Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial

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Lancet 2019; 393: 998–1008

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Summary

Background Stent retriever thrombectomy of large-vessel occlusion results in better outcomes than medical therapy alone. Alternative thrombectomy strategies, particularly a direct aspiration as first pass technique, while promising, have not been rigorously assessed for clinical efficacy in randomised trials. We designed COMPASS to assess whether patients treated with aspiration as first pass have non-inferior functional outcomes to those treated with a stent retriever as first line.

Methods We did a multicentre, randomised, open label, blinded outcome, core lab adjudicated non-inferiority trial at 15 sites (ten hospitals and four specialty clinics in the USA and one hospital in Canada). Eligible participants were patients presenting with acute ischaemic stroke from anterior circulation large-vessel occlusion within 6 h of onset and an Alberta Stroke Program Early CT Score of greater than 6. We randomly assigned participants (1:1) via a central web-based system without stratification to either direct aspiration first pass or stent retriever first line thrombectomy. Those assessing primary outcomes via clinical examinations were masked to group assignment as they were not involved in the procedures. Physicians were allowed to use adjunctive technology as was consistent with their standard of care. The null hypothesis for this study was that patients treated with aspiration as first pass achieve inferior outcomes compared with those treated with a stent retriever first line approach. The primary outcome was non-inferiority of clinical functional outcome at 90 days as measured by the percentage of patients achieving a modified Rankin Scale score of 0–2, analysed by intent to treat; non-inferiority was established with a margin of 0·15. All randomly assigned patients were included in the safety analyses. This trial is registered at ClinicalTrials.gov, number: NCT02466893.

Findings Between June 1, 2015, and July 5, 2017, we assigned 270 patients to treatment: 134 to aspiration first pass and 136 to stent retriever first line. A modified Rankin score of 0–2 at 90 days was achieved by 69 patients (52%; 95% CI 43·8–60·3) in the aspiration group and 67 patients (50%; 41·6–57·4) in the stent retriever group, showing that aspiration as first pass was non-inferior to stent retriever first line ($p_{non\text{-}inferiority}$=0·0014). Intracranial haemorrhage occurred in 48 (36%) of 134 in the aspiration first pass group, and 46 (34%) of 135 in the stent retriever first line group. All-cause mortality at 3 months occurred in 30 patients (22%) in both groups.

Interpretation A direct aspiration as first pass thrombectomy conferred non-inferior functional outcome at 90 days compared with stent retriever first line thrombectomy. This study supports the use of direct aspiration as an alternative to stent retriever as first-line therapy for stroke thrombectomy.

Funding Penumbra.

Introduction

Multiple randomised trials[1–7] have established thrombectomy as the standard of care for appropriate patients with large vessel occlusion.[8–10] These trials predominantly used stent retriever devices to do a thrombectomy. It is unclear whether the benefit observed in these trials would persist if an alternative method of thrombectomy was used. As a result, established stroke guidelines specifically recommend the use of stent retrievers to the exclusion of other thrombectomy techniques.[8,10] A direct aspiration first pass technique is an aspiration-first approach to performing thrombectomy. This technique uses a large-bore catheter to aspirate the thrombus without initially using a stent retriever. If aspiration alone is not successful, then the large-bore catheter serves as a conduit to alternatively use a stent retriever or other means to do the thrombectomy. Findings from initial single-arm studies have suggested the direct

Research in context

Evidence before this study

We searched MEDLINE for studies published between Jan 1, 2014, and Jan 1, 2019, using any combination of two of the following search terms with no language restrictions: "stroke", "thrombectomy", or "randomized trial". This search yielded ten randomised trials providing evidence that thrombectomy was superior to medical therapy for treatment of emergent large-vessel stroke. However, all but one study were primarily based upon stent retriever technology; the tenth study, THERAPY, failed to meet its primary endpoint. ASTER is the only reported trial that used aspiration thrombectomy as a first pass approach versus stent retriever as a first line approach, and it failed to meet its primary endpoint of angiographic superiority for aspiration thrombectomy as first pass. As a result, it is unclear whether the benefit of thrombectomy is unique to a single approach–stent retriever as first line or whether alternate approaches to thrombectomy would also confer a clinical benefit. Whether stent retrievers are a necessary component for successful thrombectomy is hotly debated internationally, as most clearly evidenced by the variable language used across multiple society clinical guidelines.

Added value of this study

COMPASS was a North American, prospective, multicentre, masked assessor, randomised trial assessing the non-inferiority of aspiration thrombectomy as first pass versus stent retriever as first line for large vessel occlusion. COMPASS directly addressed whether stent retrievers are necessary for successful thrombectomy, with strongly positive results.

Implications of all the available evidence

COMPASS, with the supportive but non-clinically focused ASTER results, provides level 1 data that an aspiration thrombectomy as first pass approach is non-inferior to a stent retriever as first line approach for the treatment of selected patients with acute large vessel ischaemic stroke. This finding will be of broad interest to all stroke physicians and might directly affect current stroke treatment guideline recommendations. Furthermore, these data have the potential to substantially reduce the cost of thrombectomy procedures worldwide.

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aspiration first pass approach has promising safety and clinical efficacy, with potential improvements in time and cost compared with using a stent retriever first line approach.[11,12] The technical comparability of these two approaches was also suggested when the ASTER trial,[13] a prospective randomised trial designed to show superior angiographic outcomes with direct aspiration first pass technique compared with a stent retriever as a first line approach, failed in its primary outcome, but had similar clinical results in each arm.[13]

To date there have not been any randomised trials designed specifically to assess clinical outcome with the aspiration-first approach compared with established stent retriever technology. Furthermore, there are no randomised data available on the cost differential between the two approaches, a major benefit claimed by proponents of the direct aspiration first pass technique. We designed a randomised controlled trial (COMPASS) to assess whether patients treated with the aspiration first pass approach have non-inferior functional outcomes compared with those treated with a stent retriever first line approach, and to secondarily assess for technical, clinical, and cost superiority of the aspiration-first approach.

Methods

Study design and participants

We did a prospective, multicentre, randomised, open-label, blinded outcome, core lab adjudicated, concurrent control, non-inferiority trial at 15 sites (ten hospitals and four specialty clinics in the USA and one hospital in Canada). Sites were chosen with consideration of their preferred thrombectomy method to avoid bias based on pre-existing operator philosophy. Centres were required to submit details of their 20 most recent thrombectomy cases to ensure practitioner familiarity with both approaches and to confirm preferred practices were balanced across sites (equal numbers of sites preferring both thrombectomy techniques). To ensure familiarity, each centre was required to do at least five thrombectomies with both approaches within the submitted cohort.

The study protocol and consent were initially approved by the institutional review board at the operating trial site (Medical University of South Carolina, Charleston, SC, USA). The study protocol and consent were then individually approved by the institutional review board at each participating centre. The study was registered before any patient enrolment and the active protocol and statistical analysis plan were posted for reference.

For the **statistical analysis plan** see https://clinicaltrials.gov/ct2/show/NCT02466893

Eligible participants were patients presenting with acute ischaemic stroke from large vessel occlusion within 6 h of symptom onset and an Alberta Stroke Program Early CT Score of greater than 6. These criteria were specifically chosen to mirror the majority of the patient populations of previously published trials using primarily stent retrievers.[1–4,6] All patients with internal carotid artery or middle cerebral artery (M1) occlusion who fulfilled inclusion and exclusion criteria were enrolled (appendix). Each patient or designated surrogate was required to sign an informed trial study consent form before enrolment.

See **Online** for appendix

Randomisation and masking

We randomly assigned participants (1:1) by a central web-based system to treatment with either a direct aspiration as first pass thrombectomy or stent retriever

as first line thrombectomy. Randomisation assignments were created without stratification by an outside consulting statistician to allow the study team to remain masked. All staff performing clinical examinations were certified assessors who were not involved in the study procedures. In addition, 90-day modified Rankin Scale assessors were required to be masked to the method of treatment. Masking was achieved by ensuring that 90-day assessors were not aware of the patient's randomisation assignment and did not have access to the electronic data capture system.

Procedures

Any US Food and Drug Administration (FDA)-cleared mechanical stent retriever (Solitaire, Medtronic and Trevo, and Styker; Irvine, CA, and Freemont, CA, USA, respectively) or FDA-cleared aspiration catheter (Penumbra System, Penumbra, Alameda, CA, USA) was approved for use. Detailed information regarding the types of devices used and their cost are in the appendix. Details of the study design have been published previously.[14] Sites were requested to do three passes with the assigned approach and thereafter, in cases of persistent occlusion, they were allowed to use any therapy according to physician preference. Physicians were allowed to use adjunctive technology as was consistent with their standard of care (eg, use of a balloon guide catheter, concurrent distal aspiration, etc).

Clinical and radiographic assessments were done at baseline and 24 h post-procedure. Clinical assessments, focusing on the National Institutes of Health (NIH) Stroke Scale and modified Rankin scale were also done at 7 days post-procedure or discharge, whichever came first, as well as at 30 days and 90 days. All staff doing clinical examinations were certified assessors who were not involved in the study procedures. Certification was completed through the Web DCU module (Medical University of South Carolina), which involved an instructional video followed by six test patient assessments, the same certification requirement used in other NIH-funded stroke trials.[15] Angiographic assessments were done by an independent core lab in a blinded manner. Angiographic success was defined as achieving thrombolysis in cerebral infarction (TICI) grade 2b (50–89% reperfusion), TICI 2c (90–99% reperfusion), or TICI 3 (100% reperfusion).

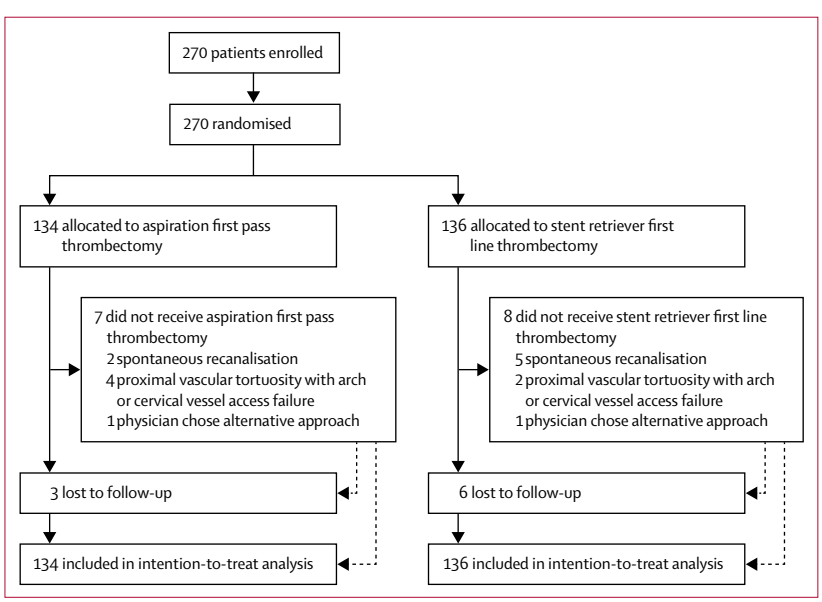

Figure 1: **Trial profile**
There were 17 protocol deviations in the aspiration first pass group: three modified Rankin scores greater than 1; 11 M2 clot location; and three tandem-cervical internal carotid artery occlusions. Additionally, there were 18 protocol deviations in the stent retriever first line group: three modified Rankin scores greater than 1; one Alberta stroke program early CT score less than 7; 11 M2 clot location; one M3 clot location; one basilar clot location; and one tandem-cervical internal carotid artery occlusion.

Outcomes

The primary study endpoint was non-inferiority of patient functional outcome (ie, the proportion of patients achieving functional independence) at 90 days, as measured by achieving 0–2 on the modified Rankin scale.[16] Secondary efficacy endpoints were assessment of time from groin puncture to TICI 2b or greater revascularisation, procedural rate of TICI 2c or greater revascularisation within 45 min of access, rate of TICI 3 revascularisation within 45 min of access, and 90-day disability assessed across the overall distribution of the modified Rankin scale. Prespecified secondary efficacy outcomes were TICI 2b or greater on first pass, rate of TICI 2b within 45 min of access, occurrence of emboli to a new territory, presence of vasospasm involving the accessed vascular tree, 90-day global disability assessed via the overall distribution of the utility weighted modified Rankin scale, reduction in stroke severity (NIH Stroke Scale) at 24 h post treatment, reduction in stroke severity (NIH Stroke Scale) at 7 days post-treatment or discharge (whichever occurred first), and Stroke Impact Score. Angiographic outcomes were analysed to facilitate comparative analysis with other trials.

Prespecified safety outcomes assessed were intracranial haemorrhage within 90 days of randomisation, asymptomatic intracranial haemorrhage at 24 h post-randomisation, symptomatic intracranial haemorrhage at 24 h post-randomisation, intracranial haemorrhage using Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria, parenchymal haematoma type 2 haemorrhage within 36 h of randomisation, clinically significant complications (pneumonia, sepsis, urinary tract infection, etc) at time of discharge or 7 days post-randomisation (whichever came first), mortality rates at 30 days post-randomisation, mortality rates at 90 days post-randomisation, device-related serious adverse events up to 48 h post-randomisation, and procedure-related serious adverse events.

Prespecified device-related procedural costs were evaluated. A comprehensive review of all available operative reports and angiographic equipment logs was

	Aspiration first pass thrombectomy (n=134)	Stent retriever first line thrombectomy (n=136)
Age (years)	71·8 (13·1)	71·1 (12·9)
Sex		
Male	43% (57/134)	50% (68/136)
Female	58% (77/134)	50% (68/136)
Medical history		
Hypertension	69% (92/134)	75% (102/136)
Diabetes	27% (36/134)	29% (40/136)
Hyperlipidaemia or hypercholesterolaemia	49% (65/134)	46% (63/136)
Atrial fibrillation	49% (65/134)	41% (56/136)
Cardiovascular disease	23% (31/134)	22% (30/136)
Current smoker	13% (18/134)	22% (30/136)
Ischaemic stroke	9% (12/134)	17% (23/136)
Haemorrhagic stroke	2% (3/134)	<1% (1/136)
Transient ischaemic attack	5% (7/134)	6% (8/136)
Current stroke event (pre-morbid modified Rankin score)		
0	81% (109/134)	77% (104/136)
1	16% (22/134)	21% (29/136)
2	2% (2/134)	<1% (1/136)
3	0	2% (2/136)
4	<1% (1/134)	0
Median NIHSS score	17 (12–21)	17 (12·5–21·0)
Mean NIHSS score	16·9 (5·8)	16·9 (6·3)
Median systolic blood pressure (mm Hg)	154 (137–176)	155 (141–181)
Mean systolic blood pressure (mm Hg)	156·7 (28·6)	160·9 (28·9)
Median ASPECT score	8 (8–9)	8 (8–9)
Mean ASPECT score	8·2 (0·7)	8·1 (0·7)
Laterality		
Left	49% (65/134)	45% (61/135)*
Right	52% (69/134)	55% (74/135)*
Site of occlusion		
Middle cerebral artery		
M1 proximal	61% (82/134)	63% (85/136)
M1 distal	14% (19/134)	11% (15/136)
M2 proximal	8% (11/134)	8% (11/136)
M3	0	<1% (1/136)
Internal carotid artery (ICA)		
Supraclinoid (ICA terminus)	13% (18/134)	15% (21/136)
Petrocavernous	<1% (1/134)	<1% (1/136)
Other		
Mid-basilar	0	<1% (1/136)
Tandem cervical ICA	2% (3/134)	<1% (1/136)
(Table 1 continues in next column)		
(Continued from previous column)		
Cervical stenosis requiring treatment	2% (3/134)	3% (4/136)
Directly admitted to a comprehensive stroke centre	56% (75/134)	57% (78/136)
Intravenous tissue plasminogen activator pre-procedure	69% (92/134)	71% (96/136)
General anaesthesia	29% (39/134)	30% (41/136)
Onset to main hospital arrival (min)	132 (86)†	133 (87)‡
Onset to qualifying imaging time (min)	149 (86)	154 (90)
Qualifying imaging to randomisation time (min)	52 (48)§	46 (34)
Randomisation to groin puncture time (min)	15 (15)	12 (14)
Onset to groin puncture time (min)	215 (81)	212 (87)
Room arrival to groin puncture time (min)	17 (12)	16 (8)
Hospital arrival to groin puncture time (min)	87 (50)†	82 (42)‡

Data are mean (SD), n (%), or median (IQR). NIHSS=National Institutes of Health stroke scale. ASPECT=Alberta stroke program early CT score. *One mid-basilar patient was incorrectly enrolled. †Six patients were hospitalised before onset and were excluded. ‡Five patients were hospitalised before onset and were excluded. §One patient was excluded because accurate time information was not available.

Table 1: **Baseline characteristics of the intention-to-treat population**

undertaken for all patients, and for each patient any device that was specifically mentioned by brand name in the operative report or for which the device log or product stickers were available was recorded. Comparative benchmark pricing was obtained from a third-party company that aggregates supply chain data from multiple hospital sources (BroadJump, LLC, Dallas, TX). As a second source of cost data, list pricing was obtained from vendor brochures and direct sources. Both methods (aggregate supply chain data and list pricing data) were then tallied and compared across the study groups. Not all devices had pricing data available in both methods; some did not have aggregate supply chain data and some did not have list pricing data. Therefore cost was analysed in two ways. First, aggregate supply chain pricing was used as the primary source, with list pricing as a supplement when aggregate supply chain data were not available. The second way primarily used list pricing with aggregate supply chain pricing supplemented when list pricing data were not available. Both analyses were done with intention-to-treat cohorts. Neither aggregate supply chain or list pricing data were available for seven items (appendix), which were low cost or rarely used devices that would not be expected to significantly affect the analysis. We evaluated device costs in US$ from a hospital perspective using reported costs from 2016 or 2017 (most recently available data used). The cost analysis was completed using a two-sided, two-sample t test ($p<0·05$) to test for the difference in means and medians between cohorts.

To help address potential bias for one approach versus another across the centres, sites were required to submit a log of their last 20 cases before enrolment, with a minimum of five cases done with each approach, thereby assuring familiarity with both. Sites were considered to

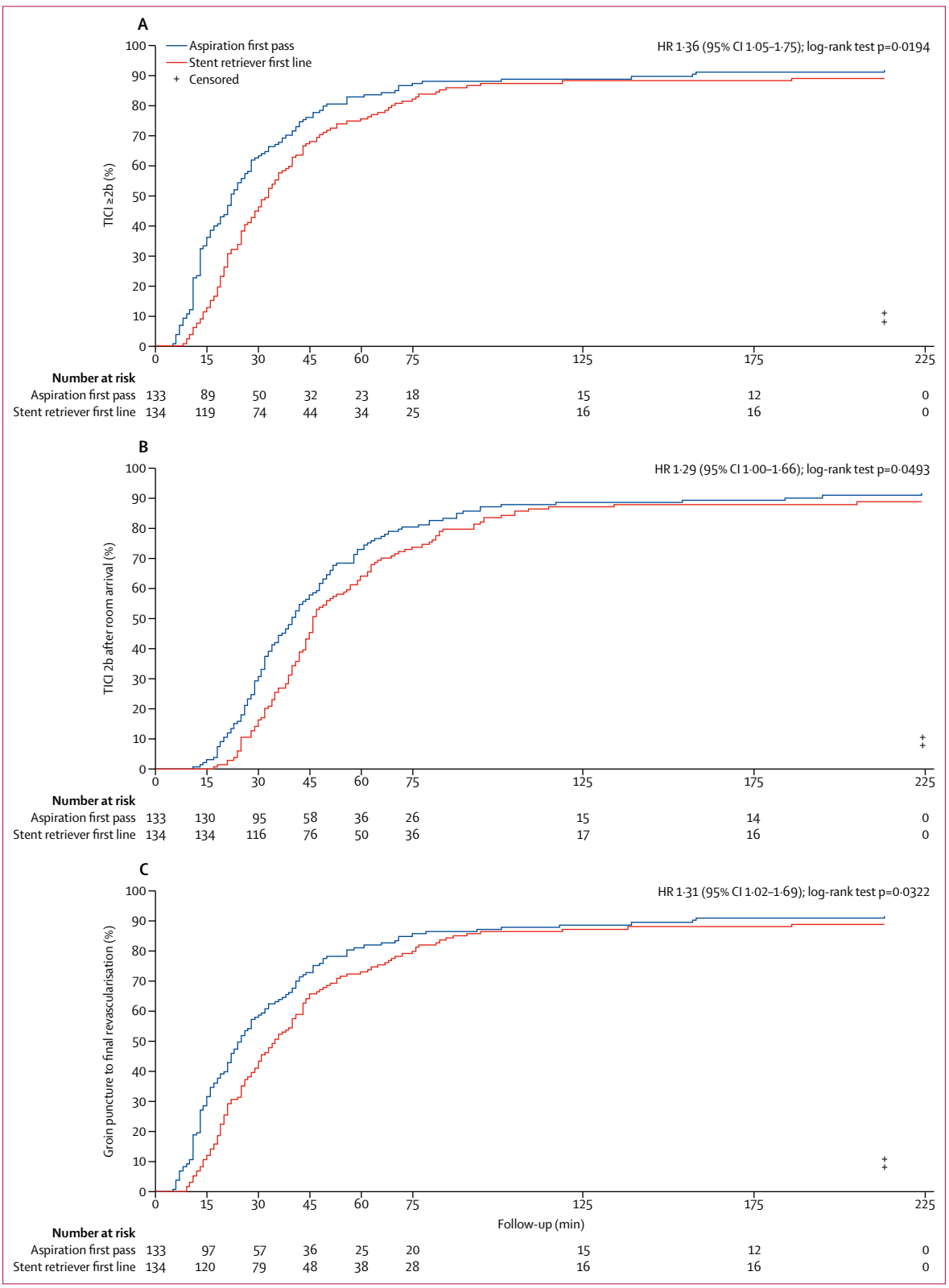

Figure 2: **Efficacy analyses***
A) Time to TICI 2b or greater. B) Analysis of room arrival to TICI 2b reperfusion. C) Groin puncture to final revascularisation. TICI=thrombolysis in cerebral infarction. *For all analyses, one patient from the aspiration first pass group was excluded because no imaging was available, and two patients from the stent retriever first line group were excluded because no time information was available.

	Aspiration first pass thrombectomy	Stent retriever first line thrombectomy	Odds ratio (95% CI)	p value
Onset to treating hospital presentation (min)	132 (86)	133 (87)	NA	..
Qualifying image to randomisation (min)	52 (48)	46 (34)	NA	..
Onset to groin puncture (min)	215 (81)	212 (87)	NA	..
Room arrival to groin puncture (min)	17 (12)	16 (8)	NA	..
Hospital arrival to groin puncture (min)	87 (50)	82 (42)	NA	..
Balloon guide	34% (45/134)	45% (61/136)	0·62 (0·38–1·02)	0·06
Distal access catheter	98% (131/134)*	87% (118/136)	6·66 (1·91–23·19)	0·001
Distal aspiration during stent retriever thrombectomy	100% (28/28)†	85% (110/128)‡	NA§	0·04
At least one stent retriever	21% (28/134)	98% (133/136)¶	0·006 (0·002–0·020)	<0·0001
More than one stent retriever	6% (8/134)	13% (17/136)	0·44 (0·18–1·07)	0·09
Room arrival time to TICI 2b reperfusion (min)	40 (35–46)	46 (44–55)	NA	0·05
Time from groin puncture to final revascularisation (min)	25 (21–30)	35 (30–41)	NA	0·03

Data are mean (SD), % (n/N), or median (95% CI). NA=odds ratio not applicable. TICI=thrombolysis in cerebral infarction. *Numerator reflects two patients with spontaneous recanalisation and one patient who had arch anatomy preventing thrombectomy. †Denominator reflects aspiration patients who had at least one stent retriever used. ‡Denominator reflects five patients with spontaneous recanalisation and three patients for whom a stent retriever was not used. §Because 100% of the aspiration first group received distal aspiration during stent retriever thrombectomy, calculating the odds ratio is not possible. ¶Numerator reflects three patients with spontaneous recanalisation; no stent retriever was opened for these patients.

Table 2: **Procedural details**

be biased if 67% or more of their patients were completed with one treatment over another.

Statistical analysis

Sample size was determined by assuming that the true proportions of patients with modified Rankin Scale outcomes of 0–2 at the 90-day follow-up visit were similar to the proportion of 32·6% from the MR CLEAN study,[1] which was chosen as the outcome rate model given its similar pragmatic design, 6-h window, absence of advanced imaging selection, and substantial population of patients treated with both FDA-approved stent retrievers (Trevo and Solitaire). The calculation was made assuming that 33% of patients receiving direct aspiration first pass and 33% of patients receiving stent retriever first line would achieve success in the primary outcome of modified Rankin Scale 0–2. A one-sided normal approximation test for non-inferiority with a margin of 15% and α=0·05 showed that 122 patients per treatment group would provide a power of 80%. To adjust for up to a 10% attrition rate, the sample was set at 135 patients per treatment group.

All statistical tests were done at the 0·05 significance level unless otherwise noted, and analyses were done using SAS version 9.4. The cost analysis was done using R version 3.4.1. We prespecified that missing modified Rankin Scale scores were handled with a last-score-carried-forward method, with two sensitivity analyses: counting missing scores as deaths and censoring missing scores. The primary endpoint was analysed using a logistic regression model with the following terms in the model: treatment, Alberta Stroke Program Early CT Score (ASPECTS) at baseline, patient age, sidedness, and any other baseline characteristic for which there was a significant difference (two-sided p value <0·05) between treatments. Under the intent-to-treat principle, all patients who were randomised were included in the analysis. The p value for the test of the null hypothesis was based on the statistic for the difference in least-squares mean for each treatment minus the non-inferiority margin of 0·15 all divided by the SEs of the difference in the least-squares means and assuming an approximate normal distribution. This margin was chosen by trial leadership to be the maximum reasonable, clinically relevant limit for the outside bound of the CI.

Secondary efficacy endpoints were analysed using a logistic regression model to test for a difference between treatments with adjustment for clot location: TICI 2b, TICI 2c, and TICI 3 or greater revascularisation within 45 min of access. In addition, time to TICI 2b or greater and room arrival to TICI 2b or greater were analysed using a Kaplan-Meier analysis.

Additional details of statistical analyses are in the statistical analysis plan. No interim analyses were planned. The protocol included requirements of safety review by a data safety monitoring board, which occurred throughout the study. The board was comprised of a neurosurgeon, neuroradiologist, and neurologist who treat stroke but were not participating in enrolment for the trial. The board could halt the study because of any safety concerns. This trial is registered with ClinicalTrials.gov, number NCT02466893.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Aspiration first pass thrombectomy (n=134)	Stent retriever first line thrombectomy (n=136)	Odds ratio (95% CI)	p value
Primary efficacy endpoint				
Modified Rankin scale score of 0–2 at 90 days	69 (52%; 43·8–60·3)	67 (50%; 41·6–57·4)	NA	0·0014*
Secondary efficacy endpoints				
Median time to TICI 2b or greater (min)	22 (19–28)	33 (28–37)	NA	0·0194
90-days global disability Modified Rankin shift	..	..	0·98 (0·64–1·51)	0·9354
0	27 (21%)	24 (19%)	..	..
1	26 (20%)	32 (25%)	..	..
2	15 (12%)	9 (7%)	..	..
3	7 (5%)	14 (11%)	..	..
4	20 (15%)	17 (13%)	..	..
5	6 (5%)	4 (3%)	..	..
6	30 (23%)	30 (23%)	..	..
TICI 2c or greater within 45 min	50% (66/133)†	44% (59/134)‡	1·3 (0·8–2·1)	0·2998
TICI 3 within 45 min	34% (45/133)†	23% (31/134)‡	1·7 (1·0–3·0)	0·0486
Secondary efficacy outcomes				
TICI 2b or greater on first pass	57% (75/131)§	51% (65/129)¶	1·32 (0·81–2·15)	0·32
TICI 2b or greater within 45 min of access	76% (101/133)†	68% (91/134)‡	1·49 (0·87–2·55)	0·17
Occurrence of emboli in a new territory	3% (4/133)†	2% (2/136)	2·08 (0·37–11·54)	0·44
Presence of vasospasm involving the accessed vascular tree	8% (10/133)†	7% (10/136)	1·02 (0·41–2·55)	1·00
90-days global disability utility weighted modified Rankin shift	0·56 (0·4; n=131)‖	0·57 (0·4; n=130)**	NA	0·76
Improved (lower) NIHSS at 24 h	7·5 (9·0; n=133)††	7·3 (8·9; n=132)‡‡	NA	0·86
Improved (lower) NIHSS at 7 days post-treatment or post-discharge	11·0 (8·5; n=117)§§	10·1 (8·7; n=121)¶¶	NA	0·42
Stroke Impact Score‖‖				
Strength	15·8 (4·7)	16·1 (4·2)	NA	0·70
Memory	30·6 (5·8)	30 (6·1)	NA	0·56
Mood	33·7 (5·9)	32·8 (5·5)	NA	0·37
Communication	31·9 (5·2)	31·6 (5·5)	NA	0·77
ADL or IADL	42·8 (10·4)	43·2 (10·8)	NA	0·82
Mobility	36·1 (10·6)	37·1 (9·7)	NA	0·57
Hand function	20·3 (6·4)	21 (5·9)	NA	0·54
Social participation	31·5 (9·0)	31 (9·6)	NA	0·74

Data are n (%, 95% CI), median (95% CI), n (%), or mean (SD). NA=odds ratio not applicable. TICI=thrombolysis in cerebral infarction. NIHSS=National Institutes of Health stroke scale. ADL=activities of daily living. IADL=instrumental activities of daily living. *Non-inferiority test. †Denominator reflects one patient with no available procedural imaging to be assessed by Core lab. ‡Denominator reflects two patients with no time information available. §Denominator reflects two patients who spontaneously recanalised and one patient with no available imaging. ¶Denominator reflects one patient for whom the practitioner chose an alternative approach, five patients who spontaneously recanalised, and one patient who did not have data. ‖Three patients did not have modified Rankin score assessments for this timepoint. **Six patients did not have modified Rankin score assessments for this timepoint. ††One patient allocated to aspiration-first thrombectomy did not have NIHSS assessment at this timepoint. ‡‡Four patients allocated to stent retriever first thrombectomy did not have NIHSS assessment at this timepoint. §§17 patients allocated to aspiration-first thrombectomy did not have NIHSS assessment at this timepoint. ¶¶15 patients did not have NIHSS assessment at this timepoint. ‖‖57 patients allocated to aspiration-first thrombectomy and 66 patients allocated to stent retriever first thrombectomy did not have Stroke Impact Score assessment at this timepoint.

Table 3: **Efficacy endpoints**

Results

Between June 1, 2015, and July 5, 2017, we enrolled 270 patients and randomly assigned 134 to direct aspiration first pass thrombectomy and 136 to stent retriever first line thrombectomy (figure 1). Of the 15 trial sites, one was activated but did not enrol (University of Miami Hospital). Six sites enrolled 25 or more patients each, and ten sites enrolled more than ten patients each. Of the 15 sites that were activated, six sites had a bias towards the aspiration first pass approach and six had a bias towards stent retriever first line. We found no bias towards either approach at the three remaining sites.

The demographic characteristics were closely matched in both cohorts, including age, sex, history of hypertension, diabetes, hyperlipidaemia, atrial fibrillation, coronary artery disease, current smoking status, and history of haemorrhagic stroke and transient ischaemic attack (table 1). The laterality and site of occlusion were also matched. One patient with basilar occlusion was erroneously enrolled in the stent retriever arm, and four patients with tandem cervical occlusions requiring

cervical revascularisation were enrolled: three in the aspiration first pass group and one in the stent retriever first line group. More than half the patients directly presented to the enrolling centre and more than two-thirds received intravenous tissue-type plasminogen activator in both groups. General anaesthesia was used in 39 patients (29%) of 134 in the aspiration first pass group and 41 (30%) of 136 in the stent retriever first line group.

Median time to TICI 2b or greater reperfusion was 11 min faster in the aspiration first pass group (p=0·0194), median time from groin puncture to final recanalisation (the last thrombectomy pass done) was 10 min faster in the aspiration first pass group (p=0·0322), and median time from arrival to the interventional suite to TICI 2b or greater reperfusion was 6 min faster in the aspiration first pass group (p=0·0477; figure 2). For the entire study population, time from room arrival to groin puncture was 16 min (SD 10), and from hospital arrival to groin puncture was 85 min (46). A balloon guide catheter was used in 34% of patients in the aspiration first pass group and 45% in the stent retriever first line group (table 2). Distal access catheters or reperfusion catheters were used in most patients in both groups. Stent retrievers were used in 21% of patients in the aspiration first pass group and 98% of patients in the stent retriever first line group.

The primary efficacy endpoint of a modified Rankin score of 0–2 at 90 days was achieved by 69 patients (52%; 95% CI 43·8–60·3) in the aspiration group and 67 patients (50%; 41·6–57·4) in the stent retriever group, showing that aspiration as first pass was non-inferior to the stent retriever first line approach ($p_{non\text{-}inferiority}$=0·0014). The absolute difference in outcome was 2·5% (95% CI –7 to 12) in favour of the aspiration first pass group suggesting that, across this patient population, it is 95% likely that the proportion of patients achieving 90-day independence with the aspiration first pass approach was no worse than 7% lower and no better than 12% higher than with the stent retriever first line approach. These results did not significantly change even if all missing data were construed as deaths or excluded (appendix). In additional sensitivity analyses (appendix), per-protocol analysis showed results consistent with the intent-to-treat analysis, with independence achieved in 61 patients (55%; 95% CI 44·8 to 63·9) in the aspiration first pass group and 60 patients (52%; 42·3 to 61·1) in the stent retriever first line group, consistent with the aspiration first pass approach being non-inferior to stent retriever first line ($p_{non\text{-}inferiority}$=0·0028). Crossover patient analysis was also consistent with aspiration first pass being non-inferior to stent retriever as first line ($p_{non\text{-}inferiority}$=0·0010). Further sensitivity analyses based on calculated site procedural bias showed that results did not change for sites that preferred one approach over another (appendix).

The secondary efficacy endpoint of 90-day modified Rankin shift, secondary efficacy outcomes, and angiographic outcomes did not differ between the groups (tables 3, 4). There were no significant differences in mortality or prespecified safety outcomes between treatment approaches (table 5).

	Aspiration first pass thrombectomy (n=134)	Stent retriever first line thrombectomy (n=136)	Odds ratio (95% CI)	p value
TICI 2b with primary modality	83% (109/131)*	81% (109/134)†	1·14 (0·60–2·14)	0·75
TICI 2b at final assessment	92% (122/133)‡	89% (121/136)	1·37 (0·61–3·11)	0·54
TICI 2c at final assessment	56% (75/133)‡	56% (76/136)	1·02 (0·63–1·65)	1·00
TICI 3 at final assessment	38% (50/133)‡	29% (39/136)	1·50 (0·9–2·5)	0·15

TICI=thrombolysis in cerebral infarction. *Denominator reflects three patients for whom the core lab was unable to assess TICI after primary modality. †Denominator reflects two patients for whom the core lab was unable to assess TICI after primary modality. ‡Denominator reflects one patient with no available procedural imaging to assess.

Table 4: **Angiographic outcomes**

Prespecified device-related procedural cost analyses showed that the aspiration first pass cohort had significantly lower device costs across all analysis methods (table 6). When using aggregate supply chain data as the primary source and list price as the secondary, the aspiration first pass group had a mean $4541 reduction (SD 7962) in the cost of devices used compared with the stent retriever first line group. When using list price as the primary source and aggregate supply chain data as the secondary source, the aspiration first pass group had a mean $5074 reduction in the cost of devices used. Information on the number of devices used in each group according to each specific device is in the appendix.

Discussion

The results showed that of patients presenting within 6 h of onset of an anterior circulation acute large vessel occlusion and an ASPECTS greater than 6, those who were treated with a direct aspiration as first pass thrombectomy approach had non-inferior functional outcome compared with those treated with a stent retriever as first line thrombectomy approach. These data confirm the non-inferiority of aspiration as first pass compared with stent retriever first line with regard to the primary efficacy endpoint of functional independence, as defined by a modified Rankin Scale score of 0–2 at 90 days. Likewise, all prespecified secondary and sensitivity clinical results were similar between the cohorts, including NIH Stroke Scale, Stroke Impact Scale, etc. These robust data, as well as previously published indirect evidence from ASTER[13] appear to support the clinical use of the aspiration first pass approach.

Additionally, core lab adjudicated angiographic outcomes between the two cohorts were similar. Prespecified angiographic efficacy endpoints and the final recanalisation categories of TICI 2b or greater, 2c or greater, and 3 were similar across both cohorts. Furthermore, prespecified safety analyses of mortality, all intracranial haemorrhage, symptomatic intracranial haemorrhage (with multiple definitions of symptomatic intracranial haemorrhage), and occurrences of serious

	Aspiration first pass thrombectomy (n=134)	Stent retriever first line thrombectomy (n=136)	Odds ratio (95%)
All-cause mortality at 3 months	22% (30/134)	22% (30/136)	1·02 (0·57–1·81)
Any identified intracranial haemorrhage	36% (48/134)*	34% (46/135)†‡	1·08 (0·65–1·78)
Symptomatic intracranial haemorrhage ≥4 NIHSS	6% (8/134)	6% (8/135)‡	1·01 (0·37–2·77)
Symptomatic intracranial haemorrhage SITS-MOST definition	3% (4/134)	3% (4/135)‡	1·01 (0·25–4·12)
Symptomatic intracranial haemorrhage at 24 h timepoint	6% (8/134)	6% (8/135)‡	1·01 (0·37–2·77)
Asymptomatic intracranial haemorrhage at 24 h timepoint	28% (38/134)	27% (37/135)‡	1·05 (0·62–1·79)
All parenchymatous haemorrhage category 2 within 36 h of randomisation	3% (4/134)	3% (4/135)‡	1·01 (0·25–4·12)
All-cause mortality at 30 days post-randomisation	17% (23/134)	16% (21/133)§	1·11 (0·58–2·11)
Intracranial haemorrhage within 90 days post-randomisation (self-reported)	22% (30/134)	18% (24/136)	1·35 (0·74–2·45)
Procedure-related serious adverse events	13% (17/134)	14% (19/136)	0·89 (0·44–1·814)
Device-related serious adverse events up to 48 h post-randomisation	0	0	NA
Clinically significant complications at time of discharge or 7 days post-randomisation			
Arrythmia	2% (2/134)	2% (2/136)	1·02 (0·14–7·31)
Congestive heart failure	0	<1% (1/136)	NA
Distal emboli	<1% (1/134)	2% (2/136)	0·50 (0·05–5·62)
Emboli to previously uninvolved territory	<1% (1/134)	0	NA
Urinary tract infection	<1% (1/134)	0	NA
Sepsis	<1% (1/134)	<1% (1/136)	1·02 (0·06–16·4)
Other infection	2% (2/134)	0	NA
Asymptomatic intracranial haemorrhage	2% (3/134)	2% (2/136)	1·53 (0·25–9·33)
Symptomatic intracranial haemorrhage	5% (7/134)	4% (5/136)	1·33 (0·41–4·3)
Intracranial vessel perforation	<1% (1/134)	0	NA
Ischaemic stroke	2% (3/134)	<1% (1/136)	3·09 (0·32–30·1)
Groin puncture site haematoma	0	<1% (1/136)	NA
Malignant cerebral oedema	<1% (1/134)	<1% (1/136)	1·02 (0·06–16·4)
Myocardial infarction	<1% (1/134)	0	NA
Neurological deterioration	4% (5/134)	4% (6/136)	0·85 (0·25–2·84)
Peripheral thromboembolic event	<1% (1/134)	<1% (1/136)	1·02 (0·06–16·4)
Peripheral bleeding or major non-intracranial haemorrhage	0	<1% (1/136)	NA
Pneumonia	2% (2/134)	0	NA
Renal failure	0	<1% (1/136)	NA
Respiratory failure	6% (8/134)	4% (6/136)	1·38 (0·46–4·08)
Worsening of pre-existing condition	3% (4/134)	2% (2/136)	2·06 (0·37–11·45)
Other	11% (15/134)	13% (17/136)	0·88 (0·42–1·85)

NIHSS= National Institutes of Health stroke scale. SITS-MOST=Safe Implementation of Thrombolysis in Stroke–Monitoring Study. NA=odds ratio not applicable. *Numerator reflects two additional patients with intracranial haemorrhage occurring at 43 and 57 h post-randomisation, compared with 24 h intracranial haemorrhage measures. †Numerator reflects one additional patient with intracranial haemorrhage occurring at 49 h post-randomisation, compared with 24 hr intracranial haemorrhage measures. ‡Denominator reflects one patient with no available imaging. §Denominator reflects three patients who were lost to follow up

Table 5: **Safety**

adverse events were consistently similar across both cohorts.

The results from this trial are similar to those from other trials of aspiration first pass versus stent retriever first line, with some differences. The ASTER trial[13] randomly assigned patients to either stent retrievers or aspiration first pass and was designed to demonstrate angiographic superiority of aspiration first pass. ASTER did not achieve its primary endpoint; there were no significant differences in modified Rankin Scale scores at 90 days despite an absolute difference slightly in favour of stent retrievers of 4·6%. Similarly, there were no significant differences in the modified treatment in cerebral ischaemia 2b to 3 rate with primary modality alone or at the end of the procedure, with absolute difference in favour of stent retrievers at end of primary modality (4·7%) and in the opposite direction at end of procedure (2·4%); differences were not statistically significant. These findings might be partly explained by the ASTER study primarily using previous-generation aspiration catheters with smaller luminal diameters (the Penumbra Ace 64), whereas in this study the Penumbra Ace 68 was used for most patients, which was the largest luminal diameter catheter approved for aspiration in the USA and Canada during the course of the trial.[17–19] Of the 15 sites that were activated, six sites had

a bias towards the aspiration first pass approach and six had a bias towards stent retriever first line.

COMPASS also showed that total device cost was significantly less with the aspiration first pass approach. This cost reduction was preserved across two different approaches to the analysis. There were limitations to this cost analysis. For example, we recorded the devices used and used national data to extrapolate costs, therefore we could have missed differences that were inherent from one centre to another. However, we were not able to obtain specific case-level primary billing or collections data from the participating centres, so a more site-specific analysis was not possible. Additionally, our analysis was based on device costs and did not take into account overall costs for the entirety of the procedure or the post-procedure hospital course. However, given that the clinical outcomes were similar between the cohorts, and procedural use of anaesthesia was similar for both groups, we expected these numbers to be similar. Perhaps the cost advantage for the aspiration as first pass approach would be less if this technique had resulted in longer procedural times and therefore increased use of interventional suite costs, but, instead, treatment times were faster in the aspiration first pass cohort. Because of the multiplicity of comparisons, these data are not conclusive, but they do suggest that the benefit obtained through lower device costs should be maintained and not abrogated by lengthened procedure times. Previously published, non-randomised data[20] support the concept of a cost advantage for the aspiration first pass approach. One study[21] compared the average costs of hospitalisation and noted a cost saving per patient of almost $20 000 with the aspiration first pass approach.

COMPASS was a pragmatic study that did not mandate use of adjunctive devices to practitioners (appendix). As a result, the study might have been limited by heterogeneity in the use of such devices. Preclusion of distal aspiration catheters entirely from the stent retriever first line group or mandatory use of balloon guide catheters in either or both groups would necessitate substantial modification of many of the enrolling physicians' current practices. There is a possibility that these adjunctive devices could have differentially affected COMPASS' outcomes. Additionally, COMPASS' enrolling sites were all highly experienced and therefore initial clinical results with aspiration first pass at other sites might not be as successful as those achieved with stent retriever first line, particularly for those practitioners who are not accustomed to the aspiration first pass approach. Furthermore, these results were specific to the types of patients assessed in this study population and the same results might not be achieved in a delayed-time window or in patients with low ASPECTS. Likewise, because COMPASS was limited to FDA-approved technologies, it is unknown whether these results will translate to other methods of aspiration (syringe or alternative pump) or other catheters. Lastly, there is inherent bias in reporting outcomes in any open-label design; however, the primary clinical outcome was measured by a masked and certified accessor. Similarly, all angiographic results were adjudicated by an independent and blinded imaging core lab.

	Aspiration first pass thrombectomy (n=134)	Stent retriever first line thrombectomy (n=136)	p value
Data primary, list price secondary ($)			
Mean	9540 (7962)	14 081 (4797)	<0·0001
Median	6633 (5937–9823)	12 790·40 (11 723–15 181)	<0·0001
Data secondary, list price primary ($)			
Mean	10 084 (8873)	15 158 (5223)	<0·0001
Median	6848 (6113–9764)	13 686 (12 715–16 548)	<0·0001

Table 6: **Aggregate supply chain cost analysis**

COMPASS establishes that the aspiration first pass approach confers non-inferior functional outcome at 90 days compared with the stent retriever first line approach. This clinical outcome was achieved with significantly lower device costs for the aspiration first pass approach. This study supports the use of the aspiration first pass approach for stroke thrombectomy, and the findings might directly affect current stroke treatment guideline recommendations.

Contributors

AS contributed to study design, data interpretation, and writing and revising the manuscript. EIL contributed to study design and writing and revising the manuscript, and collected and interpreted the data. KVS contributed to reviewing the manuscript, data interpretation, trial participation and enrolment of patients. ATR contributed to data collection, study design, and trial participation. JEDA contributed to patient enrolment, data collection, and reviewing and revising the manuscript. KMF did the core lab review and revising of the manuscript. AST, MIC, and AMS contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of the report. JTF, RADeL, and DJF contributed to the data collection, analysis, interpretation, and patient recruitment. JM contributed to the trial design and execution, data collection, analysis, interpretation, patient recruitment, and drafting of the manuscript. EG did the clinical assessment and management, and followed up patients. RAH and AAg enrolled patients into the study and reviewed the main manuscript. BKW, HRH, and MK recruited and enrolled patients and reviewed the main manuscript. DF contributed to the study design, data collection, and editing of the manuscript. AAr, BB, JE, and IL contributed to the data collection and editing of the manuscript. The initial manuscript was prepared by the trial principal investigators, with subsequent input from all study authors.

Declaration of interests

AAg reports other funding from Penumbra. JTF reports grants and non-financial support from Stryker, grants and other funding from Penumbra; grants from Microvention; and equity in Cerebrotech, and The Stroke Project. IL reports other from Penumbra, Medtronic, Stryker, Microvention, InNeuroCo, andThree Rivers. JEDA reports other and non-financial support from Penumbra and non-financial support from Medtronic. DF reports grants, non-financial support, and other funding from Penumbra, Cerenovus, and Stryker; non-financial support and other funding from Genentech and Shape Memory Medical; and grants from Siemens. JM reports other from Penumbra, Cerebrotech, Rebound Therapeutics, TSP, Lazarus Effect, Medina, Pulsar Vascular, and Blockade. MIC reports other, grants, and non-financial support from Penumbra and Pulsar Vascular; grants and non-financial support from Medtronic, Microvention, and Codman; non-financial support and other

from Blockade and non-financial support from Siemens. RAH reports other from Penumbra, Endostream, Cerebrotech, Synchron, and InNeuroCo; non-financial support from Medtronic, Microvention, Stryker, and Cerenovus; and non-financial support and other from Elum and Three Rivers Medical. KVS reports other and non-financial support from Penumbra; non-financial support from Canon Medical Systems, Medtronic, and Jacobs Institute; and other from Neurovascular Diagnostics. RADeL reports other and non-financial support from Penumbra; and non-financial support from Cerenovus and Siemens. HRH reports other from Penumbra. AMS reports other and non-financial support from Penumbra, Pulsar Vascular, and Stryker and grants, other, and non-financial support from Microvention. BB reports grants and other from Penumbra; and other from Medtronic, Stryker, Viz, and 880 Medical. EG reports other from Penumbra. AS reports non-financial support and other from Amnis Therapeutics, Serenity Medical, Silk Road Medical, Rebound Therapeutics, Penumbra Medtronic, Three Rivers Medical, Microvention, Imperative Care, Cerenovus, Endostream Medical, StimMed, Claret Medical, and Cerebrotech Medical Systems; non-financial support from Boston Scientific, Canon Medical Systems, Corindus, Guidepoint Global, Integra, Rapid Medical, Stryker, VasSol, and WL Gore & Associates; and other from Apama Medical, Blink TBI, Buffalo Technology Partners, Cardinal Health, Cognition Medical, International Medical Distribution Partners, and Viseon Spine. AAr reports other from Penumbra, Johnson and Johnson, Balt, Leica, Medtronic, Siemens, Stryker, Bendit, Cerebrotech, Endostream, Magneto, Marblehead, Neurogami, Serenity, Synchron, Triad Medical, Vascular Simulations; and grants and other from Microvention, Penumbra, Scientia, and Cerenovus. DJF reports grants, non-financial support, and other from Penumbra; non-financial support and other from Cerenovous and Medtronic; grants and non-financial support from Siemens and Microvention; and stock in Vascular Simulations and Neurogami. ATR reports other from Penumbra; and non-financial support from Microvention and Stryker. JE reports other from Penumbra, Medtronic, Stryker, and Route 92 Medical. MK reports other from Penumbra, Medtronic, and Endostream. AST reports other, grants, and non-financial support from Penumbra and Pulsar Vascular; grants and non-financial support from Codman, Microvention, and Medtronic; non-financial support and other from Blockade; and non-financial support from Siemens. KMF reports other from Penumbra and Cerebrotech. EIL reports other from Penumbra, NextGen Biologics, Rapid Medical, Cognition Medical, Three Rivers Medical, Stryker, MedX, and Endostream Medical; non-financial support and other from Claret Medical, Imperative Care, Rebound Therapeutics, StimMed, and Medtronic; and non-financial support from GLG Consulting and Guidepoint Global. BKW reports other from Penumbra.

Data sharing

The study protocol, statistical plan, and de-indentified individual data that underlie the results in this article will be available for investigators whose proposed data use has been approved by a review committee within the next 24 months. Please email ashley.friend@mountsinai.org.

Acknowledgments

The trial was an investigator-initiated and managed effort that was sponsored by Penumbra and done in North America (USA and Canada). The trial operations were executed by the research team at Medical University of South Carolina (Charleston, SC, USA). The data were acquired, stored, monitored, and interpreted by the research team at Icahn School of Medicine at Mount Sinai. Data analysis verification and confirmation was done by Biostatistical Consulting (Lexington, MA, USA). Blinded imaging core lab efforts were done by the research teams at SUNY University at Buffalo (NY, USA) and Wake Forest University (Winston-Salem, NC, USA).

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