Safety of Intravenous Thrombolysis for Acute Ischemic Stroke in Patients Receiving Antiplatelet Therapy at Stroke Onset

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Background and Purpose—Antiplatelets (APs) may increase the risk of symptomatic intracerebral hemorrhage (ICH) following intravenous thrombolysis after ischemic stroke.

Methods—We assessed the safety of thrombolysis under APs in 11 865 patients compliant with the European license criteria and recorded between 2002 and 2007 in the Safe Implementation of Treatments in Stroke (SITS) International Stroke Thrombolysis Register (SITS-ISTR). Outcome measures of univariable and multivariable analyses included symptomatic ICH (SICH) per SITS Monitoring Study (SITS-MOST [deterioration in National Institutes of Health Stroke Scale ≥4 plus ICH type 2 within 24 hours]), per European Cooperative Acute Stroke Study II (ECASS II [deterioration in National Institutes of Health Stroke Scale ≥4 plus any ICH]), functional outcome at 3 months and mortality.

Results—A total of 3782 (31.9%) patients had received 1 or 2 AP drugs at baseline: 3016 (25.4%) acetylsalicylic acid (ASA), 243 (2.0%) clopidogrel, 175 (1.5%) ASA and dipyridamole, 151 (1.3%) ASA and clopidogrel, and 197 (1.7%) others. Patients receiving APs were 5 years older and had more risk factors than AP naïve patients. Incidences of SICH per SITS-MOST (ECASS II respectively) were as follows: 1.1% (4.1%) AP naïve, 2.5% (6.2%) any AP, 2.5% (5.9%) ASA, 1.7% (4.2%) clopidogrel, 2.3% (5.9%) ASA and dipyridamole, and 4.1% (13.4%) ASA and clopidogrel. In multivariable analyses, the combination of ASA and clopidogrel was associated with increased risk for SICH per ECASS II (odds ratio, 2.11; 95% CI, 1.29 to 3.45; \( P = 0.003 \)). However, we found no significant increase in the risk for mortality or poor functional outcome, irrespective of the AP subgroup or SICH definition.

Conclusion—The absolute excess of SICH of 1.4% (2.1%) in the pooled AP group is small compared with the benefit of thrombolysis seen in randomized trials. Although caution is warranted in patients receiving the combination of ASA and clopidogrel, AP treatment should not be considered a contraindication to thrombolysis. (Stroke. 2010;41:288-294.)

Key Words: stroke ■ thrombolysis ■ antiplatelets ■ hemorrhage ■ outcome

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) within the 3-hour time window is currently one of the approved medical therapies for acute ischemic stroke. Randomized controlled trials have demonstrated the efficacy of intravenous thrombolysis for patients up to 4.5 hours after onset of acute ischemic stroke with acceptable safety profile. The most feared complication of rtPA therapy is symptomatic intracerebral hemorrhage (ICH), and concerns have been raised regarding thrombolysis after antiplatelet (AP) treatment, which patients may be under before stroke. AP drugs impair platelet function and might increase the risk of thrombolysis-related bleeding.

Previous analyses of the risk for thrombolysis-associated symptomatic ICH (SICH) after treatment with acetylsalicylic acid (ASA) yielded contradictory results. Although some studies found that ASA increases the risk for SICH, others do not report an association between ASA comedication at stroke onset and the incidence of SICH. The recently published multivariable analysis of SITS-MOST (Safe Implementation of Treatments in Stroke-Monitoring...
Study) data revealed that patients receiving ASA at stroke onset had a significantly higher rate of SICH per SITS-MOST definition but not per the National Institute of Neurological Disorders and Stroke (NINDS) definition.

Further, data on the use of clopidogrel (CLP) or combined AP treatments before thrombolysis are limited and point toward an increased risk for SICH under dual AP inhibition. A recent study assessing risk factors for thrombolysis-related SICH found that the combination of ASA and CLP particularly was associated with a significantly increased risk for SICH.

We assessed the safety of thrombolysis in patients under various AP regimens such as ASA and CLP monotherapy, or combinations of ASA with dipyridamole (DP) or CLP at stroke onset using data recorded in the prospective SITS International Stroke Thrombolysis Register (ISTR).

Methods

Study Population and Design

The SITS database is a worldwide prospective, open, multinational, multicenter audit of thrombolysis. Details of data collection and management have been published previously. Data sets include information on baseline and demographic characteristics, risk factors and medication history, baseline and follow-up stroke severity measured by National Institutes of Health Stroke Scale (NIHSS), baseline and follow-up (at 22 to 36 hours) imaging data, functional outcome assessed as modified Rankin Scale (mRS) at 3 months, and primary cause of death. The current analysis is based on the patients within the SITS registry strictly fulfilling inclusion and exclusion criteria for thrombolysis according to the terms of the rtPA conditional licensing approval. Eligible patients were between 18 and 80 years of age and received treatment within the 3-hour time window. Exclusion criteria included severe stroke defined by NIHSS \( \geq 25 \) or by baseline imaging, administration of heparin within the previous 48 hours and an elevated thromboplastin time, and previous treatment with oral anticoagulants. Recruitment of patients opened on December 25, 2002; the cut-off for the current analysis was November 15, 2007. In the SITS case report form, patients treated with ASA, DP, CLP, and other APs at stroke onset were recorded. Based on these data, we defined 7 subgroups: (1) ASA only, (2) CLP only, (3) combined ASA and DP, (4) combined ASA and CLP, (5) other AP medication (eg, triflusal), (6) any AP medication (all AP groups combined), and (7) no previous use of APs.

Outcome Measures

The main outcome measure was the incidence of SICH according to the SITS-MOST criteria (local or remote parenchymal hemorrhage type 2 on the 22- to 36-hour post-treatment imaging scan, combined with a neurological deterioration of \( \geq 4 \) points compared with baseline NIHSS or the lowest NIHSS value between baseline and 24 hours). To enable comparisons with previously published data, 2 additional definitions were used: SICH per NINDS definition (any hemorrhage plus any neurological deterioration) and per ECASS II (European-Australasian Acute Stroke Study) definition (any hemorrhage with neurological deterioration, as indicated by an NIHSS score \( \geq 4 \) than the value at baseline or the lowest value within 7 days, or any hemorrhage leading to death). Further, functional outcome (mRS 0 to 1 versus 2 to 6 for excellent recovery and 0 to 2 versus 3 to 6 for functional independence) and mortality at 3 months were compared between subgroups.

Statistical Analysis

Pearson's \( \chi^2 \) and Mann–Whitney \( U \) tests were used for comparisons of categorical and continuous variables where appropriate. For assessment of baseline characteristics, each AP group was compared with AP naïve patients separately. For categorical variables, percentage proportions were calculated by dividing the number of events by the total number of patients, excluding missing or unknown cases. Odds ratios (ORs) for the different outcome parameters were calculated using the group without AP treatment as reference group.

Multivariable analyses were performed to account for substantial baseline differences between subgroups. For each outcome variable, a separate multivariable analysis was performed. AP naïve patients were defined as reference group for calculation of ORs. All baseline and demographic characteristics shown in Table 1 were included in the multivariable model. Multivariable analyses were done by logistic regression analysis. All statistical analyses were performed using the STATISTICA software (Version 8.0).

Results

Population

Between 2002 and 2007, 11,865 patients receiving thrombolysis according to the European rtPA licensing approval were recorded in the SITS-ISTR database. Of these, 3782 (31.9%) patients received at least one AP drug (called any AP) at baseline, 7954 (67.0%) did not receive AP treatment before thrombolysis, and for 129 (1.1%) patients, data on AP treatment were unknown or missing. Of the 3782 patients who received any AP, 3016 (25.4%) received ASA, 243 (2.0%) CLP, 175 (1.5%) ASA and DP, 151 (1.3%) ASA and CLP, and 197 (1.7%) other APs. Baseline characteristics and risk factors of the patients separated by AP group are listed in Table 1. Patients with AP pretreatment were significantly older (5 years), were less likely to be functionally independent before stroke, and had a higher incidence of cardiovascular risk factors (diabetes, hypertension, atrial fibrillation, previous stroke), compared with those without AP therapy. AP-treated patients had similar stroke severity, baseline systolic blood pressure, and onset to treatment times.

Univariate Analyses

The overall incidence of SICH was 1.5% (n = 179) per SITS-MOST definition, 7.2% (n = 832) per NINDS, and 4.8% (n = 543) per ECASS II. In AP naïve patients, SICH occurred in 1.1% (n = 85) according to SITS-MOST definition, in 6.5% (n = 507) per NINDS definition, and in 4.1% (n = 317) according to ECASS II criteria (Table 2). Patients receiving any AP treatment had a risk for SICH of 2.5% (n = 94) per SITS-MOST (OR, 2.36; 95% CI, 1.76 to 3.17), 8.8% (n = 325) per NINDS (OR, 1.38; 95% CI, 1.19 to 1.60), and 6.2% (n = 226) per ECASS II (OR, 1.53; 95% CI, 1.29 to 1.82). Incidence of SICH was highest among patients receiving a combination of ASA and CLP therapy before thrombolysis, regardless of the definition (4.1% (n = 6) per SITS-MOST (OR, 3.83; 95% CI, 1.65 to 9.81); 15.2% (n = 22) per NINDS (OR, 2.51; 95% CI, 1.58 to 3.97), and 13.4% (n = 19) per ECASS II (OR, 3.47; 95% CI, 2.12 to 5.68; Table 2).

Distributions of the outcome scores at 3 months assessed by mRS are presented in Figure 1. The proportion of patients with excellent recovery (mRS 0 to 1) was 41.4% (n = 2813) in the group without previous AP drug use compared with 37.2% (n = 1239) with any AP treatment. 37.5% (n = 998) of patients under ASA, and 28.9% (n = 39) under ASA and CLP had an excellent recovery. Mortality at 3 months was higher in all AP groups, except for patients treated with ASA and DP; 10.6% (n = 727) of patients without previous AP treat-
Multivariable Analyses

To account for substantial differences in baseline and demographic characteristics between groups, multivariable logistic regression analyses were performed. Comparing any AP treatment versus no AP treatment, significantly higher odds were found for SICH per SITS MOST definition (OR, 1.28; 95% CI, 1.08 to 1.52; \( P = 0.0052 \)). However, treatment with any AP was neither associated with higher odds for SICH per NINDS or ECASS II definitions, nor with mortality or poor functional outcome (Figure 3).

The adjusted analysis of the different AP groups only revealed the combination of ASA plus CLP as a significant predictor for SICH compared with AP naïve patients per NINDS (OR, 1.74; 95% CI, 1.11 to 2.73; \( P = 0.0167 \)) definition and per ECASS II definition (OR, 2.11; 95% CI, 1.29 to 3.45; \( P = 0.0031 \)) but not per SITS-MOST criteria (Figure 3). There was no statistically significant difference in the multivariable analyses regarding odds for excellent recovery (mRS 0 to 1), independence for activities of daily living (mRS 0 to 2), or mortality at 3 months between the different AP subgroups and AP naïve patients (Figure 3).

Discussion

This observational study provides evidence that AP therapy after adjustment for baseline characteristics does not substantially increase the risk for SICH in patients treated with rtPA within 3 hours of stroke onset and according to the European licensing restrictions. The absolute excess of 1.4% of SICH per SITS-MOST definition under AP comedinations altogether did not translate into poor functional outcome or a higher mortality rate at 3 months. Thus, the net benefit of thrombolysis found in randomized controlled trials \(^2\) is maintained for patients with AP pretreatment. However, caution should be warranted in the subgroup of patients receiving the combination of CLP and ASA at stroke onset. These patients had considerably higher rates of SICH, and
the risk for SICH according to ECASS II and NINDS definitions remained significantly increased after adjustment for baseline characteristics. This is the largest series of patients investigating safety of thrombolysis on AP therapy so far. In accordance with other reports, one third of patients in the SITS registry were treated with AP drugs before thrombolysis. As reported previously, overall incidences of SICHs in our cohort were comparable to randomized controlled trial populations when similar definitions were used (NINDS 7.2% versus 8.6%; ECASS II 8.8% versus 4.8%). However, the absolute incidences of SICH varied considerably depending on the definition used. Whereas the percentage of SICH in patients using ASA and CLP was 4.1% per SITS-MOST definition, it was 13.4% according to ECASS II. Yet, the proportional increase in relation to AP naïve patients was comparable for both definitions (3.7-fold versus 3.3-fold). So far, there is no study systematically investigating the clinical meaningfulness and predictive value in terms of clinical outcomes of the different SICH definitions.

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>CLP</th>
<th>ASA+DP</th>
<th>ASA+CLP</th>
<th>Other AP</th>
<th>Any AP</th>
<th>No AP</th>
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<tr>
<td>SICH per SITS–MOST*</td>
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<td>n (%)</td>
<td>73 (2.5)</td>
<td>4 (1.7)</td>
<td>4 (2.3)</td>
<td>6 (4.1)</td>
<td>7 (3.7)</td>
<td>94 (2.5)</td>
<td>85 (1.1)</td>
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<td>OR (95% CI)</td>
<td>2.30 (1.67–3.15)</td>
<td>1.55 (0.56–4.26)</td>
<td>2.17 (0.79–5.97)</td>
<td>3.83 (1.65–8.91)</td>
<td>3.41 (1.56–7.47)</td>
<td>2.36 (1.76–3.17)</td>
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<tr>
<td>SICH per NINDS†</td>
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<td>n (%)</td>
<td>255 (8.6)</td>
<td>16 (6.7)</td>
<td>12 (6.9)</td>
<td>22 (15.2)</td>
<td>20 (10.5)</td>
<td>325 (8.8)</td>
<td>507 (6.5)</td>
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<td>OR (95% CI)</td>
<td>1.20 (1.02–1.41)</td>
<td>1.04 (0.62–1.73)</td>
<td>1.08 (0.60–1.96)</td>
<td>2.51 (1.58–3.97)</td>
<td>1.66 (1.04–2.66)</td>
<td>1.38 (1.19–1.60)</td>
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<td>SICH per ECASS II‡</td>
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<td>n (%)</td>
<td>171 (5.9)</td>
<td>10 (4.2)</td>
<td>10 (5.9)</td>
<td>19 (13.4)</td>
<td>16 (8.5)</td>
<td>226 (6.2)</td>
<td>317 (4.1)</td>
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<td>OR (95% CI)</td>
<td>1.45 (1.20–1.75)</td>
<td>1.03 (0.54–1.97)</td>
<td>1.46 (0.76–2.79)</td>
<td>3.47 (2.12–5.68)</td>
<td>2.13 (1.26–3.59)</td>
<td>1.53 (1.29–1.82)</td>
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<td>Excellent recovery§</td>
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<td>n (%)</td>
<td>998 (37.5)</td>
<td>79 (37.6)</td>
<td>63 (41.2)</td>
<td>39 (28.9)</td>
<td>60 (34.1)</td>
<td>1239 (37.2)</td>
<td>2813 (41.4)</td>
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<td>OR (95% CI)</td>
<td>0.90 (0.83–0.99)</td>
<td>0.88 (0.67–1.16)</td>
<td>1.03 (0.75–1.40)</td>
<td>0.64 (0.44–0.92)</td>
<td>0.80 (0.59–1.09)</td>
<td>0.89 (0.82–0.97)</td>
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<td>Functional independence¶</td>
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<td>n (%)</td>
<td>1425 (53.6)</td>
<td>107 (51.0)</td>
<td>102 (66.7)</td>
<td>61 (45.2)</td>
<td>88 (50.0)</td>
<td>1783 (53.5)</td>
<td>3922 (57.8)</td>
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<td>OR (95% CI)</td>
<td>0.92 (0.85–1.00)</td>
<td>0.81 (0.63–1.05)</td>
<td>1.44 (1.06–1.95)</td>
<td>0.70 (0.50–0.97)</td>
<td>0.83 (0.62–1.10)</td>
<td>0.92 (0.85–1.00)</td>
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<td>Mortality at 3m</td>
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<tr>
<td>n (%)</td>
<td>402 (15.0)</td>
<td>35 (16.1)</td>
<td>13 (8.5)</td>
<td>31 (22.8)</td>
<td>34 (19.3)</td>
<td>515 (15.3)</td>
<td>727 (10.6)</td>
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<tr>
<td>OR (95% CI)</td>
<td>1.53 (1.34–1.74)</td>
<td>1.67 (1.56–2.41)</td>
<td>0.80 (0.45–1.41)</td>
<td>2.57 (1.72–3.84)</td>
<td>2.07 (1.42–3.02)</td>
<td>1.57 (1.39–1.77)</td>
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</table>

*Local or remote parenchymal hemorrhage type 2 on the 22– to 36–hour post-treatment imaging scan, combined with a neurological deterioration of ≥4 points compared with baseline NIHSS or the lowest NIHSS value between baseline and 24 hours.
†Any hemorrhage plus any neurological deterioration.
‡Any hemorrhage with neurological deterioration, as indicated by an NIHSS score ≥4 than the value at baseline or the lowest value within 7 days, or any hemorrhage leading to death.
§mRS 0–1 at 3 months.
¶mRS 0–2 at 3 months.

Figure 1. Distribution of the scores (%) on the mRS at 3 months according to AP group.
Although treatment with any AP, and specifically ASA and the combination of ASA and CLP, was associated with higher odds for SICH, poor functional outcome, and mortality in univariate analyses, only patients receiving dual AP inhibition using ASA and CLP had a significantly increased risk for SICH per ECASS II and NINDS after adjustment for baseline characteristics. However, none of the AP regimens was identified as an independent risk factor for mortality or poor functional outcome in multivariable analyses, taking into account the substantial differences in baseline characteristics between groups. As expected, comparison of baseline characteristics confirmed that patients under AP drugs were older and frequently had several cardiovascular risk factors. Previous AP therapy was related to age, presence of risk factors, and previous vascular events. We thereby conclude that higher mortality and poor functional outcome after thrombolysis under AP comedication is not attributable to SICH but rather to other prognostically relevant factors such as age and comorbidities.

In line with our study, a recently published observational single-center study reported a significantly higher risk for SICH after thrombolysis for patients receiving AP therapy. In addition, in the same study, AP therapy was not associated with poor outcome. In contrast, previous AP use was related to age, presence of risk factors, and previous vascular events. We thereby conclude that higher mortality and poor functional outcome after thrombolysis under AP comedication is not attributable to SICH but rather to other prognostically relevant factors such as age and comorbidities.

In a recently published analysis of the SITS-MOST cohort including 6483 patients, it was shown that previous ASA treatment increased the risk for SICH per SITS-MOST definition. In the current study, ASA therapy alone did not appear as a significant predictor for any definition of SICH. That may be because the current cohort was based on SITS-ISTR population, including an additional 5000 patients. Further, the ASA group in the former analysis also comprised patients with a combination therapy (ASA and CLP and ASA and DP).

Whereas several reports provided data on safety of thrombolysis in patients under treatment with ASA, only limited data from large series of patients on pretreatment with CLP or the combination of ASA and DP or ASA and CLP have been available so far. However, previous secondary prevention studies pointed toward an increased bleeding risk for the combination therapy of ASA and CLP. In our cohort including 11,865 patients, 394 (3.3%) patients have been treated with CLP or the combination of ASA and CLP before thrombolysis. After adjustment for baseline characteristics, pretreatment with CLP alone was not an independent predictor of any of the outcome variables. In contrast, in patients receiving dual AP inhibition using ASA and CLP, the increased risk for SICH according to ECASS II and NINDS definition remained significant after adjustment for baseline characteristics. This finding is in line with the results of a
recent secondary analysis of the SAINT trials including 965 patients and analyzing risk factors for thrombolysis-related SICH found double AP therapy to be significantly associated with SICH (defined as worsening of NIHSS ≥4 points within 36 hours with evidence of hemorrhage on follow-up imaging). In that series, 43 patients were on double AP therapy, 34 of whom received the combination of ASA and CLP. Seven patients in the double AP group had SICH, all of whom were on ASA and CLP. Thus, 20.6% of patients receiving the combination of ASA and CLP experienced SICH, compared with 13.4% (per ECASS II definition) in our cohort.

However, the increased risk for SICH did not translate to worse outcome. Paralleling our results, in the study by Cucchiara et al, final clinical outcome was not influenced by AP use despite the increased risk of SICH. However, the significant increase in SICH rates found in both studies suggests that caution is demanded performing thrombolysis in this particular subgroup of patients. Before decision for thrombolysis, additional factors possibly contributing to SICH, such as elevated blood pressure, advanced age, and stroke severity, should be considered carefully in this subset of patients.

In the current study, only patients according to the strictly defined inclusion and exclusion criteria of the European rtPA conditional licensing approval were evaluated. Thus, our study does not provide information on patients who were treated within an enlarged time frame as evaluated in ECASS III or about patients ≥80 years of age. The recently pub-
lished ECASS III study, investigating the effect of rtPA in the extended time frame (3 to 4.5 hours), found a net benefit with respect to favorable functional outcome (mRS 0 to 1) of 7.2% for thrombolysis and a rate of SICH per SITS-MOST definition of 1.9% in the active treatment group. However, the effects of AP therapy on benefits from thrombolysis should not be extrapolated to patient groups treated outside the current European license criteria such as treatment beyond 3 hours and treatment of the very elderly (>80 years of age). In conclusion, these data support the use of thrombolysis in patients on AP therapy at stroke onset. However, the increased risk of SICH associated with the combination of aspirin and CLP suggests caution may need to be exercised in use of thrombolysis in this group of patients if they are at significantly increased risk of SICH because of other factors.

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References
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