Safety of intravenous thrombolysis for acute ischaemic stroke in patients receiving antiplatelet therapy at stroke onset

Jennifer Diedler, Niaz Ahmed, Marek Sykora, Maarten Uyttenboogaart, Karsten Overgaard, Gert-Jan Luijckx, Lauri Soinne, Gary A. Ford, Kennedy R. Lees, Nils Wahlgren and Peter Ringleb

1Department of Neurology, University of Heidelberg, Heidelberg, Germany
2Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
3Department of Neurology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands
4Copenhagen Stroke Unit, University Hospital of Copenhagen, Gentofte, Denmark
5Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland
6Institute for Ageing and Health, Newcastle University, Newcastle, United Kingdom
7Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom

*These authors contributed equally to the manuscript

Correspondence and reprints to:
Niaz Ahmed
SITS International Coordination Office
Karolinska Stroke Research
Department of Neurology
Karolinska University Hospital- Solna
SE-171 76 Stockholm, Sweden
Tel.: +46 8 517 756 00
Fax: +46 8 736 61 58
E-mail: niaz.ahmed@karolinska.se

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Safety of intravenous thrombolysis for acute ischaemic stroke in patients receiving antiplatelet therapy at stroke onset

Thrombolysis following AP treatment at stroke onset

2 Tables
3 Figures

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Outcome
Abstract

Background and Purpose Antiplatelets (APs) may increase the risk of symptomatic intracerebral haemorrhage (SICH) following intravenous thrombolysis after ischaemic stroke.

Methods We assessed the safety of thrombolysis under APs in 11,865 patients compliant with the European licence criteria and recorded between 2002-2007 in the SITS International Stroke Thrombolysis Register. Outcome measures of uni- and multivariable analyses included SICH per SITS-MOST (deterioration in NIHSS ≥4 plus ICH type 2 within 24 h), per ECASS-II (deterioration in NIHSS ≥4 plus any ICH), functional outcome at 3 months and mortality.

Results 3,782 (31.9%) patients had received one or two AP drugs at baseline: 3,016 (25.4%) acetylsalicylic acid (ASA), 243 (2.0%) clopidogrel, 175 (1.5%) ASA and dipyridamole, 151 (1.3%) ASA and clopidogrel, 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) 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, 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 (OR 2.11, 1.29-3.45, 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 to the benefit of thrombolysis seen in randomised trials. However, caution is warranted in patients receiving the combination of ASA and clopidogrel.

Word count: 254
Introduction

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) within the 3-h time window is currently one of the approved medical therapies for acute ischaemic stroke. Randomised controlled trials have demonstrated the efficacy of intravenous thrombolysis for patients up to 4.5 hours after onset of acute ischaemic stroke with acceptable safety profile\(^1\)-\(^7\), and large observational studies confirm treatment safety in routine clinical practice\(^8\),\(^9\). The most feared complication of rtPA therapy is symptomatic intracerebral haemorrhage (SICH) and concerns have been raised regarding thrombolysis following antiplatelet (AP) treatment which patients may be taking prior to stroke. AP drugs impair platelet function and might increase the risk of thrombolysis related bleeding.

Previous analyses of the risk for thrombolysis associated SICH after treatment with acetylsalicylic acid (ASA) yielded contradictory results. While some studies found that ASA\(^10\),\(^11\) increases the risk for SICH, others do not report an association between ASA co-medication at stroke onset and the incidence of SICH\(^12\),\(^14\). The recently published multivariable analysis of SITS-MOST (Safe Implementation of Treatments in Stroke-Monitoring Study) data\(^15\) revealed that patients receiving ASA at stroke onset had a significantly higher rate of SICH per SITS-MOST definition but not per the NINDS (National Institute of Neurological Disorders and Stroke) definition.

Data on the use of clopidogrel or combined AP treatments prior to thrombolysis is scarce\(^11\),\(^16\) and point towards an increased risk for SICH under dual AP inhibition\(^16\). However, no detailed analysis of individual AP regimens such as ASA, dipyridamole (DP) and clopidogrel (CLP) monotherapy, or combinations of ASA with DP or CLP has been published previously.

We assessed the safety of thrombolysis in patients under various APs at stroke onset using data recorded in the prospective SITS International Stroke Thrombolysis Register (ISTR; www.acutestroke.org).
Methods

Study population and design

The SITS database is a world-wide prospective, open, multinational, multicentre audit of thrombolysis. Details of data collection and management have been published previously\(^8, 9\). Datasets include information on baseline and demographic characteristics, risk factors and medication history, baseline and follow-up stroke severity measured by NIHSS (National Institutes of Health Stroke Scale), baseline and follow-up (at 22-36h) imaging data, information on functional outcome as assessed by 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 18-80 years and received treatment within the 3-hour time window. Exclusion criteria included severe stroke defined by NIHSS>25 or by baseline imaging, administration of heparin within the previous 48 hours and an elevated thromboplastin time, and prior treatment with oral anticoagulants\(^17\). 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 seven subgroups: 1) ASA only, 2) CLP only, 3) combined ASA and DP, 4) combined ASA and CLP, 5) other AP medication (e.g. triflusal), 6) any AP medication and 7) no prior use of APs.

Outcome measures

The main outcome measure was the incidence of SICH according to the SITS-MOST criteria\(^8\) (local or remote parenchymal haemorrhage type 2 on the 22-36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 h). In order to enable comparisons with previously published data, two additional definitions were used: symptomatic intracerebral haemorrhage per NINDS definition (any haemorrhage plus any
neurological deterioration\textsuperscript{1} and per ECASS II (European-Australasian Acute Stroke Study) definition (any haemorrhage 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 haemorrhage leading to death\textsuperscript{10}). Furthermore, functional outcome (mRS 0-1 versus 2-6 for excellent recovery and 0-2 versus 3-6 for functional independence) and mortality at three 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 to 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 for the different outcome parameters were calculated using the group without AP treatment as reference group.

Multivariable analyses were performed in order 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 odds ratios. 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 prior to 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 prior to stroke, and had a higher incidence of cardiovascular risk factors (diabetes, hypertension, AF, previous stroke), compared to 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 1.76-3.17), 8.8% (n=325) per NINDS (OR 1.38, 95% CI 1.19-1.60) and 6.2% (n=226, OR 1.53, 95% CI 1.29-1.82) per ECASS II. Incidence of SICH was highest among the patients receiving a combination of ASA and CLP therapy prior to thrombolysis, regardless of the definition (4.1% (n=6) per SITS-MOST (OR 3.83, 95% CI 1.65-8.91); 15.2% (n=22) per NINDS (OR 2.51, 95% CI 1.58-3.97) and 13.4% (n=19) per ECASS II (OR 3.47, 95% CI 2.12-5.68), Table 2).

Distributions of the outcome scores at three months assessed by mRS are presented in Figure 1. The proportion of patients with excellent recovery (mRS 0-1) was 41.4% (n=2813) in the group without prior AP drug use compared to 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 three months was higher in all AP groups, except for patients treated with ASA and DP. 10.6% (n=727) of patients without prior AP treatment had died after three months compared to 15.3% (n=515) with any AP treatment. Mortality in the ASA and CLP group was 22.8% (n=31) and 15.0% (n=402) under ASA alone, Table 2.
Figure 2 shows the rates of fatal SICH (per different definitions) of each subgroup. In addition we provide the data derived from the primary causes of death report forms including the categories death due to any ICH or the combination of any haemorrhage plus underlying ischaemic stroke, and the percentage of patients who had myocardial infarction or other vascular events indicated as primary cause of death. Incidence of fatal ICH regardless of the definition or database source was highest among the patients receiving the ASA and CLP combination therapy (per SITS: 0.67% (n=1) versus 0.18% (n=14) AP naïve group, $p=0.1685$; per NINDS: 7.28% (n=11) versus 2.16% (n=172), $P<0.0001$). However, consistent with their cardiovascular risk profiles, significantly more patients with ASA and CLP died because of myocardial infarction or other vascular events as compared AP naïve patients (4.64% (n=7) versus 0.80% (n=64), $P<0.0001$).

**Multivariable analyses**

In order 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 1.08-1.52, $P=0.0052$). 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 to AP naïve patients per NINDS (OR 1.74, 95% CI 1.11-2.73, $P=0.0167$) definition and per ECASS II definition (OR 2.11, 95% CI 1.29-3.45, $P=0.0031$), but not per SITS-MOST criteria (Figure 3). There was no statistically significant difference in the multivariable analyses regarding odds for excellent recovery
(mRS 0-1), independence for activities of daily living (mRS 0-2) or mortality at three 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 three 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 co-medications 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 pre-treatment. 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 prior to thrombolysis\(^11, 18, 19\). As reported previously\(^8\), overall incidences of symptomatic intracerebral haemorrhages in our cohort were comparable to randomised controlled trial populations when similar definitions were used (NINDS 7.2% versus 8.6%; ECASS II 8.8% versus 4.8%)\(^1, 7\). However, the absolute incidences of SICH varied considerably depending on the definition used. While 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.
While 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. Prior 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 co-medication is not attributable to SICH, but rather to other prognostically relevant factors such as age and co-morbidities.

In line with our study, a recently published observational single-centre study reported a significantly higher risk for SICH following thrombolysis for patients receiving AP therapy. Additionally, in the same study, AP therapy was not associated with poor outcome. In contrast, prior AP use was even independently associated with favourable outcome at three months. The authors hypothesized that AP treatment may prevent early reocclusion after thrombolytic therapy and thereby improve outcome. However, patient numbers were small: a total of 301 patients were included, 89 of them having used AP drugs (64 ASA, 22 ASA and DP, 1 DP, 1 CLP). The association with AP and favourable outcome in this previous small study was not confirmed in our large multi-centre study. However, of potential interest was the fact that patients receiving the combination of ASA and DP had the best outcomes in terms of functional independence (66.7% versus 57.8% AP naïve patients) and mortality (8.5% versus 10.6%), despite of increased incidence of SICH. Although this difference did not remain significant after adjustment for baseline characteristics, potentially beneficial effects of ASA and DP in combination with rtPA may merit further investigation. The optimal
design to investigate whether prior AP may improve outcome after thrombolysis would be a randomized controlled trial. Such a trial is currently ongoing in the Netherlands\textsuperscript{20}.

In a recently published analysis of the SITS-MOST cohort including 6483 patients it has been shown that prior ASA treatment increased the risk for SICH per SITS-MOST definition\textsuperscript{15}. In the current study, ASA therapy alone did not appear as a significant predictor for any definition of SICH. That may be due to the fact that the current cohort was based on SITS-ISTR population, including additional 5000 patients. Furthermore, the ASA group in the former analysis also comprised patients with a combination therapy (ASA and CLP, ASA and DP).

While several reports provided data on safety of thrombolysis in patients under treatment with ASA\textsuperscript{10, 12-14}, data from large series of patients on pre-treatment with CLP or the combination of ASA and DP or ASA and CLP have not been available so far. However, previous studies on secondary prevention of ischemic stroke point towards an increased bleeding risk for the combination therapy of ASA and CLP\textsuperscript{21}. In addition, a secondary analysis of the SAINT trials reports the combination of ASA and CLP to be associated with a more than 3-fold increase in SICH\textsuperscript{16}. In our cohort including 11,865 patients, 394 (3.3\%) patients have been treated with CLP or the combination of ASA and CLP prior to thrombolysis. As indicated above, patients under dual platelet inhibition were older and more frequently carried cardiovascular risk factors, making them more likely to develop poor outcome. After adjustment for baseline characteristics, pre-treatment 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. Although this did not translate into worse outcome, the significant increase in SICH rates suggests that great caution is demanded performing thrombolysis in this subgroup of patients. Prior to decision for thrombolysis, additional factors possibly contributing to SICH such as elevated blood pressure 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 that were treated within an enlarged time-window as evaluated in ECASS III or about patients older than 80 years. The recently published ECASS-III study, investigating the effect of rtPA in the extended time-window (3-4.5 hours), found a net benefit with respect to favourable functional outcome (mRS 0-1) of 7.2% for thrombolysis and a rate of sICH per SITS-MOST definition of 1.9% in the active treatment group\textsuperscript{5}. However, the effects of AP therapy on benefits from thrombolysis should not be extrapolated to patient groups treated outside the current EU Licence criteria such as treatment beyond 3 hours and treatment of the very elderly > 80 years.

In conclusion, these data support the use of thrombolysis in patients taking AP therapy at stroke onset. However, the increased risk of SICH associated with the combination of aspirin and clopidogrel 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 due to other factors.
Literature


20. [www.strokecenter.org/trials](http://www.strokecenter.org/trials), ARTIS trial.

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<th>ASA (n=3016)</th>
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*** P<0.001, ** P<0.01, * P<0.05
### Table 2  Univariate analysis of outcome parameters

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</tr>
<tr>
<td>SITS-MOST¹</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>73 (2.5)</td>
<td>2.30 (1.67-3.15)</td>
<td>4 (1.7)</td>
<td>1.55 (0.56-4.26)</td>
<td>4 (2.3)</td>
<td>2.17 (0.79-5.97)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>SICH per</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS²</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>255 (8.6)</td>
<td>1.20 (1.02-1.41)</td>
<td>16 (6.7)</td>
<td>1.04 (0.62-1.73)</td>
<td>12 (6.9)</td>
<td>1.08 (0.60-1.96)</td>
<td>22 (15.2)</td>
</tr>
<tr>
<td>SICH per</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ECASS II³</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>171 (5.9)</td>
<td>1.45 (1.20-1.75)</td>
<td>10 (4.2)</td>
<td>1.03 (0.54-1.97)</td>
<td>10 (5.9)</td>
<td>1.46 (0.76-2.79)</td>
<td>19 (13.4)</td>
</tr>
<tr>
<td><strong>Excellent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>recovery⁴</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>998 (37.5)</td>
<td>0.90 (0.83-0.99)</td>
<td>79 (37.6)</td>
<td>0.88 (0.67-1.16)</td>
<td>63 (41.2)</td>
<td>1.03 (0.75-1.40)</td>
<td>39 (28.9)</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>independence⁵</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>1425 (53.6)</td>
<td>0.92 (0.85-1.00)</td>
<td>107 (51.0)</td>
<td>0.81 (0.63-1.05)</td>
<td>102 (66.7)</td>
<td>1.44 (1.06-1.95)</td>
<td>61 (45.2)</td>
</tr>
<tr>
<td><strong>Mortality at 3m</strong></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>402 (15.0)</td>
<td>1.53 (1.34-1.74)</td>
<td>35 (16.1)</td>
<td>1.67 (1.56-2.41)</td>
<td>13 (8.5)</td>
<td>0.80 (0.45-1.41)</td>
<td>31 (22.8)</td>
</tr>
</tbody>
</table>

1 Local or remote parenchymal haemorrhage type 2 on the 22-36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more compared to baseline NIHSS or the lowest NIHSS value between baseline and 24 h
2 Any haemorrhage plus any neurological deterioration
3 Any haemorrhage with neurological deterioration, as indicated by an NIHSS score ≥ 4 than the value at baseline or the lowest value within 7 days, or any haemorrhage leading to death
4 modified Rankin Score (mRS) 0-1 at 3 months
5 mRS 0-2 at 3 months
Figure Legends

**Figure 1:** Distribution of the scores on the modified Rankin Scale at three months according to AP group, indicated in % and (n).

**Figure 2:** Causes of death, indicated as percentage of subgroup and n. The discrepancy between the percentage of patients in categories (3) and (4) as compared to group (5) are due to the fact that the data was derived from different sources within the SITS database (clinical and CT data (2,3,4) and primary cause of death report forms (1,5)).

**Figure 3:** Adjusted odds ratios for symptomatic intracerebral haemorrhage (SICH) per SITS-MOST, NINDS and ECASS II definitions and different outcome measures.