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Prospective, Multi-Centre, Single-Arm Study of Mechanical Thrombectomy using Solitaire FR in Acute Ischemic Stroke-STAR

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Abstract

Background and Purpose—Mechanical thrombectomy using stent retriever devices have been advocated to increase revascularization in intracranial vessel occlusion. We present the results of a large prospective study on the use of the Solitaire FR in patients with acute ischemic stroke.

Methods—STAR was an international, multicenter, prospective, single-arm study of Solitaire FR thrombectomy in patients with large vessel anterior circulation strokes treated within 8 hours of symptom onset. Strict criteria for site selection were applied. The primary endpoint was the revascularization rate (3TICI 2b) of the occluded vessel as determined by an independent core lab. The secondary endpoint was the rate of good functional outcome (defined as 90-day modified Rankin scale (mRS) 0–2).

Results—A total of 202 patients were enrolled across 14 comprehensive stroke centers in Europe, Canada and Australia. The median age was 72 years, 60% were female patients. The median National Institute of Health Stroke Scale (NIHSS) was 17. Most proximal intracranial occlusion was the internal carotid artery in 18%, the middle cerebral artery in 82%. Successful revascularization was achieved in 79.2% of patients. Device and/or procedure related severe adverse events were found in 7.4%. Favorable neurological outcome was found in 57.9%. The mortality rate was 6.9%. Any intracranial hemorrhagic transformation was found in 18.8% of patients, 1.5% were symptomatic.

Conclusions—In this single arm study, treatment with the Solitaire™ FR device in intracranial anterior circulation occlusions results in high rates of revascularization, low risk of clinically relevant procedural complications, and good clinical outcomes in combination with low mortality at 90 days.

Clinical Trial Registration—This study is registered with ClinicalTrials.gov, number NCT01327989.

BACKGROUND

Acute ischemic stroke is one of the major causes of morbidity and mortality among industrialized countries. Both intravenously administered tissue plasminogen activator (IV rt-PA) and local intra-arterial thrombolysis (IAT) have been shown to improve patient outcomes[1–3]. Mechanical revascularization techniques have been proposed to expand the treatment time window and enhance revascularization[4–7].

A novel class of mechanical thrombectomy (MT) devices, stent retrievers, has been recently advocated for mechanical thrombectomy in stroke treatment[5–7]. The Solitaire Flow Restoration device (Covidien/ev3, Dublin, Ireland) consists of a self-expanding stent retriever designed for thrombectomy to restore blood flow in patients with ischemic stroke due to proximal vessel occlusion[5, 7]. Results from the SWIFT trial have demonstrated that patients treated with the stent retriever (Solitaire FR device) achieved a higher revascularization rate and better neurological outcome compared to an earlier generation device (Merci Retriever, Stryker Neurovascular)[7]. Concerning the recent and upcoming randomized controlled trials (RCTs) on interventional versus systemic stroke treatment, more prospective data on real world experience with this novel technology is needed.

We describe the results of the Solitaire FR Thrombectomy for Acute Revascularization (STAR), a prospective, multi-centre, single arm trial on patients with acute ischemic anterior circulation stroke.

METHODS

Study design

The STAR trial was an international, prospective, multicentre, single-arm study. The study was designed by the principal investigators and a steering committee composed of experts in vascular neurology and interventional neuroradiology.

The study used an independent CT and MRI imaging core laboratory, a separate angiography core laboratory, and an independent clinical events committee (CEC). The CEC was responsible for the review and validation of all complications (i.e. adverse event, procedural or technical complication) that occurred over the course of the study and the subsequent classification of these complications as related to the device or procedure. The study data was independently monitored, study management was provided by the sponsor, Covidien Neurovascular.

Population

Patients were eligible if they presented within 8 hours after onset of an acute ischemic stroke due to a proximal intracranial arterial occlusion in the anterior circulation. Key inclusion criteria included the following: Age (≥ 18 and < 85 years), National Health Institutes Stroke Scale (NIHSS) score (8 – 30), modified Rankin scale (mRS ≤ 2) and documented occlusion of an anterior intracranial artery (intracranial and terminus internal carotid artery (ICA) and first and second segments of the middle cerebral artery (MCA)) on conventional angiography.

Consent was obtained from the patient or patient’s legally authorized representative prior to the interventional procedure. In instances where the patient was alone and unable to make a decision, an independent physician signed the informed consent and subsequently, the patient or representative signed a continuation form.

Patients were excluded if they had a life expectancy of less than 90 days, NIHSS > 30 or coma, sustained uncontrolled hypertension (systolic blood pressure > 185 mmHg or diastolic

blood pressure > 110 mmHg), anticoagulation with INR (International Normal Ratio) > 3.0, platelet count < 30,000, glucose > 400 mg/dL, previous stroke within 30 days, unknown time of symptom onset, seizure at the onset of stroke and associated myocardial infarction or severe infection (sepsis or endocarditis).

Imaging evaluation excluded patients with signs of intracranial hemorrhage, arteriovenous malformation (AVM) or aneurysm, early ischemic changes larger than one third of the MCA territory and/or according to ASPECT score (≤ 6 points) on CT or ASPECT score (< 5 points) according to diffusion weighted imaging (DWI), angiographic evidence of carotid dissection, complete cervical carotid occlusions, vasculitis, or arterial stenosis proximal to thrombus site that may preclude safe balloon occlusion catheter placement or safe recovery of the device.

Stroke treatment protocol

The study protocol was approved by the local ethics committee at all study sites.

Patients arriving within 4.5 hours were managed according to the center's standard protocol. The standard indication for interventional stroke treatment at each center comprised of the following:

1–Combined IV rt-PA and MT:

Patients who received any intravenous thrombolysis (e.g. failed IV rt-PA, rt-PA bolus and initial intravenous infusion) and referred to mechanical thrombectomy. Any additional intra-arterial rt-PA infusion was considered as a rescue therapy and a protocol violation for the purpose of this analysis.

2–Direct MT:

Patients with a contraindication to intravenous thrombolysis were treated directly with mechanical thrombectomy. Additionally, at some study sites, primary inclusion of patients to thrombectomy despite eligibility for intravenous thrombolysis was performed based on the local standard stroke treatment protocol.

All centers were required to maintain screening logs, which were monitored by external reviewers to ensure report of screen failures and enrollment.

Site selection

Site selection was pre-defined by the steering committee in order to get dedicated high volume stroke centers with extensive experience on stroke interventions, peri-procedural management and recovery care. Centers were required to have a 24-hour acute stroke emergency service with vascular neurology and interventional neuroradiology on call. At minimum, physicians were required to have treated 30 stroke patients and 3 cases within a 4-month period using the Solitaire device following the instructions for use. Centers were not allowed to participate in a competitive stroke study during the local enrollment phase. All centers were required to provide acute rehabilitation care to all patients.

Procedure protocol

The procedure protocol was standardized and defined per the 'instructions for use'. The use of a balloon guide catheter (BGC) and a minimum embedding time of 3 minutes with the device at the occlusion site were mandatory. Patients were included after BGC placement at the ICA.

Successful revascularization was defined as TICI ≥2b revascularization of the target territory with a maximum of three passes of the study device per vessel. After the primary endpoint outcome angiogram was performed, rescue therapy was permitted in patients in whom adequate revascularization (TICI ≥2b) had not been achieved. All cases requiring additional therapy were considered device treatment failures. Rescue therapy consisted of mechanical thrombectomy and/or intra-arterial thrombolysis at the interventionalist's discretion and according to the center's guidelines. If any rescue treatment was performed, a final procedural diagnostic angiogram was obtained. The application of anesthesia or conscious sedation followed the site's discretion.

All patients were screened for a proximal vessel occlusion, illustrated by pre-interventional imaging (CTA/MRA). Follow-up imaging was completed at 24-hours (18–30 hour window).

Experienced neurologists performed clinical neurological examinations. Modified Rankin score (mRS), National Institutes of Health Stroke Scale (NIHSS) score, were assessed at admission, 24-hour post procedure, 7–10 days or discharge and the 90-day follow up.

Imaging evaluation

All CT, MRI, and conventional angiography images were evaluated by an academic imaging core laboratory. CT or MRI studies performed prior to the thrombectomy procedure were evaluated by an independent reader (DSL) who was blinded to all angiographic and clinical data in order to confirm the imaging inclusion and exclusion criteria. Follow-up CT or MRI studies, acquired 24 h (with a tolerance of 18–30 h) post-procedure, were systematically reviewed for hemorrhagic complications and final Alberta Stroke Program Early CT Scores (ASPECTS)[8]. Hemorrhages were categorized according to the method used by Berger and colleagues in the ECASS trials[9]. The angiography images were reviewed by a different independent reader (RGN), who was blinded to all CT/MRI and clinical data, and graded with the Thrombolysis In Cerebral Infarction (TICI) grading scale[10]. TICI grade 0 was defined as no perfusion; grade 1 was defined as perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion; grade 2a was defined as perfusion of less than one the of the vascular distribution of the occluded artery; grade 2b was defined as perfusion of greater than two thirds of the vascular distribution of the occluded artery; and grade 3 was defined as full perfusion with complete filling of all distal branches (some delay was accepted in the presence of proximal vasospasm or competitive collateral flow). Revascularization outcomes were adjudicated after every single angiographic run performed after an intervention including any passes of the Solitaire device, any use of adjunctive or rescue treatments, and at the time of procedure completion. Images were reviewed for any potential angiographic complications including embolus to an uninvolved territory (embolic lesion to a territory that was not occluded initially or is not

part of the distal territory of the previous occluded territory), perforation, dissection, vasospasm, and contrast extravasation. Collateral circulation was analyzed using the ASITN/SIR Collateral Flow Grading System.

Data analysis and statistical evaluation

The primary endpoint was the revascularization rate (≥TICI 2b) of the occluded vessel after a maximum of 3 passes of the study device as determined by an independent core lab. Safety was evaluated through serious adverse events (SAEs) related to the device or the procedure, adjudicated by a clinical event committee. The secondary outcome measures included the following: 1) good neurological outcome at 90 days, defined as an mRS of 2 or less; 2) incidence of device-related and procedure-related serious adverse events; 3) time to revascularization defined as time interval from guide catheter placement to revascularization TICI ≥2b or end of the procedure in case of failed revascularization; and 4) mortality at 90 days.

Under the principles of intent to treat, the analysis population consisted of all patients who signed informed consent, met selection criteria and in whom use of the study device was attempted. The worst case scenario was assigned for patients missing primary and secondary outcome data. Patients with a missing or inconclusive final angiogram dataset were rated as TICI 0. Patients missing a 90-day mRS score were assigned mRS 6. Standard summary statistics were calculated for all study variables as appropriate to the type of data collected (e.g., continuous vs. categorical vs. ordinal). No formal hypothesis testing of overall study endpoints was prespecified; however, subgroups of interest were identified a priori and statistical comparisons between these cohorts were performed. Statistical analysis was carried out in SAS version 9.3 (SAS Institute, Cary, N.C.), a validated statistical software package.

Role of funding source

Two academic principal investigators (JG, VMP), and an academic steering committee supervised trial design and operations. The principal investigators and the steering committee interpreted the results and wrote the report. The principal investigators and the steering committee had full access to the study data and had the final decision to submit for publication. The sponsor of the study was responsible for site management, data management, and safety reporting.

This study is registered with ClinicalTrials.gov, number NCT01327989.

RESULTS

Between October 2010 and May 2012 a total of 682 patients with ischemic stroke were screened at 14 international sites (Europe, Canada and Australia). A total of 202 patients were consented and enrolled (Figure 1). Patients not included in the study were recorded and monitored to ensure consecutive evaluation and to avoid selection issues. The most common reasons for screen failures were: proximal carotid occlusion/stenosis (20.2%), intracranial occlusion location (15.7%), unknown or > 8 hour stroke symptom onset (11.5%). Nine

patients did not sign informed consent or had withdrawn consent during the course of the study.

The intention-to-treat analysis included all 202 patients. Median age of patients was 72 years, 60% female, and a median NIHSS of 17 at admission. 90-days follow up mRS was assessed in all patients. 59% of the patients received IV rt-PA prior to the mechanical procedure. Baseline demographics are summarized in Table 1.

The rate of the primary outcome (successful revascularization (TICI ≥ 2b) after ≤ 3 passes of the study device as adjudicated by independent core lab evaluation) was 79.2% (160/202). In 42 patients (20.8%), TICI 2b or greater was not achieved within the limited number of three passes (device treatment failures), in 18 of these (9%) rescue therapy was performed. Additional treatment consisted of: intra-arterial thrombolysis in 2 patients, mechanical thrombectomy in 13 patients. In 3 patients, combined intra-arterial thrombolysis and mechanical thrombectomy was performed. After rescue therapy, core lab determined that 88.1% (171/194) achieved final successful revascularization (TICI ≥2b). Median time from onset of symptoms to groin puncture was 238 min. Procedural time (guiding catheter placement to revascularization TICI ≥2b or end of the procedure) was 20 min (mean: 29 ±27). The mean number of passes with the device was 1.5. The outcome measures are summarized in Table 2.

At the 90-day follow-up visit, favorable neurological outcome (mRS 0–2) was seen in 57.9% of patients. The distribution of mRs at 90 days is illustrated in Figure 2. Most common angiographic complication in core lab evaluation was vasospasm found in 23% (45/200) of patients, and as adjudicated by the CEC, only 0.5% (1/202) were symptomatic. The frequency of total device-related and procedure-related serious adverse events was 7.4%. Any ICH was found in 18.8% patients at 24 hours and sICH occurred in 1.5% of the patients. The mortality rate was 6,9% with a higher proportion found in the male population (5%). A detailed summary of the safety outcomes is presented in Table 3. We performed an analysis between the collateral circulation and outcome and we observed that a good collateral circulation (grades 3–4 ASITN/SIR scale) correlated significantly with good (mRS-0–2) outcomes (p-0.034). Patients receiving rescue therapy showed a statistically significant lower rate of favorable outcome (33.3%, mRS 0–2) compared to the comparison to those who did not (60.3%; p=0.043). The rate of device/procedure-related SAEs was not significantly elevated in the subgroup of patients receiving rescue therapy (11.1% versus 7.2%).

DISCUSSION

The STAR study showed that the Solitaire Flow Restoration device was effective in achieving successful cerebral revascularization (TICI ≥ 2b within three passes) in patients presenting with acute ischemic stroke harboring anterior circulation proximal occlusions. Our results also demonstrated a significant improvement in patient's clinical outcomes as well as low rates of mortality and symptomatic intracranial hemorrhage. This is the largest prospective multicentre study on mechanical thrombectomy for acute ischemic stroke to date. Key elements of this study include the predefined procedure protocol, center selection,

independently monitored data acquisition and core lab review using TICI scores to define successful reperfusion.

The revascularization rates are among the highest reported in the literature[5–7], however, procedural characteristics of the study reflected the experience of study centers with mechanical thrombectomy and, particularly, with the study device. Sites selected for the study were high volume stroke centers with multidisciplinary and certified teams with experienced neurointerventionalists, vascular neurologists and neurorehabilitation facilities. Furthermore, interventionalists were required to have expertise in general stroke interventions and experience using the study device per the IFU. Most INRs in Europe had used the device for years prior to this study since clearance in April 2009[5]. Two recent randomized mechanical thrombectomy trials that were performed for FDA clearance of two stent retrievers, required few cases using the stent retriever device per site prior to enrollment[6, 7]. The impact of the experience with the study device can be observed also on the rate of device-related and procedure-related serious adverse events that was lower compared to previous studies with stent retrievers. Additionally, the number of passes, rescue treatments and the shorter procedural times were comparably lower as well.

The study showed a high rate of favorable clinical outcome, which was comparable (58 vs 55%) to a previously published retrospective Solitaire study[5, 7] reporting the initial experience with the Solitaire device as first line device in six European centers. In the SWIFT trial, treatment with the Solitaire FR device presented a favorable clinical outcome in 36%. From our point of view, the higher rate of good clinical outcome in our study can be attributed to the higher revascularization rate as well as selection of patients with exclusively anterior circulation stroke using ASPECTS score for selection, pre-stroke mRS 0–2 and comprehensive patient management after the treatment. Furthermore, our population presented a slightly lower initial NIHSS and lower relevant co-morbidities compared to other studies using stent retrievers[6, 7].

The rate of sICH was comparably low but within the range of the SWIFT trial (2%). Previous studies on other MT devices have shown higher rates of sICH[4, 11, 12]. We therefore postulate that the use of stent retrievers may impact the rate of hemorrhagic transformation. Another recent stent retriever, the Trevo device (Stryker Neurovascular, Mountain View, CA, USA) reported a 7% sICH rate, significantly lower compared to the Merci device[6]. In addition to a high revascularization rate and low rate of sICH, this STAR study demonstrated a low mortality rate at 90 days. This may be due to imaging-based patient selection, limitation to anterior circulation strokes and low complication rate. Furthermore, a subgroup analysis showed a significantly higher rate of mortality in the male study population which was unrepresented.

Our study has limitations. It was a single-arm study limited to only anterior circulation occlusions. The neurological examination was conducted by a neurologist not blinded to study device. Selection bias could not be excluded due to the study's non-randomized design. However, we used several independent committees to design the study, monitor and adjudicate outcome measurements. The recruitment rate (31%) of the present study was higher compared to previous randomized control trials on MT (SWIFT trial: 21%, Trevo

trial: 19%)[6, 7]. Baseline characteristics (age, NIHSS at admission, occlusion sites) are in line with previous studies[5–7, 11–13].

CONCLUSION

This single-arm prospective study suggests that treatment with the Solitaire™ FR device for stroke due to intracranial anterior circulation occlusions by comprehensive and experienced stroke centers results in a low risk of clinically relevant procedural and device related complications, high revascularization rates and good clinical outcomes. These data supports further investigation of this device in RCTs against best medical treatment alone.

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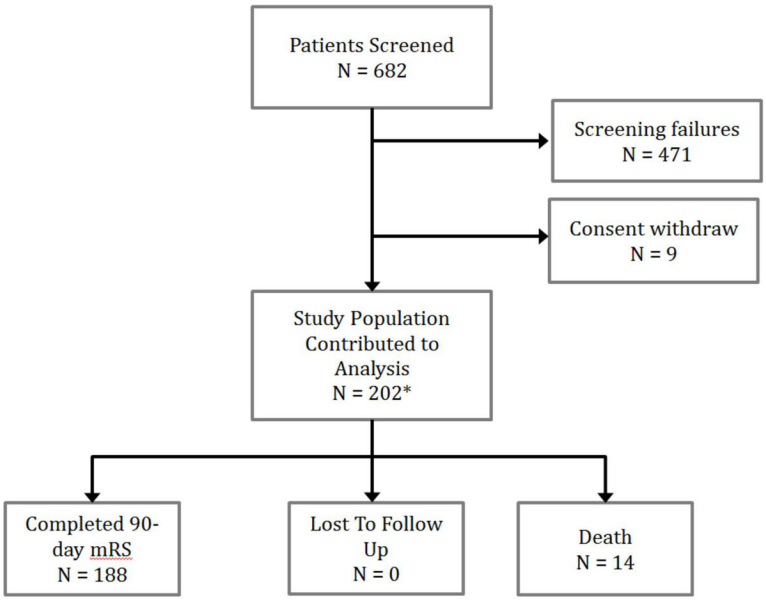

Figure 1.
Subject disposition

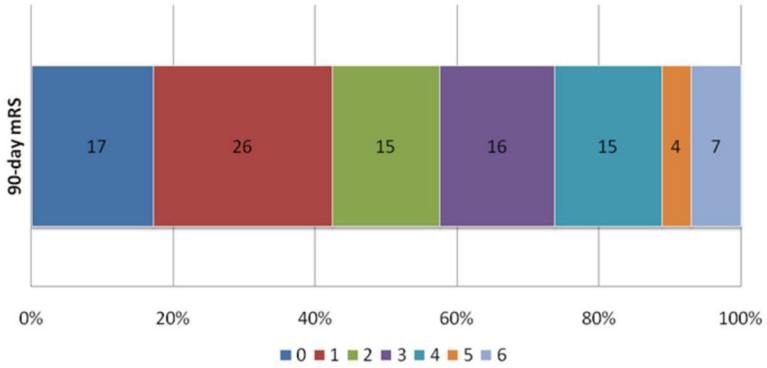

Figure 2.
Distribution of mRS at 90 days

Table 1

Baseline demographic and clinical characteristics of the patients

	Value
Age, years	
Mean	68.4 12.5
Median	72(25,86)
Sex, % female	60
NIHSS score	
Mean	16.5 4.7
Median	17 (8,26)
Pre-stroke mRS	
0	62% (125/202)
1	15% (30/202)
2	11% (22/202)
3	0.5 (1/202)
Not determined	12% (24/202)
Time from stroke onset to groin puncture, min	
Mean	251 99
Median	238 (72,714)
Stroke protocol	
Combined IV rt-PA and MT	59% (119/202)
Mechanical thrombectomy only	41% (83/202)
Hemispheric occlusion side, left	51% (101/199)
Medical history	
Diabetes mellitus	15% (30/202)
Myocardial disease	18% (36/202)
Hypertension	63% (127/202)
Atrial fibrillation	38% (77/202)
Dyslipidemia	39% (79/202)
Smoking < 1 year	11% (22/202)
Smoking > 1 year	8% (17/202)
Previous ischemic stroke	10% (21/202)
Previous hemorrhagic stroke	1% (3/202)
TIA	8% (16/202)
Most proximal occlusion location	
Intracranial ICA	18% (36/196)*
M1 middle cerebral artery	67% (131/196)*
M2 middle cerebral artery	14% (28/196)*
M3 middle cerebral artery	0.5% (1/196)*

*Core lab missing “Most proximal occlusion location” for 6 subjects.

Table 2

Outcome measures

	Total	IV-IA	IA only	P-value
Primary measure outcome				
Successful revascularization (assigned as TICI >= 2b up to 3 passes) as per core lab on available data*	84.2% (160/190)**	84.5% (93/110)	83.8% (67/80)	1.000
Successful revascularization (assigned as TICI >= 2b up to 3 passes) as per site investigator on available data*	91.1% (173/190)**	91.8% (101/110)	90.0% (72/80)	0.798
Successful revascularization (assigned as TICI > 2b up to 3 passes) as per core lab***	79.2% (160/202)	78.2% (93/119)	80.7% (67/83)	0.726
Use of rescue treatment after study device	8.9% (18/202)	9.2% (11/119)	8.4% (7/83)	1.000
Final revascularization (after rescue therapy) as per core lab****	88.1% (171/194)	87.6% (99/113)	88.9% (72/81)	0.826
Study device TICI revascularization as per core laboratory				
0	4.7% (9/190)	4.5% (5/110)	5.0% (4/80)	0.989
1	0.5% (1/190)	0.9% (1/110)	0.0% (0/80)	
2a	10.5% (20/190)	10.0% (11/110)	11.3% (9/80)	
2b	29.5% (56/190)	29.1% (32/110)	30.0% (24/80)	
3	54.7% (104/190)	55.5% (61/110)	53.8% (43/80)	
Clinical outcome				
90 day good outcome (mRS 0–2)	57.9% (117/202)	62.2% (74/119)	51.8% (43/83)	0.150

** kappa value: 0.59

*** Core lab missing primary endpoint data rated as TICI 0

**** Core lab missing primary endpoint data of eight subjects

Table 3

Safety endpoints

	Total	IV-IA	IA only	P-value
Primary				
Device or procedure-related serious adverse events	7.4% (15/202)	6.7% (8/119)	8.4% (7/83)	0.786
Procedure-related serious adverse events	5.4% (11/202)	5.9% (7/119)	4.8% (4/83)	1.000
Solitaire Device-related serious adverse events*	2.5% (5/202)	2.5% (3/119)	2.4% (2/83)	1.000
Embolus to uninvolved territory	1.0% (2/202)	0.0% (0/119)	2.4% (2/83)	0.168
Intracranial hemorrhage	1.0% (2/202)	1.7% (2/119)	0.0% (0/83)	0.513
Vessel dissection	1.0% (2/202)	0.8% (1/119)	1.2% (1/83)	1.000
Secondary				
Intracranial hemorrhage as per CEC adjudication	18.8% (38/202)	18.5% (22/119)	19.3% (16/83)	1.000
HI-1	9.4% (19/202)	8.4% (10/119)	10.8% (9/83)	0.627
HI-2	5.0% (10/202)	5.0% (6/119)	4.8% (4/83)	1.000
PH-1	3.0% (6/202)	4.2% (5/119)	1.2% (1/83)	0.404
IVH + PH-2	0.5% (1/202)	0.8% (1/119)	0.0% (0/83)	1.000
SAH	3.0% (6/202)	2.5% (3/119)	3.6% (3/83)	0.691
Symptomatic per CEC adjudication**	1.5% (3/202)	1.7% (2/119)	1.2% (1/83)	1.000
Death from any cause by 90 days	6.9% (14/202)	5.9% (7/119)	8.4% (7/83)	0.577

* One patient presented two events.

** Classified according to ECASS trials definition