Original research

Endovascular therapy in the distal neurovascular territory: results of a large prospective registry

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2020-016851).

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Received 14 September 2020
Revised 13 November 2020
Accepted 13 November 2020
Published Online First 15 December 2020

To cite: Nogueira RG, Mohammaden MH, Haussen DC, *et al*. *J NeuroIntervent Surg* 2021;**13**:979–984.

ABSTRACT

Background There is a paucity of data regarding mechanical thrombectomy (MT) in distal arterial occlusions (DAO). We aim to evaluate the safety and efficacy of MT in patients with DAO and compare their outcomes with proximal arterial occlusion (PAO) strokes.

Methods The Trevo Registry was a prospective open-label MT registry including 2008 patients from 76 sites across 12 countries. Patients were categorized into: PAO: intracranial ICA, and MCA–M1; and DAO: MCA–M2, MCA–M3, ACA, and PCA. Baseline and outcome variables were compared across the PAO vs DAO patients with pre-morbid mRS 0–2.

Results Among 407 DAOs including 350 (86.0%) M2, 25 (6.1%) M3, 10 (2.5%) ACA, and 22 (5.4%) PCA occlusions, there were 376 DAO with pre-morbid mRS 0–2 which were compared with 1268 PAO patients. The median baseline NIHSS score was lower in DAO (13 [8–18] vs 16 [12–20], P<0.001). There were no differences in terms of age, sex, IV-tPA use, co-morbidities, or time to treatment across DAO vs PAO. The rates of post-procedure reperfusion, symptomatic intracranial hemorrhage (sICH), and 90-mortality were comparable between both groups. DAO showed significantly higher rates of 90-day mRS 0–2 (68.3% vs 56.5%, P<0.001). After adjustment for potential confounders, the level of arterial occlusion was not associated with the chances of excellent outcome (DAO for 90-day mRS 0–1: OR; 1.18, 95% CI [0.90 to 1.54], P=0.225), successful reperfusion or SICH. However, DAO patients were more likely to be functionally independent (mRS 0–2: OR; 1.45, 95% CI [1,09 to 1.92], P=0.01) or dead (OR; 1.54, 95% CI [1.06 to 2.27], P=0.02) at 90 days.

Conclusion Endovascular therapy in DAO appears to result in a comparable safety and technical success profile as in PAO. The potential benefits of DAO thrombectomy should be investigated in future randomized trials.

INTRODUCTION

There is a paucity of data regarding mechanical thrombectomy (MT) in patients presenting with acute ischemic strokes (AIS) due to distal arterial occlusions (DAO). Even though over one-third of patients presenting within 24 hours of stroke symptoms have a DAO, very few DAO are currently treated with MT.[1 2] Thrombectomy in the distal vascular territory is theoretically associated with higher risks since more distal vessels have smaller calibers, thinner walls, and more tortuous courses which make them more prone to endovascular complications including perforation, dissection, and vasospasm. Moreover, as distal vessels inherently supply smaller volumes of the brain, their reperfusion is presumably associated with a lower range of benefit given the more restricted areas of tissue at risk. Therefore, DAO patients are not typically considered ideal candidates for endovascular reperfusion. Nonetheless, DAO thrombectomy may be a reasonable option, in particular, for patients with DAO involving areas of high eloquence and resulting in disabling deficits. Indeed, the current AHA Guidelines state that middle cerebral artery (MCA) M2, MCA–M3, anterior cerebral artery (ACA), and posterior cerebral artery (PCA) thrombectomy may be reasonable for carefully selected patients with AIS within 6 hours of symptom onset (level IIb).[3]

DAOs are highly underrepresented in randomized clinical trials (RCTs). For example, in the Interventional Management of Stroke III (IMS-III) trial, among subjects who underwent endovascular treatment only 8% had M3/M4 occlusions.[4] Similarly, in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, only three subjects had ACA and none had MCA–M3 occlusions.[5] Despite the growing evidence supporting the broader use of MT including the recent trials expanding its indications up to 24 hours from time last seen well and a meta-analysis suggesting the potential for a retained benefit even in the setting of large infarct sizes,[6–8] there is essentially no evidence to either support or refute endovascular treatment of DAOs.

Herein, we aim to evaluate the safety and efficacy of MT in a large prospective cohort of patients presenting with AIS in the setting of DAO and to compare their outcomes with those seen in proximal arterial occlusion (PAO) strokes.

METHODS

Trevo Retriever Registry

The Trevo Retriever Registry (ClinicalTrials.gov identifier: NCT02040259) was an international, multicenter, prospective, open-label, registry of patients who underwent MT with the Trevo stent-retriever (Stryker, Fremont, CA) as first-line therapy. The registry recruited a total of 2008 patients at 76 sites across 12 countries between November 11, 2013, and May 1, 2017. Pretreatment imaging and other entry criteria were based on local institutional protocols. The protocol was amended on March 26, 2015, to include an imaging core laboratory that was then used for central adjudication in 1599 of the 2008 (79.6%) patients of the site of vessel occlusion, pre- and posttreatment modified Thrombolysis in Cerebral Infarction (mTICI), and post-treatment imaging for hemorrhagic complications. The modified Rankin scale (mRS) assessment at 90 days was obtained in person or by telephone by a certified examiner at each site. All subjects in whom the Trevo retriever was deployed were computed in the intention-to-treat analysis. The study was funded by Stryker Neurovascular (Fremont, CA). A steering committee including academic investigators and representatives of the sponsor designed the study and led its execution. The registry was approved by the institutional review board at each site. Written informed consent was required from all enrolled patients or their designee. Additional details about the Trevo Retriever Registry methodology have been previously published elsewhere.[9]

Patient population and study analysis

The current analysis categorized Trevo Retriever Registry patients into PAO: intracranial internal carotid artery (ICA) and MCA–M1 and DAO: MCA–M2, MCA–M3, ACA, and PCA according to their primary site of occlusion (eg, patients initially presenting with PAO who subsequently had intra-procedural clot migration or embolization into the distal territory were still considered PAO). Patients' demographic data, cardiovascular risk factors such as hypertension, atrial fibrillation and diabetes mellitus, baseline National Institute of Health Stroke Scale (NIHSS) score, pre-morbid mRS, administration of intravenous tissue plasminogen activator (IV-tPA), time-from-last-seen-well (TLSW), and arterial puncture were analyzed. Descriptive analysis was provided for the overall DAO population. Baseline and outcome variables were compared across the PAO vs DAO patients with pre-morbid mRS 0–2.

Definitions for site of arterial occlusion

The MCA–M1 segment was defined as the proximal stem of the MCA including the lenticulostriate arteries and the anterior temporal artery branch. The MCA–M2 segment begins with first non-penetrator branching occurring distally to the origin of the anterior temporal artery. The anterior temporal artery is the branch of the M1 that can be identified by the confinement of its course to the anterior temporal lobe. If a branch artery exits the Sylvian fissure and supplies territory beyond the anterior temporal lobe (including the posterior temporal or inferior parietal areas), it was considered a MCA–M2 segment as opposed to an anterior temporal artery branch.[10] The MCA–M2 continues through the entire vertical course of branches up the Sylvian fissure. The MCA–M3 vessels start as the MCA branches exit from the Sylvian fissure and turn to run horizontally in the opercular regions.

Procedural characteristics

According to the inclusion criteria of the Trevo Retriever Registry, all included patients underwent MT with the Trevo stent-retriever as first-line therapy. Patients were treated either under general anesthesia or under conscious sedation according to the operator's preference.

Outcome and safety measures

Outcome variables included the rates of successful reperfusion defined as a grade 2b or more on the mTICI scale,[11] rapid neurological improvements (RNI) defined as a reduction of ≥10 on the NIHSS score or NIHSS score zero to 1, 24 hours after MT, favorable outcome (90-day mRS 0–1), and functional independence (90 day mRS 0–2). Safety measures included the rates of symptomatic intracranial hemorrhage (sICH) defined as per the ECASS 3 Trial definition (eg, any apparently extravascular blood in the brain or within the cranium associated with deterioration in NIHSS score of ≥4 points, or that led to death and that was identified as the predominant cause of the neurologic deterioration),[12] vessel perforation, emboli to a new territory, and 90-day mortality.

The first author wrote the first draft of the manuscript with the subsequent input of all co-authors. Stryker Neurovascular supplied the data and analytic support, but the company was not involved in the study design or in the preparation of the manuscript. This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

Statistical analysis

Continuous variables were reported as mean±SD or median (IQR) after normality testing with the Shapiro–Wilk test and were compared using the Mann–Whitney *U* test or *t*-test as appropriate. Categorical variables were reported as frequencies and percentages. Comparisons of categorical variables were made with Pearson X^2 or Fisher's exact tests as appropriate. Univariable analysis was performed to compare the baseline and outcome variables in patients with DAO vs those with PAO. Multivariable regression analyses were performed to evaluate the association of different variables with outcomes (90-day mRS 0–1, 90-day mRS 0–2, 90-day mortality, sICH within 48 hours post-procedure, and final mTICI2b–3) in both the overall population and patients with DAO only. Variables with $P<0.20$ in the univariate analysis and those previously described to be associated with each outcome, were entered into multiple logistic regression equations with backward variable selection. All models retained the binary covariate representing PAO vs DOA. The final models included any variable with $P\leq0.10$. Statistical analyses were performed with SAS software (version 9.4; SAS Institute Inc, Cary, NC).

RESULTS

Overall, there were 407 DAOs including 350 (86.0%) M2, 25 (6.1%) M3, 10 (2.5%) ACA, and 22 (5.4%) PCA occlusions vs 1392 PAOs including 294 (21.1%) intracranial ICA and 1098 (78.9%) M1 occlusions. Baseline characteristics, and procedural and clinical outcomes for the different subsets of the overall DAO population can be found in table 1.

A total of 376 DAO (M2: 324, 86.2%; M3: 23, 6.1%; ACA, 8, 2.1%; PCA, 21, 5.6%) and 1268 PAO (ICA: 332, 23.1%; M1: 1107, 76.9%) patients had pre-morbid mRS 0–2. Among these, DAOs had lower median baseline NIHSS score (13 [8–18] vs 16 [12–20], $P<0.001$) compared with PAO patients. There were no differences in terms of age (68.3 vs 67.9 years, $P=0.747$), sex (female, 51.1% vs 52.9%, $P=0.527$), IV-tPA use (53.1% vs 56.3%, $P=0.724$), major stroke-related risk factors, and pre-morbid mRS 0–1. Median TLSW to arterial puncture was comparable between DAO and PAO (4.2 vs 4.2 hours, $P=0.853$). There

Table 1 Baseline characteristics, procedural and clinical outcomes for the overall DAO population

	MCA–M2 (n=350)	MCA–M3 (n=25)	ACA (n=10)	PCA (n=22)
Baseline characteristics % (n)				
Age (years), mean±SD	69.1±13.5	66.7±13.9	65.9±12.8	66.2±14.3
Female	53.7 (188)	48 (12)	30 (3)	45.5 (10)
Hypertension	75.4 (264)	72 (18)	88.9 (8/9)	77.3 (17)
Atrial fibrillation	35.5 (124/349)	32 (8)	33.3 (3/9)	22.7 (5)
Diabetes mellitus	23.5 (82/349)	32 (8)	22.2 (2/9)	31.8 (7)
Previous ICAD	0.0 (0/349)	0.0 (0)	0.0 (0/9)	0.0 (0)
Baseline NIHSS score, median (IQR)	13(8–18)	11.5(7–15)	17.5(12–20)	14.0(8–16)
Pre-morbid mRS 0–1	86.7 (300/346)	95.8 (23/24)	80 (8)	90.5 (19/21)
IV-tPA use	52.9 (185)	48 (12)	66.7 (6/9)	50 (11)
TLSW to puncture (hours), median (IQR)	4.1 (2.8–6.4)	5.2 (2.9–7.8)	2.6 (2.2–5.0)	4.7 (3.5–10.7)
Time from puncture to device deployment (minutes), median (IQR)	24.0 (17.0–36.0)	27.0 (16.5–40.0)	26.0 (14.0–35.0)	32.0 (21.0–40.0)
Total procedural duration (minutes), mean±SD	54.3±30.8	63.9±27.4	49.3±30.3	61.4±33.2
Trevo 3×20 mm	41.7% (144/345)	80.0% (20/25)	60.0% (6/10)	31.8% (7/22)
Trevo 4×20 mm	43.2% (149/345)	16.0% (4/25)	40.0% (4/10)	31.8% (7/22)
Trevo 4×30 mm	11.0% (38/345)	4.0% (1/25)	0.0% (0/10)	31.8% (7/22)
Trevo 6×25 mm	4.1% (14/345)	0.0% (0/25)	0.0% (0/10)	4.6% (1/22)
Intermediate catheter	47.0% (164/349)	40.0% (10/25)	70.0% (7/10)	59.1% (13/22)
Intra-arterial lytics	52.9% (185/350)	48.0% (12/25)	66.7% (6/9)	50.0% (11/22)
Number of device passes, median (IQR)	1(1–2)	2(1–2)	1(1–2)	1(1–2)
General anesthesia	46.6% (163/350)	36.0% (9/25)	30 (3)	54.6 (12)
Procedural and clinical outcomes % (n)				
mTICI 2b–3 (Overall)	92.3% (323/350)	92.0% (23/25)	100% (10)	100% (22)
mTICI 2b–3 (IV tPA use)	93.0% (172/185)	83.3% (10/12)	100% (6/6)	100% (11/11)
mTICI 2b–3 (no IV tPA use)	91.5% (151/165)	100% (13/13)	100% (3/3)	100% (11/11)
mTICI 3 (overall)	53.7% (188)	60% (15/25)	80.0% (8)	63.6% (14)
mTICI 3 (IV tPA use)	52.4% (97/185)	41.7% (5/12)	66.7% (4/6)	63.6% (7/11)
mTICI 3 (No IV tPA use)	55.2% (91/165)	76.9% (10/13)	100.0% (3/3)	63.6% (7/11)
RNI	44.8% (151/337)	58.3 (14/24)	50 (5)	52.4 (11/21)
sICH (overall)	1.7% (6/350)	4% (1/25)	0.0% (0)	0.0% (0)
sICH (IV tPA use)	0.5% (1/185)	8.3% (1/12)	0.0% (0/6)	0.0% (0/11)
sICH (no IV tPA use)	3.0% (5/165)	0.0% (0/13)	0.0% (0/3)	0.0% (0/11)
Vessel perforation	0.4% (1/247)	5% (1/20)	0.0% (0)	0.0% (0)
Emboli to new territory	2% (7/350)	8.0% (2/25)	0.0% (0)	0.0% (0)
90-day mRS 0–2	64.9% (226/348)	72.0% (18/25)	50.0% (5)	59.1% (13)
90- day mRS 0–2 (overall)*	68.7% (222/323)	73.9% (17/23)	62.5% (5)	57.1% (12/21)
90-day mRS 0–2 (IV tPA use)*	63.4% (116/183)	75.0% (9/12)	50.0% (3/6)	54.6% (6/11)
90-day mRS 0–2 (no IV tPA use)*	66.7% (110/165)	69.2% (9/13)	33.3% (1/3)	63.6% (7/11)
90-day mortality	14.3% (50)	16.0% (4)	20.0% (2)	9.1% (2)
90-day mortality (IV tPA use)	12.4% (23/185)	16.7% (2/12)	16.7% (1/6)	18.2% (2/11)
90-day mortality (No IV tPA use)	16.4% (27/165)	15.4% (2/13)	33.3% (1/3)	0.0% (0/11)

*Subsetted to only pre-stroke mRS 0–2.
ACA, anterior cerebral artery; IV-tPA, intravenous tissue plasminogen activator; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; RNI, rapid neurological improvement; SAE, serious adverse event; sICH, symptomatic intracerebral hemorrhage; TLSW, time last seen well.

was a significantly higher use of general anesthesia in patients with DAO (46% vs 39.1%, P=0.017) and lower median number of device passes (1 [1–2] vs 1 [1–3], P=0.002) as compared with those with PAO (table 2).

The rates of successful reperfusion (mTICI2b–3) and full reperfusion (mTICI3) were comparable between DAO and PAO (92.6% vs 92.7%, P=0.90% and 55.1% vs 56.2%, P=0.706, respectively).

Table 2 Baseline characteristics, procedural and clinical outcomes in DAO vs PAO with pre-morbid mRS 0–2

	DAO (n=376)*	PAO (n=1268)*	P-value	Non-M2 DAO (n=52)*	PAO (n=1268)*	P-value
Baseline characteristics % (n)						
Age (years), mean±SD	68.3±13.5	67.9±14.9	0.747	66.4±13.4	67.9±14.9	0.428
Female	51.1 (192)	52.9 (671)	0.527	42.3 (22)	52.9 (671)	0.133
Hypertension	75.5 (283/375)	72.5 (917/1265)	0.253	78.4 (40)	72.5 (917/1265)	0.350
Atrial fibrillation	34.5 (129/374)	37 (468/1264)	0.371	27.5 (14)	37 (468/1264)	0.164
Diabetes mellitus	21.9 (82/375)	21.8 (276/1266)	0.978	27.5 (14)	21.8 (276/1266)	0.340
Previous ICAD	0.0 (0/375)	0.6 (8/1265)	0.211	0 (0)	0.6 (8/1265)	0.728
Baseline NIHSS score, median (IQR)	13 (8–18)	16 (12–20)	**<0.001**	13.5 (8–16)	16 (12–20)	0.0003
Pre-morbid mRS 0–1	93.1 (350)	91.4 (1159)	0.297	96.2 (50)	91.4 (1159)	0.310
IV-tPA use	53.1 (199/375)	56.3 (705/1252)	0.268	54.9 (28)	56.3 (705/1252)	0.843
TLSW to puncture (hours), median (IQR)	4.2 (2.8–6.7)	4.2 (3.0–6.6)	0.853	4.3 (2.8–8.4)	4.2 (3.0–6.6)	0.811
General anesthesia	46.0 (173)	39.1 (496)	**0.017**	44.2 (23)	39.1 (496)	0.459
Number of device passes median (IQR)	1 (1–2)	1 (1–3)	**0.002**	1 (1–2)	1 (1–3)	0.476
Procedural and clinical outcomes % (n)						
mTICI 2b–3	92.6 (348)	92.7 (1176)	0.900	96.2 (50/52)	92.7 (1176)	0.349
mTICI 3	55.1 (207)	56.2 (712)	0.706	63.5 (33)	56.2 (712)	0.297
RNI	47.1 (172/365)	47.4 (575/1212)	0.915	54.9 (28/51)	47.4 (575/1212)	0.296
sICH	1.3 (5)	1.6 (20)	0.731	1.9 (1/52)	1.6 (20)	0.573
Vessel perforation	0.4 (1/276)	0.8 (8/997)	0.693	0.0 (0)	0.8 (8/997)	0.691
Emboli to new territory	2.1 (8)	2.2 (28/1261)	0.914	3.9 (2/52)	2.2 (28/1261)	0.335
90 -day mRS 0–2	68.3 (256/375)	56.5 (713/1262)	**<0.001**	65.4 (34/52)	56.5 (713/1262)	0.205
90-day mortality	48 (12.8)	11 (139)	0.333	13.5 (7/52)	11 (139)	0.573

*Subsetted to only pre-stroke mRS 0–2.
ACA, anterior cerebral artery; IV-tPA, intravenous tissue plasminogen activator; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; RNI, rapid neurological improvement; SAE, serious adverse event; sICH, symptomatic intracerebral hemorrhage; TLSW, time last seen well.

Likewise, the rates of SICH, vessel perforation, and RNI were similar across both groups. The group with DAO showed a significantly higher rate of 90-day mRS 0–2 (68.3% vs 56.5%, P<0.001) and similar rates of 90-day mortality (12.8% vs 11%, P=0.333) when compared with those with PAO (table 2).

Tables 3–5 and online supplemental tables I and II depict the multivariable analysis for the predictors of mRS 0–1, mRS 0–2, and mortality at 90 days as well as successful reperfusion (mTICI2b–3) and sICH within 48 hours post-procedure, respectively. The level of arterial occlusion was not associated with the chances of excellent outcome at 90 days (DAO OR for mRS 0–1: 1.18, 95% CI [0.90 to 1.54], P=0.225), successful reperfusion (DAO OR for mTICI2b–3: 0.95, 95% CI [0.56 to 1.61], P=0.865) or sICH within 48 hours (DAO OR: 0.89, 95% CI [0.33 to 2.44], P=0.826). However, DAO patients were more likely to be functionally independent (mRS 0–2: OR, 1.45, 95% CI [1.09 to 1.92], P=0.01) or dead (OR, 1.45, 95% CI [1.06 to 2.27], P=0.02) at 90 days.

Online supplemental tables depict the multivariable analysis for the predictors of mRS 0–1, mRS 0–2, and mortality at 90

Table 3 Multivariable regression analysis for excellent outcome (90-day mRS 0–1) in the overall population

	OR	95% CI	P-value
DAO	1.18	0.90 to 1.54	0.225
Age	0.98	0.97 to 0.99	<0.0001
Baseline NIHSS score	0.90	0.88 to 0.92	<0.0001
Diabetes mellitus	0.54	0.41 to 0.72	<0.0001
Pre-morbid mRS 0–1	7.72	3.92 to 15.20	<0.0001
Post-procedure TICI 2b–3	3.10	1.90 to 5.06	<0.0001
TLSW to groin puncture	0.97	0.95 to 0.98	0.0001
Number of device passes	0.80	0.74 to 0.88	<0.0001

Table 4 Multivariable regression analysis for functional independence (90-day mRS 0–2)

	OR	95% CI	P-value
DAO	1.45	1.09 to 1.92	0.01
Age	0.97	0.96 to 0.98	<0.001
Baseline NIHSS score	0.92	0.90 to 0.94	<0.001
Hypertension	0.70	0.52 to 0.93	0.015
Diabetes mellitus	0.54	0.41 to 0.71	<0.001
General anesthesia	0.77	0.61 to 0.97	0.026
Pre-morbid mRS 0–1	4.27	2.69 to 6.77	<0.001
Post-procedure TICI 2b–3	2.94	1.89 to 4.58	<0.001
Previous ICAD	0.15	0.02 to 1.33	0.089
TLSW to groin puncture	0.98	0.97 to 1.00	0.016
Number of device passes	0.83	0.76 to 0.90	<0.001

Table 5 Multivariable regression analysis for 90-day mortality in the overall population

	OR	95% CI	P-value
DAO	1.54	1.06 to 2.27	0.023
Age	1.05	1.03 to 1.06	<0.001
Baseline NIHSS score	1.06	1.03 to 1.09	<0.001
Diabetes	1.41	0.98 to 2.03	0.062
Pre-morbid mRS 0–1	0.31	0.20 to 0.48	<0.001
Post-procedure TICI 2b–3	0.54	0.32 to 0.91	0.021

The Supplemental tables.

days as well as successful reperfusion (mTICI2b–3) and sICH within 48 hours post-procedure in the overall DAO, and in the combined MCA-M3, ACA, and PCA patients only (note that the results in this latter category are merely exploratory given its small sample size). In the DAO population, age and pre-stroke mRS 0–1 were independently associated with both mRS 0–2 and death at 90 days, whereas the baseline NIHSS score was significantly associated with 90-day functional independence and showed a strong trend toward an association with mortality. Interestingly, there was a trend toward better reperfusion (mTICI2b–3) in DAO treated under general anesthesia (OR: 2.95, 95% CI [0.95 to 9.09], P=0.061).

DISCUSSION

The Trevo Retriever Registry remains one of the largest thrombectomy registries to date. As there were no restrictions on inclusion other than the requirement of informed consent and Trevo for first-device use, it provides an unique opportunity to explore various treatment paradigms and trends, including those not properly evaluated in the recent randomized trials. The present analyses demonstrated that MT in the distal arterial territory was technically feasible and safe. Similar rates of successful reperfusion, vessel perforation, and sICH were found when compared with MT in PAOs. Despite the relatively higher rates of 90-day functional independence, our study demonstrated that DAO are not necessarily a "benign" condition. This was illustrated by the similar 90-day mortality across the two levels of arterial occlusion and poor outcomes (mRS >2) in almost one-third of the DAO patients. Moreover, the degrees of 90-day excellent outcome (mRS 0–1) were comparable across DAO and PAO after adjustment for clinical severity (eg, baseline NIHSS). Notably, DAO was associated with 90-day mortality on multivariable analysis. This is presumably related to a selection bias in the treatment decision-making process as, in general, DAO patients will have lower NIHSS scores and will only be treated if that particular NIHSS score correlates with a high degree of disability. In contrast, PAO patients are typically treated if their baseline NIHSS is equal or greater than 6 even in the presence of milder disability. As such, adjusting for baseline NIHSS may have created a bias toward greater clinical severity in the DAO group. Overall, our findings suggest that the degree of clinical severity and projected long-term disability rather than the site/level of arterial occlusion alone should guide the decision-making process regarding endovascular reperfusion. Thus, it becomes critical to formally evaluate the benefit of DAO thrombectomy in patients presenting with severe disability in future randomized trials.

While there is typically a good correlation between the level of arterial occlusion, the NIHSS score on presentation and the expected degree of long-term disability, this is not always the case, as significant imbalances can exist due to differences in the degree of collateral flow and eloquence across distinct vascular territories. PAOs with low NIHSS (eg, NIHSS 0–5) represent a common clinical dilemma and one of the remaining areas of uncertainty around the risks and benefits of endovascular treatment.[1 13 14] At the other end of the spectrum, DAOs may present with high clinical severity and projected disability. For example, a patient with a distal ACA stroke with isolated dense lower extremity monoplegia may present with a baseline NIHSS as low as 4 but left untreated will likely progress with a mRS of 4 and remain severely disabled in the long term. Similarly, disabling syndromes may occur in the setting of distal MCA occlusions causing severe aphasia or hemiplegia. Furthermore, PCA occlusion could present with low NIHSS but with potentially life-altering consequences due to visual impairment or alexia.[15] The practical truth is that patients do not really care about either their site of occlusion or baseline NIHSS score but rather about the degree of disability they will have to face for the rest of their lives.

Despite the public health impact of DAO, there is little consensus in terms of the treatment indications and even on the definitions of DAO. Historically, the classification of the MCA and its branches has been based on microsurgical anatomy.[16] As such, the original definitions were not designed to optimally correlate with the degree of clinical severity and eventual infarct size of the occluded vessels. This led to the subsequent development of more pragmatic classifications based on branching patterns.[10 17 18] However, the definitions for the different levels of arterial occlusion continue to be problematic. For instance, the lack of standardized definitions for the MCA–M2 segment has not only contributed to its exclusion from many RCTs but had also resulted in misclassifications and erroneous patient inclusions that have led to selection bias as seen in the SWIFT PRIME and REVASCAT trials where M2 occlusions represented about 10% of the trial population (19 and 18 patients, respectively) despite an exclusion criterion for M2 occlusions.[19 20] This reinforces the concept that M2 occlusions represent a highly heterogenous group ranging from small branches with relatively low eloquence to "M1-like M2 occlusions". Not surprisingly, there is high variability in the existing data. A previous observational study demonstrated that, in the absence of reperfusion treatment, the overall natural history of M2 occlusions is poor, with only half of the patients achieving good outcomes. In alignment with our findings, this study also highlighted that, after the adjustment for age, baseline NIHSS score, and degree of collateral flow, the level of arterial occlusion across ICA vs MCA–M1 vs MCA–M2 had no impact on long-term functional outcomes.[21] A patient-level data meta-analysis of seven RCTs from the HERMES collaboration including 130 MCA–M2 occlusions showed a significant benefit to endovascular treatment over medical management in terms of 90-day mRS 0–2 (adjusted OR 2.39, 95% CI 1.08 to 5.28).[22] Notably, while the HERMES M2 analysis highlighted that the treatment benefit varied according to both the dominance pattern (dominant M2, n=73; adjusted OR 4.08, 95% CI 1.08 to 15.48) and proximal vs distal level of occlusion (proximal M2, n=116; adjusted OR 2.68, 95% CI 1.13 to 6.37), a subgroup analysis of the MR CLEAN Registry demonstrated that the effect of reperfusion status on functional outcome was comparable between M1 (n=759) and both dominance patterns of M2 occlusions (n=175) (common OR, 1.27; 95% CI [1.06 to 1.53] for dominant M2; cOR, 1.32 [0.93–1.87] for nondominant M2; and cOR, 1.35; [1.24–1.46] for M1 occlusions).[23] Recently, there have been new attempts to standardize the definitions for the level of arterial occlusion. Goyal

et al adopted the definition of medium-vessel occlusions for occlusions that meet specific criteria related to vessel anatomy (involvement of MCA–M2/M3, ACA–A2/A3, and PCA–P2/P3), size (1–3 mm vessel diameter), and associated clinical deficit (NIHSS ≥5 and/or disabling deficit).[24] Similarly, Saver et al have defined the level of occlusion on the basis of both vessel size and vessel distance/tortuosity with "medium vessels" operationally defined as cerebral arteries with lumen diameters between 0.75 and 2.0 mm, and distal vessels defined as those beyond the M1 segment of the MCA or the basilar artery.[25]

Although our findings are consistent with previous studies demonstrating the feasibility and safety of MT in DAO,[26 27] it is important to again acknowledge that DAO MT is at least theoretically associated with higher risks, given the previously discussed anatomic peculiarities of the distal arteries. However, small distal vessels are safely navigated for the treatment of various cerebrovascular diseases in which the treatment benefit is presumably lower than that of AIS involving similar territory. For instance, flow diverters have been increasingly used to treat unruptured aneurysms in the distal arteries.[28 29] Moreover, despite the fact that intravenous thrombolysis (IVT) is more effective in DAO than PAO, not all patients with DAO are eligible for IVT either due to its many contraindications or delayed presentation times. Notably, IVT trials in the extended window have either failed to demonstrated benefit (DIAS1-4, DEDAS, EPITHET)[30 31] or had an underrepresentation of the DAO population (only ~30% of subjects in EXTEND-IV).[32] These findings reinforce the need to further explore endovascular means for distal artery reperfusion. Finally, another interesting finding of our study was the association between the number of device passes with sICH (OR, 1.24, 95% CI [1.00 to 1.53], P=0.047). This is consistent with a report from the ASTER trial demonstrating that more than three stent-retriever passes was an independent predictor of parenchymal hematoma (adjusted OR, 9.24; 95% CI, 2.65 to 32.13).[33]

Our study possesses all the limitations inherent to any analysis that is retrospective in nature. As approximately 86% of all DAO patients in our analysis had M2 occlusions, caution should be taken to not simply generalize all of our findings to the M3, ACA, and PCA territories. Moreover, the inclusion of all types of M2s may have further diluted the significance of our findings as dominant M2 vessels may more closely approximate to PAO/MCA-M1 occlusions rather than DAOs. Since the ASPECTS system does not compute lesions in the ACA or PCA territories, we were not able to properly quantify or make adjustments for baseline infarct burden. The lack of a control medical treatment arm does not allow for the exploration of treatment benefit. Other limitations of the Trevo Retriever Registry, including the potential for selection bias, have been previously detailed elsewhere.[9] The main strength of the present study is the inclusion of a robust number of primary DAOs with the demonstration of a good safety profile, while also highlighting that stroke prognosis is dictated by the clinical severity on presentation rather than the level of occlusion in isolation.

CONCLUSIONS

Endovascular therapy may be safely performed in the distal cerebrovascular bed with no clear evidence of any additional safety concerns (including vessel perforation or sICH) as compared with PAO thrombectomy, while yielding similarly high rates of reperfusion (mTICI 2b–3:~93%). DAO can result in significant morbidity and mortality with a similar adjusted impact on outcomes as compared with PAO. The potential benefits of DAO thrombectomy should be investigated in future randomized trials.

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Funding The Trevo Retriever Registry was funded by Stryker Neurovascular.

Competing interests RGN reports consulting fees for advisory roles with Stryker Neurovascular, Cerenovus, Medtronic, Phenox, Anaconda, Genentech, Biogen, Prolong Pharmaceuticals, and Imperative Care, and stock options for advisory roles with Brainomix, Viz-AI, Corindus Vascular Robotics, Vesalio, Ceretrieve, Astrocyte, and Cerebrotech. DCH is a consultant for Stryker and Vesalio, and holds stock options at Viz.AI. RG has ownership interest/royalties from UpToDate and is a consultant for Stryker, Medtronic, and Rapid Medical. AK is a consultant for Stryker. JDE is a consultant for Penumbra, Medtronic, and Stryker. ARM is a proctor for Stryker and consultant for InNeuroCo. AS reports research grants from, and is consultant for, Stryker. MAT is a consultant for Stryker, Rapid Medical, Balt USA, and Medtronic. MRF is a consultant for Nico Corporation. BWB is a consultant for Stryker, Penumbra, Medtronic, Cerenovus, Route 92 Medical, and Artio Medical, and has stock/stock options/equity in Penumbra, Viz.ai, Rapid Medical, Route 92 Medical, Artio Medical, 880 Medical, and Marblehead Medical. PJ is a consultant for Stryker. BMB, is a consultant for Stryker. DL is a consultant for Cerenovus, Genentech, Medtronic, Rapid Medical, Stryker, and Vesalio. EV is a consultant for Stryker, patent holder and scientific advisor for Penumbra, is a Trice consultant, and holds a Mizuho patent.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data-sharing anonymized data from the study are available upon reasonable request to the corresponding author.

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