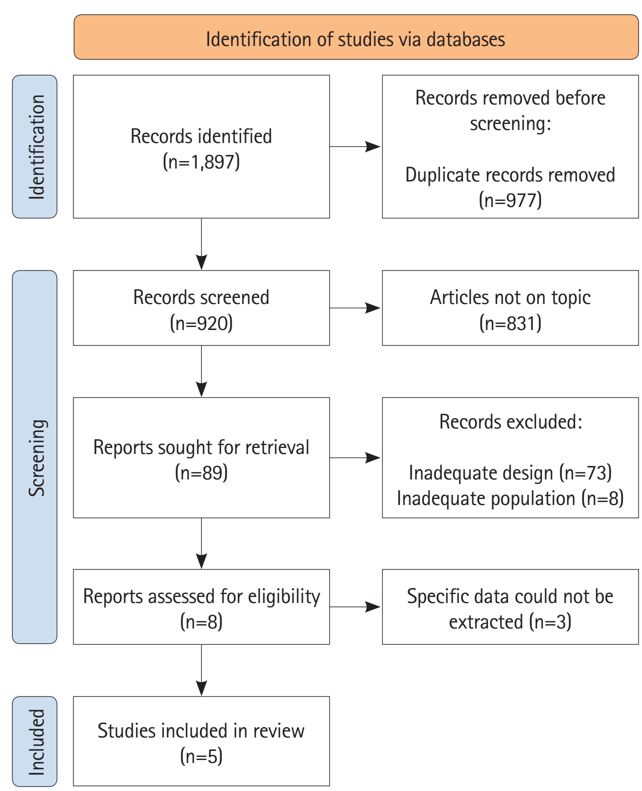
Supplementary Material. Systematic review and meta-analysis on endovascular treatment for distal-M2 occlusions

A recent consensus statement defining distal and medium vessel occlusions (DMVOs) highlighted the peculiar nature of the M2-segment of the middle cerebral artery (MCA) that experts do not firmly classify as a DMVO or large vessel occlusion (LVO).[1] The diameter of the M2-segment ranges from 1.1 mm to 2.4 mm, with a proximal segment very close in diameter to the M1-segment (around 3 mm), especially for a dominant branch, and a distal segment closer to the M3-segment (1.1 mm to 1.5 mm).[1-3] Additional awareness has been raised about the high variability of the M1-segment anatomy and its branching patterns so that some proximal-M2 occlusions are described functionally as "M1-like."[4-6] Distinguishing between proximal-M2 occlusions and distal-M2 occlusions seems reasonable and clinically relevant, as we could consider this segmentation to be the threshold between LVOs and DMVOs.

In addition to the ETIS (Endovascular Treatment for Ischemic Stroke) study, we performed a comprehensive systematic search of PubMed, MEDLINE, Embase, and Cochrane databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] on endovascular treatment (EVT) for distal-M2 strokes. No written review protocol was prepared, and the review was not registered before its realization. We used the keywords: "thrombectomy," "endovascular treatment," "stroke," "occlusion," "M2," and "distal" combined with Boolean operators to increase search sensitivity and specificity. Initial screening and study selection were performed using Covidence (Veritas Health Innovation, Melbourne, Australia), a web application for systematic reviews, by two independent reviewers. We included articles published in the English language between the inception of each database and March 2022, reporting EVT of acute ischemic stroke due to primary distal-M2 occlusion. Articles reporting fewer than five cases and cadaveric, animal, or *in vitro* studies were excluded. Articles reporting patients with distal-M2 occlusion among other occlusion locations were assessed in full text to determine whether data specific to distal-M2 could be separately extracted. If not possible, these studies were excluded. Centers and periods of each study were assessed, and those with overlapping populations were excluded while maintaining the article with the most recent and complete dataset to avoid the risk of multiplicity. Information extracted from each study included sample size, age, treatment modality, percentage of patients receiving intravenous thrombolysis, National Institutes of Health Stroke Scale (NIHSS) at admission, time from symptoms onset to puncture, rate of successful recanalization, rate of symptomatic intracranial hemorrhage (sICH), clinical outcomes, and mortality at 90 days. A favorable outcome was defined as achieving a modified Rankin Scale (mRS) ≤2. Successful recanalization and sICH were considered according to the definition provided in each study. Muszynski et al.[8] reported data on 67 distal-M2 occlusions from the ETIS registry; therefore, we pooled this article with the most recent data from the ETIS registry and labeled it as "current series" in the meta-analysis. An assessment of the risk of bias for each study was made independently by the two reviewers.

In the meta-analysis, estimated rates of reperfusion, good clinical outcome, sICH, and mortality at 90 days were weighted for each study sample size. Odds ratios (ORs) and 95% confidence intervals (CIs) for pooled data for good recanalization, sICH, favorable outcomes, and mortality were also calculated. The extent of heterogeneity among studies was assessed with an I^2 test. Pooled analyses were performed with fixed effect and DerSimonian and Laird random-effects models. All analyses were completed using Stata 17 (StataCorp, College Station, TX, USA), RStudio version 1.4.1106 (https://posit.co/), and the R General Package for Meta-Analysis (version 6.0-0; R Foundation for Statistical Computing, Vienna, Austria).



Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study search and inclusion adapted from the PRISMA 2020 flow diagram template.[7]

Supplementary Table 1. Quality assessment of the studies included in the meta-analysis

Study (year)	Main limitations
Tomsick et al.[11] (2017)	Open-label, M2 occlusion retrospectively assessed, incomplete outcome data, risk of selective outcome reporting
de Castro Afonso et al.[12] (2019)	Retrospective design, open-label, single center, small sample size, no control arm.
Ivan et al.[9] (2020)	Retrospective design, open-label, single center, no control arm, incomplete outcome data.
de Havenon et al.[10] (2021)	Open-label, no control arm
Current series	Open-label, no control arm

Supplementary Table 2. Judgements about each risk of bias item for each included study in the meta-analysis

	Tomsick et al.,[11] 2017	de Castro Afonso et al.,[12] 2019	Ivan et al.,[9] 2020	de Havenon et al.,[10] 2021	Current series
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and personal (performance bias)					
Blinding of outcome assessors					
Incomplete outcome data (attrition bias)					
Selective outcome reporting					
Other bias					

Green indicates a low risk of bias. Red indicates a high risk of bias.

Supplementary Table 3. Demographic, procedural and outcome data of the studies included in the meta-analysis

	Tomsick et al.[11]	de Castro Afonso et al.[12]	Ivan et al.[9]	de Havenon et al.[10]	Current series
Year	2017	2019	2020	2021	2022
Study design	Multicenter, retrospective (IMS III)	Single center, prospective	Single center, retrospective	Multicenter, retrospective (ARISE II)	Multicenter, prospective
Country	North America, Australia, Europe	Brazil	Germany	United States, Europe	France
Number of patients	28	8	23	30	157
Age (yr), mean (SD)	NA	69.2 (NA)	73 (13.3)	71.2 (12)	71 (15)
Female	NA	14 (45)	34 (59.6)	27 (47.4)	74 (47.1)
Intravenous thrombolysis	NA	19 (63.3)	43 (75.4)	57 (100)	84 (54.2)
NIHSS, median (IQR)	NA	15.5 (7.5)	11 (NA)	14 (6)	12 (11)
ASPECTS, median (IQR)	NA	9.5 (2.5)	10 (NA)	10 (1)	9 (3)
Time from symptom onset to treatment (min)	NA	261 (104) (mean, SD)	227 (70) (mean, SD)	208 (80) (mean, SD)	260 (130) (median, IQR)
Time from puncture to recanalization (min)	NA	47.5 (29.8) (median, IQR)	68 (42) (mean, SD)	NA	35 (31) (median, IQR)
Complete or partial recanalization	8 (28.6)	8 (100.0)	NA	27 (90.0)	111 (84.7)
mRS ≤2 at 90 days	NA	4 (50.0)	NA	23 (76.7)	61 (46.2)
sICH	NA	NA	5 (22)	NA	7 (5.2)
Mortality at 90 days	NA	3 (37.5)	3 (13) (mortality during hospitalization)	3 (10)	22 (16.7)

Demographic and procedural data are reported for all M2 occlusions in the study as specific data on distal-M2 occlusions were not available. Outcome data are specific to distal-M2 occlusions. Data are presented as number (%) unless otherwise indicated.
IMS III, Interventional Management of Stroke III trial; ARISE II, Analysis of Revascularization in Ischemic Stroke with EmboTrap trial; SD, standard deviation; NA, not available; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.

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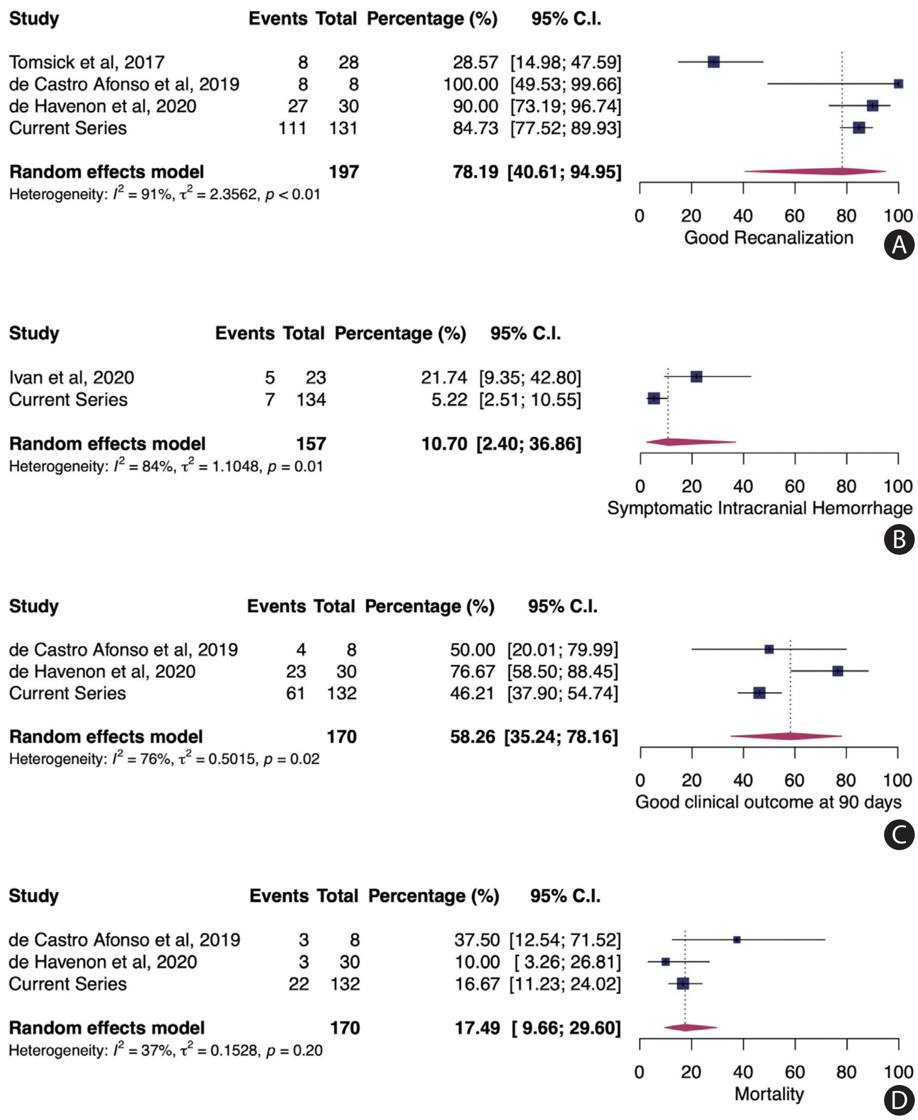

Supplementary Figure 2. Forest plots from the pooled data of the meta-analysis for (A) successful recanalization; (B) symptomatic intracranial hemorrhage; (C) 90-day favorable outcome; and (D) 90-day all-cause mortality.[9-12] Good recanalization and symptomatic intracranial hemorrhage are reported according to the original study definition. Good clinical outcome is defined as mRS ≤2 at 90 days. mRS, modified Rankin Scale; CI, confidence interval.

The research identified 1,897 records related to the keywords chosen. After removal of duplicates (n=977), articles not on the topic (n=831), articles with inadequate design (n=73), inadequate population (n=8), and articles in which specific data could not be extracted (n=3), five studies were finally included in the review[8-12] (PRISMA flowchart is detailed in Supplementary Figure 1).

The outcome data on EVT for distal-M2 occlusions reported by each article is highly heterogenous and susceptible to bias (quality assessment table and judgment about risk of bias are available in Supplementary Tables 1 and 2). Demographic, procedural, and outcome data for each study are detailed in Supplementary Table 3. For each article, except the current series, demographic and procedural data are reported for all M2-occlusions, as specific data on distal-M2 occlusions were not available. In the pooled analysis, the percentage for partial or complete recanalization was 78.19% (95% CI 40.61–94.95); the percentage for sICH was 10.70% (95% CI 2.40–36.86); the percentage for favorable outcome was 58.26% (95% CI 35.24–78.16); and the percentage for mortality at 90 days was 17.49% (95% CI 9.66–29.60). Forest plots for all four major outcomes are available in Supplementary Figure 2.

The systematic review of the literature and meta-analysis is limited by the heterogeneity of the definitions of the distal-M2 segment. The most common definition, and the one used by the ETIS registry, is to define distal-M2 as "distal to the mid-Sylvian point" (Muszynski et al.,[8] de Havenon et al.,[10] and Menon et al.[13]). Other definitions encountered in the literature include: "immediately proximal to or at the M2–M3 junction" (Romano et al.[14]

and Haussen et al.[15]), "second half of an M2 branch" (de Castro Afonso et al.[12]), "after 1-cm within the middle cerebral artery bifurcation" (Ospel et al.[16]), and "distal M2 branches" (Ivan et al.[9]). Tomsick et al.[11] created a new segmentation system dividing the MCA into trunk, division, division-branch, and branch, which has been criticized by other authors.[6] This lack of consensus on the definition of the distal-M2 segment of the MCA makes it hard to draw definite conclusions from the pooled data of the meta-analysis as it is highly susceptible to selection bias.

The other main issue we encountered in the elaboration of the meta-analysis was the overall poor and heterogeneous reporting of outcome data on distal-M2 thrombectomy, which could be explained by the fact that distal-M2 occlusions were not the main focus of these articles.

The recanalization rate for distal-M2 occlusions is high across the studies included, between 84.7% and 100%, with the exception of Tomsick et al.[11] (29%). Their results can be explained by the fact that they are drawn from a *post-hoc* analysis of IMS III, one of the early RCT that did not show an additional benefit of EVT over best medical treatment alone. This low reperfusion rate may be explained by the fact that most of the devices used in this study were first-generation mechanical thrombectomy devices, considered today as obsolete.[17]

In conclusion of this review, EVT seems safe and effective across studies resulting in a high recanalization rate; however, prospective randomized studies are needed. A collective effort to better define the distal-M2 segment must be made, especially for future RCTs.

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