Low- Versus Standard-Dose Alteplase in Patients on Prior Antiplatelet Therapy

The ENCHANTED Trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study)

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Background and Purpose—Many patients receiving thrombolysis for acute ischemic stroke are on prior antiplatelet therapy (APT), which may increase symptomatic intracerebral hemorrhage risk. In a prespecified subgroup analysis, we report comparative effects of different doses of intravenous alteplase according to prior APT use among participants of the international multicenter ENCHANTED study (Enhanced Control of Hypertension and Thrombolysis Stroke Study).

Methods—Among 3285 alteplase-treated patients (mean age, 66.6 years; 38% women) randomly assigned to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) intravenous alteplase within 4.5 hours of symptom onset, 752 (22.9%) reported prior APT use. Primary outcome at 90 days was the combined end point of death or disability (modified Rankin Scale [mRS] scores, 2–6). Other outcomes included mRS scores 3 to 6, ordinal mRS shift, and symptomatic intracerebral hemorrhage by various standard criteria.

Results—There were no significant differences in outcome between patients with and without prior APT after adjustment for baseline characteristics and management factors during the first week; defined by mRS scores 2 to 6 (adjusted odds ratio [OR], 1.01; 95% confidence interval [CI], 0.81–1.26; *P*=0.953), 3 to 6 (OR, 0.95; 95% CI, 0.75–1.20; *P*=0.662), or ordinal

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mRS shift (OR, 1.03; 95% CI, 0.87–1.21; *P*=0.770). Alteplase-treated patients on prior APT had higher symptomatic intracerebral hemorrhage (OR, 1.82; 95% CI, 1.00–3.30; *P*=0.051) according to the safe implementation of thrombolysis in stroke-monitoring study definition. Although not significant (*P*-trend, 0.053), low-dose alteplase tended to have better outcomes than standard-dose alteplase in those on prior APT compared with those not using APT (mRS scores of 2–6; OR, 0.84; 95% CI, 0.62–1.12 versus OR, 1.16; 95% CI, 0.99–1.36).

Conclusions—Low-dose alteplase may improve outcomes in thrombolysis-treated acute ischemic stroke patients on prior APT, but this requires further evaluation in a randomized controlled trial.

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Intravenous alteplase (recombinant tissue plasminogen activator) is the only approved medical reperfusion treatment in patients with acute ischemic stroke (AIS); and the earlier the treatment is given, the greater the proportional benefit.[1] Because ≤40% of AIS patients have regularly taken antiplatelet therapy (APT), mainly aspirin, at the time of intravenous alteplase,[2–4] a harmful interaction between these 2 agents may reduce the net benefit of thrombolysis treatment. Two recent meta-analyses of randomized controlled trials and cohort studies have both reported that APT use at the time of alteplase significantly increases the risk of symptomatic intracerebral hemorrhage (sICH).[5,6] Pan et al[6] reported that his was associated with a reduced probability of good outcome (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.73–1.01; *P*=0.06), although others have not reported any clear attenuation of the clinical benefit.[7] However, the ARTIS trial (APT in Combination With Recombinant Tissue Plasminogen Activator in Thrombolysis in Ischemic Stroke), the only randomized trial of de novo aspirin with standard-dose alteplase versus standard-dose alteplase alone, was terminated prematurely because of an excess sICH in the combination arm (absolute difference, 2.8%; 95% CI, 0.2–5.4; *P*=0.04).[8]

Concerns over the risk of sICH with intravenous alteplase have led to lower doses being used in many AIS patient groups, particularly Asians,[9] after a dose of 0.6 mg/kg was approved for use in Japan. The ENCHANTED study (Enhanced Control of Hypertension and Thrombolysis Stroke Study) was designed to evaluate the effectiveness of low dose (0.6 mg/kg body weight) compared with a standard dose (0.9 mg/kg) of intravenous alteplase in patients with AIS who fulfill guideline-recommended criteria for thrombolysis treatment.[10] Although the ENCHANTED trial failed to meet its primary noninferiority outcome, a prespecified subgroup analysis identified a borderline significant interaction (*P*=0.052) between prior APT use and alteplase dose on the primary outcome—the conventional binary separation of scores of 2 to 6 that define death or disability on the modified Rankin Scale (mRS).[10] We report herein, more details of the balance of benefits and risks of alteplase according to prior APT use and potential modification of effects by use of low-dose alteplase.

Materials and Methods

Patients

The ENCHANTED trial is an international, multicenter, prospective, randomized, open-label, blinded-end point trial that used a 2×2 quasi-factorial design to assess the effectiveness of low- versus standard-dose alteplase in the completed arm and more intensive versus guideline-recommended control of blood pressure in the ongoing arm, full details of which are outlined elsewhere.[10] This analysis considers the alteplase dose arm where 3310 patients with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for thrombolysis treatment administered within 4.5 hours of symptom onset were randomly assigned to receive low-dose (0.6 mg/kg; 15% as bolus, 85% as infusion during 1 hour) or standard-dose (0.9 mg/kg; 10% as bolus, 90% as infusion during 1 hour) intravenous alteplase. The study protocol was approved by the appropriate ethics committee at each participating center, and written informed consent was obtained from the patient or an appropriate surrogate.

Procedures

Key demographic and clinical characteristics, including the prior use of aspirin or another APT agent, were recorded at the time of enrollment. Stroke severity was measured using the National Institutes of Health stroke scale at baseline, 24 hours, and at day 7 (or earlier, on discharge from hospital). Uncompressed digital images of all baseline and follow-up digital computed tomography, magnetic resonance imaging, and angiogram images were collected in DICOM format (Digital Imaging and Communications in Medicine) on a CD-ROM identified only with the patient's unique study number and analyzed centrally for any intracranial hemorrhage by independent assessors blinded to clinical data, treatment, and date and sequence of scan. Assessors graded any identified hemorrhage as intracerebral using a range of standard definitions (Materials section in the online-only Data Supplement) and subarachnoid, intraventricular, subdural, or other.

The primary clinical outcome was the combined end point of death or disability at 90 days, defined by scores of 2 to 6 on the mRS. Other efficacy outcomes included an ordinal mRS shift and the combined end point of death or major disability (mRS scores of 3–6) at 90 days. The secondary (safety) outcome was sICH, defined according to several criteria from other studies (Materials section in the online-only Data Supplement).

Statistical Analysis

The association of prior APT on global functional outcome was estimated using ordinal logistic regression after the assumption of proportionality of the odds was confirmed from a likelihood ratio test. Logistic regression models were used to estimate associations for all the other outcomes. Adjustments were made for the prespecified minimization and baseline covariates and additionally for aspects of management during the first 7 days after hospital admission. In patients with and without prior APT, the heterogeneity of alteplase treatment effects was tested by adding interaction terms to the statistical models. 2-sided *P* values were reported, and *P*<0.05 was considered statistically significant. The SAS, version 9.3, (SAS Institute, Cary, NC) was used for the analysis.

Results

Baseline Characteristics

These analyses included 3285 patients (38% women; mean age, 66.6 years) in whom the presence or absence of prior APT use

was recorded (Figure I in the online-only Data Supplement); 752 (22.9%) patients reporting the use of prior APT at baseline. Those with prior APT were older, and more likely to be of non-Asian ethnicity, had baseline imaging changes indicative of more severe cerebral infarction, and were diagnosed with a presumed cardioembolic or other stroke pathology (Table I in the online-only Data Supplement). Patients on prior APT were also more likely to have associated comorbidity (including hypertension, previous stroke, coronary artery or other cardiac disease, or risk factors, including atrial fibrillation, diabetes mellitus, and hypercholesterolemia) and to be on statin therapy (Table I in the online-only Data Supplement). However, with the exception of a history of hypercholesterolemia and use of statins, there were no baseline imbalances between the use of low-dose or standard-dose alteplase in patients on prior APT (Table). Overall, patients with prior APT were treated more quickly after the onset of symptoms and received a higher bolus alteplase dose, but there were no other significant differences in thrombolysis-associated management (Table II in the online-only Data Supplement).

Prior APT and Outcome

Prior APT was associated with a worse 90-day clinical outcome, whether defined by mRS scores of 2 to 6 (unadjusted OR, 1.38; 95% CI, 1.17–1.63; $P<0.001$), 3 to 6 (OR, 1.33; 95% CI, 1.13–1.58; $P<0.001$), or ordinal shift (OR, 1.41; 95% CI, 1.22–1.63; $P<0.001$), or mortality alone (OR, 1.46; 95% CI, 1.12–1.89; $P=0.005$; Table III in the online-only Data Supplement). However, after adjustment for the minimization criteria and important baseline variables at the time of randomization, and subsequently for imbalances in management during the first 7 days of hospital admission, there were no significant differences in these outcomes between patients with and without prior APT (Table III in the online-only Data Supplement). Prior APT was also associated with an increased risk of sICH across most definitions (Table IV in the online-only Data Supplement).

Prior APT and Alteplase Dose

Although not significant, low-dose alteplase tended to have more favorable 90-day outcomes in patients on prior APT compared with those without prior APT, defined by mRS scores of 2 to 6 (unadjusted OR, 0.84; 95% CI, 0.62–1.12 versus OR, 1.16; 95% CI, 0.99–1.36, respectively; *P*-trend, 0.053), 3 to 6 (OR, 0.80; 95% CI, 0.60–1.08 versus OR, 1.10; 95% CI, 0.93–1.30]; *P*-trend, 0.065; Table V in the online-only Data Supplement), or as an ordinal mRS shift analysis (OR, 0.76; 95% CI, 0.59–0.88 versus OR, 1.07; 95% CI, 0.93–1.23; *P* interaction, 0.023; Figure 1). Conversely, for those patients without prior APT—77% of the ENCHANTED population—standard-dose alteplase was associated in a trend toward more favorable outcome (Table V in the online-only Data Supplement). Importantly, there was reduced mortality by 5.0% (−0.05 to 9.95) and 1.1% (−1.13 to 3.40) in patients with and without prior APT (*P* interaction, 0.23) treated with low-dose compared with standard-dose alteplase, but no significant differences in sICH across a broad range of definitions (Figure 2; Table VI in the online-only Data Supplement).

Discussion

These additional analyses of the ENCHANTED trial related to the patient subgroup on prior APT have shown that, albeit not significant, a trend toward more favorable clinical outcomes with low-dose as compared with standard-dose intravenous alteplase, warranting further evaluation in a randomized controlled trial. Patients on prior APT account for at least one quarter of the thrombolysis-eligible AIS population, as indicated by an international stroke thrombolysis registry,[2] the United States Get With the Guidelines quality improvement registry,[4] and participants in the ENCHANTED trial, and are at significantly higher risk of sICH[3] and poor outcome[11] compared with other patients who receive alteplase. This figure may increase further with the aging of population and data suggesting benefits of early use of aspirin in reducing the risk of secondary ischemic events after transient ischemic attack or minor ischemic stroke.[12]

Our findings are consistent with previous studies of patients on prior APT being at greater risk of thrombolysis-associated sICH, in part, related to the greater co-occurrence of other risk variables, such as older age, statin use, cardiac disease, atrial fibrillation, and diabetes mellitus.[4,5] Although higher sICH with APT may explain much of the association with worse functional outcome after AIS, the presence of greater comorbidity is also likely to be particularly relevant.[13] The Get With the Guidelines registry showed that aspirin monotherapy was associated with increased sICH after adjustment for baseline imbalances (adjusted OR, 1.18; 95% CI, 1.10–1.28).[4]

The ENCHANTED trial allowed for a randomized assessment of the comparative effects of low-dose versus standard-dose alteplase in patients on prior APT. Concerns of a higher risk of sICH have led to a wide range of doses of intravenous alteplase being used in many Asian countries in relation to perceived risks and affordability of the treatment.[9] Although 3 studies—2 registries[14,15] and 1 observational[16]—have specifically evaluated outcomes by dose of alteplase in Asian populations, only Chao et al[16] reported a trend toward an adverse effect of prior APT on outcome. In particular, use of clopidogrel or ticlopidine, but not aspirin, was associated with an increased risk of sICH on multivariate analysis. However, only 3.4% and 4.0% of patients in the low- and standard-dose groups, respectively, were on these agents, and no beneficial effect of low-dose alteplase in patients on prior APT was observed.[16] Nonetheless, as low-dose alteplase in the ENCHANTED trial was associated with lower sICH, this may be considered an important treatment option in such patients, despite the absence of any clear reduction in sICH in those patients on prior APT.

Some authors have suggested that prior APT may result in less severe strokes, by limiting the size of the occluding thrombus and subsequent risk of embolization,[17] improving recanalization,[18] or the microcirculation of the ischemic penumbra through inhibition of platelet-derived vasoconstrictors (eg, thromboxane A2),[19] and of potential anti-inflammatory and neuroprotective effects.[20] Most recently, a retrospective analysis of a large multicenter registry of 10 433 patients indicated better outcomes in those on prior APT after atherothrombotic stroke, but not after cardioembolism or small vessel occlusion, and only in patients without hemorrhagic transformation.[21] However,

Table. Baseline Characteristics by Randomized Treatment Among Patients on Prior Antiplatelet Therapy

	Randomized Treatment Group		
	Low-Dose (n=407)	Standard-Dose (n=345)	*P* Value
Time from stroke onset to randomization, h; mean (SD)	2.6 (0.9)	2.7 (0.9)	0.084
Women, n (%)	160 (39.3)	136 (39.4)	0.976
Age, y; mean (SD)	71.0 (11.1)	71.9 (11.2)	0.310
≥80, n (%)	84 (20.6)	80 (23.2)	0.399
Ethnicity, Asian	186 (45.7)	138 (40.0)	0.116
Clinical features			
Systolic BP, mm Hg; mean (SD)	148.4 (18.8)	149.9 (20.3)	0.309
Diastolic BP, mm Hg; mean (SD)	82.4 (13.2)	82.3 (12.9)	0.857
Heart rate, bpm; mean (SD)	79.7 (18.1)	78.1 (15.6)	0.186
NIHSS score*			
Median (Q1, Q3)	8 (5–15)	8 (5–14)	0.836
≥14, n (%)	112 (27.5)	91 (26.4)	0.725
GCS score, median (Q1, Q3)†	15 (13–15)	15 (14–15)	0.568
Visible early ischemic changes on brain imaging, n (%)	124 (30.5)	90 (26.1)	0.185
Mass effect on brain imaging, n (%)	8 (2.0)	5 (1.5)	0.588
Medical history			
Hypertension, n (%)	321 (78.9)	263 (76.2)	0.367
Currently treated hypertension, n (%)	301 (74.0)	243 (70.4)	0.282
Previous stroke, n (%)	125 (30.7)	122 (35.4)	0.176
Coronary artery disease, n (%)	148 (36.4)	107 (31.0)	0.123
Valvular or other heart disease, n (%)	57 (14.0)	47 (13.6)	0.880
Atrial fibrillation confirmed on ECG, n (%)	128 (31.5)	92 (26.7)	0.151
Diabetes mellitus, n (%)	107 (26.3)	89 (25.8)	0.878
Hypercholesterolemia, n (%)	165 (40.5)	112 (32.5)	0.022
Current smoker, n (%)	64 (15.8)	58 (16.9)	0.685
Pre-stroke function without any symptoms (mRS=0)	282 (69.3)	227 (65.8)	0.308
Warfarin anticoagulation, n (%)	10 (2.5)	3 (0.9)	0.096
Statin or other lipid lowering agent, n (%)	216 (53.2)	152 (44.0)	0.013
Final diagnosis at time of hospital separation			
Nonstroke, n (%)	16 (4.0)	10 (2.9)	0.442
Presumed stroke pathology, n (%)			
Large artery occlusion because of significant atheroma	115 (29.8)	112 (33.8)	0.323
Small vessel or perforating vessel lacunar disease	56 (14.5)	56 (16.9)	
Cardioembolism	133 (34.5)	95 (28.7)	
Other or uncertain pathogenesis	82 (21.2)	68 (20.5)	

Data are n (%), mean (SD), or median (Q1, Q3). The P values are based on χ^2, Student *t* test, or Wilcoxon signed-rank test. BP indicates blood pressure; GCS, Glasgow coma scale; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

†Scores on the GCS range from 15 (normal) to 3 (deep coma).

Ricci et al[22] found no association of previous aspirin use with baseline stroke severity in the third international stroke trial. Additionally, Pan et al[6] did not demonstrate increased recanalization rate in patients on prior APT in their meta-analysis. In ENCHANTED trial, more patients in the prior APT group had atrial fibrillation and a final diagnosis of cardioembolic stroke, features which may suggest a lower efficacy of low-dose alteplase because of proximal vessel occlusion and greater clot burden. Nonetheless, low-dose alteplase was associated with better clinical outcome on shift analysis of 90-day mRS.

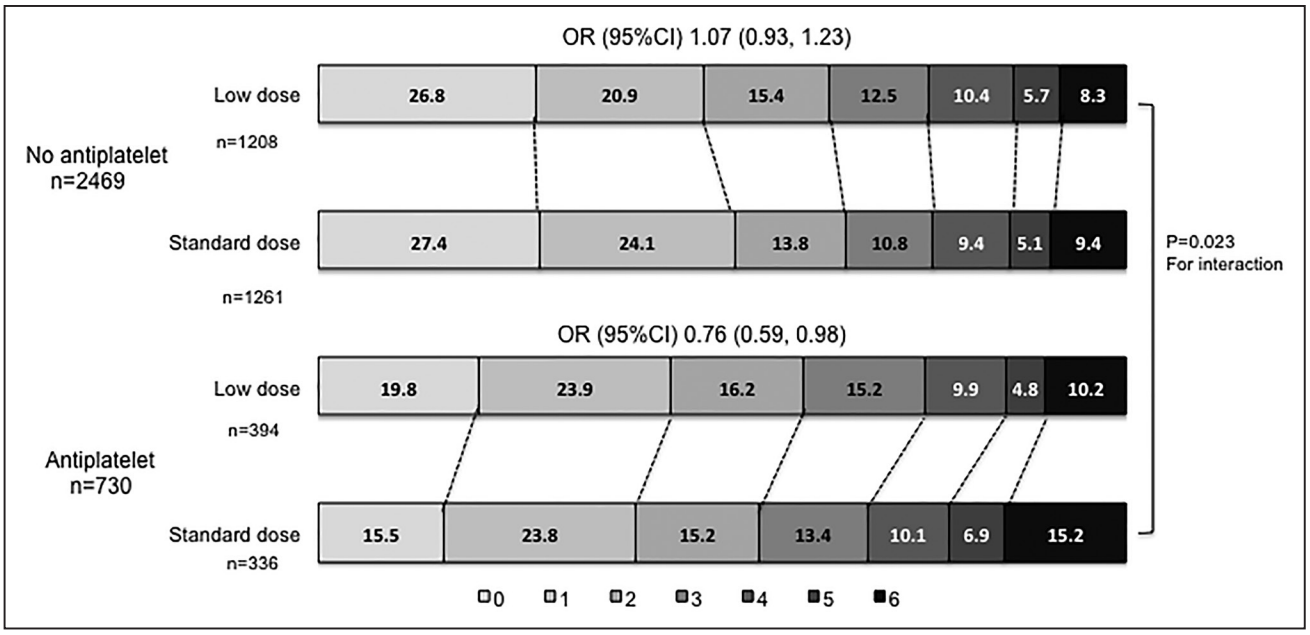

Figure 1. Global functional outcome at 90 days in patients with and without prior antiplatelet therapy by randomized treatment. The figure shows the raw distribution of scores on the modified Rankin Scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms; 1, symptoms without clinical significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. Unadjusted odds ratios (ORs; and 95% confidence intervals [CIs]) are provided for ordinal shift of mRS between low- and standard-dose intravenous alteplase by patients with and without prior use of antiplatelet therapy and acute ischemic stroke.

On the basis of these current data, many study protocols and guidelines have recommended that APT be avoided for at least 24 hours after the use of alteplase.[23] Although higher sICH was seen with de novo use of aspirin at the time of thrombolysis in the ARTIS trial,[8] only 3 (0.53%) episodes of sICH (according to the SITS-MOST definition [Safe Implementation of Thrombolysis in Stroke-Monitoring Study]) occurred among 571 patients who also received antithrombotic therapy (antiplatelet or heparin) within the first 24 hours after thrombolysis in the ENCHANTED trial. These numbers are too small to offer a reliable assessment of risk or to assess differences according to variable doses of alteplase. However, the Cochrane review of thrombolysis trials concluded that the odds of mortality increases with early administration of APT; the majority of this risk occurring in the first 24 hours.[24]

Another important aspect of APT in AIS relates to the type, number, and combination of prior agents for which the data are scarce, but a significant dose response in relation to the number of antiplatelet agents prescribed has been reported.[5,6] A higher sICH risk was noted in thrombolysis-treated patients on combination therapy, in particular aspirin and clopidogrel, who were registered in the Virtual International Stroke Trials Archive database.[25] Such an association was also noted in the SITS International Stroke Thrombolysis Register[3] and the Get With the Guidelines registry cohort where the combination aspirin and clopidogrel were associated with a number needed to harm of 60 compared with 147 for aspirin monotherapy.[4] Nonetheless, low number of patients and sICH in all these studies limits the reliability of these data and the recommendations that can be made for clinical practice. Moreover, uncertainty exists over the role of newer antiplatelet agents in the setting of thrombolysis for AIS, although a small pilot phase trial demonstrated the safety of a GP IIb/IIIa (glycoprotein IIb/IIIa) inhibitor with low-dose alteplase.[26] Being a pragmatic academic study, ENCHANTED is unable to provide any information about the relation of type, dose, combination, duration, indication, and timing of the last dose of APT before thrombolysis to adverse outcomes, although it would seem reasonable to assume that aspirin monotherapy was the most commonly prescribed antiplatelet regimen used in participating countries.

Other limitations of our study include those related to an open-label trial, despite our efforts to minimize reporting bias, concealment of treatment allocation, rigorous assessment of adverse events, and blinded evaluation of clinical outcomes using established criteria. Because the ENCHANTED trial included patients with generally milder stroke severity with a slightly longer treatment delay from onset than in previous trials[1] or registries,[27] there may be concerns over the generalizability of these data, whereas imprecision in the estimates of the treatment effect may have arisen from the timing and interobserver variability in scoring of the mRS.[28]

Conclusions

Our study suggests that the use of low-dose, as compared with standard-dose, intravenous alteplase may be associated with improved clinical outcome in patients who were on prior APT. Therefore, we consider a formal evaluation of low- versus standard-dose alteplase in a randomized controlled trial of patients on prior APT is warranted. In addition, the potential beneficial effects of low-dose alteplase in other patient groups considered at high risk of sICH could be considered.[29]

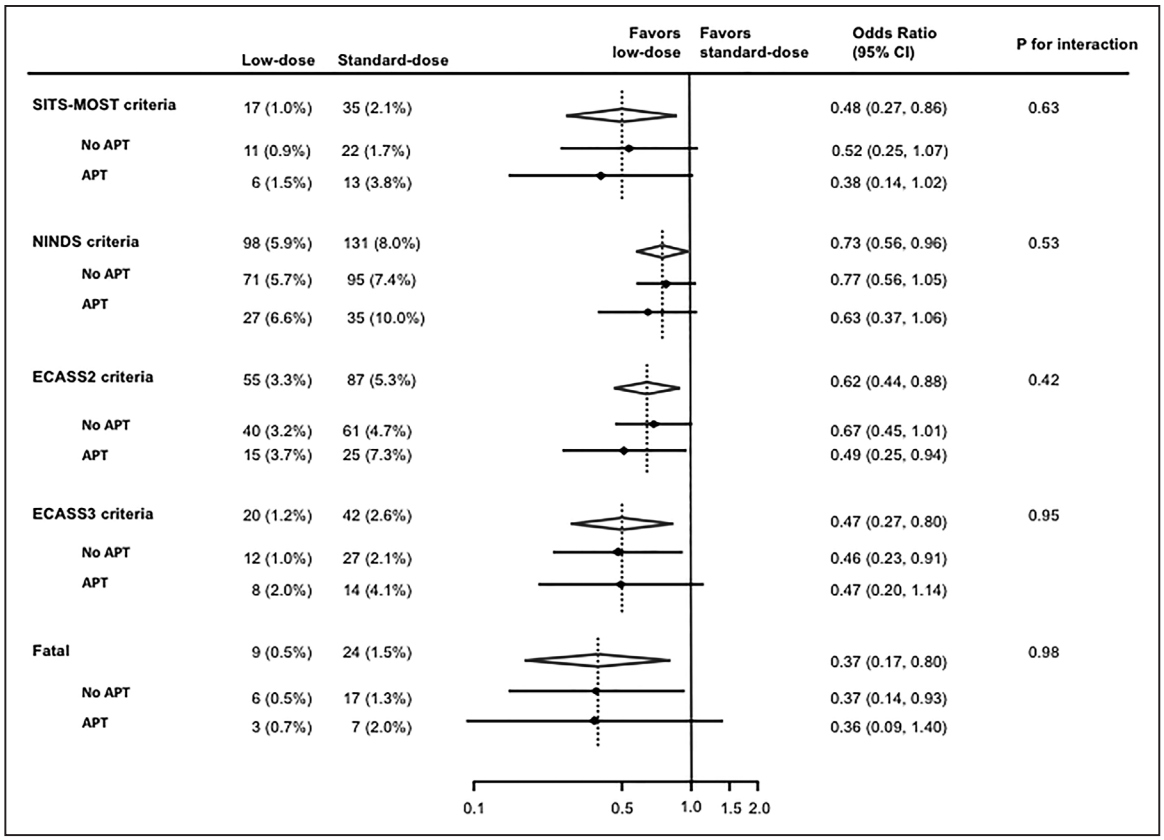

Figure 2. Symptomatic intracerebral hemorrhage in patients with and without prior antiplatelet use, by randomized treatment. The figure shows the rates of symptomatic intracerebral hemorrhage (sICH) on follow-up neuroimaging for patients treated with low-dose and standard-dose intravenous alteplase for acute ischemic stroke, overall and for patients with and without prior antiplatelet therapy (APT). Definitions of sICH shown include SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study), NINDS (National Institute of Neurological Disorders and Stroke), ECASS2 and ECASS3 (European Cooperative Acute Stroke Study 2 and 3), and fatal. The overall effect is represented by the open diamond for each sICH definition. For subcategories, black diamonds represent point estimates and horizontal lines represent 95% confidence intervals (CIs).

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Low- Versus Standard-Dose Alteplase in Patients on Prior Antiplatelet Therapy: The ENCHANTED Trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study)

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on behalf of the ENCHANTED Investigators

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SUPPLEMENTAL MATERIAL
Low- versus standard-dose alteplase in patients on prior antiplatelet therapy: the ENCHANTED trial
Robinson TG et al

Definitions of Symptomatic Intracerebral Hemorrhage

For intracererbal hemorrhage, bleeding was coded as HI1 (small petechiae along infarct margins), HI2 (confluent petechiae within infarcted area without space-occupying effect), PH1 (blood clot(s) in <30% of infarcted area with slight space-occupying effect) and PH2 (blood clot(s) in >30% of infarcted area with substantial space-occupying effect). In addition, independent assessors were asked to adjudicate if hemorrhage was the predominant cause of neurological worsening, and if there was evidence of midline shift. These assessments enabled the following definitions of symptomatic intracerebral hemorrhage (sICH) to be adjudicated: Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST): large or remote parenchymal ICH (type 2, defined as greater than 30% of the infarcted area affected by hemorrhage with mass effect or extension outside the infarct) combined with neurological deterioration ($\geq$4 points on the NIHSS) or leading to death within 24 to 36 hours [Wahlgren et al, 2007]; any ICH associated with neurological deterioration ($\geq$1 point change in NIHSS score) from baseline or death within 24 to 36 hours (NINDS) [NINDS Study Group, 1995]; any ICH with neurological deterioration ($\geq$4 points on the NIHSS) from baseline or death within 24 to 36 hours (ECASS2) [Hacke et al, 1998]; any ICH with neurological deterioration ($\geq$4 points increase on the NIHSS) from baseline or death within 36 hours (ECASS3) [Hacke et al, 2008]; either significant ICH (local or distant from the infarct) or significant hemorrhagic transformation of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment (IST3) [IST-3 Collaborative Group, 2012]; and fatal ICH, any type 2 parenchymal ICH and death within 7 days.

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Supplemental Table I: Baseline characteristics by prior antiplatelet use

	Antiplatelet agent		P value
	No (n=2533)	Yes (n=752)	
Time from stroke onset to randomization (hrs), mean (SD)	2.8 (0.9)	2.6 (0.9)	0.0003
Female, n (%)	949 (38)	296 (39)	0.347
Age (years), mean (SD)	65 (13)	71 (11)	<0.0001
≥80, n (%)	308 (12)	164 (22)	<0.0001
Ethnicity, Asian	1750 (69)	324 (43)	<0.0001
Clinical features			
Systolic BP (mmHg), mean (SD)	149 (20)	149 (20)	0.715
Diastolic BP (mmHg), mean (SD)	85 (13)	82 (13)	<0.0001
Heart rate (beats per minute), mean (SD)	79 (15)	79 (17)	0.844
NIHSS score*			
Median (Q1, Q3)	8 (5-14)	8 (5-14)	0.670
≥14, n (%)	646 (26)	203 (27)	0.412
GCS score†, median (Q1, Q3)	15 (14-15)	15 (13-15)	0.815
Visible early ischemic changes on brain imaging, n (%)	556 (22)	214 (29)	0.0002
Mass effect on brain imaging, n (%)	34 (1)	13 (2)	0.433
Medical history			
Hypertension, n (%)	1478 (58)	584 (78)	<0.0001
Currently treated hypertension, n (%)	951 (38)	544 (72)	<0.0001
Previous stroke, n (%)	341 (14)	247 (33)	<0.0001
Coronary artery disease, n (%)	223 (9)	255 (34)	<0.0001
Valvular or other heart disease, n (%)	130 (5)	104 (14)	<0.0001
Atrial fibrillation confirmed on ECG, n (%)	416 (16)	220 (29)	<0.0001
Diabetes Mellitus, n (%)	449 (18)	196 (26)	<0.0001
Hypercholesterolemia, n (%)	278 (11)	277 (37)	<0.0001
Current smoker, n (%)	647 (26)	122 (16)	<0.0001
Pre-stroke function without any symptoms (mRS=0)	2163 (86)	509 (68)	<0.0001
Warfarin anticoagulation, n (%)	69 (3)	13 (2)	0.125
Statin or other lipid lowering agent, n (%)	247 (10)	368 (49)	<0.0001
Final diagnosis at time of hospital separation			
Non-stroke, n (%)	71 (3)	26 (4)	0.376
Presumed stroke pathology, n (%)			<0.0001
Large artery occlusion due to significant atheroma	1042 (44)	227 (32)	
Small vessel or perforating vessel lacunar disease	559 (23)	112 (16)	
Cardio-embolism	413 (17)	228 (32)	
Other or uncertain etiology	378 (16)	150 (21)	

Data are n (%), mean (SD), or median (Q1, Q3). The P values are based on Chi-square, T test, or Wilcoxon signed-rank test

NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow coma scale, mRS: modified Rankin scale, CT: computerized tomography, MRI: magnetic resonance imaging

*Scores on the National Institutes of Health stroke scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficits.

† Scores on the Glasgow coma scale (GCS) range from 15 (normal) to 3 (deep coma)

Supplemental Table II: Use of alteplase and other management details during the first 7 days of hospital admission in patients with and without prior antiplatelet therapy

	Anti-platelet agent		P value
	No (n=2533)	Yes (n=752)	
Thrombolysis treatment			
Body Weight			
Patients with estimated body weight prior to alteplase, n(%)	2533 (100.0)	752(100.0)	
Estimated measurement prior to alteplase use (kg), mean (SD)	69.3 (14.2)	71.5(14.8)	0.0002
Patients with direct measured body weight after alteplase use, n(%)	2302 (90.9)	666(88.6)	0.0589
Direct measured body weight after alteplase use (kg), mean (SD)	68.7 (14.3)	71.2(14.9)	0.0001
Alteplase given			
Any given, n(%)	2499 (98.7)	742(98.7)	0.979
Bolus dose (mg), mean (SD)	6.2 (1.8)	6.4(1.4)	0.0021
Infusion over 60 mins dose (mg), mean (SD)	45.7 (14.0)	45.8(14.0)	0.766
Time from randomization to treatment (mins), median (Q1, Q3)	5.8 (2.1-12.0)	5.0(2.0-9.5)	0.0031
Recruited in China	9.5 (3.5-17.7)	9.2(4.3-19.8)	0.386
Not recruited in China	4.1 (1.4-7.5)	4.3(1.6-7.4)	0.715
Time from stroke onset to treatment, median (Q1, Q3)	173 (130-220)	161.5(116-210)	<0.0001
Recruited in China	200 (161-236)	200(160-230)	0.617
Not recruited in China	145 (110-190)	147(110-195)	0.815

	Anti-platelet agent		P value
	No (n=2533)	Yes (n=752)	
Management			
Cerebral angiogram undertaken, n(%)	127 (5.0)	44 (5.9)	0.364
Occluded cerebral vessel identified, n(%)	115 (91.3)	36 (81.8)	0.0867
Endovascular clot retrieval used, n(%)	91 (71.7)	33 (75.0)	0.668
Any intravenous BP lowering treatment in first 24 hours, n(%)	620 (24.6)	172 (23.0)	0.358
Any intravenous BP lowering treatment in days 2-7, n(%)	465 (18.7)	146 (19.6)	0.599
Systolic BP at 24 hours (mmHg), mean (SD)	136.7 (19.5)	136.6 (20.4)	0.833
Intubation and ventilation, n(%)	126 (5.1)	44 (5.9)	0.379
Fever occurrence, n(%)	450 (18.1)	168 (22.5)	0.0077
Fever treated, n(%)	383 (17.3)	135 (21.0)	0.0303
Nasogastric feeding given, n(%)	429 (17.3)	154 (20.6)	0.0371
Patient mobilized by therapist, n(%)	1010 (40.7)	443 (59.3)	<0.0001
Compression stockings used, n(%)	202 (8.1)	81 (10.9)	0.0209
Subcutaneous heparin used, n(%)	460 (18.2)	167 (22.2)	0.0131
Any antithrombotic agent (antiplatelet or heparin) used in first 24 hours, n(%)	434 (17.2)	137 (18.3)	0.482
Intravenous traditional Chinese medicine administered, n(%)	799 (32.2)	140 (18.7)	<0.0001
Intravenous steroids administered, n(%)	59 (2.4)	18 (2.4)	0.957
Hemicraniectomy performed, n(%)	26 (1.1)	9 (1.2)	0.714
Any neurosurgery performed, n(%)	76 (3.0)	37 (4.9)	0.0112
Any stroke unit admission, n(%)	1448 (58.3)	526 (70.5)	<0.0001
Any intensive care unit admission, n(%)	617 (24.8)	155 (20.8)	0.0225
Any rehabilitation given, n(%)	1176 (47.3)	464 (62.1)	<0.0001
Decision to withdrawal active care, n(%)	59 (2.4)	26 (3.5)	0.0975

Data are n (%), mean (SD), or median (IQR). The P values are based on Chi-square, T test, or Wilcoxon signed-rank test

BP: blood pressure

Supplemental Table III: Major outcomes at 90 days in patients with and without prior antiplatelet therapy

	Antiplatelet agent							
	No	Yes	OR	P value	AOR[1]	P value	AOR[2]	P value
Death or disability (mRS score 2+3+4+5+6)	1244/2469 (50.4)	426/730 (58.4)	1.38 (1.17-1.63)	<0.001	1.05 (0.85-1.28)	0.672	1.01 (0.81-1.26)	0.953
Death or major disability (mRS score 3+4+5+6)	884/2469 (35.8)	311/730 (42.6)	1.33 (1.13-1.58)	<0.001	0.96 (0.78-1.19)	0.732	0.95 (0.75-1.20)	0.662
Death (mRS score 6)	219/2533 (8.7)	91/752 (12.1)	1.46 (1.12-1.89)	0.005	0.91 (0.67-1.25)	0.568	1.15 (0.80-1.65)	0.449
mRS categories (unadjusted)		.	1.41 (1.22-1.63)	<0.001	1.03 (0.87-1.21)	0.751	1.03 (0.87-1.21)	0.770
0	669/2469 (27.1)	130/730 (17.8)						
1	556/2469 (22.5)	174/730 (23.8)						
2	360/2469 (14.6)	115/730 (15.8)						
3	287/2469 (11.6)	105/730 (14.4)						
4	245/2469 (9.9)	73/730 (10.0)						
5	133/2469 (5.4)	42/730 (5.8)						
6 (death at 90 days)	219/2469 (8.9)	91/730 (12.5)						

mRS, modified Rankin scale; AOR, adjusted odds ratio.

[1]Adjusted analysis for minimization variables including NIHSS score and time from onset to randomization, and baseline variables: age sex, ethnicity, pre-morbid mRS (0 or 1), warfarin anticoagulant, any history of stroke, coronary artery disease, diabetes mellitus, atrial fibrillation, and randomized treatment (low- vs. standard-dose alteplase).

[2]Additionally adjusted for management variables: fever occurrence, nasogastric feeding, patient mobilized by therapist, compression stockings used, subcutaneous heparin used, intravenous traditional Chinese medicine administered, any neurosurgery performed, any stroke unit admission, any intensive care unit admission, and any rehabilitation given.

Supplemental Table IV: Symptomatic intracerebral hemorrhage according to standard definitions in patients with and without prior antiplatelet therapy

Symptomatic ICH	Antiplatelet					
	No (n=2533)	Yes (n=752)	OR	P value	AOR[1]	P value
SITS-MOST criteria	33 (1.3)	19 (2.5)	1.96 (1.11-3.47)	0.020	1.82 (1.00-3.30)	0.051
NINDS criteria	166 (6.6)	62 (8.2)	1.28 (0.95-1.74)	0.101	1.19 (0.87-1.64)	0.282
ECASS2 criteria	101 (4.0)	40 (5.3)	1.35 (0.93-1.97)	0.115	1.31 (0.88-1.94)	0.182
ECASS3 criteria	39 (1.5)	22 (2.9)	1.93 (1.14-3.27)	0.015	1.82 (1.05-3.17)	0.034
IST-3 criteria	56 (2.2)	27 (3.6)	1.65 (1.03-2.63)	0.036	1.48 (0.91-2.40)	0.117
Clinician-reported	206 (8.1)	81 (10.8)	1.36 (1.04-1.79)	0.025	1.13 (0.85-1.51)	0.390
Fatal	23 (0.9)	10 (1.3)	1.47 (0.70-3.10)	0.311	1.37 (0.63-2.99)	0.434
Adjudicated any ICH	406 (16.0)	164 (21.8)	1.46 (1.19-1.79)	<0.001	1.35 (1.08-1.68)	0.007
Any ICH	457 (18.0)	180 (23.9)	1.43 (1.18-1.74)	<0.001	1.32 (1.07-1.63)	0.010
Death or neurological deterioration in first 24 hours	207 (8.2)	61 (8.1)	0.99 (0.74-1.34)	0.958	0.96 (0.70-1.30)	0.777
Death or neurological deterioration in first 7 days	306 (12.1)	94 (12.5)	1.04 (0.81-1.33)	0.756	0.98 (0.76-1.27)	0.902

ICH, intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study; NINDS, National Institute of Neurological Disorders and Stroke; ECASS, European Co-operative Acute Stroke Study; IST, International Stroke Trial; AOR, adjusted odds ratio.

[1]Adjusted analysis baseline NIHSS score, age, time from onset to randomization (<3 vs. ≥3 hr), pre-morbid use of aspirin, atrial fibrillation, and randomized treatment (low-dose vs. standard-dose).

Supplemental Table V: Major outcomes at 90 days in patients with and without prior antiplatelet use by randomized treatment

Outcome	Randomized treatment, n(%)		OR	P value for trend
	Low-dose	Standard-dose		
Death or disability (mRS score 2+3+4+5+6)				0.053
No antiplatelet	632/1208 (52.3)	612/1261 (48.5)	1.16 (0.99-1.36)	
Antiplatelet	222/394 (56.4)	204/336 (60.7)	0.84 (0.62-1.12)	
Death or major disability (mRS score 3+4+5+6)				0.065
No antiplatelet	446/1208 (36.9)	438/1261 (34.7)	1.10 (0.93-1.30)	
Antiplatelet	158/394 (40.1)	153/336 (45.5)	0.80 (0.60-1.08)	
Death (mRS score 6)				0.229
No antiplatelet	100/1240(8.1)	119/1293(9.2)	0.87 (0.66-1.14)	
Antiplatelet	40/407(9.8)	51/345(14.8)	0.63 (0.40-0.98)	

mRS denotes modified Rankin scale, OR odds ratio.

All estimates are based on shift to a less favorable outcome.

Supplemental Table VI: Symptomatic intracerebral hemorrhage and other adverse outcomes in patients with and without prior antiplatelet use by randomized treatment

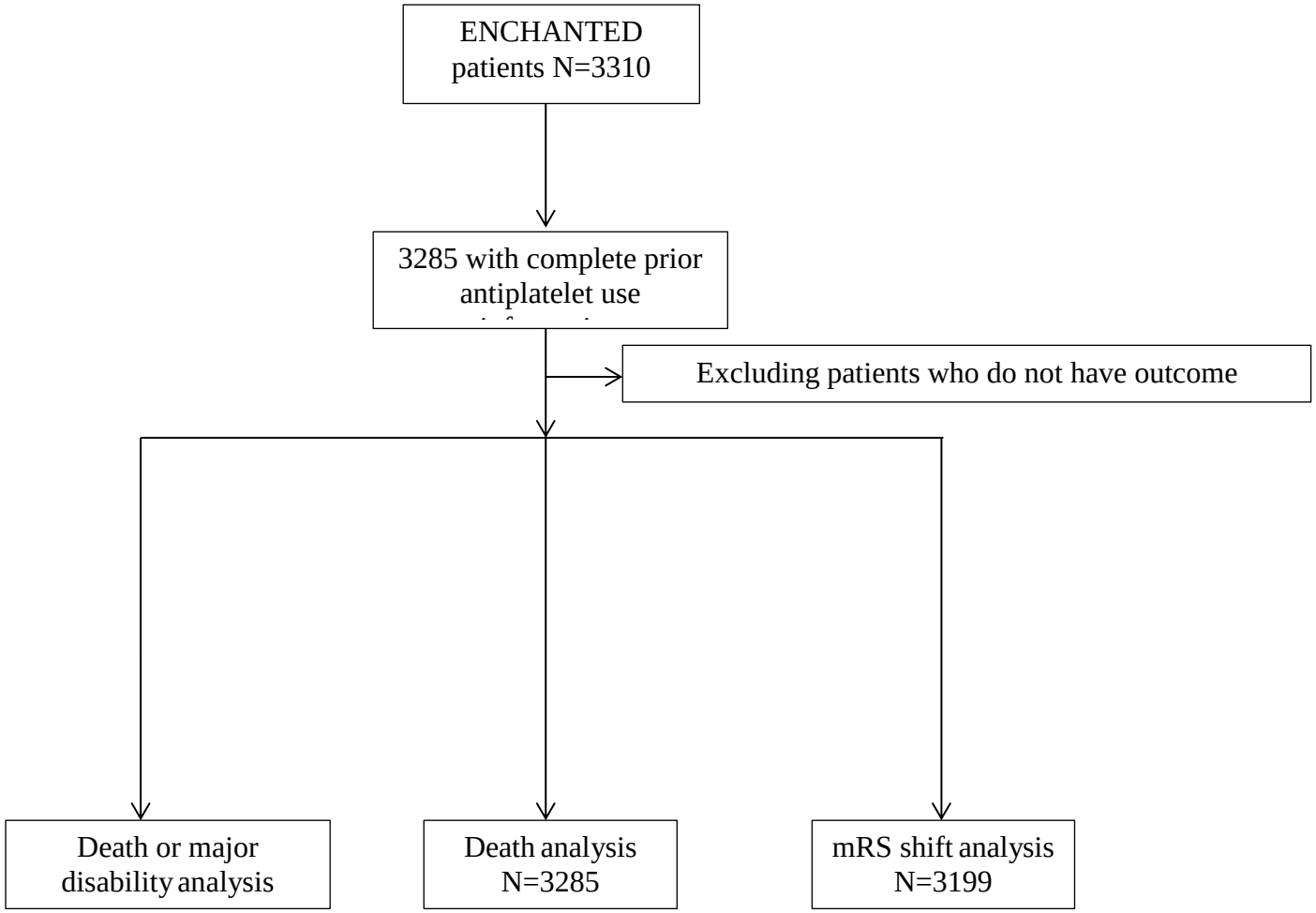
Symptomatic ICH	Low-dose	Standard-dose	OR	P value
SITS-MOST criteria				0.627
No antiplatelet	11/1240 (0.9)	22/1293 (1.7)	0.52 (0.25-1.07)	
Antiplatelet	6/407 (1.5)	13/345 (3.8)	0.38 (0.14-1.02)	
NINDS criteria				0.530
No antiplatelet	71/1240 (5.7)	95/1293 (7.4)	0.77 (0.56-1.05)	
Antiplatelet	27/407 (6.6)	35/345 (10.0)	0.63 (0.37-1.06)	
ECASS2 criteria				0.420
No antiplatelet	40/1240 (3.2)	61/1293 (4.7)	0.67 (0.45-1.01)	
Antiplatelet	15/407 (3.7)	25/345 (7.3)	0.49 (0.25-0.95)	
ECASS3 criteria				0.952
No antiplatelet	12/1240 (1.0)	27/1293 (2.1)	0.46 (0.23-0.91)	
Antiplatelet	8/407 (2.0)	14/345 (4.1)	0.47 (0.20-1.14)	
IST-3 criteria				0.875
No antiplatelet	21/1240 (1.7)	35/1293 (2.7)	0.62 (0.36-1.07)	
Antiplatelet	12/407 (3.0)	15/345 (4.4)	0.67 (0.31-1.45)	
Clinician-reported				0.250
No antiplatelet	98/1240 (7.9)	108/1293 (8.4)	0.94 (0.71-1.25)	
Antiplatelet	37/407 (9.1)	44/345 (12.8)	0.68 (0.43-1.09)	
Fatal				0.983
No antiplatelet	6/1240 (0.5)	17/1293 (1.3)	0.37 (0.14-0.93)	
Antiplatelet	3/407 (0.7)	7/345 (2.0)	0.36 (0.09-1.40)	
Adjudicated any ICH				0.662
No antiplatelet	189/1240 (15.2)	217/1293 (16.8)	0.89 (0.72-1.10)	

Antiplatelet	88/216 (21.6)	76/345 (22.0)	0.98 (0.69-1.38)	
Any ICH				0.870
No antiplatelet	214/1240 (17.3)	243/1293 (18.8)	0.90 (0.74-1.10)	
Antiplatelet	95/407 (23.3)	85/345 (24.6)	0.93 (0.67-1.30)	
Death or neurological deterioration in the first 24 hours				0.047
No antiplatelet	103/1240 (8.3)	104/1293 (8.0)	1.04 (0.78-1.38)	
Antiplatelet	25/407 (6.1)	36/345 (10.4)	0.56 (0.33-0.96)	
Death or neurological deterioration in the first 7 days				0.137
No antiplatelet	146/1240 (11.8)	160/1293 (12.4)	0.95 (0.74-1.20)	
Antiplatelet	42/407 (10.3)	52/345 (15.1)	0.65 (0.42-1.00)	

ICH: intracerebral hemorrhage; SITS-MOST: Safe Implementation of Thrombolysis in Stroke Monitoring Study; NINDS: National Institute of Neurological Disorders and Stroke; ECASS: European Co-operative Acute Stroke Study; IST: International Stroke Trial, OR: odds ratio.

Figure Legends

Supplemental Figure I: Flow chart


ENCHANTED
patients N=3310
3285 with complete prior
antiplatelet use
Excluding patients who do not have outcome
Death or major
disability analysis
Death analysis
N=3285
mRS shift analysis
N=3199