

# Low dosis of alteplase, for ischemic stroke after Enchanted and its determinants, a single center experience

Dosis reducida de alteplase en el accidente cerebrovascular isquémico después del estudio *Enchanted* y sus determinantes, una experiencia de un solo centro

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## ABSTRACT

**Background:** Low-dose alteplase (LrtPA) has been shown not to be inferior to the standard-dose (SrtPA) with respect to death/disability. **Objective:** We aim to evaluate the percentage of patients treated with LrtPA at our center after the ENCHANTED trial and the factors associated with the use of this dosage. **Methods:** Prospective study in consecutive patients with an acute stroke admitted between June 2016 and November 2018. **Results:** 160 patients were treated with intravenous thrombolysis, 50% female; mean age 65.4±18.5 years. Of these, 48 patients (30%) received LrtPA. In univariate analysis, LrtPA was associated with patient's age ( $p=0.000$ ), previous modified Rankin scale scores (mRS) ( $p<0.000$ ), hypertension ( $p=0.076$ ), diabetes mellitus ( $p=0.021$ ), hypercholesterolemia ( $p=0.19$ ), smoking ( $p=0.06$ ), atrial fibrillation ( $p=0.10$ ), history of coronary artery disease ( $p=0.06$ ), previous treatment with antiplatelet agents ( $p<0.000$ ), admission International Normalized Ratio-INR ( $p=0.18$ ), platelet count ( $p=0.045$ ), leukoaraiosis on neuroimaging ( $p<0.003$ ), contraindications for thrombolytic treatment ( $p=0.000$ ) and endovascular treatment ( $p=0.027$ ). Previous relevant bleedings were determinants for treatment with LrtPA. Final diagnosis on discharge of stroke mimic was significant ( $p=0.02$ ) for treatment with SrtPA. In multivariate analysis, mRS (OR: 2.21; 95%CI 1.37–14.19), previous antiplatelet therapy (OR: 11.41; 95%CI 3.98–32.70), contraindications for thrombolysis (OR: 56.10; 95%CI 8.81–357.80), leukoaraiosis (OR: 4.41; 95%CI 1.37–14.10) and diagnosis of SM (OR: 0.22; 95%CI 0.10–0.40) remained independently associated. **Conclusions:** Following the ENCHANTED trial, LrtPA was restricted to 30% of our patients. The criteria that clinicians apply are based mostly on clinical variables that may increase the risk of brain or systemic hemorrhage or exclude the patient from treatment with lytic drugs.

**Keywords:** Acute Stroke; Therapeutic Thrombolysis; Thrombolytic Therapy.

## RESUMEN







**Introducción:** Dosis reducidas de trombolítico (LrtPA) podrían no ser inferiores en muerte/discapacidad. **Objetivo:** Evaluar el porcentaje de pacientes tratados con LrtPA en nuestro centro después del ensayo ENCHANTED, y los factores asociados con el uso de esta dosis. **Métodos:** Estudio prospectivo de pacientes consecutivos con infarto cerebral ingresados entre junio de 2016 y noviembre de 2018. **Resultados:** 160 pacientes fueron tratados con trombólisis intravenosa, 50% mujeres; edad media 65,4±18,5 años. 48 casos (30%) recibieron LrtPA. En el análisis univariado, LrtPA se asoció con la edad del paciente ( $p=0,000$ ), escala de Rankin modificadas (mRS) ( $p<0,000$ ), hipertensión arterial ( $p=0,076$ ), diabetes mellitus ( $p=0,021$ ), hipercolesterolemia ( $p=0,19$ ), tabaquismo ( $p=0,06$ ), fibrilación auricular

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**Authors' contributions:** AMB: developed the study idea, collected the data, participated in the statistical calculations and wrote the manuscript. GC: participated in the statistical calculations approve the final manuscript. EM: collected the data, and approve the final manuscript. EM, AR, JA, VVO, PMV and PML: developed the study idea, collected the data, and approve the final manuscript.

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( $p=0,10$ ), antecedentes de enfermedad coronaria ( $p=0,06$ ), tratamiento previo con antiplaquetarios ( $p<0,000$ ), *International Normalized Ratio*-INR ( $p=0,18$ ), recuento de plaquetario ( $p=0,045$ ), leucoaraiosis en neuroimagen ( $p<0,003$ ), contraindicaciones para el tratamiento trombolítico ( $p=0,000$ ) y tratamiento endovascular ( $p=0,027$ ). Las hemorragias previas relevantes fueron determinantes para el tratamiento con LrtPA. El diagnóstico al alta de imitador de accidente cerebrovascular fue significativo ( $p=0,02$ ) para el tratamiento con dosis estándar. El análisis multivariado demostró que mRS (OR: 2,21; IC95% 1,37–14,19), tratamiento antiplaquetario previo (OR: 11,41; IC95% 3,98–32,7), contraindicaciones para trombólisis (OR: 56,1; IC95% 8,81–357,8), leucoaraiosis (OR: 4,41; IC95% 1,37–14,1) y un diagnóstico de imitador de accidente cerebrovascular (OR: 0,22; IC95% 0,1–0,40) fueron asociados con la dosis recibida. **Conclusiones:** LrtPA está restringido al 30% de nuestros pacientes. Los criterios para tomar esta decisión se basan en variables que podrían aumentar el riesgo de hemorragia cerebral/sistémica o excluir al paciente del tratamiento con fármacos líticos.

**Palabras clave:** Accidente Cerebrovascular; Terapia Trombolítica; Terapia Trombolítica.

## INTRODUCTION

The recombinant tissue plasminogen activator (rtPA) within 4.5 h of acute ischemic stroke (AIS) onset improves the possibility of a good outcome<sup>1,2,3,4</sup>; however, rtPA could also increase the risk of symptomatic intracranial hemorrhage (sICH)<sup>5,6</sup>, which is associated with poor clinical outcomes<sup>1</sup>.

In a meta-analysis, the low-dose alteplase (LrtPA) has been shown not to be inferior compared to the standard-dose (SrtPA) with respect to death and disability outcomes at 90 days<sup>7</sup>, although the ENCHANTED trial<sup>8</sup> was negative for its primary outcome (death or disability at 90 days), there were fewer sICH patients receiving LrtPA.

This study aimed to investigate what percentage of patients were treated with LrtPA at our research center after the ENCHANTED trial, and the variables associated with the use of LrtPA.

## METHODS

In this prospective study, patients with AIS admitted to *Clínica Alemana* between June 2016 and November 2018 were evaluated by the neurologist on call. Age, sex, pre-stroke modified Rankin Scale score (mRS), cerebrovascular risk factors, previous use of antiplatelet, anticoagulants or relevant previous extracranial bleeding (defined as “that required transfusion, hospitalization, or surgery”) or brain bleedings were recorded as part of our prospective stroke registry (RECCA). The time from AIS onset to arrival at the emergency room (ER), defined as the last time the patient was known to be free from neurological deficit, was registered, as well as the severity of the stroke assessed with the National Institutes of Health Stroke Scale (NIHSS), serum glucose, systolic blood pressure (SBP), and diastolic blood pressure (DBP) on admission before the rtPA bolus.

Patients were then studied with a neuroimaging protocol<sup>9</sup>, consisting of a non-contrast brain computed tomography (NCCT), spiral Computed Tomographic Angiography of the cervical and intracranial arteries (CTA) and then a diffusion-weighted image (DWI). If a CTA could not be obtained, an acute magnetic resonance angiography was performed.

Patients eligible for rtPA were treated within a 4.5-hour time window; the bolus was usually administered immediately after the NCCT scan and before the results of blood parameters were received, or the CTA and DWI were performed.

In the case of a wake-up stroke (WUS), they were treated with rtPA if the AIS was not visible on parenchymal hyperintensity on fluid-attenuated inversion recovery magnetic resonance imaging (MRI) (FLAIR) that was added to the imaging protocol for this specific group of patients.

Patients treated with rtPA were evaluated during thrombolytic treatment with transcranial Doppler.

The information obtained from the imaging protocol were NCCT and DWI ASPECTS, presence of hyperdense artery sign and of leucoaraiosis defined as hypodensity with initial confluency of lesions or large confluent lesions on the white matter of NCCT scans. The presence of a relevant intracranial large vessel occlusion and the thrombolysis in brain ischemia (TIBI) ultrasound classification<sup>10</sup>, at the beginning of the rtPA treatment for the symptomatic arterial territory.

At our institution, the dosage established for the rtPA treatment is 0.9 mg/kg with a maximum of 90 mg. There is no pre-established protocol for LrtPA (0.6 mg/kg), allowing its use according to the clinical criteria of the emergency neurologist.

The dose used in every thrombolytic treatment was recorded, as well as the reasons for the LrtPA dose use. If a patient treated with rtPA had any contraindication for this treatment, this information was registered. Patients who presented with relevant intracranial large-vessel disease are usually treated with bridging therapy with thrombectomy.

After acute treatment, patients were admitted to the Stroke Unit, where telemetric monitoring and echocardiographic examinations were performed; additional evaluations were performed to detect infrequent causes of AIS.

In order to simulate a real-world stroke-treating scenario, stroke mimics (SM) were not excluded from the study analysis.

Symptomatic intracranial hemorrhage was defined as any intraparenchymal, subarachnoid, or intraventricular hemorrhage in post-rtPA treatment NCCT associated with an increase of  $\geq 4$  points on the NIHSS according to the ECASS criteria<sup>11</sup>.

The Ethics Committee of *Universidad del Desarrollo, Clínica Alemana de Santiago* approved the registry protocol, and patients or their relatives provided written informed consent.

## Statistical analysis

The numbers of patients treated with LrtPA were calculated with 95% confidence intervals (95%CI).

Univariate analysis was performed using  $\chi^2$  for frequency data to evaluate the associations of LrtPA with age, gender, basal mRS, cerebrovascular risk factors, and the presence of WUS. Previous treatment with antiplatelet agents, a history of relevant systemic or brain bleedings, contraindications for rtPA treatment, admission NIHSS, SBP, and DBP. Other factors considered were international normalized ratio and platelet count on admission, ASPECT score on NCCT and DWI, the presence of leukoaraiosis on brain NCCT, the hyperdense arterial sign or the presence of intracranial occluded vessels on CTA. The TIBI ultrasound scale at the beginning of the rtPA drip, bridging endovascular treatment and a final diagnosis of SM at discharge.

A logistic regression analysis was performed for those variables associated ( $p < 0.25$ ) in the univariate analysis.

## RESULTS

Within the period covered by this study, from June 2016 to November 2018, 174 patients with an AIS of less than 4.5 hours from the onset of symptoms and 29 additional cases with WUS arrived to the ER. Forty-three patients did not undergo thrombolytic treatment for a variety of reasons: 13 cases because of anticoagulation medication in use, 15 WUS demonstrated lesions on MRI FLAIR, seven patients had deficits that were considered too mild to require treatment, and finally eight patients were not treated for other reasons.

Overall, 160 patients were treated with rtPA (50% women; mean age  $65.4 \pm 18.5$  years), with a door to needle time of  $45.8 \pm 25.0$  minutes. Forty-eight patients (30%; 95%CI 23.1–37.8) were treated with the LrtPA (0.6 mg/kg body) and the remaining 112 cases (70%; 95%CI 76.9–62.2) were treated with SrtPA.

The baseline characteristics of these groups and the univariate analysis correlating LrtPA dosage with clinical and radiological variables are shown in Table 1.

**Table 1.** Univariate analysis correlating low-dose alteplase dosage with the clinical and radiological variables.

	Srt-PA n=112 (70%)	Lrt-PA n=48 (30%)	p-value
Mean age, years (SD)	60.3 ( $\pm 18.5$ )	77.4 ( $\pm 13.5$ )	0.000
Stroke	96	47	0.02
Stroke mimic	16	1	
Wake up stroke (%)	9 (8)	5 (10.4)	0.76
Previous			
Rankin (median)	0.4	1.3	0.000
Rankin > 2 (number of patients)	5	8	

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**Table 1.** Continuation.

	Srt-PA n=112 (70%)	Lrt-PA n=48 (30%)	p-value
Women (%)	56 (50)	24 (50)	0.56
Hypertension (%)	74 (66)	24 (50)	0.076
Diabetes mellitus (%)	24 (21.4)	19 (39.6)	0.021
Hypercholesterolemia (%)	30 (26.7)	18 (37.5)	0.19
Tobacco (%)	14 (12.5)	12 (25)	0.062
Heart failure (%)	9 (8.0)	6 (12.5)	0.38
Atrial fibrillation (%)	10 (8.9)	9 (18.7)	0.10
Coronary heart disease	10 (8.9)	13 (27)	0.006
Previous antiplatelet	16 (14.2)	30 (62.5)	0.000
rtPA contraindications	2 (1.8)	11 (22.9)	
Systolic pressure > 180	0	3	
Previous anticoagulant	2	2	0.000
MI in previous three months	0	3	
AIS in the previous three months	0	1	
Platelet count < 100.00	0	1	
Relevant hemorrhages	0	2 (5)	Determinant
Time to ER, minutes mean $\pm$ SD	118.5 (143.6)	133.1 (174.5)	0.57
Admission NIHSS			
Mean	8.9	8	0.49
Median	5	5	
Door to needle time (minutes)	44 (23.8)	49.9 (27.5)	0.17
Systolic BP, mm Hg	145.4	150.5	0.26
Diastolic BP, mm Hg mean (SD)	85.5	83.2	0.42
Blood glucose, mg/dL, mean	116.8	122.2	0.37
INR	1.11	1.14	0.18
Platelet count (mean)	238.82	203.31	0.045
NCCT leukoaraiosis (%)	13 (11.6%)	16 (33.3)	0.003
Hyperdense arterial Sign (%)	22 (19.6)	7 (14.5)	0.5
DWI			
ASPECTS mean	8.7	8.8	0.68
ASPECT < 7 (n)	12	5	
Arterial occlusion on CTA	51 (47.2)	19 (40.4)	0.48
TIBI scale on TCD (mean)	3.9	3.8	0.58
TIBI 0–3 (n)	27	11	
Planned thrombectomy	27 (24.1)	4 (8.3)	0.028

Srt-PA: standard-dose alteplase; Lrt-PA: low-dose alteplase; SD: standard deviation; rtPA: thrombolytic therapy; MI: myocardial infarction; AIS: acute ischemic stroke; ER: emergency room; NIHSS: National Institute of Health Stroke Scale; BP: blood pressure; INR: International Normalized Ratio; NCCT: non-contrast brain computed tomography; DWI: diffusion-weighted magnetic resonance imaging; CTA: cervical and intracranial arteries; TIBI: thrombolysis in brain ischemia; TCD: transcranial Doppler.

Variables that reached significance were patient age on admission ( $p=0.000$ ), mRS before stroke ( $p<0.000$ ), chronic arterial hypertension ( $p=0.076$ ), *diabetes mellitus* ( $p=0.021$ ), hypercholesterolemia ( $p=0.19$ ), smoking ( $p=0.062$ ), atrial fibrillation ( $p=0.10$ ), history of coronary artery disease ( $p=0.006$ ), previous treatment with antiplatelet agents ( $p<0.000$ ), International Normalized Ratio-INR ( $p=0.18$ ), platelet count on admission ( $p=0.045$ ), leukoaraiosis ( $p<0.003$ ), presence of contraindications for thrombolytic treatment ( $p=0.000$ ), and endovascular treatment ( $p=0.028$ ). The presence of a previous major bleeding was a determinant for treatment with LrtPA and was not incorporated in the multivariate analysis. The final diagnosis of SM on discharge ( $p=0.02$ ) was statistically associated with treatment with SrtPA.

In the multivariate analysis (Table 2), previous mRS (OR: 2.1; 95%CI 1.36–3.334;  $p=0.001$ ), use of antiplatelet treatment (OR: 11.4; 95%CI 3.98–32.7;  $p<0.000$ ), contraindications for thrombolytic treatment (OR: 56.1; 95%CI 8.81–357.0;  $p<0.000$ ), presence of leukoaraiosis (OR: 4.4; 95%CI 1.37–3.34;  $p=0.001$ ), and discharge diagnosis of SM (OR: 0.22; 95%CI 0.1–0.40;  $p=0.049$ ) remained significant.

Six patients (3.7%; 95%CI 1.5–8.3) experienced ICH during the study; 4 of these were in the SrtPA group and 2 in the LrtPA; this difference was not statistically significant ( $p=0.57$ ).

The neurologist on call when the patient arrived and week *versus* weekend did not influence the dosage of rtPA chosen by the neurologist on call to treat the patient (Supplemental Table 1).

## DISCUSSION

Following the ENCHANTED trial, SrtPA was the most frequent dosage used in our institution. LrtPA was used in less than one out of every three patients treated with systemic lytic drugs. Probably, the lower percentage of patients treated with 0.6 mg/kg of alteplase is explained by the fact that in ENCHANTED LrtPA was associated with lower death rates although with more patients surviving with severe residual disability<sup>8</sup>.

**Table 2.** Multivariate analysis of predictors for use of low dosages of thrombolytic therapy.

	OR	95%CI	p-value
Previous Rankin score (>2)	2.1	1.35–3.34	0.001
Previous use of antiplatelet	11.4	3.98–32.70	0.000
Contraindication for rtPA	56.1	8.81–357.80	0.000
Presence of leukoaraiosis	4.4	1.37–14.10	0.013
Stroke mimic	0.2	0.10–0.4	0.049

OR: Odds Ratio; 95%CI: 95% confidence interval; rtPA: thrombolytic therapy.

The criteria used to select the patients that were treated with LrtPA are mostly clinical, such as a previous mRS, the use of antiplatelet treatments, antecedents of previous significant hemorrhage, or conditions that contraindicated the use of rtPA.

Previously physically dependent patients were not admitted in thrombolytic trials<sup>11</sup>. A multicenter rtPA register<sup>12</sup> demonstrated an under-representation of such patients, who constituted 6.6% of the entire group. The patients included in the study were older, had more severe strokes, and were more often already on antithrombotic medications, additionally being more likely to have poorer outcomes than independent patients<sup>12</sup>.

The treatment of this group of patients with a lower dose of rtPA instead of excluding them from thrombolytic therapy, could perhaps merit a study in the future.

Patients who were previously treated with antiplatelet therapy had, in our experience, a high probability of being treated with LrtPA. This feature was probably related to the results of observational studies that reported increased incidences of sICH among patients treated with rtPA receiving antiplatelet treatment<sup>13</sup>. Additionally, the results of the ARTIS trial<sup>14</sup> showed that the administration of aspirin and alteplase was independently associated with sICH. Furthermore, a subgroup analysis of the ENCHANTED trial showed that antiplatelet treatment could compromise the safety of rtPA in AIS patients<sup>15</sup>. A recent meta-analysis adjusted for age and severity of stroke found no significant association<sup>16</sup>; a future study aimed at analyzing these relations seems desirable.

Patients who had contraindications for rtPA were frequently not treated with thrombolytic drugs in our center. From 32 patients with contraindications for alteplase, only 13 received this treatment and more than 80% were treated with LrtPA. The group of patients who did not receive thrombolytic drugs were mainly patients treated with anticoagulants or who had recently undergone a major surgery (less than a week); those who were treated appear in Table 1. Of those who were under anticoagulant medication, two received Prothrombin Complex Concentrate (PCC) before the thrombolysis, in the other two cases it was not clear if the patients had taken the dose of Apixaban indicated that day, and it was therefore decided to thrombolize with LrtPA.

Contraindications for the administration of rtPA originated as exclusion criteria in major stroke trials, which aimed at selecting patients showing the maximal benefit with optimal safety<sup>1,11,17</sup>. Additionally, the majority of these criteria were based on the opinion of experts, and their scientific basis is weak<sup>18</sup>.

Patients who had contraindications for rtPA may have a tendency to more favorable three-month outcomes associated with alteplase treatment *versus* no treatment<sup>19</sup>.

None of our patients treated with standard or LrtPA experienced cerebral or systemic bleeding. Perhaps, and in very specific cases, LrtPA could be considered as an option for



treatment for these patients; however there is still no evidence to support this idea.

A history of previous significant hemorrhage was determinant for treatment with LrtPA in our ER. The use of LrtPA was probably seen by the neurologist, although without firm evidence, as an opportunity for decreasing the risk of a new bleeding episode.

Only those patients discharged with a final diagnosis of SM had a high probability of being treated with SrtPA. These patients are usually younger, have lower NIHSS, less cerebrovascular risk factors, and use antiplatelet treatments infrequently compared to stroke patients<sup>20</sup>; these factors could be associated with a lower level of anxiety with respect to episodes of sICH when treated with rtPA.

Our patients were subjected to extensive image evaluations in the ER: NCCT, CTA, DWI, and transcranial Doppler (TCD); leukoaraiosis was the only radiological element related with the use of LrtPA. This could be explained by a few factors, Firstly, the presence of leukoaraiosis is associated with an increased risk of sICH and poor functional outcomes after thrombolysis<sup>21</sup>. In the second place, rtPA bolus and the dosage of lytic therapy is decided in our institution after

the NCCT scan, but before the CTA, DWI, and TCD evaluations, which exclude these imaging techniques from the decision-making process. Finally, five patients among those who had leukoaraiosis on NCCT had suffered head trauma at the time of admission with soft tissue injury. However, their brain NCCT showed no evidence of bleeding. ICH has been describe when AIS patients with head trauma are treated with rtPA<sup>22</sup>.

Our study has limitations. It is a small-sized, single-centered experience. Of our patients, 11% were SM. The mRS at 90 days in both groups were not compared. Furthermore, we only recorded the presence of previous antiplatelet use, not having registered what drug was used. Finally, we participated in the ENCHANTED trial, and as a consequence we could be biased toward the use of LrtPA, especially in difficult cases, which may not have been treated with standard dosages.

In conclusion, after the ENCHANTED trial, the use of LrtPA has been restricted to a limited proportion of patients. In our study, the use of LrtPA depended mainly on elements that were thought to increase the risk of sICH and to exclude them from rtPA treatment.

## References

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995 Dec;333(24):1581-7. <https://doi.org/10.1056/NEJM199512143332401>
2. Goyal M, Demchuk AM, Menon BK, Easa M, Rempe J, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015 Feb;372(11):1019-30. <https://doi.org/10.1056/NEJMoa1414905>
3. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015 Jan;372(1):11-20. <https://doi.org/10.1056/NEJMoa1411587>
4. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007 Jan;369(9558):275-82. [https://doi.org/10.1016/S0140-6736\(07\)60149-4](https://doi.org/10.1016/S0140-6736(07)60149-4)
5. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. *Stroke*. 2012 Nov;43(11):2904-9. <https://doi.org/10.1161/STROKEAHA.112.665331>
6. Pan X, Zhu Y, Zheng D, Liu Y, Yu F, Yang J. Prior antiplatelet agent use and outcomes after intravenous thrombolysis with recombinant tissue plasminogen activator in acute ischemic stroke: a meta-analysis of cohort studies and randomized controlled trials. *Int J Stroke*. 2015 Apr;10(3):317-23. <https://doi.org/10.1111/ij.12431>
7. Liu H, Zheng H, Cao Y, Pan Y, Wang D, Zhang R, et al. Low- versus standard-dose intravenous tissue-type plasminogen activator for acute ischemic stroke: an updated meta-analysis. *J Stroke Cerebrovasc Dis*. 2018 Apr;27(4):988-97. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.11.005>
8. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N Engl J Med*. 2016 Jun;374(24):2313-23. <https://doi.org/10.1056/NEJMoa1515510>
9. Brunser AM, Lavados PM, Cárcamo DA, Hoppe A, Olavarría A, Díaz V, et al. Additional information given to a multimodal imaging stroke protocol by transcranial Doppler ultrasound in the emergency room: a prospective observational study. *Cerebrovasc Dis*. 2010 Aug;30(3):260-6. <https://doi.org/10.1159/000319068>
10. Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, et al. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke*. 2001 Jan;32(1):89-93. <https://doi.org/10.1161/01.str.32.1.89>
11. 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 Oct;352(9136):1245-51. [https://doi.org/10.1016/s0140-6736\(98\)08020-9](https://doi.org/10.1016/s0140-6736(98)08020-9)
12. Gensicke H, Strbian D, Zinkstok SM, Scheitz JF, Bill O, Hametner C, et al. Intravenous thrombolysis in patients dependent on the daily help of others before stroke. *Stroke*. 2016 Feb;47(2):450-6. <https://doi.org/10.1161/STROKEAHA.115.011674>
13. Uyttenboogaart M, Luijckx GJ. Intravenous thrombolysis for patients with ischaemic stroke on antiplatelet therapy: a blessing in disguise? *Eur J Neurol*. 2010 Feb;17(2):177-8. <https://doi.org/10.1111/j.1468-1331.2009.02851.x>
14. Zinkstok SM, Beenen LF, Majoie CB, Marquering HA, de Haan RJ, Roos et al. Early deterioration after thrombolysis plus aspirin in acute stroke: a post hoc analysis of the Antiplatelet Therapy in Combination with Recombinant t-PA Thrombolysis in Ischemic Stroke trial. *Stroke*. 2014 Oct;45(10):3080-2. <https://doi.org/10.1161/STROKEAHA.114.006268>

15. Robinson TG, Wang X, Arima H, Bath PM, Billot L, Broderick JB, et al. Low- versus standard-dose alteplase in patients on prior antiplatelet therapy: the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study). *Stroke*. 2017 Jul;48(7):1877-83. <https://doi.org/10.1161/STROKEAHA.116.016274>
16. Tsivgoulis G, Katsanos AH, Zand R, Sharma VK, Köhrmann M, Giannopoulos S, et al. Antiplatelet pretreatment and outcomes in intravenous thrombolysis for stroke: a systematic review and meta-analysis *J Neurol*. 2017 Jun;264(6):1227-35. <https://doi.org/10.1007/s00415-017-8520-1>
17. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset: alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. *Stroke*. 2002 Feb;33(2):493-5. <https://doi.org/10.1161/hs0202.102599>
18. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist*. 2015 Jul;5(3):110-21. <https://doi.org/10.1177/1941874415578532>
19. Frank B, Grotta JC, Alexandrov AV, Bluhmki E, Lyden P, Meretoja A, et al. VISTA Collaborators. Thrombolysis in stroke despite contraindications or warnings? *Stroke*. 2013 Mar;44(3):727-33. <https://doi.org/10.1161/STROKEAHA.112.674622>
20. Tsivgoulis G, Alexandrov AV, Chang J, Sharma VK, Hoover SL, Lao AY, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. *Stroke*. 2011 Jun;42(6):1771-4. <https://doi.org/10.1161/STROKEAHA.110.609339>
21. Kongbunkiat K, Wilson D, Kasemsap N, Tiamkao S, Jichi F, Palumbo V, et al. Leukoaraiosis, intracerebral hemorrhage, and functional outcome after acute stroke thrombolysis. *Neurology*. 2017 Feb;88(7):638-45. <https://doi.org/10.1212/WNL.0000000000003605>
22. Meguro T, Higashi H, Nishimoto K. Acute subdural hematoma after intra-arterial thrombolysis for acute ischemic stroke--case report. *Neurol Med Chir (Tokyo)*. 2005 Dec;45(12):627-30. <https://doi.org/10.2176/nmc.45.627>