

SYSTEMATIC REVIEW/META-ANALYSIS

Neurointervention

Endovascular Thrombectomy for Carotid Pseudo-occlusion in the Setting of Acute Ischemic Stroke: A Comparative Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: The effective treatment for acute ischemic stroke (AIS) patients with cervical internal carotid pseudo-occlusion (cICA-PO) requires comprehensive research on the safety and outcomes of endovascular thrombectomy (EVT). However, there is limited data available, highlighting the need for further research to ensure better treatment strategies and improve the quality of care for these patients.

PURPOSE: This study aims to assess the management and outcomes in this population group compared to patients with true carotid occlusion.

DATA SOURCES: Following the PRISMA guidelines, a comprehensive systematic review was conducted using PubMed, Embase, Web of Science, and Scopus from data base inception to November 2023.

STUDY SELECTION: The size of the included studies ranged from 16 patients to 146 patients. Through the 4 full-text articles, a total of 259 patients were collected. We

compared outcomes between patients with cICA-PO compared to patients with true carotid occlusions undergoing EVT due to AIS. We excluded studies with patients with carotid pseudo-occlusion without stroke, review articles, duplicate studies, overlapped data that included the same patients presented in another included study, case reports, case series with fewer than 5 patients, and meeting abstracts that did not contain the outcomes of interest. We did not pose any limitations regarding sample size or patients' characteristics.

DATA ANALYSIS: We utilized the R statistical software (V.4.3.1; R package meta, R Foundation for Statistical Computing, Vienna, Austria) to conduct the analysis of all the data obtained. We calculated the odds ratio (OR) for binary variables, and the corresponding 95% confidence interval (CI). To synthesize the data, random-effect models, as well as forest plots were generated to visually represent the synthesis of the data. Additionally, we assessed heterogeneity using Cochran's Q and I^2 tests. A P-value less than 0.05 for the Q statistic or I^2 more than 50% suggests significant heterogeneity. Based on a small number of studies (less than 10), the assessment of publication bias could not be reliably performed.

DATA SYNTHESIS: This meta-analysis encompassed data from 4 studies. Patients with cICA-PO and AIS who underwent EVT (n = 135) exhibited lower rates of functional independence (OR 0.35, 95% CI 0.20-0.61, p= <0.001) compared to patients with true occlusions (n = 103), as well as successful recanalization rates (OR 0.39, 95% CI 0.20-0.74, p=0.004). In addition, the cICA-PO group experienced higher mortality and sICH compared to the group with true carotid occlusions (OR 2.62, 95% CI 0.21-7.24, and OR 2.23, 95% CI 1.00-4.95, p= 0.049, respectively).

LIMITATIONS: Individual patient data was not available. Studies were a retrospective design and some of the studies had small sample sizes. The included studies in our meta-

analysis did not exclude patients with tandem occlusions which might influence the results of the comparison.

CONCLUSIONS: As compared to patients with true carotid occlusion, the cICA-PO group with AIS undergoing EVT presented poor outcomes with lower functional independence and successful recanalization, as well as higher sICH and mortality rates.

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Summary section:

Previous literature:

Pseudo-occlusion (PO) of the cervical internal carotid artery (ICA) refers to an isolated occlusion of the intracranial ICA that appears as an extracranial ICA occlusion on computed tomography angiography (CTA) or digital subtraction angiography because of blockage of distal contrast penetration by a stagnant column of unopacified blood. Previous studies have

found that cICA-PO patients compared to true cICA occlusion patients have a lower chance of successful recanalization, lower rates of favorable functional outcome (mRS 0-2) and mortality, likely due to the heavier clot burden in cICA-PO cases.

Key findings: This meta-analysis of four studies, encompassing 135 patients, demonstrated EVT in AIS patients with cICA-PO with consistent results with lower rates of successful recanalization and worse functional outcome (mRS 0-2) compared to those with true cICA occlusion. EVT in AIS patients with cICA-PO also found to have higher risks of sICH and mortality as compared to AIS patients with true cICA occlusion.

Knowledge advancement: To improve outcomes in these patients, it's essential to optimize the vascular imaging modalities to help differentiate between cICA-PO and true ICA occlusion in acute settings. This will allow for better decision-making and tailored preparation for EVT procedures based on the actual level of the ICA occlusion.

Conflict of Interest Statement

R.K. has the following conflicts: Research support from: Cerenovus Inc, Medtronic, Endovascular Engineering, Frontior Bio, Sensome Inc, Endomimetics, Ancure LLC, Neurogami Medical, MIVI Biosciences, Monarch Biosciences, Stryker Inc, Conway Medical, Pireus Medical, and Bionau Labs outside the submitted work. He holds the following research grants Research Grants: NIH (R01NS076491, R44NS107111, R43NS110114 and R21NS128199) and NSF (081215707) outside the submitted work.

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Medtronic, Balt, and Inera Therapeutics; has served on the Data Safety Monitoring Board for Vesalio; and received royalties from Medtronic outside the submitted work.

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INTRODUCTION

Carotid pseudo-occlusion (cICA-PO) refers to an apparent occlusion of the cervical internal carotid artery on CT angiography or digital subtraction angiography due to unopacified stagnant blood flow in a patent artery caused by a distal intracranial occlusion. It is often mistaken for true occlusions on CT angiography due to their similar imaging findings. Pseudo-occlusion occurs in 6%–15% of patients with acute ischemic stroke (AIS) (1), and according to a study published in 2022 suggests that cICA-PO is associated with an increased risk of reperfusion failure and poor outcome after endovascular treatment (EVT) compared with true occlusion (2). Even though ICA PO is a fairly common scenario, existing studies have been only performed in small population sizes, requiring further evidence to evaluate the role of this imaging finding in patients with AIS. Therefore, the purpose of this Systematic review and Meta-analysis is to assess the management and outcomes of patients who underwent EVT with pseudo-occlusion compared to true occlusion in the setting of acute stroke.

MATERIALS AND METHODS

Search Strategy

For this systematic review and meta-analysis, a systematic review of the literature was conducted within Nested Knowledge Autolit software version 1.46 (Nested Knowledge), using PubMed, Embase, Web of Science, and Scopus from data base inception to November 2023.⁷ Based on each database, different combinations of possible keywords and/or Medical Subject Headings terms were used for that purpose. Keywords and Medical Subject Headings terms included *carotid pseudo-occlusion or pseudoocclusion, stroke*. The full search strategy is provided in the supplement material. Moreover, we did an extensive manual search through the references of the included articles to retrieve any missed papers. This study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (3).

Screening Process and Eligibility Criteria

We included all original studies fulfilling our predetermined Population, Intervention, Comparator, and Outcomes approach. The population was patients with Carotid pseudo-occlusion in the setting of acute stroke, the intervention was EVT, and the control group was patients with true occlusion in the presence of AIS.

We excluded studies with patients with carotid pseudo-occlusion without stroke, review articles, duplicate studies, overlapped data that included the same patients presented in another included study, case reports, case series with fewer than 5 patients, and meeting abstracts that did not contain the outcomes of interest. We did not pose any limitations regarding sample size or patients' characteristics.

Data Extraction

Two authors (M.T, T.M and K.V) performed the title and abstract screening against the predefined criteria. This was followed by a full-text screening of any retained studies of the first screening step. In both stages, the senior author (D.F.K) was consulted to resolve any conflicts in the decisions.

Data extraction was also performed with AutoLit software. The extracted data included study characteristics, baseline data of included patients, and outcomes of interest. Two authors (M.T and T.M) independently completed the extraction, which was subsequently evaluated for consensus by a third author (S.G).

Risk of Bias

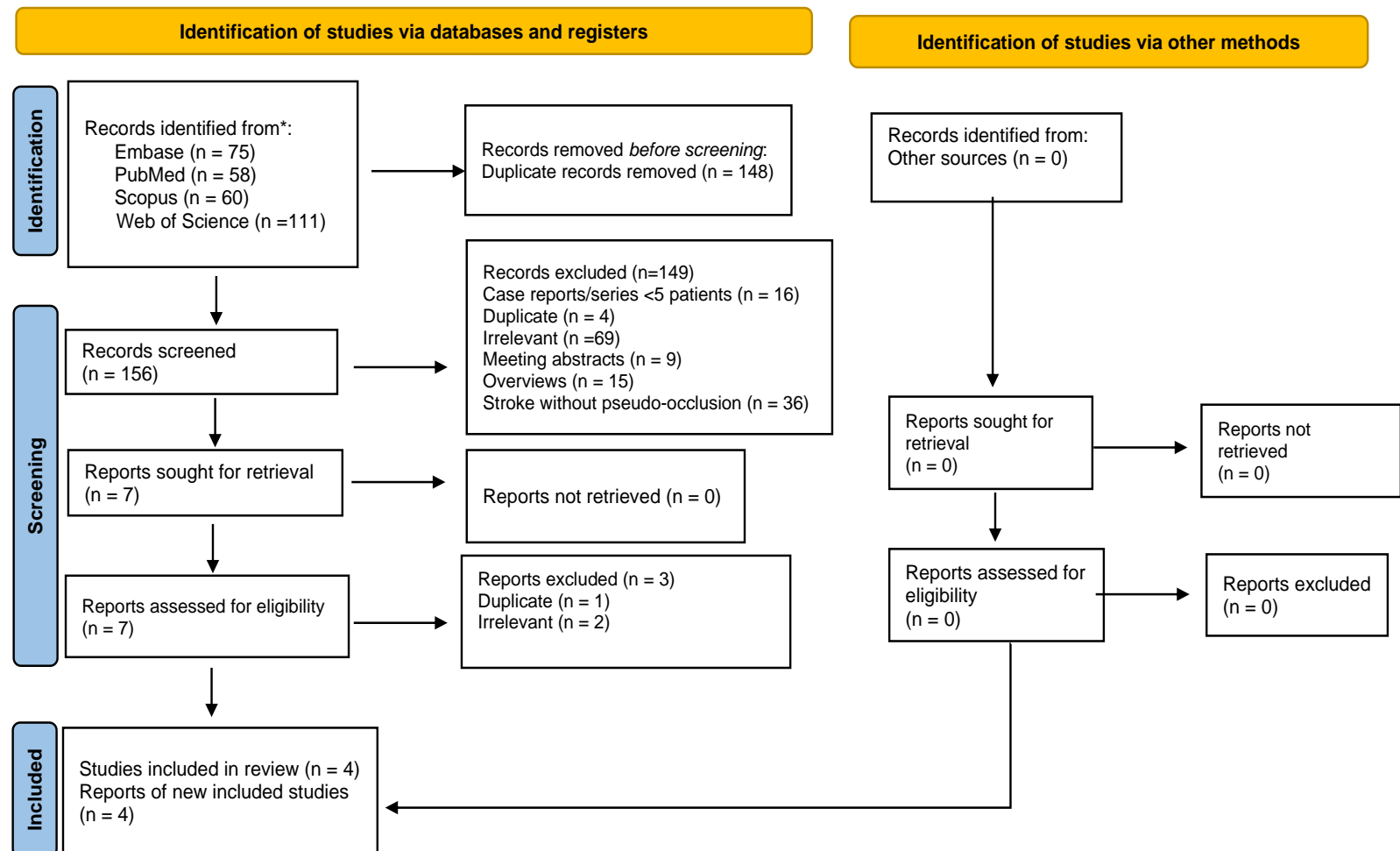
To evaluate the potential bias in the observational, non-randomized studies included in our analysis, we employed the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (4). The tool assesses seven distinct domains of bias, including confounding, selection of participants in the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Our assessment yielded an overall judgment of the risk of bias, which we categorized as low, moderate, serious, or critical.

Statistical Analysis

We utilized the R statistical software (V.4.3.1; R package meta, R Foundation for Statistical Computing, Vienna, Austria) to conduct the analysis of all the data obtained. We calculated the odds ratio (OR) for binary variables, and the corresponding 95% confidence interval (CI). To synthesize the data, random-effect models, as well as forest plots were

generated to visually represent the synthesis of the data. Additionally, we assessed heterogeneity using Cochran's Q and I^2 tests. A P-value less than 0.05 for the Q statistic or I^2 more than 50% suggests significant heterogeneity. Based on a small number of studies (less than 10), the assessment of publication bias could not be reliably performed.

Figure 1. Prisma 2020 Flow diagram.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

RESULTS

Search and screening results.

The search strategy yielded a total of 304 studies, after removing duplicates the remaining 156 studies were further screened. There was a total of 7 studies selected for the title and abstract screening. Eventually, 4 studies were determined to satisfy our inclusion criteria with the appropriate report of outcomes of interest and data was then extracted from these studies.

Study characteristics and risk of bias

All 4 included studies used a retrospective design. The size of the included studies ranged from 16 patients to 146 patients. Through the 4 full-text articles, a total of 259 patients were collected.

Moderate RoB was found in 3 of the 4 articles and was determined in 1 study to have a critical RoB. Domains of most concerns across studies were: bias due to the selection of participants and measurement outcomes. Patient characteristics, including age, sex, comorbidities, presence of tandem occlusions, site of occlusion, management, and baseline National Institutes of Health Stroke Scale (NIHSS) score, are detailed in the Table.1

Outcomes

Functional Independence

Three studies involving 129 patients compared the rates of mRS 0-2 at 90 days between patients with cICA-PO and those with true occlusion undergoing EVT for AIS. The analysis indicated a lower rate of functional independence in the cICA-PO group (OR: 0.35, 95% CI 0.20-0.61, $p <$

0.001). Notably, no heterogeneity was observed among these studies ($I^2 = 0\%$, $p = 0.763$; Figure 1).

Recanalization rate

The meta-analysis of four studies, encompassing 135 patients, evaluated successful recanalization (TICI 2b-3) in EVT-treated patients. The analysis revealed lower rates of recanalization in the cICA-PO group compared to the true carotid occlusion group (OR 0.39, 95% CI 0.20-0.74, $p = 0.004$). No significant heterogeneity was detected among these studies ($I^2 = 45\%$, $p = 0.140$; Figure 2).

Symptomatic Intracranial Hemorrhage (sICH)

In four studies involving 139 patients, rates of sICH were compared between the two groups. cICA-PO patients undergoing EVT exhibited significantly higher rates of sICH compared to those with true carotid occlusions (OR=2.23, 95% CI 1.00-4.95, $p = 0.049$). No heterogeneity was observed among these studies ($I^2 = 0\%$, $p = 0.876$; Figure 3).

Mortality

Four studies involving 135 patients compared mortality rates between the two groups. It was found that cICA-PO patients had a significantly higher mortality rate compared to those with true carotid occlusion (OR 2.62, 95% CI 0.21-7.24), with no heterogeneity noted among these studies ($I^2 = 0\%$, $p = 0.001$; Figure 4).

DISCUSSION

Our systematic review and meta-analysis included 4 studies with a total of 259 patients, and our results indicated that EVT in AIS patients with cICA-PO had lower rates of successful recanalization and favorable functional outcome (mRS 0-2 at 90 days) as compared with AIS patients with true cICA occlusion. Furthermore, EVT in AIS patients with cICA-PO were found to have higher risks of sICH and mortality as compared to AIS patients with true cICA occlusion. These results were consistent with the results of the studies by Jang et al. (5) and Ni et al. (2) which have larger sample sizes than the rest of the included studies (6, 7).

The phenomenon of cICA-PO refers to the presence of unopacified column of blood in the cICA that might be perceived as extracranial ICA obstruction, while it is in fact an isolated intracranial ICA occlusion causing stagnation of blood in the patent extracranial portion of the ICA (8, 9). Pseudo-occlusion and true occlusion are two different conditions that may only share the common imaging finding of lack of ICA filling. It is very difficult to differentiate with absolute certainty cICA-PO from true occlusion of the cICA on CT angiography (1). This imposes a crucial challenge in clinical practice from both decision-making and technical standpoints. In terms of decision-making, AIS patients with cICA-PO presenting in the late window of EVT might be deemed not to be good candidates for EVT given the falsely overestimated time needed to overcome the perceived extracranial cICA occlusion. From the technical standpoint, differentiating PO from true occlusion of the extracranial ICA might influence the choice of the EVT material including guiding sheaths, percutaneous transluminal angioplasty balloons, and distal access catheters (1).

The lower rate of successful recanalization in cICA-PO patients as compared with true cICA occlusion is likely due to the heavier clot burden in case of cICA-PO (2, 10, 11), and lower rates

of successful recanalization are associated with lower rates of favorable functional outcome (mRS 0-2) and mortality (12). Furthermore, the heavier clot burden with large clots in the distal ICA segment in cICA-PO might be associated with poor filling of the collateral circulation (10) which is known to be associated with higher rates of poor functional outcomes (13, 14). Therefore, it is pivotal to optimize the vascular imaging modalities to enable differentiation between cICA-PO and true ICA occlusion in acute settings, which will allow for better decision-making and tailored preparation for EVT procedure according to the actual level of the ICA occlusion. Moreover, these findings indicate the need for further investigation into the underlying causes of these deficient outcomes.

According to the literature, ICA-PO can also be compared to distal ICA due to their similar disease process and imaging presentations. However, certain imaging characteristics may suggest pseudo-occlusion on CTA, such as an ipsilateral occluded intracranial ICA bifurcation (carotid T-occlusion) and good contrast filling of the carotid bulb followed by a gradual contrast decay. Furthermore, the imaging presentation of isolated distal ICA occlusion demonstrates patency of the cervical ICA carotid terminus. The results between these two groups indicated that cICA-PO is also associated with poorer outcomes. (1, 8, 15, 16).

Table 1. Demographics and baseline characteristics of patients with carotid pseudo-occlusion and true occlusion in the setting of acute ischemic stroke.

Study	Criteria	No. of px per group			Age mean±SD or median (IQR).			Sex %			Tandem occlusions %			Etiology %			Comorbidities %			IVT%			NIHSS 1		
		Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Duijsens et. al 2015	Group 1. cICA-PO Group 2. cICA-TO	6	10		61.8 (38-84)			M 43.8			100%	100%								50	90		15 (11-17)	14 (3-22)	
Jang et, al 2022	Group 1.cICA-PO Group 2.cICA-TO Group 3.dICA-O	32	14	21	72.8			M 53.7			6.30%	71.40%		Cardioembolic 81.3 Atheroembolic 6.3	Cardioembolic 21.4 Atheroembolic.3	Cardioembolic 71.4 Atheroembolic9.5	A-fib 46.9 HTN 78.1 DM 1134.4 HLD 56.3 Previous stroke 28.1 OAC 12.5 APT 37.5 Smoker 6.3	A-fib 14.3 HTN 78.6 DM II 14.3 HLD 35.7 Previous stroke 14.3 OAC 0 APT 35.7 Smoker 71.4	A-fib 42.9 HTN 57.1 DM II 28.6 HLD 42.9 Previous stroke 23.8 OAC 28.6 APT 33.3 Smoker 4.8	31.3	35.7	38.1	16 (12-21)	11 (7.5-13.5)	13 (10.5-15.5)
Ni et al, 2023	Group 1.cICA-PO Group 2. cICA-TO	79	67		72 (11.6)	65 (12.4)		F 53.2	F 5.4		68.70%	81.00%	5%	Cardiomebolic 72.1 Atherosclerosis 24.1 Dissection 3.8	Cardiomebolic 32.8 Atherosclerosis 72.1 Dissection 9		A-fib 53.2 HTN 68.4 DM II 22.8 HLD 6.3 Previous stroke 15.2 Smoker 20.3 CAD 20.3	A-fib 23.9 HTN 56.7 DM II 26.9 HLD 13.4 Previous stroke 17.9 Smoker 20.3 CAD 16.4		34.2	32.8		19 (13-24)	15 (11-21)	
Choi et al, 2020	Group 1. cICA-PO Group 2. cICA-TO	18	12		76.5 (73.0-84.0)	74.5 (66.5-81.5)		M 40	M 30		Present (% not defined)	Present (% not defined)		Cardiomebolic 2.2 Atherosclerosis 16.7 Others 11	Cardiomebolic 25 Atherosclerosis 75 Others 0										

cICA-PO cervical internal carotid pseudo-occlusion; cICA-TO, cervical internal carotid true occlusion; dICA-O, distal internal carotid occlusion QR, interquartile range; IVT, intravenous thrombolysis; SD, standard deviation; M, male; F, female; HLD, hyperlipidemia; OAC, oral anticoagulant; APT antiplatelet.

Strengths and Limitations

Our meta-analysis provides a larger sample of patients to provide a comprehensive analysis of all published literature regarding the outcomes of EVT in cICA-PO patients in the setting of AIS. However, our study has a few limitations. First, a low number of studies met our inclusion criteria. Second, all of the studies were a retrospective design and some of the studies had small sample sizes. Therefore, this meta-analysis may contain insufficient data to allow generalization. Furthermore, access to individual patient data was not available, which resulted in restrictions on the level of analysis that could be performed. Lastly, it is to be noted that the included studies in our meta-analysis collected patients with and without tandem occlusions which might influence the results of the comparison. For instance, the studies by Jang et al. (5) and Ni et al. (2) reported higher percentages of tandem occlusions within the true ICA occlusion patients as compared with the cICA-PO patients. This is a pivotal point to be taken into consideration given that the EVT outcomes might be better in tandem occlusion patients than in isolated carotid occlusion patients from both successful recanalization and functional independence standpoints (17).

Conclusion

Patients undergoing EVT for AIS with cICA-PO have poor outcomes. This is most likely due to heavy clot burden and poor recanalization rates that lead to lower favorable functional outcomes and greater rates of mortality and sICH. The accurate and timely diagnosis of cICA-PO from true carotid occlusions is crucial as it influences the treatment and possess a worse prognosis than true occlusion. We recommend further research should be conducted with precise definitions regarding the presence of tandem lesions as they may affect the outcomes. In

addition, studies should be conducted to identify underlying causes of these poor outcomes and improve management guidelines in such settings.

Ethics approval

Ethics approval was not required for this study.

Informed consent

Informed consent was not required for this study.

Funding

None.

ACKNOWLEDGMENTS

None.

Figure legends

Figure 1. PRISMA Flowchart Detailing the Literature Review Process.

Figure 2. Forest Plot of Rates of Functional Independence.

Figure 3. Forest Plot of Rates of Successful Recanalization.

Figure 4. Forest Plot of Rates of sICH.

Figure 5. Forest Plot of Rates of Mortality

Supplementary Materials Legends:

Supplementary Figure 1. Overall Risk of Bias

Supplementary Figure 2. Risk of Bias Domains

Figure 2. Forest Plot of Rates of Functional Independence

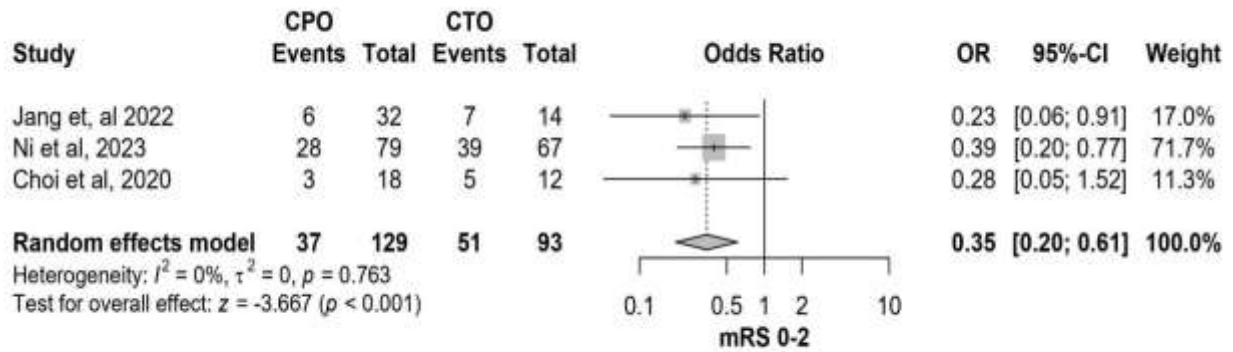


Figure 3. Forest Plot of Rates of Successful Recanalization

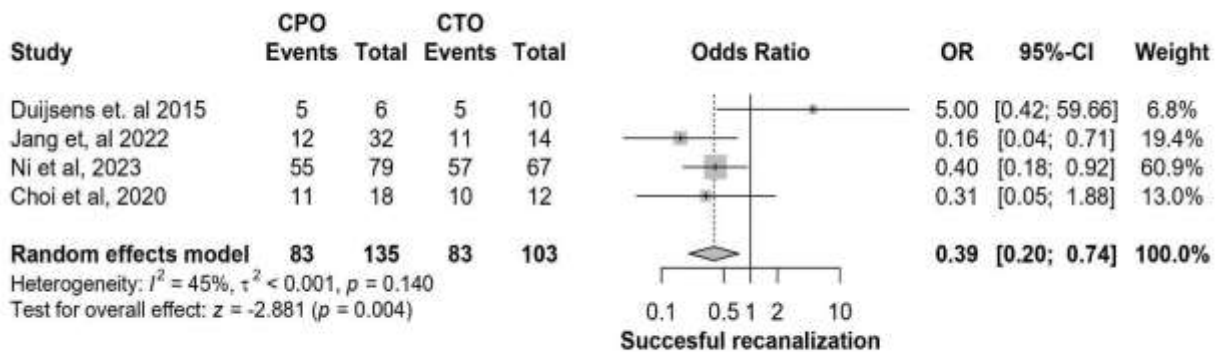


Figure 4. Forest Plot of Rates of sICH

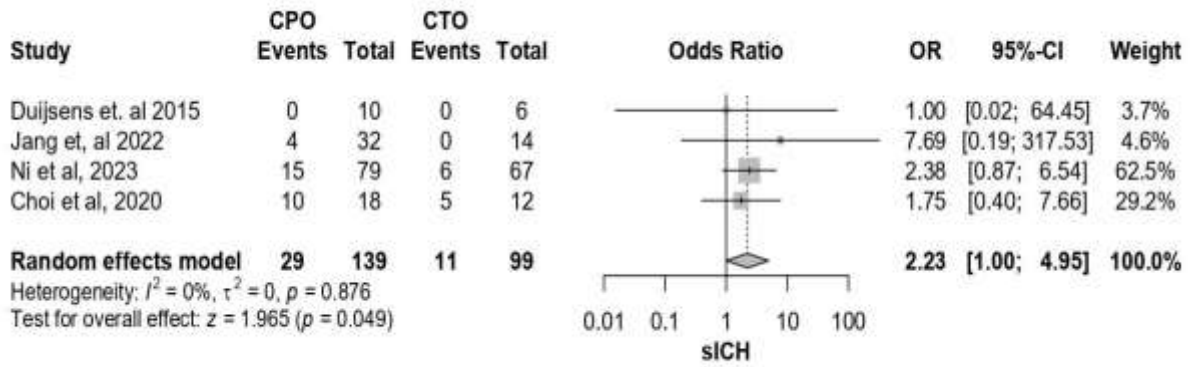
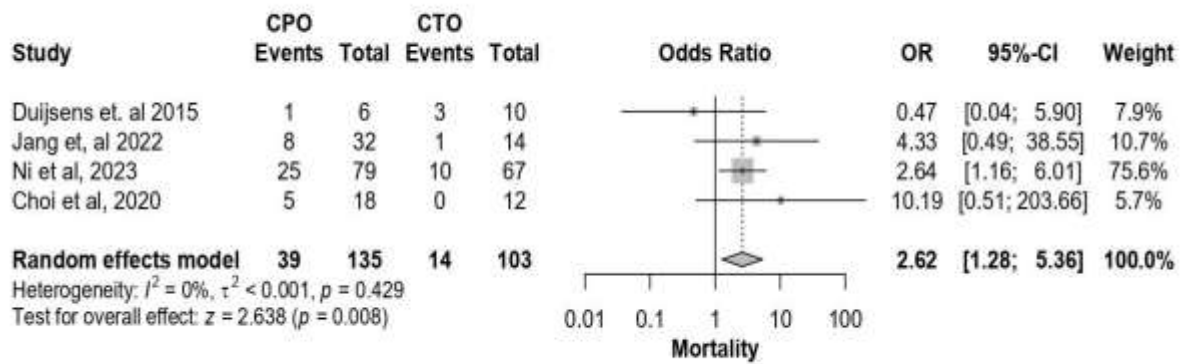


Figure 5. Forest Plot of Rates of Mortality



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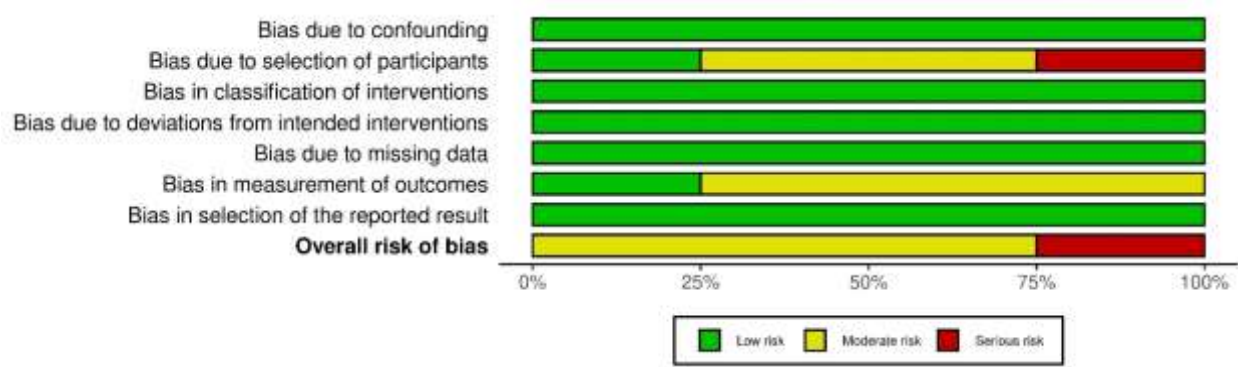
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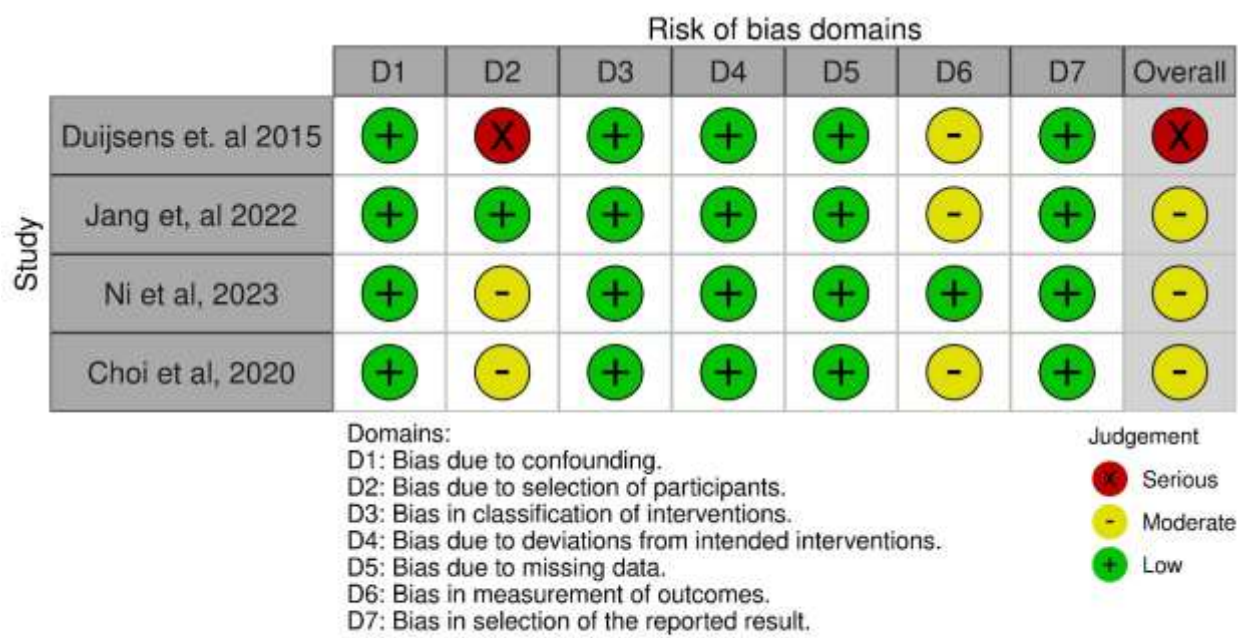
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SUPPLEMENTAL FILES

Supplementary Figure 1. Overall Risk of Bias



Supplementary Figure 2. Risk of Bias Domains



Detailed search strategy

Embase

1974 to present. (carotid and (pseudo-occlusion or pseudoocclusion) and stroke).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 75.

Web of Science Search Strategy (v0.1)

Database: All Databases

Entitlements:

- WOS: 1900 to 2023
- BCI: 1969 to 2023
- CCC: 1998 to 2023
- DRCI: 1993 to 2023
- DIIDW: 1993 to 2023
- KJD: 1980 to 2023
- MEDLINE: 1950 to 2023
- PPRN: 1991 to 2023
- PQDT: 1637 to 2023
- SCIELO: 2002 to 2023
- ZOOREC: 1993 to 2023

Searches: (carotid) AND (pseudo-occlusion OR pseudoocclusion) AND (stroke) (Topic) and Preprint Citation Index (Exclude – Database)

Date Run: Tue Nov 28 2023 15:34:44 GMT-0600 (Central Standard Time)

Results: 115

Scopus

Advanced search

ITL-ABS-KEY((carotid) AND (pseudo-occlusion OR pseudo-occlusion) AND (stroke))

PubMed

("carotid") AND (pseudo-occlusion OR pseudoocclusion) AND (stroke)