ORIGINAL RESEARCH

Acute carotid stenting in patients undergoing thrombectomy: a systematic review and meta-analysis

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ABSTRACT

Background The benefit of acute carotid stenting compared with no stenting on clinical outcomes among patients with tandem lesions (TL) undergoing endovascular thrombectomy (EVT) remains unknown.

Methods We conducted a systematic review and meta-analysis of studies comparing acute carotid stenting versus no stenting among TL patients undergoing EVT with regards to 90 day modified Rankin Scale (mRS) score, symptomatic intracerebral hemorrhage (sICH), and mortality. Four reviewers screened citations for eligibility and two assessed retained studies for risk of bias and data extraction. A random effects model was used for the synthesis of aggregated data.

Results 21 studies (n=1635 patients) were identified for the systematic review; 19 were cohort studies, 1 was a post-hoc analysis of an EVT trial, and 1 was a pilot randomized controlled trial. 16 studies were included in the meta-analysis. Acute stenting was associated with a favorable 90 day mRS score: OR 1.43 (95% CI 1.07, 1.91). No significant heterogeneity between studies was found for this outcome ($I^2=17.0$%; $\chi^2=18.07, p=0.26$).

There were no statistically significant differences for 3 month mortality (OR 0.80 [95% CI 0.50, 1.28]) or sICH (OR 1.41 [95% CI 0.91, 2.19]).

Conclusions This meta-analysis suggests that among TL patients undergoing EVT, acute carotid stenting is associated with a greater likelihood of favorable outcome at 90 days compared with no stenting.

Patients with tandem lesions (TL)—that is, stroke with an acute intracranial anterior circulation occlusion and an ipsilateral cervical internal carotid artery (c-ICA) high grade stenosis or occlusion—constitute about 15% of patients undergoing endovascular thrombectomy (EVT). Patients with TL present a unique therapeutic challenge and tend to have worse outcomes than patients with isolated intracranial occlusions. In these patients, intracranial thrombus. When EVT is performed in TL patients, treatment strategies vary according to clinical, anatomical, and technical considerations, as well as physician preference.

Two main approaches exist: the first is to traverse the c-ICA lesion, perform intracranial clot retrieval, and leave the c-ICA largely untreated for possible endarterectomy or stenting in the ensuing days or weeks. The second is to recanalize the c-ICA more definitively using stenting during the EVT procedure, either prior to or following intracranial thrombectomy. These two treatment strategies exemplify the competing risks that must be balanced in TL patients—that is, ischemic stroke progression or recurrence on the one hand, and intracranial hemorrhage on the other. Without randomized controlled trial data to guide therapeutic decisions, both approaches are widely used in clinical practice. Thus while we do not know which is superior, neither approach can truly be considered the standard of care or experimental therapy.

To determine if existing data might support the superiority of one approach over the other with regards to functional outcomes, we conducted a systematic review and meta-analysis of the literature.

METHODS

Protocol and eligibility criteria

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All published randomized controlled trials, cohort studies, case control studies, and case series evaluating endovascular treatment of adults with acute anterior circulation strokes due to TL were eligible for inclusion. Abstracts, case reports, or case series with fewer than six participants, comments, reviews, and meta-analyses were excluded. Tandem lesions were defined as high grade stenosis (70–99%) or occlusion of the c-ICA with ipsilateral occlusion of the distal ICA and/or middle cerebral artery. Only studies published between 2000 and 2018 that reported outcomes both for patients undergoing acute c-ICA stenting and patients undergoing intracranial thrombectomy alone were included. There were no initial restrictions concerning country or language of publication. The primary outcome was a favorable modified Rankin Scale (mRS) score of 0–2 at 3 months. Secondary outcomes were symptomatic intracranial hemorrhage (sICH) and mortality at 3 months.

Search strategy

The search strategy was designed in collaboration with a medical librarian having expertise in systematic reviews (DZ). The following electronic databases were searched: Ovid EMBASE, EBSCO...
CINAHL, Complete, Ovid MEDLINE, Web of Science, Google Scholar, and Open Grey. The following search keywords were used to target selected studies: Carotid, Thrombectomy, thrombectomy, thrombolysis, thromboendarterectomy, stent, angioplasty (see online supplementary appendix e-1 for detailed search strategy). Additionally, we searched the bibliographies of all of the included studies to find additional studies. The most recent literature search was completed on February 19, 2020.

**Study selection**

Reviewers (GJ, ML, AYP, CS) independently screened each title/abstract using a free online systematic review application (https://rayyan.qcri.org). Full text articles were obtained when identified by any reviewer as potentially relevant to the research question. Full text articles were then independently screened by two reviewers and the reasons for any exclusions were recorded. Disagreements about eligibility were resolved by consensus.

**Protocol approval**

No ethics approval was required for this systematic review and meta-analysis.

**Data collection and risk of bias**

Data collection was completed by one author (GD) and reviewed by a second (AYP) using a data extraction instrument designed specifically for this review. Demographic data for each included study were collected when available, including number of participants, age, sex, initial National Institutes of Health Stroke Scale score, Alberta Stroke Program Early CT Score (ASPECTS), key vascular comorbidities (hypertension, diabetes, smoking, dyslipidemia, atrial fibrillation), etiology of the ICA lesion (atherosclerosis, embolism, dissection), site of intracranial occlusion, use of IV thrombolysis, use of antiplatelet agents or anticoagulation, and the thrombectomy device used. For stented patients, the order of stenting relative to intracranial thrombectomy (before, or after) was also documented when specified. Corresponding authors were contacted when data relevant to the primary and secondary outcomes were not included in the original publication (four of seven authors responded).

Risk of bias was evaluated for the individual studies using a customized quality assessment tool designed based on recommendations from the Ottawa Non-Randomized Studies Workshop and Cochrane Handbook for Systematic Reviews of Interventions. Each quality criterion was rated as having a low, high, or unclear risk of bias.

**Data synthesis and analysis**

A random effects model was chosen for the synthesis of aggregated data. In order to compare acceptably homogeneous data, studies were included in the meta-analysis only when outcome data respected our prespecified time frame (mRS score and mortality at 90 days). Summary effect measures (ORs) were calculated using data extracted from primary studies and were compared using 95% CIs.

Heterogeneity between studies was evaluated with visual assessment of forest plots, as well as I² and χ² tests. We defined important inter-study heterogeneity as an I² test result of >50% and a χ² test result of <0.1. Reporting bias was assessed using funnel plots for each outcome of interest. Analyses were performed with R Studio (V1.2) using the meta package (V 4.9-5; https://www.rdocumentation.org/packages/meta).

**Subgroup analyses**

Subgroup analyses were conducted when at least three studies were available for each variable of interest. Studies were divided according to year of publication (before or after 2017 to capture studies conducted before and after the era of modern thrombectomy devices), total number of participants included (<50 or ≥50), order of stenting relative to thrombectomy among stented patients (≥50% of stented patients in study stented before thrombectomy vs >50% of patients stented after thrombectomy), and study design (observational study vs randomized controlled study).

**Data availability**

Data are available on reasonable requests by qualified investigators to the corresponding author.

**RESULTS**

**Study selection**

Study selection and reasons for study exclusion are detailed in the PRISMA flow diagram (figure 1). A total of 1715 articles were identified through database searching, and one was identified through other sources (bibliographic hand search); 1556 records were screened after removal of duplicates, of which 204 full texts were assessed for eligibility. A total of 21 studies, including 1635 patients (974 with acute stenting and 661 without), were included in our systematic review (online supplementary table e-1).

Two studies were prospective cohort studies,7 8 eight were retrospective cohort studies,10 9-13 nine were retrospective cohort studies from prospectively collected databases,16-24 one was a post hoc analysis of a randomized controlled trial,25 and one was a pilot randomized controlled trial.26 Data regarding study population, management, and follow-up duration are summarized in online supplementary table e-1. One study included patients with posterior circulation TL which were excluded from our analysis.10 Stenting was compared with angioplasty or no acute treatment of the c-ICA in 13/21 studies and with multiple different treatment regimens in 6/21 studies. Management of the c-ICA lesion in patients without acute stenting was not specified in 2/16 studies.9 19 Most (14/21) studies compared patients according to acute intervention on c-ICA regardless of type of intervention,24 and one conducted a multivariate analysis of predictors of functional independence without direct comparison between patients undergoing acute c-ICA stenting or not.21 In three studies, intracranial lesions were treated with intra-arterial tissue plasminogen activator alone11-13 while the others used a combination of thrombolysis and thrombectomy. ASPECTS score was inconsistently reported in the included studies. However, apart from one study where ASPECTS was significantly higher in participants in the stenting subgroup compared with the no stenting group,13 the scores were comparable between treatment groups when reported. Antiplatelet and anticoagulation treatment regimens were widely variable and inconsistently reported in the included studies, precluding meaningful analysis of this component of patient management.

Risk of bias assessment was summarized in online supplementary table e-1. Allocation of intervention was performed in most studies (20/21) according to the treating physicians, making the risk of selection bias high. One study26 was randomized but
3Dufort, et al. J NeuroIntervent Surg 2020;0:1–6. doi:10.1136/neurintsurg-2020-015817

Ischemic stroke

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for literature search and study selection.

mRS, modified Rankin Scale.

crossover of two patients from the stenting group to the no stenting group make the risk of selection bias uncertain. Performance bias risk was considered high in retrospective studies (17/21) where concealment of intervention allocation was unlikely, and in two open label studies. Most studies were at low risk of detection bias for mortality and sICH (17/21), and of unclear risk for mRS score (13/21). Most studies were at low risk of detection bias for mortality and sICH (17/21), and of unclear risk for mRS score (13/21). However, evaluation of outcome at differing time points between patients made 4/21 studies at high risk of detection bias for these outcomes. Only 3/21 studies mentioned blinding of staff assessing mRS at follow-up. Risk of attrition bias was high in 3/21 studies excluding patients without outcome data at 3 months but was otherwise of low or unclear risk. Selective reporting bias risk was unclear in most studies (20/21), but likely to be high as in most observational studies, and high in one that was a post hoc analysis of previously published data.

Narrative synthesis of included studies

Narrative examination was completed for all studies included in our systematic review. Two studies reported statistically significant favorable mRS scores at 90 days and one of these also reported significantly lower mortality for patients with acute c-ICA stenting compared with no stenting. Statistically significant favorable mRS scores at 90 days were found in one study for participants with c-ICA patency at 24 hours compared with no patency at 24 hours and in another study comparing patients with acute c-ICA stenting with antithrombolytic medication compared with no stenting. Sample size was too small for statistical analysis in 5/15 studies.

Meta-analysis of included studies

Sixteen studies were included in the meta-analysis of the primary outcome (mRS score 0–2 at 3 months). Four studies were excluded because of mRS data outside our prespecified time frame and one because of unavailable data. Stenting was associated with a favorable mRS score at 3 months (OR 1.43 (95% CI 1.07, 1.91)) (figure 2). No significant heterogeneity between studies was found for this outcome ($I^2=17.0\%$; $\chi^2=18.07$, $p=0.26$). There were no statistically significant differences for 3 month mortality (OR 0.80 (95% CI 0.50, 1.28)) or for sICH (OR 1.41 (95% CI 0.91, 2.19)), although the direction of the association suggested lower odds of death and higher odds of sICH with stenting (figure 3).

Sensitivity analyses

Subgroup analyses for year of publication, number of patients, timing of stenting relative to thrombectomy, and study design had no significant effect on the results (data not shown). Funnel
Our meta-analysis is the first to demonstrate a statistically significant difference in functional outcome at 90 days favoring acute c-ICA stenting in TL patients undergoing EVT. This result is likely driven by the inclusion of two large and more recent multicenter series that both suggested better outcomes with acute stenting.15 A cumulative funnel plot analyzing studies according to year of publication suggested progressively better mRS outcomes over time. This may reflect improvements in techniques for both intracranial recanalization and c-ICA stenting as well as the higher quality of more recently published series.

Although not statistically significant, there was a trend suggesting lower mortality in patients undergoing acute stenting, possibly related to lower stroke recurrence and better functional outcomes or perhaps reflecting a selection bias favoring more aggressive acute c-ICA lesion treatment of patients felt by the treating team to have a better prognosis. Conversely, there appeared to a trend towards higher rates of sICH among stented patients, likely explained by earlier and more aggressive use of antithrombotic agents as well as the possibility of an increased risk of reperfusion injury. Similar to a previous meta-analysis,28 the order of stenting relative to thrombectomy was not associated with functional outcome in our study. There are, however, theoretical advantages to c-ICA stenting after thrombectomy, including shorter intracranial recanalization times and avoidance of potential snagging of the retrievable stent in the struts of an already deployed carotid ICA stent. Stenting of the c-ICA earlier in the procedure also subjects the patient to potential hemodynamic instability due to baroreceptor activation while cerebral perfusion is still impaired by the presence of intracranial occlusion. Furthermore, in some cases, merely traversing the c-ICA lesion with catheters to access the intracranial thrombus is sufficient to dilate the stenosis or occlusion and potentially obviate a clear indication for stenting. However, sometimes specific technical circumstances dictate that access to the intracranial circulation requires antegrade stenting.

The current meta-analysis has limitations, the most important of which is that primarily uncontrolled observational, often retrospective, studies were included, all of which had at least a moderate risk of bias while only one small randomized trial was identified. Furthermore, older studies included may not reflect contemporary EVT techniques and may thus be less applicable to

### Table: Functional Independence at 90 Days

| Study (author, year) | Stent mRS 0–2 | No stent mRS 0–2 | Odds ratio | OR | 95% CI | Weight |
|----------------------|--------------|-----------------|------------|----|--------|--------|
| Dufort g, et al. J NeuroIntervent Surg 2020;0:1–6. doi:10.1136/neurintsurg-2020-015817 |

**DISCUSSION**

This systematic review and meta-analysis suggests an association between acute c-ICA stenting and better 3 month functional outcome in patients with TL undergoing EVT for acute stroke. To date, no large randomized controlled trials have been completed addressing the question of optimal c-ICA management in acute stroke patients with TL. While the current meta-analysis is limited almost exclusively to prospective and retrospective observational studies, contrary to previously published meta-analyses, we included only studies comparing stented and non-stented patients and also captured more recent, larger cohorts. Four main meta-analyses of smaller case series have been published,19 27–29 most with relatively few patients not having undergone acute stenting and only two reporting whether acute ICA stenting was associated with different clinical outcomes than no stenting.

Data from the HERMES collaboration provides clear evidence that patients with TL benefit from EVT, without regard to how the c-ICA lesion is addressed.30 As EVT becomes ever more widespread, it is necessary to further refine its use in specific subpopulations, including patients with TL. There are putative advantages for both acutely stenting the c-ICA and for foregoing acute stenting during EVT. Acute c-ICA stenting may more effectively treat the cause of stroke, favor intracranial clot lysis, and decrease the risk of recurrence while improving overall cerebral perfusion. However, foregoing acute c-ICA stenting can avoid early administration of antiplatelet agents which may increase the risk of intracranial hemorrhage in the immediate post-recanalization phase, particularly in patients having received IV thrombolysis or having a large core of infarction.31 32 Furthermore, stent placement carries an inherent risk of in-stent thrombosis which may confer a worse prognosis.33 34 An international survey of stroke experts highlighted this therapeutic uncertainty, with 75% of respondents having equipoise regarding optimal acute management of c-ICA stenosis in TL patients.
current practice. Factors that may have influenced both the decision to stent and overall outcomes, including baseline ASPECTS, type of antiplatelet agents used, and etiology of c-ICA lesions (atherosclerosis vs dissection) were not systemically reported in the included series. Nevertheless, unlike previous reviews, our meta-analysis is strengthened by the inclusion of recent, large multicenter prospective cohorts and only studies that explicitly compared acute stenting with no acute stenting.

While this large meta-analysis of observational data suggests an advantage of acute c-ICA stenting during EVT for TL patients, only randomized trials comparing acute stenting with no acute stenting will provide more definitive evidence to guide optimal management for these patients. Two forthcoming trials (TITAN (NCT03978988) and EASI-TOC (NCT04261478)) are expected to address this important clinical question.

Contributors
GD: data acquisition, data analysis, and interpretation, and writing and revising the manuscript. BYC: data acquisition, data analysis, and interpretation. GJ: design and conceptualization of the study, data acquisition, data analysis, and interpretation, and revising the manuscript. MK: statistical analysis and data interpretation, and writing and revising the manuscript. ML: data acquisition, data analysis, and interpretation. BR: statistical analysis and interpretation, CS: design and conceptualization of the study, data acquisition, data analysis, and interpretation, and revising the manuscript. DZ: study design and data acquisition. AYP: design and conceptualization of the study, data acquisition, data analysis, and interpretation, and revising the manuscript.

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Competing interests
AYP is the principal investigator for a forthcoming trial of patients with tandem lesions, Endovascular Acute Stroke Intervention–Tandem OCclusion study (EASI-TOC), for which he has received a networking grant from the Canadian Stroke Trials for Optimized Results (CaSTOR) initiative.

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REFERENCES

1. Jadad AR, Moher D, Gotzsche PC, et al. Emergent management of tandem lesions in acute ischemic stroke. Stroke 2019;50:428–33.

2. Rubiera M, Ribot M, Delgado-Mederos R, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke 2006;37:2301–5.

3. Jacquin G, Poppe AY, Labrie M, et al. Lack of consensus among stroke experts on the optimal management of patients with acute tandem occlusion. Stroke 2019;50:1254–6.

4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

5. Ouzzani M, Hammady H, Fedorowicz Z, et al. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. Res Synth Methods 2013;4:63–77.

6. Wells GA, Shea B, Higgins JP, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.

7. Li W, Chen Z, Dai Z, et al. Management of acute tandem occlusions: Stent-retriever thrombectomy with emergency stenting or angioplasty. J Int Med Res 2018;46:2578–86.

8. Bricout N, Peronsonic T, Ferrigno M, et al. Day 1 extracranial internal carotid artery patency is associated with good outcome after mechanical thrombectomy for tandem occlusion. Stroke 2018;49:2520–2.

9. Alpor S, Gelenen P. Endovascular treatment of acute tandem occlusion strokes and stenting first experience. J Clin Neurosci 2018;47:328–31.

10. Laberrie M-A, Ducroux C, Civelli V, et al. Endovascular management of extracranial occlusions at the hyperacute phase of stroke with tandem occlusions. J Neurointerv Surg 2018;10:533–539.

11. Li A-H, Wang Y-H, Kao H-F, et al. Aggressive recanalization of internal carotid artery occlusion in patients with NIHSS>20 and poor collateral circulation: preliminary report. Int J Cardiol 2012;161:97–102.

12. Srivastava A, Goyal M, Sty B, et al. Microcatheter navigation and thrombolysis in acute symptomatic cervical internal carotid occlusion. AJNR Am J Neuroradiol 2006;27:774–9.

13. Wang H, Lanzino G, Fraser K, et al. Urgent endovascular treatment of acute symptomatic occlusion of the cervical internal carotid artery. J Neurosurg 2003;99:972–7.

14. Eker OF, Bühlmann M, Dargazani C, et al. Endovascular treatment of atherosclerotic tandem occlusions in anterior circulation stroke: technical aspects and complications compared to isolated intracranial occlusions. Front Neurol 2018;9:1046.

15. Papapanagiotou P, Haussen DC, Turman E, et al. Carotid stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke with tandem lesions. JACC Cardiovasc Interv 2018;11:1290–9.

16. Blaisiau A, Gawlitzka M, Manceau P-F, et al. Mechanical thrombectomy for tandem occlusions of the internal carotid artery-results of a conservative approach for the extracranial lesion. Front Neurol 2018;9:928.

17. Fahed R, Redjim H, Blanc R, et al. Endovascular management of acute strokes with tandem occlusions. Cerebrovasc Dis 2016;41:298–305.

18. Machi P, Lobotesis K, Maldonado IL, et al. Endovascular treatment of tandem occlusions of the anterior cerebral circulation with solitaire FR thrombectomy system. Initial experience. Eur J Radiol 2012;81:3479–84.

19. Sadeh-Gonik U, Tau N, Friesenmann T, et al. Thrombectomy outcomes for acute stroke patients with anterior circulation tandem lesions: a clinical registry and an update of a systematic review with meta-analysis. Eur J Neurol 2018;25:693–700.

20. Sallustio F, Motta C, Koch G, et al. Endovascular stroke treatment of tandem occlusion: a single-center experience. J Vasc Interv Radiol 2017;28:543–9.

21. Hernández-Fernández F, Del Valle Pérez JA, Garcia-Garcia J, et al. Simultaneous angioplasty and mechanical thrombectomy in tandem carotid occlusions. Incidence of reocclusions and prognostic predictors. J Stroke Cerebrovasc Dis 2020;29:104578.

22. Kang D-H, Kim Y-W, Hwang Y-H, et al. Endovascular recanalization of tandem carotid occlusion: definition, clinical aspects, and outcomes. J Neurointerv Surg 2019;126:e1268–74.

23. Kim B, Kim BM, Bang OY, et al. Carotid artery stenting and intracranial thrombectomy for tandem cervical and intracranial artery occlusions. Neurosurgery 2020;86:213–20.

24. Wallocha M, Chapot R, Nordmeyer H, et al. Treatment methods and early neurologic improvement after endovascular treatment of tandem occlusions in acute ischemic stroke. Front Neurol 2019;10:127.

25. Assis Z, Menon BK, Goyal M, et al. Acute ischemic stroke with tandem lesions: technical endovascular management and clinical outcomes from the ESCAPE trial. J Neurointerv Surg 2018;10:429–33.

26. Poppe AV, Jacquin G, Stafpi C, et al. A randomized pilot study of patients with tandem carotid lesions undergoing thrombectomy. J Neuroradiol 2019. doi:10.1016/j.neurad.2019.08.003. [Epub ahead of print: 26 Sep 2019].

27. Sivan-Hoffmann R, Gory B, Armony X, et al. Stent-retriever thrombectomy for acute anterior ischemic stroke with tandem occlusion: a systematic review and meta-analysis. Eur Radiol 2017;27:247–54.

28. Pires Coelho A, Lobo M, Gouveia R, et al. Endovascular treatment of symptomatic occlusion of the cervical internal carotid artery. J Neurointerv Surg 2016;8:288–8.

29. Wilson MP, Murad MH, Krings T, et al. Management of tandem occlusions in acute ischemic stroke - intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis. J Neurointerv Surg 2018;10:721–8.

30. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723–31.

31. Heck DG, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. J Neurointerv Surg 2015;7:170–5.

32. Zhu F, Labreuche J, Haussen DC, et al. Hemorrhagic transformation after thrombectomy for tandem occlusions. Stroke 2019;50:516–9.

33. Pop R, Zinchenko I, Quenardelle V, et al. Predictors and clinical impact of delayed stent thrombosis after thrombectomy for acute stroke with tandem lesions. AJNR Am J Neuroradiol 2018;40:533–39.