Effect of Age on Arterial Recanalization and Clinical Outcome in Thrombolyzed Acute Ischemic Stroke in CLOTBUST Cohort

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Abstract

Background and Aims: Despite the evidence from randomized clinical trials, the effectiveness of intravenous tissue recombinant plasminogen activator (IV-tPA) for elderly patients ($\geq$80 yrs) with acute ischemic stroke (AIS) is often an important consideration in clinical practice. We evaluated the effect of older age on arterial recanalization, timing of recanalization and outcome in thrombolysed AIS patients. **Methods:** Consecutive AIS patients treated with IV-tPA and transcranial Doppler (TCD) examination within 3 hours of symptom-onset were included. Thrombolysis in Brain Ischemia (TIBI) flow-grading system was used to interpret TCD findings of persistent occlusion, re-occlusion and complete recanalization within 2 hours of IV-tPA bolus. Poor functional outcome was defined by modified Rankin score of 3 or more. Univariate and multiple logistic regression analyses were performed to assess the effect of age on clinical and TCD outcome measures. **Results:** The study included 361 patients (elderly = 85, <80 yrs = 276). Median age was 68 years (range 18-91 years). Compared to the elderly, younger patients (<80 years) were more females (63.5% versus 41.3%), had higher baseline National Institute of Health Stroke Scale score (17.5 versus 16.0 points) and shorter time from symptom-onset to IV-tPA bolus (median 136.6 versus 139.7 minutes). No significant differences were noted between the site of arterial occlusion, TCD outcome measures or time of complete recanalization between the 2 groups. More patients aged < 80 years achieved good functional outcome (51.9% versus 31.8% in the older age group; *P* = 0.004). IV-tPA induced recanalization and symptomatic intracranial hemorrhage were similar in the 2 groups. Multivariate logistic regression showed elderly age as an independent predictor of poor outcome (adjusted OR 2.5, 95%CI 1.26-4.95; *P* = 0.008). **Conclusion:** Elderly AIS patients achieve relatively poor functional outcome after IV-tPA despite similar rates of arterial recanalization. However, there is no increase in the hemorrhagic risk. Perhaps, decision for IV thrombolysis in elderly patients should be made cautiously.

Keywords: Ischemic stroke, old age, recanalization, thrombolysis, transcranial Doppler

Introduction

World's population is aging rapidly, both in developing and the developed countries. Similar pattern is noted in the proportion of persons aged 80 years or more. Accordingly, a recent report by United Nations showed that the proportion of patients aged more than 80 years increased from 7% in 1950 to 14% in 2013.[1]

Age remains an important risk factor for ischemic stroke (IS). After the age of 55 years, stroke rates double for each successive 10 years. Importantly, 30% of IS occur in patients aged $\geq$80 years.[2,3] In the Rotterdam study, the incidence of stroke in elderly men ranged from 1.7 (95% CI 0.4-0.6) per 1000 persons in the age group 55-59 years to 69.8 (95% CI 22.5-216.6) in the age group 95 years and above.[4] Despite the increased incidence of stroke with advancing age, initial clinical trials on stroke thrombolysis excluded or under-recruited patients older than 80 years of age.[5]

Intravenously administered tissue plasminogen activator (IV-tPA) remains the only approved drug treatment for acute IS in the 3-hour window (in the US), with the number needed to treat of 8 to reverse 1 stroke completely at 3 months.[6] However, the effectiveness of IV-tPA in elderly acute IS patients ($\geq$80 yrs)

is often an important consideration in clinical practice. The main concern for IV-tPA use in elderly patients is the safety as well as the uncertainty about efficacy despite clinical trials. Heuschmann *et al.* found that patients above 75 years of age were at more than double risk of intracranial bleeding compared to patients aged less than 55 years (10.3% versus 4.9%).[7] On the contrary, Bates *et al.* reported similar outcomes and no increase in hemorrhage in patients aged more than 80 years as compared to the younger patients treated with IV-tPA for acute IS.[8] Furthermore, a subgroup analysis of National Institute

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of Neurological Disorders and Stroke (NINDS) tPA stroke trial did not find a significant influence of age on the risk of intracranial hemorrhage.[9]

Intracranial arterial recanalization induced by IV-tPA is an important determinant of functional recovery in acute IS. However, it has been evaluated in very few previous studies. Transcranial Doppler (TCD) is an excellent bedside monitoring tool that enables non-invasive continuous monitoring of the arterial patency during intravenous thrombolysis.[10] TCD can quickly detect the presence of an occlusion[11] as well as recanalization, if it occurs.[12-15] In addition, continuous TCD monitoring may safely augment tPA induced arterial recanalization with a trend toward an increased rate of functional recovery.[16] We evaluated whether age affects the recanalization rate, symptomatic intracranial hemorrhage (SICH) and functional outcome in the CLOTBUST extended database.

METHODS

This is a retrospective study of consecutive patients who presented with acute stroke in a less than 3-hour window in four major stroke centers in North America and Europe from 2000 to 2003. Patients received standard intravenous rt-PA therapy (0.9 mg/kg dose, maximum 90 mg, 10% bolus, 90% continuous infusion) which was initiated within the first 3 hours after symptom onset according to the NINDS protocol.[6] Patients enrolled in clinical trials of ultrasound enhanced intravenous rt-PA thrombolysis were included into this analysis as well as those treated in a 3-6 hour window using ethics committee approved protocols.[16]

Except for the upper age limit, inclusion and exclusion criteria were according to the NINDS trial protocol.[6] The decision of treating physicians for the administration of intravenous t-PA was not based on the ultrasound findings. Patients with no occlusion on TCD or no temporal window were excluded from our study population.

Additional inclusion criterion for this study was the demonstration of proximal arterial occlusion by TCD, which included the M1 and M2 segments of middle cerebral artery (MCA), terminal internal carotid artery (TICA), tandem lesions of ICA and MCA, posterior cerebral artery (PCA), vertebral artery (VA) and basilar artery (BA) according to criteria previously validated by our group.[17,18] Our TCD criteria for proximal MCA occlusion had 91% sensitivity and 98% specificity, when compared with contrast angiography. Patients with no occlusion on TCD (considered as lacunar strokes) were excluded from the study.

Before IV-tPA bolus, an experienced sonographer, credentialed by the American Society of Neuroimaging and TCD Flow Grading Examination (Health Outcomes Institute, 2000), identified the residual flow signals at the presumed thrombus location using the Thrombolysis in Brain Ischemia (TIBI) flow-grading system.[11] The 2-MHz TCD transducer was

positioned at a constant angle of insonation with a standard head frame (Marc series; Spencer Technologies) and used for continuous monitoring for 2 hours. The depth with the worst residual TIBI flow signal was selected for continuous TCD monitoring (starting before tPA bolus and lasting up to 2 hours) or intermittent evaluation every 10-20 minutes, according to the previously published Institutional Review Board-approved protocol.[16]

TCD waveforms were interpreted from the real-time display at the bedside. TCD findings during the monitoring were defined as persistent arterial occlusion, partial recanalization and complete recanalization. Arterial recanalization on TCD was determined using previously validated criteria.[15] Recanalization on TCD was graded as 'complete', 'partial' or 'none', according to the TIBI criteria. Briefly, complete recanalization was diagnosed when a normal waveform with low-resistance stenotic signal appeared at the selected depth of insonation (TIBI 4 or 5). These flow findings correlate with unobstructed passage of contrast agent on angiography.[15] Partial recanalization was diagnosed if the abnormal signals (high resistance dampened signals or flattening of the systolic upstroke with "blunted" waveform) were seen (TIBI 2 or 3). No change in the abnormal flow signals indicated absence of recanalization or persistent occlusion (TIBI 0 or 1).

Standard monitoring of vital signs (blood pressure, pulse oximetry and heart rhythm) was performed during intravenous thrombolysis. National Institute of Health Stroke Scale (NIHSS) was assessed at baseline and during the first 2 hours. This was performed by the treating neurologist who was not directly involved in TCD monitoring. All neurologists who performed serial neurological examinations in the emergency room were certified in the NIHSS scoring. The NIHSS scores were reassessed at 24 hours.

Patients were divided into 2 groups, based on age (<80 versus ≥80 years old or the elderly group). Various baseline characteristic (gender, baseline NIHSS, blood glucose, systolic blood pressure, time from symptom-onset to IV-tPA treatment and time of recanalization) were recorded in both age groups. Outcome measures included recanalization status and time of recanalization on TCD, SICH (defined by appearance of blood on the computerized tomography (CT) scan and ≥ 4 NIHSS points worsening within first 3 days). Modified Rankin Scale (MRS) was used to define the functional recovery at 3 months, assessed by a neurologist who was not aware of TCD findings. Poor functional outcome was defined as MRS scores of ≥3.[18]

Statistical analyses

The analysis was performed with SPSS 21.0 software (SPSS Inc). Univariate analysis was performed by using two-sample Student's t-tests, Pearson Chi-square test, and Fisher exact test whenever appropriate. Non-parametric test (Mann Whitney) was used for analyzing time to recanalization. Multivariable logistic regression analyses were carried out to assess the predictors of poor outcome (with their odds ratios and confidence intervals), SICH and complete recanalization,

after controlling for common stroke risk factors (age, sex, SBP, onset-to-IV- tPA time, baseline NIHSS, diabetes mellitus and sonothrombolysis. A level of $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 361 patients were included in the study. While 85 (23.5%) patients were ≥80 years old, 276 (76.6%) patients were <80 years of age. Baseline characteristic of the study population are shown in Table 1. Briefly, the median age (SD) of the study population was 68 (range 18-91) years. The elderly group had a higher proportion of females (63.5% versus 41.3% in the age group <80 years). Median (range) baseline NIHSS was 17 (10-31) points among the elderly group and 16 (9-33) in <80 years group. The median time from symptom-onset-to-IV-tPA in elderly group was 145 (range 82-180) minutes and 139 (range 78-180) minutes in patients <80 years of age ($P = 0.079$). Cardioembolism was the underlying stroke mechanism in 45 patients (52.9%) in elderly and 125 patients (45.5%) in <80 years.

Baseline TCD revealed occlusion of the proximal M1 MCA in 48 patients (56.5%) in the elderly group and 128 patients (46.4%) in <80 years age group, tandem ICA/ MCA occlusion in 7 patients (8.2%) in elderly group and 54 patients (19.6%) in <80 years age group. Based on TCD flow findings at the end of 2 hours after IV-tPA bolus, persistent occlusion was noted in 55 (64.7%), reocclusion in 12 (14.1%) and complete recanalization in 18 (21.2%) patients in the elderly group as compared to 156 (56.5%), 41 (14.9%) and 79 (28.6%) patients, respectively ($P = 0.348$). Median time for re-occlusion of the index artery was 98 minutes (range 71-118 minutes).

There was no difference in the time of recanalization (from IV-tPA bolus) in the elderly age group (median 22 minutes; range 16-84 minutes) as compared to the patients aged <80 years (median 20 minutes; range 16-78 minutes; $P = 0.146$). Patients with <80 years age group were further dichotomized into <56 years (n = 62) and 56-79 years (n = 214), to evaluate whether there was any difference in the timing of recanalization from symptom-onset. Interestingly, the mean (SD) or median (range) time of recanalization (from symptom-onset) among patients aged <50 years was longer [153.9 ± 82 minutes and 112 (94-168) minutes, respectively; $P = 0.076$] as compared to the patients aged 56-79 years [121.6 ± 64 minutes and 101 (94-148) minutes, respectively; $P = 0.068$] [Figure 1]. Real time TCD monitoring

Table 1: Baseline characteristics of the study population (*n*=361)			
Factors	Age ≥80 yrs (*n*=85)	Age <80 yrs (*n*=276)	*p*
Gender			<0.001
Male	31 (36.5%)	162 (58.7%)	
Female	54 (63.5%)	114 (41.3%)	
Median NIHSS at presentation (range)	17 (10-31)	16 (9-33)	0.574
Median Time to IV-tPA bolus in minutes (range)	145 (82-180)	139 (78-180	0.079
Median Time to recanalization after tPA bolus in minutes (range)	22 (16-84)	20 (16-78)	0.146
Mean CT ASPECT (SD)	8.6±1.6	8.4±1.8	0.667
Median Pre-tPA systolic blood pressure in mm Hg (range)	156 (117-178)	159 (124-180)	0.738
Median blood Glucose in mg/dL (range)	126 (92-284)	144 (78-276)	0.061
Symptomatic intracranial hemorrhage- *n* (%)	6 (7.1%)	22 (8%)	0.783
TOAST classification			0.045
Large artery atherosclerosis	18 (21.2%)	73 (26.5%)	
Cardioembolism	45 (52.9%)	125 (45.5%)	
Small artery disease	3 (3.5%)	1 (0.4%)	
Stroke of other determined etiology	0 (0%)	7 (2.5%)	
Stroke of undetermined etiology	19 (22.4%)	69 (25.1%)	
Site of intracranial occlusion- *n* (%)			0.072
M1 MCA	48 (56.5%)	128 (46.4%)	
M2 MCA	22 (25.9%)	76 (27.5%)	
Terminal ICA	7 (8.2%)	9 (3.3%)	
Tandem (ICA/MCA)	7 (8.2%)	54 (19.6%)	
BA	1 (1.2%)	4 (1.4%)	
PCA/VA	0 (0%)	3 (1.1%)	
ACA	0 (0%)	2 (0.7%)	
TCD flow finding at 2-hrs after IV-tPA bolus- *n* (%)			0.348
Persistent occlusion	55 (64.7%)	156 (56.5%)	
Re-occlusion	12 (14.1%)	41 (14.9%)	
Complete recanalization	18 (21.2%)	79 (28.6%)	

ACA- anterior cerebral artery; BA- basilar artery; ICA- internal carotid artery; MCA-middle cerebral artery; PCA- posterior cerebral artery; VA- vertebral artery

findings of partial and complete recanalization in 2 patients during IV thrombolysis are shown in Figure 2.

Poor functional outcome (MRS ≥3) at 3 months was noted in 45 (68.2%) in elderly patients as compared to 112 (48.1%) in <80 years age group (*P* = 0.004). The incidence of SICH was similar in both groups.

After adjustment of gender, stroke severity, baseline Glucose, time to tPA treatment and systolic blood pressure, elderly patient had higher chances of poor functional outcome (adjusted OR 2.5, 95% CI 1.3-4.9; *P* = 0.008) [Table 2] despite similar rates of complete recanalization (adjusted OR 0.74, 95% CI 0.4-1.4, *P* = 0.34). [Table 3].

Table 2: Multiple logistic regression for independent predictors of poor outcome (mRS 3 or more)

Factors	Adjusted Odds ratio	95% CI for Adjusted Odds ratio	*P*
Age ≥80 yrs	2.501	1.264-4.951	0.008
Gender	0.969	0.56-1.660	0.909
Systolic blood pressure	1.013	1.001-1.025	0.038
Baseline glucose	1.005	1.001-1.009	0.016
Baseline NIHSS	1.184	1.119-1.253	<0.001
Stroke onset-to-tPA bolus time	1.009	1.001-1.017	0.023

Table 3: Multiple logistic regression for independent predictors of complete recanalization

Factors	Adjusted Odds ratio	95% CI for Adjusted Odds ratio	*P*
Age ≥80 yrs	0.743	0.402-1.373	0.343
Gender	1.034	0.627-1.704	0.896
Systolic blood pressure	0.981	0.970-0.993	0.001
Baseline glucose	0.993	0.989-0.998	0.004
Baseline NIHSS	0.909	0.867-0.952	0.000
Stroke onset-to-tPA bolus time	1.005	0.998-1.012	0.148

DISCUSSION

Our study showed that elderly patients have similar rates of arterial recanalization with intravenous thrombolysis with tPA. However, the functional outcomes were relatively poorer among the elderly acute IS patients.

Our study provides information on recanalization rate and timing of recanalization in elderly patients compared to patients <80 years. Rates of complete recanalization as well as the timing of recanalization after IV-tPA bolus were similar in both age groups. We believe that the observed higher rates of poor outcome were related to the higher prevalence of cardiovascular risk factors, especially atrial fibrillation and hypertension.[19-21]

The primary aim of thrombolysis in acute IS is recanalization of an occluded intracranial artery, which is an important predictor of stroke outcome as timely restoration of regional cerebral perfusion helps salvage threatened ischemic tissue. Mainly due to logistic reasons, very few clinical trials have monitored recanalization rates during or at completion of intravenous thrombolysis. Data regarding recanalization rates, modality of imaging and outcomes from some of the major trials is presented in Table 4.[22-26] Short therapeutic window, low rates of recanalization and only modest benefits with IV-tPA have prompted a quest for alternative approaches to restore blood flow in an occluded artery in acute ischemic stroke. As a result, endovascular clot retrieval evolved as a very effective treatment for achieving arterial recanalization and improving functional outcomes, both as a bridging treatment for patients failing to respond to IV-tPA as well as a stand-alone treatment for patients with acute IS.[27]

SICH remains a dreaded complication after intravenous thrombolysis for acute IS and an important determinant of poor functional outcomes in thrombolysed acute IS patients. However, we did not observe any increased SICH among our elderly stroke cohort. A previous smaller observational study showed that SICH increased with age from 4.9% in patients <55 years to 10.3% in patients aged ≥75 years.[7] In
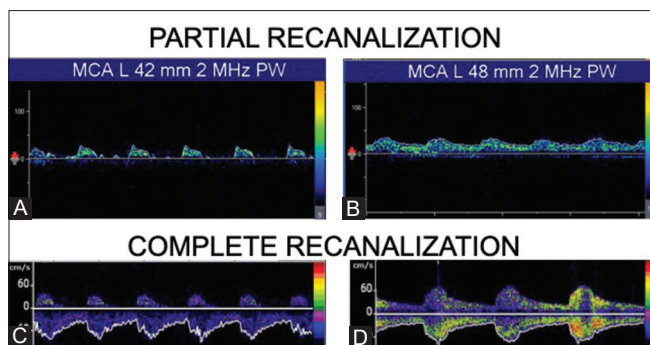
Table 4: Rates of arterial recanalization with intravenous thrombolysis, imaging modality and outcomes in some of major clinical trials

TRIAL	Treatment	Number of patients	Highest reported recanalization rate (%)	Assessment method	SICH %	mRS ≥3 *n* (%)
CLOTBUST[16]	IV-tPA+TCD	63	38		3.8	49
	IV-tPA	63	13	TCD		
TRUMBI[22]	IV-tPA+Ultrasound	14	29.3		35.7	72
	IV-tPA	12	50.0	MRA	0	60
DEFINITY[23]	IV-tPA+TCD+microbubbles	12	83.3 (complete=50 Partial=33.3)	TCD	0	60 (data for only 5 subjects)
TUCSON active arm[24]	IV-tPA+TCD+microspheres	23	65.2 (complete=56 Partial=9.2)	TCD	13	26
DIAS[25] (3-9 hours) Active arm	IV-Desmoteplase	75	49	MRA-complete or partial recanalization	12	61
DIAS 4 active arm[26]	IV-Desmoteplase	135	52.1	CTA/MRA	4.8	59

Figure 1: Longitudinal changes in transcranial Doppler (TCD) spectra during intravenous thrombolysis. A 54 years old Indian man presented with right-sided weakness and aphasia of sudden-onset (NIHSS score 19 points). Intravenous tissue plasminogen activator (tPA) bolus was injected at 154 minutes after symptom-onset. Pre-tPA bolus TCD (panel A) showed high resistance minimal flow (TIBI grade 1) signals in the proximal left middle cerebral artery (MCA). At 26 minutes, TIBI flow signals improved to grade 2 (panel B- note the blunted systolic upstroke), which was accompanied by clinical improvement (NIHSS 7 points). TIBI 2 flow spectra persisted (partial recanalization) during the thromolytic infusion. Panel C shows the flow signals from right MCA in a 46 years old Chinese man who presented with left sided weakness for 120 minutes. Note high resistance flow signals (TIBI 1) above the baseline from proximal MCA and high flow signals from ipsilateral anterior cerebral artery (showing flow diversion). At 22 minutes after IV-tPA bolus, the flow signals in right MCA improved to normal flow (TIBI 5 in panel D), consistent with complete recanalization. This was accompanied by rapid clinical recovery (NIHSS decreased to 2 points)

our study, SICH in the elderly age group was seen in 7.1% patients and 8% in the younger age group. This observation is in accordance with the Canadian Alteplase for Stroke Effectiveness Study (CASES) study, which had a large sample size (4.4% in ≥80 yrs versus 4.6% in <80 yrs).[28] Our finding are similar to a previous study of IV and/or IA thrombolysis for acute IS, which did not find any difference in SICH in elderly patients (12.8%) compared to patients <80 years (10.4%).[21]

Elderly patients with acute IS have a higher in-hospital morbidity as well as 3-month mortality. The findings of some of the recent studies are similar to our observations of increased mortality at discharge and at 90 days, as well as less favorable outcome despite similar rates of arterial recanalization in elderly patients.[29,30] We strongly believe that the poor outcome in elderly patients treated with various revascularization therapies cannot be attributed to age alone, rather multiple factors like comorbid conditions, preexisting disability and stroke severity may account for it.

Certain limitations of this study need to be acknowledged. First, this is a retrospective analysis of a prospective collaborative data set. Therefore, it is prone to the effect of confounders. We tried to eliminate this possible influence by adjusting for common known confounders. Although, we provide additional TCD findings of arterial occlusion and recanalization during intravenous thromolysis, these may still be considered operator-dependent despite the extensive
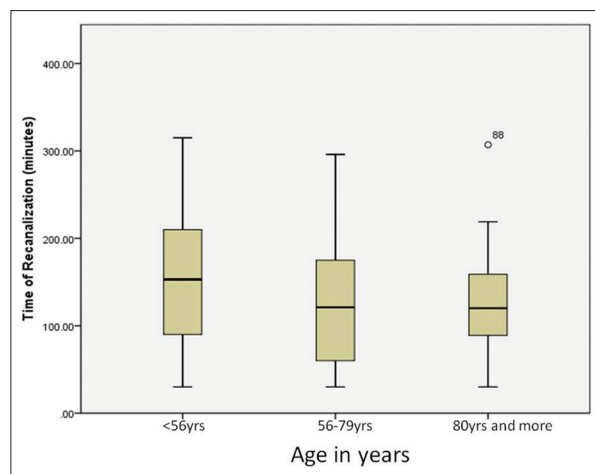

Figure 2: Median time of arterial recanalization among various age groups

training and credentialing of the sonographers involved in this study.

In conclusion, elderly patients have higher rate of poor outcome despite good rates of arterial recanalization and no increased risk of SICH with IV-tPA thrombolysis. We strongly feel that there is a need to identify factors unique to the age which lead to relatively poor outcome in acute ischemic stroke patients despite thrombolysis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Ageing; 2013.
2. Di Carlo A, Lamassa M, Pracucci G, Basile AM, Trefoloni G, Vanni P, *et al*. Stroke in the very old: Clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke 1999;30:2313-9.
3. The World Bank. World Development Report. New York: Oxford University Press; 1993.
4. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. J Neurol Neurosurg Psychiatry 2003;74:317-21.
5. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, *et al*. A prospective study of acute cerebrovascular disease in the community: The Oxfordshire community stroke project 1981–86, I: Methodology, demography and incident cases of first ever stroke. J Neurol Neurosurg Psychiatry 1988;51:1373-80.

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;333:1581-7.

7. Heuschmann PU, Kolominsky-Rabas PL, Roether J, Misselwitz B, Lowitzsch K, Heidrich J, *et al*. Predictors of in-hospital mortality in patients with acute ischemic stroke treatedwith thrombolytic therapy. JAMA 2004;292:1831-8.

8. Tanne D, Gorman MJ, Bates VE, Kasner SE, Scott P, Verro P, *et al*. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: The tPA stroke survey experience. Stroke 2000;31:370-5.

9. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. Stroke 1997;28:2109-18.

10. Alexandrov AV, Demchuk AM, Wein TH, Grotta JC. Yield of transcranial Doppler in acute cerebral ischemia. Stroke 1999;30:1604-9.

11. Demchuk A, Burgin SW, Christou I, Felberg R, Barber P, Hill M, *et al*. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, easy recovery, and mortality in patients treated with intravenous tissue plasminogen activator. Stroke 2001;32:89-93.

12. Alexandrov AV, Demchuk AM, Felberg RA, Christou I, Barber PA, Burgin WS, *et al*. High rate of complete recanalization and dramatic clinical recovery during tPA infusion when continuously monitored with 2-MHz transcranial Doppler monitoring. Stroke 2000;31:610-4.

13. Alexandrov AV, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: Sonographic classification and short-term improvement. Circulation 2001;103:2897-902.

14. Felberg RA, Okon NJ, El-Mitwalli A, Burgin WS, Grotta JC, Alexandrov AV. Early dramatic recovery during intravenous tissue plasminogen activator infusion: Clinical pattern and outcome in acute middle cerebral artery stroke. Stroke 2002;33:1301-7.

15. Burgin WS, Malkoff M, Felberg RA, Demchuk AM, Christou I, Grotta JC, *et al*. Transcranial Doppler ultrasound criteria for recanalization after thrombolysis for middle cerebral artery stroke. Stroke 2000;31:1128-32.

16. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, *et al*.; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170-8.

17. Demchuk AM, Christou I, Wein TH, Felberg R, Malkoff M, Grotta JC, *et al*. The accuracy and criteria for localizing arterial occlusion with transcranial Doppler. J Neuroimaging 2000;10:1-12.

18. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, *et al*. Specific transcranial Doppler flow findings related to the presence and site of arterial occlusion. Stroke 2000;31:140-6.

19. Lindley RI, Wardlaw JM, Sandercock PA, Rimdusid P, Lewis SC, Signorini DF, *et al*. Frequency and risk factors for spontaneous hemorrhagic transformation of cerebral infarction. J Stroke Cerebrovasc Dis 2004;13:235-46.

20. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, *et al*. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455-61.

21. Pundik S, McWilliams-Dunnigan L, Blackham KL, Kirchner HL, Sundararajan S, Sunshine JL, *et al*. Older age does not increase risk of hemorrhagic complications after intravenous and/or intra-arterial thrombolysis for acute stroke. J Stroke Cerebrovasc Dis 2008;17:266-72.

22. Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, *et al*. Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: Increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: Results of a phase II clinical trial. Stroke 2005;36:1441-6.

23. Alexandrov AV, Mikulik R, Ribo M, Sharma VK, Lao AY, Tsivgoulis G, *et al*. A pilot randomized clinical safety study of sonothrombolysis augmentation with ultrasound-activated perflutren-lipid microspheres for acute ischemic stroke. Stroke 2008;39:1464-9.

24. Molina CA, Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, *et al*. Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial. Ann Neurol 2009;66:28-38.

25. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, *et al*. DIAS Study Group. The Desmoteplase in acute ischemic stroke trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36:66-73.

26. von Kummer R, Mori E, Truelsen T, Jensen JS, Grønning BA, Fiebach JB, *et al*. DIAS-4 Investigators. Desmoteplase 3 to 9 hours after major artery occlusion stroke: The DIAS-4 trial (Efficacy and safety study of desmoteplase to treat acute ischemic stroke). Stroke 2016;47:2880-7.

27. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, *et al*. HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: Ameta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-31.

28. Sylaja PN, Cote R, Buchan AM, Hill MD. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian alteplase for stroke effectiveness study. J Neurol Neurosurg Psychiatry 2006;77:826-9.

29. Chandra RV, Leslie-Mazwi TM, Oh DC, Chaudhry ZA, Mehta BP, Rost NS, *et al*. Elderly patients are at higher risk for poor outcomes after intra-arterial therapy. Stroke 2012;43:2356-61.

30. Sharobeam A, Cordato D, Manning N, Cheung A, Wenderoth J, Cappelen-Smith C. Functional outcomes at 90 days in octogenarians undergoing thrombectomy for acute ischemic stroke: A prospective cohort study and meta-analysis. Front Neurol 2019;10:254.