Journal of Neurology (2020) 267:1585–1593
https://doi.org/10.1007/s00415-019-09474-y

REVIEW

Endovascular therapy versus intravenous thrombolysis in cervical artery dissection-related ischemic stroke: a meta-analysis

Jueying Lin[1] · Yawei Liang[2] · Juexin Lin[2]

Received: 19 April 2019 / Revised: 10 July 2019 / Accepted: 11 July 2019 / Published online: 18 July 2019

Abstract

Background The purpose of our meta-analysis is to evaluate the endovascular therapy (EVT) in patients with cervical artery dissection (CAD)-related acute ischemic stroke (AIS) by comparing its efficacy and safety with the ones of intravenous thrombolysis (IVT).

Methods A systematic search on EVT to CAD-related ischemic stroke is performed. The meta-analysis models are applied to calculate either the risk ratio (RR) with 95% confidence interval (CI) or pooled proportions with 95% CI of favorable functional outcome (mRS = 0–2), excellent functional outcome (mRS = 0–1), symptomatic intracranial hemorrhage (SICH), mortality and recurrent stroke between EVT and IVT in CAD-related stroke. The differences between the two treatment groups are analyzed by the pooled odds ratio value and Chi-squared test.

Results A total of 190 patients given EVT and 139 IVT-alone patients are included. By comparing EVT alone and IVT alone, patients treated with EVT alone are more likely to experience favorable outcomes than those treated with IVT alone (71.2% vs 53.4%). Besides, there is no significant difference in excellent functional outcome, SICH, mortality and recurrent stroke between the EVT-alone and IVT-alone groups (all $P > 0.05$). Towards general EVT (EVT with or without IVT), the outcomes are not significantly different from those of IVT alone except for a higher mortality rate (10.2% vs 3.2%).

Conclusion Based on our findings, EVT is considered to be more efficacious than IVT for CAD-related AIS patients. Although EVT alone tends to be safe and promising, its safety needs to be further evaluated, particularly for EVT separating from IVT therapy.

Keywords Cervical artery dissection · Ischemic stroke · Endovascular therapy · Intravenous thrombolysis · Meta-analysis

Introduction

As the World Health Organization reported in 2016, strokes are one of the leading causes of death worldwide [1]. Compared to the other main causes, such as high blood pressure, high cholesterol, smoking and obesity, the CAD, as a rare but under-diagnosed cause of ischemic strokes, receives relatively less attention. Although only 2% of ischemic stroke cases are caused by CAD on average [2], this ratio boosts to 10–25% in young patients with age below 50 years [3]. The stroke could still cause disability or even mortality for the timely treatment. As such severity, particularly in the young, it is vital and urgent to discover favorable treatments. IVT has been proved to be a reperfusion therapy to AIS. Due to the induction of recanalization of the thrombosis and distal emboli, perfusion of cerebral blood flow is restored [4], which leads to nonwithholding of IVT in patients with CAD [5]. Thanks to this favorableness, a recent meta-analysis was conducted to evaluate IVT in patients with CAD-related AIS and revealed that the safety and efficacy of thrombolysis were observed similarly as those in patients with stroke from the other causes [6]. However, the presence of tandem internal carotid artery occlusion was demonstrated to predict poor outcome after IVT independently [7]. Lavallée et al. [8] also showed that CAD patients with tandem middle cerebral

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09474-y) contains supplementary material, which is available to authorized users.

✉ Jueying Lin
lin_jueying@hotmail.com

1 Emergency Department, Zhongshan Hospital Xiamen University, No. 201, South Hubin Street, Siming District, Xiamen 361000, Fujian, People's Republic of China

2 Department of Statistics, University of South Carolina, Columbia, SC, USA

artery occlusion stroke generally experienced a worse outcome and a lower rate of recanalization when treated with intravenous rt-PA than those received stent-assisted endovascular thrombolysis. Encouraged by the success in several case reports and case series on the feasibility and safety [8–20], EVT could be suggested as a complementary option to IVT in patients with CAD-related AIS including thrombectomy, stent implantation, intra-arterial thrombolysis (IAT), and angioplasty. More recently, the superiority of EVT over IVT is further demonstrated in randomized controlled trials (RCTs) [21–24]. We, therefore, conjecture that EVT would have better performance than IVT alone in CAD-related AIS. The goal of this meta-analysis is to assess the efficacy and safety of EVT compared with commonly recognized IVT treatment in patients with CAD-related AIS. However, most of the related studies [12, 14, 15, 19, 25] focused on EVT either with or without IVT as reperfusion therapy in CAD-related AIS without clear separations. Therefore, two meta-analyses are conducted in our study. First one is to compare the outcomes in the general-EVT group (as long as patients receive EVT) with those in the IVT-alone group (patients receive IVT alone). To diminish bias due to having IVT treatment in the general-EVT group, we perform the second meta-analysis by comparing the outcomes in the EVT-alone group (patients receive EVT alone) with those in the IVT-alone group, for which the data is limited.

Methods

Search strategy

We systematically search PubMed, EMBASE, Cochrane Library, and Web of Science databases as of June 2019. Queries conducted in each database are the combination of the following keywords: ("carotid artery dissection" or "vertebral artery dissection" or "cervical artery dissection") and ("stroke" or "brain ischemia" or "brain infarction") and ("endovascular treatment" or "thrombectomy" or "stent" or "intra-arterial thrombolysis" or "IAT" or "angioplasty" or "thrombolysis" or "IVT" or "intravenous thrombolysis" or "recombinant tissue plasminogen activator" or "rtPA"), without any imposition of language. In addition, the reference list of each obtained article is manually examined to avoid any loss of relevant data.

Selection criteria

Each included study has to meet the following criteria: (1) investigation of EVT (with or without IVT) in patients with CAD-related AIS must be either the main focus or subgroup analysis of the study. (2) The AIS is diagnosed according to WHO protocols [26]. (3) The CAD is extracranial dissection, without other artery dissection extending, of which the diagnosis should be confirmed with the imaging examinations. (4) It must be an observational study.

In addition, articles with small sample sizes (<3) are excluded from consideration. Duplicate publications and studies with overlapping data are also removed.

All the studies and reference lists are reviewed independently by the authors.

Data extraction and quality assessment

Let the IVT-alone group denote the patients who receive IVT only. Patients dealt with the treatment of EVT alone (e.g., IAT) or IVT followed by EVT are combined in the general-EVT group, while the EVT-alone group denotes the patients receiving EVT only. Data on the baseline characteristics, safety, and efficacy parameters from each pooled study are extracted independently by the authors, with discrepancies resolved through discussion or consulting original author. The baseline characteristics are extracted from selected studies directly including author, publication year, country, treatment type (general EVT/EVT alone/IVT alone), patients number, and stroke severity (NIHSS scores). Efficacy of each group is estimated by the proportion of favorable functional outcome (modified Rankin Scale, mRS = 0–2) and excellent functional outcome (mRS = 0–1). Safety of two treatments is assessed by comparing three pairs of pooled rates including SICH, mortality and recurrent stroke. Finally, articles are evaluated according to the standard checklist of Strengthening the Reporting of Observational Studies in Epidemiology, which is commonly used in observational studies and systematic reviews [27, 28]. In the meanwhile, non-qualified articles are excluded.

Statistical methods

Meta-analysis is conducted using the Review Manager (RevMan) Version 5.2 software and R software. Heterogeneity between studies is tested by the I^2 statistic, where the I^2 statistic is defined as the percentage of variation across studies caused by heterogeneity [29, 30]. A fixed-effects model will be applied when the I^2 value is less than 50%, which indicates the homogeneity. In contrast, a random-effects model is adopted when $I^2 > 50\%$, because of the significance of heterogeneity. A potential subgroup analysis could be conducted if necessary. We use the funnel plot and Egger's test to detect the potential publication bias (in Egger's test, $P > 0.05$ implies no significant publication bias). The pooled OR (associated 95% CI) and Chi-squared test of the pooled proportion in adverse events (SICH, mortality, and recurrent stroke) and outcomes (favorable functional outcome and excellent functional outcome) are calculated by R software for the purpose of comparison (general EVT vs IVT alone or EVT alone vs IVT alone). The 0.05 significance level is used throughout this article.

Results

Literature search and baseline characteristics of the eligible studies

The flow of the systematic study review process is illustrated in Fig. 1. We identify 483 literature through the initial comprehensive literature search. After removing duplicates, screening the titles and abstracts, assessing eligible criteria and evaluating qualities, only 14 studies meet our predefined inclusion criteria [8, 11–20, 25, 31, 32].

The EVT in patients of CAD-related AIS is studied by all eligible articles, of which nine also contain the study of IVT [8, 11–14, 17, 25, 31, 32]. In total, 329 patients of CAD-related AIS are included in the meta-analysis, of which 190 patients are treated with EVT (190 treated EVT with or without IVT, 59 treated with EVT alone) and 139 patients are treated with IVT alone. The baseline characteristics and

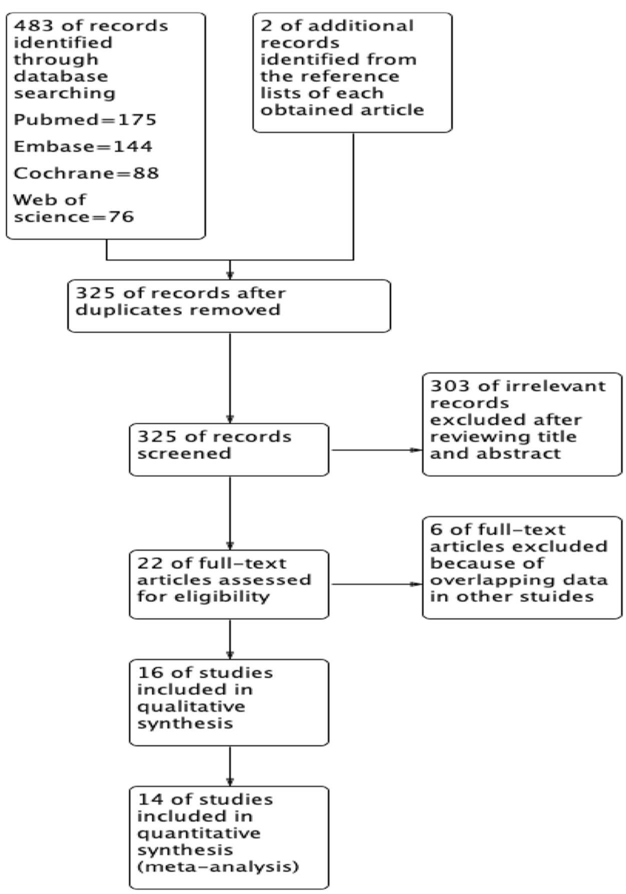

Fig. 1 Study flow diagram

the outcomes of each involved study, as well as the author information, are summarized in Table 1. Some irrelevant factors, including age, sex, race, vascular risk factors, location of dissection and onset to treatment time, are dropped because of their uniformity across studies. However, the NIHSS scores at presentation in Vergouwen et al. [13] appear to be inconsistent with those from other studies. To prevent the baseline bias of stroke severity, we consider using the adjusted NIHSS scores from the original manuscript (Vergouwen et al. [13]).

Result of meta-analysis

A popular way of comparing outcomes in the EVT and IVT groups among studies is to carry out a classic meta-analysis via a fixed (random)-effects model. However, the classic meta-analysis for nine studies [8, 11–14, 17, 25, 31, 32] (studied on both EVT and IVT groups) results in no statistically significant difference in either efficacy or safety. A possible reason might be that the number of patients is not large enough to draw any conclusion (37 of EVT-alone patients, 139 of IVT-alone patients). As a remedy, we include more EVT cases by adding additional five studies [15, 16, 18–20] which do not contain the IVT-alone case, then compare the two treatments by adopting the meta-analysis of proportions, which does not require the paired comparison in groups for each study. The idea is to first estimate the proportions of outcome from two groups separately, then perform a two-sample proportion test to compare the estimated proportions. In what follows, we present the results of the meta-analysis of pooled proportion for all 14 selected studies.

In concern of the impact of stroke severity on the prognosis of treatment, a subgroup meta-analysis of NIHSS score is performed for nine literature studying both EVT and IVT (see Appendix B for details). The first primary focus of our analysis is to compare the efficacy of EVT and IVT. To accomplish this, the mRS score is used to assess the prognosis of AIS in terms of the functional outcome [33]. Particularly, we consider the favorable functional outcome and the excellent functional outcome. The second primary focus is to compare the safety of two treatments. For this purpose, we analyze the SICH, mortality, and recurrent stroke. Since the SICH criteria vary across studies, we perform a subgroup analysis to examine the heterogeneity of different criteria in Appendix C.

For the assessment of efficacy, the likelihood of experiencing the favorable functional outcome and the excellent functional outcome at a period time follow-up (mostly 3 months) after stroke are compared in three treatment groups, respectively, in Table 2. The fixed-effects models are applied in the analysis because of low heterogeneity ($I^2 < 50\%$, $P > 0.05$) observed. The pooled proportion of favorable functional outcome in general-EVT group,

Table 1 Baseline characteristics and outcomes of the eligible studies

Author	Year	Country	Treatment type	Sample size, *N*	Stroke severity (NIHSS)	Proportion of favorable functional outcome (mRS = 0–2)	Proportion of excellent functional outcome (mRS = 0–1)	Proportion of SICH	Proportion of mortality	Proportion of recurrent stroke	Follow-up duration (months)
Baumgartner [11]	2008	Switzerland	EVT alone	4	17.5	2/4	NA	NA	NA	NA	3
Baumgartner [11]	2008	Switzerland	IVT alone	14	17.5	6/14	NA	NA	NA	NA	3
Engelter [12]	2012	Switzerland	General EVT	13	NA	5/13	NA	0/13	0/13	NA	3
Engelter [12]	2012	Switzerland	IVT alone	55	NA	32/55	NA	0/55	0/55	NA	3
Lavallée [8]	2007	France	EVT alone	6	17	6/6	4/6	0/6	0/6	0/6	15
Lavallée [8]	2007	France	IVT alone	4	16.3	1/4	1/4	0/4	1/4	0/4	15
Dziewas [31]	2003	Germany	EVT alone	2	NA	1/2	0/2	0/2	0/2	0/2	6
Dziewas [31]	2003	Germany	IVT alone	3	NA	2/3	2/3	0/3	0/3	0/3	6
Arnold [32]	2002	Switzerland	EVT alone	11	23	6/11	6/11	0/11	2/11	0/11	3
Arnold [32]	2002	Switzerland	IVT alone	19	18.9	8/19	7/19	1/19	2/19	0/19	3
Vergouwen [13]	2009	Netherlands	General EVT	2	20	1/2	1/2	0/2	1/2	NA	6
Vergouwen [13]	2009	Netherlands	EVT alone	1	24	1/1	1/1	0/1	0/1	NA	6
Vergouwen [13]	2009	Netherlands	IVT alone	2[a] (4)	14[a] (9.8)	2/2[a]	1/2[a]	0/2[a]	0/2[a]	NA	6
Jensen [14]	2017	USA	General EVT	24	13	13/20	NA	1/24	4/24	NA	3
Jensen [14]	2017	USA	IVT alone	11	10	3/5	NA	0/11	1/11	NA	3
Traenka [17]	2018	Switzerland	General EVT	38	16	15/38	9/38	5/38	6/38	NA	3
Traenka [17]	2018	Switzerland	EVT alone	13	NA	7/13	2/13	1/13	2/13	NA	3
Traenka [17]	2018	Switzerland	IVT alone	24	14.5	13/24	5/24	0/24	0/24	NA	3
Crespo Araico [25]	2017	Spain	General EVT	11	12	7/11	NA	NA	1/11	NA	3
Crespo Araico [25]	2017	Spain	IVT alone	7	11	4/7	NA	NA	0/7	NA	3
Marnat [15]	2018	France, Switzerland	General EVT	34	17.3	23/34	14/34	2/34	3/34	0/34	3
Fields [16]	2012	USA	General EVT	10	16	8/10	5/10	0/10	0/10	NA	3
Fields [16]	2012	USA	EVT alone	8	16.3	7/8	4/8	0/8	0/8	NA	3
Quintana [18]	2016	Spain	EVT alone	11	13.6	10/11	9/11	0/11	0/11	NA	3
Haussen [19]	2015	USA	General EVT	21	17.4	15/21	NA	0/21	2/21	1/21	3
Lekoubou [20]	2010	France	EVT alone	3	12	3/3	2/3	NA	0/3	NA	1

[a]The adjusted NIHSS scores are obtained from the original data of the literature

Table 2 Meta-analysis of the pooled proportion of outcomes between the EVT group and IVT group in CAD-related AIS

Outcomes	Treatment type	Number studies	Heterogeneity	Effected models of meta-analysis	Result of meta-analysis [pooled proportion (95% CI)]
Favorable functional outcome	General EVT	14	$I^2=44\%$; $P=0.29$	Fixed	61.8% (56.8%; 66.6%)
	EVT alone	9	$I^2=28\%$; $P=0.67$	Fixed	71.2% (58.4%; 81.3%)
	IVT alone	9	$I^2=0\%$; $P=0.90$	Fixed	53.4% (44.9%; 61.7%)
Excellent functional outcome	General EVT	9	$I^2=48\%$; $P=0.10$	Fixed	42.7% (34.1%; 51.8%)
	EVT alone	8	$I^2=47\%$; $P=0.22$	Fixed	50.9% (37.9%; 63.8%)
	IVT alone	5	$I^2=0\%$; $P=0.51$	Fixed	30.8% (19.8%; 44.5%)
SICH	General EVT	11	$I^2=32\%$; $P=1.00$	Fixed	4.7% (2.3%; 9.0%)
	EVT alone	7	$I^2=0\%$; $P=1.00$	Fixed	1.9% (0.3%; 12.4%)
	IVT alone	7	$I^2=0\%$; $P=1.00$	Fixed	0.8% (0.1%; 5.8%)
Mortality	General EVT	13	$I^2=0\%$; $P=0.99$	Fixed	10.2% (6.6%; 15.5%)
	EVT alone	8	$I^2=2\%$; $P=1.00$	Fixed	7.3% (2.8%; 17.8%)
	IVT alone	8	$I^2=46\%$; $P=1.00$	Fixed	3.2% (1.2%; 8.2%)
Recurrent stroke	General EVT	5	$I^2=0\%$; $P=0.57$	Fixed	0.4% (0.0%; 3.1%)
	EVT alone	3	$I^2=0\%$; $P=1.00$	Fixed	0.0% (0.0%; 5.0%)
	IVT alone	3	$I^2=0\%$; $P=1.00$	Fixed	0.0% (0.0%; 3.6%)

EVT-alone group and IVT-alone group are 61.8% (95% CI 56.8–66.6%), 71.2% (95% CI 58.4–81.3%) and 53.4% (95% CI 44.9–61.7%), respectively (Table 2). In other words, patients treated with EVT alone are more likely to experience a favorable outcome at the 3-month follow-up than those treated with IVT alone. The difference is statistically significant (pooled OR 2.157, 95% CI 1.117–4.168, $\chi^2=4.639$, $P=0.031$, Table 3). However, the difference in the same benchmark is not significant between general-EVT and IVT-alone groups (pooled OR 1.383, 95% CI 0.881–2.170, $\chi^2=1.679$, $P=0.195$, Table 3). On the other hand, the pooled proportion of excellent functional outcome is 42.7% (95% CI 34.1–51.8%) in general-EVT group, 50.9% (95% CI 37.9–63.8%) in EVT-alone group and 30.8% (95% CI 19.8–44.5%) in IVT-alone group (Table 2). It shows that there is no significant difference in 3 months post-treatment excellent functional outcome between any pair of groups (general EVT vs IVT alone: pooled OR 1.679, 95% CI 0.839–3.359, $\chi^2=1.692$, $P=0.193$; EVT alone vs IVT alone: pooled OR 2.333, 95% CI 1.058–5.148, $\chi^2=3.685$, $P=0.055$; Table 3). To summarize, in terms of efficacy, the outcome of EVT alone in patients of CAD-related AIS is more favorable than that observed from IVT-alone group.

To assess the safety of treatments, we analyze the pooled proportion of SICH, mortality and recurrent stroke. The fixed-effects models are applied due to the lack of

Table 3 The pooled OR (95% CI) and χ^2 test in outcomes between EVT group and IVT group in CAD-related AIS

Outcomes	Type of EVT	Proportion, %		Pooled OR (95% CI)	Chi-squared test	
		EVT	IVT alone		χ^2	P value
Favorable functional outcome	General EVT	61.3 (114/186)	53.4 (71/133)	1.383 (0.881, 2.170)	1.679	0.195
	EVT alone	71.2 (42/59)	53.4 (71/133)	2.157 (1.117, 4.168)	4.639	0.031
Excellent functional outcome	General EVT	42.7 (50/117)	30.8 (16/52)	1.679 (0.839, 3.359)	1.692	0.193
	EVT alone	50.9 (28/55)	30.8 (16/52)	2.333 (1.058, 5.148)	3.685	0.055
SICH	General EVT	4.8 (8/165)	0.7 (1/142)	7.185 (0.888, 58.163)	3.265	0.071
	EVT alone	1.8 (1/52)	0.7 (1/142)	2.765 (0.170, 42.026)	1.168962e−30[a]	1.000[a]
Mortality	General EVT	10.2 (19/186)	3.2 (4/125)	3.441 (1.142, 10.374)	4.396	0.036
	EVT alone	7.3 (4/55)	3.2 (4/125)	2.373 (0.571, 9.855)	0.687	0.407
Recurrent stroke	General EVT	1.4 (1/74)	0 (0/26)	NA[a]	1.797553e−31[a]	1.000[a]
	EVT alone	0 (0/19)	0 (0/26)	NA[a]	5.495905e−32[a]	1.000[a]

[a]Note that the results of pooled OR and Chi-squared test are not reliable because only a few occurrences of recurrent stroke (1 or 0 for EVT group and none for IVT-alone group) and SICH (1 for EVT-alone group and IVT-alone group) observed

significance in heterogeneity ($I^2 < 50\%$, $P > 0.05$). As presented in Table 2, the pooled proportion of SICH, mortality and recurrent stroke in general-EVT group are 4.7% (95% CI 2.3–9.0%), 10.2% (95% CI 6.6–15.5%), and 0.4% (95% CI 0.0–3.1%), respectively; those in EVT-alone group are 1.9% (95% CI 0.3–12.4%), 7.3% (95% CI 2.8–17.8%), and 0.0% (95% CI 0.0–5.0%), respectively; those in IVT-alone group are 0.8% (95% CI 0.1–5.8%), 3.2% (95% CI 1.2–8.2%), and 0.0% (95% CI 0.0–3.6%), respectively. By performing Chi square test for heterogeneity, one could conclude that there is no significant difference in SICH or mortality between EVT-alone group and IVT-alone group (pooled OR 2.765, 95% CI 0.170–42.026, $\chi^2 = 0.001$, $P > 0.05$, for SICH; pooled OR 2.373, 95% CI 0.571–9.855, $\chi^2 = 0.687$, $P > 0.05$, for mortality; Table 3). Although the difference of SICH between the general-EVT group and IVT-alone group is negligible (pooled OR 7.185, 95% CI 0.888–58.163, $\chi^2 = 3.265$, $P > 0.05$), we observe that the general-EVT group exhibits significantly higher mortality than the IVT-alone group (pooled OR 3.441, 95% CI 1.142–10.374, $\chi^2 = 4.396$, $P = 0.036$). Due to the lack of records in recurrent stroke in IVT-alone group, neither pooled OR nor Chi-squared test in Table 3 is accurate. Therefore, in terms of safety, the performances including SICH, mortality and recurrent stroke of EVT alone in patients of CAD-related AIS are similar to those observed from IVT-alone group, while the general EVT results in higher mortality to CAD-related AIS patients compared to IVT alone.

From the result of Egger's test (Table 4), one could conclude that there is no obvious publication bias in functional outcomes and adverse events (Egger's test $P > 0.05$). In addition, the publication bias is not present in our study since the symmetric inverted funnel shape is observed in the funnel plot (Fig. 2).

Discussion

The benefit of efficacy and safety of EVT in patients experiencing AIS has been shown in previous studies [21–24]. However, the effect of EVT in patients of CAD-related AIS is still uncertain. To the best of our knowledge, most studies in this area are small series or case reports without any RCT or meta-analysis included. Hence, it is worthwhile to undertake a superior approach by combining results of comparable research studies through a meta-analysis. Moreover,

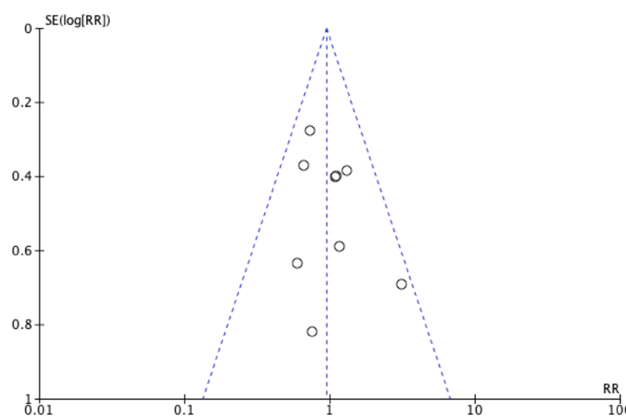

Fig. 2 Funnel plot

Table 4 Publication bias in our meta-analysis (Egger's test)

Events	Treatment type	Number studies	Egger's test	
			t value	*P* value
Favorable functional outcome	General EVT	14	0.745	0.470
	EVT alone	9	1.639	0.145
	IVT alone	9	− 0.065	0.950
Excellent functional outcome	General EVT	9	1.284	0.240
	EVT alone	8	− 0.031	0.977
	IVT alone	5	1.013	0.386
SICH	General EVT	11	− 2.174	0.058
	EVT alone	7	− 0.181	0.863
	IVT alone	7	− 0.265	0.802
Mortality	General EVT	13	− 1.200	0.256
	EVT alone	8	− 1.807	0.121
	IVT alone	8	− 1.273	0.250
Recurrent stroke	General EVT	5	− 0.206	0.850
	EVT alone	3	NaN[a]	NA[a]
	IVT alone	3	NaN[a]	NA[a]

[a]Note that the results of Egger's test of recurrent stroke in EVT-alone group and IVT-alone group are not reliable because there is no occurrence of recurrent stroke in these two groups

thrombolysis has been demonstrated to be a treatment option for CAD patients experiencing a stroke [34]. Consequently, we conduct meta-analyses to assess the efficacy and safety of EVT in patients of CAD-related AIS and compare it to IVT.

From the perspective of pathophysiology, CAD is the presence of intramural hemodynamics and abnormalities in the structure of the arterial wall involving the carotid or vertebral artery [35, 36]. Due to the increased risk of extension of underlying intramural hematoma, aneurysm rupture and predisposition to subarachnoid hemorrhage, receiving IVT might be dangerous to stroke patients with the setting of CAD [37]. Although the safety of IVT in patients of CAD-related AIS has been proved under repeated clinical practices [1, 3, 7, 20, 32], the efficacy of IVT is still in concern because of the poor outcome and the low rate of recanalization [7, 8]. More recently, the research attention has shifted to the investigation of arterial interventional therapy [8–20, 23, 25, 31, 32]. These studies demonstrate the feasibility of EVT in CAD-related AIS patients. Another recent study reveals the equivalent efficacy of IAT (a type of EVT) in patients of CAD-related AIS and other stroke patients [14]. Driven by those cheerful findings in EVT, we perform a meta-analysis to compare it with IVT in patients of CAD-related AIS.

Through the meta-analysis of comparing the EVT-alone group and the IVT-alone group, we have two observations. (1) For the efficacy assessment, we find the pooled proportion of favorable functional outcome and excellent functional outcome from EVT-alone group (71.2% and 50.9%, respectively) are significantly higher than those from IVT-alone group (53.4% and 30.8%, respectively). (2) For the safety evaluation, pooled SICH proportion, overall mortality and recurrent stroke proportion in EVT-alone group (1.9%, 7.3%, and 0.0%, respectively) are detected to be similar to (not significantly different from) those in IVT-alone group (0.8%, 3.2%, and 0.0%, respectively). When it comes to the comparison of general-EVT group and IVT-alone group, (1) the advantage in the efficacy of receiving general EVT is not significant, where the pooled proportion of favorable functional outcome and excellent functional outcome are 61.8% and 42.7%, respectively; (2) towards safety, the general-EVT group is even worse than the IVT-alone group by providing a similar pooled SICH proportion (4.7%), a significantly higher mortality rate (10.2%) and a similar recurrent stroke proportion (0.4%). Beyond the meta-analysis, the subgroup analysis of NIHSS score (Appendix B) shows that the effect of initial stroke severity on the efficacy of EVT could be negligible. Similarly, the subgroup analysis of SICH (Appendix C) shows that the difference in SICH criteria would not introduce heterogeneity.

It is not surprising to see the superiority of EVT alone to IVT alone in CAD-related AIS patients. A potential factor leading to this result might be the presence of an obstructive lesion in the carotid or vertebral artery, which is a common symptom in hemodynamic problems of CAD. Due to the presence of tandem occlusion, CAD patients often present with carotid severe stenosis and a regional decease of cerebral perfusion pressure, which would increase the risk of rethrombosis after incomplete recanalization. Tandem occlusion in carotid or vertebral artery is associated with worse outcomes and lower chance of recanalization after IVT than isolated cerebral lesions [7, 38]. However, interventional therapy could improve the above condition by providing a higher likelihood of achieving successful reperfusion and a lower chance of complications [8, 11, 19]. Therefore, with those favorable insights of EVT from aforementioned studies, it is rational to observe a better outcome of EVT in our meta-analysis and expect a better clinical outcome of EVT than that of IVT in patients with CAD-related AIS. In particular, for the tandem lesion patients, we would suggest trying a more aggressive intervention.

Towards a broader view of the EVT, the outcomes of the general-EVT group are not significantly different from those of IVT-alone group except for a higher mortality rate. Since the general-EVT group consists of patients treated by EVT either with or without IVT, the unclear proportion of mixed IVT and EVT hinders us to investigate the real reason for observing a higher mortality rate. Future interesting studies would be to investigate whether EVT exists mutual effect (such as bleeding or other complications) to IVT in patients with CAD-related AIS, and thereby increases the mortality risk.

There's no doubt that the current meta-analysis has several limitations. First, although the included studies are all in high quality, the selection of subjects and collection of clinical data can still be biased since none of the studies is a randomized controlled trial. Instead, they are all retrospective designed observational studies. Second, because of the novelty of our topic, the studies on EVT of CAD-related AIS are rare and of small sample sizes. Albeit 14 reports have been included, the total number of patients involved in our meta-analysis is still not a large scale. In addition, the type of antithrombotic drug used after onset is not available, which might influence the hemorrhagic adverse events [39].

Conclusions

Based on our findings, EVT is considered to be more efficacious than IVT for CAD-related AIS patients. Although EVT alone tends to be safe and promising, its safety needs to be further evaluated, particularly for EVT separating from IVT therapy. Since our meta-analysis results are from an indirect comparison, further large-scale randomized clinical studies are necessary to assess whether EVT can be recommended as a routine treatment for patients with CAD-related AIS.

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

Appendix A: The authors

Name	Location	Role	Contribution
Jueying Lin	Zhongshan Hospital Xiamen University, Xiamen	Author	Design study; searched literatures; extraction of data; analyzed the data; drafted the manuscript for intellectual content
Yawei Liang	University of South Carolina, Columbia	Author	Searched literatures; extraction of data; analyzed the data; drafting and revision of manuscript
Juexin Lin	University of South Carolina, Columbia	Author	Analyzed the data by statistics; drafting and revision of manuscript

Appendix B: Subgroup meta-analysis of NIHSS

The analysis is conducted with a threshold at 20 (no NIHSS, NIHSS 9–19, and NIHSS ≥ 20). As shown in the data, patients with less severe stroke tend to receive more benefits from ET than simple IVT. Nevertheless, we do not have enough evidence to conclude a statistically significant difference between two treatment groups (RR 0.67, 95% CI 0.35–1.30, $P = 0.24$, for no NIHSS strata; RR 1.02, 95% CI 0.72–1.46, $P = 0.89$, for NIHSS 9–19 strata; RR 2.09, 95% CI 0.57–2.06, $P = 0.80$, for NIHSS ≥ 20 strata; ESM Figure B) or among the NIHSS subgroups (heterogeneity test of subgroups: $I^2 = 0\%$, $P > 0.05$, ESM Figure B).

Appendix C: Subgroup meta-analysis of SICH criteria

Most selected studies fall in three of widely used SICH criteria: NINDS criteria [40], SITS criteria [41], European Cooperative Acute Stroke Study (ECASS II) criteria [42]. For those studies without clear definition on SICH, we contact the authors for clarification and classify the SICH criteria according to their response. But for those without responses, we mark them as a separate group "no clear definition". Then a subgroup meta-analysis of SICH is conducted across all SICH standards (NINDS, SITS, ECASS II, no clear definition), which results in non-heterogeneity of its different standards ($I^2 = 11.3\%$, $P > 0.05$, ESM Figure C).

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, on behalf of the American Heart Association Statistics Committee, and Stroke Statistics Subcommittee et al (2017) Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 135:e229–e445
2. Schievink SI (2001) Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 345(6):898–906
3. Vergouwen MD (2012) Intravenous thrombolysis in ischaemic stroke secondary to cervical artery dissection: safe but not effective? Eur J Neurol 19(9):1155–1156
4. Wardlaw JM, Murray V, Berge E, del Zoppo GJ (2014) Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 7:CD000213. https://doi.org/10.1002/14651858.CD000213.pub3
5. Wardlaw JM, Murray V, Berge E et al (2009) Thrombolysis for acute ischaemic stroke. Cochrane Libr 4:CD000213. https://doi.org/10.1002/14651858.CD000213.pub2
6. Zinkstok SM, Vergouwen MD, Engelter ST et al (2011) Safety and functional outcome of thrombolysis in dissection-related ischemic stroke: a meta-analysis of individual patient data. Stroke 42(9):2515–2520
7. Rubiera M, Ribo M, Delgado-Mederos R et al (2006) Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke J Cereb Circ 37(9):2301
8. Lavallée PC, Mazighi M, Saint-Maurice JP et al (2007) Stent-assisted endovascular thrombolysis versus intravenous thrombolysis in internal carotid artery dissection with tandem internal carotid and middle cerebral artery occlusion. Stroke 38(8):2270–2274
9. Lewis JB, Merwick A, Laoide RÓ et al (2013) Therapeutic decision making in acute stroke due to carotid artery dissection: a potential role for percutaneous vascular intervention following intravenous thrombolysis. Case Rep Vasc Med 2013:121696. https://doi.org/10.1155/2013/121696
10. Janjua N, Qureshi AI, Kirmani J et al (2006) Stent-supported angioplasty for acute stroke caused by carotid dissection. Neurocrit Care 4(1):47–53
11. Baumgartner RW, Georgiadis D, Nedeltchev K et al (2008) Stent-assisted endovascular thrombolysis versus intravenous thrombolysis in internal carotid artery dissection with tandem internal carotid and middle cerebral artery occlusion. Stroke 39:e27–e28
12. Engelter ST, Dallongeville J, Kloss M et al (2012) Thrombolysis in cervical artery dissection–data from the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) database. Eur J Neurol 19(9):1199–1206
13. Vergouwen MD, Beentjes PA, Nederkoorn PJ (2009) Thrombolysis in patients with acute ischemic stroke due to arterial extracranial dissection. Eur J Neurol 16:646–649
14. Jensen J, Salottolo K, Frei D et al (2017) Comprehensive analysis of intra-arterial treatment for acute ischemic stroke due to cervical artery dissection. J Neurointerventional Surg 9(7):654–658. https://doi.org/10.1136/neurintsurg-2016-012421

15. Marnat G, Bühlmann M, Eker OF et al (2018) Multicentric experience in distal-to-proximal revascularization of tandem occlusion stroke related to internal carotid artery dissection. Am J Neuroradiol 39(6):1093–1099
16. Fields JD, Lutsep HL, Rymer MR et al (2012) Endovascular mechanical thrombectomy for the treatment of acute ischemic stroke due to arterial dissection. Interv Neuroradiol J Peritherapeutic Neuroradiol Surg Proced Relat Neurosci 18(1):74
17. Traenka C, Jung S, Gralla J et al (2018) Endovascular therapy versus intravenous thrombolysis in cervical artery dissection ischemic stroke—results from the SWISS registry. Eur Stroke J 3(1):47–56. https://doi.org/10.1177/2396987317748545
18. Murias Quintana E, Vega Valdés P, Morales Deza E et al (2016) Endovascular reconstruction of internal carotid artery dissection in patients with acute ischemic stroke using the Wingspan stent. Interv Neuroradiology J Peritherapeutic Neuroradiol Surg Proced Relat Neurosci 22(6):700–704
19. Haussen DC, Jadhav A, Jovin T et al (2015) Endovascular management vs intravenous thrombolysis for acute stroke secondary to carotid artery dissection: local experience and systematic review. Neurosurgery 78(5):709
20. Lekoubou A, Cho TH, Nighoghossian N et al (2010) Combined intravenous recombinant-tissular plasminogen activator and endovascular treatment of spontaneous occlusive internal carotid dissection with tandem intracranial artery occlusion. Eur Neurol 63(4):211–214
21. Berkhemer OA, Fransen PS, Beumer D et al (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 372(1):11
22. Goyal M, Demchuk AM, Menon BK et al (2015) Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 372(11):1019–1030
23. Jovin TG, Chamorro A, Cobo E et al (2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 372(24):2296–2306
24. Saver JL, Goyal M, Bonafe A et al (2015) Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 372(24):2285–2295
25. Crespo Araico LA, Vera Lechuga R, Cruz-Culebras A et al (2019) Reperfusion therapy in patients with acute ischaemic stroke caused by cervical artery dissection. Neurologia 34(3):153–158. https://doi.org/10.1016/j.nrl.2016.11.005
26. WHO Special Report (1989) Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on stroke and other cerebrovascular disorders. Stroke 20(10):1407–1431
27. Vandenbroucke JP, von Elm E, Altman DG et al (2014) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 12(12):1500–1524. https://doi.org/10.1016/j.ijsu.2014.07.014
28. Elm EV, Altman DG, Egger M et al (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. Der Internist 49(6):688–693
29. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
30. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
31. Dziewas R, Konrad C, Dräger B et al (2003) Cervical artery dissection-clinical features, risk factors, therapy and outcome in 126 patients. J Neurol 250(10):1179–1184
32. Arnold M, Nedeltchev K, Sturzenegger M et al (2002) Thrombolysis in patients with acute stroke caused by cervical artery dissection: analysis of 9 patients and review of the literature. Arch Neurol 59(4):549–553
33. Broderick JP, Adeoye O, Elm J (2017) Evolution of the Modified Rankin Scale and its use in future stroke trials. Stroke 48(7):2007–2012. https://doi.org/10.1161/STROKEAHA.117.017866
34. Lin J, Sun Y, Zhao S, Xu J, Zhao C (2016) Safety and efficacy of thrombolysis in cervical artery dissection-related ischemic stroke: a meta-analysis of observational studies. Cerebrovasc Dis 42(3–4):272–279. https://doi.org/10.1159/000446004
35. Schievink WI, Wijdicks EF, Kuiper JD (1998) Seasonal pattern of spontaneous cervical artery dissection. J Neurosurg 89(1):101–103
36. Benninger DH, Georgiadis D, Kremer C et al (2004) Mechanism of ischemic infarct in spontaneous carotid dissection. Stroke 35(2):482–485
37. Engelter ST, Brandt T, Debette S et al (2007) Antiplatelets versus anticoagulation in cervical artery dissection. Stroke 38(9):2605–2611
38. Kim YS, Garami Z, Mikulik R et al (2005) Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. Stroke 36(4):869–871
39. Lyrer P, Engelter S (2010) Antithrombotic drugs for carotid artery dissection. Cochrane Database Syst Rev 10:CD000255. https://doi.org/10.1002/14651858.CD000255.pub2
40. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333:1581–1587
41. Wahlgren N, Ahmed N, Dávalos A et al (2007) Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 369(9558):275–282
42. Trouillas P, von Kummer R (2006) Classification and pathogenesis of cerebral hemorrhages after thrombolysis in ischemic stroke. Stroke 37:556–561