A systematic review and meta-analysis on the outcomes of carotid endarterectomy after intravenous thrombolysis for acute ischemic stroke

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ABSTRACT

Background: Intravenous thrombolysis (IVT) is the mainstay of treatment for patients presenting with acute ischemic stroke, whereas carotid endarterectomy (CEA) is indicated in patients with symptomatic carotid stenosis. However, the impact of prior IVT on the outcomes of CEA (IVT-CEA) is not clear. The aim of this study was to determine whether IVT may create additional stroke and death risk for CEA, compared with CEA performed in the absence of a history of recent IVT, and to determine the optimal timing for CEA after IVT.

Methods: We conducted a systematic review and meta-analysis of studies comparing the outcomes of IVT-CEA vs CEA, using the Medline, Embase, and Cochrane databases.

Results: We included 11 retrospective comparative studies, in which 135,644 patients underwent CEA and 2070 underwent IVT-CEA. The pooled rate of perioperative stroke was 4.2% in the IVT-CEA group and 1.3% in the CEA group (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.12-1.58; $P = .21$), with a high heterogenicity ($I^2 = 93\%$). The rate of stroke/death was 5.9% in patients undergoing IVT-CEA 1.9% in those receiving CEA only (OR, 0.42; 95% CI, 0.15-1.14; $I^2 = 92\%$; $P = .09$); after exclusion of studies including TIA as presenting symptom, stroke/death risk was 3.6% in IVT-CEA and 3.0% in CEA (OR, 1.42; 95% CI, 0.80-2.53; $I^2 = 50\%$; $P = .11$). The risk of stoke decreased with a delay in the performance of CEA ($P = .268$). Using results of the metaregression, the calculated delay of CEA that allows for a <6% risk was 4.6 days. Compared with CEA, patients undergoing IVT-CEA had a significantly higher risk of intracranial hemorrhage (2.5% vs 0.1%; OR, 0.11; 95% CI, 0.06-0.21; $I^2 = 28\%$; $P < .001$) and neck hematoma requiring reintervention (3.6% vs 2.3%; OR, 0.61; 95% CI, 0.43-0.85; $I^2 = 0\%$; $P = .003$).

Conclusions: In patients presenting with an acute ischemic stroke, CEA can be safely performed after a prior endovenous thrombolysis, maintaining a stroke/death risk of <6%. After IVT, CEA should be deferred for ≥5 days to minimize the risk for intracranial hemorrhage and neck bleeding. (J Vasc Surg 2024;■:1-7.)

Keywords: Carotid endarterectomy; Carotid stenosis; Cerebral hemorrhage; Hematoma; Meta-analysis; Stroke; Thrombolytic therapy

Stroke is currently the second leading cause of death in Europe[1] and the fourth cause in the United States.[2] More than 50% of stroke survivors suffer from significant disability and limitation in their daily life activities, with significant impact on the quality of life and health care resources use. Thrombolysis with intravenous tPA (IVT) is considered today the mainstay of treatment for patients presenting with acute ischemic stroke that meet the inclusion criteria.[3,4] Its use has been progressively increasing through the last years, in particular as a result of the extension of the therapeutic window from 3.0 to 4.5 hours, and the worldwide efforts to create coordinated regional stroke care systems with the aim to provide dedicated efficient diagnostic/therapeutic protocols to patients presenting with an acute ischemic stroke.[2-4] Among patients receiving thrombolysis, >50% will have a vessel recanalization, and a significant clinical benefit will occur in one-third. However, there remains a non-negligible risk of intracranial hemorrhage (ICH), which occurs in 6% of patients.[5]

Extracranial carotid stenosis accounts for approximately 20% of all ischemic strokes.[2] After the first index ischemic event, a substantially high risk of recurrent stroke still persists if the carotid stenosis is left

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untreated.[1,6-8] For this reason, carotid endarterectomy (CEA) is indicated in symptomatic patients with an extracranial carotid stenosis of 50% to 99%, preferentially within 14 days.[1] The rational of an early CEA is to prevent further ischemic events through the removal of the source of thromboembolic debris and to restore a normal perfusion pressure to the ischemic penumbra in the brain.[1,3] Despite a possible increased risk of ICH and reperfusion syndrome in case of early CEA, the risk/benefit ratio of CEA seems to be optimal during the first 2 weeks after the index event, and CEA may be performed with favorable outcomes also during the first 48 hours after a transient ischemic attack (TIA) or stroke.[1]

This parallel tendency of an early CEA and the increasing use of IVT has exposed vascular surgeons to the clinical situation of performing CEA in patients previously treated with IVT (IVT-CEA). However, the safety of IVT-CEA has not been investigated extensively. The aim of this systematic review and meta-analysis was to determine whether IVT may provide additional risks to CEA (compared with CEA in the absence of recent IVT) and what is the optimal timing of CEA after IVT to balance the risk of stroke recurrence vs the risk of perioperative CEA hemorrhagic complications.

METHODS

Search method. The aim was to identify studies comparing the outcomes obtained with CEA alone vs carotid endarterectomy after intravenous thrombolysis (CEA-IVT) in patients with acute stroke. A literature search was conducted through the PubMed (MEDLINE) database, Embase, and Cochrane CENTRAL using the following exploded MeSH terms and keywords: carotid endarterectomy, carotid intervention, carotid surgery, thrombolysis, thrombolytic therapy, and stroke. An additional manual review of references from relevant articles was conducted.

Studies were identified, screened, and selected according to the PRISMA study flow diagram. The abstracts of studies retrieved using the automatic and manual search strategy were screened independently by two reviewers to identify studies that potentially met the inclusion criteria. The full texts of these potentially eligible studies were screened independently for eligibility by two reviewers; any eventual disagreement was be resolved by consensus.

Studies on mechanical thrombectomy, intraoperative thrombolysis, or carotid artery stenting (CAS) were excluded; only studies published in the English language were considered. Case reports or series including <10 patients, editorials, previous reviews, and meta-analyses without original data were excluded. Noncomparative studies reporting only the outcomes CEA-IVT, or those including patients treated for complete extracranial carotid occlusion were excluded. The study was registered in the PROSPERO database (CRD42020178962).

End points. The study end points were perioperative stroke, death, combined stoke/death, intracerebral hemorrhage (ICH) and any bleeding requiring re-intervention. The outcomes were compared between CEA and IVT-CEA. The clinical impact of the timing of CEA after IVT on stroke/death was also investigated. Periprocedural events were considered to be those occurring within a 30-day time frame after the procedure.

Statistical methods. For each of the included studies, raw data (number of patients who developed an end point in the intervention and control group) were extracted. These were crossed checked and any discrepancies were solved before the data were transferred to the statistical programs. Review Manager (RevMan, version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) software was used for the analysis. Statistical analyses were performed with RevMan, which performed the meta-analyses, produced Forest plots, and provided inconsistency (I^2) statistics that evaluated heterogeneity within the studies. A nonsignificant P value for the Cochrane Q statistic indicated that there was no significant statistical heterogeneity between studies. An I^2 value of 0% indicated no heterogeneity, whereas larger values were consistent with increasing heterogeneity. In case of statistically significant I^2, indicative of substantial heterogeneity, a random effects model was chosen, instead of the fixed effect model. In case of outcomes measures using >10 studies, a funnel plot with Egger's and Begg's test were used to assess for publication bias. The impact of CEA timing after IVT was assessed through a metaregression analysis, using the R software (R Foundation for Statistical Computing, Vienna, Austria). The metaregression equation had a negative slope, indicating a decreasing odds of stroke or death with a longer time interval between IVT and CEA. The metaregression equation was used to calculate the time interval between IVT and CEA that gives a predicted risk of stroke or death of <6%, considering that for rare events the odds ratio is approximately the same as the risk ratio. Also, a 95% prediction interval for stroke or death risk after 2 days was calculated using the same equation.

RESULTS

The literature search provided 1669 records, of which 754 were duplicates and 867 were excluded after abstract screening. Of the remaining 50 studies, 39 were excluded after obtaining the full text. Reason for exclusion were the following: 4 studies did not match the study design, 5 studies included patients undergoing CAS or aggregated cohorts of CAS and CEA, 21 studies did not include patients undergoing IVT, 1 study included patients treated for carotid occlusion, 2 studies analysed the effect of intra-arterial IVT, 6 studies compared patients undergoing IVT and IVT

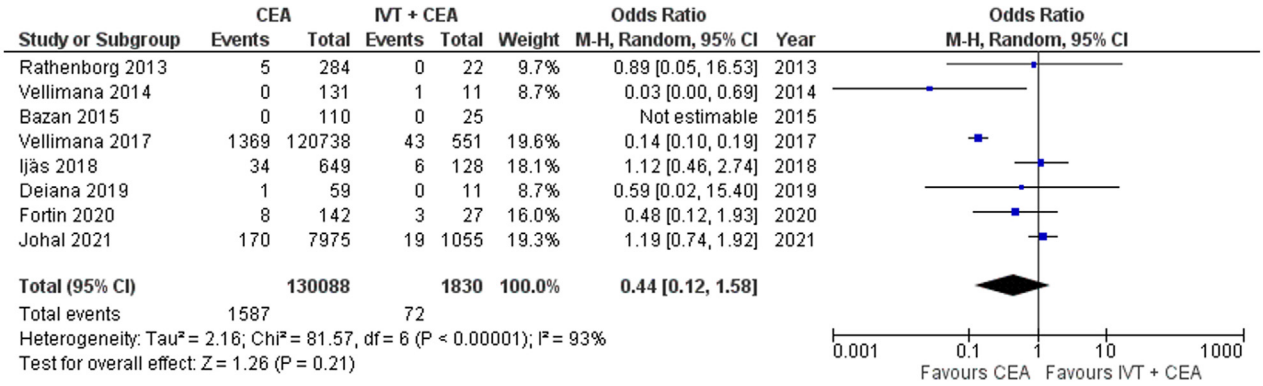

Fig 1. Forest plot for periprocedural stroke risk in patients with stroke undergoing carotid intervention after thrombolysis or without thrombolysis. *CEA*, carotid endarterectomy; *CI*, confidence interval; *IVT*, intravenous thrombolysis; *M-H*, Mantel–Haenszel. Odds ratios based on random effects model.

plus CEA. This process left 11 studies that were finally included for qualitative analysis and quantitative syntheses in the meta-analysis[9-19] (Supplementary Fig 1, online only).

A summary of the included studies is reported in Supplementary Table I (online only). A total of 326,682 patients were collected, including 135,644 treated by CEA alone and 2070 by IVT-CEA. All patients in the IVT-CEA group had an ischemic stroke as the index event at presentation. All patients in the control group undergoing CEA without prior thrombolysis had a symptomatic carotid stenosis[1,3,8]; only stroke was selected as index event in four studies,[13,16,18,19] whereas both stroke and TIA were included in seven studies.[9-12,14,15,17]

Qualitative analyses. Vellimana et al[15] reported a significantly increased risk of 30 day ICH, stroke, and death in the IVT- CEA group. Similarly, an increased risk of postoperative ICH[11] and 30-day mortality[13] were reported when CEA was performed after IVT. In one study,[19] there was a significant increased risk of neck hematoma after IVT. In seven studies IVT, before CEA did not impact the rate of postoperative stroke, mortality ICH, or neck bleeding.[9,10,12,14,16-18]

Postoperative stroke and stroke/death. The pooled rate of perioperative stroke was 4.2% in the IVT-CEA group and 1.3% in the CEA group (OR, 0.44; 95% CI, 0.12-1.58; $P = .21$) (Fig 1), with a high heterogenicity ($I^2 = 93\%$). The rate of stroke/death was 5.9% in patients undergoing IVT-CEA and 1.9% in those receiving CEA only (reference IVT-CEA, OR 0.42; 95% CI, 0.15-1.14; $I^2 = 92\%$; $P = .09$) (Fig 2). There was a high heterogenicity and a low risk for publication bias (Egger's test; $P = .373$; Begg's test; $P = .242$) (Supplementary Fig 2, online only).

The definition of perioperative stroke was not standardized in all the included studies. The presence of stroke was defined at discretion of the treating physician in most cases.[9-14,16-19] Vellimana et al[15] based the diagnosis of post-procedural stroke on the *International Classification of Diseases*, 9th edition, Clinical Modification, diagnostic code 997.02 (iatrogenic cerebrovascular infarction or hemorrhage).

A sensitivity analysis was performed after exclusion of studies with TIA as presenting symptom before CEA in the CEA group.[9-12,17] This led to a 3.6% stroke/death rate in IVT-CEA and 3.0% in CEA (reference IVT-CEA; OR, 1.42; 95% CI, 0.80-2.53; $I^2 = 50\%$; $P = .11$).

Intracerebral hemorrhage. Compared with CEA, patients undergoing IVT-CEA had a significantly higher risk of ICH (2.5% vs 0.1%; reference IVT-CEA, OR, 0.11; 95% CI, 0.06-0.21; $I^2 = 28\%$; $P < .001$) (Fig 3). Specific rates of ICH were retrievable in seven studies[11-15,17,18]; a clear definition of ICH was reported only in Bazan et al[12] and Vellimana et al,[11] who defined ICH based on clinical worsening of the neurological condition confirmed by hemorrhage using computed tomography scans or magnetic resonance imaging.

Any bleeding requiring intervention. In patients undergoing IVT-CEA there was a significantly higher risk of periprocedural neck hematoma requiring reintervention (3.6% vs 2.3%; reference IVT-CEA, OR, 0.61; 95% CI, 0.43-0.85; $I^2 = 0\%$; $P = .003$) (Fig 4).

Timing of CEA. The timing between IVT and CEA was not reported uniformly in the selected studies. Ahmed et al[13] had a median time from thrombolysis to CEA of 7.5 days; 64% of patients underwent CEA within 14 days from thrombolysis, 12% within 20 days, and 12% within 50 days. In the study by Bazan et al,[12] >50% of patients in the IVT-CEA group underwent revascularization within 72 hours. Deiana et al[17] and Fortin et al[18] reported a median time from IVT to revascularization of 8 days. In the report by Gunka et al,[14] the median time interval between IVT and CEA was 2 days, and 46% of patients underwent CEA within 24 hours from IVT. Ijäs et al[16] reported a median time from IVT to CEA of 9 days, with 5.5% undergoing CEA within 24 hours, 15.6% within

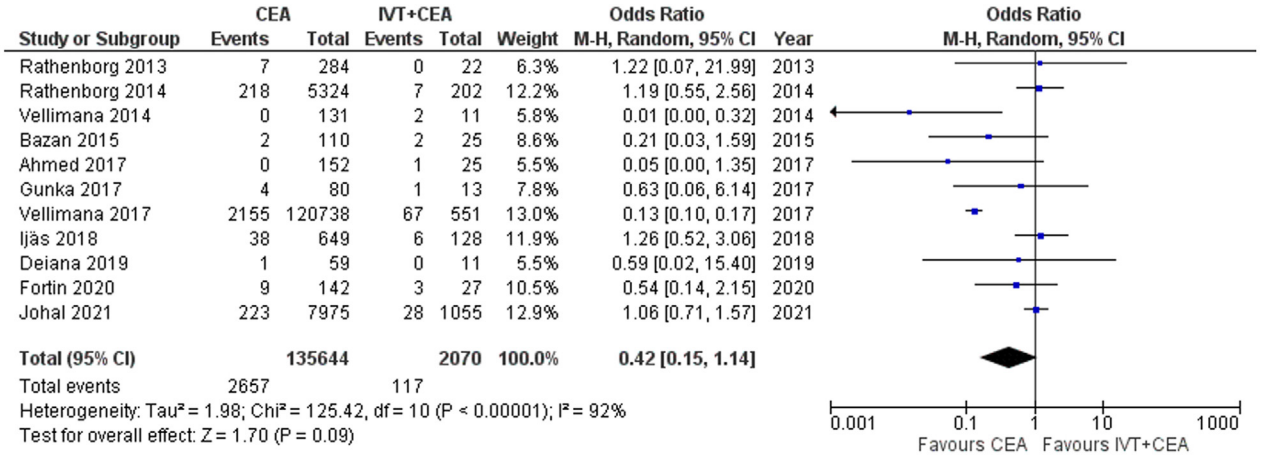

Fig 2. Forest plot for periprocedural stroke and death risk in patients with stroke undergoing carotid intervention after thrombolysis or without thrombolysis. *CEA*, carotid endarterectomy; *CI*, confidence interval; *IVT*, intravenous thrombolysis; *M-H*, Mantel–Haenszel. Odds ratios based on random effects model.

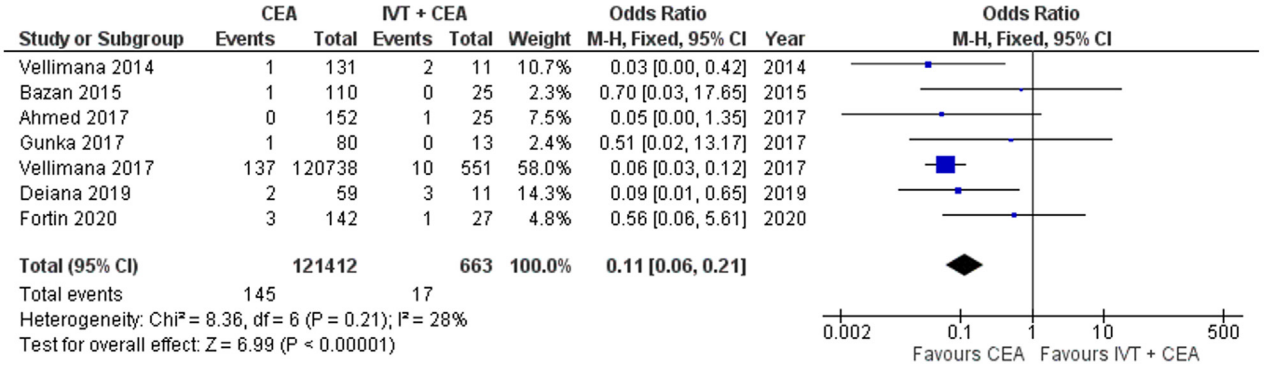

Fig 3. Forest plot for periprocedural intra-cerebral hemorrhage risk in patients with stroke undergoing carotid intervention after thrombolysis or without thrombolysis. *CEA*, carotid endarterectomy; *CI*, confidence interval; *IVT*, intravenous thrombolysis; *M-H*, Mantel–Haenszel. Odds ratios based on fixed effects model.

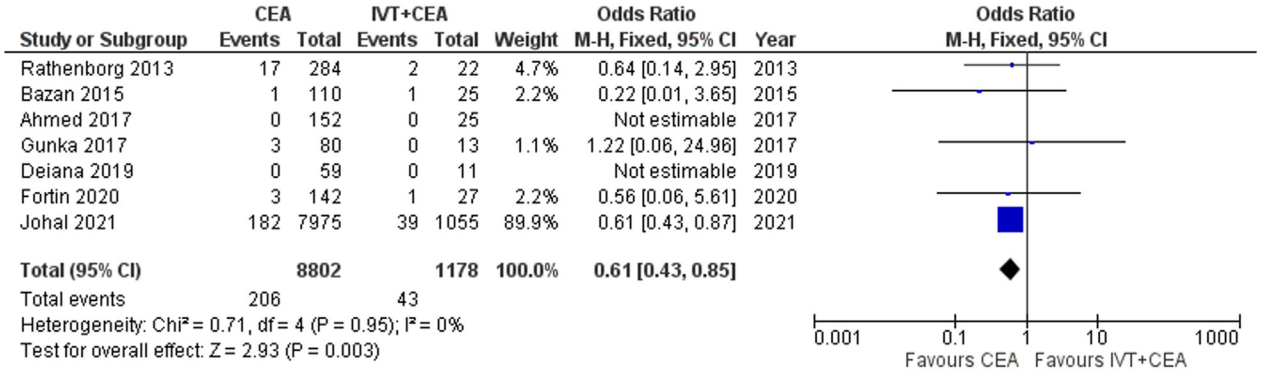

Fig 4. Forest plot for periprocedural local-hematoma risk in patients with stroke undergoing carotid intervention after thrombolysis or without thrombolysis. *CEA*, carotid endarterectomy; *CI*, confidence interval; *IVT*, intravenous thrombolysis; *M-H*, Mantel–Haenszel. Odds ratios based on fixed effects model.

48 hours, and 68.0% within 2 weeks from IVT. Johal et al[19] reported a median time from symptom to CEA of 10 days in the IVT cohort.

A few studies specifically reported the impact of CEA timing after IVT. Rathenborg et al[10] observed a stroke rate of 3.5% (95% CI, 1.69-6.99) among patients having

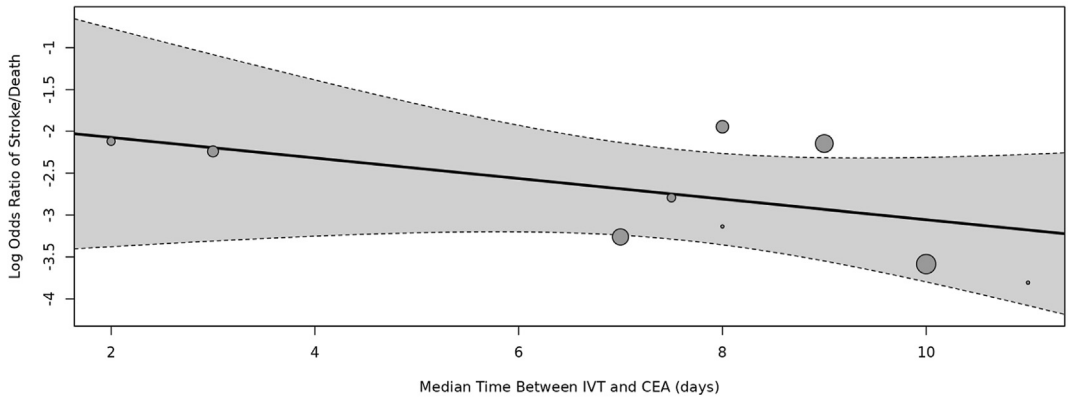

Fig 5. Bubble plot with fitted meta-regression line and 95% confidence intervals (CIs) showing an inverse relationship between logarithmic odds ratio of periprocedural stroke and death risk and time interval between thrombolysis and carotid endarterectomy (*CEA*). Bubble sizes vary with inverse of within study variance (weight in a fixed effect meta-analysis; $P = .268$).

IVT-CEA, with an increased risk if CEA was performed within 7 days (5.1%; 95% CI, 1.74-13.91) compared with 14 days (3.4%; 95% CI, 1.33-8.39). Vellimana et al[15] reported a progressive decrease in the risk of stroke and ICH in patients undergoing IVT-CEA; achieving a risk comparable with CEA without IVT at day 6. Ijäs et al[16] found no association between perioperative or postoperative ischemic stroke and the time between IVT and CEA ($P = .656$). Johal et al[19] found similar rates of stroke in IVT-CEA vs CEA if surgery was performed within the first 5 days from symptoms (2.3% vs 2.0%); however, neck hematomas were more common in patients undergoing IVT-CEA undergoing surgery within 5 days (2.0% vs 4.5%; $P = .042$). The metaregression analysis on the impact of time from IVT on stroke/death is displayed in Fig 5. There was an inverse relation between delay from IVT and stroke/death, which was not statistically significant ($P = .268$). Using the metaregression equation, the calculated delay of CEA that allows for a <6% risk was 4.6 days. The predicted stroke/death risk after 2 days was 7.8% (95% prediction interval, 2.0%-39.3%).

DISCUSSION

This systematic review and meta-analysis investigated the current outcomes of CEA after IVT, comparing the results with those receiving CEA without IVT. Overall IVT, did not impact the cumulative end point of stroke and death significantly (5.9% vs 1.9%; reference IVT-CEA; OR, 0.42; 95% CI, 0.15-1.14; $P = .09$), but was associated with an increased risk of ICH (2.5% vs 0.1%; reference IVT-CEA, OR, 0.11; 95% CI, 0.06-0.21; $P < .001$) and neck bleeding (3.6% vs 2.3%; reference IVT-CEA, OR, 0.61; 95% CI, 0.43-0.85; $P = .003$).

Current guidelines recommend CEA within 14 days from the index event in patients presenting with symptomatic carotid stenosis, granted a perioperative risk of stroke and death of <6%.[1,8] However, the perioperative risk of patients presenting with amaurosis fugax or TIA vs stroke may substantially differ. Patients with stroke suffer from a higher perioperative stroke rate, especially if CEA is performed within 48 hours, owing to the presence of the ischemic penumbra, the damage to the blood-brain barrier, and the greater severity of symptoms.[20-22] IVT may increase CEA perioperative risk additionally by facilitating hemorrhagic transformation of the brain infarct,[11,15] potentially questioning the actual benefit of CEA in this subset of patients. In our analysis, the pooled rate of stroke/death in the IVT group was 5.9%, falling within the 6% threshold recommended by the guidelines.[1,8] Nevertheless, the stroke rate was higher than CEA alone (1.9%); however, there was a high heterogenicity of results. After inclusion of only patients presenting with stroke (excluding those presenting with TIA or amaurosis), the rate of stroke/death was approximately 3% for both groups (reference IVT-CEA, OR, 1.42; 95% CI, 0.80-2.53; $P = .11$), with a lower heterogenicity ($I^2 = 50\%$). In our meta-analysis, it was not possible to correlate the results with the size of the infarct and ischemic penumbra and the severity of stroke, although this factor may be a major determinant of outcomes, as recently reported by Hayson et al,[23] who found that with tissue plasminogen activator (tPA) use before CEA/CAS was not related to stroke/hemorrhagic conversion. However, there was a significantly higher mortality in case of CEA/CAS with prior IVT ($P < .001$), that was strictly related to the severity of stroke, regardless of whether patients received tPA or not. Given that patients undergoing IVT are usually characterized by worse symptoms and larger brain infarct,[24] the specific additional risk provided by prior IVT is still difficult to assess based on our meta-analysis.

In our meta-regression, there was a trend toward a progressive decrease in stroke/death with the delay from IVT, with a calculated waiting time after IVT of 5 days to

achieve a <6% stroke/death risk. The half-life of tPA used in IVT is 4 to 7 minutes, and it may be reasonable to expect a complete drug clearance within 24 to 48 hours. However, the detrimental effect of IVT on CEA outcomes may persist also after tPA administration through two main mechanisms: IVT-related ICH may occur after 24 hours from alteplase administration in ≥20% of patients,[25] and IVT may cause cerebral microbleeds (in 15%-27% of patients)[3] that are not clinically evident, but represent an hallmark of blood-brain barrier damage and may predispose to ICH and other neurological complications in patients undergoing CEA. Nevertheless, IVT is not the only factor contributing to the stroke risk these patients; the presence of an infarcted brain area,[22] CEA early timing,[20,21] and severity of symptoms[26,27] are well-established risk factors for adverse neurological events after CEA. Another possible confounding factor is that the timing of CEA after IVT was not standardized, and it was not possible to understand the reason for early CEA vs more delayed CEA. It is possible that, in these situations, the choice for an early CEA after thrombolysis was dictated by recurrent or worsening symptoms, and this factor might have biased the results leaning toward worsened outcomes in those patients undergoing early interventions. Also, it is unclear if the effect of CEA timing is related to the time interval from IVT or from the index neurological event, because they essentially coincide, considering that IVT is performed in all cases within 4.5 h from stroke.

The results of our study are in line with a prior review by Kakkos et al.[24] They analyzed 25 studies on both CAS and CEA, including also case series with 1 to 10 patients, as well as noncomparative studies. Similar to our results, CEA outcomes in patients receiving IVT vs no IVT, periprocedural death/stroke was nonsignificantly higher after IVT (4.3% vs 1.5%), but ICH was significantly higher after IVT (2.2% vs 0.12%), as was local hematoma formation (3.6% vs 2.26%). Their meta-regression analysis demonstrated an inverse association between the time interval from IVT to undergoing CEA and the risk of periprocedural stroke/death ($P = .032$). Since 2021, no new randomized or comparative studies have been published. To minimize the risk of bias and to focus our analysis only to CEA, we included only comparative studies with ≥10 patients, excluding case series/reports and studies in which it was not possible to discriminate the results in CEA vs CAS.

Overall our interpretation of the results is that recent IVT provides an additional risk for CEA stroke/death that is driven essentially by ICH in patients operated in the early period (<5 days) after thrombolysis.[10,15,16,19,24] After this hazardous period of time, the risks of IVT-CEA may be comparable with those of CEA without prior thrombolysis. In clinical decision-making, the risk of IVT-CEA complications within 5 days should be weighed carefully against the risk for a recurrent stroke after IVT, without correction of the carotid stenosis. Ijäs et al,[16] in a multicenter registry including 128 IVT-CEA, described a 5.5% incidence of recurrent stroke or progression of symptoms while waiting for CEA, occurring after a median of 4 days from IVT. Further studies are necessary to determine which is the rate of recurrent stroke during the first 5 days after thrombolysis and to clarify which is the optimal timing of CEA in patients treated by IVT. In patients subjected to CEA after tPA, a perioperative care protocol that minimizes the risk for ICH should be adopted, and a repeated cerebral imaging (by computed tomography scan or magnetic resonance imaging) should be obtained before CEA to exclude patients with hemorrhagic evolution; future clinical investigations are required also to clarify which is the optimal approach in terms of operative technique, shunt use, blood pressure control, and antiplatelet and anticoagulation regimen.

The main limitation of this systematic review and meta-analysis was that there were no randomized controlled trials, and only retrospective comparative studies were included. The control groups of patients receiving only CEA were heterogenous, and included not only patients presenting with a stroke, but also TIA. The difference in outcomes of IVT-CEA vs CEA may reflect a different baseline patients selection, with higher stroke severity in patients undergoing IVT, larger brain infarction size, and worse functional outcome[24]; however, the currently available literature did not allow for an in-depth analysis of these aspects. Furthermore, the perioperative antiplatelet, anticoagulation, and heparin reversal protocols were not specified consistently, although they may have an important effect on hemorrhagic complications. In addition, other clinical factors, such as brain infarction size, blood pressure control, CEA operative technique, and shunt use, may have an important role in postoperative stroke and ICH,[1,3,21] but could not be investigated in our study fully. Finally, this review focused on the impact of IVT, because this modality represent the mainstay of treatment for acute ischemic stroke and may be associated with an increased risk of ICH; the outcomes of CEA after endovascular thrombectomy were not investigated.

CONCLUSIONS

In patients presenting with an acute ischemic stroke, CEA can be safely performed after a prior endovenous thrombolysis, maintaining a stroke/death risk of <6%. Nevertheless, patients undergoing CEA after IVT had an increased risk for ICH and neck bleeding, especially if CEA was performed within 5 days from the index stroke. CEA should be deferred for ≥5 days; further studies are necessary to clarify in which patients the risk/benefit ratio of IVT-CEA justifies a carotid intervention within the first 5 days and to investigate how to minimize the risk for hemorrhagic complications after IVT-CEA.

AUTHOR CONTRIBUTIONS

Conception and design: FS
Analysis and interpretation: FS, CZ, MM, AX, CD, FG, MP, MA
Data collection: FS, CZ, AX, EC
Writing the article: FS
Critical revision of the article: FS, CZ, MM, AX, EC, CD, FG, MP, MA
Final approval of the article: FS, CZ, MM, AX, EC, CD, FG, MP, MA
Statistical analysis: FS
Obtained funding: Not applicable
Overall responsibility: FS

DISCLOSURES

None.

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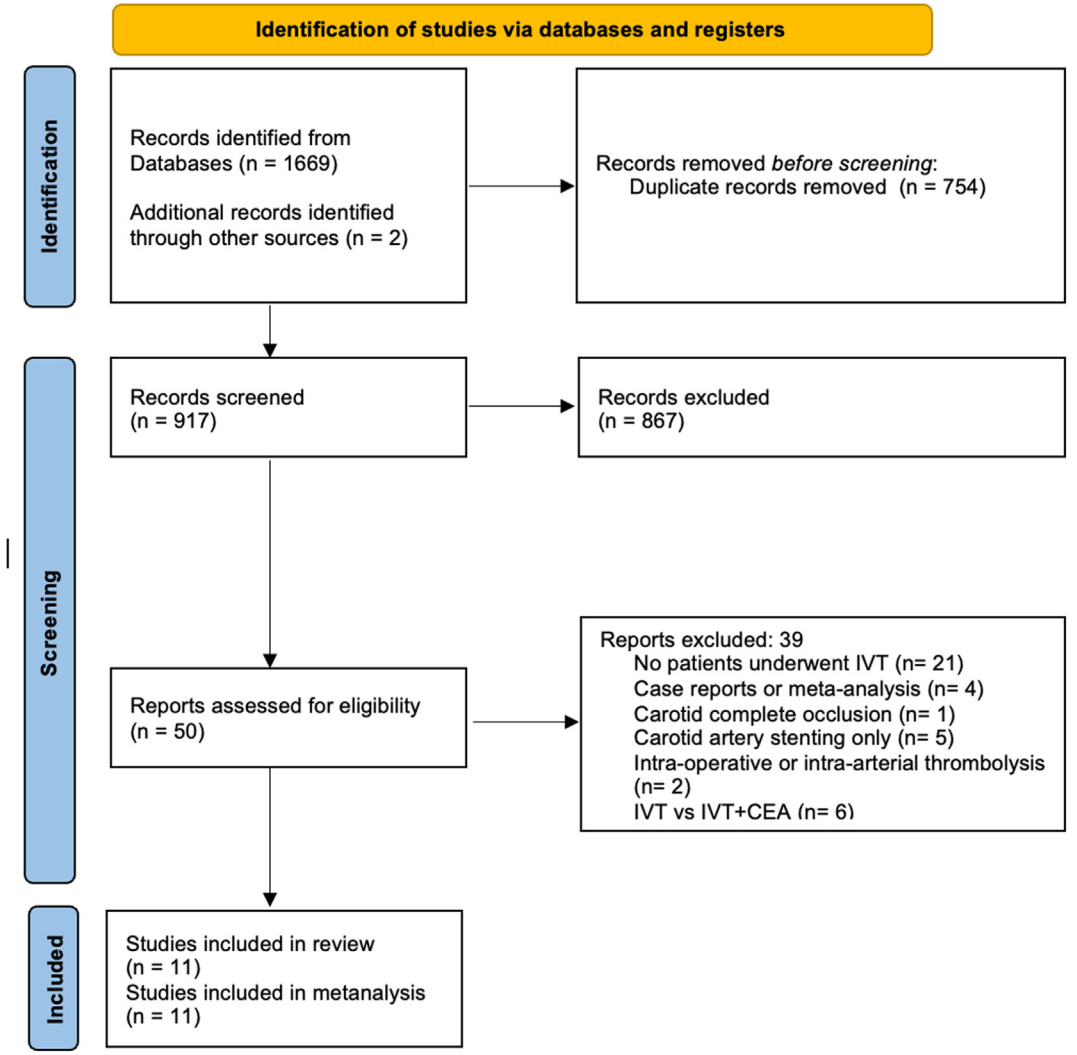
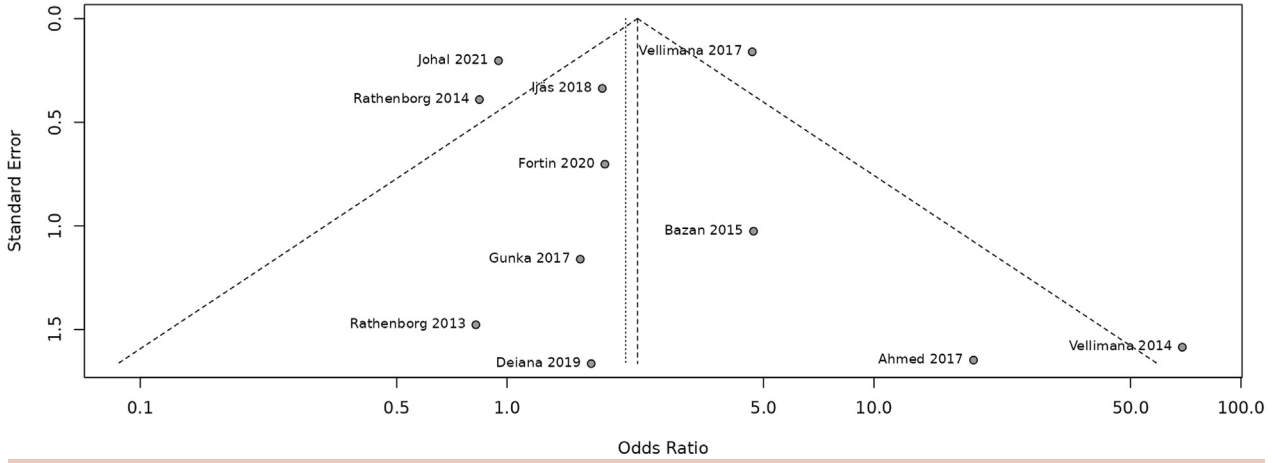
Supplementary Table (online only). Characteristics of the patients in the 11 studies included in the meta-analysis

Study	No. of patients	CEA	IVT-CEA	Age, years	Males	Hypertension	Diabetes mellitus	Dyslipidemia	Time from thrombolysis to revascularization, days	Stroke/death after CEA, %	Stroke/death after IVT-CEA, %
Rathenborg, 2013	306	284	22	70 (median)	211	NA	NA	NA	11 (median)	2.4	0
Rathenborg, 2014	5526	5324	202	71 (median)	3654	4117	1078	NA	NA	4.1	3.5
Vellimana, 2014	142	131	11	66.5 (median)	79	97	68	62	NA	0.7	18.2
Bazan, 2015	135	110	25	69 (mean)	67	154	78	129	3 (mean)	1.6	8.0
Ahmed, 2017	177	152	25	68 (mean)	NA	NA	NA	NA	7.5 (median)	0	4.0
Gunka, 2017	93	80	13	67 (median)	70	81	39	58	2 (median)	5.0	7.7
Vellimana, 2017	310,257	120,738	551	72 (mean)	168,529	238,898	96,179	NA	NA	1.7	7.8
Ijäs, 2018	777	649	128	69 (median)	NA	NA	NA	NA	9 (median)	5.8	10.2
Deiana, 2019	70	59	11	70 (median)	54	60	18	46	8 (median)	5.1	27.3
Fortin, 2020	169	142	27	68 (mean)	108	117	47	121	8 (median)	6.3	11.1
Johal, 2021	9030	7975	1055	71 (mean)	6128	6699	2239	7924	NA	2.4	2.1

CEA, Carotid endarterectomy; *IVT*, intravenous thrombolysis; *NA*, not available.



Supplementary Fig 1 (online only). PRISMA flowchart. *CEA*, carotid endarterectomy; *IVT*, intravenous thrombolysis.



Supplementary Fig 2 (online only). Funnel plot representing the composite outcome of stroke/death.