Evaluation of stroke thrombectomy including patients where IV thrombolysis is contraindicated or has failed: a randomised trial of two novel thrombectomy devices

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ABSTRACT

Background

Study was a PROBE design phase II randomised controlled trial in. We assessed trial feasibility and technical efficacy and safety of two novel thrombectomy devices –ERIC™ (a retriever device) and SOFIA™ (a distal access catheter) – used alone or in combination depending on operator preference.

Methods

Four UK neuroscience centres enrolled adults with proximal large artery occlusion (LAO) stroke on imaging where arterial puncture was achievable within 5.5h [8.5h for posterior circulation] of symptom onset; NIHSS ≥6 with limited ischaemic change on CT imaging. Randomisation was 2:1 into intervention arm (ERIC™ and/or SOFIA™). Patients and core lab were blinded to allocation. Primary outcome was independent core lab adjudication of reperfusion (modified TICI scale). Secondary outcomes were modified Rankin score (mRS) at 90 and 365 days (independence & shift analysis), 30-day mortality, symptomatic ICH (sICH), procedural complications, NIHSS change.

Results

Sixty-six patients were enrolled. TICI 2B/3 reperfusion was achieved in 72% in intervention compared with 90% in control arm on intention to treat (ITT) analysis (p=0.2) and 78% compared with 86% on per protocol analysis (p=0.7). Functional independence at 90 days was 40% (intervention) compared with 43% (control) on ITT analysis (p=1.0). sICH rates were low at 0% and 5% respectively (p=0.3). 30-day mortality was 9% intervention compared with 14% control (p=0.7).

Conclusion

Study indicated feasibility of a phase II RCT trial approach for assessing new thrombectomy devices. In a broad LAO stroke population ERIC™ and SOFIA™ were not statistically different from control devices. Larger trials are needed.

Keywords

Mechanical thrombectomy; Stent retriever; Distal aspiration catheter; ERIC™; SOFIA™

BACKGROUND

In large artery occlusive (LAO) stroke, successful recanalisation of the occluded artery can be achieved by intravenous thrombolysis (IVT) in from <10% (ICA) to 40% (M2 MCA) of patients; reflecting volume of thrombus to be degraded.[1] There are a substantial number of contraindications to IVT.[1,2] Clinical outcomes are most favourable with earlier reperfusion and diminish steeply with increasing onset-to-treatment time.[2] Intra-arterial clot extraction (commonly termed mechanical thrombectomy or MT) has become established as the standard of care in LAO stroke.[3] Any delays to recanalisation, including longer procedure duration, diminish the benefit of reperfusion therapy.[4]

Most recent thrombectomy RCTs predominantly or exclusively used stent-retrievers.[5-12] Many of the current devices were not purposely designed for thrombectomy being based on stents designed as an adjunct to endovascular coiling of intracranial aneurysms and found fortuitously to be useful in stroke. These devices may fail to access or be effective in arteries that are distal, tortuous (more common in elderly patients) or occluded by a long thrombus (more common in patients who fail to respond to IVT). The MicroVention ERIC™ retriever device was specifically designed for MT with features that they claim may facilitate the access of distal and tortuous vessels and the retrieval of long segment thrombi.[13,14] These features include longer length (than the original generation of stent-retrievers); multiple connecting but flexibly linked clot retriever cages.[13] There may be no need for ERIC to stay open for several minutes to engage the clot as with standard stent-retrievers and so there is the potential to save time with every pass.[14]

An alternative to stent-retrievers for performing MT is aspiration, whereby a large-bore distal aspiration catheter (DAC) is used to aspirate the thrombus directly. If aspiration alone is unsuccessful, then the DAC can be used to deploy a stent-retriever rapidly to assist removal of the thrombus. Again, many of the current DACs used for MT were initially designed for assisting aneurysm treatments. The MicroVention SOFIA™ DAC was designed with the aim to provide easier navigation very distally in tortuous vessels and around bifurcations by design adaptations made particularly to the distal segment of the DAC. It is available as 5F or 6F (SOFIA+) bores and in a range of lengths. Although a handful of small non-randomised studies support the efficacy and safety of ERIC™ and SOFIA™ in MT[15, 16] these novel devices have not been evaluated in any randomised trials to date. Both devices are CE marked.

In multiple RCTs, MT results in far higher recanalisation rates than IVT and achieves significantly better clinical outcomes overall, with no increased risk of symptomatic intracerebral haemorrhage (sICH) and a trend to lower mortality.[4-11] However, these trials have tended to specifically exclude or, if allowed, have included few very elderly patients (>80y) – for example, a median of 68y in the HERMES meta-analysis[3] versus 76y in the UK-based national stroke registry (containing data from >414,000 stroke patients).[17] Many trials excluded or substantially under-represented patients with contraindications to IVT[7,8,10,11] despite this population accounting for up to 50% of all acute stroke patients in routine practice.[18]

Many operators advocate a combination of aspiration DAC along with stent retriever in thrombectomy. That conceptual approach underpinned the concept of investigating in this RCT whether the novel ERIC™ retriever and SOFIA™ DAC thrombectomy devices can be utilised safely and technically successfully in a real-world heterogeneous population with acute LAO stroke and to

inform the design of a definitive phase III clinical trial. However, reflecting a range of operator preferences and practices and pragmatic considerations around study costs in UK units, the use of combination therapy (DAC+retriever) was encouraged but not mandated.

METHODS

Study design and participants

This study was a multicentre, prospective, phase II, single-blinded RCT (ISRCTN 15698516) running in four English neuroscience centres. Ethical approval was provided by a UK Multicentre Research Ethics Committee. Participating centres were required to have hyperacute stroke service and neurointerventionists undertaking regular cerebral endovascular interventional procedures including MT. Safety was overseen and assessed at regular intervals by an Independent Data Monitoring Committee. The trial was designed to indicate recanalisation rate and procedural safety. A 2:1 allocation ratio was used given that the control group was recruited primarily to provide an unbiased benchmark of MT technical efficacy and adverse events in participating centres. It was not powered to statistically prove differences between the experimental and control groups using formal hypothesis testing.

Eligible participants were male and non-pregnant female patients aged ≥18 years presenting with acute ischaemic stroke from LAO (confirmed by CTA or MRA) with a clinically significant neurological deficit as assessed by an NIHSS score ≥6. Patients were also required to have been independent prior to the stroke (estimated baseline mRS 0-2) and expected to be able to be followed-up at 12 months. As up to 10% of UK thrombectomy cases are for occlusions in the posterior circulation, it was felt appropriate to include these; nor was there any strong rationale to exclude them in a device comparison trial.

Additionally, patients were eligible for the study where CT demonstrated no extensive hypodensity (either <1/3 MCA territory or ASPECTS score ≥6) and where randomisation and commencement of thrombectomy (i.e. groin puncture) was possible within 90 minutes of diagnosis of LAO on vascular imaging and within 5.5 hours (anterior circulation) or 8.5 hours (posterior circulation) of stroke symptom onset. Detailed inclusion and exclusion criteria are provided in supplemental material ii. At the time STABILISE recruited (before DAWN/DEFUSE-3 reported), the 6h timeline for anterior circulation intervention was used because it accorded with UK national guidelines for thrombectomy indications in non-advanced brain imaging triage practice. Informed consent or assent for enrolment in the study was gained from eligible patients or next of kin. Participants eligible for IVT received treatment up to 4.5 hours after symptom onset regardless of trial allocation.

Randomisation and blinding

Trial participants were randomised to either novel thrombectomy device (intervention arm) or a standard thrombectomy device (control arm) in a 2:1 ratio and were blinded to their allocation. Randomisation was stratified on age (≤65 versus >65) and NIHSS (6-15 versus ≥16).

In the intervention arm, the initial attempt at thrombectomy was made with the SOFIA^{TM} and/or ERIC^{TM} devices (full range of sizes/lengths available) as per neurointerventionist preference, within the device instructions for use (IFU). If the device failed to achieve adequate recanalisation (TICI 2b

or better) within 3 passes, the interventionist could elect to use any other second generation or later CE-marked device(s) approved for thrombectomy. In the control arm, the initial attempt at thrombectomy was made with an existing CE-marked MT device as per local protocol. If adequate recanalisation was not achieved within three passes the interventionist could elect to use any other CE-marked devices, including the novel SOFIA^{TM} or ERIC^{TM} devices in the best interests of the patient. A crossover was defined where an allocated treatment arm device was not deployed first. Deployment of a 2nd device after less than 3 passes (other than in a deliberate combined type approach) was determined as a minor protocol deviation rather than a crossover.

Participants were assigned a unique identification number and randomisation was performed using a central internet-based randomisation system hosted by the Clinical Trials Unit.

Procedures

Thrombectomy procedures were all carried out by experienced consultant neurointerventionists. General anaesthesia (GA) or local anaesthesia (LA) and conscious sedation (CS) was used as per local operating procedure. MT procedures were commenced within 90 minutes of confirmation of LAO ischaemic stroke on imaging and within 5.5 hours (anterior circulation) or 8.5 hours (posterior circulation) of onset. Interventionists used adjunctive CE-marked devices/technology as was consistent with their normal standard of care. Further information regarding thrombectomy devices used are detailed in the Supplemental Table i. Baseline pre-procedure and post-procedure digital subtraction angiography (DSA) images were acquired.

Post-procedure, participants were assessed for NIHSS at 24h (22-36h), 72h (± 8h) and 7 days (± 2d). Brain imaging with MRI and MRA was performed at 24h (22-36h) hours post-procedure. Blinded mRS assessment by participants or their carers was performed at 90 (± 3) days and 365 (± 10) days via a standardised structured postal questionnaire, telephone interview or clinic visit (Rankin Focused Assessment (RFA) assessors were suitably qualified and blinded to participant allocation). Adverse events were assessed at each post-procedure follow-up point. Trial visits coincided with routine clinical follow-up to improve likelihood of compliance; non-attendance prompted follow-up by telephone.

Outcomes

The primary outcome was the proportion of participants in each arm achieving adequate recanalisation based on the STIR II modified Thrombolysis In Cerebral Infarction grade 2b or 3 (TICI) scale[19], as determined by an independent blinded core laboratory expert assessment of pre-procedure and post-procedure (final run) DSA images (Prof J Byrne, Nuffield Dept. of Surgical Sciences, University of Oxford).

Pre specified secondary outcomes assessed study feasibility, clinical outcome and procedural safety. Study feasibility was defined by the proportion of identified eligible patients that were randomised and enrolled in the study and the number lost to follow-up. Clinical outcomes were assessed by the mRS distribution at 90 days and 365 days (assessed both as an ordinal measure and dichotomised as favourable (0-2) and unfavourable (3-6)). Patient completed Rankin questionnaire or where unable their next of kin or main carer completed on their behalf. Procedural safety was determined by the following post-procedural measures: the presence of sICH (defined using SITS-MOST criteria[20]) on imaging at 24-hour post-procedure, neurological deterioration of ≥ 4 points on the NIHSS from

baseline at 24 hours post-procedure, any groin haematoma or any other extracranial haemorrhage requiring surgery, transfusion or prolonged hospital stay; any other clinical complications deemed procedural by the interventionist responsible, and deaths within 30 days attributable to a procedural event.

Statistical analysis

Sample size calculation was performed as follows. The primary outcome measure was recanalisation. and the number of patients was based on achieving a specified recanalisation rate in the novel (intervention) device group, with acceptable error levels, which would justify further research of the devices. As an indication, assuming a recanalisation rate of <75% to reject ERIC^{TM} or SOFIA^{TM} (p0) and a recanalisation rate of >90% to justify further investigation of ERIC^{TM} or SOFIA^{TM} (p1), recruiting a minimum of 67 patients to the intervention arm would allow α and β error levels of 2.5% and 10% respectively (Fleming-A'Hern single stage early phase trial methodology[21]). Assuming a worse than anticipated drop-out rate of 20% over 12-months increased the initial recruitment target to 80 patients.

Feasibility was reported descriptively as i) acceptability: defined as the total number of patients randomised as a proportion of those identified as eligible to participate; ii) feasibility of the procedure: defined as time to thrombectomy and duration of thrombectomy; iii) compliance to data collection procedures at 3 and 12 months.

Intention to treat (ITT) and per protocol (PP) analyses were performed for primary and secondary outcomes. The ITT analysis included all randomised eligible patients analysed according to the allocation group. The PP analysis excluded patients who did not receive the allocated device as their first treatment option. Fisher exact or t -test was applied to binary outcome measures.

Role of the funding source

The funders (Newcastle University Biomedical Research Centre and Microvention Terumo) 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.

RESULTS

Of 141 LAO patients screened March 2015–Jan 2018, 52 were ineligible. Sixty-seven of the 89 screen –eligible patients were enrolled (a 73% conversion rate). Sixty-nine patients were consented in four UK centres and 67 randomised (two patients randomised were subsequently identified to be ineligible); see Figure 1. One patient was identified during a monitoring visit not to have any assent or consent forms (missing) and was therefore withdrawn at sponsor request as a randomisation error, leaving 66 patients in the trial. The main reasons for ineligibility were occlusion site (11), excess time since onset (7), not independent pre stroke (6). Forty-five patients were allocated to the intervention arm (SOFIA^{TM} and/or ERIC^{TM} to be used first) and 21 to control arm (standard device to

be used first). Eight patients had recanalised by time of DSA and no thrombectomy device deployment was required (balanced between arms). In two intervention arm patients the procedure was abandoned as target artery access for thrombectomy could not be achieved. In total, 37/45 patients in the intervention arm and 14/21 in the control arm received the MT intervention as allocated. Clinical follow up at both 90 and 365 days was attained in 64/66 (97%).

Baseline demographics and patient characteristics are described in Table 1. Groups were generally well matched for a small phase II study except that atrial fibrillation was commoner in intervention arm. Procedural details and process timelines are also described in Table 1. There were no significant differences between the two groups in terms of type of anaesthesia (Chi^2 p=0.10), t-PA (Chi^2 p=0.75), time from onset to puncture (t-test p=0.80) and procedure time (t-test p=0.65). Supplementary table i records all the device deployments in each case.

Table 1: Baseline variables, process and procedural details

		Intervention- ERIC/SOFIA N = 45	Control- standard devices N= 21
Age	Median (IQR) <=65 >65	72 (58-78) 16 (36%) 29 (64%)	72 (63-81) 7 (33%) 14 (67%)
Gender	Female	18 (40%)	7 (33%)
Pre stroke mRS	0-1 2 3-5	39 (87%) 6 (13%) 0	21 (100%) 0 0
Side of large vessel occlusion	Left Right Both (e.g. POCS)	20 (44%) 24 (53%) 1 (2%)	12 (57%) 9 (43%) 0
Past medical history	Stroke Heart disease HBP DM	3 (7%) 14 (31%) 27 (60%) 6 (13%)	4 (19%) 4 (19%) 10 (48%) 3 (14%)

	AF Prior CEA/stent	18 (40%) 0	4 (19%) 1 (5%)
NIHSS	Median (IQR) 6-15 16 or more	18 (13-23) 19 (42%) 26 (58%)	19 (12-24) 7 (33%) 14 (67%)
Received IVT		36 (82%)	17 (81%)
Occlusion site* *occlusion may extend over multiple arterial segments	ICA (intracranial) M1 M2 BAO PCA P1 VA Other	15 (40%) 36 (80%) 12 (27%) 2 (4%) 1 (2%) 2 (4%) 0	9 (43%) 16 (76%) 6 (29%) 1 (5%) 0 0 1 (5%)
Anaesthesia	GA CS LA only NA**	8 (18%) 25 (57%) 11 (25%) 1	7 (33%) 6 (29%) 8 (38%) 0
Any IA tpA	Yes No NR NA*	3 (7%) 39 (93%) 2 1	1 (5%) 19 (95%) 1 0
Onset to Randomisation	Mean (SD) minutes	194.9 (69.5)	191.7 (77.9)
Onset to Puncture	Mean (SD) minutes NA*	217.0 (62.4) 1	221.5 (78.1) 0

Procedure time	Mean (SD) minutes	55.4 (24.8)	58.9 (36.8)
Devices used^	Device as allocated	37 (82%)	14 (67%)
	Multiple devices used	13 (29%)	2 (10%)
Device crossover		1 (to stent-retriever)	4 (all to SOFIA)
No MT required		5	3
Unable to access (target artery)		2	0

Heart disease is a composite of any one or more of: ischaemic heart disease/previous MI/stenting/CABG

^ see Supplemental material Table i for complete list of devices used

Primary trial outcome was technical efficacy of recanalisation achieved on the mTICI scale– see Table 2. In two patients DSA images could not be obtained from the enrolling centre and so those patients were classed as missing. Good to complete recanalisation (TICI 2B-3) was achieved in 31/43 in the intervention arm (72%; 95% CI 57-83) compared with 18/21 (86%; 95% CI 70-97) in the control arm. However, this difference was not significant, p=0.19. On a per protocol basis there were no substantial differences in TICI 2B-3, at 29/37 (78%; 95% CI 63-89) vs 12/14 (86%; 95% CI 60-96) for intervention and control arms respectively, p=0.71. The thrombectomy "as treated" analysis is provided in supplemental material.

Table 2: angiographic core lab assessed outcomes

ANGIOGRAPHIC Assessment Intention To Treat		Intervention- ERIC/SOFIA N = 45	Control- standard MT devices N= 21
mTICI <u>pre</u> thrombectomy	0-1	37 (86%)	17 (81%)
	2a	4 (9%)	0
	2b	2 (5%)	1 (5%)
	2c	0	1 (5%)[+]
	3	0	2 (10%)[+]
	NR*	2	0

mTICI post thrombectomy	0-1	5 (12%)	0 (0%)
	2a	7 (16%)	2 (10%)
	2b	9 (21%)	4 20%)
	2c	12 (28%)	9 (45%)
	3	10 (23%)	5 (25%)
	NR*	2	1

*Notes *indicates cases where Images were not supplied*

+ We were not able to confirm with individual operators why device was deployed in these cases. It is presumed they disagreed with core lab pre procedure TICI assignment of 2c/3

Three patients in the control arm, but none in the intervention arm, had good perfusion before treatment (as assessed by the core lab) yet a MT device was deployed (see table 2). In all three the mTICI grade was unchanged post procedure. Overall, regarding the primary endpoint, good reperfusion was achieved as expected at 77% compared with 71% in the HERMES meta-analysis[3] despite the current trial being less selective and much more of an "all-comers" trial than most of the trials included in HERMES.

The current trial was not designed to investigate comparative details of device performance such as time-to-capture clot and clot fragmentation, which are more appropriate for bench-top studies. There was a higher rate of second MT device usage in the intervention arm (13/45, 29%) than in the control arm (2/21, 10%) – see Table 1 and supplementary table i. However, device crossovers were appreciably higher in the control arm (4; 19%) compared with the intervention arm (1; 2%). There was a small procedural time saving of 4.5 minutes in the intervention over control arm but this was not significant (p = 0.65).

Clinical and safety outcomes are presented in Table 3. The absolute difference in mRS 0-2 between groups at 90 days on ITT analysis was very small and not statistically different at 3% (95% CI -20 to 28; p = 1.00). On PP analysis, difference was minimal at 1%. At 365 days there was a reversal of this small difference, now in favour of the intervention arm, but again not statistically significant– see Table 3. Pre-defined safety outcomes were: mortality at 30-days, symptomatic ICH and NIHSS increase of 4 or more points within 24h of MT procedure (Table 3). Mortality at both 30 and 90 days was in line with that expected; sICH rate was low (0-5%), as was substantial deterioration in NIHSS – three cases.

Table 3 Clinical and safety outcomes

ITT analysis		Intervention-ERIC/SOFIA N = 45	Control standard MT devices N= 21	
90 day mRS	0-1	11 (26%)	6 (29%)	
	2	6 (14%) 40%	3 (14%) 43%	Exact P=1.0
	3	9 (21%)	4 (19%)	

	4-5 6 Lost To Follow Up	12 (28%) 5 (12%) 2	3 (14%) 5 (24%) 0	
365 day mRS	0-1 2 3 4-5 6 LTF	11 (26%) 6 (14%) 40% 9 (21%) 10(23%) 7 (16%) 2	6 (29%) 1 (5%) 33% 5 (24%) 3 (14%) 6 (29%) 0	Exact p=0.8
PP analysis		N = 37	N = 14	
90 day mRS	0-1 2 3 4-5 6 LTF	10 (28%) 6 (17%) 44% 6 (17%) 9 (25%) 5 (14%) 1	3 (21%) 3 (21%) 43% 1 (7%) 2 (14%) 5 (36%) 0	Exact p=1.0
365 day mRS	0-1 2 3 4-5 6 LTF	10 (29%) 4 (11%) 40% 7 (20%) 7 (20%) 7 (20%) 2	3(21%) 1 (7%) 29% 2(14%) 2 (14%) 6 (43%) 0	Exact p=0.5
30 day mortality	Dead LTF	4 (9%) 1	3 (14%) 0	Exact p =0.7
NIHSS increase of 4+ ≤24h	No	42 (93%)	21 (100%)	Exact p=0.6
	Yes	3 (7%)	0	
Symptomatic ICH*	Yes	0 (0%)	1 (5%)	Exact p= 0.3
Procedural complication[$]	Yes • Vessel rupture/SAH • ENT • Puncture site related	4(9%) 2 0 2	3 (14%) 0 1 2	Exact p= 0.7
	No	41 (91%)	18 (86%)	

**Two patients in the intervention group did not have any post-op imaging (one case sedated and intubated, one case patient unable to lie flat due to respiratory problems)*

[$] This is any complication recorded and does not mean the complication resulted in clinical sequelae

NIHSS and Age subgroup analyses are reported in the supplemental material as they were used for stratification of groups on randomisation.

DISCUSSION

The current trial assessed novel thrombectomy devices using a robust pragmatic RCT design with blinded assessment of primary angiographic and clinical outcomes. Randomised assessment of new neurointerventional devices is usually lacking or delayed for many years whereas STABILISE began soon after the ERIC™ device was CE-marked. Given that 73% of screen eligible patients were randomised, complete follow-up was achieved in 97% and that mean stroke onset-to-thrombectomy time (3h 39 minutes) and thrombectomy procedure duration (56 minutes) were acceptable (and in line with the literature), the study has confirmed the feasibility of phase II randomised controlled device trials in the field of thrombectomy. These data would facilitate planning of a definitive phase III trial.

The heterogeneous population enrolled is widely clinically representative increasing generalisability. We included 22% (15/67) of older patients (> 80 years) and those with contraindications to IVT (20%). These groups have often been excluded or very under-represented in prior thrombectomy trials but comprise a significant proportion of the clinical population. As in most pragmatic surgical trials, the interventionist was not blinded to the type of device used but the core lab was. Patients were also blinded to allocation. The trial was not designed to compare experimental and control groups with formal hypothesis testing, which is best suited to a phase III trial.

We recruited fewer participants (67) than the trial target (80) due to initial slow uptake of the trial at the different sites and lower-than-predicted thrombectomy activity. Site set-up and initiation was slow mainly due to negotiations between individual hospital R&D departments and the device supplier and separate contracting of sites with both CTU & study sponsor. Over an average of 15 months of screening per centre, four large Neuroscience centres with a combined catchment population of ~12 million (or >20% of the English population) only collectively accepted 141 patients for MT, reflecting a number of factors. These include pathways for referral and transport that were poorly developed, disappointingly low &/or slow identification of LAO in primary stroke centres, MT services not formally commissioned for most of this period and, as a result, at the time of trial recruitment none of the participating units operated 24/7 thrombectomy services. Had all LAO cases in their catchment populations been identified and referred then ~2000 should have been screened over this period.[22]

Overall, good reperfusion was achieved as expected at 77% with no statistical difference between the arms on ITT, PP or an “As Treated” basis. In comparison, the previous HERMES trials MR CLEAN and REVASCAT achieved rates of 59% and 66% respectively; these trials had recruitment approaches close to that of the current trial (i.e. no CTP, MRI or CT collateral scoring selection and allowing recruitment of patients with either a contraindication to, or a failure to respond to, IVT).[5,9]

In this real world, heterogeneous patient population enrolment, the dichotomised 90-day functional independence (mRS 0-2) results were also similar to MR CLEAN & REVASCAT trials. Overall, functional independence rate (mRS 0-2) at 90 days was 40% (26/64) in the current trial versus 33% and 44% in the EVT arms of MR CLEAN & REVASCAT respectively. To place that in context, MR CLEAN and REVASCAT both had a slightly lower median NIHSS (17) and appreciably lower median age (66) on randomisation than the current trial (median NIHSS 18, median age 72), both factors that are

independent predictors of clinical outcome. Furthermore, the ICA occlusion rate exceeded 40% in the current trial compared with 26% in both MR CLEAN and REVASCAT. So occlusions were generally larger and more proximal in the current trial, another factor associated with both poorer recanalisation and worse clinical outcomes. So, for the population recruited, the current trial clinical and recanalisation outcomes compare very satisfactorily with the most appropriate (as regards patient population) prior comparator randomised trials.[5,9]

Process times were broadly comparable between the current trial groups and other similar MT trials. There was an imbalance in the type of anaesthesia with more GA in the control arm. It is uncertain whether GA is, or is not, associated with worse outcomes – the evidence being contradictory between three small single centre RCTs[23-25] and a large meta-analysis of other RCTs.[26]

Reassuringly there were no safety concerns identified with either of the novel devices. Event rates were broadly similar in both arms with no statistical differences and in line with, or indeed below, expected rates. [4,8] 30-day mortality is more likely to be procedure-related and this was low at 11% (7/66). For comparison it was 16% in recent COMPASS trial[27] and overall 90-day mortality was in line with most previous trials at 15% (10/66).[3] The overall sICH rate was lower (1.5%) than most trials (3%-4.4%)[3,10,11,27] but this may simply reflect the play of chance with small numbers.

The ERASER study was a prospective, multicenter, single-arm (virtual 2-arm) study that also evaluated the effectiveness of ERIC in combination with SOFIA in stroke patients with ICA or M1 MCA occlusions. The primary end point was the volume of saved tissue.[28] The patient population was more select than STABILISE (in ERSAER all were <4.5h, all received IVT and all had favourable CTP profile) but excellent clinical and TICI results were achieved. The requirement for a second thrombectomy device in ERASER was broadly in line with that in STABILISE (13% versus 19%). However, the novel ERASER design without an actual control group or the complexity of a RCT aided rapid centre initiation and recruitment. It may therefore be that this methodology is preferable in the early clinical evaluation of novel devices.

Conclusions

The current trial confirms the feasibility of a PROBE design phase II RCT trial approach to assessing novel devices and technical developments in stroke thrombectomy. The ERIC™ and SOFIA™ thrombectomy device arm had technical, safety and clinical outcomes in line with those expected in the broad LAO stroke population enrolled and these were not statistically different from the control device arm. Further larger studies are warranted.

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Ethics Approval

Written informed Patient Consent/Assent was obtained and multicentre ethics approval was obtained (North East England REC A Ref 14/NE/0113).

Data sharing

Fully anonymised data from this trial will be available to the scientific community subject to appropriate ethics approval and Trial Steering Committee agreement. Requests for anonymised data should be directed to the Chief Investigator. Trial protocol can be obtained via Newcastle University Clinical Trials Unit. Ultimately we intend to seek permission to archive data in the VISTA Thrombectomy repository.

Author contributions: PMW & GAF designed the trial, obtained funding, were co-chief Investigators. EAC & PMW obtained ethical approval. BG was trial statistician. EAC and PMW with RL coordinated follow-up; PMW, EAC, BG, GAF and AM drafted the manuscript. All authors revised it for important intellectual content. AD, JY, GS and RS were local Principal investigators, recruited patients and directed data accrual.

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REFERENCES

1. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010;41:2254–8.
2. Emberson J, Lees K, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *The Lancet* 2014;384:4–10.
3. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *The Lancet* 2016;387:1723–1731.
4. Saver JL, Goyal M, van der Lugt A, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *JAMA* 2016;317:1279-1288.
5. Berkhemer OA, Puck SS, Fransen PS, et al. A randomized trial of intra-arterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372: 11–20.
6. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009–1018.
7. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372: 1019–1030.
8. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs t-PA alone in stroke. *N Engl J Med* 2015;372: 2285–2295.
9. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372: 2296–2306.
10. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15: 1138–1147.
11. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2016;88:38–44.
12. Mocco J, Zaidat OO, von Kummer R, et al. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. *Stroke* 2016;47:2331-2338.
13. Raoult H, Redjem H, Bourcier R, et al. Mechanical thrombectomy with the ERIC retrieval device: initial experience. *J Neuroint Surg* 2017; 9:574-577
14. Steglich-Arnholm et al. 2017 Mechanical thrombectomy with the embolus retriever with interlinked cages in acute ischemic stroke: ERIC, the new boy in the class. Am J Neuroradiol 2017; 38: 1356–1361
15. Stampfl, S. *et al.* Initial experience with a new distal intermediate and aspiration catheter in the treatment of acute ischemic stroke: clinical safety and efficacy. *J Neurointerv Surg 2016;* 8:714–8
16. Kahles, T. *et al.* Mechanical Thrombectomy Using the New ERIC Retrieval Device Is Feasible, Efficient, and Safe in Acute Ischemic Stroke: A Swiss Stroke Center Experience. *Am J Neuroradiol* 2016;37:114–9
17. Sentinel Stroke National Audit programme Clinical Audit April 2013-March 2018 https://www.strokeaudit.org/Documents/National/Clinical/Apr2017Mar2018/Apr2017Mar2018-AnnualReport.aspx page 10; accessed 30/08/2019.
18. Frank B, Grotta JC, Alexandrov AV, et al. Thrombolysis in Stroke Despite Contraindications or Warnings? *Stroke* 2013;44:727-733.

19. Wintermark M, Albers GW, Broderick JP, et al. Acute Stroke Imaging Research Roadmap II. *Stroke* 2013; 44:2628-263
20. Wahlgren N, Ahmed N, Davalos A, *et al*. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82
21. Ahern RPA. Sample size tables for exact single-stage phase II designs. *Statistics in Medicine* 2001;20:859-866
22. McMeekin P, White PM, Martin J, et al. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. *Eur Stroke J* 2017; 2(4):319-326.
23. Schonenburger S, Uhlmann L, Hacke W, et al. Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. *J Am Med Assoc* 2016;316:1986-1996.
24. Simonsen CZ, Yoo AJ, Sorenson LH, et al. Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke A Randomized Clinical Trial. *JAMA Neurol* 2018;75:470-477
25. Lowhagen LP, Rentzos A, Karlsson JE, et al. General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke: The AnStroke Trial (Anesthesia During Stroke). *Stroke* 2017;48:1601-1607.
26. Campbell B, van Zwam W, Goyal M et al. Effect of General Anaesthesia on functional outcome among patients with anterior circulation ischaemic stroke undergoing Endovascular Thrombectomy versus standard care: a meta-analysis of individual patient Data from seven randomised controlled trials. *Lancet Neurology* 2018;17:47-53.
27. Turk A, Siddiqui A, Fifi JT, et al. 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 *Lancet* 2019;393:998-1008.
28. Fiehler J, Thomalla G, Bernhardt M et al. ERASER A Thrombectomy Study With Predictive Analytics End Point. *Stroke. 2019 May;50(5):1275-1278*

Figure 1: CONSORT Diagram