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Arterial Occlusive Lesions Recanalize More Frequently in Women Than in Men After Intravenous Tissue Plasminogen Activator Administration for Acute Stroke

Sean I. Savitz, MD; Gottfried Schlaug, MD, PhD; Louis Caplan, MD; Magdy Selim, MD, PhD

Background and Purpose—Previous reports suggest that women achieve better outcome than men after intravenous thrombolysis for ischemic stroke. Coagulation and fibrinolysis differ between sexes. These findings prompted us to investigate possible gender differences in arterial recanalization after intravenous tissue plasminogen activator (IV tPA).

Methods—We identified 100 consecutive patients who presented with acute ischemic stroke and received IV tPA within 6 hours of onset. Only patients with large artery anterior circulation strokes, as determined by MRI/MRA or CT/CTA before treatment, who had follow-up vascular study within 72 hour after treatment were included. We compared demographics, clinical features, admission medications, symptom-to-needle and treatment-to-repeat vascular imaging times, baseline National Institutes of Health Stroke Severity score, radiological and laboratory data, stroke mechanism, and outcome between the sexes.

Results—39 patients met all inclusion/exclusion criteria (22 men and 17 women). The recanalization rate was significantly higher in women (94% versus 59%; $P=0.02$). This difference remained statistically significant after excluding patients whose strokes were attributed to internal carotid artery occlusive lesions, and when the analysis was limited to those treated within 3 hours of stroke onset. All other confounding variables did not differ significantly between the sexes.

Conclusions—In our cohort, vascular occlusive lesions were more likely to recanalize in women than men in response to IV tPA. These preliminary findings need to be validated in larger prospective studies. (***Stroke***. 2005;36:1447-1451.)

Key Words: gender ■ outcome ■ stroke ■ thrombolysis

A pooled analysis of 2178 patients who participated in the National Institute of Neurological Disorders and Stroke (NINDS) study,[1] the Second European Cooperative Acute Stroke Study (ECASS II),[2] and Alteplase Thrombolysis for Acute Non-interventional Therapy in Acute Ischemic Stroke (ATLANTIS) trial[3] showed that women, treated with intravenous (IV) tissue-plasminogen activator (tPA) within 6 hours of stroke onset had better functional outcome after 90 days compared with men.[4] Age, conventional risk factors, stroke severity, symptom-to-needle time, blood pressure, and extent of hypoattenuation on baseline computed tomography did not account for this gender-dependent differential functional outcome.[4]

Early recanalization after thrombolysis is associated with better clinical outcome by salvaging penumbral brain tissue.[5–6] Gender differences in coagulation and fibrinolysis have been reported in acute ischemic stroke and other vascular disorders.[7–8] Such differences could theoretically influence arterial recanalization resulting from treatment with tPA and affect functional outcome after ischemic stroke. The cerebral vasculature was not routinely evaluated after tPA administration to assess for successful recanalization in any

of these trials. Therefore, we aimed to investigate if treatment with IV tPA within 6 hours of ischemic stroke onset results in a higher frequency of arterial recanalization in women than in men.

Materials and Methods

Study Design and Patient Selection

We reviewed our prospectively collected stroke database and identified 100 consecutive patients treated with thrombolysis within 6 hours of ischemic stroke symptom onset. Patients treated between 3 to 6 hours after stroke onset (n=13) were part of 2 experimental trials using typical IV tPA dosing in the extended time window; no preselection was applied. We included only patients who received standard IV tPA for a stroke within the vascular distribution of an imaging-documented occlusion of the internal carotid artery (ICA), middle cerebral artery (MCA), or both (ICA/MCA), and who had a repeat vascular study within 72 hours after tPA. Each patient received 0.9 mg/kg of IV tPA (maximum 90 mg) according to the NINDS guidelines.[1] Patients were excluded if they had a small vessel or posterior circulation stroke (n=6) or arterial dissection (n=3), if they received intra-arterial (IA) tPA (n=15) or other experimental thrombolytic or neuroprotective therapies (n=5), if they did not have a vascular imaging study before treatment (n=5) or a vascular occlusion of a major cerebral vessel on imaging (n=5), or if they did not have a follow-up vascular study (n=22).

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Data Collection and Clinical Evaluation

We retrieved the following data for each patient: (1) demographics; (2) risk factors for stroke (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease [CAD], atrial fibrillation, and smoking); (3) admission blood pressure (BP) and temperature; (4) blood glucose, basic coagulation parameters, and hematocrit levels at admission; (5) medications on admission, with particular attention to antiplatelets, anticoagulants, lipid-lowering agents, and estrogen replacement therapy (HRT); (6) the National Institute of Health Stroke Scale (NIHSS) score[1] at baseline and within 72 hours of tPA administration, as recorded by stroke-trained neurologists certified in its application; (7) stroke-onset-to-treatment time; (8) treatment-to-repeat vascular imaging time; (9) radiological data; (10) length of hospitalization (LOH); (11) discharge status; and (12) functional status at discharge and 30 to 45 days, as assessed by modified Rankin scale (mRS).

Imaging

Either brain MRI or CT scans were used to determine the presence of an anterior circulation stroke or to exclude hemorrhage before administering tPA. The presence of large artery occlusion was assessed by MRA or CTA. All patients who were treated between 3 and 6 hours after stroke onset (n=13) had MRI/MRA with diffusion-weighted and perfusion-weighted imaging (DWI/PWI). An experienced researcher, blinded to patient's identity, measured the volumes of DWI lesions. Specific sequence details of MRI/MRA and CT/CTA and volumetric measurements have been previously described.[9,10]

We used a thrombolysis in myocardial infarction (TIMI) flow grades-derived scale[11,12] to assess the presence and degree of arterial recanalization on post-treatment MRAs/CTAs. One neuroradiologist, blinded to clinical history, interpreted the images. A vessel was considered not recanalized if no flow signal was detected (*TIMI0*); partially recanalized if a minimal flow signal was seen beyond the area of arterial occlusion, but not in most of the vascular bed distal to it (*TIMI1*) or if a more robust, but incomplete, flow signal was seen beyond the occlusion site and the distal vascular bed (*TIMI2*); and completely recanalized if a flow signal of normal intensity was detected on MRA/CTA (*TIMI3*).[11] Five patients had transcranial Doppler (TCD) studies within 72 hours after tPA. Insonation of the intracranial vessels was obtained as described by Aaslid et al.[13] An experienced ultrasonographer used the parameters described by Demchuk et al[14] for the grading of a normal, narrowed, or occluded vessel.

Assessment of Degree of Functional and Neurological Recovery

We determined neurological improvement, defined as a decrease of ≥4 points in the NIHSS within 72 hours after tPA compared with the baseline NIHSS. We allocated patients on discharge to 1 of 4 categories: patients returned home with or without services, transferred to an acute rehabilitation facility, transferred to a chronic care facility, or died in-house. In addition, mRS scores were collected on discharge and at 30 to 45 days.

Statistical Analysis

Patients were divided into 2 groups based on their sex. Data are summarized as mean±SD or percentages, as appropriate. Statistical significance for intergroup differences was assessed by Student t test for continuous variables and Fisher exact test for categorical comparisons. $P<0.05$ was regarded significant.

Results

Patient Characteristics (Demographic and Clinical Features)

Thirty-nine patients met all inclusion/exclusion criteria: 17 women (44%) and 22 men (56%) were treated with IV tPA within 6 hours of a stroke secondary to a documented stenosis or occlusion of the ICA plus MCA or the MCA alone. Table 1 lists demographics and clinical features. There were no significant differences between men and women in any of these variables. The majority of our patients were whites and had a higher median age (73 years) compared with NINDS, ATLANTIS, and ECASS II trials' cohorts. Only 1 woman was using HRT before stroke onset. A lower percentage of women were using antiplatelets and statins, compared with men, at the time of stroke onset. These differences were not significant. All patients who were using warfarin at stroke onset had a subtherapeutic international normalization ratio (INR). Two women (12%) and 3 men (14%) were started on intravenous heparin before their repeat vascular imaging.

Table 2 summarizes imaging findings, stroke mechanism, NIHSS, and symptom-to-needle time. There were no significant differences in any of these variables. Thirty-seven patients (16 women and 21 men) had MRI/MRA and 2 patients (1 man and 1 woman) had CT/CTA at baseline. Five patients (2 women, 3 men) had TCD after treatment with tPA. The mean time from tPA administration-to-repeat vascular study was 36±20 hours in women and 27±18 hours in men (P=0.14, t-test).

Outcomes

The recanalization rate for MCA and ICA/MCA occlusive lesions was 94% (59% complete; 35% partial) in women

TABLE 1.   Demographics and Baseline Clinical Features

	Women (n=17)	Men (n=22)	P
Age, mean±SD	71±18	75±11	0.36
Race, % white	88	95	0.57
Hypertension	76	68	0.72
Diabetes	6	18	0.36
Hyperlipidemia	41	59	0.34
Tobacco	24	23	0.62
CAD	29	54	0.19
Atrial fibrillation	29	27	1.00
Admission BP, mm Hg	157±49	154±58	0.95
SBP, mean±SD	77±24	80±15	0.94
DBP, mean±SD			
Admission HCT, %	38±4	40±10	0.09
Admission glucose, mg/dL	115±22	116±26	0.84
Admission PT, sec	12.6±1.2	13.4±1.3	0.08
PTT, sec	25.3±2.8	24.3±2.7	0.32
Medications			
Beta blockers, %	24	32	0.72
ACE inhibitors, %	10	6	0.57
HRT, %	6	N/A	0.43
Antiplatelets, %	18	31	0.46
Warfarin, %	18	14	1.00
Statins, %	12	23	0.44

ACE indicates angiotensin-converting enzyme; BP, blood pressure; CAD, coronary artery disease; DBP, diastolic blood pressure; HCT, hematocrit; HRT, hormone replacement therapy; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 2.   Radiological Data, Stroke Mechanisms, and Time Parameters

	Women	Men	P
Baseline NIHSS, mean±SD	15±4	17±6	0.21
Vessel Occlusion			
MCA (M1 or M2)	70%	59%	0.52
ICA/MCA	30%	41%	0.52
Stroke Subtype*			
Cardioembolic	71%	73%	1.00
Large artery	18%	27%	0.7
Other	6%	0%	0.18
Undetermined	6%	0%	0.18
Symptom-to-needle time (min), mean±SD	211±84	185±63	0.33
Initial infarct (DWI) volume, cm^3	34.7±55.4	32.4±52.8	0.8
Follow-up DWI volume	44.3±61.6	62.2±92.4	0.4

*Note that lacunar strokes were excluded.

versus 59% (36% complete; 23% partial) in men (*P*=0.02, Fisher exact test). This gender difference in recanalization remained statistically significant even after excluding patients whose strokes were attributed to ICA/MCA occlusive lesions (5 women and 9 men). The recanalization rate in women with isolated MCA occlusive lesions was 100% (67% complete; 33% partial) versus 61% (54% complete; 7% partial) in men (*P*=0.02). Table 3 lists the degrees of recanalization according to TIMI grades.

Results were similar when the analysis was limited to the subgroup of patients who received tPA within 3 hours from stroke onset (11 women and 15 men). The overall recanalization rate was 100% in women (TIMI3=64%; TIMI2=27%; TIMI1=9%) versus 60% in men (TIMI3=40%; TIMI2=20%; *P*=0.02). Again, the difference in recanalization remained statistically significant after excluding patients whose strokes were attributed to ICA/MCA occlusive lesions (2 women and 6 men), in which 100% of women recanalized versus 55% of men (*P*=0.03).

Twelve women (71%) and 17 men (77%) had their vascular imaging repeated within 24 hours of tPA administration. In this subgroup, the recanalization rate for MCA and ICA/MCA occlusive lesions was also 100% in women (TIMI3=60%; TIMI2=20%; TIMI1=20%) versus 55% in men (TIMI3=33%; TIMI2=22%; TIMI0=45%; *P*=0.01).

As Table 2 indicates, there were no significant differences in mean baseline DWI lesion volumes between women and

TABLE 3.   Recanalization Status According to TIMI Grades

	MCA+ICA/MCA Occlusion		Isolated MCA Occlusions	
	Women	Men	Women	Men
TIMI Grade	n=17	n=22	n=12	n=13
TIMI3	10 (59%)	8 (36%)	8 (67%)	7 (54%)
TIMI2	4 (23%)	4 (18%)	3 (25%)	1 (8%)
TIMI1	2 (12)	1 (5%)	1 (8%)	0
TIMI0	1 (6%)	9 (41%)	0	5 (38%)

men. Women had smaller lesion volumes on scans after tPA, but this difference was not statistically significant.

Seventy percent of women (12/17) showed neurological improvement, defined as a decrease of ≥4 points on NIHSS within 72 hours of treatment with tPA, compared with 36% (8/22) of men (*P*=0.04). The mean LOH for women was 7±3 days (range 3 to 17) versus 7±4 days (range 3 to 21) for men (*P*=0.9, *t*-test). Forty-one percent of women versus 27% of men were discharged home (*P*=0.5), whereas more men died in hospital (27% versus12%; *P*=0.4). With regard to patients' functional outcome, 65% of women and 36% of men had a mRS ≤2 (*P*=0.05) on discharge. Seven patients (3 women and 4 men) were lost to follow-up after discharge. Among the remaining subjects, 67% of women versus 43% of men (*P*=0.3) had a comparable mRS at 30 to 45 days.

Discussion

In this cohort of stroke patients, arterial recanalization after IV tPA for anterior circulation strokes was more frequent among women than men despite comparable age, blood pressure, symptom-to-needle time, and stroke mechanism. In addition, neurological improvement within 72 hours of treatment occurred significantly more frequently in women.

Several anatomical, pathophysiological, and biochemical factors could potentially account for the observed difference in response to tPA between sexes. The site and mechanism of vascular occlusion may influence the response to thrombolytic therapy. Fibrin-rich embolic occlusions, often seen with cardioembolism, are thought to recanalize more often than platelet-rich thromboses on pre-existing atherosclerotic lesions.[15–16] An approximately equal percentage of women and men in the present study had cardioembolic strokes according to TOAST classification.[17]

We have previously shown that stroke patients with isolated MCA occlusions have a higher rate of recanalization after IV tPA compared with patients who had ICA/MCA occlusions.[10] Although a higher percentage of men than women had ICA/MCA occlusions in the present study, the gender-based differential response to tPA remained statistically significant even after excluding patients whose strokes were attributed to ICA occlusive lesions.

Variations in blood pressure and viscosity can cause physiological and hemodynamic changes, which might impact clot formation and/or recanalization. High BP may facilitate the passage of clots and reperfusion. In contrast, hyperglycemia and hyperchromia might increase blood viscosity, facilitating clot formation and impeding recanalization. We found no difference in admission blood pressure, glucose, or basic coagulation parameters between sexes, suggesting that the observed difference in recanalization was not related to these variables. There was a nonsignificant trend toward a lower hematocrit level in women. This could have facilitated the effects of thrombolysis. There was an equal incidence of tobacco use in both genders. This is noteworthy because smoking increases fibrinogen levels and platelets aggregation, resulting in a relatively hypercoagulable state.[18]

Positive interactions between medications could have augmented the thrombolytic effects of tPA in some of our

patients. Cardiac studies have shown that concomitant use of antithrombotics with IV tPA leads to higher coronary patency rates.[19,20] We found no significant differences in the percentage of patients using various antihypertensives including angiotensin-converting enzyme inhibitors, statins, antiplatelets, or anticoagulants at the time of tPA administration. We also excluded patients who had endovascular interventions including intra-arterial tPA or received other experimental stroke therapies from our study. This indicates that the observed gender difference in recanalization after tPA is unlikely to be related to other concomitant treatments.

Estrogen status can alter the balance between coagulation and fibrinolysis. Gebara et al[21] found that premenopausal women with high estrogen status and postmenopausal women using HRT had lower levels of plasminogen activator inhibitor (PAI-1) antigen and thus greater fibrinolytic potential, compared with patients with low estrogen status such as men and postmenopausal women not using HRT. Similarly, the Atherosclerosis Risk in Communities study showed that the levels of PAI-1 antigen were lower in current users of HRT than in nonusers.[22] Eighty-two percent of women in our study were postmenopausal, and only one was using HRT. Therefore, the potential influence of estrogen on the fibrinolytic status of our patients was limited.

The gender-based differential response to tPA could be attributed to enhanced endogenous fibrinolytic activity in women compared with men. Differences between sexes in biomarkers of coagulation and fibrinolysis have been reported in patients with acute stroke and cardiovascular disorders. Regulation of endogenous fibrinolysis involves multiple complex interactions.[23–25] Some evidence suggests that the effectiveness of IV tPA for acute stroke is enhanced in patients who have the apolipoprotein (apo) E2 phenotype.[26] There is a gender difference in the effects of apoE2 polymorphism on plasma levels of lipoprotein A, which are higher in women with apoE2 than in men.[27] Future studies are required to elucidate the biochemical mechanisms underlying higher recanalization rates after tPA in women.

Our study has limitations imposed by its small sample size and retrospective nature. Earlier angiographic studies reported a recanalization rate of 25% to 66% within 24 hours of IV tPA treatment for carotid artery territory stroke.[28,29] More recent studies using MRA[11] and TCD[5] reported that recanalization occurred within 48 hours in 70% to 92% of patients treated with IV tPA. Although the overall recanalization rate in our study (74%) is more or less in line with these studies, we acknowledge that our small sample size may have led us to overestimate the rate of recanalization. Similarly, the assessment of recanalization up to 72 hours may have led us to overestimate the true rate of thrombolysis-induced recanalization. Spontaneous arterial recanalization has been reported in ≈32% of patients during the first 24 hours after onset of anterior circulation stroke, increasing up to 50% by the fourth day.[30] The impact of spontaneous recanalization as a confounding variable is likely minimal because 29 of our 39 patients were re-evaluated for recanalization within the first 24 hours after tPA administration, and the observed gender-based differential response to tPA remained statistically significant when the analysis was limited to these patients.

There are technical differences between MRA, CTA, and TCD, which could potentially influence assessment of recanalization and its degree. The impact of these various modalities on our results is unclear.

Neurological improvement within 72 hours of treatment was significantly more frequent in women compared with men, and more women had a favorable outcome on discharge. However, we did not find a significant difference in functional outcome at 30 to 45 days. One explanation is that most women recovered significantly before discharge as opposed to men who recovered more slowly. Although LOH did not differ between men and women, LOH depends on several factors unrelated to clinical conditions such as insurance and family preference. Overall, there was less DWI lesion growth in women than men and a nonsignificant trend toward smaller infarct volumes after treatment in women, despite approximately equal initial infarct volumes between the sexes. The lack of consistent results regarding clinical outcome measures is possibly a result of our small sample size.

In conclusion, we found that arterial occlusive lesions were more likely to recanalize in women than in men after IV tPA for acute stroke in this small cohort of patients. The role of gender on the effects of IV tPA may have important therapeutic implications. Gender may be an important variable in the decision to pursue more aggressive thrombolytic approaches such as combining IV with IA tPA or mechanical clot retrieval in men. Our findings are preliminary and need to be validated in larger-scale, prospective, controlled studies.

References

1. Tissue plasminogen activator for acute ischemic stroke. The NINDS rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581–1587.
2. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke. Second European-Australasian Acute Stroke Study Investigators. *Lancet.* 1998;352:1245–1251.
3. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Alteplase for ischemic stroke 3 to 5 hours after symptom-onset. The ATLANTIS Study: a randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. *JAMA.* 1999;282:2019–2026.
4. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke. A pooled analysis of randomized clinical trials. *Stroke.* 2005;36:62–65.
5. Molina CA, Montaner J, Abilleira S, Arenillas JF, Ribo M, Huertas R, Romero F, Alvarez-Sabin J. Time course of tissue plasminogen activator-induced recanalization in acute cardioembolic stroke: a case-control study. *Stroke.* 2001;32:2821–2827.
6. Felberg RA, Okon NJ, El-Mitwalli A, Burgin WS, Grotta JC, Alexandrov AV. Early dramatic recovery during intravenous t-PA infusion: clinical pattern and outcome in acute middle cerebral artery stroke. *Stroke.* 2002; 33:1301–1307.
7. Kain K, Catto AJ, Carter AM, Young J, Bamford J, Bavington J, Grant PJ. Decreased fibrinolytic potential in South Asian women with ischaemic cerebrovascular disease. *Br J Haematol.* 2001;114:155–161.

8. Kain K, Carter AM, Bamford JM, Grant PJ, Catto AJ. Gender differences in coagulation and fibrinolysis in white subjects with acute ischemic stroke. *J Thromb Haemost*. 2003;1:390–392.

9. Schlaug G, Benfield A, Baird AE, Siewert B, Lovblad KO, Parker RA, Edelman RR, Warach S. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. *Neurology*. 1999;53:1528–1537.

10. Linfante I, Llinas RH, Selim M, Chaves C, Kumar S, Parker RA, Caplan LR, Schlaug G. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous t-PA. *Stroke*. 2002;33:2066–2071.

11. Neumann-Haefelin T, du Mesnil de Rochemont R, Fiebach JB, Gass A, Nolte C, Kucinski T, Rother J, Siebler M, Singer OC, Szabo K, Villringer A, Schellinger PD; Kompetenznetz Schlaganfall Study Group. Effect of incomplete (spontaneous and postthrombolytic) recanalization after middle cerebral artery occlusion: a magnetic resonance imaging study. *Stroke*. 2004;35:109–114.

12. The Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I findings: TIMI Study group. *N Engl J Med*. 1985;312:932–936.

13. Aaslid R, Markwalder TM, Nornes H. Noninvasive TCD recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57:769–774.

14. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, Alexandrov AV. Specific TCD flow findings related to the presence and site of arterial occlusion. *Stroke*. 2000;31:140–146.

15. Niessen F, Hilger T, Hoehn M, Hossmann KA. Differences in clot preparation determine outcome of rt-PA treatment in experimental thromboembolic stroke. *Stroke*. 2003;34:2019–2024.

16. Zivin JA, Fisher M, DeGirolami U, Hemenway CC, Stashak JA. Tissue plasminogen activator reduces neurological damage after cerebral embolism. *Science*. 1985;230:1289–1292.

17. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. 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.

18. Ernst E. Fibrinogen: its emerging role as a cardiovascular risk factor. *Angiology*. 1994;45:87–93.

19. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with t-PA for acute myocardial infarction. Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med*. 1990;323:1433–1437.

20. Willerson JT, Golino P, McNatt J, Eidt J, Yao SK, Buja LM. Role of new antiplatelet agents as adjunctive therapies in thrombolysis. *Am J Cardiol*. 1991;67:12A–18A.

21. Gebara OC, Mittleman MA, Sutherland P, Lipinska I, Matheney T, Xu P, Welty FK, Wilson PW, Levy D, Muller JE, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation*. 1995;91:1952–1958.

22. Shahar E, Folsom AR, Salomaa VV, Stinson VL, McGovern PG, Shimakawa T, Chambless LE, Wu KK. Relation of hormone-replacement therapy to measures of plasma fibrinolytic activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation*. 1996;93: 1970–1975.

23. Nordenhem A, Wiman B. Tissue plasminogen activator antigen in plasma: correlation with different tPA/inhibitor complexes. *Scand J Clin Lab Invest*. 1998;58:475–483.

24. Kooistra T, Schrauwen Y, Arts J, Emeis JJ. Regulation of endothelial cell t-PA synthesis and release. *Int J Hematol*. 1994;59:233–255.

25. Pradhan AD, LaCroix AZ, Langer RD, Trevisan M, Lewis CE, Hsia JA, Oberman A, Kotchen JM, Ridker PM. Tissue plasminogen activator antigen and D-dimer as markers for atherothrombotic risk among healthy postmenopausal women. *Circulation*. 2004;110:292–300.

26. Broderick J, Lu M, Jackson C, Pancioli A, Tilley BC, Fagan SC, Kothari R, Levine SR, Marler JR, Lyden PD, Haley EC Jr, Brott T, Grotta JC. Apolipoprotein E phenotype and the efficacy of intravenous t-PA in acute ischemic stroke. *Ann Neurol*. 2001;49:736–744.

27. Horita K, Eto M, Saito M, Nakata H, Iwashima Y, Ito H, Takahashi M, Kondo A, Morikawa A, Makino I. Effects of apolipoprotein E polymorphism on plasma lipoprotein(a) levels. *Artery*. 1993;20:324–336.

28. Rother J, Schellinger PD, Gass A, Siebler M, Villringer A, Fiebach JB, Fiehler J, Jansen O, Kucinski T, Schoder V, Szabo K, Junge-Hulsing GJ, Hennerici M, Zeumer H, Sartor K, Weiller C, Hacke W; Kompetenznetzwerk Schlaganfall Study Group. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke*. 2002;33:2438–2445.

29. Nighoghossian N, Hermier M, Adeleine P, Derex L, Dugor JF, Philippeau F, Ylmaz H, Honnorat J, Dardel P, Berthezene Y, Froment JC, Trouillas P. Baseline magnetic resonance imaging parameters and stroke outcome in patients treated by intravenous t-PA. *Stroke*. 2003;34:458–463.

30. Kassem-Moussa H, Graffagnino C. Nonocclusion and spontaneous recanalization rates in acute ischemic stroke: a review of cerebral angiography studies. *Arch Neurol*. 2002;59:1870–1873.