

## ORIGINAL RESEARCH

# The impact of general anesthesia, baseline ASPECTS, time to treatment, and IV tPA on intracranial hemorrhage after neurothrombectomy: pooled analysis of the SWIFT PRIME, SWIFT, and STAR trials

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## ABSTRACT

**Background** Despite the proven benefit of neurothrombectomy, intracranial hemorrhage (ICH) remains the most serious procedural complication. The aim of this analysis was to identify predictors of different hemorrhage subtypes and evaluate their individual impact on clinical outcome.

**Methods** Pooled individual patient-level data from three large prospective multicenter studies were analyzed for the incidence of different ICH subtypes, including any ICH, hemorrhagic transformation (HT), parenchymal hematoma (PH), subarachnoid hemorrhage (SAH), and symptomatic intracranial hemorrhage (sICH). All patients ( $n=389$ ) treated with the Solitaire device were included in the analysis. A multivariate stepwise logistic regression model was used to identify predictors of each hemorrhage subtype.

**Results** General anesthesia and higher baseline Alberta Stroke Program Early CT score (ASPECTS) were associated with a lower probability of any ICH (OR 0.36,  $p=0.003$ ), (OR 0.80,  $p=0.032$ ) and HT (OR 0.54,  $p=0.023$ ), (OR 0.78,  $p=0.001$ ), respectively. Longer time from onset to treatment was associated with a higher likelihood of HT (OR 1.08,  $p=0.001$ ) and PH (OR 1.11,  $p=0.015$ ). Intravenous tissue plasminogen activator (IV-tPA) was also a strong predictor of PH (OR 7.63,  $p=0.013$ ). Functional independence at 90 days (modified Rankin Scale (mRS) 0–2) was observed significantly less frequently in all hemorrhage subtypes except SAH. None of the patients who achieved functional independence at 90 days had sICH.

**Conclusions** General anesthesia and smaller baseline ischemic core are associated with a lower probability of HT whereas IV-tPA and prolonged time to treatment increase the risk of PH after neurothrombectomy.

**Trial registration numbers** SWIFT-NCT01054560; post results, SWIFT PRIME-NCT01657461; post results, STAR-NCT01327989; post results.

Given the overwhelming benefit of thrombectomy in selected patients with AIS due to anterior circulation large vessel occlusion (LVO),<sup>2–4</sup> endovascular treatment (EVT) has been established as a standard of care in this patient population.<sup>5,6</sup> However, intracranial hemorrhage (ICH) remains the most dreaded complication of any acute revascularization therapy for AIS, and its potential occurrence requires careful risk versus benefit assessment in individual patients. Despite ample existing data demonstrating the hemorrhagic risk after intravenous and intra-arterial thrombolysis, little is known about the procedural and clinical factors associated with ICH incidence after contemporary thrombectomy with stent retriever. Identification of risk factors associated with ICH has the potential to further improve procedural safety and efficacy and guide patient selection in practice and future research. The clinical impact of various hemorrhage subtypes after EVT with stent retrievers has also not been well delineated. The purpose of this study was to identify the clinical, radiological, and procedural variables that may be predictive of various subtypes of ICH following mechanical thrombectomy.

## METHODS

### Patient selection

All patients who underwent EVT with the Solitaire device in the STAR ( $n=202$ ), SWIFT ( $n=89$ ), and SWIFT PRIME ( $n=98$ ) trials were included in this pooled analysis. All trials were large prospective multicenter studies involving patients with AIS with anterior circulation emergent large vessel occlusion (ELVO). The detailed designs, methods, and results of each individual trial have been previously published.<sup>7–10</sup> All three study protocols were approved by the local ethics committee at each of the participating sites. All patients were enrolled after an informed consent form had been signed or country-specific requirements had been met for enrollment without explicit informed consent in emergency circumstances.

### Data collection

Outcome data were adjudicated by an independent imaging/angiography core laboratory and a Clinical



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## Ischemic Stroke

Events Committee (CEC). The core laboratory assessors were blinded to clinical outcome. Variables scored by the core laboratory and CEC were: location of occlusion, final revascularization grades, collaterals grading, Alberta Stroke Program Early CT score (ASPECTS), presence of ICH with corresponding subtypes, and other adverse events. In SWIFT and SWIFT PRIME, the assessors were blinded to study group assignments. The data were collected and provided by Medtronic Neurovascular. The company had no role in the design, conduct, analysis, or reporting of the present study.

### ICH categorization

Different ICH subtypes were categorized by the core laboratory and CEC according to the European Cooperative Acute Stroke Study (ECASS) III definition as: (a) hemorrhagic transformation within the ischemic territory (HT), a category which included both hemorrhagic infarct (HI) and parenchymal hematoma (PH); and (b) symptomatic intracranial hemorrhage (sICH), defined as any PH, subarachnoid hemorrhage (SAH), or intraventricular hemorrhage (IVH) associated with death, or worsening of National Institutes of Health Stroke Scale score (NIHSS) by  $\geq 4$  within 24 hours.<sup>11</sup> Other imaging core laboratory-adjudicated ICH categories included: SAH, remote intracranial hemorrhage, and IVH. All the above referenced ICH subtypes were already categorized by the CEC and core laboratory for each individual trial and provided to us for the present analysis. From the pathophysiological perspective, we analyzed HT (including all HI and PH and excluding SAH) as a separate category, which most likely represents post-reperfusion hemorrhage and less likely involves other potential mechanisms such as vessel dissection and wire perforation. The presence of any ICH was also categorized and analyzed separately. In the present study, all six separate hemorrhage subtypes (any ICH, HI, HT, PH, SAH, and sICH) were correlated with 15 candidate baseline clinical, imaging, and procedural variables (tables 1 and 2).

### Statistical analysis

Standard descriptive statistics were employed, including means, SD and medians for continuous variables and frequency distributions for categorical variables. For unadjusted between-group comparisons, t-tests were used for continuous variables and

**Table 2** Key baseline patient characteristics of the studied cohort

Characteristic	Result
Female, % (n/N)	55% (214/389)
Age, mean $\pm$ SD (median)	67.1 $\pm$ 12.6 (70)
NIHSS, mean $\pm$ SD (median)	16.8 $\pm$ 4.7 (17)
General anesthesia, % (n/N)	56% (217/389)
Number of device passes, mean $\pm$ SD (median)	1.7 $\pm$ 1.0 (1)
ASPECTS, mean $\pm$ SD (median)	8.3 $\pm$ 1.7 (9)
IV-tPA, % (n/N)	66% (258/389)
M1 occlusion, % (n/N)	67% (249/373)
ICA occlusion, % (n/N)	19% (71/389)
ICA, internal carotid artery.	

Fisher's exact test for categorical variables. Multivariate stepwise logistic regression was used to identify predictors of any ICH and individual hemorrhage subtypes using the list of candidate predictors cited in table 1. Univariate analyses were run for each individual variable. Predictors with univariate p values  $<0.20$  were included in the multivariable analyses. Stepwise selection with entry criteria of  $p<0.2$  and retention criteria of  $p<0.05$  were used to obtain the final regression model. Odds ratios were derived from these models and presented along with their 95% CIs and corresponding p values. Fisher's exact test was used to compare the frequency of functional independence, defined as modified Rankin Scale (mRS) score of 0–2 at 90 days, among subgroups of patients with and without ICH and subtypes of ICH. Additional logistic regression, adjusted for baseline ASPECTS, was performed to compare ICH subtypes with 90-day functional independence. For all statistical analyses, two-tailed p values are presented, with values  $<0.05$  considered statistically significant. Analyses were conducted in SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA) and R Version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). Table 2 represents the distribution of key baseline patient characteristics of the studied cohort.

## RESULTS

### Clinical and procedural predictors of ICH risk

Any ICH was observed in 84/389 (21.6%), HT in 75/389 (19.3%), HI in 54/389 (14%), PH in 21/389 (5.4%), SAH in 9/389 (2.3%), and sICH only in 4/389 (1%) of the analyzed patients. The most significant predictors of separate hemorrhage subtypes based on both univariate and multivariate analyses are shown in table 3. Both ASPECTS and general anesthesia (GA) had a strong inverse association with any ICH (ASPECTS: OR 0.80, 95% CI 0.66 to 0.98,  $p=0.032$ ; GA: OR 0.36, 95% CI 0.18 to 0.71,  $p=0.003$ ) and HT (ASPECTS: OR 0.78, 95% CI 0.68 to 0.91,  $p=0.001$ ; GA: OR 0.54, 95% CI 0.31 to 0.92,  $p=0.023$ ). Collateral grade was also inversely associated with any ICH, but this association did not reach statistical significance ( $p=0.057$ ). Time to treatment was a significant hemorrhage predictor, with longer times increasing the risk of HT (OR 1.08, 95% CI 1.03 to 1.12,  $p=0.001$ ) and PH (OR 1.11, 95% CI 1.02 to 1.20,  $p=0.015$ ). IV-tPA use prior to thrombectomy was also a significant predictor of PH (OR 7.63, 95% CI 1.52 to 17.35,  $p=0.013$ ). No significant predictors of SAH and sICH were identified, although a non-significant inverse association between sICH and platelet count was noted (OR 0.98, 95% CI 0.96 to 1.0,  $p=0.084$ ).

**Table 1** Baseline variables included in the analysis

Clinical variables	Procedural variables
Age	General anesthesia
NIHSS	Collateral grade*
Hypertension	Number of device passes
DM	Final TICI
Hyperglycemia (BS >140 mg/dL)	Rescue therapy†
Atrial fibrillation	
INR	
Platelet count	
ASPECTS	
IV-tPA	

\*Collateral grading was based on the ASITN scale.<sup>61</sup>

†Any additional endovascular therapy after failed thrombectomy with Solitaire.

ASPECTS, Alberta Stroke Program Early CT score; DM, diabetes mellitus; INR, international normalized ratio; IV-tPA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

**Table 3** Predictors of hemorrhage subtypes: pertinent findings from the multivariate analysis

Predictor	OR	Lower CI	Upper CI	P value
Any ICH (HI, PH, SAH, and sICH)				
ASPECTS	0.80	0.66	0.98	0.032
General anesthesia	0.36	0.18	0.71	0.003
Collateral grade	0.71	0.50	1.01	0.057
Hemorrhagic transformation within the ischemic territory (HI and PH)				
ASPECTS	0.78	0.68	0.91	0.001
General anesthesia	0.54	0.31	0.92	0.023
Onset to groin puncture (per 15 min)	1.08	1.03	1.12	0.001
Parenchymal hematoma (PH)				
IV r-tPA	7.63	1.52	17.35	0.013
Onset to groin puncture (per 15 min)	1.11	1.02	1.20	0.015

ASPECTS, Alberta Stroke Program Early CT Score; HI, hemorrhagic infarct; ICH, intracranial hemorrhage; IV=tPA, intravenous tissue plasminogen activator; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage.

#### Analysis of clinical outcome based on ICH subtype

Among all patients treated with Solitaire in this dataset, 210/378 (55.6%) were functionally independent at 90 days. The frequency of different hemorrhage subtypes seen within this group is shown in table 4. Additional adjusted analysis was performed to eliminate potential confounding between large ischemic core (low ASPECTS) and the occurrence of various ICH subtypes. Overall, patients with any ICH ( $p<0.001$ ), HT ( $p<0.001$ ), HI ( $p=0.002$ ), and PH ( $p=0.002$ ) were much less likely to have functional independence at 90 days than those who did not have hemorrhage. No significant difference in terms of functional independence was observed in patients with SAH ( $p=0.46$ ). None of the patients with sICH were independent at 90 days table 5.

#### DISCUSSION

The findings of our study provide insights regarding pathophysiological mechanisms and risk factors associated with various hemorrhagic subtypes after contemporary thrombectomy with Solitaire and their individual impact on functional independence.

**Table 4** Clinical outcome

ICH subtype	Functional independence* with ICH	Functional independence without ICH	P value
Any ICH (HT, PH, SAH, sICH)	32.1% (27/84)	61.4% (183/298)	<0.001
HT (HI+PH)	30.7% (23/75)	60.9% (187/307)	<0.001
HI	33.3% (19/57)	58.8% (191/325)	<0.001
SAH	44.4% (4/9)	55.2% (206/373)	0.74
PH	19.0% (4/21)	57.1% (206/361)	0.001
sICH	0.0% (0/4)	55.6% (210/378)	0.040

Of the 389 patients in this study, ICH information was available in 382 and mRS information was available in 378 patients.

\*Functional independence is defined as mRS 0–2.

HI, hemorrhagic infarct; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage.

**Table 5** Clinical outcome adjusted for baseline ASPECTS by logistic regression

ICH subtype	Adjusted odds ratio (aOR) for mRS 0–2 outcome (95% CI)*	P value
Any ICH (HT, PH, SAH, sICH)	0.31 (0.19, 0.53)	<0.001
HT (HI+PH)	0.30 (0.17, 0.52)	<0.001
HI	0.38 (0.21, 0.70)	0.002
SAH	0.60 (0.16, 2.30)	0.46
PH	0.18 (0.06, 0.54)	0.002
sICH†	NA (NA)	NA

ICH on mRS 0–2 outcomes while controlling for (and therefore independent of) any effect of baseline ASPECTS on clinical outcome. Results are concordant with univariate modeling unadjusted for ASPECTS (table 4).

\*The analysis shown above displays the adjusted odds ratio (aOR) for the occurrence of mRS 0–2 in the presence of each ICH subtype shown, adjusted for ASPECTS score at baseline. The adjustment for ASPECTS is included to avoid confounding between low ASPECTS and subsequent ICH. The aOR shown represents the effect of

†Adjusted modeling could not be performed due to sparse data (n=4 in sICH group).

#### Impact of general anesthesia

Our study is the first to report an inverse association between GA and the occurrence of ICH in the setting of neurothrombectomy. Although GA did not impact the most severe hemorrhage subtypes (sICH and PH), these findings provide signals about its protective effect against hemorrhage that warrant further exploration. While no definitive explanation regarding the relationship between GA and ICH can be drawn from our data, there are several theoretical possibilities: (1) less patient motion in the setting of GA with more precise intracranial navigation and lower chance of microvascular avulsion; (2) protective effect of anesthetic medications against cerebral ischemic reperfusion injury<sup>12–15</sup>; (3) reduced pain and agitation with lower chance of blood pressure surges and uncontrolled hypertension, which is an independent risk of HT.<sup>16</sup> In addition, hypotension that frequently occurs with GA during thrombectomy may also protect the ischemic tissue against HT after reperfusion. However, it is also important to emphasize that hypotension can be deleterious to the cerebral collateral circulation prior to revascularization. Profound hemodynamic and ventilation changes in the setting of GA have been associated with worse outcome after thrombectomy,<sup>17</sup> and are likely key factors leading to an overall worse outcome seen in multiple retrospective case series and post hoc analyses correlating GA with worse clinical outcome.<sup>18–23</sup> In contrast, three single-center prospective randomized studies exploring the difference between GA and conscious sedation (CS) demonstrated equivalence in their primary outcomes.<sup>24–26</sup> Furthermore, two of these three recent trials showed superiority in terms of functional independence of GA over CS as a secondary outcome.<sup>24–26</sup> All three trials had specific GA protocols with well-defined ventilation and blood pressure targets designed to minimize the risk of collateral failure prior to endovascular revascularization. Accordingly, two recent meta-analyses involving newer thrombectomy devices demonstrated inconclusive results regarding the clinical benefit of either procedural method of sedation.<sup>27–28</sup> Given the prior confounding data, the most recent guidelines for early management of AIS specifically outlined the need for further randomized data to identify the best anesthetic technique.<sup>6</sup> Our findings of the protective effect of GA against ICH further contribute to the existing clinical equipoise regarding the optimal method of sedation during EVT.

### Impact of baseline ASPECTS

The size of the baseline ischemic core is a well-established predictor of hemorrhagic risk with intravenous and endovascular reperfusion.<sup>29–33</sup> The strong association of baseline ASPECTS with any ICH and HT in our study reaffirms these previous data and further establishes the ischemic volume as one of the most important factors influencing hemorrhage after reperfusion. Cerebral collateral circulation, which is inversely proportional to the ischemic core volume, is another important and well-known variable associated with an increased risk of HT after intra-arterial therapies for AIS<sup>33–35</sup> and also was linked to ICH in our study. Both variables demonstrate the increased susceptibility of the ischemic core tissue to HT after thrombectomy.

### Impact of time to treatment

Prolonged time from onset to treatment is one of the main determinants of clinical outcome in all AIS therapies.<sup>36–38</sup> The well-established pathophysiologic paradigm is that progression of the ischemic core lesion in the setting of LVO is highly dependent on the temporal dynamic evolution of collateral circulation, which fails over time.<sup>39</sup> As discussed above, ischemic core volume and collaterals are potent predictors of HT. Ischemia-induced blood-brain barrier disruption,<sup>40</sup> activation of metalloproteinases,<sup>41</sup> and formation of free radicals<sup>42</sup> rendering the ischemic brain susceptible to hemorrhage are proportionally related to the degree and size of the ischemic changes and occur at maximum intensity within 6–24 hours after onset.<sup>43,44</sup> Thus, the association between time to treatment and hemorrhagic risk in our study is not surprising as it likely represents the increased vulnerability of the ischemic brain tissue to reperfusion hemorrhage in the setting of prolonged ischemia. Similar findings have been reported in previous studies: prolonged time from onset to EVT has been associated with an increased risk of basal ganglionic hemorrhage and sICH.<sup>32,33</sup> Experience with faster intravenous thrombolysis further supports this notion: in a study involving over 70 000 patients, reduction of door-to-needle time for IV-tPA administration after implementation of national quality initiatives resulted in a significant decrease in the incidence of ICH.<sup>45</sup>

### Impact of IV-tPA

Similar to GA, the data regarding the benefit of bridging IV-tPA therapy in the setting of EVT for ELVO is a topic of ongoing controversy and debate.<sup>46</sup> The main reason supporting its use is improved recanalization and potential avoidance of thrombectomy, particularly in patients with distal and smaller clots.<sup>47</sup> However, the small chance of recanalization after early administration of IV-tPA for LVO in comprehensive or thrombectomy-ready centers may be obviated by rapid endovascular revascularization. A small single-center study demonstrated equivalent outcomes with EVT alone versus IV-tPA/EVT bridging therapy.<sup>48</sup> Another consideration against bridging therapy in ELVO patients is the increased cost of IV-tPA.<sup>49</sup> In addition, the coagulopathy induced by the tPA clearly accentuates the hemorrhagic risk after reperfusion.<sup>50,51</sup> These post-thrombolytic hemostasis changes have been correlated with cardioembolic infarcts,<sup>52</sup> which comprise most of the LVO etiology and further raise the concern of an augmented risk of hemorrhage after EVT. Unlike the other predictors, IV-tPA was uniquely associated with PH in our study. PH has been considered as a separate entity due to its highest impact on clinical outcome among all hemorrhagic subtypes,<sup>53</sup> which further emphasizes the potentially hazardous effect of bridging IV-tPA therapy in conjunction with EVT. A similar finding of a higher PH risk with IV-tPA

from ‘real-world’ non-randomized retrospective data involving older generation devices was reported by Nogueira *et al.*<sup>54</sup> As such, our findings contribute to the existing data of the increased hemorrhagic risk of IV-tPA, reaffirm the controversy regarding the utility of IV-tPA in the setting of ELVO, and support the need for a well-powered randomized multicenter trial comparing bridging therapy versus EVT alone.

### Impact of ICH subtypes on outcome

We explored the incidence of functional independence (mRS 0–2) with ICH versus the incidence of functional independence without ICH for each hemorrhagic subtype. Although this analysis involved simple univariate comparisons, it provides important information regarding the potential impact of each type of hemorrhage on clinical outcome. All hemorrhage subtypes were associated with a lower likelihood of independent clinical outcome, except for SAH. This finding replicates prior data, emphasizing that the imaging finding of SAH alone without parenchymal involvement and/or clinical deterioration may not have a significant long-term clinical impact.<sup>55–57</sup>

None of the currently used definitions of sICH optimally predict functional outcome.<sup>58</sup> The data regarding the long-term clinical effect of different radiographic subtypes are also unclear. While PH has been cited as the most potentially hazardous to clinical outcome,<sup>53</sup> HI has been considered a relatively ‘benign’ entity and even correlated with improved outcome as a marker of early reperfusion after IV-tPA in some studies.<sup>59</sup> Conversely, more detailed analyses have identified asymptomatic HI-2 as an independent predictor of poor outcome after IV-tPA and EVT.<sup>54,60</sup> Our data support the notion that any ICH, HI, and HT can have a potential impact on functional outcome, even if considered asymptomatic by trial definitions. However, our findings also highlight that the stringent definition of sICH used in this dataset (any PH, SAH, or IVH associated with death or worsening of NIHSS score by  $\geq 4$  within 24 hours) and recent thrombectomy trials has the strongest impact on functional outcome as none of the patients with sICH achieved mRS 0–2 at 90 days.

### Limitations

Our study has several limitations. The main limitation is the relatively small number of symptomatic hemorrhages in the dataset as the patient population included in the three trials is highly selected and may not represent ‘real-world’ experience. Another important drawback is the difference in the design of the three studies, conducted in three different continents over a time span of 4 years. Although all patients were treated with the same device, these factors introduce potential heterogeneity in the analyzed data due to differences in patient population and neurointerventional practices. In addition, our clinical outcome data were derived on the basis of analyses adjusted only for baseline ASPECTS, instead of multivariate regression, focusing only on individual hemorrhage effect and excluding other important clinical and procedural variables. However, the goal of the outcome analysis was to analyze the clinical effect of each ICH subtype compared with all other hemorrhages rather than identifying overall predictors of clinical outcome.

### CONCLUSIONS

Detailed knowledge regarding the factors associated with hemorrhage occurrence after endovascular reperfusion for AIS may improve procedural safety and outcomes. Our data demonstrate that lower baseline ASPECTS, delayed time to treatment, and

bridging IV-tPA are significant predictors of ICH after thrombectomy with Solitaire. This report also provides novel evidence that GA minimizes the peri-procedural hemorrhagic risk and may be a safer alternative to CS in the proper institutional settings. These findings could be applied for better patient selection in current practice and indicate the need for randomized data addressing the benefit of bridging therapy with IV thrombolysis and the optimal method of sedation in endovascular treatment of AIS.

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**Correction notice** Since this article was first published online first, a change has been made to the conclusion section of the abstract.

**Contributors** The main author interpreted the data, drafted the original manuscript version, reviewed all suggestions provided by all co-authors, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All co-authors provided substantial contribution to the interpretation of the provided data. All co-authors also contributed with revisions to the original draft, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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## Correction: *The impact of general anesthesia, baseline ASPECTS, time to treatment, and IV tPA on intracranial hemorrhage after neurothrombectomy: pooled analysis of the SWIFT PRIME, SWIFT, and STAR trials*

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This article has been corrected since it was published Online First. The affiliation for Dr Jan Gralla has been updated to the University Institute of Diagnostic and Interventional Neuroradiology, University Hospital Bern, Inselspital, University of Bern, Switzerland.

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