast computed tomography (CT), with follow-up brain imaging ≈24 hours after treatment and additional imaging when clinically indicated. Transcranial Doppler ultrasound was used to monitor middle cerebral artery (MCA) flow in some cases during alteplase infusion.

We defined significant END as a drop in NIHSS score of 4 points or more within 72 hours after presenting stroke. SICH was considered to be the cause when a parenchymal hematoma (PH1 or PH2)[7] was present on posttreatment CT. ERIS was diagnosed when there was both clinical and imaging evidence of ischemic stroke in an independent arterial territory, so as to exclude deficits explainable by arterial reocclusion, proximal extension, or distal embolism of the original thrombus. Cases of deterioration without either SICH or recurrent ischemic stroke were considered to be related to the incident stroke.

Statistical Analysis

Descriptive statistics present normally distributed variables as mean±SD and nonnormally distributed variables as median and interquartile range. Proportions are given with 95% CIs. Binary logistic regression was undertaken with the dependent variables of ERIS or SICH and independent variables that included atrial fibrillation (AF), hypertension, age, smoking, NIHSS score, prior anticoagulant/antiplatelet use, diabetes, and previous history of transient ischemic attack or stroke. Variables were entered into a forward stepwise conditional model.

Results

Data from 228 consecutive patients were reviewed. Clinical characteristics are summarized in Table 1. AF (persistent, paroxysmal, or transient) was documented in nearly one third of all patients (32.4%). Thirty-four patients (15%; 95% CI, 10% to 19.5%) developed neurologic deterioration within 72 hours of treatment, 10 (4.4%) due to SICH, 6 (2.6%) with evidence of ERIS, and 18 patients (8%) with neither cause, therefore attributed to evolution of their incident stroke.

Table 2 compares the demographic and premorbid clinical data among the 3 groups of END patients. Premorbid AF was notably common (83.3%) in those with ERIS, and conversely, the incidence of ERIS was significantly higher (Table 1) in those with documented AF (6.8%; 95% CI, 2.6% to 15.2%) compared with those without a history of AF (0.6%; 95% CI, 0% to 3.9%; odds ratio=11.1; 95% CI, 1.27 to 96.7, $P=0.0146$) and also accounted for 5 of 12 cases of END in patients with AF (42%), compared with only 1 of 22 cases of END in those without AF (odds ratio=15.0; 95% CI, 1.49 to 151.3; $P=0.0136$). In logistic regression, only a history of AF was associated with ERIS (odds ratio=11.1; 95% CI, 1.27 to 96.7; $P=0.029$). END due to SICH was associated with prior anticoagulant use and a history of diabetes.

Table 3. Demography, Clinical Features, and Outcomes of Patients Who Developed ERIS After IV rt-PA

Case	Sex/ Age, y	History of AF	Other Vascular Risk Factors	Antiplatelet Use Before Admission	OCSP	NIHSS	ECG on Admission	Pretreatment CT	Onset-to-Treatment Time, min	Symptoms of Recurrent Stroke	Time From Treatment Onset to Recurrent Stroke, min	Follow-Up CT	Other Investigation and Management	Final Outcome (Days From Onset)
1	F/80	PAF	IHD, smoking	Clopidogrel	L PACS	13	NSR	L MCA EIC	160	Coma, extension of 4 limbs	80	L MCA infarct, hyperdense BA	Angiography and IA thrombolysis of BA	Death (6)
2	M/64	No	HTN, smoking	No	R TACS	18	NSR	Recent L occipital infarct, hyperdense R MCA	210	Coma, extension of 4 limbs	60	R MCA infarct, hyperdense L MCA	TCD: Low R MCA flow, microemboli	Death (3)
3	M/62	Permanent AF	HOCM	No	R TACS	19	AF	Nil	165	New contralateral hemiparesis	45	Normal	CTA: occluded L MCA, recanalized R MCA	Death (2)
4	F/79	PAF with pacemaker	IHD, migraine, DVT	Aspirin	L PACS	4	PAF	Nil	205	Coma, extension of 4 limbs	3 days	L MCA infarct, hyperdense BA	CTA: normal (before deterioration)	Death (10)
5	M/74	PAF with pacemaker	IHD, HTN, DM, CHF, smoking	Clopidogrel	L PACS	13	AF	Nil	150	Coma, new contralateral hemiparesis	40	L MCA and PCA acute infarcts	CTP: L MCA ischemia, no PCA ischemia, CTA: L MCA anterior branch occlusion and irregular calcific atheroma occluding L VA	Death (15)
6	F/73	PAF	HTN, hyperlipidemia	Aspirin	R PACS	11	NSR	Nil	165	Seizures, coma, new contralateral hemiparesis	3 days	R MCA early infarct	MRI (DWI): L acute MCA and R subacute MCA infarctions	Death (11)

OCSP indicates Oxfordshire Community Stroke Project; PAF, paroxysmal AF; IHD, ischemic heart disease; HTN, hypertension; HOCM, hypertrophic obstructive cardiomyopathy; DVT, deep venous thrombosis; DM, diabetes mellitus; CHF, congestive heart failure; L, left; PACS, partial anterior circulation stroke; R, right; TACS, total anterior circulation stroke; NSR, normal sinus rhythm; EIC, early ischemic changes; BA, basilar artery; PCA, posterior cerebral artery; IA, intra-arterial; TCD, transcranial Doppler; CTA, CT angiography; CTP, CT perfusion; VA, vertebral artery; MRI, magnetic resonance imaging; and DWI, diffusion-weighted imaging.

The clinical features of the 6 cases of ERIS are detailed in Table 3. On admission, 5 of 6 had documented AF (4 paroxysmal and 1 permanent). The specific reasons for prior pacemaker use in 2 cases were not documented. There was no evidence of acute or recent myocardial ischemia on the admission ECG. All patients died 2 days to 2 weeks after first stroke (mean, 8 days). In 4 cases, deterioration occurred suddenly during or immediately after IV alteplase infusion, and 2 cases occurred 3 days later. In 5 cases, there was a reduced level of consciousness. Examples of supporting imaging studies are shown in the Figure.

Discussion

The incidence of END after IV rt-PA treatment in our series (15%) is consistent with that reported by others, but we found a higher incidence of ERIS than has been reported previously. Although the incidence of ERIS was low and certainly should not delay thrombolysis in suitable patients, ERIS accounted for a significant proportion of deterioration and was only slightly less frequent than SICH. A strong association with AF was also noted.

Secondary embolism after systemic thrombolysis, including ischemic stroke, is recognized as an uncommon complication of thrombolysis for acute myocardial ischemia,[8–14] prosthetic valvular thrombosis,[15–18] or massive pulmonary embolism[19] and has been presumed to occur as a consequence of the disintegration of preexisting intracardiac or valvular thrombus. Preexisting left ventricular thrombus has been documented by echocardiography before ischemic stroke complicating thrombolysis for acute myocardial ischemia,[10,13] with a disappearance or reduction in thrombus volume after stroke. Possible embolization to other vascular beds has also been reported after IV rt-PA for ischemic stroke, including acute myocardial infarction,[20,21] peripheral arterial embolism,[22] or embolism to the external carotid artery.[23] Embolic sources include intracardiac (intraventricular, intra-atrial, or valvular) or proximal aortic[14] thrombus. In most previously reported cases, the embolic event occurred during or soon after rt-PA infusion, consistent with the majority of our cases.

Although the presence of intracardiac thrombi has been suggested as a relative contraindication for thrombolysis for stroke, secondary embolic stroke after systemic thrombolysis is rare, even in the presence of known intraventricular thrombi[24] (no strokes in 37 consecutive patients treated with streptokinase for acute myocardial ischemia[24] and 1 late ischemic stroke among 5 consecutive cases after IV rt-PA for acute stroke[25]).

Applying our definition of ERIS, which attempts to exclude cases of proximal extension, reocclusion, or distal embolization in the same vascular territory, we identified only 5 cases in the literature.[26–29] Mechanisms of stroke

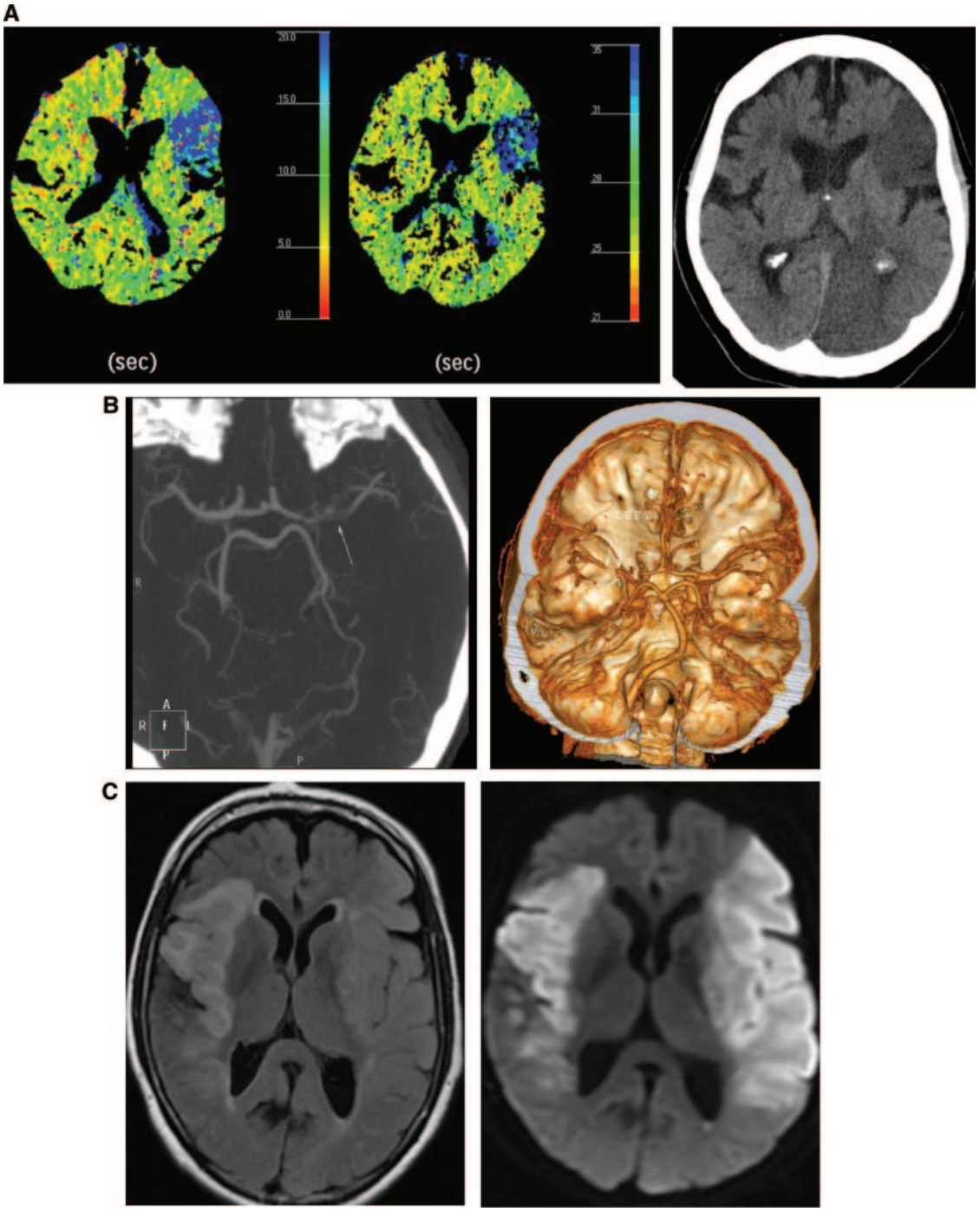

Figure. A, Case 5, presented with symptoms of left MCA territory ischemia and CTP (a, b), confirming increased mean transit time in the left frontal cortex with no other hypoperfusion. C, Noncontrast CT scan 24 hours after deterioration with ischemic changes in both the left MCA and posterior cerebral artery territories. B, CT angiography in case 3 after clinical deterioration shows recanalization of the right MCA (presenting symptomatic vessel) and a proximal left MCA filling defect, consistent with the development of a new contralateral hemiparesis. C, Magnetic resonance imaging of case 6 performed after acute deterioration occurred with generalized seizures 3 days after treatment. T2 fluid-attenuated inversion recovery (a) and diffusion-weighted (b) imaging shows a subacute right MCA infarction (presenting stroke) and an acute left MCA infarct.

recurrence included calcific embolism from an aortic valve.[26] In only 2 cases was AF documented.[27,29] However, a central embolic source was inferred from multifocal thrombotic vessel occlusions in 2 others.[28] Alternative mechanisms such as proximal arterial thrombi have been present in other cases with a history of paroxysmal AF.[30]

Documented AF was unusually prevalent in our patients and was associated with ERIS. This mechanism accounted for 42% of END cases after thrombolysis in AF patients. Most events caused sudden neurologic deterioration with impaired consciousness and occurred during or shortly after rt-PA infusion. Without echocardiography, the source is specula-

tive, and although the time course and clinical associations are consistent with fragmentation of preexisting intra-atrial clot by rt-PA, we cannot exclude the possibility of embolism from other sources known to be common in patients with AF, such as aortic arch atheroma, or intraventricular thrombus secondary to myocardial infarction, although we found no ECG evidence of recent myocardial ischemia in any case.

The single case in our series without documented AF had clinical and radiological evidence of preceding multiple-territory ischemic events, including recent transient ischemic attack, and had multiple, hyperintense, transient signals consistent with emboli during transcranial Doppler monitoring, implicating a central embolic source. In case 5, an irregular, occlusive, calcific thrombus of the vertebral artery was documented before recurrent ipsilateral posterior cerebral artery infarction, so artery-to-artery embolism is a possible alternative mechanism.

Admission ECG did not show AF in all cases in our series, and medical records provided evidence of prior diagnosis. Previous reports of ERIS documented definite AF in only 2 of 5 cases, but this may only reflect limited availability of previous medical history. The low sensitivity of single ECG recordings for paroxysmal AF diagnosis is recognized.[31]

The uniformly poor outcome of ERIS almost certainly reflects recognition bias in favor of severe events. Because only a small proportion of new ischemic lesions detected on diffusion-weighted magnetic resonance imaging are associated with clinical events,[32] the true incidence of new events in other arterial territories can be determined only by imaging studies before and after thrombolysis. AF is recognized as a poor prognostic factor for acute ischemic stroke, in the severity of presentation and early mortality, either with[33,34] or without[35–38] thrombolysis. Although other factors such as hemodynamic instability and poorer cerebral perfusion may be contributory,[1,39] ERIS might also be a mechanism for this poor prognosis among rt-PA–treated patients.

The implications for patient management are ambiguous in the absence of a clear therapeutic intervention at present for either prevention or rescue therapy. Echocardiographic screening of patients would delay thrombolysis, and it assumes a cardiac source for emboli that is unproven. Transesophageal studies would be required to seek an atrial or atrial appendage clot. The presence of AF on admission ECG alone is insensitive, with low sensitivity and specificity. Both the early timing of deterioration in several of our cases and the increased risk of ICH as part of the natural history of cardioembolic stroke suggest that early introduction of anticoagulants or antithrombotic therapy after IV rt-PA in patients with AF, even with documented intracardiac thrombus, would unlikely be safe or effective. Awareness of second embolic stroke may allow clinicians to consider interventional treatment approaches in individual cases, which may be justified in the light of a poor prognosis.

Disclosures

None.

References

1. Alawneh JA, Moustafa RR, Baron JC. Hemodynamic factors and perfusion abnormalities in early neurological deterioration. *Stroke*. 2009;40:e443–e450.
2. Weimar C, Mieck T, Buchthal J, Ehrenfeld CE, Schmid E, Diener HC. Neurologic worsening during the acute phase of ischemic stroke. *Arch Neurol*. 2005;62:393–397.
3. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. *J Neurol Neurosurg Psychiatry*. 1990;53:824–829.
4. Grotta JC, Welch KM, Fagan SC, Lu M, Frankel MR, Brott T, Levine SR, Lyden PD. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. *Stroke*. 2001;32:661–668.
5. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology*. 2002;59:862–867.
6. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
7. Larrue V, von Kummer RR, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke*. 2001;32:438–441.
8. Stafford PJ, Strachan CJ, Vincent R, Chamberlain DA. Multiple microemboli after disintegration of clot during thrombolysis for acute myocardial infarction. *BMJ*. 1989;299:1310–1312.
9. Lescure M, Lagorce P, Caussanel JP, Malbec M. Myocardial infarction, late fibrinolysis and resolving cerebral embolism. *Ann Cardiol Angeiol (Paris)*. 1993;42:25–27.
10. Bautista RE. Embolic stroke following thrombolytic therapy for myocardial infarction in a patient with preexisting ventricular thrombi. *Stroke*. 1995;26:324–325.
11. Sloan MA, Price TR, Terrin ML, Forman S, Gore JM, Chaitman BR, Hodges M, Mueller H, Rogers WJ, Knatterud GL, Braunwald E. Ischemic cerebral infarction after rt-PA and heparin therapy for acute myocardial infarction: the TIMI-II pilot and randomized clinical trial combined experience. *Stroke*. 1997;28:1107–1114.
12. Chang GY. An ischemic stroke during intravenous recombinant tissue plasminogen activator infusion for evolving myocardial infarction. *Eur J Neurol*. 2001;8:267–268.
13. Chang MC, Lee AY, Chang WF, Chen TJ. Embolic cerebral infarction and gastrointestinal hemorrhage following thrombolytic therapy for acute myocardial infarction. *Echocardiography*. 2002;19:139–141.
14. De Simone N, Sassone B, Vinelli S, Pancaldi LG, Di Pasquale G. Non-hemorrhagic stroke, of possible aortoembolic origin, in the course of acute myocardial infarct treated with thrombolysis. *Ital Heart J Suppl*. 2002;3:344–348.
15. Pape LA, Love DG, Gore JM. Massive thromboembolic stroke and death after fibrinolytic therapy of St. Jude prosthetic mitral valve thrombosis: documentation by transthoracic Doppler echocardiography. *Am Heart J*. 1994;128:406–409.
16. Serafini O, Bisignani G, Plastina F. Acute dysfunction from thrombosis of a prosthetic mitral valve: thrombolysis with rt-PA in the clinical emergency phase. *G Ital Cardiol.* 1998;28:387–391.
17. Koca V, Bozat T, Sarikamis C, Akkaya V, Yavuz S, Ozdemir A. The use of transesophageal echocardiography guidance of thrombolytic therapy in prosthetic mitral valve thrombosis. *J Heart Valve Dis*. 2000;9:374–378.
18. Lengyel M, Vandor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis*. 2001;10:636–649.
19. Braceya TS, Langrisha C, Darbyb M, Soara J. Cerebral infarction following thrombolysis for massive pulmonary embolism. *Resuscitation*. 2006;68:135–137.
20. Meissner W, Lempert T, Saeuberlich-Kniggeb S, Bocksch W, Pape UF. Fatal embolic myocardial infarction after systemic thrombolysis for stroke. *Cerebrovasc Dis*. 2006;22:213–214.
21. Mehdiratta M, Murphy C, Al-Harthi A, Teal PA. Myocardial infarction following t-PA for acute stroke. *Can J Neurol Sci*. 2007;34:417–420.
22. Gomez-Beldarrain M, Telleria M, Garcia-Monco JC. Peripheral arterial embolism during thrombolysis for stroke. *Neurology*. 2006;67:1096–1097.
23. Yasaka M, Yamaguchi T, Yonehara T, Moriyasu H. Recurrent embolization during intravenous administration of tissue plasminogen activator in acute cardioembolic stroke: a case report. *Angiology*. 1994;45:481–484.
24. Kontny F, Dale J, Hegrenaes L, Lem P, Søberg T, Morstøl T. Left ventricular thrombosis and arterial embolism after thrombolysis in acute

anterior myocardial infarction: predictors and effects of adjunctive antithrombotic therapy. *Eur Heart J*. 1993;14:1489–1492.
25. Derex L, Nighoghossian N, Perinetti M, Honnorat J, Trouillas P. Thrombolytic therapy in acute ischemic stroke patients with cardiac thrombus. *Neurology*. 2001;57:2122–2125.
26. Kissela BM, Kothari RU, Tomsick TA, Woo D, Broderick J. Embolization of calcific thrombi after tissue plasminogen activator treatment. *J Stroke Cerebrovasc Dis*. 2001;10:135–138.
27. Lai CC, Hu CJ. A left MCA territory infarction during intravenous recombinant tissue plasminogen activator therapy for right MCA territory ischaemic stroke. *Emerg Med J*. 2006;23:e11.
28. Georgiadis D, Engelter S, Tettenborn B, Hungerbühler H, Luethy R, Müller F, Arnold M, Giambarba C, Baumann CR, von Büdingen HC, Lyrer P, Baumgartner RW. Early recurrent ischemic stroke in stroke patients undergoing intravenous thrombolysis. *Circulation*. 2006;114:237–241.
29. Yalcin-Cakmakli G, Akpinar E, Topcuoglu MA, Dalkara T. Right internal carotid artery occlusion during intravenous thrombolysis for left middle cerebral artery occlusion. *J Stroke Cerebrovasc Dis*. 2009;18:74–77.
30. Anderson CD, Bergman DL, Bernstein RA. Recurrent artery-to-artery embolism during intravenous t-PA therapy for acute ischemic stroke. *Neurocrit Care*. 2005;3:54–56.
31. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke*. 2004;35:1647–1651.
32. Kang DW, Latour LL, Chalela JA, Dambrosia J, Warach S. Early ischemic lesion recurrence within a week after acute ischemic stroke. *Ann Neurol*. 2003;54:66–74.
33. Kimura K, Iguchi Y, Yamashita S, Shibazaki K, Kobayashi K, Inoue T. Atrial fibrillation as an independent predictor for no early recanalization after IV-t-PA in acute ischemic stroke. *J Neurol Sci*. 2008;267:57–61.
34. 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.
35. Kaarisalo MM, Immonen-Räihä P, Marttila RJ, Salomaa V, Kaarsalo E, Salmi K, Sarti C, Sivenius J, Torppa J, Tuomilehto J. Atrial fibrillation and stroke: mortality and causes of death after the first acute ischemic stroke. *Stroke*. 1997;28:311–315.
36. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke*. 2001;32:2333–2337.
37. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology*. 2003;22:118–123.
38. Kimura K, Minematsu K, Yamaguchi T, for the Japan, Multicenter Stroke Investigators' Collaboration (J-MUSIC). Atrial fibrillation as a predictive factor for severe stroke and early death in 15 831 patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2005;76:679–683.
39. Porebska A, Nowacki P, Safranowb K, Nowik M. Hemodynamic blood flow disturbances in the middle cerebral arteries in patients with atrial fibrillation during acute ischemic stroke. *Clin Neurol Neurosurg*. 2008;110:434–440.