Stroke

CLINICAL AND POPULATION SCIENCES

Endovascular Treatment for Acute Ischemic Stroke in Children

Experience From the MR CLEAN Registry

Adriaan C.G.M. van Es, MD, PhD; Maayke A.W. Hunfeld, MD; Ido van den Wijngaard, MD, PhD; Ulrike Kraemer, MD, PhD; Marc Engelen, MD, PhD; Boudewijn A.A.M. van Hasselt, MD; Puck S.S. Fransen, MD, PhD; Diederik W.J. Dippel, MD, PhD; Charles B.L.M. Majoie, MD, PhD; Aad van der Lugt, MD, PhD; Bart J. Emmer, MD, PhD; for the MR CLEAN Registry Investigators

BACKGROUND AND PURPOSE: Multiple trials have shown the efficacy and safety of endovascular therapy (EVT) of acute ischemic stroke in adults. Trials in children are lacking and only case reports and case series exist. However, the long-term outcome of children with acute ischemic stroke can be devastating with significant mortality and morbidity. In this study, we describe the safety and efficacy of EVT in children with anterior circulation acute ischemic stroke who were included in the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands).

METHODS: Patients under the age of 18 years who were treated with EVT for acute ischemic stroke between March 2014 and July 2017 were retrospectively reviewed up to 6 months after EVT. Nine children, aged 13 months to 16 years (median 14 years, interquartile range, 3–15 years), underwent EVT. Stroke cause was thromboembolism in children with end-stage heart failure on left ventricular assist device (4 of these 9 cases). Median time from onset to imaging was 133 minutes. Four children received intravenous alteplase before EVT, with median onset to needle time of 165 minutes. In all but one patient, EVT was technically successful. No major periprocedural complications occurred.

RESULTS: At 24 hours after EVT, 3 children completely recovered and 4 children showed partial recovery (median National Institutes of Health Stroke Scale, 3.5), whereas 2 patients on left ventricular assist device died within the first week due to the occurrence of multiple strokes. One patient on left ventricular assist device developed a fatal massive intracranial hemorrhage and another child died due to left ventricular assist device-related complications. Among the 5 stroke survivors, all had a favorable outcome (modified Rankin Scale score, 0–2) at 6 months follow-up.

CONCLUSIONS: EVT of children with acute ischemic stroke seems safe and feasible. However, these findings should be interpreted with caution as more and larger studies are needed to clarify the trade-off between risks and benefits of this treatment.

Key Words: endovascular procedures ■ ischemic stroke ■ pediatrics

The incidence of arterial stroke in children is estimated at 1.6/100.000 children per year.[1,2] Although the long-term clinical outcome in young patients is favorable due to the plasticity of the infant brain, it is also known that pediatric stroke results in significant mortality (7%–14%)[3,4] and morbidity (up to 70%).[5,6] Pediatric stroke has a profound impact on patients and their family as these children suffer from life-long deficits that have an important impact on the quality of life and participation in life. Furthermore, the burden for society is high as the lifetime cost of care after stroke is likely greater for a child than an adult.[7]

Correspondence to: Adriaan C.G.M. van Es, MD, PhD, Department of Radiology, Leiden University Medical Center PO BOX 9600, 2300 RC Leiden, the Netherlands. Email a.c.g.m.van_es@lumc.nl

For Sources of Funding and Disclosures, see page 787.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
EVT	endovascular therapy
IQR	interquartile range
LVAD	left ventricular assist device
mTICI	modified Treatment in Cerebral Infarction
NIHSS	National Institutes of Health Stroke Scale

See related article, p 789

Multiple trials have shown the efficacy and safety of endovascular therapy (EVT) for acute ischemic stroke (AIS) caused by the occlusion of a large intracranial vessel (large vessel occlusion) in the anterior circulation.[8,9] However, these findings are confined to the adult population as the inclusion criteria of these studies required patients to be at least 18 years of age. Nevertheless, the positive results of these trials are increasingly being extrapolated to the pediatric population. The 2015 American Heart Association/American Stroke Association Focused Update of the 2013 *Guidelines for the Early Management Patients With Acute Ischemic Stroke Regarding Endovascular Treatment* states that EVT with stent retrievers may be reasonable for some patients under the age 18 years with a stroke caused by a large vessel occlusion who can be treated within 6 hours of symptom onset (Class IIb; Level of Evidence C).[10]

Evidence from randomized controlled trials for the use of EVT in the pediatric population is lacking and due to the ethical and clinical difficulties in randomizing pediatric stroke patients, such a trial is not expected to be initiated soon. Future guideline recommendations for the use of EVT in the pediatric patient population will, therefore, be based on expert opinions and clinical experience from case series and observational cohorts. Until now, the number of reported cases of EVT in children suffering from a stroke caused by the occlusion of a large intracranial vessel in the anterior circulation is low. A recent review revealed 70 cases in which EVT in the anterior circulation was performed. Furthermore, it was shown that data regarding the youngest children are even more scarce as only 12 cases of children younger than 5 years that underwent EVT were identified.[11] Such a review of case reports is likely to suffer from publication bias as unsuccessful procedures are less likely to be published. In a recently published large retrospective study, 63 children with AIS due to a large vessel occlusion in the anterior circulation who received EVT were identified. In this study, EVT seemed feasible and safe; furthermore, neurological outcome was favorable in most cases.[12]

In this study, we present prospectively gathered data of 9 patients with an age under 18 years from the MR CLEAN Registry who were treated with mechanical thrombectomy for an occlusion in the anterior circulation. The MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) is an ongoing, prospective, multicenter, observational study for stroke intervention centers that perform EVT in the Netherlands. Knowledge drawn from these nine cases will help defining the role of EVT in the treatment of pediatric AIS.

METHODS

The MR CLEAN Registry is an ongoing, prospective, multicenter, observational study for stroke intervention centers that perform EVT in the Netherlands. The study protocol was evaluated by a central medical ethics committee, and permission to carry out the study as a registry was granted. Patients who were treated with EVT for AIS after the final MR CLEAN trial randomization on March 16, 2014, were registered. For this study, the MR CLEAN Registry database (up till July 19, 2017) was searched for all patients with an age under 18 years old at the date of the endovascular procedure. One of the cases was previously published as a case report.[13] Because of the sensitive nature of the data collected for this study, data cannot be made available.

RESULTS

Patients

In total 9 children who underwent EVT between March 2014 and July 2017 were included in this study. Baseline characteristics of these patients are given in Table 1. Patients (4 boys, 5 girls) were between 13 months and 16 years old (median 14 years, interquartile range [IQR], 3–15 years). All patients presented with severe stroke symptoms including hemiparesis. The median pediatric National Institutes of Health Stroke Scale (NIHSS) at presentation was 17 (IQR, 9.5–19.5). Large vessel occlusion was demonstrated with CTA in all of the cases, additional MRI was performed in 2 patients. Only patients with ischemic stroke caused by large vessel occlusion in the anterior circulation were included in the study with the M1 segment of the middle cerebral artery as the most common occlusion location (n=6). Median time from onset to imaging was 133 minutes (IQR, 115–183 minutes). Median time from onset to groin puncture was 265 minutes (IQR, 164–320 minutes). One patient presented with a wake-up stroke and the time of onset could not be determined.

Stroke. 2021;52:781–788. DOI: 10.1161/STROKEAHA.120.030210

Table 1. Patients Characteristics

Case	Age, y	Underlying pathology	Sex (M/F)	Symptoms	pedNIHSS before EVT	Imaging	Occlusion location	Onset to			Recanalization (mTICI)	Outcome	
								Imaging, min	IV, min	Groin puncture, min		Short term (24 h after EVT)	Long term (6 mo after EVT)
1	13 mo	DCM, LVAD	F	Paralysis arm R Paresis leg R	8*	CT/CTA	M1 Left	102	n.a.	160	2B	pedNIHSS 4*	†
2	18 mo	DCM, LVAD	M	Hemiparesis R	7*	CT/CTA	T-top left	205	n.a.	390	2B	pedNIHSS 13*	†
3	3	DCM, LVAD	F	Gaze deviation L Aphasia Paralysis arm R Paresis leg R	17	CT/CTA	T-top left	287	n.a.	300	2B	Partial recovery‡	†
4	10	DCM, LVAD	F	Gaze deviation L Aphasia Facial paresis R Paralysis arm R Paresis leg R	20	CT	M1 left	65	n.a.	129	3	pedNIHSS 3	†
5	14	Unknown	M	Neglect Dysarthria Paralysis Arm L Paresis Leg L	19	CT/CTA	M1 right	131	143	168	3	pedNIHSS 3	Mild spasticity arm L mRS 1
6	14	Atrial Myxoma	M	Gaze deviation L Hemiplegia R Aphasia	21	CT/CTA /CTP	M1 left	128	240	300	2B	pedNIHSS 13	mRS 2
7	16	PFO	F	Hemiparesis L Facial paralysis L	11	CT/CTA MRI/ MRA	M2 right	160§	180	230	3	pedNIHSS 1	Complete recovery mRS 0
8	15	Unknown	M	Hemiparesis R Aphasia	12	CT/CTA TA MRI/ MRA	M1 left	135§	150	340	2B	pedNIHSS 4	Mild paresis arm R, mild speech disturbances mRS 2
9	16	VSD	M	Hemiparalysis L	19	CT/CTA	M1 right	‖	n.a.	‖	2B	pedNIHSS 4	Fine motor skills Reduced L hand mRS 1

CT indicates computed tomography; CTA, CT angiography; CTP, CT perfusion; DCM, dilated cardiomyopathy; EVT, endovascular therapy; F, female; LVAD, left ventricular assist device; M, male; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction score; n.a., not applicable; pedNIHSS, pediatric National Institutes of Health Stroke Scale; PFO, persistent foramen ovale; and VSD, ventricular septum defect.

*Unclear whether the pedNIHSS can be reliably used in patients younger than 2 y old.

†Patient died.

‡Due to deep sedation and intubation it was impossible to score the pedNIHSS. The hemiparesis did improve short term.

§Onset to CT, additional MRI was performed before endovascular therapy was initiated.

‖Wake-up stroke, last seen at midnight.

Recanalization Treatment

Intravenous Thrombolysis

Four children received intravenous alteplase before EVT with a median onset- to-thrombolysis time of 165 minutes. The 4 children on left ventricular assist device (LVAD) did not receive intravenous alteplase due to therapeutic anticoagulation therapy to prevent clotting formation associated with the LVAD. One child did not receive intravenous alteplase due to the unknown time of symptom onset.

Endovascular Treatment

Groin Access

In the oldest patient, the procedure was performed using local anesthesia in the groin. All other procedures were performed under general anesthesia. The common

femoral artery was used for arterial access in all cases. The size of the introducer sheath was chosen based on the caliber of the common femoral artery. For the 3 youngest children (13 months, 17 months, and 3 years old), a 4F (radial) sheath was used, whereas in the oldest children, an 8F introducer sheath was used.

Cervical Access

In children younger than 10 years of age, a 4F diagnostic vertebral catheter was predominantly used as a guiding catheter. Due to the absence of vessel tortuosity and atherosclerotic plaques in children, this catheter could be easily positioned in the cervical internal carotid artery just below the skull base. In one patient (case 1, 13 months old), a 4F SOS-Omni catheter was used as a guiding catheter due to an acute angle of the proximal left internal carotid artery sharing a common origin with the brachiocephalic trunk. In the children older than 10 years of age, the diameter of the internal carotid artery was considered large enough to host an 8F balloon guiding catheter. Before thrombectomy, the balloon on the guiding catheter (filled with saline and contrast, 1:1) was carefully inflated under fluoroscopy.

Intracranial Procedure

The stent retriever with the smallest diameter (Trevo 3×20 mm) was preferred in children younger than 10 years of age, although a 4×20 mm stent retriever was used in a 3-year-old (case 3) after the 3×20 mm stent retriever failed to remove the thrombus. In the older children, the same stent retrievers as commonly used for M1 occlusions in adults were preferred (Trevo 4×20 mm and Embotrap 5x21 mm). The diameter of the M1 in the oldest patient (case 9; 16 years old) was large enough to accommodate a large-bore 5F distal access catheter for thrombus aspiration. Adequate recanalization (modified Treatment in Cerebral Infarction score [mTICI] score [modified Treatment in Cerebral Infarction score] 2B or better) was achieved in 8 patients (mTICI 3; n=3, mTICI 2B; n=5) with a median of 2 attempts to remove the thrombus. Only one case resulted in suboptimal recanalization (mTICI 2A; n=1). Mean procedure time, defined as the time between groin puncture and recanalization, was 53 minutes.

Closure of the Common Femoral Artery

The puncture site was closed by manual compression. Except for the oldest patient (case 9), no vascular closure device was used.

The technical details of the endovascular procedures are summarized in Table 2. EVT performed in 2 very young patients (case 1 and case 3) are illustrated in, respectively, Figure 1 and Figure 2.

Periprocedural Complications

No intracranial bleeding was reported directly after EVT. One patient developed a pseudoaneurysm of the common femoral artery which could be treated successfully with thrombin injection. No other periprocedural complications were reported.

Short-Term Outcome

Within 24 hours after EVT, 8 out of the 9 patients showed neurological recovery (see Table 1). In one of these patients, the pediatric NIHSS could not be assessed as the patient was sedated and intubated. One of the patients deteriorated in the 24 hours after EVT (pediatric NIHSS from 7 to 13). Median pediatric NIHSS after EVT was 4 (IQR, 3–8.5).

Long-Term Outcome

Long-term outcome (up to 6 months follow-up) was poor for all 4 patients on LVAD as all died due to LVAD-related complications. In 3 of these LVAD patients, neurological complication were the cause of death. Two patients died within the first week after EVT due to the occurrence of multiple ischemic strokes in both hemispheres. As these

Table 2. Technical Details of the Performed Endovascular Procedures

Patient	Age, y	Body weight, kg	Sheath	Guiding catheter	Distal access catheter	Stent retriever	No. of runs	Procedure time (min)	Recanalization (mTICI)	Procedural complication
1	13 mo	11	4F radial sheath	4F Slos-Omni	…	Trevo 3×20	3	65	2B	Pseudoaneurysm AFC
2	17 mo	10	4F radial sheath	4F vertebral	…	Trevo 3×20	2	60	2A	…
3	3	13	4F short introducer sheath	4F vertebral	…	Trevo 3×20 Trevo 4×20	2	54	2B	…
4	10	27	5F short introducer sheath	4F vertebral	…	Trevo 4×20	1	40	3	…
5	14	70	8F short introducer sheath	8F flowgate balloon guiding	Catalyst 6	Trevo 4×20	2	50	3	…
6	14	59	6F short introducer sheath	5F guider softtip	…	Solitaire 4×20	1	34	2B	…
7	16	65	6F short introducer sheath	5F guiding	…	Trevo 4×20	1	45	3	…
8	15	100	8F short introducer sheath	8F balloon guiding	…	Embotrap	3	66	2B	…
9	16	60	8F short introducer sheath	8F guiding	ACE60	Aspiration	4	65	2B	…

AFC indicates common femoral artery; and mTICI, modified Treatment in Cerebral Infarction score.

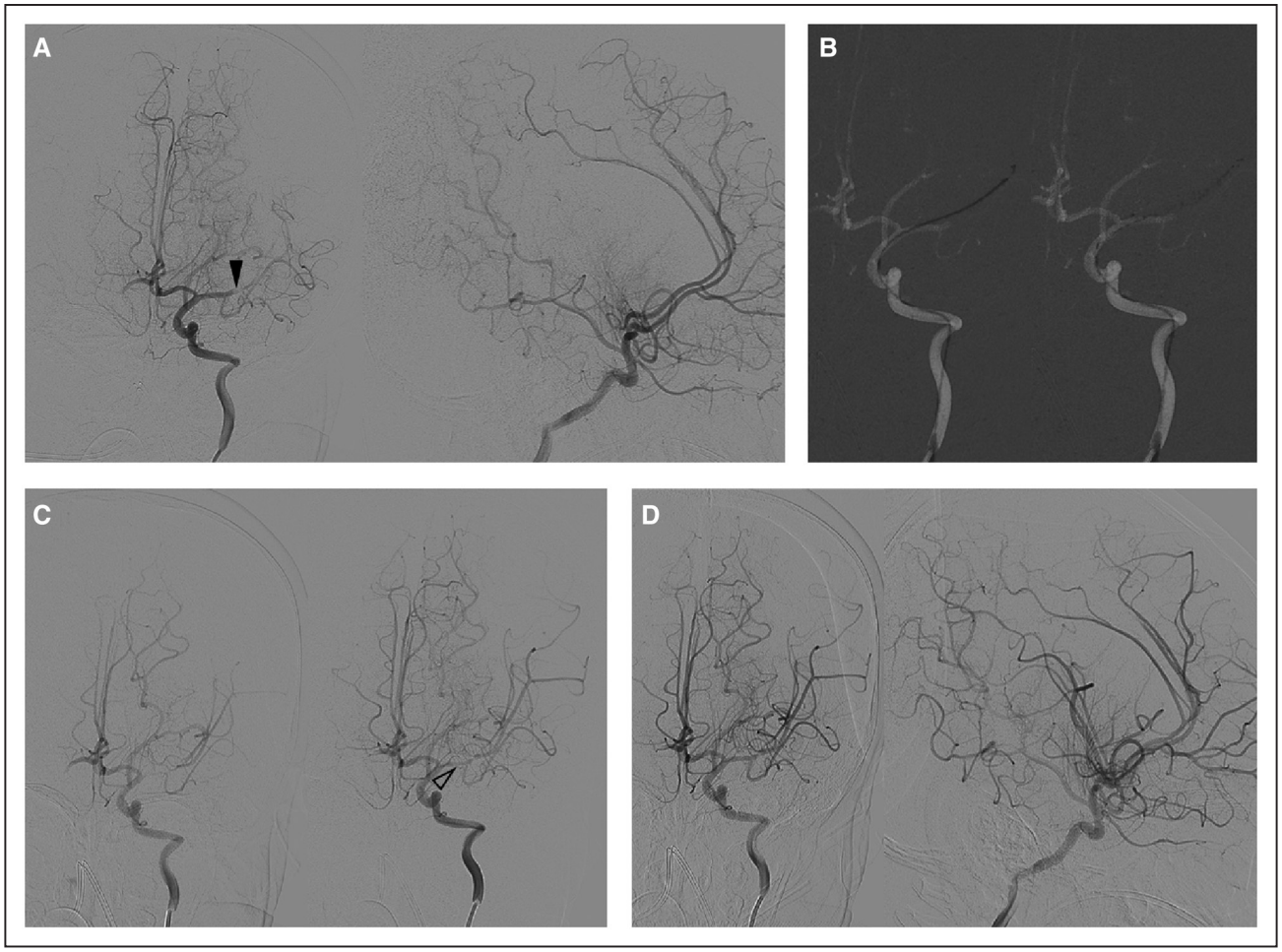

Figure 1. Digital subtraction angiography images recorded during the endovascular treatment of patient 1 (13 mo old female). **A**, (anteroposterior and lateral view) shows an occlusion of the distal M1 segment on the left (arrowhead). **B**, After crossing the thrombus with a Pro 18 microcatheter a 3×20 Trevo thrombectomy stent is advanced inside the microcatheter. The stent is deployed so that the most proximal part of the working area of the stent is covering the thrombus. **C**, After one thrombectomy attempt, the thrombus has moved to the proximal M1 segment (**left** anteroposterior view). After the third thrombectomy attempt (second attempt not shown), the thrombus has been removed from the M1 segment; however, vasospasms remain (**right** anteroposterior view). **D**, (anteroposterior and lateral view) Control angiography after 4 min of waiting with a continuous 0.9% NaCl flush over the guiding catheter shows almost complete resolution of the spasms and a modified Treatment in Cerebral Infarction score 2B recanalization.

infarcts occurred in vascular territories other than the territory of the with EVT treated vessel in combination with a known source for the emboli in both patients (proven atrial thrombi in one patient and thrombus accumulation in the LVAD of the other patient), these ischemic complications were considered related to the underlying dilated cardiomyopathy. Another patient on LVAD developed a massive intracranial hemorrhage with major neurological deficits 8 days after EVT and died 14 days later. This hemorrhage was located in the territory of the revascularized left middle cerebral artery. Although we cannot exclude the possibility that revascularization contributed to this ICH, we think that it was rather due to LVAD complications as a noncontrast enhanced computed tomography reveal multiple fluid, fluid levels in this hemorrhage, a finding consistent with anticoagulant induced coagulopathy associated with the LVAD. No ischemic changes were seen in the middle cerebral artery territory. Contrary to this, all 5 patients who were not on an LVAD had a favorable clinical outcome (modified Rankin Scale score, 0–2) 6 months after the AIS (see Table 1 and Figure 3).

DISCUSSION

This consecutive case series adds to the growing body of evidence indicating that EVT of ischemic stroke in children seems safe and feasible. The previously reported good recanalization rates are confirmed by our case series showing excellent technical results with successful recanalization (≥ mTICI 2B) in all but one of the cases with only one minor periprocedural complication. In patients with AIS and a dilated cardiomyopathy requiring an LVAD, the clinical outcome seems determined by this severe underlying disease. Favorable clinical outcome (modified Rankin Scale score ≤ 2) was reached in all of the other 5 treated patients. Although these findings are

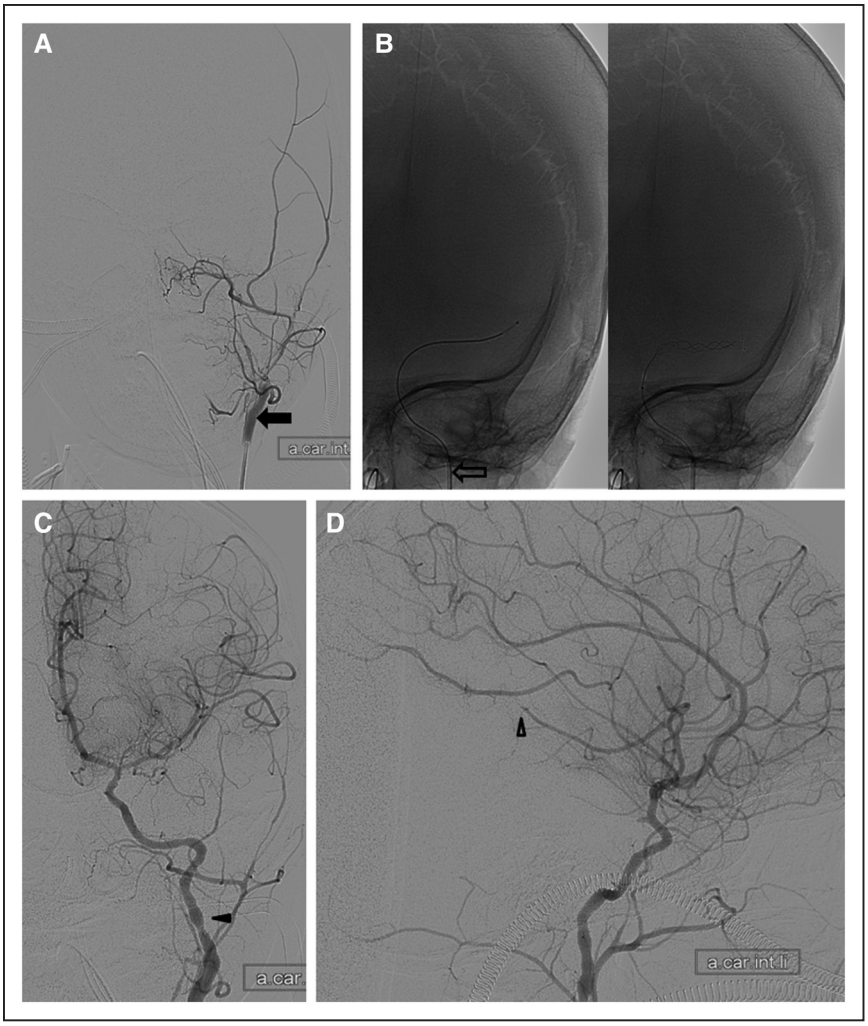

Figure 2. Digital subtraction angiography images recorded during the endovascular treatment of patient 3 (3 y old female).
A, Before treatment contrast injection in the left common carotid artery (anteroposterior image) shows normal filling of the external carotid artery. However, contrast stasis is noted in the proximal internal carotid artery (ICA; arrow). This finding is compatible with an outflow obstruction due to a large thrombus in the carotid T-top. **B**, A 4F vertebral catheter is positioned in the distal ICA below the skull base (open arrow) and the M1 segment is navigated with a Pro 18 microcatheter. Subsequently, a 3×20 mm Trevo thrombectomy stent is deployed. **C**, Contract injection in the left ICA (anteroposterior view) shows restoration of the flow to the left hemisphere after 2 thrombectomy attempts. Furthermore, a patent ICA is observed with only mild vasospasm (arrowhead). **D**, The lateral view of the digital subtraction angiography shows a modified Treatment in Cerebral Infarction score 2B recanalization with only a single distal embolus (open arrowhead).

in line with the Save Childs Study, these result, particularly regarding safety, should be interpreted with caution as our series is small, and no control group is available. However, it should be noted that the data presented in the present study has been prospectively gathered and is less likely to suffer from selection bias and missing data compared with previously published studies with a retrospective design.

Although a randomized controlled trial investigating the safety and efficacy of EVT in the pediatric population is desirable, it is highly unlikely that such a trial can be completed as a low inclusion rate is to be expected. This has multiple reasons. First, the incidence of stroke is lower in the pediatric population compared with the adult population. Second, contrary to adults, the most important cause for stroke in children is not thromboembolism but arteriopathies, acute and chronic systemic disorders, acute and chronic head and neck disorders, and prothrombotic states.[2] Third, in most cases, the diagnosis of a pediatric stroke can be delayed as multiple factors can make recognition of AIS in children challenging.[1] However, an accurate and timely diagnosis can be made by the experienced clinician.

These difficulties in diagnosing AIS stroke in children are thought to contribute to long time to treatment reported for endovascular treated children with AIS (13.7 hours with a maximum of 72 hours).[14] The difficulty of completing a randomized controlled trial in the pediatric stroke population was demonstrated by the termination of the TIPS trial (Thrombolysis in Pediatric Stroke), investigating intravenously administered intravenous alteplase for the treatment of AIS in children, in 2013 due to lack of accrual.[15] Therefore, integration of EVT in the guidelines for pediatric AIS will have to be based on the best available evidence consisting of case reports, case series, and expert opinions.

In our study, we used the PedNIHS as measure for short-term clinical outcome. The pediatric NIHSS, a modified scale of the adult NIHSS, is suitable for children from 2 until 18 years.[16] Two children in our cohort were younger than 2 years (13 and 18 months), and one child older than 3 years was sedated and intubated making it difficult to perform the pediatric NIHSS very accurately. Many items are not applicable for the young and sedated children as they are unable to obey comments or answer questions.

 Stroke. 2021;52:781–788. DOI: 10.1161/STROKEAHA.120.030210

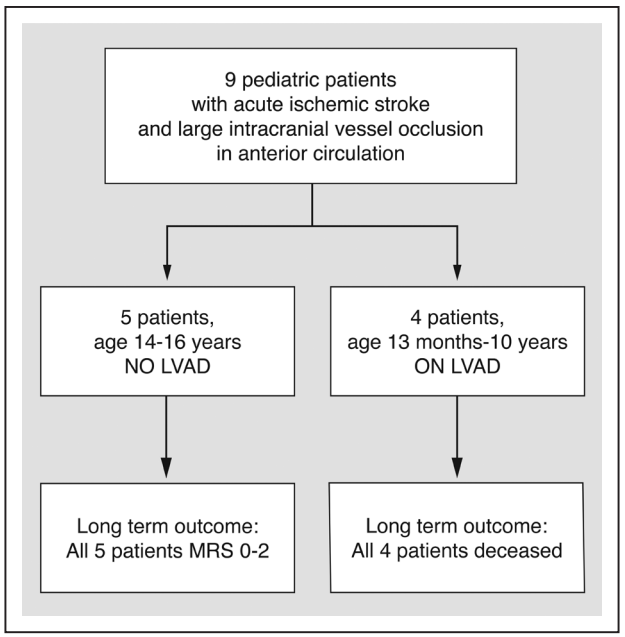

Figure 3. Long-term outcome (up to 6 mo) after endovascular therapy for intracranial large vessel.
LVAD indicates left ventricular assist device; and mRS, modified Rankin Scale.

With regards to the technical execution, EVT in the pediatric population does not seem to pose insurmountable challenges to the interventionalist as the reported procedure times and revascularization rates are at least equal, if not better, when compared with the adult population.[17] However, some difficulties gaining arterial access (common femoral artery) in the youngest patients with an LVAD can be expected due to the small caliber of this artery. Furthermore, our series illustrates that all endovascular procedures can be performed using materials commonly available in stroke centers performing EVT in the adult population. Therefore, no special preparation is needed, and the interventionalist is able to work with materials familiar to him or her.

EVT in young patients with an LVAD deserves special attention as 4 of our patients were on LVAD due to end-stage heart failure and awaiting heart transplant. Early identification of ischemic stroke and treatment might limit the neurological deficits caused by the stroke and could reduce the risk of hemorrhage in the ischemic part of the brain as these patients are on antithrombotic therapy. In addition, neurological deficits as a result of AIS would limit the eligibility of these patients for a heart transplant. Because of this, we considered these patients eligible for endovascular therapy in the case of an AIS despite very young age and severe illness. It is known that the risk of stroke in children on LVAD is high (21%–29%) due to a high risk of developing thrombi.[18,19] The Erasmus MC has an in-house protocol for children on LVAD admitted to the Pediatric Intensive Care Unit of Sophia Children's Hospital Erasmus MC in Rotterdam, a nationwide pediatric cardiac transplant center with ≈5 children on LVAD per year. This protocol has been developed to quickly detect, diagnose, and treat AIS. Collaboration with other pediatric cardiac transplant centers and international agreement on treatment protocols is essential.

CONCLUSIONS

Our case series suggests that EVT in the pediatric population seems feasible and safe. As an randomized controlled trial is unlikely to be conducted, prospective international population-based registries are needed to corroborate the benefit of EVT in the treatment of AIS in children.

ARTICLE INFORMATION

Received April 13, 2020; final revision received September 28, 2020; accepted November 16, 2020.

Affiliations

Department of Radiology and Nuclear Medicine, Leiden University Medical Center, the Netherlands (A.C.G.M.v.E.). Department of Radiology and Nuclear Medicine (A.v.d.L.) and Neurology (M.A.W.H., D.W.J.D.), Erasmus University Medical Center, Rotterdam, the Netherlands. Department of Neurology, Haaglanden Medical Center (HMC), The Hague, the Netherlands (I.v.d.W.). Department of Intensive Care and Pediatric Surgery, Erasmus MC-Sophia Children's Hospital University Medical Center, Rotterdam, the Netherlands (U.K.). Department of Radiology and Nuclear Medicine (B.A.A.M.v.H.) and Neurology (P.S.S.F.), Isala, Zwolle, the Netherlands. Department of Radiology and Nuclear Medicine (C.B.L.M.M., B.J.E.) and Neurology (M.E.), Academic Medical Center (AMC), Amsterdam, the Netherlands.

Acknowledgments

A special thanks to Dick Tibboel for his useful comments.

Sources of Funding

None.

Disclosures

Dr Majoie received funds from TWIN Foundation (related to this project, paid to institution) and from Netherlands Cardiovascular Research Initiative/Dutch Heart Foundation, Stryker, European Commission, Health Evaluation Netherlands (unrelated; all paid to institution). He is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical imaging analysis. Dr van der Lugt reports research grants from Stryker, Penumbra, Medtronic, and Cerenovus, all paid to the institution. The other authors report no conflicts.

REFERENCES

1. Mittal SO, ThatiGanganna S, Kuhns B, Strbian D, Sundararajan S. Acute ischemic stroke in pediatric patients. *Stroke.* 2015;46:e32–e34. doi: 10.1161/STROKEAHA.114.007681
2. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T, Parker AP, Wassmer E, Wraige E, Amin S, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neurol.* 2014;13:35–43. doi: 10.1016/S1474-4422(13)70290-4
3. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol.* 2000;15:316–324. doi: 10.1177/088307380001500508
4. Goeggel Simonetti B, Cavelti A, Arnold M, Bigi S, Regényi M, Mattle HP, Gralla J, Fluss J, Weber P, Hackenberg A, et al. Long-term outcome after arterial ischemic stroke in children and young adults. *Neurology.* 2015;84:1941–1947. doi: 10.1212/WNL.0000000000001555
5. Elbers J, deVeber G, Pontigon AM, Moharir M. Long-term outcomes of pediatric ischemic stroke in adulthood. *J Child Neurol.* 2014;29:782–788. doi: 10.1177/0883073813484358
6. Christerson S, Strömberg B. Childhood stroke in Sweden I: incidence, symptoms, risk factors and short-term outcome. *Acta Paediatr.* 2010;99:1641–1649. doi: 10.1111/j.1651-2227.2010.01925.x

7. Gardner MA, Hills NK, Sidney S, Johnston SC, Fullerton HJ. The 5-year direct medical cost of neonatal and childhood stroke in a population-based cohort. *Neurology*. 2010;74:372–378. doi: 10.1212/WNL.0b013e3181cbcd48
8. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
9. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
10. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi AA, Kidwell CS, et al; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American stroke association. *Stroke*. 2015;46:3020–3035. doi: 10.1161/STR.0000000000000074
11. Bhatia K, Kortman H, Blair C, Parker G, Brunacci D, Ang T, Worthington J, Muthusami P, Shoirah H, Mocco J, et al. Mechanical thrombectomy in pediatric stroke: systematic review, individual patient data meta-analysis, and case series. *J Neurosurg Pediatr*. 2019;24:558–71.
12. Sporns PB, Sträter R, Minnerup J, Wiendl H, Hanning U, Chapot R, Henkes H, Henkes E, Grams A, Dorn F, et al. Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the save ChildS study. *JAMA Neurol*. 2020;77:25–34. doi: 10.1001/jamaneurol.2019.3403
13. van den Wijngaard I, Wermer M, van Walderveen M, Wiendels N, Peeters-Scholte C, Lycklama À Nijeholt G. Intra-arterial treatment in a child with embolic stroke due to atrial myxoma. *Interv Neuroradiol*. 2014;20:345–351. doi: 10.15274/INR-2014-10026
14. Cobb MIH, Laarakker AS, Gonzalez LF, Smith TP, Hauck EF, Zomorodi AR. Endovascular therapies for acute ischemic stroke in children. *Stroke*. 2017;48:2026–2030. doi: 10.1161/STROKEAHA.117.016887
15. Bigi S, Dulcey A, Gralla J, Bernasconi C, Melliger A, Datta AN, Arnold M, Kaesmacher J, Fluss J, Hackenberg A, et al. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol*. 2018;83:1125–1132. doi: 10.1002/ana.25242
16. Ichord RN, Bastian R, Abraham L, Askalan R, Benedict S, Bernard TJ, Beslow L, Deveber G, Dowling M, Friedman N, et al. Interrater reliability of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) in a multicenter study. *Stroke*. 2011;42:613–617. doi: 10.1161/STROKEAHA.110.607192
17. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949
18. Jordan LC, Ichord RN, Reinhartz O, Humpl T, Pruthi S, Tjossem C, Rosenthal DN. Neurological complications and outcomes in the Berlin Heart EXCOR® pediatric investigational device exemption trial. *J Am Heart Assoc*. 2015;4:e001429. doi: 10.1161/JAHA.114.001429
19. Fraser CD Jr, Jaquiss RD, Rosenthal DN, Humpl T, Canter CE, Blackstone EH, Naftel DC, Ichord RN, Bomgaars L, Tweddell JS, et al; Berlin Heart Study Investigators. Prospective trial of a pediatric ventricular assist device. *N Engl J Med*. 2012;367:532–541. doi: 10.1056/NEJMoa1014164