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Endovascular treatment of primary M3 occlusion stroke in clinical practice: analysis of the German Stroke Registry

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Abstract

Background Endovascular treatment (ET) options for acute stroke due to distal middle cerebral artery occlusions are rapidly evolving, but data on outcome and safety are sparse. We therefore performed an analysis of patients undergoing ET for primary M3 occlusions in routine clinical practice in a nationwide registry.

Methods Patients enrolled between 01/20 and 12/21 in the prospective, multicenter German Stroke Registry-Endovascular Treatment (GSR-ET) were screened for mechanical thrombectomy performed for primary M3 occlusion. We analyzed neurological deficit as measured by the National Institute of Health Stroke Scale (NIHSS), symptomatic intracranial hemorrhage (sICH), thrombectomy technique, successful reperfusion (modified Thrombolysis in Cerebral Infarction [mTICI] score of 2b-3) and functional outcome as measured by the modified Rankin Scale (mRS) at discharge and 90 days.

Results Out of 5574 patients, 11 patients (0.2%, median age 80 years, 54.5% female) underwent ET for primary M3 occlusion. All patients had pre-admission mRS ≤ 1 , median NIHSS on admission was 8, and successful reperfusion was achieved in 6/11 patients (54.5%). While no vasospasm, dissection or perforation was reported, symptomatic intracranial hemorrhage occurred in 2 patients (18.2%). Favorable outcome (mRS ≤ 2) was achieved in 6/11 patients (54.5%) at 90-day follow-up.

Conclusions ET for primary M3 occlusions is rarely performed. While technically feasible, the procedure's potential benefits must be carefully weighed against its associated risks, including clinically relevant complications. Caution and further research is needed to optimize patient selection for this intervention.

Trial Registration GSR-ET; ClinicalTrials.gov Identifier: NCT03356392; Trial Registration Date: 11/29/2017.

Keywords Stroke, Endovascular treatment, Mechanical thrombectomy, MeVo, Clinical outcome

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Introduction

Endovascular treatment (ET) has become the standard of care for acute stroke caused by large vessel occlusion (LVO) [1]. Increasing clinical experience and evidence are emerging for ET as a treatment option for distal occlusions of the middle cerebral artery (MCA) [2–4]. According to current guidelines, there is class IIb evidence that ET "may be reasonable" in selected patients with occlusions of the MCA segment 2 or MCA segment 3 [5]. While ET is generally favored over best medical therapy for primary M2 occlusions [4, 6, 7], ET for primary M3 occlusion stroke (M3OS) is more challenging: First, there is an increased risk of complications, such as perforation, dissection and vasospasm, due to the longer route into small-diameter vessels [8]. Second, the neuronal "tissue at risk" is smaller, resulting in a potentially smaller loss of function when compared to proximal occlusions. Third, it remains unclear whether additional ET is beneficial in patients receiving intravenous thrombolysis (IVT) for primary M3OS. On the other hand, primary M3OS can lead to devastating clinical deficits, especially in eloquent areas.

Accordingly, ET in the M3 segment has been performed only in selected cases to date. Small case series have demonstrated the technical feasibility [9–11], but there are no larger case series of primary M3OS, and results of randomized trials comparing ET with best medical therapy are lacking. Therefore, we here aimed to investigate feasibility, safety parameters, and outcomes of M3OS in a large multicenter German thrombectomy registry.

Methods

We used data from the German Stroke Registry – Endovascular Treatment (GSR-ET; ClinicalTrials.gov identifier: NCT03356392). The GSR-ET is an ongoing, academic, open-label, multicenter registry of consecutive patients with acute ischemic stroke undergoing ET. The study was conducted in accordance with the Declaration of Helsinki and was approved centrally by the Institutional Review Board of the Ludwig-Maximilians-University Munich (689–15) and by local institutional review boards. Detailed methods of the GSR-ET have been published previously [12, 13].

Primary M3 occlusion was defined as proof of occlusion of the MCA distal to the M2/M3 junction and proximal to the M4 junction within the (opercular) M3 segment [14] on initial imaging or peri-interventional proof of M3 occlusion on angiography. Secondary occlusions such as migrated proximal LVO, peri-interventionally displaced or fragmented thrombus material, and multilobar occlusions on initial imaging were excluded.

The item of M3 occlusion was introduced into the registry database in January 2020. For the current analysis, the registry data were used from the introduction of that item until December 31, 2021. For suspected M3OS cases, the treating centers were asked to re-evaluate the initial imaging and angiography for anatomic location of the MCA occlusion and whether the inclusion criterion of primary M3OS was met. In addition, information on thrombectomy technique, employed device and complications was requested.

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and outcome and premorbid disability were rated by the modified Rankin Scale (mRS). Baseline infarct size was assessed using the Alberta Stroke Program Early CT Score (ASPECTS). Reperfusion success was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b–3 [15]. Intracranial hemorrhage (ICH) following stroke and reperfusion therapy was classified according to the Heidelberg Bleeding Classification [16]. Symptomatic intracranial hemorrhage (sICH) was defined as intracranial hemorrhage on 24-h follow-up CT and at least a 4-point increase in NIHSS [17]. Stroke etiology was rated according to the TOAST classification [18].

The neurological endpoints were functional outcome measured by mRS at discharge and at 90-day follow-up [1]. Secondary endpoints were the rate of good functional outcome defined as mRS 0–2 at 90-day follow-up, NIHSS at 24 h and at discharge, periprocedural complications (dissection, perforation, vasospasm), sICH, in-hospital-mortality and mortality at 90-day follow-up.

Missing data were not imputed for this analysis. Standard descriptive statistics were provided. Statistical calculations were performed using R (R version 4.2.1, R core team 2022).

Results

A total of 5574 patients treated with ET were included in the registry between January 2020 and December 2021. Of those, M3 occlusion was documented in 57 cases and isolated M3 occlusion was identified in 20 cases from 9 centers (Supp. Figure 1). After re-evaluation of these cases, 11 were confirmed to have primary M3 occlusion (example shown in Fig. 1). Thus, primary M3OS accounted for 0.2% of all ETs performed.

The median age was 80 years (interquartile range (IQR), 65.5–85.5) and 54.5% were female (Table 1). All patients were functionally independent prior to treatment (mRS ≤ 1) and 63.6% were fully independent (mRS 0). The median NIHSS score was 8 (IQR, 6.5–11) and the median ASPECT score was 10 (IQR, 9–10). Interestingly, the occluded vessel was located in the left hemisphere in all cases.

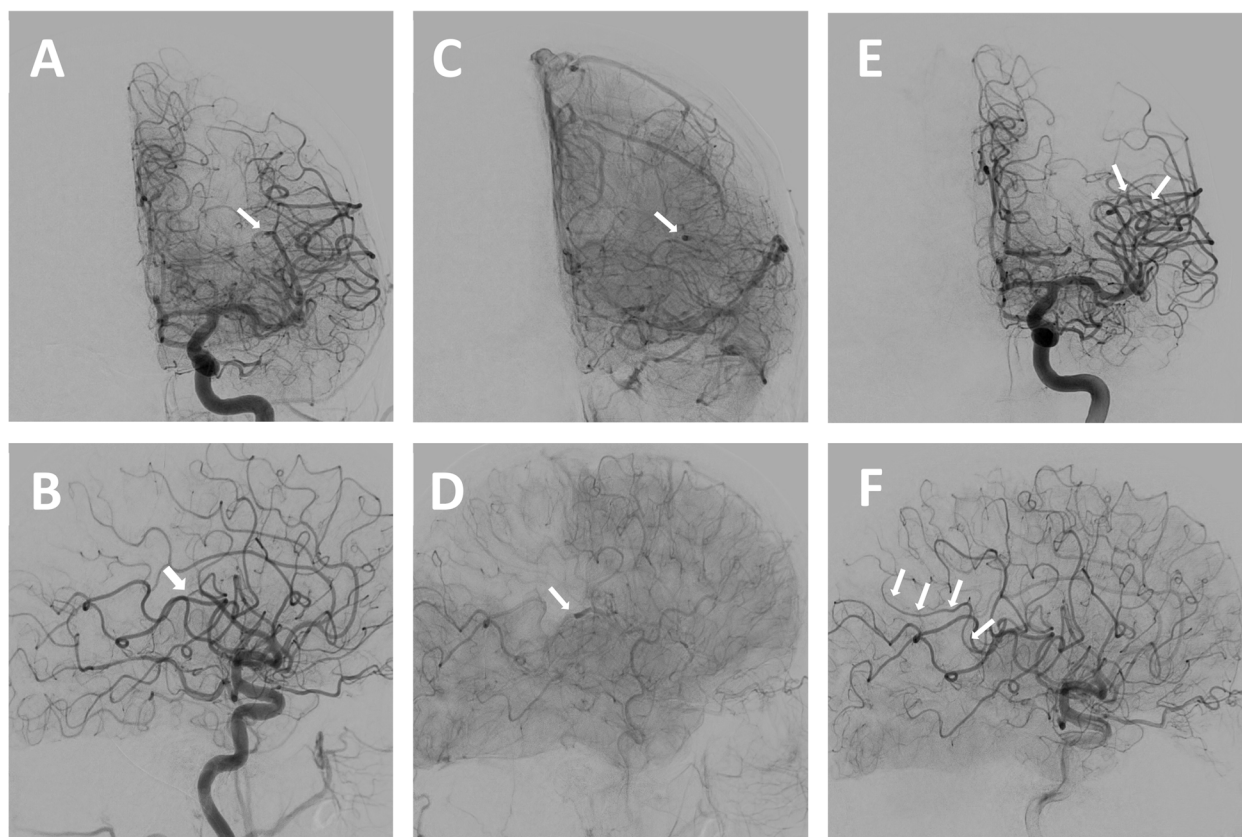


Fig. 1 Endovascular treatment for primary M3 occlusion stroke. Initial run (**A** (PA), **B** (lateral): arterial, **C** (PA), **D** (lateral): parenchymal phase) demonstrates M3-occlusion (→) with parietal perfusion deficit and full reperfusion of the branch (→→) after stent retriever thrombectomy (**E**, **F**)

Eight of 11 patients (72.7%) underwent ET under general anesthesia. The median number of thrombectomy maneuvers was 1 (IQR, 1–2). Successful reperfusion (i.e., mTICI score $\geq 2b$) was achieved in 6 out of 11 cases (54.5%). All patients were treated at larger centers, recruiting between 167 and 212 cases at the respective year.

No complications in terms of perforation, vasospasm or device malfunction were reported. In a single case, there was a clot migration into the distal vessels. 3 cases showed class 3c subarachnoid hemorrhage (SAH). sICH occurred in 2 cases, and both patients eventually died. 6 of 11 patients (54.5%) received IVT. One additional case not receiving IVT due to prior anticoagulation was periprocedurally treated with 10 mg of rtPA i.a. due to incomplete recanalization. Complete recanalization was not achieved (mTICI 2a) and follow-up imaging revealed sICH and SAH.

Stent retriever thrombectomy combined with distal aspiration was the preferred technique, performed in 72.7% of cases (8/11), whereas stent retriever thrombectomy was used in 2 cases and direct aspiration in only 1 case. Small lumen microcatheters and dedicated small

stent retrievers were used in all stent retriever cases. Details of pre- and periprocedural times and clinical characteristics are given in Table 1 and in the Supplemental Material.

The most common stroke etiology according to the TOAST classification was cardioembolism in 54.5% of cases. Rare causes were paroxysmal nocturnal hemoglobinuria and embolization from an M1 aneurysm, each occurring in one case. Etiology was undetermined in 3 cases.

Functional independence at 90-day follow-up was achieved in 54.5% (6/11) of all patients. Excellent functional outcome (mRS 0–1) was achieved in 4 cases (36.4%). In-hospital mortality was 9.1% (1/11) with one additional death during follow-up. Of note, successful reperfusion was not achieved in either of the deceased patients.

Discussion

Our case series, reporting on patients with primary M3OS, provides insight into the real-world application of ET in a challenging setting. ET for primary M3OS is rarely performed, accounting for only 0.2% in

Table 1 Main baseline and outcome characteristics of patients undergoing endovascular treatment for primary M3 occlusion stroke

	Age	Sex	Pre-morbid mRS	NIHSS	ASPECTS	Occluded vessel Initial Imaging	Side	IVT	Occluded vessel DSA	M3 branch	Final mTICI	sICH	Etiology	Discharge mRS	d90 mRS
1	87	m	1	10	10	M3	left	no	prox. M3	Truncus-superior	0	no	cardioembolism	4	4
2	88	f	0	14	10	M3	left	yes	M3 and A. pericallosa	NA	0	no	cardioembolism	5	5
3	67	f	1	12	9	distal M2	left	no	M3	Parietal	2b	no	cardioembolism	2	2
4	64	f	0	6	9	M2/M3 junction	left	yes	M2/M3 junction	Parietal	0	yes	cardioembolism	6	6
5	80	m	1	3	10	none	left	no	M3	Truncus superior	2a	yes	paroxysmal nocturnal hemoglobinuria	4	6
6	77	m	0	3	10	M3	left	no	M2/M3 junction	Fronto-parietal	3	no	undetermined	2	3
7	55	m	0	7	10	prox. M2	left	yes	prox. M3	Parietal	3	no	undetermined	NA	0
8	88	f	0	12	10	prox. M3	left	yes	prox. M3	Parietal	2b	no	cardioembolism	1	1
9	80	m	0	4	10	M3	left	yes	M2/M3 junction	Parietal	0	no	embolisation from M1 aneurysm	3	2
10	84	f	1	8	10	M3	left	no	M3	Parietal	3	no	cardioembolism	2	1
11	32	f	0	7	10	M3	left	yes	M3	Frontal	3	no	undetermined	1	0

Abbreviations: ASPECTS Alberta Stroke Program Early CT Score, NA not available, NIHSS National Institutes of Health Stroke Scale, IVT intravenous thrombolysis, mTICI modified Thrombolysis in Cerebral Infarction score, mRS modified Rankin Scale, sICH symptomatic intracranial hemorrhage

our registry. While the incidence of primary M3OS is unknown, distal vessel occlusions represent 20–40% of strokes [8], suggesting that only highly selected patients underwent ET in our large nation-wide registry representing approximately 16% of all ET in Germany during the study period [19]. Our data show a clear trend in the selection of eligible patients for ET for primary M3OS: These patients were functionally independent prior to stroke, clinically severely affected and had no or only little infarct demarcation on pre-interventional imaging. Exclusively left hemispheric occlusions combined with high NIHSS scores suggested that eloquent branches were affected, leading to the clinical decision that potential benefits outweighed risks in these cases.

The feasibility of ET in primary M3OS is emphasized by the rate of successful recanalization and functional independence at follow-up, which was achieved in both 55%. Final mTICI score $\geq 2b$ was observed in 5 out of 6 patients who achieved a good clinical outcome (mRS 0–2) at 90 days. This may suggest that prompt recanalization remains the key factor in patients' functional improvement in distal/medial vessel occlusions, as previously demonstrated in LVO strokes. Notably, recanalization rates were much lower than those observed in large studies of proximal vessel occlusion stroke [1]. Although only experienced high-volume centers were involved in this study, there seems to be a relevant safety risk in performing ET for primary M3OS as subarachnoid hemorrhage was observed in almost 30% of cases. We speculate that the longer and more tortuous route of the catheter into the small and often winding M3 segment may have led to perforation, as perforation is twice as likely in medium and distal occlusions compared to large vessel occlusion thrombectomy [20].

The risk–benefit balance of ET in M3OS also depends on the administration of IVT: When IVT is administered, clinicians tend to omit ET for distal vessel occlusions [21]. This practice is supported by higher recanalization rates of IVT in distal occlusions than in proximal occlusions [22]. However, contrary to previous assumptions, Saver et al. highlighted that IVT in distal vessel occlusions results in only 30–50% resolution of the visualized thrombi [8]. Therefore, medium and distal vessel occlusions are the next frontier of ET and highly clinically relevant, as they account for 20–40% of all strokes [8].

Increasing technical innovations such as microstent retrievers and the use of smaller and potentially more flexible microcatheters constantly expand the indications for and the overall technical success of ET. Accordingly, difficult discussions about performing ET for primary M3 occlusions will increase in the clinical routine.

In addition to the limitations inherent to a retrospective multicentric cohort study, the main limitation is

the low number of included M3OS patients despite our registry representing approx. 16% of all ET performed in Germany during the study period [19]. Further, as only 0.2% of patient in the GSR-ET underwent ET for M3OS, it is not possible to make a statement on patient outcomes based on this highly selected population, and there was no control group of patients not undergoing ET. Further research is warranted to fully understand the efficacy and safety of ET for M3OS. The ESCAPE MeVO (NCT05151172), DISCOUNT (NCT05030142), DISTALS (NCT05152524), and DISTAL (NCT05029414) randomized controlled trials comparing ET for medium and distal vessel occlusion stroke with best medical therapy are currently recruiting. These trials will hopefully provide important decision support for ET in distal MCA occlusion stroke. Until then, ET for primary M3 occlusion requires a thoughtful risk–benefit analysis.

Conclusion

Thrombectomy for isolated M3 occlusion stroke is technically feasible, albeit rarely performed. Its potential benefits should be judiciously balanced against its inherent risks, including the occurrence of clinically relevant complications. Prudent patient selection and refinement of interventional devices are imperative to optimize treatment outcomes. Further collaborative research, encompassing large-scale randomized controlled trials, is warranted to refine the selection criteria for distal middle cerebral artery thrombectomy in clinical practice.

Abbreviations

ASPECTS	Alberta Stroke Program Early CT Score
ET	Endovascular treatment
IVT	Intravenous thrombolysis
GSR-ET	German Stroke Registry – Endovascular Treatment
LVO	Large vessel occlusion
M3OS	Primary M3 occlusion stroke
MCA	Middle cerebral artery
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis in Cerebral Infarction
NIHSS	National Institutes of Health Stroke Scale
sICH	Symptomatic intracranial hemorrhage

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s42466-024-00330-7>.

Supplementary Material 1: Supplementary Table 1. Baseline, periprocedural and outcome characteristics of patients undergoing endovascular treatment for primary M3 occlusion stroke.

Supplementary Material 2: Supplementary Table 2. Endovascular treatment characteristics of patients with primary M3 occlusion stroke.

Supplementary Material 3: Supplementary Fig. 1. Flow diagram for patient inclusion.

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Trial registration

clinicaltrials.gov NCT03356392. Participants or their legal representatives gave informed consent as described in the initial study protocol [12].

Authors' contributions

Felix J. Bode, Franziska Dorn, and Johannes M. Weller designed the study; Niklas M. Beckonert, Felix J. Bode, and Johannes M. Weller conducted the literature research. Johannes M. Weller analyzed the data. Niklas M. Beckonert wrote the first draft of the manuscript. Gabor C. Petzold, Felix J. Bode, Franziska Dorn, and Johannes M. Weller revised the manuscript and figures. All authors were involved in patient recruitment and data collection, reviewed and revised the manuscript, and approved the final version of the manuscript.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was centrally approved by the institutional review board of the Ludwig-Maximilians University Munich (689–15) and institutional review boards according to local regulations.

Consent for publication

Not applicable.

Competing interests

NMB received travel grants from Sanofi and Viatrix. FD is a consultant/proctor for Cerenovus/Johnson&Johnson, Balt, Cerus Endovascular and Phenox. She received speaker's honoraria from Acandis, Stryker, Cerenovus/Johnson&Johnson, Asahi and research support from Cerenovus/Johnson&Johnson. MDC reports grants from the Werner Otto Stiftung outside the submitted work. All other authors report no conflicting interests.

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