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Safety and outcomes of routine endovascular thrombectomy in large artery occlusion recorded in the SITS Register: An observational study

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Background and objective. We aimed to evaluate the safety and outcomes of thrombectomy in anterior circulation acute ischaemic stroke recorded in the SITS–International Stroke Thrombectomy Register (SITS-ISTR) and compare them with pooled randomized controlled trials (RCTs) and two national registry studies.

Methods. We identified centres recording ≥10 consecutive patients in the SITS-ISTR with at least 70% of available modified Rankin Scale (mRS) at 3 months during 2014–2019. We defined large artery occlusion as intracranial internal carotid artery, first and second segment of middle cerebral artery and first segment of anterior cerebral artery. Outcome measures were functional independence (mRS score 0-2) and death at 3 months and symptomatic intracranial haemorrhage (SICH) per modified SITS-MOST.

Results. Results are presented in the following order: SITS-ISTR, RCTs, MR CLEAN Registry and German Stroke Registry (GSR). Median age was 73, 68, 71 and 75 years; baseline NIHSS score was 16, 17, 16 and 15; prior intravenous thrombolysis was 62%, 83%, 78% and 56%; onset to reperfusion time was 289, 285, 267 and 249 min; successful recanalization (mTICI score 2b or 3) was 86%, 71%, 59% and 83%; functional independence at 3 months was 45.5% (95% CI: 44–47), 46.0% (42–50), 38% (35–41) and 37% (35–41), respectively; death was 19.2% (19–21), 15.3% (12.7–18.4), 29.2% (27–32) and 28.6% (27–31); and SICH was 3.6% (3–4), 4.4% (3.0–6.4), 5.8% (4.7–7.1) and not available.

Conclusion. Thrombectomy in routine clinical use registered in the SITS-ISTR showed safety and outcomes comparable to RCTs, and better

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functional outcomes and lower mortality than previous national registry studies.

Keywords: real-world registry, stroke, thrombectomy.

Introduction

Randomized controlled trials (RCTs) have demonstrated the benefit of thrombectomy with second-generation devices (mainly stent retrievers) over medical therapy alone among patients with anterior circulation acute ischaemic stroke due to large artery occlusions (LAO) [1–6]. Thrombectomy results in a high rate of arterial recanalization and significantly improves functional outcomes at 3 months with no increase in mortality [7, 8].

Currently, thrombectomy devices are approved by the US Food and Drug Administration for use up to 8 h after symptom onset, and Canadian guidelines additionally recommend thrombectomy for selected patients up to 12 h after symptom onset [9–11]. Recently published results of the DAWN [12] and DEFUSE 3 [13] trials demonstrated that thrombectomy can be effective in selected patients up to 24 h after being last seen without acute stroke symptoms. International guidelines recommend treatment 6–16 h if within DAWN or DEFUSE-3 criteria, and 16-24 if within DAWN criteria [14, 15]. After the publication of first positive trial on endovascular thrombectomy [1], most of the trials were prematurely stopped for ethical reasons [2–6]. Although meta-analyses of these trials show benefit of endovascular thrombectomy over standard medical care [7, 8], additional data on real-world experience of endovascular thrombectomy are desirable to verify whether the results of RCTs hold true in routine clinical practice. Moreover, published data are limited on thrombectomy in routine clinical practice, in particular international data on treatment safety and outcomes. The SITS (Safe Implementation of Treatment in Stroke)–International Stroke Thrombectomy Registry (ISTR) has been collecting international data on endovascular thrombectomy in routine clinical practice since 2014.

Aim

We aimed to evaluate the safety and outcomes of thrombectomy in patients with anterior circulation acute ischaemic stroke with LAO as recorded in the SITS-ISTR, compared with patients in the active arms of RCTs [8] and two national thrombectomy registry studies [16, 17].

Methods

Data source

We collected data from the SITS-ISTR, an ongoing prospective academic-driven multinational registry for centres using thrombectomy for the treatment of acute ischaemic stroke.

Centre selection

Centres recording at least 10 consecutive patients in the SITS-ISTR and each with at least 70% of complete data for 3-month outcomes during the period of 1 January 2014 to 3 September 2019 were included in the study.

Patient selection

Acute ischaemic stroke patients with CT/MRI angiography verified anterior circulation LAO defined as intracranial internal carotid artery (ICA), first (M1) and second (M2) segment of the middle cerebral artery and first segment of the anterior cerebral artery (A1) were included in the analysis.

HERMES data [8], MR CLEAN Registry [16] and German Stroke Registry (GSR) [17] results were collected from their respective publications.

Variables

Baseline and demographic characteristics including cerebrovascular risk factors, medication at stroke onset, stroke severity using the National Institutes of Health Stroke Scale (NIHSS) score and pre-stroke disability using the modified Rankin Scale (mRS) score, site of occlusion, brain imaging prior to treatment, type of anaesthesia, recanalization status according to modified thrombolysis in cerebral infarction (TICI) score, blood pressure, NIHSS at 2, 24 h and 7 days or discharge (whatever comes first) following treatment, follow-up brain imaging scans at 22–36 h after treatment and any other extra imaging scans to assess for haemorrhagic transformation, mRS at 3 months were the study variables. Haemorrhagic transformation was categorized using the SITS-MOST [18] definitions into haemorrhagic infarction (HI) type 1,

HI2, parenchymal haemorrhage (PH) type 1, PH2, remote PHr1 and PHr2.

Outcome parameters

Primary endpoints

For efficacy: Functional independence at 3 months (defined as a mRS 0-2).

For safety: Symptomatic intracranial haemorrhage (SICH) according to the modified SITS-MOST) and mortality within 3 months. SITS-MOST [16] was defined as ≥4-point increase in NIHSS from baseline to 24 h or death within 24 h and PH2 or PHr2 or in the 22–36 h post-EVT imaging scans. In the modified SITS-MOST, any subarachnoid haemorrhage in the 22–36 h post-thrombectomy imaging scans was added to the definition.

Definitions of SICH varied between SITS, RCTs and the MR CLEAN Registry. The GSR publication did not report SICH data.

Secondary endpoints

1. SICH per ECASS II [19] defined as ≥4-point increase in NIHSS from baseline to 7 days or death within 7 days and any haemorrhagic transformation categorized using the ECASS trial definitions (HI1, HI2, PH1, PH2, PHr1 and PHr2) in the post-EVT imaging scans.
2. Proportion of patients with excellent recovery (mRS score 0–1) at 3 months.
3. Proportion of patients with NIHSS score 0–2 at 24 h.
4. Proportion of patients with major early neurological recovery at 24 h, defined as a reduction in NIHSS score from baseline of at least 8 points or reaching 0–1; and change in NIHSS score from baseline to 24 h.
5. NIHSS score at 24 h (mean, median).
6. NIHSS score change from baseline to 24 h (mean change, median change).
7. PH2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 22–36 h or any extra imaging scans.
8. All-cause death at 3 months.
9. Recanalization of the occluded artery, defined as at least TICI 2b flow in the treated territory after procedure.
10. Time from stroke onset to recanalization to any TICI.

Statistical analysis

Descriptive statistics for the baseline and demographic data are presented for the SITS-ISTR cohort and published results of the pooled active arms of the RCTs. Unknown or missing values were excluded from the denominator when calculating proportions in the SITS-ISTR. Proportions and 95% confidence intervals for outcomes were calculated and presented for comparison with the corresponding proportion in the active arm of the pooled RCTs and two national registries. The 95% confidence intervals for proportions were calculated using the Wilson procedure with a correction for continuity according to methods described by Newcombe [20]. Outcomes were compared between patients treated with thrombectomy according to stroke symptom onset to arterial puncture time.

Sensitivity analyses were undertaken on data from centres that had lower rates of complete data for 3-month outcome (70–94%) compared with centres that had a high rate (≥95%) of 3-month complete data.

All analyses were performed using STATISTICA 13.1 and SPSS v.25.

Ethics

Ethical approval or patient consent for participation in the SITS-ISTR differed among participating countries. Ethical approval and patient consent were obtained in countries that required this, while other countries approved the register for conduct as an anonymized audit. The SITS Register was approved by the Ethics Committee in Stockholm, Sweden.

Results

Figure 1 shows the study flow chart. In total, 6350 patients from 16 countries and 42 centres were included in the final analysis. The rate of mRS availability at 3 months was 86%. Appendix S1 shows the contributing countries, centres and centre coordinators.

Table 1 shows the baseline and demographic characteristics. SITS thrombectomy patients were older than in HERMES and the MR CLEAN Registry, but younger than in the GSR, and more often had a history of hypertension and diabetes mellitus

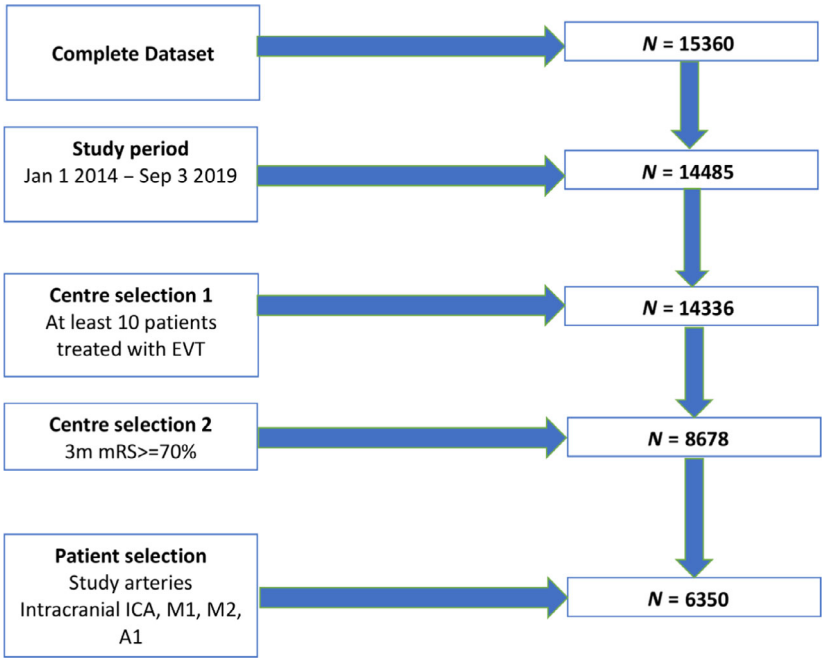

Fig. 1 *Study flow chart.*

compared with HERMES and the MR CLEAN Registry, but less often than GSR patients. Gender distribution, baseline stroke severity, history of atrial fibrillation and blood glucose were similar between the groups. SITS-ISTR patients had a higher proportion of M2 occlusion compared with HERMES and the MR CLEAN Registry, but a lower proportion than in the GSR. SITS-ISTR patients had a lower proportion of prior treatment with intravenous thrombolysis (IVT) than HERMES and the MR CLEAN Registry, but higher than GSR patients. In SITS-ISTR, stroke onset to IVT initiation was longer than in HERMES and the MR CLEAN Registry. Stroke onset to reperfusion time was comparable between SITS-ISTR and HERMES; however, MR CLEAN had a shorter time to reperfusion (median 267 min).

Table 2 shows the main outcome results. The rates of functional independence and mortality at 3 months and SICH were similar between SITS-ISTR and HERMES. MR CLEAN Registry and GSR patients had lower rates of functional independence and higher rates of mortality than SITS-ISTR and HERMES. Most of the secondary outcomes were also similar between SITS-ISTR and HERMES. The rate of successful recanalization was similar between SITS-ISTR and GSR and higher than in HERMES and the MR CLEAN Registry. Figure 2 shows the distribution of mRS scores at 3 months.

Of the entire study population, among 5459 patients (86%) with available 3-month mRS, 95% ($N = 5201$) had available arterial puncture time. Among these patients, arterial puncture was done in 80% of cases within 6 h of symptom onset, 8% within >6–8 h, 6% within >8-12 h and 6% within >12–24 h. Table 3 shows the distribution of primary outcomes across timing strata.

In a sensitivity analysis, we examined results in centres with at least 95% available 3-month outcome (21 centres with 3151 patients) and compared with centres with 70–94% available 3-month data (21 centres with 3199 patients). Functional independence was 44.2% vs. 47% ($P = 0.04$) and mortality was 19.8% vs. 18.4% ($P = 0.19$), SICH per modified SITS-MOST was 3.5% vs. 3.8% ($P = 0.64$), excellent outcome was 30% vs. 31.9% ($P = 0.14$), type 2 parenchymal haemorrhage was 4.2% vs. 4.6%, $P = 0.46$, and patients without prior IVT were 60.9% vs. 63.3% ($P = 0.04$) in the centres with ≥95% 3-month data

Table 1 *Baseline and demographic characteristics of patients in the SITS-ISTR, patients in active arms of pooled RCTs and two national registries*

Characteristic Median (IQR)/% (*N*)	SITS-ISTR	HERMES Data	MR CLEAN Registry	German Stroke Registry (GSR)
Age (years)	73 (63–80)	68 (57–77)	71 (60–80)	75 (64–82)
Women	50.5% (3209/6350)	48%	46.7% (694)	50.4% (1328)
Hypertension	68% (4273/6315)	56%	50.7% (745/1488)	75.7% (1976/2612)
Diabetes mellitus	19% (1220/6313)	13%	17.2% (255/1488)	21.1% (550/2612)
Atrial fibrillation	31% (1940/6308)	33%	22.3% (327/1488)	40.9% (1067/2606)
Previous stroke	11% (686/6314)	–	16.8% (249/1488)	–
Smoking	22% (1351/6069)	31%	22.9% (338/1488)	15.2% (349/2289)
NIHSS	16 (11–20)	17 (14–20)	16 (11–20)	15 (10–19)
Blood glucose (mmol L^{-1})	6.7 (5.8–8.1)	6.6 (5.9–7.8)	Not available	Not available
Systolic blood pressure	150 (130–166)	Not available	Not available	Not available
Diastolic blood pressure	80 (70–90)	Not available	Not available	Not available
Intracranial internal carotid artery	16% (1022/6350)	21%	22% (313/1488)	26% (666/2565)
First segment of MCA (M1)	67% (4259/6350)	69%	58% (825/1488)	53.6% (1374/2565)
Second segments of the MCA (M2)	16.8% (1057/6350)	8%	12.3% (175/1488)	20.1% (516/2565)
Other/ACA	0.2% (12/6350)	2%	1.9% (27/1488)	3.4% (86/2565)
Treatment with IV tPA	62.1% (61–63%) (3944/6350)	83%	78% (1161/1488)	55.8% (1457/2610)
Onset to IV tPA	120 (90–174)	100 (75–133)	80 (62–120)	–
Onset to reperfusion	289 (208–405)	285 (210–362)	267 (217–331)	249 (191–325)

NIHSS, National Institute of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; IV tPA, intravenous tissue plasminogen activator.

compared with centres with 70–94% available 3-month data.

Discussion

In this 5-year observational, retrospective study of a large, multinational cohort of anterior circulation AIS patients with intracranial LAO treated with thrombectomy in routine clinical practice, we found that the treatment outcomes are comparable with the active arms of the HERMES and national registries. SICH rates, neurological improvement within 24 h and functional independence at 3 months showed similar results between SITS thrombectomy-treated patients and HERMES. However, we observed a higher point estimate for death within 3 months in the SITS thrombectomy patients compared with the HERMES data. This may be partly explained by the older age (median difference 5 years) in SITS thrombectomy patients compared with patients in the RCTs. We did not have access to individual patient data from the HERMES and therefore were unable to perform formal statistical testing and multivariate analysis to adjust for baseline differences between SITS-ISTR and HERMES data. For the main outcome results, we calculated 95% confidence intervals (CI). Although there are some differences in point estimates, the 95% CIs overlap for primary and most of the secondary outcome parameters, indicating that results are similar.

When comparing with the MR CLEAN Registry [16] and GSR [17], we observed a higher frequency of

Table 2 *Main outcomes in the SITS-ISTR compared with pooled RCTs and two national registries*

Outcomes % (95% CI) *n*/*N*	SITS-ISTR	HERMES data	MR CLEAN Registry	German Stroke Registry (GSR)
Primary outcomes				
mRS 3m 0–2	45.5% (44–47) 2485/5459	46% (42.1–49.9) 291/633	37.9% (35–41) 517/1363	36.9% (35–41) 854/2316
SICH per modified SITS-MOST	3.6% (3–4) 218/5983	4.4% (3.0–6.4) 28/634[a]	5.8% (4.7–7.1) 86/1488[b]	–
Death within 3m	19.2% (19–21) 1086/5670	15.3% (12.7–18.4) 97/633	29.2% (27–32) 398/1363	28.6% (27–31) 662/2316
Secondary outcomes				
SICH per ECASS-II	6.8% (6–7) 365/5396	4.4% (3.0–6.4) 28/634[c]		–
mRS 3m 0-1	30.9% (29.7–32.1) 1686/5459	26.9% (23.5–30.5)	18.9% 258/1363	26.3% 610/2316
Parenchymal haematoma type 2 at 24 h	4.4% (3.9–4.9) 263/6003	5.1% (3.6–7.2)	–	13.2%[d] 349/2637
Successful recanalization (mTICI score 2b or 3)	85.7% (85–87) 4573/5339	71% (66.6–74.2)	58.7% 743/1266	83% 1857/2236
NIHSS 24 h, Mean (SD) Median (IQR)	10.2 (8.4) 8 (3–16)	10.4 (8.7) 8 (3–16)	–	–
NIHSS Improvement ≥8p or NIHSS 0-1 at 24 h	44.1% (43–45) 2351/5336	50.2% (46.1–54.2)	–	–
NIHSS change 0–24 h Mean (SD)/Median (IQR)	−5.2 (7.7) −5 (−11 to 0)	−6.4 (8.2) −7 (−12 to −1)	–	–

[a]Definitions varied between RCTs in the HERMES.
[b]MR CLEAN Registry used the Heidelberg criteria.
[c]RCTs definition did not include petechial haemorrhagic infarction.
[d]Any haemorrhage at 24-h imaging.

functional independence at 3 months in the SITS-ISTR and lower rate of death within 3 months and SICH (3% vs. 5.8%, $P < 0.001$, not available for GSR). The better outcomes in the SITS-ISTR than in the MR CLEAN Registry and GSR could partly be explained by higher proportions of patients with ICA occlusion in the two latter (28% and 26% vs. 17% in the SITS-ISTR [21]. Moreover, the SITS-ISTR patients had higher proportions of successful recanalization (TICI2b/3), at 86%, compared with HERMES at 71% and the MR CLEAN Registry at 59%. Recanalization is one of the most important predictors for 3-month functional outcome. Meanwhile, the MR CLEAN Registry employs central independent adjudication for recanalization grade, which may give a more conservative estimate [16].

When comparing with HERMES, some known prognostic factors for long-term outcome were unfavourable in the SITS-ISTR population: higher age, higher frequency of hypertension and diabetes mellitus, and longer onset to IVT treatment time than in the HERMES data. On the other hand, some prognostic factors were favourable for the SITS-ISTR population, such as a lower proportion of smoking history and higher proportion of distal (M2) occlusion. However, stroke severity as measured by NIHSS score, history of atrial fibrillation and blood glucose were similar between the SITS thrombectomy and HERMES. SITS-ISTR and GSR patients were older and had a higher frequency of cardiovascular risk factors compared with the MR CLEAN Registry. Patients in the SITS-ISTR also had a higher proportion of M2 occlusions

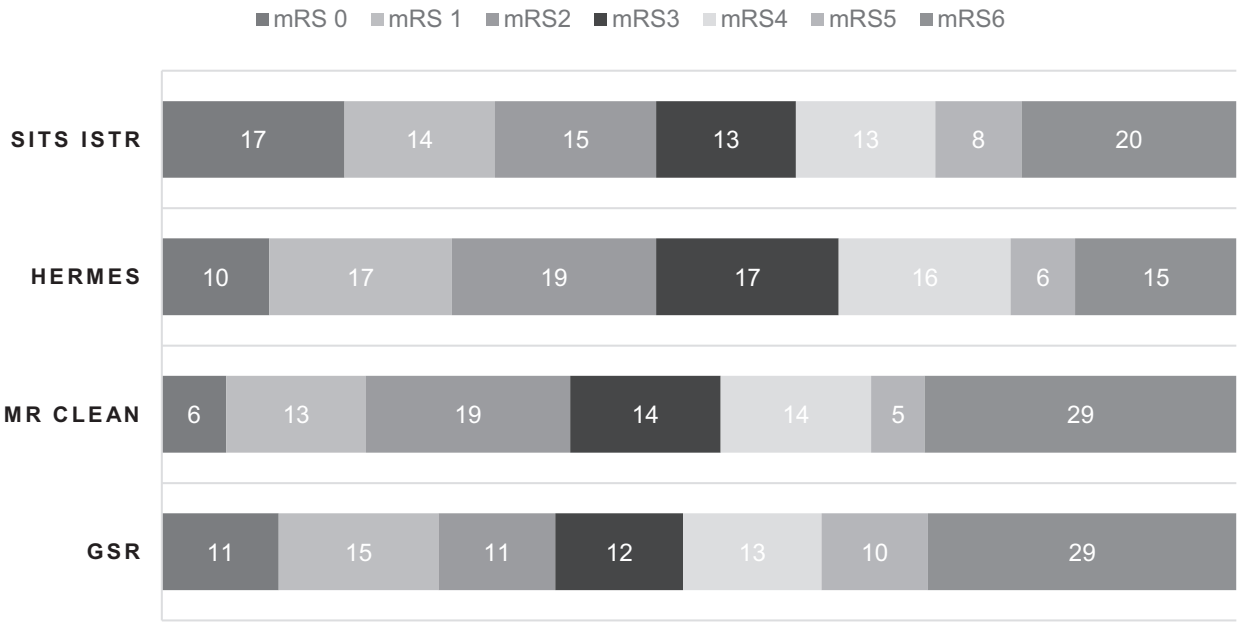

Fig. 2 *Outcomes per the modified Rankin Scale (mRS) at three-month follow-up in the SITS-ISTR, HERMES data, MR CLEAN Registry and German Stroke Registry (GSR) cohorts.*

Table 3 *Primary outcomes in the SITS-ISTR according to time from onset to arterial puncture*

	<6 h, 4772/6019 (80%)	6–8 h, 470/6019 (8%)	8–12 h, 388/6019 (6%)	12–24 h, 389/6019 (6%)	*P*-value
mRS 3m 0-2	46%	43%	48%	41%	0.17
SICH per modified SITS-MOST	3.9%	3.7%	4.8%	3.5%	0.83
Death within 3m	20%	17%	20%	19%	0.37

compared with the MR CLEAN Registry, which may contribute to better outcome in the former.

Parenchymal hematoma type 2 (PH2) and SICH rates were comparable between the SITS-ISTR and HERMES. In the pooled RCTs, the definition of SICH varied across the individual trials. Our primary definition of SICH was per the modified SITS-MOST definition [18]. We also presented additional SICH per the ECASS-II definition for the SITS-ISTR [19]. As expected, the point estimate of SICH per ECASS-II rate was higher in the SITS-ISTR than SICH defined in the pooled RCT; however, the ECASS-II definition includes petechial haemorrhagic infarction, in which the RCTs did not include in their SICH definition. For both SICH definitions, our observed 95% CI overlaps with the SICH in the HERMES data. These divergences in definitions used for SICH render the results difficult to compare.

In the SITS-ISTR population, a higher proportion received thrombectomy without prior IVT, compared with HERMES and the MR CLEAN Registry, but slightly lower than in the GSR. Thus, both SITS and GSR cohorts included more patients with IVT contraindications, such as unknown onset time or time since last seen well >4.5 h.

In SITS-ISTR, arterial puncture was done within 6 h after stroke onset in the majority of cases (80%). Overall, there was no statistically significant

difference in outcomes between the groups according to onset to puncture time. Time remains an important factor for good functional outcome.

We did not observe any significant differences in functional outcomes and mortality at 3 months between centres categorized by their availability of 3-month data. Although some centres did not achieve >70% completeness, the overall 3-month data availability is 86% for the study population, which is acceptable for a registry-based observational study.

Important limitations of our study should be considered. These include the observational design. We used published results from the HERMES collaboration for comparison due to lacking access to individual patient data. Another limitation is the missing data at various time points. Interpretation of our results requires caution, due to likely influence of case mix. Lack of central adjudication of imaging data is another limitation of our study. Selection bias for centres with lower proportion of 3-month available data is an important issue and a potential limitation of our study, as is the 14% rate of missing outcome data within the retained population. Other limitations include absence of on-site monitoring and source data verification, and the unblinded assessment of outcomes, which may be susceptible to investigator bias.

The strength of our study is the large number of patients from an international registry, with data contributed by 42 centres in 16 countries over more than 5 years of real-life clinical practice.

In conclusion, safety and outcome after thrombectomy in routine clinical use for anterior circulation ischaemic stroke are similar to that in randomized clinical trials. SITS-ISTR patients had a higher functional outcome and lower mortality than two studies based on large national stroke registries.

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Conflicts of interest

N. Ahmed is the Chairman of SITS International, which receives a grant from Boehringer Ingelheim for the SITS–International Stroke Thrombolysis Register and from Stryker, Covidien and Phenox in collaboration with Karolinska Institutet for the SITS-OPEN study. M Mazya holds the position of Research and Network Executive of SITS International. R. Herzig has received honoraria from Boehringer Ingelheim as a member of an Advisory Board (regarding dabigatran). K. Lees has received fees and expenses from Boehringer Ingelheim for lectures and for serving on data monitoring committees. R. Mikulik has received fees from Boehringer Ingelheim for lectures. D. Toni is a member of an Advisory Board (regarding dabigatran) and has received speaker honoraria from Boehringer Ingelheim. A.P Nunes has received fees from Boehringer Ingelheim for lectures. Other authors have no disclosure.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Country (number of centres), Centre name (Centre Coordinator).

