Impact of collateral circulation status on favorable outcomes in thrombolysis treatment: A systematic review and meta-analysis

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Abstract. Collateral circulation affects the prognosis of patients with acute ischemic stroke (AIS) treated by thrombolysis. The present study performed a systematic assessment of the impact of the collateral circulation status on the outcomes of patients receiving thrombolysis treatment. Relevant full-text articles from the Cochrane Library, Ovid, Medline, Embase and PubMed databases published from January 1, 2000 to November 1, 2016 were retrieved. The quality of the studies was assessed and data were extracted by 2 independent investigators. The random-effects model was used to estimate the impact of good vs. poor collateral circulation, as well as baseline characteristics, on the outcome within the series presented as risk ratios. Subgroup analyses explored the potential factors that may interfere with the effects of the collateral circulation status on the outcome. A total of 29 studies comprising 4,053 patients were included in the present meta-analysis. A good collateral circulation status was revealed to have a beneficial effect on favorable functional outcome (modified Rankin scale, 0-3 at 3-6 months; P<0.001) and a higher rate of recanalization (P<0.001) compared with poor collateral circulation. Good collateral circulation was also associated with a lower rate of symptomatic intracranial hemorrhage (P<0.01), a lower rate of mortality (P<0.01) and a smaller infarct size (P<0.01). In conclusion, good collateral circulation was demonstrated to have a favorable prognostic value regarding the outcome for patients with AIS receiving thrombolysis treatment. Assessment of collateral circulation and penumbra area during pre-treatment imaging within an appropriate time-window prior to thrombolytic therapy will therefore improve the identification of AIS patients who may benefit from thrombolysis treatment.

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Introduction

Stroke is a severe health issue worldwide. Available treatments are limited and it is currently the second leading cause of death (1). Prompt thrombolytic therapy is critical for improving the clinical prognosis of patients with acute ischemic stroke (AIS). The collateral circulation is a major factor affecting the effect of thrombolytic therapy and good collateral circulation significantly influences the prognosis of patients, thereby preventing and delaying permanent neurological damage (2). The collateral circulation maintains the blood supply to the infarction area prior to recanalization after AIS (3). It also prevents the expansion of the infarct size, provides a better clinical prognosis, increases the rate of recanalization and potentially prolongs the time window prior to the requirement of endovascular treatment (ET) (4-7). In addition, good collateral circulation reduces the risk of hemorrhagic transformation (HT) and mortality after thrombolysis therapy (8).

A previous systematic review by Leng *et al* (9) analyzed the available evidence on the correlations between collateral circulation and the outcomes in patients with AIS following intravenous thrombolysis therapy (IVT). However, it did not include studies in which endovascular treatment was used. In the present study, the relevant literature published until November 2016 was systematically reviewed and a meta-analysis was performed to evaluate the association between collateral circulation determined prior to thrombolytic treatment and outcomes.

Materials and methods

Reporting and definitions. The relevant studies were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-Analysis of Observational Studies in Epidemiology (10,11). The definition of good or poor collateral circulation status prior to treatment was in accordance with that in the primary studies; for studies classifying the collateral status in >2 categories, it was categorized as good and poor in the present analysis by adopting the dichotomization methods from other primary studies using the same imaging modality to gauge the collateral status. The outcomes, including good recanalization/reperfusion, HT, final infarct size, mortality and the favorable functional outcome at 3-6 months, were defined in the studies.

Information sources. Potentially eligible studies as full-text articles, published from January 2000 to November 2016, were identified through a search of the Cochrane Library, Ovid, Embase, Medline and PubMed databases. The search was restricted to articles published in English language. In brief, the search terms included 'stroke', 'collateral', 'thrombolysis', 'thromboly' and 'endovascular'. A manual search was also performed by checking the references of pertinent review articles and relevant original research articles.

Study selection and eligibility criteria. The criteria for the included studies were as follows: i) Case-control, cohort or randomized controlled trial (RCT) studies on patients (>18 years of age) with acute ischemic stroke; ii) collateral circulation status was evaluated prior to the initiation of thrombolysis treatment; iii) The correlation between pre-treatment collateral circulation status and outcome in patients with AIS was described. Animal studies, non-RCTs and duplicate reports were excluded.

Data collection and parameters. All titles and abstracts were initially screened by one investigator to identify potentially relevant studies for inclusion. Relevant studies were retrieved in full text and reassessed by two researchers to determine the eligibility for inclusion with regard to publication characteristics, study populations, patient demographics, onset-to-treatment time, mode of thrombolysis therapy, methods to assess the collateral circulation status, methods to define successful reperfusion and/or recanalization and definition of HT.

Statistical analysis. Cochrane RevMan (version 5.3; The Cochrane Institute, London, UK) was used for analyzing the data. The impact of good vs. poor pre-treatment collateral circulation on the outcomes was evaluated by a fixed-effects model if the heterogeneity was low or the random-effects model with the results expressed as the risk ratio (RR) and 95% confidence interval (CI). For the clinical or imaging outcomes, subgroup analyses were performed with stratification by different sample sizes, prescribed durations of thrombolysis treatment, median baseline National Institutes of Health Stroke Scale (NIHSS), treatment type and mean (or median) age. To assess the publication bias, a visual inspection of the funnel plot was applied in the analysis of any assessed variable.

Inter-study and -subgroup heterogeneities were evaluated by χ^2 and I^2 statistics ($P<0.10$ and $I^2 >50\%$ was considered to indicate significant heterogeneity). A sensitivity analysis was also performed by removing individual trials from the meta-analysis.

Results

Study selection and characteristics. The selection of the studies identified through the literature search was

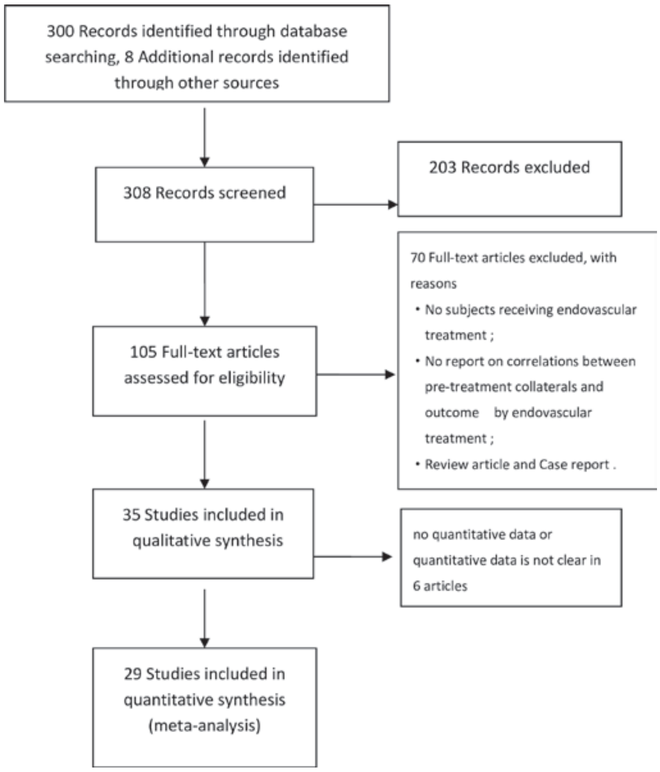

Figure 1. Schematic representation of the screening and selection of studies for inclusion in the present meta-analysis.

schematically represented in a flowchart illustrated in Fig. 1. Of the 308 records retrieved from several databases and manual searches, 29 primary studies comprising 4,053 subjects were included in the systematic review, of which 12 were retrospective studies, 17 were prospective studies, 7 were multicenter studies and 22 were single-center studies. A total of 9 studies described the treatment with IVT alone, and in the other 20 studies, patients received IVT with subsequent ET or ET only (Table I) (7,8,12-38). All of the studies used tissue plasminogen activator for the thrombolysis treatment, while that by Christoforidis *et al* (7) used tissue plasminogen activator, urokinase and pro-urokinase. The duration of thrombolysis treatment was 3-6 h in 12 studies and >6 h in 5 studies, extending up to 12 h. However, the time window was not prescribed in 6 of the studies. The assessment of the pre-treatment collateral circulation status was performed using different imaging methods, which were computed tomography (CT) angiography in 22 studies (7,8,12,14,15,17,18,22-35,37), while others included digital subtraction angiography (13,36), fluid-attenuated inversion recovery imaging (19,21), and CT or magnetic resonance perfusion imaging (16,20,38) (Table I).

Favorable functional outcome. The present review included 22 studies (comprising 2,608 subjects) that reported on functional outcome. The rate of favorable functional outcome [modified Rankin scale (mRS) 0-3 at 3-6 months] was doubled in the GC statue group as compared with that in the PC group (RR=2.33; 95% CI, 1.95-2.78; P<0.001; Fig. 2). This effect of good collateral circulation did not differ significantly between the studies (Cochran's Q=36.47; P=0.02; I^2=42%). In the subgroup analyses presented in

Table I. Summary of the characteristics of the primary studies.

									Collateral circulation grading					
											Dichotomized collateral status			
First author	Country	Year	Sample size (n)	Thrombolysis type	Mean age (years)	Median NIHSS at baseline	Duration of IVT (h)	Mean interval from onset to treatment (min)	Imaging modality	Grading method	Good	Poor	Study quality[a]	(Refs.)
García-Tornel	Canada	2016	108	IVT, ET	70	17	8	215	CTA	University of Calgary collateral circulation scale (0-5)	4-5	0-1	A	(12)
Angermaier	Germany	2011	25	ET	67	14	6	244	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(13)
Bang	USA/Korea	2011	222	ET	65	16	UNK	UNK	DSA	ASITN/SIR collateral circulation graded on a 5-point scale (0-4)	2-4;	0-1	A	(8)
Berkhemer	Netherlands	2016	231	ET	UNK	UNK	6	UNK	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(14)
Brunner	Germany	2014	246	IVT	74	14	3 or 4.5	160	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(15)
Calleja	Spain	2013	54	IVT	73	10	4.5 or >4.5 based on imaging	237	CTP	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(16)
Christoforidis	USA	2008	104	ET	68	16	12	285	DSA	LCC graded on a 5-point scale (1-5)	1-2	3-5	A	(7)
Fanou	Canada	2015	395	IVT, ET	72	14	4.5	147	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(17)
Gerber	Germany	2016	93	IVT, ET	69	17	UNK	252	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(18)
Kufner	Germany	2015	62	IVT	71	11	4.5	UNK	FLAIR MRI	Number of sections of FLAIR with hyperintense vessels	≤4	>4	A	(19)
Lee	Korea	2000	17	IVT	63	15	3 or 7	UNK	CTP	Percentage of severe Vdeficit in MCA territory	≤erc	33-50%	A	(20)

Table I. Continued.

									Collateral circulation grading					
											Dichotomized collateral status			
First author	Country	Year	Sample size (n)	Thrombolysis type	Mean age (years)	Median NIHSS at baseline	Duration of IVT (h)	Mean interval from onset to treatment (min)	Imaging modality	Grading method	Good	Poor	Study quality[a]	(Refs.)
Lee	USA	2009	52	IVT	69	8	3	UNK	FLAIR MRI	Distal hyperintense vessels (none/ subtle/prominent)	Prominent[b]	None[b]	A	(21)
Lima	USA	2010	196	IVT, ET	69	13	UNK	UNK	CTA	LCC graded on a 5-point scale (1–5)	UNK	UNK	A	(22)
Menon	North America, Australia, Europe	2015	185	IVT, ET	UNK	UNK	3	UNK	CTA	LCC in ACA-MCA and PCA-MCA regions (0-10)	6-10	0-5	A	(23)
Marks	USA	2014	60	IVT, ET	64	19	12	360	MRI	Collateral Flow Grading System with a 4-point scale (0-4)	3-4	0-2	A	(24)
Miteff	Australia	2009	92	IVT, ET	74	17	6	UNK	CTA	LCC graded into 3 categories (good, moderate, poor)	Good	Moderate, poor	A	(25)
Nambiar	Canada	2013	84	IVT, ET	65	14	3 for IVT	UNK	CTA	rLMC score based on ASPECTS	rLMC score (11-20)	rLMC score (0-10)	A	(26)
Ramaiah	Australia	2013	87	IVT, ET	66	18	UNK	329	CTA	LCC graded on a 4-point scale (0-3)	3	0-2	A	(27)
Saarinen	Finland	2014	105	IVT	69	13	3	132	CTA	LCC graded on a 5-point scale (0-4)	2-4	0-1	A	(28)
Sallustio	Italy	2016	135	IVT, ET	69	UNK	UNK	UNK	CTA	LCC graded on a 4-point scale (0-3)	2-3	0-1	A	(29)
Mangiafico	Italy	2014	103	ET	61	20	3-6	270	CTA	Careggi collateral score 6 categories (0-5)	2-5	0-1	A	(30)
van Seeters	Netherlands	2016	484	IVT, ET	66	13	9	361	CTA	Collateral filling of Vterritory of the affected MCA or MCA branch territory	≥ran	<50%	A	(31)

Table I. Continued.

First author	Country	Year	Sample size (n)	Thrombolysis type	Mean age (years)	Median NIHSS at baseline	Duration of IVT (h)	Mean interval from onset to treatment (min)	Collateral circulation grading: Imaging modality	Grading method	Dichotomized collateral status: Good	Poor	Study quality[a]	(Refs.)
Sheth	USA	2016	117	IVT, ET	UNK	UNK	UNK	UNK	DSA	ASITN/SIR collateral circulation graded on a 5-point scale (0-4)	3-4	0-2	A	(32)
Shin	Korea	2014	43	ET	UNK	UNK	6	UNK	CTA	Graded on CTA and delayed contrast CECT axial MIP imaging on a 4-point scale	2-3	0-1	A	(33)
Souza	USA	2012	197	IVT, ET	67	15	9	UNK	CTA	LCC graded on a 4-point scale (0-3)	1-3	0	A	(34)
Sung	Korea	2014	30	IVT, ET	61	16	8	324	DSA	LCC graded on a 5-point scale (0-4)	UNK	UNK	A	(35)
Yeo	Singapore	2015	200	IVT	63	19	UNK	155	CTA	LCC by four different scores (i.e., the Miteff system, scores 1-3)	2-3	1	A	(36)
Zhang	China	2016	80	IVT	68	13	6	195	CTA	rLMC score (rLMC-P and rLMC-M)	rLMC-P >11 rLMC-M>16	rLMC-P ≤11 rLMC-M ≤MM	A	(37)
Zhang	China	2016	66	IVT	UNK	UNK	6	UNK	PWI	ATD was defined as the velocity of collateral flow	ATD <2.3 sec	ATD ≥TD sec	A	(38)

[a]The study quality was graded as A or B, with a Newcastle-Ottawa Scale of ≥6 or <6, respectively. [b]The collateral status was classified into more than two categories in the primary study but was dichotomized in the present study for analysis. Careggi collateral score were based on the extension of anterograde filling of the anterior cerebral artery and retrograde filling of middle cerebral artery territory in anteroposterior projection. ASITN/SIR, the American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; DSA, digital subtraction angiography; FLAIR, fluid-attenuated inversion recovery; ICC, intraclass correlation; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion-weighted imaging; UNK, unknown; ET, endovascular treatment; ATD, arrival time delay; LCC, leptomeningeal collateral circulation; rLMC-P/M, regional leptomeningeal collateral circulation score on peak phase/ temporally fused intensity projections.

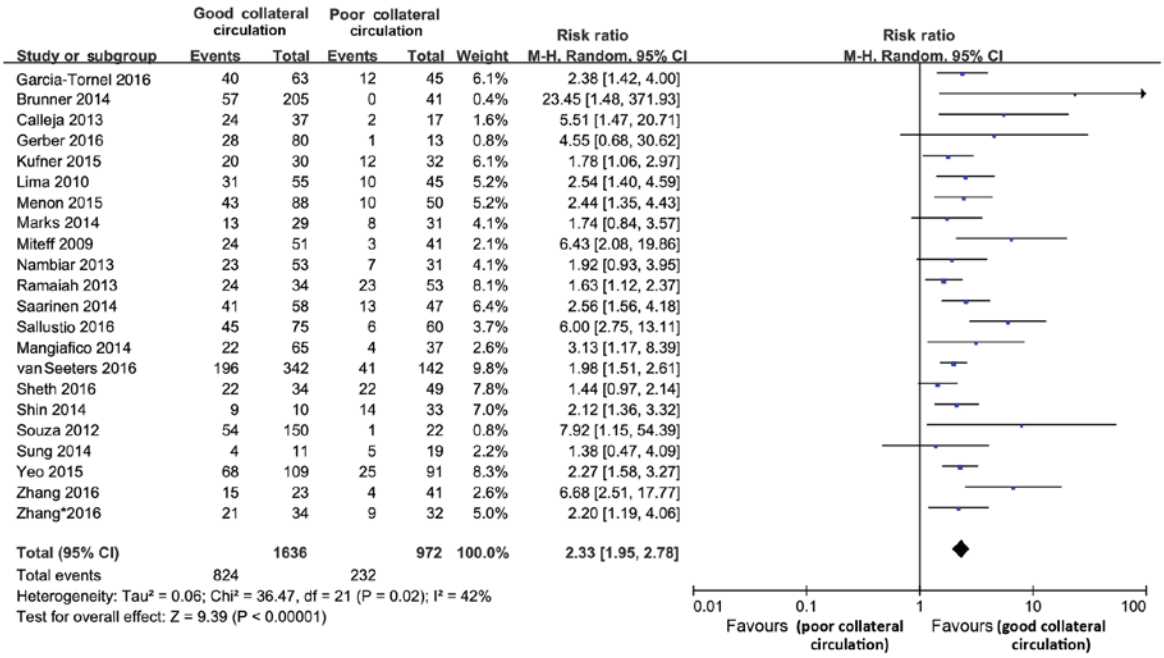

Figure 2. Forest plot presenting the estimation of the overall effect of good vs. poor pre-treatment collateral circulation status on primary outcome, a favorable functional outcome at 3 or 6 months, in patients with AIS receiving thrombolysis therapy in 23 studies. The studies are aligned by the effect size. A favorable functional outcome was defined as an mRS of 0-2 at 3 months in 19 studies, mRS of 0-1 at 3 or 6 months in the study by Yeo *et al* (36), mRS of 0-3 at 3 months in the study by Sheth *et al* (32) and mRS of 0-2 at 6 months in the study by Lima *et al* (22). CI, confidence interval; M-H, Mantel-Haenszel; mRS, modified Rankin Scale; df, degrees of freedom.

Table II, the beneficial effect of good collateral circulation did not differ significantly between the subgroups of studies stratified by a median NIHSS at baseline of ≤ or >13 (Cochran's Q=0.48; P=0.49; I^2=0%); a sample size of < or ≥100 subjects (Cochran's Q=1.56; P=0.21; I^2=35.8%); a mean (or median) age of < or ≥70 years (Cochran's Q=1.94; P=0.16; I^2=48.6%); treatment type (IVT alone, IVT+ET or ET alone; Cochran's Q=0.75; P=0.69; I^2=0%); or duration of IVT treatment (4.5, 4.5-6 h or >6 h; Cochran's Q=2.46; P=0.29; I^2=18.6%).

HT. In 8 of the studies (12,13,15,29,30,33,36,37), HT was defined as symptomatic intracranial hemorrhage in cases with a 4-fold increase in the NIHSS score (ECASS II study) (39), while it was defined differently in 3 studies (7,16,24); however, the definition was unclear in the 4 remaining studies (8,20,27,32). In a total of 1,436 subjects, HT was evaluated from any follow-up CT or magnetic resonance imaging performed within 24 h after treatment until the time-point of discharge. The risk of HT was decreased in the pretreatment good collateral circulation group (RR=0.57; 95% CI, 0.48-0.68; P<0.001; Fig. 3), and no significant heterogeneity was observed between studies in the analysis of HT (Cochran's Q=17.21, P=0.25; I^2=19%) (Fig. 3). Subgroup analyses were performed to assess the outcomes of the different treatment types in patients with good and poor collateral circulation (Table III). The most significant effect was observed in patients administered IVT treatment alone (Cochran's Q=6.63; P=0.04; I2=69.8%). The RRs of good vs. poor collateral status for HT were 0.43, 0.47 and 0.73 for studies with treatment types IVT alone, IVT and ET and ET alone, respectively.

Mortality. The present review included 9 studies (1,108 subjects) that assed mortality. Compared with the PC group, a good collateral circulation status significantly lowered the risk of mortality by thrombolysis treatment (RR=0.29, 95% CI, 0.22-0.37; P<0.01). This effect differed significantly between the studies (Cochran's Q=16.41; P=0.04; I^2=51%). According to the subgroup analyses, such effects were more significant in studies with a sample size of <100 subjects (Cochran's Q=6.07; P=0.01; I^2=83.5%), as the RRs of good vs. poor collateral circulation status for mortality were 0.17 and 0.37, respectively (Fig. 4).

Recanalization or reperfusion. The present review included 13 studies (comprising 1,265 subjects) that reported on recanalization or reperfusion. In comparison with the poor collateral circulation status, good collateral circulation was significantly associated with elevated the rates of good recanalization/reperfusion (RR=1.42; 95% CI, 1.20-1.68; P<0.001; Fig. 5), and this effect was significantly different between the studies (Cochran's Q=20.33; P=0.06; I^2=41%). According to the subgroup analyses, such effects were more significant in studies with successful recanalization (thrombolysis in cerebral infarction score of 2b/3 or other definitions; Cochran's Q=6.97; P=0.008; I^2=85.7%; Fig. 5).

Final infarct volume. The final infarct volume was determined by diffusion-weighted imaging in the studies by Sheth *et al* (32) and Lee *et al* (21) and by CT in the studies by García-Tornel *et al* (12) and Angermaier *et al* (13). The good collateral circulation group displayed a significantly lower final infarct volume than the poor collateral circulation group [mean difference=-100.11; 95% CI, -(118.97-81.25); P<0.01]; however, no significant heterogeneity was identified between the studies (Cochran's Q=2.57; P=0.046; I^2=0%) or between the subgroups (Cochran's Q=0.87; P=0.35; I^2=0%) (Fig. 6).

Table II. Subgroup analyses for favorable functional outcome at 3-6 months.

				Inter-study heterogeneity			Inter-subgroup heterogeneity		
Subgroup	Number of studies	Number of subjects	RR (95% CI)	Cochran's Q statistics	P-value	I^2 statistics (%)	Cochran's Q statistics	P-value	I^2 statistics (%)
Mean (or median) age (years)	19	2,413	2.68 (2.33,3.09)	37.58	0.004	52	1.94	0.16	48.6
≥70	5	562	3.38 (2.35,4.87)						
<70	14	1,851	2.55 (2.19,2.97)						
Median (or mean) baseline NIHSS	17	2,143	2.45 (2.12,2.84)	23.93	0.09	33	0.48	0.49	0
≥13	11	1,274	2.59 (2.09,3.20)						
<13	6	869	2.33 (1.91,2.84)						
Sample size	22	2,608	2.46 (2.16,2.79)	36.47	0.02	42	1.56	0.21	35.8
≥100%	10	1,790	2.61 (2.20,3.08)						
<100	12	818	2.22 (1.83,2.68)						
Prescribed duration of treatment (h)	15	1,856	2.32 (1.92,2.80)	18.03	0.21	22	2.46	0.29	18.6
≤4.5	5	635	2.24 (1.61,3.12)						
4.5-6	5	367	3.18 (1.90,5.35)						
>6	5	854	2.03 (1.63,2.54)						
Treatment type	22	2,608	2.33 (1.95,2.78)	36.47	0.02	42	0.75	0.69	0
IVT alone	7	797	2.67 (1.87,3.80)						
IVT + ET	13	1,666	2.22 (1.75,2.81)						
ET alone	2	145	2.27 (1.51,3.41)						

RR, risk ratio; CI, confidence interval; IVT, intravenous thrombolysis; ET, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale.

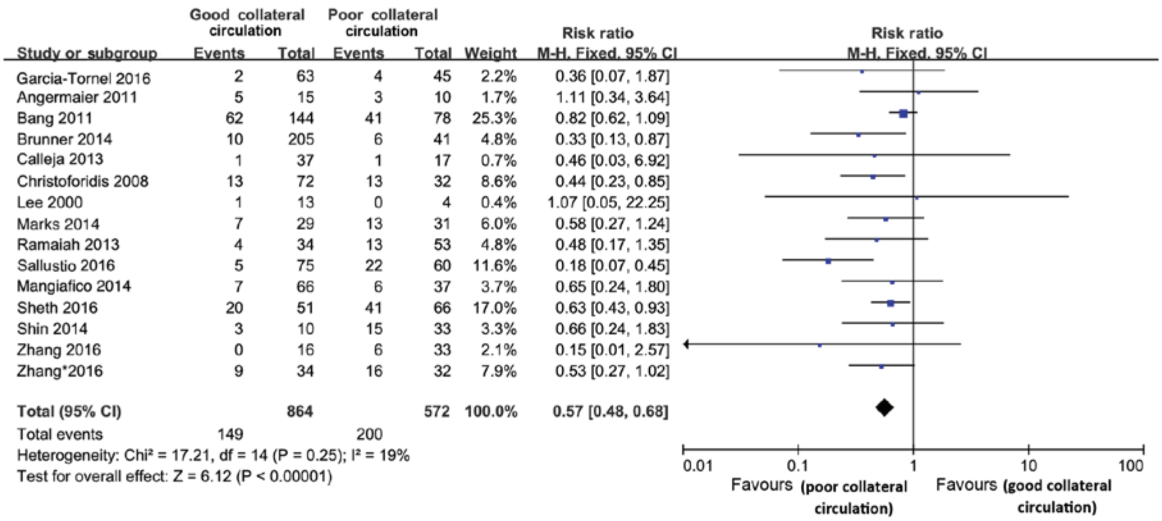

Figure 3. Forest plot presenting the estimation of the overall effects of good vs. poor pre-treatment collateral circulation status on HT. HT was defined according to the SITS-MOST definition by Calleja *et al* (16). HT was defined as a new hyperattenuated region identified on any follow-up CT scan before patient discharge in the study Christoforidis *et al* (7). HT for parenchymal hematoma formation (PH1 and PH2) was evaluated from any follow-up CT or magnetic resonance image undertaken within 7 days of stroke onset by Marks *et al* (24). HT, hemorrhagic transformation; CT, computed tomography; CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

Discussion

The collateral circulation connects the cerebral arteries to maintain penumbra perfusion and provide alternative routes for blood flow prior to achievement recanalization/reperfusion in patients with AIS. The predictive value of the collateral circulation status regarding the outcome in such patients has been demonstrated in various studies (6,7,35,40-42); however, these studies display certain differences, including imaging evaluation methods and types of thrombolysis therapy. The literature, including baseline features of collateral status and effects of determining outcomes, was systematically reviewed in the present study. The beneficial effects of good collateral circulation regarding the favorable functional outcome at 3-6 months have been demonstrated (12,16,26,32,43-45), without any significant difference among various durations of thrombolysis (4.5 h, 4.5-6 h or >6 h) and among different treatment types (ET alone, ET+IVT or IVT alone). These phenomena may be explained by the following two points: First, good collateral circulation may have improved the delivery of thrombolysis to both sides of the thrombus, while limiting any extension of the occlusion (25), facilitated adequate preservation of the penumbra until effective reperfusion was reached and increased the efficacy of aggressive ET applied to patients beyond 6 h as per the clinical risk of futile recanalization (46). Second, patients with poor collateral circulation status had a relatively low rate of favorable functional outcomes due to the low amount of salvageable tissue to be reperfused beyond 6 h.

To the best of our knowledge, the present study was the first to systematically review and meta-analyze the correlation between collateral circulation status and final infarct volume. The results indicated that the collateral circulation score predicted the final infarct volume, which was negatively associated with an increased collateral blood supply that improved oligemic peri-infarct tissue perfusion to reduce infarct core expansion and maintain the viable tissue eligible for recovery of function for a prolonged duration, as also outlined in a previous study (47). According to the results of the present study, good collateral circulation also lowered the risk of HT and mortality and enhanced the rate of recanalization/reperfusion. Such effects were independent of variability in estimation methods of collateral circulation, type of thrombolysis therapy and treatment duration, which was in disagreement with the results provided by McVerry *et al* (48), who indicated that inconsistencies in evaluating the collateral blood flow may lead to an underestimation of the effect of the collateral circulation on the outcome of patients with AIS.

According to recent RCT studies, ET has achieved a higher efficiency as compared with IVT (49-53). The putative factors for this change are the use of stent-retriever device technology, a reduction in time delay between admission and groin puncture and the use of neuroimaging modalities for documenting vessel occlusion and patient selection (54); however, the impact of collateral status on the outcome in different treatment types had remained to be subjected to a comparative analysis. The present study revealed that good collateral circulation may have beneficial effects in both treatment types; although ET may be more effective and reliable owing to technological developments, while IVT alone also achieved favorable functional outcomes for patients with a good collateral circulation status.

Evaluation of the collateral circulation status and penumbra area prior to treatment are critical for identifying patients with AIS are likely to benefit from thrombolysis treatment. In addition, collateral circulation scores and the penumbra area should be evaluated alongside the application of the imaging methods for improved accuracy and a timely decision regarding the application of IVT. In addition, certain assessment manuals, including the Houston Intraarterial Therapy (54) and the Totaled Health Risks in Vascular Events score (55), should be jointly considered for improving the selection of patients for whom thrombolysis treatment is likely to be beneficial rather than harmful.

Table III. Subgroup analyses for the outcomes of different treatment types in patients with good vs. poor collateral circulation.

				Inter-study heterogeneity			Inter-subgroup heterogeneity		
Outcome	Number of studies	Number of subjects	RR (95% CI)	Cochran's Q statistics	P-value	I^2 statistics (%)	Cochran's Q statistics	P-value	I^2 statistics (%)
HT	15	1,436	0.57 (0.48, 0.68)	17.21	0.25	19	6.63	0.04	69.8
IVT alone	5	432	0.43 (0.25, 0.72)						
IVT + ET	5	507	0.47 (0.34, 0.63)						
ET alone	5	497	0.73 (0.57, 0.93)						
Mortality	9	1,108	0.29 (0.22, 0.37)	16.41	0.04	51	3.66	0.16	45.4
IVT alone	2	310	0.24 (0.14, 0.42)						
IVT + ET	6	696	0.27 (0.20, 0.36)						
ET alone	1	103	0.53 (0.27, 1.03)						
Recanalization	13	1,265	1.48 (1.31, 1.68)	20.33	0.06	41	0.63	0.73	0
IVT alone	1	54	2.02 (0.92, 4.42)						
IVT + ET	9	1,041	1.47 (1.29, 1.67)						
ET alone	3	170	1.46 (0.94, 2.28)						

RR, risk ratio; CI, confidence interval; IVT, intravenous thrombolysis; ET, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale; HT, hemorrhagic transformation.

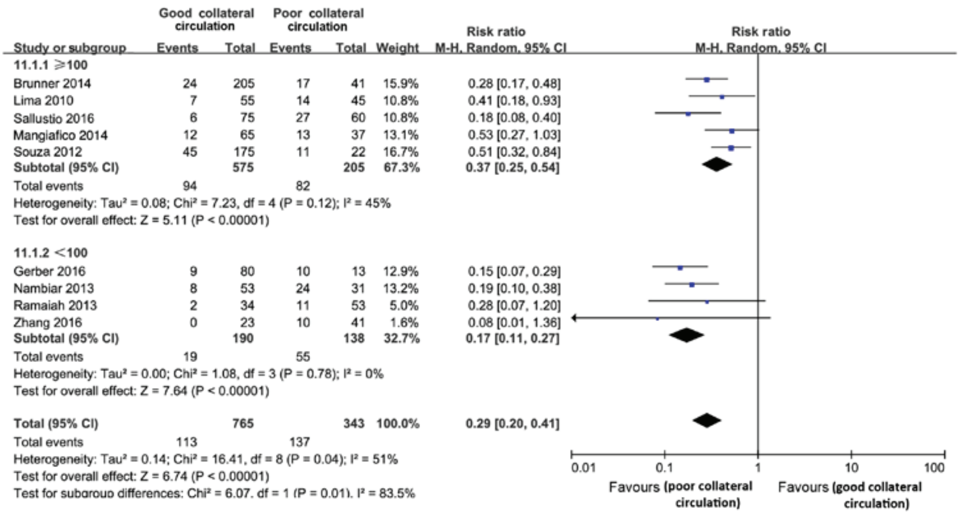

Figure 4. Forest plot presenting the estimation of the overall effects of good vs. poor pre-treatment collateral circulation status on mortality. Mortality was determined at 3 months in 6 studies, at 1 month in 1 study and at the end of the hospitalization period in 2 studies. CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

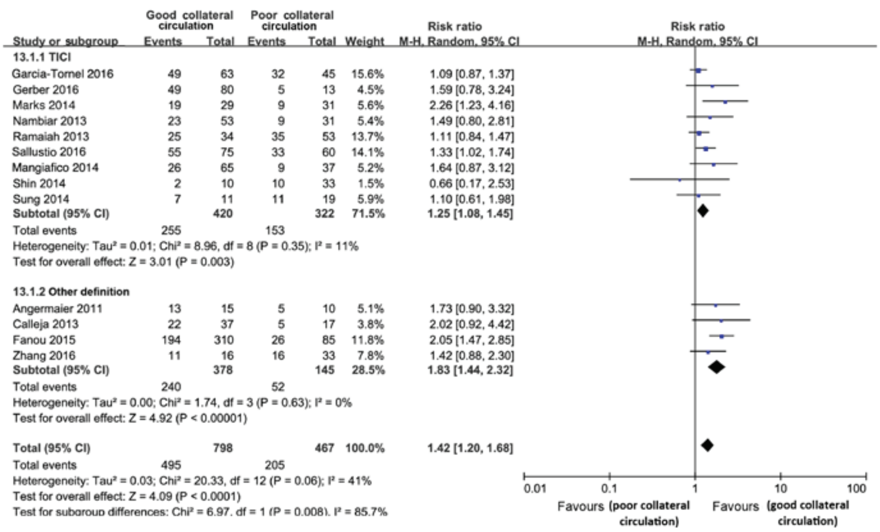

Figure 5. Forest plot presenting the estimation of the overall effects of good vs. poor pre-treatment collateral circulation status on good recanalization or reperfusion. Thrombolysis in myocardial infarction scores were 2-3 in the studies by Angermaier *et al* and Fanou *et al* (13,17), thrombolysis in brain ischemia scores were 4-5 in the study by Calleja *et al* (16) and arterial occlusive lesion scores were 2-3 in the study by Zhang *et al* (37). CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom; TICI, thrombolysis in cerebral infarction.

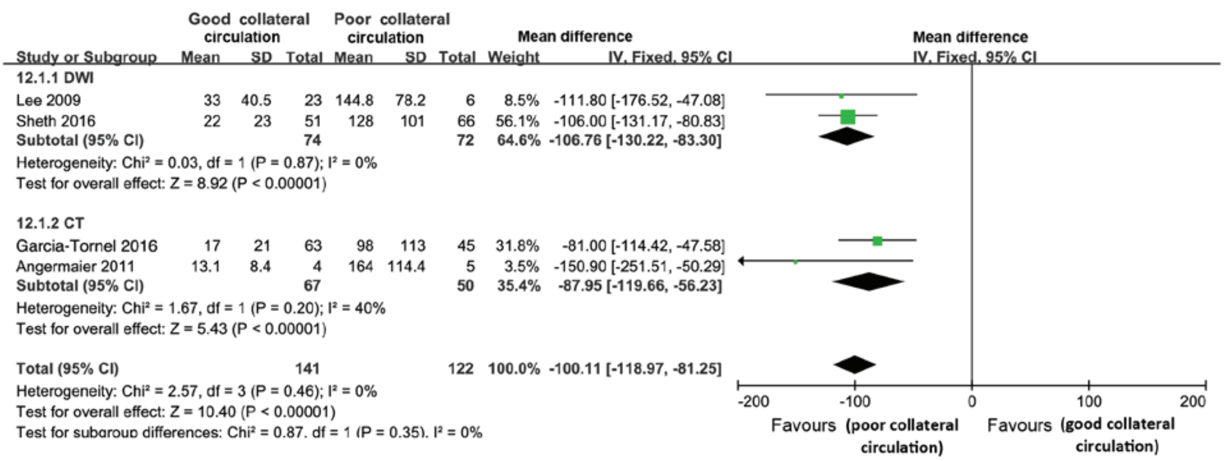

Figure 6. Forest plot presenting the estimation of the overall effects of good vs. poor pre-treatment collateral circulation status on the final infarct size. SD, standard deviation; IV, inverse variance; CI, confidence interval.

However, the present meta-analysis had several limitations: First, the patients included in this systematic review did not only have anterior circulation ischemic stroke but also with posterior circulation ischemic stroke, which may have resulted in prognosis evaluation bias; second, the present study had other heterogeneities, including differences in ethnicity and treatment compliance after recanalization, and the effects of good collateral circulation are probably restricted to certain subgroups of patients, which requires further exploration. Third, a sampling bias may have been present, as an English language restriction was imposed on the literature search due to which the studies published in other languages were neither identified nor included, thereby reducing the broadness of the analysis. Also, in the present study the effect was more significant in the subgroup of other definitions (TIMI, TIBI or AOL scores) than in the TICI subgroup. The number of studies included in the two groups was different, therefore resulting in a bias between the two groups. Unifying the evaluation and reporting standards for revascularization would benefit horizontal and longitudinal comparisons among IVT or ET studies in the future.

In conclusion, a good collateral circulation status may lead to a favorable 3-6-month functional outcome, a better recanalization or reperfusion rate, a smaller infarct core, a lower HT rate and a lower risk of mortality after thrombolysis treatment for various durations in patients with AIS. In clinical practice, it may be worth considering the collateral circulation status, penumbra assessment and onset-to-treatment time for optimally identifying suitable patients who are likely to benefit from thrombolysis treatment.

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