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SYSTEMATIC REVIEW AND META-ANALYSIS

Acute Carotid Artery Stenting Versus Balloon Angioplasty for Tandem Occlusions: A Systematic Review and Meta-Analysis

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BACKGROUND: Despite thrombectomy having become the standard of care for large-vessel occlusion strokes, acute endovascular management in tandem occlusions, especially of the cervical internal carotid artery lesion, remains uncertain. We aimed to compare efficacy and safety of acute carotid artery stenting to balloon angioplasty alone on treating the cervical lesion in tandem occlusions. Similarly, we aimed to explore those outcomes' associations with technique approaches and use of thrombolysis.

METHODS AND RESULTS: We performed a systematic review and meta-analysis to compare functional outcomes (modified Rankin Scale), reperfusion, and symptomatic intracranial hemorrhage and 3-month mortality. We explored the association of first approach (anterograde/retrograde) and use of thrombolysis with those outcomes as well. Two independent reviewers performed the screening, data extraction, and quality assessment. A random-effects model was used for analysis. Thirty-four studies were included in our systematic review and 9 in the meta-analysis. Acute carotid artery stenting was associated with higher odds of modified Rankin Scale score ≤2 (odds ratio [OR], 1.95 [95% CI, 1.24–3.05]) and successful reperfusion (OR, 1.89 [95% CI, 1.26–2.83]), with no differences in mortality or symptomatic intracranial hemorrhage rates. Moreover, a retrograde approach was significantly associated with modified Rankin Scale score ≤2 (OR, 1.72 [95% CI, 1.05–2.83]), and no differences were found on thrombolysis status.

CONCLUSIONS: Carotid artery stenting and a retrograde approach had higher odds of successful reperfusion and good functional outcomes at 3 months than balloon angioplasty and an anterograde approach, respectively, in patients with tandem occlusions. A randomized controlled trial comparing these techniques with structured antithrombotic regimens and safety outcomes will offer definitive guidance in the optimal management of this complex disease.

Key Words: carotid artery ■ carotid occlusive disease ■ intervention ■ reperfusion ■ stroke

Tandem occlusions (TOs) involve high-grade stenosis or occlusion of the cervical internal carotid artery (ICA) and concomitant intracranial large-vessel occlusion. These lesions represent 10% to 20% of all strokes,[1] and are associated with poor prognosis, severe disability, and mortality when left untreated.[2] Acute TOs have shown poor response to intravenous thrombolysis (IVT), with recanalization rates <10%.[3] A subgroup analysis of the Highly Effective Reperfusion Using Multiple Endovascular Devices meta-analysis found mechanical thrombectomy (MT) may be beneficial for LVOs resulting from TOs. However, there was

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CLINICAL PERSPECTIVE

What Is New?

- Cervical carotid stenting is found to be an effective treatment for tandem occlusions, showing better functional outcomes and reperfusion rates when compared with balloon angioplasty.
- Performing mechanical thrombectomy before cervical recanalization was observed to be the most effective approach (retrograde approach).
- Moreover, intravenous thrombolysis in patients receiving cervical carotid stenting was observed to be safe, without an increased risk of symptomatic intracranial hemorrhage.

What Are the Clinical Implications?

- Acute cervical carotid stenting after cerebral reperfusion is a reasonable therapeutic option for patients with intracranial large-vessel occlusion and concomitant cervical tandem occlusions.
- A multicenter randomized clinical trial is the natural next step to achieve a standard of care paradigm.

Nonstandard Abbreviations and Acronyms

BA	balloon angioplasty
CAS	carotid artery stenting
ICA	internal carotid artery
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
MT	mechanical thrombectomy
sICH	symptomatic intracranial hemorrhage
TO	tandem occlusion

a paucity of data in regard to the management of the concomitant cervical lesion.[4]

Endovascular management of TOs widely varies according to clinical and technical considerations and proceduralist's preference.[5] Revascularization of the cervical lesion could be performed in an acute or a deferred manner. When performed acutely, carotid artery stenting (CAS)±balloon angioplasty (BA) is a definitive treatment strategy, performed before or following intracranial MT. Acute BA, suction aspiration of the cervical segment, or MT alone implicate a deferred treatment with endarterectomy or stenting in the following days or weeks. Each treatment carries potential risks that are taken into consideration when selecting the best treatment method. For instance, acute CAS involves the risk of symptomatic intracranial hemorrhage (sICH) associated with antithrombotic use in freshly reperfused brain tissue and stent thrombosis.[6,7] In contrast, deferred cervical revascularization can be done in a more planned and secure setting.[8] Although it avoids the immediate need for antithrombotics and potential sICH risk,[5] it carries the risk of stroke recurrence and/or progression.[9]

Recent studies suggest a benefit in functional outcomes and reperfusion rates when CAS and MT are performed emergently, without increased rates of sICH.[10–12] Moreover, Anadani et al found IVT was not associated with an increased risk of hemorrhagic transformation.[11] Nevertheless, data from randomized controlled trials on optimal management, procedural features, and safety outcomes are still missing, and all the above-mentioned approaches are used in clinical practice.[5]

We aimed to compare the efficacy and safety of CAS±angioplasty with BA alone of the cervical ICA in treating TOs through an aggregated data meta-analysis of the recent literature. Additionally, we aimed to explore the association of the technique approaches (anterograde and retrograde) with the functional and safety outcomes and IVT with sICH.

METHODS

Search Strategy and Selection Criteria

This systematic review and meta-analysis follows the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* guidelines. We executed a comprehensive literature search using a combination of Medical Subject Headings terms and free text for the concepts of "tandem occlusion," "thrombectomy," "stent," "acute stroke," and "carotid artery disease" in the MEDLINE database, Embase, and the Web of Science from January 2015 through May 2020. We included studies from 2015 that included the randomized controlled trials supporting the benefit of MT as the standard treatment for acute large-vessel occlusionstarted at that time. Complete search strategy is detailed in Data S1.

We searched for studies assessing patients presenting with acute high-grade stenosis (70%–99%) or occlusion of the cervical ICA with ipsilateral occlusion of the distal ICA and/or middle cerebral artery treated with MT and endovascular treatment of the extracranial ICA (CAS and/or BA). Inclusion criteria were randomized controlled trials, cohort and cross-sectional studies, case series with ≥10 patients, and case-control studies reporting clinical outcomes (modified Rankin Scale [mRS] scores), complications (sICH, embolization, and death), and reperfusion rates. We only included publications with full text in English. We excluded animal models, protocols, reviews, studies with <10 patients, case reports, and other meta-analyses. When we encountered studies with multiple reports

from the same patient cohort, we kept the report with the higher number of patients and longer follow-up times. Furthermore, we searched the references of all the included studies to find additional studies.

Two independent reviewers initially screened all identified records by reading all titles/abstracts using a free online application for systematic reviews (https://rayyan.qcri.org/). Then, potentially relevant articles were reviewed as full text. The reviewers performed data extraction from these studies and cross-checked the extracted data. Disagreements in any of these steps were resolved after discussion or with a third senior reviewer when needed.

Identified studies from the literature search were then further evaluated for inclusion in the meta-analysis. For the main meta-analysis on the best cervical technique, we only included studies with complete data that compared our outcomes of interest between acute CAS±BA and BA alone. Similarly, for best order of treatment we included studies with acute CAS that compared the outcomes between anterograde and retrograde approaches. Finally, for evaluating the association of IVT status with sICH, we included studies with acute CAS with both IVT groups.

Baseline Data and Outcome Variables

From each study, we collected demographic information, including number of participants, age, sex, race and ethnicity, comorbidities (hypertension, atrial fibrillation, dyslipidemia, diabetes, coronary artery disease, ICA stenosis), smoking status, initial assessment at presentation, use of IVT, stroke workflow metrics (onset to arrival, onset to puncture, onset to revascularization, and puncture to revascularization), location of the intracranial occlusion, type of endovascular interventions, number of patients undergoing each type of treatment, first endovascular approach (anterograde when proximal ICA occlusion was treated first and retrograde when intracranial occlusion was treated first), devices used (stent and balloon type, embolic protection device), concurrent medications (tissue-type plasminogen activator, anticoagulants, and antiplatelets), procedure-related complications (new stroke, hemorrhage, hemodynamic impairment, acute stent thrombosis), technical success rates of carotid revascularization, and outcome variables. We separately extracted data of interest about the TO revascularization approach and technique including revascularization order in patients undergoing CAS (anterograde versus retrograde), patients with stenting, and patients with angioplasty only as available.

The primary outcome was functional outcomes scored by mRS at 90 days. We dichotomized the results as good (0–2) and poor (3–6) outcomes. Secondary efficacy outcomes included reperfusion status assessed by the modified Thrombolysis in Cerebral Infarction grading system. Safety outcomes included sICH as defined by each study and mortality at 90 days.

Study Quality and Risk of Bias Assessment

We evaluated the quality of the studies using tools according to the study's design. For cohorts with control groups, we used the risk of bias in nonrandomized studies of interventions tool,[13] with the overall risk of bias rated as low, moderate, serious, and critical. Single-arm cohorts were evaluated using the National Institutes of Health quality assessment tool for before–after (pre–post) studies with no control group,[14] with the overall risk of bias rated as good, fair, and poor.

Statistical Analysis

A revised Cochrane risk of bias in randomized trials tool[15] was used for randomized controlled trials with the overall risk of bias rated as low, some concerns, and high risk.

We used a random-effects model (Mantel-Haenszel method) for combining cumulative event rates to account for heterogeneity (I^2) between studies to directly compare the efficacy and safety outcomes between CAS and BA alone. Summary effect measures (odds ratios [ORs]) were calculated using data extracted from primary studies and were compared using 95% CIs and prediction intervals. Similarly, we compared the same outcomes after classifying the patients undergoing CAS by first endovascular approach (anterograde versus retrograde) and IVT status (received or not).

Finally, we evaluated the heterogeneity between studies with visual assessment of forest plots, as well as χ^2 test. We defined important interstudy heterogeneity as an I^2 test result of >50% and a χ^2 test result of <0.1. Analysis was conducted using Review Manager 5.[16] Publication bias was graphically assessed by funnel plot inspection and analyzed by Egger test conducted in R software (R Foundation for Statistical Computing) for Windows version 3.5.2.

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

RESULTS

Literature Search and Study Selection

We initially identified 1404 articles through database searching, and 1105 records were screened after duplicates were removed, of which 59 full texts were assessed for eligibility. Twenty-five studies were excluded, 18 of them reported different endovascular

approaches or techniques for treating the cervical ICA grouped (CAS, BA, flow diversion, no CAS, or no acute treatment), 3 analyzed MT of TOs without cervical revascularization, 2 had different outcomes of interest, and 2 grouped TOs and isolated ICA. Finally, 34 studies including 3014 patients with TOs (2482 CAS and 245 BA) were included in our systematic review (Table S1), and 9 were included in our meta-analysis assessing the best endovascular technique for TOs. Screening and selection of studies are detailed in the flow diagram (Figure 1).

Studies included in the review contained the primary outcome and at least 1 of the other outcomes of interest. Thirty-three studies were retrospective cohort studies (22 single-center and 11 multicenter), and 1 was a single-center pilot randomized controlled trial study.[17] Of the 33 cohort studies, 17 were from prospectively collected databases. Fifteen studies evaluated outcomes of CAS±BA,[7,10–12,18–28] and 1 evaluated BA-alone outcomes without comparison groups.[8] Two studies compared CAS in TOs to isolated proximal ICA stenosis,[6,29] 2 compared CAS in TOs with MT in isolated LVOs,[30,31] 3 compared CAS with other endovascular techniques combined in TOs,[32–34] 1 compared CAS with carotid endarterectomy,[35] and 9 compared CAS to BA.[9,36–43]

Characteristics of the studies included in the systematic review are summarized in Table S1. Studies were heterogenous on type of intervention, use of embolic protection device (6/34), antiplatelet regimen, information on concurrent management (heparin and antiplatelets), definition of sICH and any intracranial hemorrhage (8/34), and outcome evaluations (15/34 evaluated in stent thrombosis or reocclusion). The type of endovascular approach was reported in most of the studies, but only 4 studies explored the best first approach (anterograde versus retrograde) and compared our outcomes of interest between both groups. Antiplatelet therapy was inconsistently reported in the included studies, and only 4 studies of patients undergoing CAS reported sICH rates in patients with and without IV tissue-type plasminogen activator use.

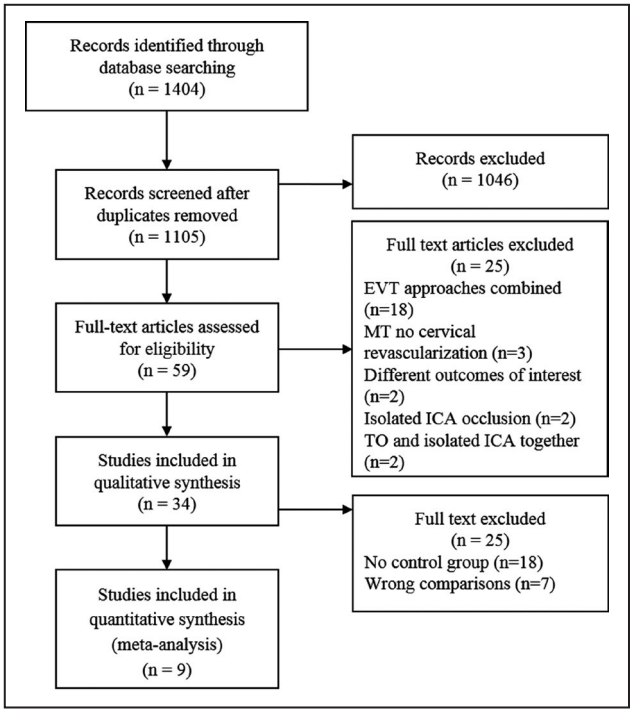

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.
EVT indicates endovascular therapy; ICA, internal carotid artery; MT, mechanical thrombectomy; and TO, tandem occlusion.

Qualitative Analysis

Of the 20 retrospective studies with control groups included in the systematic review and meta-analysis assessed by the risk of bias in nonrandomized studies of interventions tool, 11 studies had moderate overall risk of bias assessments, and 9 had serious overall risk of bias assessments (Figure S1A). When the bias was assessed per domain, 6 studies had serious risk because of missing data at the 3-month follow-up, 6 had serious risk of confounding bias, and 1 had risk because of the classification of the interventions. Only 1 study[42] mentioned a blinded assessment of mRS score at follow-up (Figure S1B).

Studies with no comparison group assessed by the pre–post tool were of variable quality rating, most of them were rated fair (10/14) to good (3/14), but 1 was rated poor[27] because of unclear objectives and inclusion criteria, not including all the eligible participants, small sample size, and loss at follow-up (Table S2). The randomized pilot trial by Poppe et al had some concerns of bias because of deviation from the intended intervention and in the measurement of the outcome (Table S3).

Meta-Analysis of Included Studies

For assessing the best endovascular technique, we included 9 studies in the meta-analysis of the primary outcome. Stenting was associated with favorable mRS scores at 3 months (OR, 1.95 [95% CI, 1.24–3.05]) (Figure 2A).[9,36–43] The 95% prediction interval, however, ranged from 0.69 to 5.48, indicating some uncertainty with the treatment effect of CAS on functional outcome. No significant heterogeneity between studies was found for this outcome (I^2=31.0%, χ^2=11.65, P=0.17). Eight studies were included in the meta-analysis of the reperfusion outcome; CAS was associated with higher odds of Thrombolysis in Cerebral Infarction grade 2b-3 (OR, 1.89 [95% CI, 1.26–2.83]), with no significant heterogeneity between studies (I^2=30.0%, χ^2=10.01, P=0.19), although the 95% prediction interval ranged from 0.55 to 6.66 (Figure 2B).[9,36–38,40–43] There were

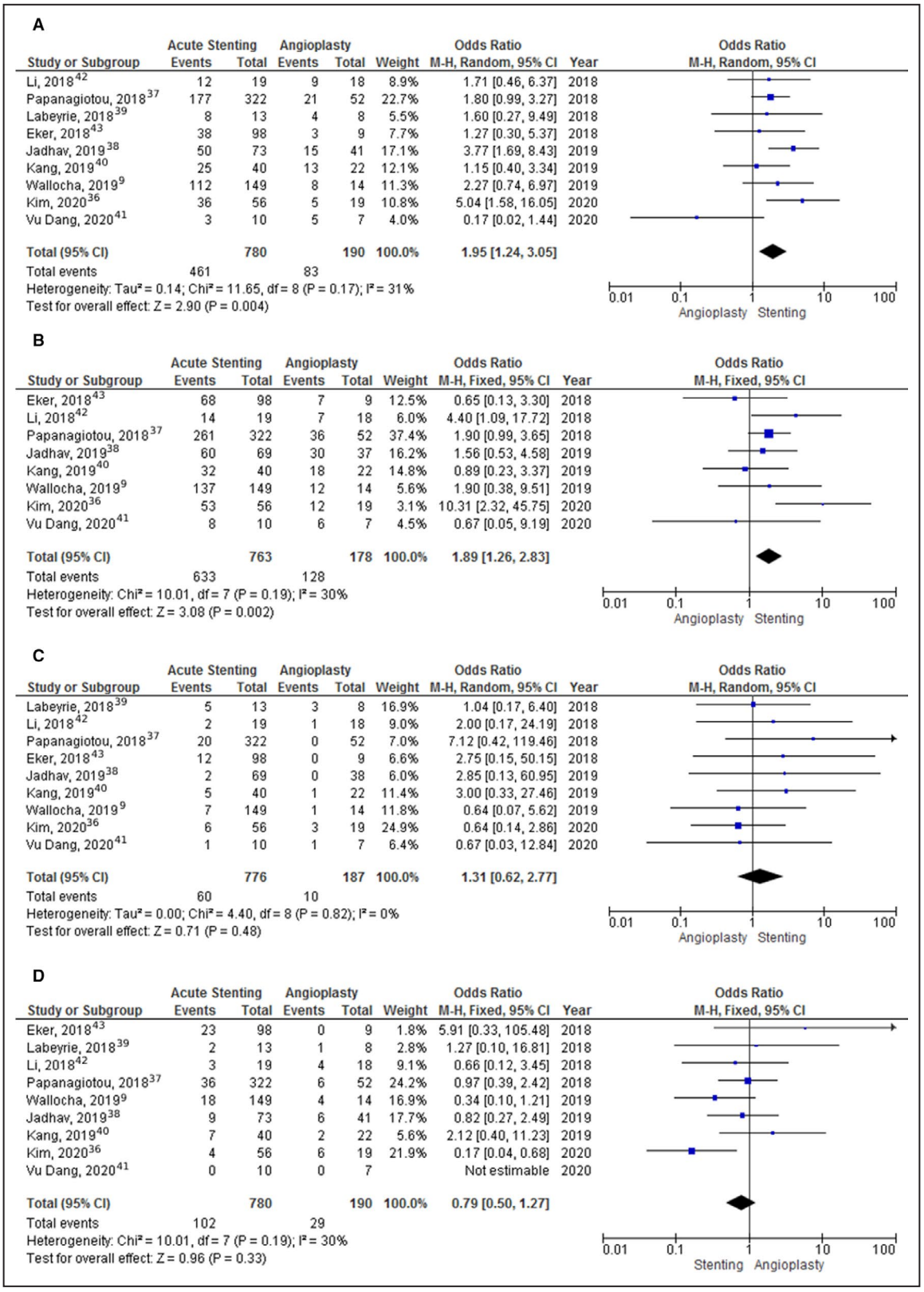

Figure 2. Meta-analysis of (A) good functional outcome at 90 days (modified Rankin Scale score of 0–2), (B) good reperfusion status Thrombolysis in Cerebral Infarction grade 2b-3, (C) symptomatic intracranial hemorrhage, and (D) mortality in patients with acute stenting vs balloon angioplasty.
M-H indicates Mantel-Haenszel.

no statistically significant differences in mortality at 3 months (OR, 0.79 [95% CI, 0.50–1.27]) or sICH (OR, 1.31 [95% CI, 0.62–2.77]), although the direction of the association suggested lower odds of death and higher odds of sICH with stenting (Figure 2C and 2D).[9,36–43]

A total of 4 studies provided data to compare safety and efficacy outcomes based on anterograde and retrograde approaches.[12,22,25,40] The meta-analysis of the primary outcome showed the retrograde approach was associated with higher odds of favorable mRS scores at 3 months (OR, 1.72 [95% CI, 1.05–2.83]) with no heterogeneity (I^2=0%, χ^2=0.79, P=0.85) and Thrombolysis in Cerebral Infarction grade 2b-3 (OR, 3.18 [95% CI, 1.50–6.74]) with no significant heterogeneity (I^2=18%, χ^2=3.66, P=0.30). There were no statistically significant differences on mortality at 3 months (OR, 0.84 [95% CI, 0.40–1.77]) or sICH (OR, 0.81 [95% CI, 0.29–2.33]) between approaches (Figure 3A through 3D).[12,22,25,40]

A total of 4 studies provided data for comparing our safety outcome in patients treated with CAS, MT, and IV tissue-type plasminogen activator to patients treated with CAS and MT alone.[10,11,19,23] The meta-analysis showed no statistically significant difference in the rates of sICH between both groups (OR, 0.66 [95% CI, 0.19–2.30]) (Figure S2).

No evidence of publication bias was found by inspecting the funnel plots and Egger test in most of the outcomes, except for the comparison on successful reperfusion stratified by the best first approach, which demonstrated a significant asymmetry by Egger test (P=0.02) (Figures S3 through S5).

DISCUSSION

This systematic review and meta-analysis demonstrates that acute cervical CAS in patients presenting with TOs is effective and safe in the setting of MT. Patients treated with CAS have significantly better reperfusion rates and 3-month functional outcomes, without a significant increase in the rates of sICH or mortality. A retrograde approach might have better functional outcomes and reperfusion rates as well. Finally, receiving IVT does not increase the sICH rates in patients who undergo CAS.

Our meta-analysis attempted to address a common and controversial matter during the endovascular treatment of the proximal ICA in TOs.[44] As previously shown by our published international survey, emergent CAS±angioplasty and BA with local aspiration seem to be equally preferred techniques (41% versus 38%).[5] Certainly, both CAS and BA have advantages and risks to consider when facing a TO. Because of the wide variety of factors to weigh, proceduralists currently retain full discretion over individual case technique selections, which leads to wide practice variability.[45] CAS seems more effective in treating the cervical ICA lesion and directly treating the cause of the stroke when atherosclerotic plaques or dissections are the culprits. Thus, it decreases the risk of stroke recurrence immediately[9] while improving cerebral reperfusion, clot lysis, or even allowing spontaneous intracranial reperfusion,[22,24,46] at the expenses of a potential risk for acute stent thrombosis and the need for early antithrombotic therapy.[47] On the other hand, BA may prevent futile stenting in patients with poor outcomes[8] and the need of antithrombotics, but with the shortcoming of a potential risk of thrombus formation and stroke recurrence.[37,48,49] In our analysis, CAS demonstrated an association with better functional outcomes at 3 months, and despite the concerns about increased risk of sICH in association with CAS, we did not find an increase in its rates or mortality. Similarly, our results showed no statistical difference in sICH rates between patients undergoing CAS with and without IVT. Our results are in agreement with previous TITAN (Thrombectomy In Tandem Lesion) study reports of hemorrhagic transformation and support a more aggressive treatment using acute stenting with dual antithrombotic regimen.[37,50]

Initial studies reported pooled data of patients with TOs treated with MT±CAS and compared the recanalization rates and functional and safety outcomes with outcomes from patients with isolated intracranial large-vessel occlusiontreated with MT, which confirmed the benefit of MT in TOs, as previously published in the Goyal et al collaboration.[4,28,51,52] Other meta-analyses compared patients undergoing CAS with patients with no stenting, including in the latter several modalities angioplasty±aspiration, suction alone, flow diversion, and clot wire-disruption as treatment modalities.[1,53] For instance, Dufort et al combined multiple cervical treatment regimens (BA, aspiration, and CAS) and patients with no acute treatment in the nonstenting cohort. Despite this heterogeneity, they found similar results to ours, favoring CAS over no stenting in regard to functional independence (OR, 1.43 [95% CI, 1.07–1.91]); however, BA effect size could not be evaluated separately.[53] Interestingly, the Wilson et al meta-analysis compared CAS with BA, but they found no differences in efficacy and safety outcomes. The discrepancy with our study might be explained by the fact that they did not incorporate 2 recent studies, 1 of them a large single-center cohort of 163 patients that showed early neurological improvements in their CAS group.[9] Furthermore, they included noncomparative retrospective studies that only assessed 1 of the techniques without comparison groups (13 CAS and 3 BA studies), which might have introduced additional heterogeneity (I^2 ≥50% for each technique and functional outcome).[51] In our meta-analysis, we exclusively included studies that defined the endovascular revascularization procedures performed in the proximal ICA (CAS or BA) and compared both techniques on our outcomes of

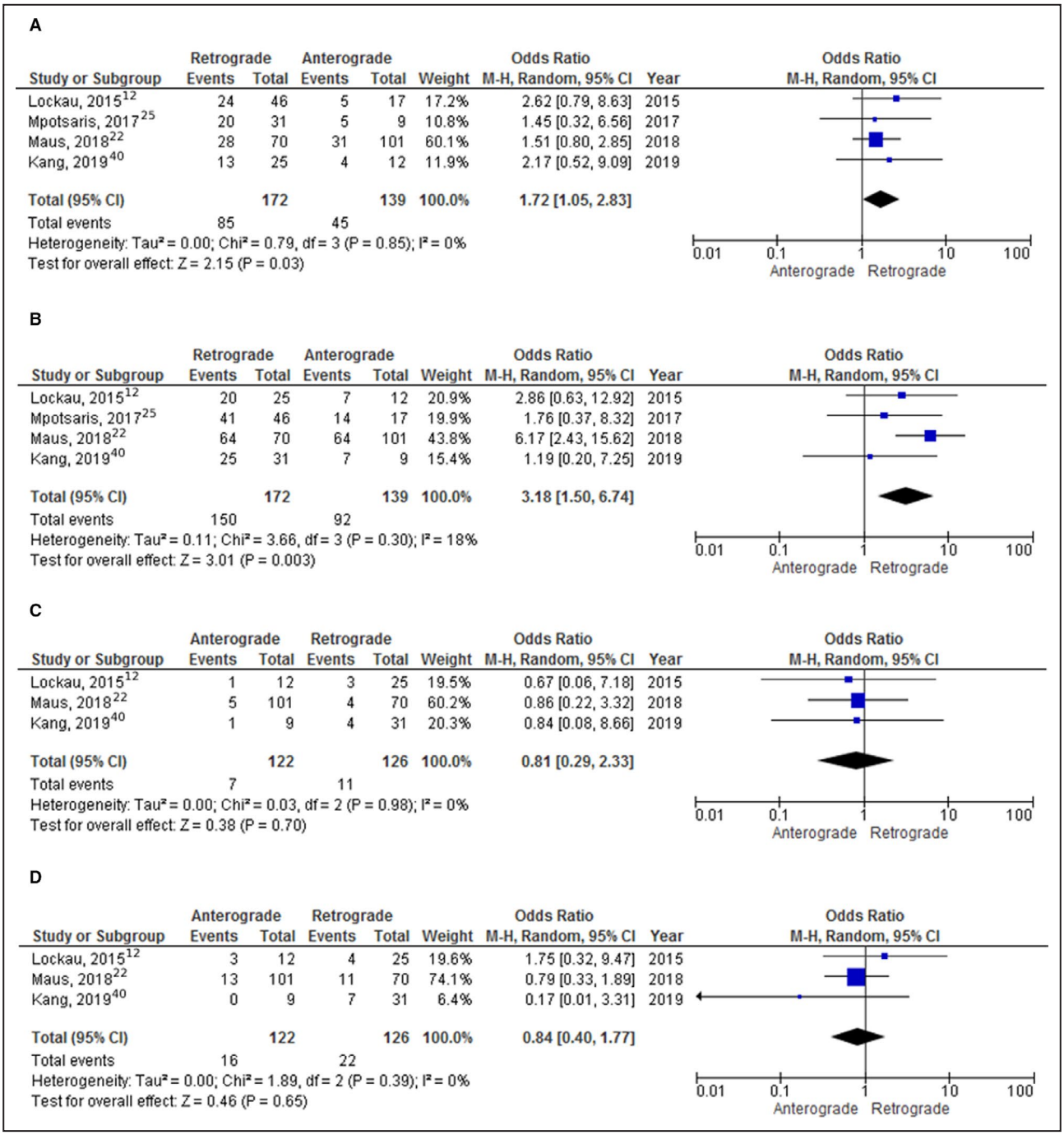

Figure 3. Meta-analysis of (A) functional outcome at 90 days (modified Rankin Scale score of 0–2), (B) good reperfusion status Thrombolysis in Cerebral Infarction grade 2b-3, (C) symptomatic intracranial hemorrhage, and (D) mortality in patients with an anterograde vs retrograde approach.
M-H indicates Mantel-Haenszel.

interest. Similarly, the studies defined the degree of ICA stenosis (70%–99%) in their methodology, all of these to decrease heterogeneity. More importantly and considering that MT became the standard of care in 2015, our meta-analysis comprises all large recent studies to account for the expected acquired improvement in endovascular treatment techniques over time that might have favored outcomes for CAS.

The order in which the cervical and intracranial lesions should be treated has been under investigation because of the various reasons for preferring one approach over the other.[12,54] Favorable outcomes in the retrograde approach might relate to faster reperfusion times of the intracranial LVO. Additionally, it involves a decreased risk of distal embolization and hemodynamic instability. Yet the steno-occlusive lesion may be difficult to access

intracranially and restrict technical success of the intracranial MT. Our meta-analysis is the first to demonstrate an association of the retrograde approach with good functional outcomes and successful reperfusion in patients undergoing CAS. Previously, Wilson et al reported no statistical differences between the approaches; however, their approach groups included studies with BA, aspiration, or CAS as neck recanalization techniques and were not directly comparing each technique, resulting in significant heterogeneity (I^2=63%).[51] We included 4 studies of only patients undergoing CAS in evaluating this subject and reported revascularization rates and good functional outcome.[12,22,25,40] Despite our significant results, it is important to recognized that many confounders play a role in the outcomes of interest, such as infarct core, collateral vasculature, time to reperfusion, and grade of stenosis of the proximal ICA, which were not collected in all the aforementioned studies. Maus et al in their international multicenter study found a successful reperfusion rate of 92% in their retrograde cohort; however, the rate of favorable outcome was only 44%.[22]

Our study has several limitations. First, almost all the studies included in our systematic review (33/34) have a retrospective design. Allocation to intervention and concomitant management were decided by treating physicians. Factors that may have influenced both decisions, including premorbid functional state, stroke severity, type of antiplatelet agents used, and cause of stroke were not systematically reported in the included series. Additionally, more patients were treated with CAS than BA alone, which makes the studies heterogeneous and potentially biased. Furthermore, the definition of outcomes and protocols varied across the different studies. We also observed wide PIs when analyzing the primary outcomes. This may have been favored by the small number of studies reflecting some uncertainty about the effects of the techniques. Moreover, they may indicate the existence of settings where stenting has a suboptimal effect. The antithrombotic regimen was not regularly reported in most of the studies. Some multicenter studies even differed between their center's protocols.

All these aspects should be considered when interpreting the results of our analysis. However, our meta-analysis has the strength of comparing acute stenting versus BA only and includes the most recent TO cohorts with severe stenosis ≥70%. We suggest a prospective evaluation of both techniques, and an optimal antithrombotic regimen before and after emergent CAS in the acute stroke setting should be further evaluated.

CONCLUSIONS

Acute CAS of the proximal ICA lesion in TOs is effective and safe. CAS and a retrograde approach have higher odds of successful reperfusion and good functional outcomes at 3 months than BA and an anterograde approach, respectively. CAS seems safe even in patients who received IVT, with no increase of sICH rates. Hence, an aggressive management of TOs should be considered in clinical practice. However, there are still insufficient data about stent patency and antithrombotic therapy that might influence the evaluated outcomes. The limitations of this meta-analysis may pave the way for a definitive, multicenter, high-quality randomized controlled trial evaluating both techniques, where structured antithrombotic regimens and systematically measured efficacy and safety outcomes will provide more guidance in the optimal management of this complex disease.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S3
Figures S1–S5

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS Search strategy

Database: MEDLINE

((((("Carotid Stenosis"[MeSH Terms] AND "Carotid Artery, Internal" [MeSH Terms] OR (internal carotid [Text Word] OR ICA [Text Word]) AND (occlusion [Text Word] OR occluded [Text Word] OR ICAO [Text Word])) AND (acute stroke[MeSH Terms]) OR CVA [Text Word] OR "acute cerebrovascular accident" [MeSH Terms] OR stroke [Text Word] AND (thrombectomy[MeSH Terms]) OR MECHANICAL THROMBECTOMY [Text Word])) AND (stent [MeSH Terms] OR "TANDEM occlusion" [TEXT WORD]))) AND ("2015"[Date - Publication] : "2020"[Date - Publication])

Total: 572 references

Database: EMBASE

('internal carotid artery occlusion'/exp OR 'carotid artery disease'/exp OR 'tandem occlusion') AND ('cerebrovascular accident'/exp OR stroke:ab,ti) AND ('mechanical thrombectomy'/exp OR 'thrombectomy':ab,ti) AND [2015-2020]/py

Total: 699 references

Database: WEB OF SCIENCE

((TS=("carotid artery occlu*" OR "internal carotid*") AND (TS=("acute stroke" or "cerebrovascular accident")) AND (TS=("mechanical thrombectomy" OR "stent" or "thrombectomy")))) AND DOCUMENT TYPES: (Article OR Review) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2015-2020

Total: 133 references

Table S1. Characteristics of the studies included in the systematic review.

Study ID	Design	Primary outcomes	N	Interventions	Endovascular approach	IV tpA	FU (%)	Antithrombotic regimen	Additional outcomes
Yilmaz, 2017, Germany	Retrosp, SC	SICH (ECASS II within 24h) mRS-DC	47	aCAS (n=47) DLS (20), SLS (27)	Antero	51 %	72h	Previous APT (-): 500mg IV ASA before stent. CPD at discretion.	Stent patency (by US): TF 37% SLS, 50% DLS.
Pfaff, 2019, MN (Europe)	Retrosp, MC (7)	SICH (ECASS II/III) mRS-DC. TICI	160	aCAS (n=160) DLS	Antero (73.1%) Retro (26.9%)	61 %	72h	Post procedural: ASA alone/ ASA+ CPD or ticagrelor.	Acute TF (20.6%) and occlusion at 72h and previous APT.
Maus, 2017, MN	Retrosp, MC (4), PCDB	SICH (≥4pts) mRS-DC - 90d. TICI	197	aCAS (n=197)	Antero (55.3%) Retro (44.7%)	58 %	90d (81 %)	APT differed between centers.	Effect of contralateral CS (-).
Lucena, 2016, Brazil	Retrosp, SC	SICH (SITS-MOST ≥4pts at 72h) mRS 90d TICI	20	aCAS (n=20)	Antero	60 %	90d 100 %	Dual APT started at 24h after CAS for 3m.	

Heck, 2015, Usa	Retrosp, SC, PCDB	SICH (SITS-MOST) mRS 90d TICI	23	aCAS (n=23)	Antero	30 %	90d 100 %	ACT or APT at discretion.	
Anadani, 2019, MN	Retrosp, MC, TITAN Registry, PCDB	SICH (ECASS II) mRS 90d. TICI	205	aCAS (n=205)	Antero (66.8%) Retro (33.2%)	60 %	90d	APT differed between centers. PO meds: NA	
Park, 2019, Korea	Retrosp, SC	SICH (ECASS III at 24h) mRS 90d TICI	42	aCAS (n=42)	Antero	69 %	90d	tPA (+): dual APT after 24h. tPA (-): dual APT load and maintenance.	Stenosis vs. complete occlusion of ICA.
Lockau, 2015, Germany	Retrosp, SC	SICH (≥4pts at 18±6 h) mRS 90d TICI	37	aCAS (n=37)	Antero (32%) Retro (67.6%)	54 %	90d	APT (-): bolus tirofiban, then for 24h. Dual APT load and for 3m.	Early neurological improvement.
Maus, 2018, Germany	Retrosp, MC (4) PCDB	SICH (≥4pts) mRS 90d. TICI	171	aCAS (n=165) (6 SRC after CAS, no MT)	Antero (59%) Retro (41%)	62 %	90d (88 %)	APT on each center. Used: tirofiban, ASA, abciximab.	Best first approach

Spiotta, 2015, USA	Retrosp, SC	SICH mRS 90d. TICI	16	aCAS (n=16)	Antero	50 %	90d 100 %	IA Abciximab (0.25 mg/ kg) at CAS. Dual APT load and maintenance.	
Yoon, 2015, China	Retrosp, MC (2) PCDB	SICH (≥4pts) mRS 90d TICI	42	aCAS (n=42) (7 SRC after CAS)	Antero	64 %	90d	45% URK in MT Dual APT by NGT immediately PO, for 3m.	Predictors for favorable outcome. In-stent thrombosis (1).
Mpotsaris, 2017, Germany	Retrosp, SC	SICH (ECASS 18±6 h). mRS 90d	63	aCAS (n=63)	Antero (27%) Retro (73%)	52 %	90d (97 %)	Abciximab bolus, followed by dual APT for 3m after 12–24h NCCT	
Steglich-Arnholm, 2015, Denmark	Retrosp, SC	SICH (≥4pts at 24h) mRS 90d TICI	62	aCAS (n=47) 15 SRC after CAS	NA	85 %	90d	Load of IV ASA and/or GPIIb/IIIa (eptifibatide or abciximab). Dual APT after FU imaging.	Stent patency: 8 TF, 4 occlusions at 90d Early clinical improvement 72h.
Behme, 2015, Germany	Retrosp, MC (4) PCDB	SICH (ECASS) mRS 90d TICI	170	aCAS (n=170)	Antero (89%) Retro (11%)	72 %	90d	APT on each center.	Risk factors for SICH

Cohen, 2015, Israel	Retrosp, SC	SICH (≥4pts at 36h) mRS 90d and 6 months TICI	24	aCAS (n=24)	Antero	42 %	90d (77 %) 6 m 90%	Previous APT (-): ASA 300mg. After (-) CT, added CPD 300mg. dual APT for 2m.	
Sadeh-Gonik, 2018, France	Retrosp, SC PCDB	SICH (≥4pts at 24h) mRS 90d TICI	46	aCAS (n=12)	Retro	76 %	90d (93 %)	NA	
Fahed, 2016, France	Retrosp, SC	SICH (ECASII at 24h and 72h) mRS 90d. TICI	70	aCAS (n=37) No stent (n=33)	NA	49 %	90d (96 %)	CAS: IV ASA bolus followed by a dual APT if (-) 24h NCCT	NIHSS at 24h and 7d
Bucke, 2018, Germany	Retrosp, SC PCDB	SICH (SWIFT PRIME at 24h) mRS 90d TICI	107 1LVO 222 TO	aCAS (n=222) LVO MT (n=849)	Antero	24 %	90d	IV dual APT or Ticagrelor load prior to CAS (at discretion)	

Rodriguez-Lopez, 2018, Spain	Retrosp, SC	mRS 90d TICI	66	aCAS (n=33) MT alone (33)	Retro	54 %	90d	NA	
Runck, 2019, Germany	Retrosp, SC	SICH (ECASS) TICI	66	aCAS+ MT (45) aCAS not TO (21)	Antero (80%) Retro (20%)	64 %	DC	APT (-): ASA after CAS and PO tirofiban. At 4h before cessation of the infusion, a ticagrelor load, then for min 6w and ASA for 6m.	In-stent thrombosis (22%).
Maurer, 2015, Germany	Retrosp, SC	SICH (24h) mRS DC TICI	43	aCAS (n=38), BA (n=5)	Antero	88 %	DC	Loading dose of CPD or ticagrelor	
Lescher, 2015, Germany	Retrosp, SC	SICH mRS 90d TICI	39	aCAS (n=09), BA (n=30)	Retro	74 %	90d	CPD load before CAS. Maintenance dual APT the next day.	
Akpinar, 2017, Turkey	Retrosp, SC PCDB	SICH (≥4pts) mRS TICI	15	BA (n=15), Delayed 7-10d CAS (n=10)	Antero	53 %	7–10, 30 and 90 days	CAS (+): dual APT 5d before CAS.	
Slawski, 2018, USA	Retrosp, SC PCDB	SICH (≥4pts) mRS 90d. TICI	45 TO. 39 Tx	aCAS (n=27), CEA (n=12)	Retro	46 %	90d	CAS: Dual APT before EPD. Low-dose heparin (2000-3000 U).	Re-occlusion 3/12. In-stent thrombosis (US 24h)

								CEA: ASA and a heparin bolus (5000 U).	
Poppe, 2019, Canada	RCT pilot study. SC	SICH (ECASS II at 24h) mRS 90d TICI	24	aCAS (n=11), BA (n=02)	Antero (18%) Retro (82%)	75 %	90d 100 %	No strict rec. tpA(+): ASA if (-) APT or CPD if (+) Dual APT after imaging at 6–24h. tpA(-): dual APT immediately PO.	PO stenosis
Kim, 2019, Korea	Retrosp, MC (17) PCDB	SICH mRS 90d TICI	955 MT, 75 TO	aCAS (n=56), BA (n=19)	Antero (90%) Retro (10%)	56 %	90d	CAS: PO APT on each center.	Re-occlusion (9%) Factors of success TICI
Papanagiotou, 2018, MN	Retrosp, MC (18) TITAN registry	SICH (≥4pts at 24h) mRS 90d TICI	482	aCAS (n=322), BA (n=52) MT alone (108)	Antero	61 %	90d	APT depended on each center.	Efficacy and safety outcomes according to APT type.
Jadhav, 2018, USA	Retrosp, MC (55) PCDB STRATIS	SICH (SWIFT PRIME at 24h) mRS 90d	147	aCAS (n=80), BA (n=43), delayed CAS (n=24)	Antero (47%) Retro (53%)	74 %	90d (93 %)	NA	Predictors of good outcomes in TO, and predictors of aCAS.

	Registry	TICI							
Labeyrie, 2018, France	Retrosp, SC PCDB	ICH (ECASS > 1 at 48h) mRS 90d TICI	49	aCAS (n=16), BA (n=9). Coils (n=12), Medical (n=13)	NA	67 %	90d (86 %)	Before stent positioning: IV ASA + CPD by NGT, then for 3m *additional IV anti-GP IIb/IIIa at discretion.	Early embolic recurrence (9/64). Stroke recurrence at 30 days.
Kang, 2019, Korea	Retrosp, SC PCDB	SICH (≥4pts at 24h) mRS 90d TICI	62	aCAS (n=40), BA (n=22)	Antero (22%) Retro (78%)	40 %	90d 1y	Neurologist's discretion: Immediate/ delayed (>1h) Dual /single APT	Long-term stent patency
Vu Dang, 2020, Vietnam	Retrosp, SC	ICH (Heidelberg 18±6 h) mRS 90d TICI	17	aCAS (n=10), BA (n=07)	Antero	59 %	90d	4000 UI heparin at CAS. Dual APT for 3m, then ASA.	Early clinical improvement at 24h
Li, 2018, China	Retrosp, SC	SICH (Heidelberg at 36h) mRS 90d TICI	37	aCAS (n=19), BA (n=18)	NA	32 %	90d	tpA(+): dual APT after 24h and for min 3m. tpA(-): dual APT load and maintenance.	In-stent stenosis at 3m (1/11)

Walloch a, 2019, Germany	Retrosp, SC PCDB	SICH (≥4pts) mRS 90d TICI	163	aCAS (n=149), BA (n=14)	Antero (52%) Retro (48%)	55 %	90d-5y (97 %)	CAS: IV ASA. IV heparin in some procedures. CPD 24h after. Dual APT for 4w, followed by mono-APT	Stent patency: acute re-occlusion 5.4%
Eker, 2018, Switzerland	Retrosp, MC (2) PCDB	SICH (≥4pts at 24h) mRS 90d TICI	121 TO 456 LVO	aCAS (n=98), BA (n=9), delayed CAS (n=14)	Antero (38%) Retro (62%)	52 %	90d (97 %)	IV ASA prior to CAS. Dual APT after (-) NCCT within 24h	Acute in-stent thrombosis (2/98)

aCAS stands for acute carotid artery stenting; ACT, anticoagulation therapy; Antero, anterograde; APT, antiplatelet therapy; ASA, acetylsalicylic acid; ATS, atorvastatin; BA, balloon angioplasty; CEA, carotid endarterectomy; CPD, clopidogrel; CS, carotid stenosis; d, days; DC, discharge; DLS, dual layer stent; ECASS II, European Cooperative Acute Stroke Study II; EPD, embolic protection device; FU, follow up; h, hours; IA, intra-arterial; IV, intravenous; LVO, large vessel occlusion; m, months; MC, multicenter; min, minimum; MN; multinational; mRS, Modified Rankin Scale; MT, mechanical thrombectomy; NA, not available; NCCT, non-contrast computerized tomography; NGT, nasogastric tube; NIHSS, The National Institutes of Health Stroke Scale; PCDB, prospectively collected database; PO, post-operative; RCT, randomized controlled trial; rec, recommendations; retro, retrograde; Retrosp, retrospective; SC, single center; SICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SLS, single layer stent; SRC, spontaneous recanalization; SWIFT PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial; TF, thrombus formation; TICI, thrombolysis in cerebral infarction; TO, tandem occlusion; tpA, tissue plasminogen activator; Tx, treatment; U, units; URK, urokinase; US, ultrasound; w, weeks; and y, year.

Table S2. Risk of bias assessment of studies included in the systematic review without control group.

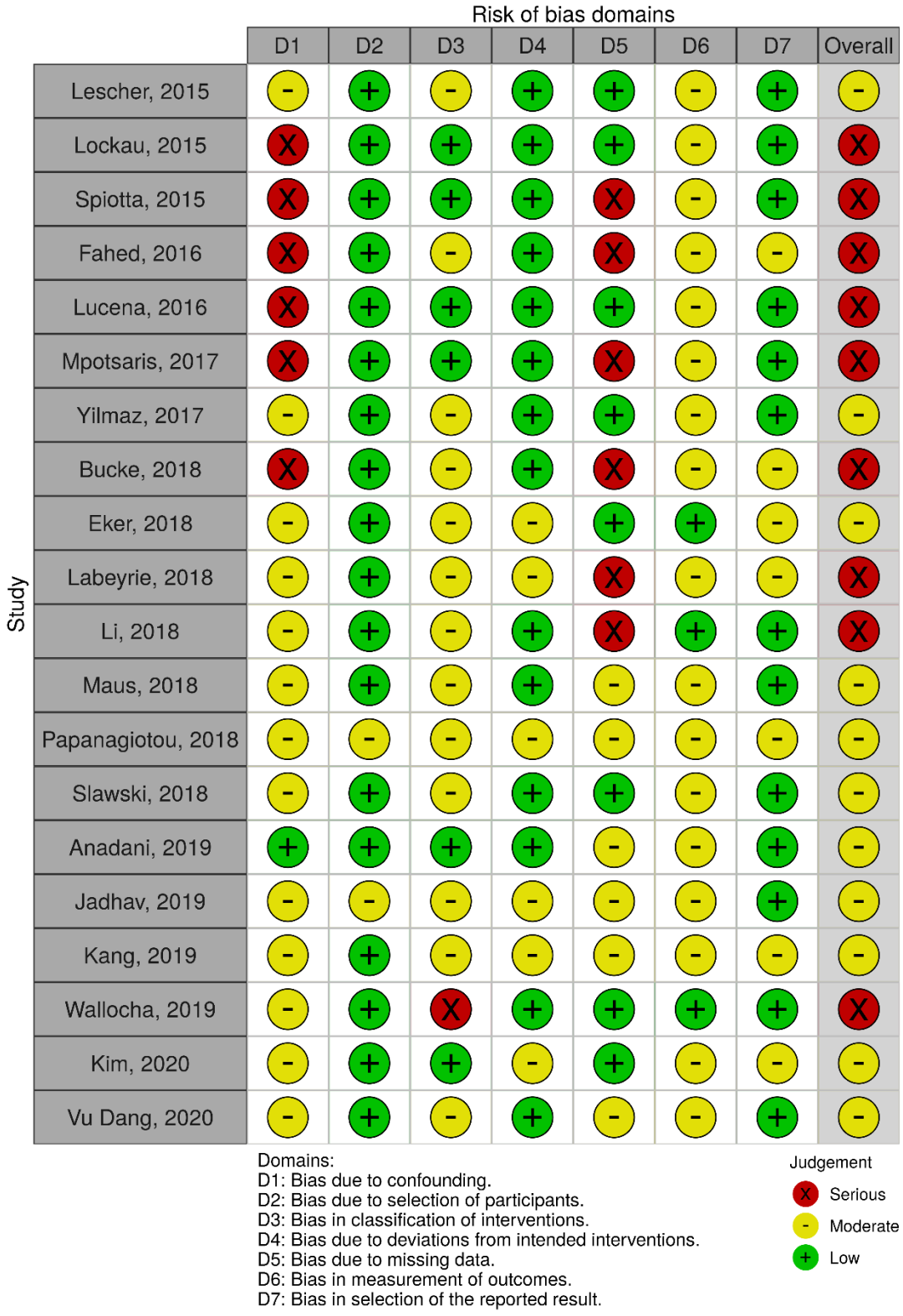
National Institute of Health Quality Assessment Tool for before-after (pre-post) Studies	
Study ID	Quality rating
Akpinar, 2017	Fair
Pfaff, 2019	Fair
Heck, 2015	Fair
Park, 2019	Fair
Maus, 2017	Good
Yoon, 2015	Good
Runck, 2019	Fair
Rodriguez-Lopez, 2018	Fair
Steglich-Arnholm, 2015	Fair
Sadeh-Gonik, 2018	Fair
Maurer, 2015	Fair
Behme, 2015	Good
Cohen, 2015	Poor

Table S3. Risk of bias assessment, RoB2 tool

Cochrane risk of bias in randomized trials (RoB 2)- Poppe, 2019	
Domain	Classification
Randomization process	Low
Deviations from intended interventions	Some concerns
Missing outcome data	Low
Measurement of the outcome	Some concerns
Selection of the reported result	Low
Overall Bias	Some concerns

Figure S1. Risk of bias assessment of studies included in the systematic review and meta-analysis – ROBINS I (A) summary per study. (B) summary per domain.

A



B

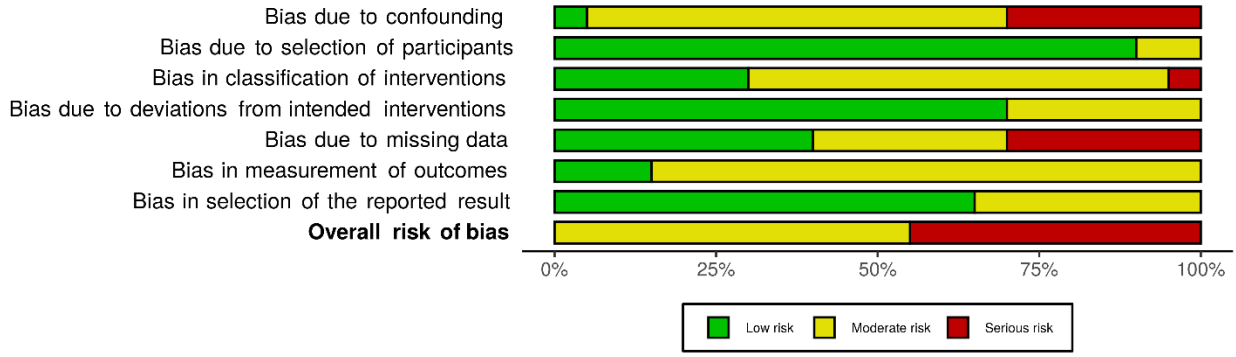


Figure S2. Meta-analysis of Symptomatic intracranial hemorrhage (sICH) in patients with acute stenting with of intravenous tissue plasminogen activator (IV tpA) versus without IV tpA.

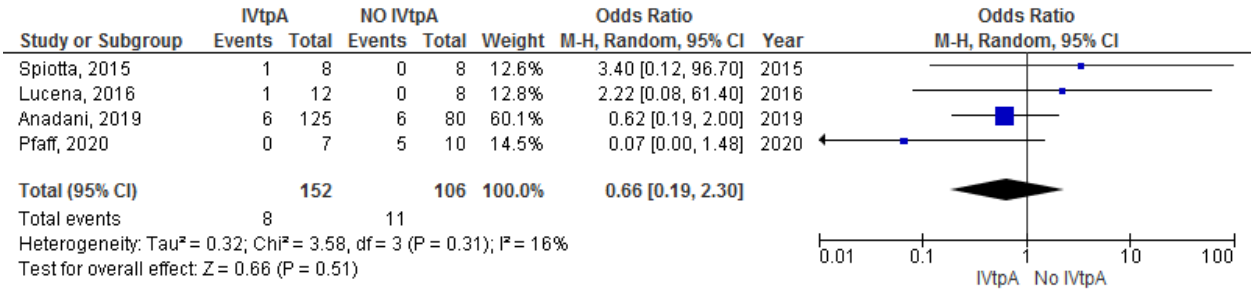
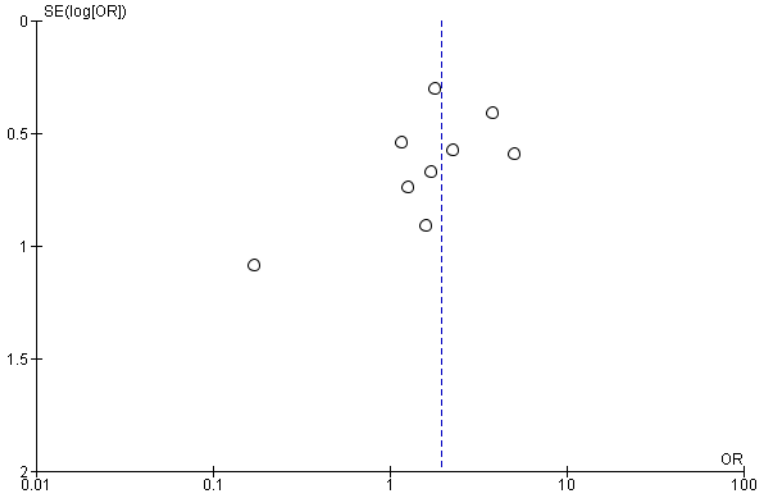
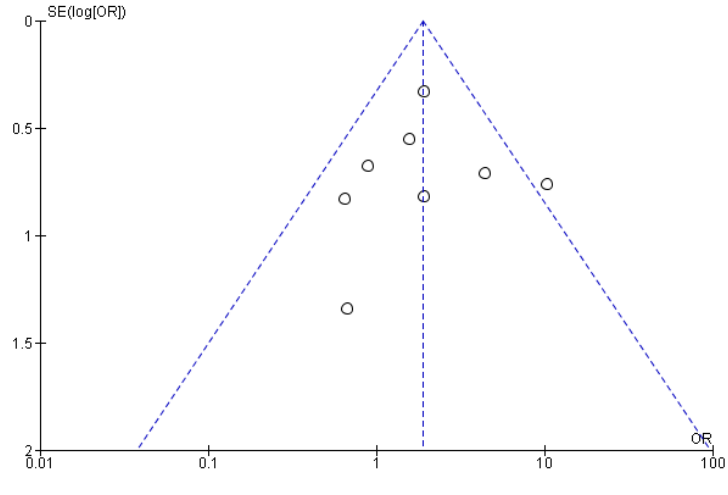


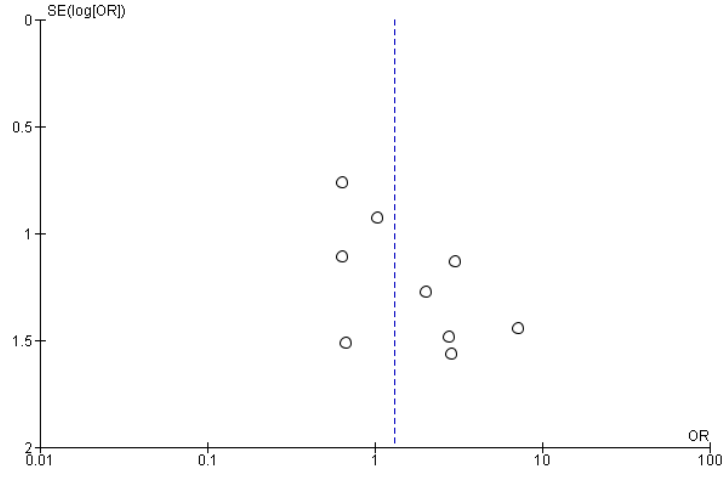
Figure S3. Funnel plots and Egger´s test results for (A) functional outcome at 90 days (modified Rankin Scale (mRS) score of 0–2), (B) good reperfusion status Thrombolysis in Cerebral Infarction (TICI) 2b-3, (C) Symptomatic intracranial hemorrhage (sICH), and (D) mortality as outcomes in acute stenting versus angioplasty studies showing no asymmetry.



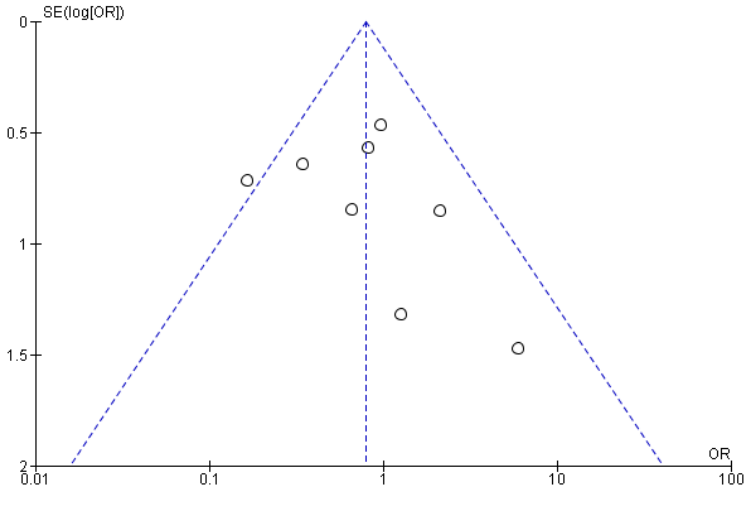
A Egger's test: p=0.27



B Egger's test: p=0.87

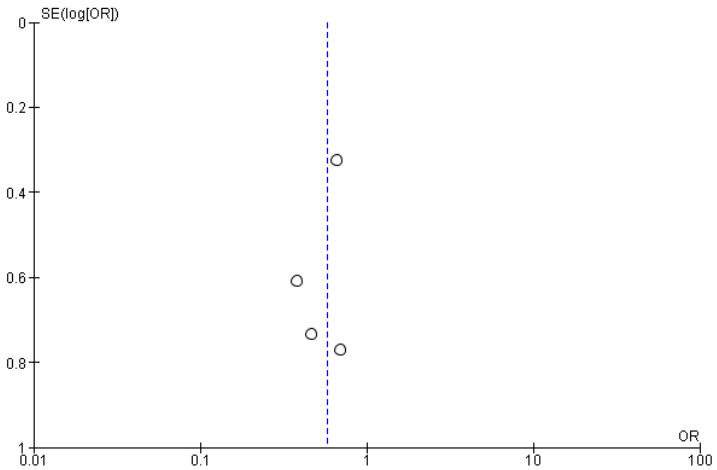


C Egger's test: p=0.06

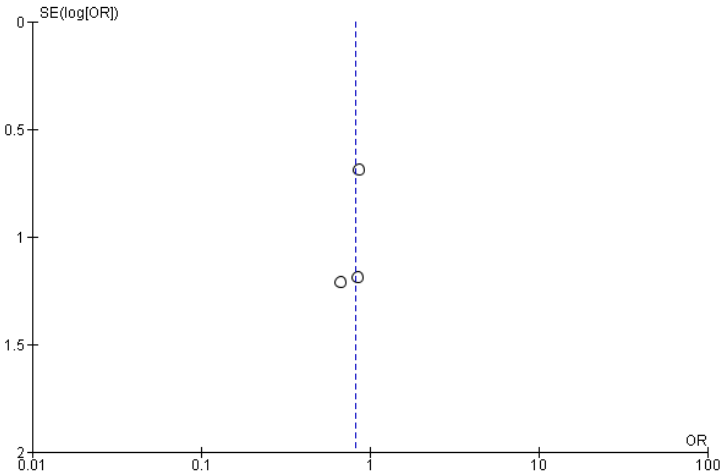


D Egger's test: p=0.54

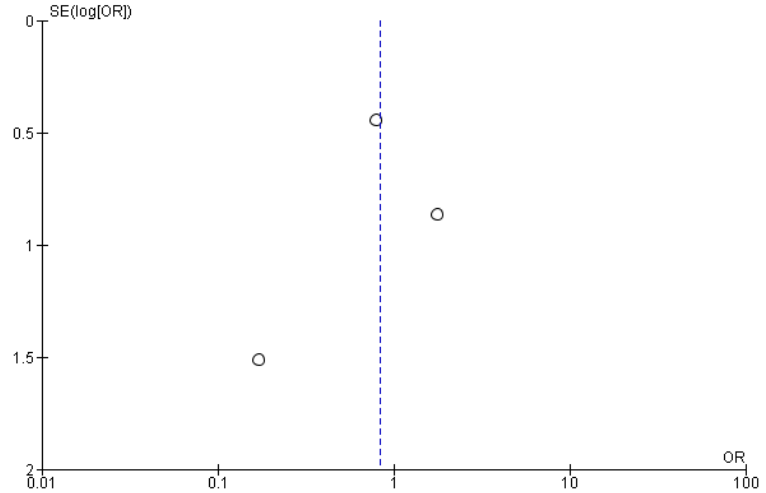
Figure S4. Funnel plots and Egger´s test results for (A) functional outcome at 90 days (modified Rankin Scale (mRS) score of 0–2), (B) Symptomatic intracranial hemorrhage (sICH), (C) mortality as outcomes in anterograde versus retrograde approach studies showing no asymmetry,



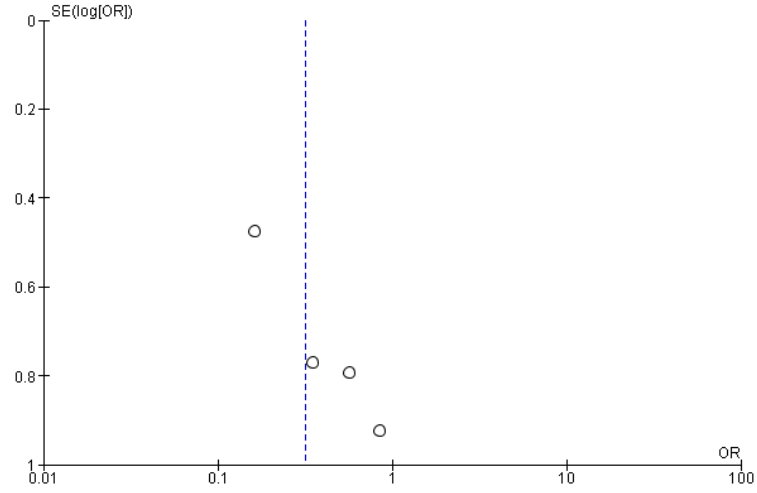
A Egger's test: p=0.43



B Egger's test: p=0.52



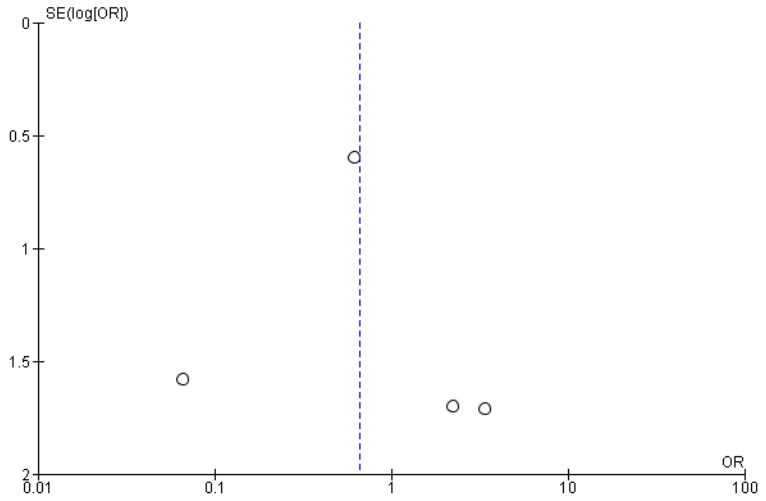
C Egger's test: p=0.79



D Egger's test: p=0.02

and (D) good reperfusion status Thrombolysis in Cerebral Infarction (TICI) 2b-3 showing asymmetry and possible bias.

Figure S5. Funnel plot and Egger´s test result for Symptomatic intracranial hemorrhage (sICH) as outcome in patients with acute stenting with of intravenous tissue plasminogen activator (IV tpA) versus without IV tpA showing no asymmetry.



Egger's test: p=0.88