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Primary results from the CLEAR study of a novel stent retriever with drop zone technology

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ABSTRACT

Background Challenges to revascularization of large vessel occlusions (LVOs) persist. Current stent retrievers have limited effectiveness for removing organized thrombi. The NeVa device is a novel stent retriever designed to capture organized thrombi within the scaffold during retrieval.

Objective To evaluate the safety and effectiveness of revascularization of acute LVOs with the NeVa device.

Methods Prospective, international, multicenter, single-arm, Investigational Device Exemption study to evaluate the performance of the NeVa device in recanalizing LVOs including internal carotid artery, M1/M2 middle cerebral artery, and vertebrobasilar arteries, within 8 hours of onset. Primary endpoint was rate of expanded Treatment in Cerebral Ischemia (eTICI) score 2b–3 within 3 NeVa passes, tested for non-inferiority against a performance goal of 72% with a −10% margin. Additional endpoints included first pass success and 90-day modified Rankin Scale (mRS) score 0–2. Primary composite safety endpoint was 90-day mortality and/or 24-hour symptomatic intracranial hemorrhage (sICH).

Results From April 2021 to April 2022, 139 subjects were enrolled at 25 centers. Median National Institutes of Health Stroke Scale (NIHSS) score was 16 (IQR 12–20). In the primary analysis population (n=107), eTICI 2b–3 within 3 NeVa passes occurred in 90.7% (97/107; non-inferiority P<0.0001; post hoc superiority P<0.0001). First pass eTICI 2b–3 was observed in 73.8% (79/107), with first pass eTICI 2b67–3 in 69.2% (74/107) and eTICI 2c–3 in 48.6% (52/107). Median number of passes was 1 (IQR 1–2). Final eTICI 2b–3 rate was 99.1% (106/107); final eTICI 2b67–3 rate was 91.6% (98/107); final eTICI 2c–3 rate was 72.9% (78/107). Good outcome (90-day mRS score 0–2) was seen in 65.1% (69/106). Mortality was 9.4% (13/138) with sICH in 5.0% (7/139).

Conclusions The NeVa device is highly effective and safe for revascularization of LVO strokes and demonstrates superior first pass success compared with a predicate performance goal.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mechanical thrombectomy for large vessel occlusion (LVO) stroke is the standard of care; however, revascularization in the context of organized thrombi remains a challenge.

WHAT THIS STUDY ADDS

⇒ Our investigation demonstrates that the NeVa stent retriever is highly effective and safe in the treatment of LVO stroke. In particular, substantial reperfusion within three passes, first pass success, 90-day good clinical outcomes, and a composite of mortality and symptomatic intracranial hemorrhage at 24 hours with the NeVa are all equivalent or better than predicate devices.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The NeVa stent retriever offers a safe and effective alternative to available thrombectomy devices, and shows superior first pass success when compared with a predicate performance goal.

Trial registration number NCT04514562.

BACKGROUND

Despite the proven benefit of stent retrievers, challenges to rapid revascularization of large vessel occlusions (LVOs) in patients with acute ischemic stroke persist. First pass reperfusion is associated with the best clinical outcomes following thrombectomy.[1 2] Latest generation devices yield first pass substantial reperfusion (eTICI 2b–3) in only half of cases.[3 4] A likely reason is that current stent retrievers have limited effectiveness for removing organized, firm thrombi, which are typically fibrin-rich.[5]

The NeVa thrombectomy device (Vesalio LLC, Nashville, USA) is a novel stent retriever designed with openings in the basket cell structure ('drop zones') intended to capture organized thrombi within the central scaffold during retrieval.

The CLEAR study aimed to evaluate the safety and effectiveness of revascularization of acute LVOs with the NeVa device.

METHODS

Study design

The data supporting the findings of this study are available on reasonable request and with approval of the CLEAR investigators. The CLEAR study was a prospective, multicenter, open-label, single-arm, Food and Drug Administration (FDA)-regulated Investigational Device Exemption study to evaluate the safety, performance, and effectiveness of the NeVa device for recanalizing LVOs including the internal carotid artery, M1/M2 middle cerebral artery, and vertebrobasilar arteries, within 8 hours of stroke onset. The primary study hypothesis was to demonstrate the substantial equivalence of the NeVa stent retrievers to other commercially available devices. The performance goal was based on two recent premarket studies of the EmboTrap (ARISE II study) and Tigertriever (TIGER study) devices.[3 4]

The study leadership included a Clinical Events Committee (CEC) and an imaging core laboratory. The CEC consisted of three physicians who adjudicated key prespecified adverse events. Information on key adverse events including death during the trial, serious adverse events through 24 hours postintervention, or unexpected adverse device effects was sent to the CEC to determine procedure and device relatedness. The imaging core laboratory (Eppdata, Hamburg, Germany) provided independent assessment of digital subtraction angiography (DSA) imaging obtained during endovascular treatment to determine the presence and location of the LVO, degree of reperfusion after each recanalization attempt (as applicable after the first through the sixth attempt), and final reperfusion. De-identified images were sent electronically from the site to the core laboratory.

Population and participating centers

Informed consent was obtained from the patients or their legally authorized representatives. Eligible patients had to be aged 18 years or older and younger than 85 years with acute ischemic stroke due to an LVO of the internal carotid artery, middle cerebral artery M1 or proximal M2 segment, vertebral artery, basilar artery, anterior cerebral artery, or posterior cerebral artery demonstrated on DSA. Thrombectomy had to be initiated within 8 hours. Other key inclusion criteria included failed IV tissue plasminogen activator (tPA) therapy (initiated within 3 hours of last known well) or contraindication to IV tPA, baseline National Institutes of Health Stroke Scale (NIHSS) score 8–25, pre-stroke modified Rankin Scale (mRS) score 0–1, and imaging demonstrating a small–moderate baseline infarct volume, defined as non-contrast CT Alberta Stroke Program Early CT Score (ASPECTS) 6–10, or ischemic core volume ≤50 mL on CT perfusion or MRI diffusion imaging. In cases of failed IV tPA, there was no waiting period to establish treatment failure; patients with persistent deficits were taken immediately for endovascular treatment. Key exclusion criteria were acute intracranial hemorrhage, and stenosis or occlusion in a proximal vessel requiring treatment or preventing access to the thrombus. Full inclusion/exclusion criteria are provided in online supplemental table 1).

A total of 25 sites (16 sites in the USA and nine sites outside the USA) were initiated and enrolled 139 subjects (online supplemental table 2).

Procedures

The NeVa stent retrievers consist of a self-expanding nitinol scaffolding attached to a push wire that can be delivered through a microcatheter. The device scaffolding contains drop zone openings that are intended to capture organized thrombus within the scaffolding. Depending on the model, an expandable tip incorporates two or three drop zones. Multiple configurations of the NeVa stent retrievers were available during the study.

DSA with anteroposterior and lateral views was performed at the beginning of the intervention to document baseline occlusion location, after each thrombectomy pass, and at procedure end. Perfusion status was assessed using the expanded Treatment in Cerebral Ischemia (eTICI) score. The first three device passes, if applicable, were required to be performed with the NeVa stent retriever, after which non-NeVa device therapy was allowed. In cases where an eTICI score 2b–3 was obtained after the first or second NeVa pass, non-NeVa device therapy could be performed for the third pass for residual distal occlusions below the recommended size range for NeVa (<2 mm). The same Neva device could be used for up to three passes for a maximum of six passes per vessel in total. A smaller-sized NeVa device could be used for residual distal occlusions, where appropriate, during the first three attempts. Rescue therapy was defined as when the initial target vessel occlusion required treatment with an approved non-NeVa stent retriever or direct aspiration catheter.

Intravenous conscious sedation or general anesthesia was administered to ensure subject safety and comfort. Proximal balloon guide catheter aspiration or local aspiration through a distal access catheter or both for flow control during the thrombectomy was at the treating physician's discretion. Mechanical pump aspiration was not permitted until after the third NeVa pass.

Outcomes

Analysis populations

The intention-to-treat (ITT) population consisted of all subjects in whom a NeVa device was introduced into their vasculature, regardless of the ability to reach the target location. The safety population was the same as the ITT Population.

The modified ITT (mITT) population was a subset of the ITT population, in which subjects were treated with the M1S, 5.5, or the T-3S NeVa devices (the devices for which FDA clearance was sought; online supplemental table 3) for the primary occlusion, and who met eligibility criteria. Study eligibility deviations were reviewed and determined prior to database lock. As prespecified in the statistical analysis plan, the analysis of the primary and secondary effectiveness endpoints was performed on the mITT population while safety data were reported for the ITT population.

Primary effectiveness endpoint

The study primary endpoint was the rate of eTICI 2b-3 (substantial reperfusion) achieved within three NeVa passes for the primary LVO, as determined by the core laboratory.

Primary safety endpoint

In the initial protocol, the primary safety endpoint was 90-day stroke-related mortality. On regulatory request, this endpoint was amended to include 90-day all-cause mortality and/or

symptomatic ICH (sICH) at 24 hours postprocedure using the European Cooperative Acute Stroke Study (ECASS) III definition (any intracranial hemorrhage associated with ≥4 point increase in NIHSS score or death that is attributable to the hemorrhage).[6] This composite endpoint was used in the recent TIGER study, where the incidence of all-cause mortality at 90 days and/or sICH at 24 hours postprocedure in TIGER was 17.7% in their mITT analysis.[3]

Secondary endpoints

Secondary effectiveness endpoints included core laboratory-adjudicated rate of first pass successful reperfusion (eTICI 2b–3) and excellent reperfusion (eTICI 2c–3), core laboratory-adjudicated reperfusion rate to eTICI 2b–3 and to eTICI 2c–3 at procedure end (after all thrombectomy attempts), and the proportion of subjects treated with the NeVa devices with good clinical outcomes (90-day mRS score 0–2).

Secondary safety endpoints were the incidence of neurological deterioration (≥4 point increase in NIHSS score from baseline to day 5–10 postintervention or discharge, whichever was earlier), and the incidence of procedure- and device-related serious adverse events (SAEs) through 24 hours postintervention as adjudicated by the CEC and defined as vessel perforation or dissection, sICH, embolization to a new territory, access site complication requiring surgical repair or blood transfusion, intraprocedural mortality, in vivo device breakage, or any other complications adjudicated by the investigator and sponsor to be related to the procedure.

Statistical analysis

The primary statistical hypothesis was to demonstrate non-inferiority of the NeVa device against a performance goal based on comparator devices for achieving an eTICI score ≥2b following three or fewer passes using only the NeVa for the primary LVO, as determined by the core laboratory. This hypothesis was tested in the mITT population (prespecified effectiveness population). The performance goal of a 72% rate of success was updated during the course of the study and represented the average success rate observed in the two most recent FDA premarket clearance submissions (weighted by sample size),[3 4] and the non-inferiority margin was set at 10% to be consistent with the aforementioned predicate device submissions. The primary hypothesis was tested with a one-sided exact binomial test, comparing the observed primary study endpoint with the performance goal minus the non-inferiority margin (ie, 72%–10%, or 62%) using a significance level of 2.5%. If non-inferiority was demonstrated, a post hoc test of superiority would be performed, using an exact binomial test comparing the observed primary study endpoint with the performance goal of 72%. The primary study endpoint was also evaluated between subgroups according to occlusion site, NeVa device model, the use of flow control strategies (balloon guide catheter or intermediate catheter), use of IV tPA, use of antithrombotics (heparin or antiplatelet medication), sex, and geographic location (in the USA vs outside the USA) using a Fisher's exact test for equality of proportions.

The primary safety endpoint of 90-day all-cause mortality and/or 24-hour sICH in the ITT population (prespecified safety population) was compared against a performance goal of 17.7%. No formal statistical testing was conducted for the safety analyses. For the secondary effectiveness endpoints in the mITT population, the rates of first pass eTICI≥2b and eTICI≥2c were compared with performance goals from the TIGER study (57.8% and 41.4%, respectively).[3] Similarly, the rates of eTICI≥2b and eTICI≥2c after all passes were compared with the corresponding TIGER rates (95.7% and 71.8%, respectively). The 90-day mRS score 0–2 rate in the mITT population was compared against the 54.7% rate in TIGER. To control study-wise type I error as required by the FDA, hypothesis testing of the key secondary endpoints was conducted using a gatekeeping procedure, wherein the secondary effectiveness analyses would be performed only if the primary effectiveness endpoint comparison was statistically significant. The secondary analyses used two-sided exact binomial tests, each with an α of 0.05, and proceeded according to a prespecified closed fixed-sequence procedure, which is described below. This sequential procedure controls the overall type I error at the 5% level and does not require adjustment of the α level of each hypothesis test.

1. Non-inferiority of the NeVa stent retriever, then
2. Comparison of the rate of eTICI score ≥2b after the first pass of the NeVa device with the TIGER rate of 57.8%. If the comparison achieved statistical significance at the two-sided 0.05 level, then
3. Comparison of the rate of eTICI score ≥2b after all passes with the TIGER rate of 95.7%. If the comparison achieved statistical significance at the two-sided 0.05 level, then
4. Comparison of the rate of eTICI score 2c–3 after all passes with the TIGER rate of 71.8%. If the comparison achieved statistical significance at the two-sided 0.05 level, then
5. Comparison of the proportion of subjects treated with the NeVa devices with 90-day good clinical outcomes (mRS score ≤2) with the TIGER rate of 54.7%.

If at any step defined above, the comparison was not statistically significant at the two-sided 0.05 level, then the remaining comparisons in the stated hierarchy would be considered nominal, descriptive, and exploratory.

RESULTS

From April 1, 2021 to April 28, 2022, 139 subjects (ITT population) consented to take part in the study and were treated at 16 centers in the USA (n=79; 56.8%)) and 9 centers outside the US (n=60; 43.2%). (online supplemental figure 1) The mITT population consisted of 107 subjects, including 73 (68.2%) at 16 USA sites and 34 (31.8%) at 9 sites outside the USA. Reasons for excluding patients from the mITT population included major protocol deviations (ie, eligibility criteria not met) in 20 subjects and a non-mITT NeVa device used in 12 subjects (online supplemental table 4).

Baseline characteristics of the ITT and mITT populations are shown in table 1. In the ITT population, mean±SD age was 66.7±12.8 years; 65 (46.8%) were female. Median NIHSS score was 16 (IQR 12–20). Median ASPECTS was 9 (IQR 8–10). The mean ischemic core volume was 17.7±18.4 mL for MRI (n=30) and 18.0±26.4 mL for CT perfusion (n=49). IV tPA was administered in 71 (51.1%) subjects.

Occlusions were 14 (10.1%) internal carotid artery, 86 (61.9%) M1, 37 (26.6%) M2, 1 (0.7%) basilar, and 1 (0.7%) posterior cerebral artery in the ITT population. The median time from last known well to arterial puncture was 202 min (IQR 138–294 min). General anesthesia was used in 36.7% (51/139), and in most cases femoral access was used (95.7%; 133/139). Flow-control strategies included balloon guide catheter (BGC) alone in 14.4% of procedures, local aspiration alone in 64.0%, combined BGC and local aspiration in 15.1%, and none in 6.5%. Among the ITT population, three patients (2.2%) underwent extracranial lesion aspiration, and two patients (1.4%) each underwent angioplasty prior to or after intracranial intervention and stent placement (table 1; online supplemental table 5).

Table 1 Baseline and procedural characteristics of the intention-to-treat and modified intention-to-treat populations

Parameter	ITT/safety (n=139)	mITT (n=107)
Age, mean (SD)	66.7 (12.8)	65.1 (13.2)
Female sex, n (%)	65 (46.8%)	45 (42.1%)
Ethnicity, n (%)		
Hispanic or Latino	4 (2.9%)	3 (2.8%)
Not Hispanic or Latino	101 (72.7%)	84 (78.5%)
Not reported	34 (24.5%)	20 (18.7%)
Race, n (%)		
White	89 (64.0%)	72 (67.3%)
Black	25 (18.0%)	22 (20.6%)
Asian	1 (0.7%)	1 (0.9%)
Not reported	24 (17.3%)	12 (11.2%)
Pre-stroke mRS score, median (IQR)	0 (0–1)	0 (0–0)
Baseline NIHSS score, median (IQR)	16 (12–20)	16 (12–20)
Baseline CT ASPECTS		
Number of subjects	106	92
Median (IQR)	9 (8–10)	9 (8–10)
Baseline MRI ischemic core		
Number of subjects	30	12
mL, mean (SD)	17.7 (18.4)	14.4 (11.0)
mL, median (IQR)	13 (5.4–26.0)	14 (5.5–24.0)
Baseline CT perfusion ischemic core		
Number of subjects	49	42
mL, mean (SD)	18.0 (26.4)	17.5 (25.5)
mL, median (IQR)	7 (0–28.0)	8 (0–28.0)
Medical history, n (%)		
Hypertension	103 (74.1%)	79 (73.8%)
Diabetes	35 (25.2%)	29 (27.1%)
Atrial fibrillation	62/138 (44.9%)	43/106 (40.6%)
Dyslipidemia	58 (41.7%)	43 (40.2%)
Smoking	39 (28.1%)	27 (25.2%)
Previous MI/CAD	24 (17.3%)	19 (17.8%)
Previous stroke	24/138 (17.4%)	21/106 (19.8%)
Previous TIA	9 (6.5%)	6 (5.6%)
IV tPA administration, n (%)	71 (51.1%)	59 (55.1%)
Primary occlusive lesion location, n (%)		
Intracranial ICA	14 (10.1%)	10 (9.3%)
MCA-M1	86 (61.9%)	66 (61.7%)
MCA-M2	37 (26.6%)	30 (28.0%)
Basilar	1 (0.7%)	1 (0.9%)
PCA	1 (0.7%)	0 (0.0%)
Occlusion side (left)	71 (51.1%)	57 (53.3%)
Significant (>70%) extracranial stenosis proximal to primary lesion	2 (1.4%)	0 (0.0%)
Procedural characteristics		
Last known well to arterial puncture (min), median (IQR)	202 (138–294)	181 (131–252)
General anesthesia, n (%)	51 (36.7%)	43 (40.2%)
Flow control strategies		
BGC use only, n (%)	20 (14.4%)	14 (13.1%)
Intermediate catheter use only, n (%)	89 (64.0%)	69 (64.5%)
BGC+intermediate catheter use, n (%)	21 (15.1%)	17 (15.9%)

ASPECTS, Alberta Stroke Program Early CT Score; BGC, balloon guide catheter; CAD, coronary artery disease; ICA, internal carotid artery; ITT, intention-to-treat population; MCA, middle cerebral artery; MI, myocardial infarction; mITT, modified intention-to-treat population; mL, milliliters; mRS, modified Rankin Scale; NIHHS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

Primary effectiveness endpoint and reperfusion results

In the primary analysis mITT population, the NeVa device achieved eTICI 2b–3 within three NeVa passes and without rescue therapy in 90.7% (97/107; 95% CI 83.6% to 94.8%), which was significantly higher than the non-inferiority goal of 62% (non-inferiority P<0.0001) and the performance goal of 72% (post hoc superiority P<0.0001); see figure 1A. Subgroup analyses of the primary endpoint are shown in online supplemental table 6). The only significant difference was in sex, with 97.8% (44/45) women and 85.5% (53/62) men achieving eTICI 2b–3 within three NeVa passes without rescue (exploratory P=0.04).

The rate of eTICI 2c–3 within three NeVa passes and without rescue therapy was 68.2% (73/107). First pass eTICI 2b–3 was observed in 73.8% (79/107; 95% CI 64.8% to 81.2%), compared with the performance goal of 57.8% (P=0.0008). First pass eTICI 2c–3 rate was 48.6% (52/107; 95% CI 39.3% to 58.0%), versus the performance goal of 41.4% (exploratory P=0.13). Median number of passes was 1 (IQR 1–2).

In the mITT population, the proportion of subjects with an eTICI score ≥2b following all passes without rescue was 95.3% (102/107; 95% CI 89.5% to 98.0%), compared with the performance goal of 95.7% (exploratory P=0.85). The rate of eTICI sore ≥2b following all passes including rescue was 99.1% (106/107; 95% CI 94.9% to 99.8%). The frequency of eTICI score ≥2c following all passes without rescue was 71.0% (76/107; 95% CI 61.8% to 78.8%), which was also similar to the performance goal of 71.8% (exploratory P=0.86). eTICI score ≥2c after all passes including rescue was observed in 72.9% (78/107; 95% CI 63.8% to 80.4%).

Angiographic results in the ITT population were similar (table 2).

Primary safety endpoint

In the ITT/safety population, the rate of the primary composite safety endpoint of 90-day all-cause mortality and/or 24-hour sICH was 12.2% (17/139; 95% CI 7.8% to 18.7%), which was numerically less than the performance goal of 17.7%. A total of 13 patients (9.4%) had died by day 90, 7 patients (5.0%) experienced sICH within 24 hours of the procedure, and 17 patients (12.2%) experienced at least one of these events.

Secondary endpoints

One subject was lost to 90-day follow-up. In the mITT population; good outcome (90-day mRS score 0–2) was seen in 65.1% (69/106), compared with the performance goal of 54.7% (exploratory P=0.03); see figure 1B. Additional clinical effectiveness endpoints are shown in table 2.

Secondary and additional safety endpoints are shown in table 3. Neurological deterioration was observed in four patients

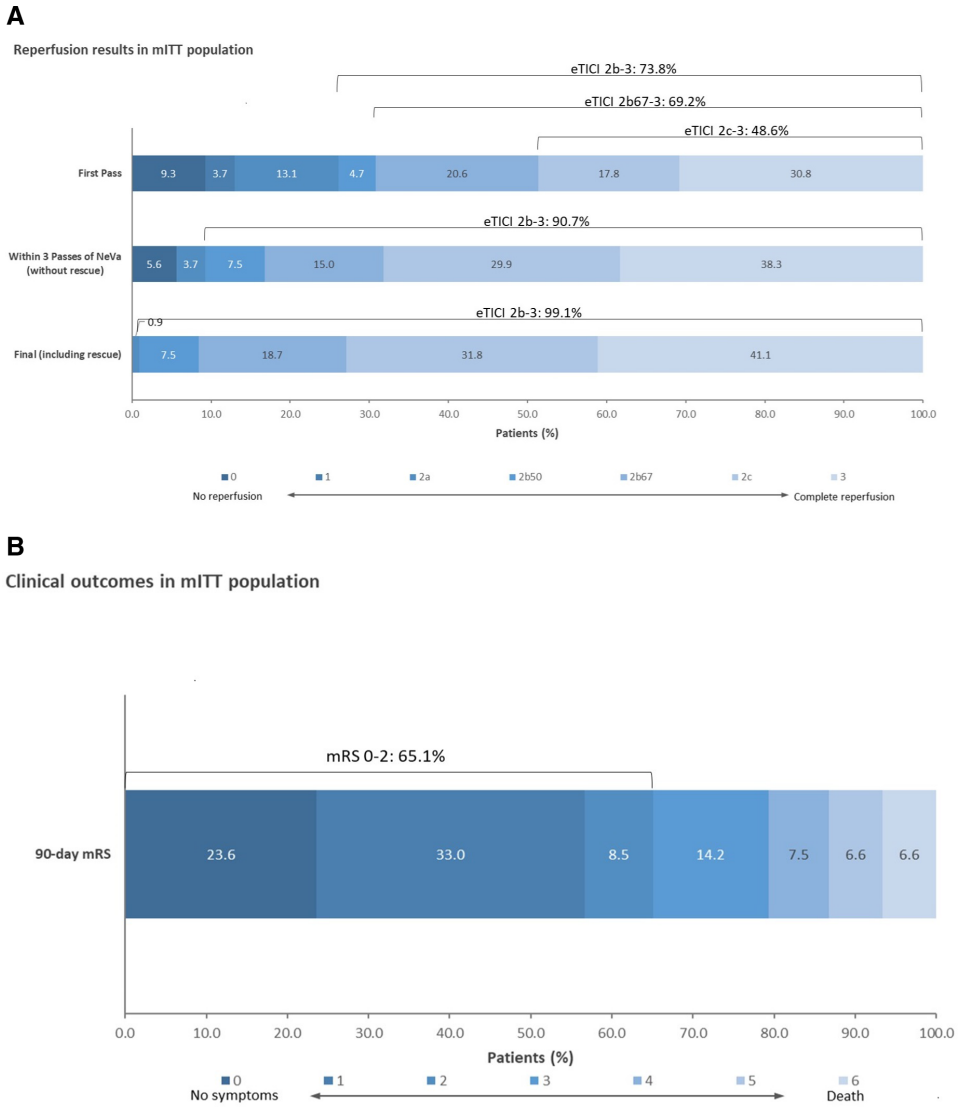

Figure 1 Reperfusion results and clinical outcomes in the modified intention-to-treat (mITT) population. (A) Distribution of expanded Treatment in Cerebral Ischemia (eTICI) scores after the first NeVa pass, after up to three NeVa passes (without rescue therapy), and after all treatments. (B) Distribution of 90-day functional outcomes on the modified Rankin Scale (mRS). mRS was available for 106 of the 107 subjects in the mITT group.

(2.9%; 95%CI 1.1% to 7.2%). Eight SAEs occurred in eight subjects (5.8%) deemed definitely or possibly procedure-related, and of these, six SAEs in six subjects (4.3%) deemed definitely or possibly NeVa device-related. The NeVa-related SAEs consisted of vasospasm (n=2), asymptomatic subarachnoid hemorrhage (n=1), symptomatic subarachnoid hemorrhage (n=2), and vessel perforation resulting in symptomatic intraparenchymal hemorrhage (n=1). No unexpected adverse device effects were reported. Additional information on CEC-adjudicated adverse events is provided in the online supplemental materials. Safety comparison between the ITT and mITT populations is shown in online supplemental table 10).

DISCUSSION

This prospective, multicenter study confirms that the NeVa stent retrievers are highly effective and safe for the revascularization of large vessel occlusions in acute ischemic stroke. The NeVa device alone achieved substantial reperfusion within three passes in 9 out of 10 patients, exceeding both the predefined non-inferiority threshold and the performance goal based on the regulatory trials of the predicate EmboTrap and TIGER devices. In addition, this trial confirms that the NeVa device is superior to the predicate device performance goal for first pass successful reperfusion (eTICI 2b–3) in prespecified hierarchical testing. The NeVa stent retrievers achieved first pass eTICI 2b–3 in more than 7 out of 10 patients. This rate was more than 15% higher than TIGER and more than 20% higher than ARISE II.[3 4]

The high rates of substantial and rapid reperfusion in the CLEAR study translated to 90-day functional independence in more than 6 out of 10 patients, which was superior to the performance goal in exploratory testing and compares favorably with other device registration studies. The CLEAR population was similar to these comparator studies in the important baseline characteristics of age, NIHSS score, premorbid mRS score, extent of baseline ischemic injury (ASPECTS), rate of IV tPA pretreatment, and occlusion level[3 4 7 8] (online supplemental table 11). Slightly more M2 occlusions and shorter time from last seen normal to arterial puncture in CLEAR might have further contributed to the favorable outcomes.

Virtually all CLEAR patients (99%) underwent substantial reperfusion by the end of the procedure. Notably, the vast majority (95%) of the primary occlusions were treated only with

Table 2 Core laboratory-adjudicated reperfusion endpoints and clinical outcomes in intention-to-treat and modified intention-to-treat populations

Parameter	mITT (n=107)*	ITT/safety (n=139)
Primary effectiveness endpoint		
Successful reperfusion (eTICI 2b–3) within three NeVa passes without rescue, n (%)	97 (90.7%)	125 (89.9%)
95% Wilson Score CI	(83.6%, 94.8%)	(83.8%, 93.9%)
Secondary angiographic endpoints		
Successful reperfusion (eTICI 2b–3) after first pass, n (%)	79 (73.8%)	95 (68.3%)
Excellent reperfusion (eTICI 2c–3) after first pass, n (%)	52 (48.6%)	65 (46.8%)
Successful reperfusion (eTICI 2b–3) after all passes without rescue, n (%)	102 (95.3%)	132 (95.0%)
Excellent reperfusion (eTICI 2c–3) after all passes without rescue, n (%)	76 (71.0%)	104 (74.8%)
eTICI outcomes within three passes without rescue		
eTICI 2c–3 within three passes without rescue, n (%)	73 (68.2%)	100 (71.9%)
eTICI 2b67–3 within three passes without rescue, n (%)	89 (83.2%)	117 (84.2%)
0: No flow	6 (5.6%)	8 (5.8%)
1: Penetration, but not distal branch filling	0 (0.0%)	0 (0.0%)
2a: Partial reperfusion with incomplete (< 50%) or slow distal branch filling	4 (3.7%)	6 (4.3%)
2b50: Reperfusion of 50–66% of the territory	8 (7.5%)	8 (5.8%)
2b67: Reperfusion of 67–89% of the territory	16 (15.0%)	17 (12.2%)
2c: Reperfusion of 90–99% of the territory	32 (29.9%)	43 (30.9%)
3: Complete or 100% reperfusion	41 (38.3%)	57 (41.0%)
Other angiographic outcomes		
eTICI 2b67–3 after first pass, n (%)	74 (69.2%)	89 (64.0%)
eTICI 3 after first pass, n (%)	33 (30.8%)	42 (30.2%)
Use of rescue therapy†, n (%)	4 (3.7%)	5 (3.6%)
Final eTICI 2b-3 including rescue, n (%)	106 (99.1%)	137 (98.6%)
Final eTICI 2b67–3 including rescue, n (%)	98 (91.6%)	126 (90.6%)
Final eTICI 2c–3 including rescue, n (%)	78 (72.9%)	106 (76.3%)
Final eTICI grade with rescue		
0: No flow	0 (0.0%)	0 (0.0%)
1: Penetration, but not distal branch filling	0 (0.0%)	0 (0.0%)
2a: Partial reperfusion with incomplete (< 50%) or slow distal branch filling	1 (0.9%)	2 (1.4%)
2b50: Reperfusion of 50–66% of the territory	8 (7.5%)	11 (7.9%)
2b67: Reperfusion of 67–89% of the territory	20 (18.7%)	20 (14.4%)
2c: Reperfusion of 90–99% of the territory	34 (31.8%)	45 (32.4%)
3: Complete or 100% reperfusion	44 (41.1%)	61 (43.9%)
Time from arterial puncture to first device pass (min), median (IQR)	18 (11–25)	18 (11–25)
Procedure duration (min), median (IQR)	32 (20–51)	35 (22–52)
Number of passes, median (IQR)	1 (1–2)	1 (1–2)
Secondary clinical endpoint		
90-day good outcome (mRS score 0–2), n (%)	69/106 (65.1%)	87/138 (63.0%)
95% Wilson Score CI	(55%, 74%)	(54%, 71%)
Other clinical outcomes		
NIHSS score at 24 hours, median (IQR)	4 (1–8)	4 (1–10)
NIHSS score change from baseline to 24 hours, median (IQR)	–10 (–15 to –5)	–9 (–15 to –5)
NIHSS score at earlier of 5–10 days or discharge, median (IQR)	2 (0–5)	2 (0–6)
NIHSS score change from baseline to 5–10 days or discharge, median (IQR)	–11 (–17 to –8)	–11 (–17 to –7)

*mITT was the primary effectiveness population.
†Rescue therapy is defined as when the initial target vessel occlusion required treatment with an approved non-NeVa stent retriever or direct aspiration catheter.
eTICI expanded Treatment in Cerebral Ischemia; ITT, intention-to-treat population; mITT, modified intention-to-treat population; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale.

Table 3 Safety endpoints in the intention-to-treat population

Parameter	Total (n=139)
Primary safety composite endpoint	
Percent of subjects deceased at day 90 and/or experiencing sICH at 24 hours postprocedure, n (%)	17 (12.2%)
95% CI	(7.8% to 18.7%)
Secondary and other safety endpoints	
Percent of subjects deceased at day 90	13/138* (9.4%)
	(95% CI 5.6% to 15.5%)
Percent of subjects experiencing sICH at 24 hours postprocedure	7 (5.0%)
	(95% CI: 2.5% to 10.0%)
Percent of subjects with ≥4 point increase in NIHSS score at 24 hours postprocedure	7 (5.0%)
	(95% CI 2.5% to 10.0%)
Percent of subjects with ≥4 point increase in NIHSS score at day 5–10/discharge	4 (2.9%)
	(95% CI 1.1% to 7.2%)
Procedure-related serious adverse events, n (%)	8 (5.8%)
NeVa device-related serious adverse events, n (%)	6 (4.3%)

*One subject lost to follow-up at day 90.
.NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

the NeVa device. The rate of rescue therapy was approximately 4%. The high rate of first pass successful reperfusion and the low use of rescue devices in CLEAR support the idea that NeVa is effective across the spectrum of thrombus types, including firm, highly organized thrombi, which are often recalcitrant to stent retriever thrombectomy. Traditional stent retrievers have difficulty sufficiently embedding within firm thrombi to allow for effective retrieval.[5] The NeVa device addresses this challenge by capturing organized thrombi en bloc through openings in the stent structure known as drop zones.

BGC use has been associated with higher rates of first pass and final revascularization, shorter procedure times, and better clinical outcomes.[9] Flow arrest may also reduce the chances of distal embolization and embolization to a new territory. BGC use was low in CLEAR (29.5%), which was similar to the TIGER study (29.9%) and much less than in ARISE II (73.6%). Despite the paucity of BGCs, NeVa resulted in superior revascularization rates, fast times to reperfusion (median procedure duration of 32 min, median of one pass), and no cases of emboli to new territory, which further supports the effectiveness of the drop zone technology for more complete, three-dimensional thrombus capture within the stent scaffolding.

There is growing adoption of eTICI 2c–3 as an effectiveness benchmark.[2] Using this more rigorous threshold, the first pass eTICI 2c–3 rate of 48.6% after one pass in CLEAR was numerically higher than both TIGER (41.4%) and ARISE II (40%). Recent work suggests that a more optimal reperfusion target may be eTICI 2b67–3. A re-adjudication of angiographic data from the HERMES (Highly Effective Reperfusion Evaluation in Multiple Endovascular Stroke trials) meta-analysis demonstrated significantly better outcomes after 2b67 (67–89%) reperfusion than after 2b50 (50–66%), and outcomes between 2c and 2b67 were nearly identical with a common OR for mRS score shift of 1.02 (95% CI 0.70 to 1.46; P=0.934).[10] Unlike previous device registration trials, CLEAR captured prospective core laboratory evaluation of eTICI 2b67. Using this updated benchmark, the NeVa device yielded impressive rates of eTICI 2b67–3: 69.2% after one pass, 83.2% after three passes (without rescue), and 91.6% at procedure end.

The safety outcomes of the NeVa device were in line with the predicate device studies. The 5% rate of symptomatic hemorrhage in CLEAR was slightly more than TIGER (1.7%) but similar to ARISE II (5.3%). The 9.4% 90-day mortality was also equivalent to ARISE II (9.0%) and less than TIGER (18.1%). These results support a favorable benefit–risk profile of the NeVa device for large vessel thrombectomy.

Limitations

The primary limitation of this study was the absence of an active comparator device with randomized allocation. The single-arm design of CLEAR used an objective performance goal derived from previous device studies. This design limits the precision of individual device comparisons. Additionally, the study design prevented clinical and imaging adjudication blinded to device type. To limit bias, clinical raters were certified in the endpoint evaluations and were blinded to the details and outcome of the thrombectomy procedure, and a core imaging laboratory was used for the angiographic and imaging endpoints.

CONCLUSIONS

In this prospective, multicenter trial of a novel stent retriever designed for three-dimensional thrombus capture, the NeVa device achieved substantial reperfusion within three passes in 9 out of 10 patients, confirming non-inferiority over the prespecified performance goal and demonstrating superiority over historical rates reported in recent regulatory trials of established devices. In addition, this trial confirmed that NeVa is superior to a predicate device performance goal for first pass successful reperfusion, which was achieved in more than 7 out of 10 patients in the study. Functional independence at 90 days was achieved in two-thirds of CLEAR patients.

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