The impact of leptomeningeal collaterals in acute ischemic stroke

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Systematic Review

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Abstract

Objectives: Leptomeningeal collaterals provide an alternate pathway to maintain cerebral blood flow in stroke to prevent ischemia, but their role in predicting outcome is still unclear. So, our study aims at assessing the significance of collateral blood flow (CBF) in acute stroke.

Methods: Electronic databases were searched under different MeSH terms from Jan 2000 to Feb 2019. Studies were included if there was available data on good and poor CBF in acute ischemic stroke (AIS). The clinical outcomes included were modified rankin scale (mRS), recanalization, mortality, and symptomatic intracranial hemorrhage (sICH) at 90 days. Data was analyzed using random-effect model.

Results: A total of 47 studies with 8,194 patients were included. Pooled meta-analysis revealed that there exist 2-fold higher likelihood of favorable clinical outcome (mRS≤2) at 90 days with good CBF compared with poor CBF (RR: 2.27; 95%CI: 1.94-2.65; p<0.00001) irrespective of the thrombolytic therapy [RR with IVT: 2.90; 95%CI: 2.14-3.94; p<0.00001, and RR with IAT/EVT: 1.99; 95% CI: 1.55-2.55; p<0.00001]. Moreover, there exists 1-fold higher probability of successful recanalization with good CBF (RR: 1.31; 95% CI: 1.15-1.49; p<0.00001). However, there was 54% and 64% lower risk of sICH and mortality respectively in patients with good CBF in AIS (p<0.00001).

Conclusions: The relative risk of favorable clinical outcome is more in patients with good pretreatment CBF. This could be explained due to better chances of recanalization, combined with lesser risk of intracerebral hemorrhage in good CBF status.

Introduction

Reversing the trend of morbidity caused by ischemic stroke in our modern era has still proven difficult and; thus, poses a significant global burden. It is widely known that adequate blood flow to the brain by removing the clot forms the theoretical basis for management. Therefore, thrombolytic therapies in the form of intravenous (IVT) or intra-arterial (IAT) aim for clot disruption, thus re-establishing the circulation. The therapeutic implications of such interventions have been enhanced further by the presence of bypass vascular network channels, which provides an alternate pathway for cerebral blood flow to prevent permanent neurological damage. Hence, these pial collaterals prolongs the time window for treatment after stroke and reduces the hemorrhagic transformation. Thus, determination of collateral status before establishing any treatment is appealing because the coherence with adequate intervention can be improved. Consequently, there exists various ways to identify collateral circulation in the brain after acute ischemic stroke, although the effect of number of collaterals on clinical outcomes has not been assessed.

To determine whether good or poor collateral blood flow (CBF) has any impact on clinical outcome in AIS, we reviewed randomized controlled trials, case-control, prospective cohort and retrospective studies in...
adult patients receiving different thrombolytic therapies.

Methods

Study selection:

Randomized controlled trials, case-control studies, prospective cohort studies and retrospective studies studying the collateral status in patients with AIS who received IA/EVT± IV thrombolytic therapy. We excluded case series and case report studies from our systematic review. Articles were retrieved from January 2000 till February 2019. Various data bases were searched which included PubMed, Cochrane, EMBASE and Google Scholar. The MeSH headings included “collateral circulation”, “thrombolytic therapy”, and “stroke”. The reviewers were not incognizant with regards to the author’s name and institution, journals of publication, or study results. No language barriers were imposed. Eligibility assessment was performed independently by one reviewer (NF) in an unblinded manner. Disagreement between the reviewers was resolved by consensus. However, if still there was no agreement then third party (AS) would decide. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline for our meta-analysis.

Data abstraction:

Information was extracted from the studies included on: (1) baseline characteristics of studies (type of study, number of patients, mean age, NISS score, and inclusion criteria); (2) Collateral status (methodology, collateral definition, number of collaterals); (3) Thrombolytic therapies (types of therapies); (4) Clinical outcome in good versus poor CBF (mRS at 90 days, sICH, mortality, and recanalization). The definition of collateral scores and method of collateral scoring depended upon the included studies and are described in detail in Table 1. For the definition of our systematic review we defined good CBF as 50–100% collateral filling of the ischemic area while <50% collateral filling was defined as poor CBF.

The meta-analysis was performed using random-effect model by computing OR and 95% confidence interval for each study determining the outcome. The primary outcome was modified rankin scale mRS at 90 days (good clinical outcome = 0–2) in good CBF versus poor CBF in acute ischemic stroke. Secondary outcomes included mortality, recanalization and sICH.

Statistical analysis:

Review Manager Program version 5 as provided by Cochrane Library was used to perform Statistical analyses. The data from each study was extracted from the articles and placed in this software to perform a pooled meta-analysis and sub-group analysis.
Pooled meta-analysis on good versus poor CBF irrespective of type of treatment followed by dichotomization into IVT and IAT/EVT was evaluated using random-effect model. Subgroup analysis was performed with mortality, sICH, and recanalization. To assess the publication bias, funnel plot was also applied. The RR from separate studies were combined by the random-effects meta-analysis according to the Mantel-Haenszel method, which is also valid for paired RR. Heterogeneity between studies was assessed by the Breslow-Day χ² test and I² statistic.

**Results**

A total of 2685 articles were reviewed from the above-mentioned electronic literature. 160 articles were retrieved and analyzed; ultimately 47 articles which met the inclusion criteria were included in our meta-analysis. Table 1 shows characteristics of included studies. Table 2 indicates the types of interventions and clinical outcomes. Table 3 identifies the results of all included studies.

A total of 8,194 patients were included in our meta-analysis with good and poor collaterals receiving either IVT, IAT or EVT for acute ischemic stroke. The median age of the included patients was 68 (54–78) with NIHSS score at the time of presentation as 15 (18–21).

Pooled analysis of all included studies: Patients with acute ischemic stroke with good CBF had a more than 2-fold higher likelihood of having good outcome (mRS 0–2 at 90 days) in comparison to patients with stroke having poor CBF (RR: 2.27; 95%CI: 1.94–2.65; p<0.00001) as indicated in Figure 1 Panel A. Furthermore, patients with good pretreatment collaterals receiving intra venous thrombolysis showed around 3-fold higher risk of better outcome as compared to patients with poor collaterals (RR: 2.90; 95%CI: 2.14–3.94; p<0.00001) as demonstrated in Figure 1 Panel B. In addition, patients with good collaterals who received thrombolysis either intrarterial or mechanical had approximately 2-fold higher risk of favorable outcome compared to patients with pre-treatment poor collaterals (RR: 1.99; 95% CI: 1.55–2.55; p<0.00001) as shown in Figure 1 Panel C.

Further sub group analysis based upon the status of recanalization was performed based upon the pretreatment collaterals status, it was found that patients with good collaterals showed 1-fold higher likelihood of complete recanalization as compared to poor collaterals RR of Recanalization: 1.31; 95% CI: 1.15–1.49; p<0.00001 (Figure 2)

Compared to poor collateral status, good pretreatment collaterals had 54% less relative risk of sICH at 90 days. The RR of sICH: 0.46; 95% CI: 0.35–0.60; p<0.00001 (Figure 3)

Further sub group analysis was done comparing the collateral status with mortality. We found that patients with good collateral status has 64% less risk of mortality at 3-months compared to patients with poor collateral status irrespective of the type of thrombolysis. The RR of mortality: 0.36; 95%CI: 0.27–0.48; p<0.00001 (Figure 4).
Statistical heterogeneity was further assessed using funnel plot, revealing asymmetrical distribution in the funnel plot. This could be due to publication bias, but we tried to minimize it by searching the unpublished literature as well. Though no study was included from the grey literature in our meta-analysis.

**Discussion**

Overall, there was a strong evidence of relationship between the collateral circulation and clinical outcomes in patients with AIS. This can be explained due to the fact that the expansion or reduction of penumbral tissue, immediately after the stroke, depends on collateral status\(^\text{55}\).

**Clinical outcomes:**

In our meta-analysis, we demonstrated that the presence of good CBF was associated with increased likelihood of favorable clinical outcome, which validates the previous meta-analysis\(^\text{24}\) (mRS at 3–6 months; \(p<0.0001\)). In addition, further analysis showed that there was higher probability of predicting better neurological outcome with either IVT or IAT/EVT. Our results, however, are contradictory to recent trial of DEFUSE 3\(^\text{54}\), which showed that good CBF does not predict the neurological status. Previous studies also revealed that IAT/EVT is efficient in clot-retrieval in stroke, combined with better neurological outcome\(^\text{59–61}\).

The degree of collateral circulation is essential to be determined prior to thrombolytic therapy. This status helps to determine the expansion of infarct, degree of reperfusion and efficacy of treatment. Although endovascular treatment is considered to be the treatment of choice for acute large-vessel occlusion, however, it was found that patients with poor collaterals had more odds of unfavorable clinical outcome (onset-to-puncture time: 300, 59% versus 300, 32%; OR, 0.24; \(P\ .011\); puncture-to-reperfusion time: 60, 73% versus 60, 32%; OR, 0.21, \(P\ .011\)) as compared to those with good collaterals\(^\text{63–64}\). Therefore, collateral circulation helps in minimizing the neurological damage by limiting the extent of infarction as it maintains the viability of the penumbral tissue.

**Recanalization:**

Our study suggests that recanalization was better achieved in patients with good pretreatment collateral status (\(p<0.00001\)). This can be explained as collateral circulation sustain downstream perfusion and enhances ante grade perfusion to the distal arteries\(^\text{57}\). Besides, it increases the delivery of thrombolytic agents to the clot itself from different sides, thus increasing the efficacy of treatment\(^\text{57}\).

In previous literature, it was found that mechanical thrombectomy has higher rate of recanalization than IV treatment alone; like in a randomized trial EXTEND-IA, it was found that >90% recanalization was found in patients who received endovascular thrombectomy than those who received rt-PA\(^\text{58}\). MR CLEAN
and ESCAPE trial also demonstrated the same findings that there are low complications rate with endovascular treatment.

Mortality and sICH: Our meta-analysis revealed the there was reduction in mortality with good CBF than poor CBF (p<0.00001). Though in previous study it was found that recanalization did not independently affect the mortality (p>.15), thus collateral status plays indispensable role in decreasing the mortality as evident in previous studies. Our study identified significant reduction in sICH in good CBF compared to poor CBF, this could be explained as collaterals limits the growth of infarct core before revascularization. This ultimately helps in reducing the risk of hemorrhagic transformation.

Our study has several limitations. Firstly, there is a possibility of selection and publication bias in our systematic review, since only two reviewers carried out this part of the process. They might therefore be more influenced by the positive trial results than by the negative ones. However, we tried to limit such bias using the following steps: a gray literature review, in which we reviewed the abstracts from several meetings in order to capture any RCT that was presented as an abstract but not published because of a negative result. Second, in our meta-analysis there were different scales used to assess and define collateral circulation into good and poor CBF, therefore, resulting in a bias between two groups. Third, in our meta-analysis we didn't only restrict to anterior circulation stroke but also included posterior circulation stroke as well, this might have resulted in sampling bias. Fourth, there must be difference in ethnicity and co-morbidities, which might have led to sampling bias.

**Conclusion**

In conclusion, our meta-analysis points to a signal-of-efficacy of good CBF in the management of patients with acute ischemic stroke. However, further studies including randomized controlled trials are required to determine the effectiveness of thrombolytic therapy depending upon the collateral status.

**Abbreviations**

AIS: acute ischemic stroke; ASITN: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR); ASPECTS: Alberta Stroke Program Early CT score; CBF: Collateral Blood Flow; CTP: Computed Tomography Perfusion; CTA: Computed Tomography Angiography; CAOSD: Coronary Artery Septal Occlusion Defect; DSA: Digital subtraction Angiography; IV: Intravenous; ICA: Internal Carotid Artery; LMC: Leptomeningeal Collateral Grading; MRI: Magnetic Resonance Imaging; MCA: Middle Cerebral Artery; MRP: Magnetic Resonance Perfusion; mRS: modified rankin scale; NIHSS: National Institute of Health Stroke Scale; PROACT: Prolyse in Acute Cerebral Thromboembolism; rCBV: LVOS: Large vessel occlusion stroke; relative cerebral blood volume; RR: Relative Risk; sICH: symptomatic intracranial hemorrhage

**Declarations**
Competing interests: The authors declare no competing interests.

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### Tables

**Table 1: Baseline Characteristic of Various Studies**
| Trial or Study | Patients (n) | Age (Mean) | NIHSS score (Median) | Inclusion Criteria | Collateral Scoring | Collateral Score Definition |
|---------------|--------------|------------|----------------------|--------------------|-------------------|----------------------------|
| Lee et al 2000 | 17           | 63         | 15                   | Acute middle cerebral artery (MCA) territory ischemic stroke within 3 hours after onset and were treated with IV recombinant tissue plasminogen activator (rt-PA). | CTP                | MCA territory perfusion deficit |
| Kim DJ et al 2008 | 13          | 60         | 13                   | Anterior and Posterior Circulation Ischemic Stroke | DSA                | Graded as sufficient, moderate and poor |
| Miteff F et al 2009 | 92         | 74         | 17                   | 1. Anterior circulation stroke with IV thrombolysis is within 6 hours of stroke  
2. Repeat perfusion/infarct volume imaging at 24 hours | CTA                | Good collaterals: entire MCA distal to occluded segment reconstituting with contrast  
Poor collaterals: distal MCA reconstituted partially |
| Lee et al 2009 | 52           | 69         | 8                    | Acute middle cerebral artery (MCA) territory ischemic stroke within 3 hours after onset and | FLAIR MRI          | Distal hyperintense vessels on MRI slices |
were treated with IV recombinant tissue plasminogen activator (rt-PA).

| Authors          | Year | Patients | Age (Mean) | Follow-Up (Median) | Imaging Modality | Description                                                                 |
|------------------|------|----------|------------|--------------------|-----------------|-----------------------------------------------------------------------------|
| Lima F et al 2010| 2010 | 741      | 69         | 13                 | CTA             | Complete occlusion of the intracranial internal carotid artery (ICA) and/or the middle cerebral artery (MCA-M1 or M2 segments) |
| Angermaier et al | 2011 | 25       | 68         | 14                 | CTA             | Anterior Circulation Ischemic Stroke                                        |
| Park et al 2011  | 2011 | 58       | 63         | 12                 | PWI             | Anterior circulation stroke with IV tPA and baseline MRI                   |

Leptomeningeal collateral pattern was graded as a three category less than contralateral unaffected side (score 1-2), equal to contralateral unaffected side (score 3) and greater than contralateral unaffected side (scores 4-5). rCBV ratio by comparing the blood volume of the ischemic lesion with that of the corresponding unaffected contralateral region (i.e. ipsilateral divided by
| Study                  | N  | Mean | SD | Key Points                                                                 |
|-----------------------|----|------|----|-----------------------------------------------------------------------------|
| Bang et al 2011       | 222| 65   | 17 | ASITN collateral flow grading system                                         |
| Choi et al 2011       | 55 | 64   | 15 | Pial Collateral Score                                                        |
| Gallimanis et al 2012 | 623| 64   | 15 | Graded as none, poor or good                                                 |
| Souza et al 2012      | 197| 67   | 21 | CS: 0= absent collaterals in >50% of an MCA M2 branch territory; 1= diminished collaterals in >50% of an MCA M2 branch territory; 2= diminished collaterals in <50% of an MCA M2 branch territory; 3= collaterals equal to the contralateral hemisphere; and 4= increased collaterals |
| Rai et al 2012        | 89 | 68   | 15 | Graded as sufficient, moderate and poor                                      |
| Calleja et al 2012    | 54 | 73   | 10 | Leptomeningeal                                                              |
| Study | Patients | Controls | Duration | Imaging Modality | Description |
|-------|----------|----------|----------|------------------|-------------|
| Ichijo M et al 2012<sup>16</sup> | 50 | 78 | 15 | TOF-MRA | Acute proximal MCA occlusion patients who were treated with IV rtPA within 3 hours of symptom onset. |
| Ramaiah et al 2014<sup>17</sup> | 78 | 66 | 18 | CTA | Acute ischemic stroke with intracranial ICA and/or MCA occlusions who received intra-arterial therapy. |
| | | | | | Collateral statuses were divided into 4 categories: score 0 absence of contrast reaching the cortical surface of the affected hemisphere; score 1 contrast reaching the cortical surface but not the Sylvian fissure; score 2 contrast reaching the Sylvian fissure but opacifying 50% of hemisphere; score 3 contrast reaching the Sylvian fissure and opacifying 50% of the |
| Study                          | CTV | Age Range | ISH | Procedure                                      | Description                                                                 |
|-------------------------------|-----|-----------|-----|-----------------------------------------------|-----------------------------------------------------------------------------|
| Nambiara V et al 2014         | 84  | 65.2      | 14  | M1 segment MCA with or without intracranial ICA occlusions | Collateral status by use of the rLMC score (0–20) was trichotomized into 3 groups: good (17–20), intermediate (11–16), and poor (0–10) |
| Saarinen et al 2014           | 105 | 69        | 13  | Anterior Circulation Ischemic Stroke with IV tPA and CTA | Leptomeningeal collateral circulation grading                                |
| Brunner et al 2014            | 246 | 74        | 14  | NINDS protocol                                | Leptomeningeal collateral grading                                            |
| Al-Ali et al 2014             | 28  | 62        | NA  | Anterior Circulation Ischemic Stroke          | Capillary Index Score                                                       |
| Marks MP et al DEFUSE 2014    | 60  | 63        | 18  | 1. Patients started endovascular treatment within 12 hours of ictus and 1.5 hours of the baseline MRI 2. ICA-M1 occlusion | Collateral score using a prior 5 point scale, from 0 (no collateral flow) to 4 (complete/rapid collaterals to entire ischemic territory). |
| Liebeskind IMS-III et al 2014 | 276 | 69        | 17  | Anterior and Posterior Circulation Ischemic Stroke | ASITN collateral flow grading                                               |
| Liebeskind SWIFT et           | 119 | 67        | 18  | Anterior and                                 | ASITN collateral                                                            |
| Study | Flow grading | Methodology | Flow grade |
|-------|--------------|-------------|------------|
| Mangiafico et al 2014 | Posterior Circulation Ischemic Stroke | DSA | Collateral circulation score |
| Chen et al 2015 | Anterior Circulation Ischemic Stroke | CTP | Collateral Flow Score |
| Sung SM et al 2015 | Acute M1 occlusion | CTA | A score of zero indicated absent collateral supply to the occluded MCA territory. A score of 1 indicated collateral supply filling ≤50% but >0% of the occluded MCA territory. A score of 2 was given for collateral supply filling >50% but <100% of the occluded MCA territory. A score of 3 was given for 100% collateral supply of the occluded MCA territory |
| Fanou et al 2015 | Anterior Circulation Ischemic Stroke | CTA | Collateral Flow 0-3 |
| Study                | Participants | Age Mean | Age SD | NIHSS | Eligibility Criteria                                                                 |
|----------------------|--------------|----------|--------|-------|--------------------------------------------------------------------------------------|
| Menon BK et al 2015  | 656          | 70       |        | M1 MCA± Intracranial ICA occlusion | CTA Score 0-1 ischemic territory, Scores ≥ 2 indicates a good collateral status |
| Kufner A et al 2015  | 62           | 71       | 11     | IV-tPA within 4.5 hours of symptom onset, had MR imaging before and within 24 hours after treatment | FLAIR MRI Hyperintense vessels on MRI sections |
| Hwang et al 2015     | 207          | 68       | 17     | Anterior Circulation Ischemic Stroke | DSA ASITN collateral flow grading system |
| Singer et al 2015    | 148          | 71       | 20     | Posterior Circulation Ischemic Stroke | DSA ASITN collateral flow grading system |
| Study | Sample Size | Age | Grade | Method | Grading System |
|-------|-------------|-----|-------|--------|----------------|
| Singer et al 2015 | 160 | 72 | 15 | Anterior Circulation Ischemic Stroke | DSA |
| Zhang S et al 2016 | 80 | 69 | 13 | M1 ± internal carotid artery (ICA) occlusion | 4D CTA |
| Seeters TV et al 2016 | 484 | 66.6 | 13 | 1. acute ischemic stroke of less than 9-h duration 2. confirmed occlusion in the M1 or M2 segment of the MCA on admission CTA | CTA |
| Tan BYQ et al 2016 | 300 | 65.5 | 18 | 1. Anterior Ischemic Stroke (AIS) as proven by CTA | ASPECTS scoring |
| Sheth sa et al 2016 | 117 | 68 | 19 | Acute cerebral ischemia within the anterior circulation underwent conventional angiography | DSA |

- **ASPECTS scoring**: ASPECTS score \( \leq 5 = \) poor collateral status and ASPECTS \( \geq 8 \) as good collaterals.

- **DSA grading system**: ASITN collateral flow grading system.

- **Collateral Grading Score**: Poor leptomeningeal collateral status was defined as \( \leq 50 \% \) collateral filling of the perfusion territory of the affected MCA or MCA branch territory.
persistence of some of the defect), 2 (rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory), 3 (collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase), and 4 (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion).

| Garcia-Tornel A et al | 108 | 69.6 | 17 | University of Calgary Collateral Grading (0-5) |
|-----------------------|-----|------|----|---------------------------------------------|
| 2016                  |     |      |    | Occlusion of the proximal segment of the middle cerebral artery (M1 MCA) or terminal intracranial carotid artery (TICA) |
| Study                  | N  | Mean Age | Intervention                          | Imaging Modality | Description                                                                 |
|-----------------------|----|----------|---------------------------------------|------------------|-----------------------------------------------------------------------------|
| Sallustio F et al 2016 | 135| 69       | Extracranial and intracranial arteries of patients with M1 segment middle cerebral artery (MCA) occlusion with or without internal carotid artery (ICA) occlusion. | CTA              | Collateral status on CTA we adopted a scale from 0 to 3 derived from the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (0: no collaterals; 1: collaterals to the periphery of ischemia; 2: collaterals filling 50–100% of ischemic area; 3: collaterals filling 100% of ischemic area). |
| Gersing AS et al 2017  | 115| 70.3     | Patients undergoing Mechanical Thrombectomy in Middle cerebral artery occlusion (M1) | CTA              | Regional Leptomeningeal collateral score 0 = no collaterals; 1 = less compared with the same region of the contralateral hemisphere; and 2 = equal or prominent collaterals compared with the same region of |
| Study                  | n   | Mean Age | Sex Ratio | MRI Technique | TIA | Details                                                                 |
|------------------------|-----|----------|-----------|---------------|-----|-------------------------------------------------------------------------|
| Son JP et al 2017 41   | 73  | 65       | NA        | MRP           | NA  | (1) subjects who presented within 6 hours of symptom onset; (2) subjects who underwent serial brain MRI, including diffusion-weighted imaging (DWI), MRP, and MR angiography (MRA), at admission and at day 7; (3) subjects who had a NIH Stroke Scale (NIHSS) score of 4 or more points at admission; and (4) subjects with internal carotid artery and/or proximal MCA (M1 segment) occlusion associated with symptoms on admission MRA |
| Nordmeyer H et al 2017 42 | 87  | 72.5     | 15        | CTA           | Tan score was used: A score of 0 indicated |
| Study | N | Low | High | CTAs |
|-------|---|-----|------|------|
| Madelung CF et al 2017 | 187 | MCA occlusion receiving thrombolytic therapy | CTA | 1: Comparison to contralateral; 2: Percentage of collateral supply filling the occluded MCA territory; and 3: Extent of contrast visualized distal to the occlusion |
| Rebello LC et al 2017 | 122 | Patients with (i) a past medical history or in-hospital diagnosis of AF or (ii) CASOD on conventional angiography and (iii) anterior circulation LVOS involving the intracranial internal | CTA | 0, absent collaterals in >50% of the affected territory; 1, diminished collaterals in >50% of the affected territory; 2, diminished collaterals in <50% of the affected territory; 3, collaterals equal to |
carotid artery (ICA) and/or proximal middle cerebral artery (MCA) M1 and/or M2 segments who (d) underwent pre-intervention in-house computed tomography angiography (CTA) were included.

| Study                  | N    | Mean Age | Cases | Description                                                                                     |
|------------------------|------|----------|-------|------------------------------------------------------------------------------------------------|
| Dankbaar JW et al 2018 | 188  | 68.3     | 15    | Occluded M1 segment (with or without extension in the intracranial ICA or M2 branches) on admission CTA |
| Kim BM et al 2018      | 554  | 67.3     | 14    | Acute stroke due to occlusion of intracranial ICA, MCA M1 or proximal M2                        |
| Wang F et al 2018      | 270  | 71.26    | 14    | Primary acute ischemic stroke with an onset of the first episode within the previous 4.5 h and (2) had an occlusion of the internal |
carotid artery (ICA) or of the proximal (M1) or distal (M2) segments of the middle cerebral artery (MCA)

| Study            | n  | Collateral Score | Treatment | Imaging     | Collateral Grade |
|------------------|----|------------------|-----------|-------------|------------------|
| Park JS et al 2018 | 119 | 72.2             | 1. Acute Ischemic Stroke treated with EVT | CTA          | Good collateral score LMC score: 17-20; Poor collateral score: 0-10 |
| Havenon DA et al 2019 | 130 | 71               | 1. Endovascular therapy after acute ischemic stroke | CTA          | Leptomeningeal Collateral Grading |

**TABLE 2: TYPES THROMBOLYTIC THERAPIES AND CLINICAL OUTCOME**

**Abbreviations:**
- ASITN: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR)
- ASPECTS: Alberta Stroke Program Early CT score
- CTP: Computed Tomography Perfusion
- CTA: Computed Tomography Angiography
- CAOSD: Coronary Artery Septal Occlusion Defect
- DSA: Digital subtraction Angiography
- IV: Intravenous
- ICA: Internal Carotid Artery
- LMC: Leptomeningeal Collateral Grading
- MRI: Magnetic Resonance Imaging
- MCA: Middle Cerebral Artery
- MRP: Magnetic Resonance Perfusion
- NIHSS: National Institute of Health Stroke Scale
- PROACT: Prolyse in Acute Cerebral Thromboembolism
- rCBV: LVOS: Large vessel occlusion stroke; relative cerebral blood volume
| Trial or Study | Therapies | Good versus Poor Collaterals | Clinical Outcome | Recanalization | sICH |
|---------------|-----------|-----------------------------|------------------|----------------|------|
| Lee et al 2000 | IVT: 17   | 9: 4                        | NA               | NA             | NA   |
| Kim DJ et al 2008 | EVT      | 6: 3                        | -mRS at 90 days  | NA             | NA   |
| Miteff F et al 2009 | IVT: 60  | 51: 41                       | -mRS at 90 days  | Thrombolysis in Cerebral Infarction: Grade 1: Minimal perfusion 2: Partial perfusion 2a:<2/3rd filling 2b:complete filling but slow rate 3: Complete perfusion | NA   |
|                | EVT: 32   |                             | -absolute infarct expansion |                |      |
| Lee et al 2009 | IVT: 52   | 20/14                       | NA               | NA             | NA   |
| Lima F et al 2010 | IVT: 8    | 55:96:45                    | -mRS at 30 days  | NA             | NA   |
|                | EVT: 9    |                             |                  |                |      |
|                | Combined: 13 |                   |                  |                |      |
| Angermaier et al 2011 | EVT | 15: 10                       | -sICH            | NA             | NA   |
| Park et al 2011 | IVT: 36   | 37: 21                       | - Recanalization | An improvement in the TIMI grade from the baseline to arterial obstruction by ≥ 2 points | Any sign of hemorrhage on follow-up CT or MRI scans associated with clinical deterioration of 4 points on the NIHSS |
|                | EVT: 22   |                             | -SICH            |                |      |
| Bang et al 2011 | EVT | 144: 78                       | -sICH            | NA             | Signs of hemorrhage on follow-up |
| Study                     | Treatment | mRS at 90 days | mRS at 90 days | Mortality | Mortality |
|--------------------------|-----------|----------------|----------------|-----------|-----------|
| Choi et al 2011          | EVT       | 29: 26         | -              | NA        | NA        |
| Gallimanis et al 2012    | EVT       | 316: 69        | -              | NA        | NA        |
| Souza et al 2012         | IVT: 49   | 22/197 CS=0,   | 67/197 CS=2,   | NA        | NA        |
|                          | EVT: 82   | 40/197 CS=1,   | 42/197 CS=3,   | -         | -         |
|                          |           | 67/197 CS=2,   | 26/197 CS=4.   | -         | -         |
|                          | No Reperfusion Therapy 66/197 | | | | |
| Rai et al 2012           | EVT       | 62: 27         | -              | NA        | NA        |
| Calleja et al 2012       | IVT: 40   | 34:53          | -              | Thrombolysis in Cerebral Infarction | NA |
|                          | EVT: 13   |                | -              | -         | -         |
|                          |           | -              | -              | -Sich     | -         |
|                          |           | -              | -              | -TICI     | -         |
| Ichijo M et al 2012      | IVT: 54   | 37: 17         | NA             | NA        | NA        |
| Ramaiah et al 2014       | IVT: 50   | 20: 30         | NA             | NA        | NA        |
| Nambiar V et al 2014     | IVT: 105  | 47: 58         | -              | NA        | NA        |
| Saarien et al            | IVT: 105  |                | -              | NA        | NA        |
| Year  | Study          | Treatment  | Time  | Outcome 1 | Outcome 2 | Outcome 3 |
|-------|----------------|------------|-------|-----------|-----------|-----------|
| 2014  | Brunner et al  | IVT: 246   | 171: 41 | -sICH     | NA        | NA        |
|       | 2014           |            |       |           |           |           |
|       | Al-Ali et al   | IVT: 15/55:18/58 | 29:31 | -Clinical outcome at 90 days | TICI 2B partial reperfusion of >50% of occluded artery | N/A |
|       | 2014           |            |       |           |           |           |
|       | Marks MP et al | EVT: 28    | 13: 15 | -mRS at 90 days | NA        | NA        |
|       | DEFUSE         |            |       |           |           |           |
| 2014  | Liebeskind IMS-III et al | EVT | 96: 180 | -mRS at 90 days | NA | NANA |
|       | 2014           |            |       | -sICH     |           |           |
|       | -mortality     |            |       |           |           |           |
|       | Liebeskind SWIFT et al | EVT | 35: 71 | -mRS at 90 days | NA | NA |
|       | 2014           |            |       | -mortality |           |           |
|       | Mangiafico et al | EVT | 65: 37 | -mRS at 90 days | NA | NA |
|       | 2014           |            |       | -sICH     |           |           |
|       | -mortality     |            |       |           |           |           |
|       | Chen et al     | EVT | 25: 50 | -mRS at 90 days | NA | NA |
|       | 2015           |            |       | -sICH     |           |           |
|       | -mortality     |            |       |           |           |           |
|       | Sung SM et al  | IVT: 20    | 11:19 | -mRS at 90 days | Thrombolysis in Cerebral Infarction (TICI) scale (graded as 0 for absent perfusion, 1 for minimal distal perfusion, 2 for partial perfusion, and 3 for complete perfusion) | Any intracranial hemorrhage associated with ≥4 point’s increase on the NIHSS. |
|       | 2015           |            |       | -TICI     |           |           |
|       |                |            |       | -sICH     |           |           |

**Notes:**
- mRS: Modified Rankin Scale
- sICH: Symptomatic Intracerebral Hemorrhage
- TICI: Thrombolysis in Cerebral Infarction
- N/A: Not available
| Study                          | Intervention | N | TICI | mRS at 90 days | sICH | Mortality at 90 days |
|-------------------------------|--------------|---|------|---------------|------|---------------------|
| Fanou et al 2015 33           | NA           | 310:85 | -mRS at 90 days | Thrombolysis in M1 score, in which a score of ≥2 equals a good collateral status | NA | NA |
| Menon BK et al 2015 34        | IVT:59       | NA | -mRS at 90 days | NA | NA |
| Kufner A et al 2015 35        | IVT: 62      | 30/31 | -TICI 2b-3 | NA | NA |
| Hwang et al 2015 36           | EVT          | 131: 76 | -mRS at 90 days | -sICH | -mortality |
| Singer et al 2015 (Singer OC) | EVT          | 41: 83 | -mRS at 90 days | NA | NA |
| ENDOSTROKE E 37               | EVT          | 78: 82 | -mRS at 90 days | NA | NA |
| Zhang S et al 2016 39         | IVT          | 23/41 | -mRS at 90 days | -TICI 2b-3 | -mortality at 90 days |
| Seeters TV et al 2016 40      | IVT/EVT/Combined | 342:142 | -mRS at 90 days | NA | NA |
| Tan BYQ et al 2016 41         | IVT          | 143: 97 | -mRS | -sICH | -Mortality |
| Study                        | Treatment | Collateral | mRS at 90 days | TICI | sICH | Follow upMeasurements |
|------------------------------|-----------|------------|----------------|------|------|-----------------------|
| Sheth sa et al 2016          | Good      | IV Tpa:21; IA tPA:7; Thrombectomy:41 | 54:66 | N/A | N/A | Hemorrhagic transformatio was categorized as hemorrhagic infarctions or parenchymal hematomas |
|                             | Poor      | IV Tpa:22; IA-Tpa:9; Thrombectomy:55 |       |     |     |                       |
| Garcia-Tornel A et al 2016   | IVT: 56   |            | mRS at 90 days |      |      | Early clinical improvement or deterioration was defined by a decrease or an increase of ≥4 points from baseline on the NIHSS at 24 h |
|                             | EVT: 82   |            |                |      |      | Symptomatic intracranial hemorrhage (sICH) in cases with a 4-point increase in the NIHSS score |
| Sallustio F et al 2016       | IVT: 51.6:66.6 |        | mRS at 90 days |      |      | Symptomatic intracranial hemorrhage (sICH) in cases with a 4-point increase in the NIHSS score |
|                             | EVT: 115  |            |                |      |      |                       |
| Gersing AS et al 2017        | IVT: 83   |            | -NIHSS         | NA   | NA   |                       |
|                             | EVT: 115  |            | -mRS at 90 days|      |      |                       |
|                             |           |            | -TICI          |      |      |                       |
|                             |           |            | -sICH          |      |      |                       |
| Son JP et al 2017            | IVT: 4    |            | -Infarct volume| NA   | NA   |                       |
|                             | EVT: 19   |            | -TICI 2b-3     |      |      |                       |
|                             | Combined: 41 |      |                |      |      |                       |
| Nordmeyer H et al 2017       | IVT: 29   |            | -sICH          | TICI 2b-3 was considered as complete recanalization | Any intracranial hemorrhage observed on control NCCT associated with an increase of 4 points or more on NIHSS score |
| Study                        | IVT | EVT | Combined | Infarct Growth | mRS at 90 days | Mortality at 90 days | TICI 2b-3 |
|------------------------------|-----|-----|----------|----------------|----------------|----------------------|-----------|
| Madelung CF et al 2017 48    | 126 | 5   | 56       | NA             | NA            | NA                   | NA        |
| Rebello LC et al 2017 49     | 44  | 97  | 94:28    | NA             | Infarct growth | NA                   | TICI 2b-3 |
| Dankbaar JW et al 2018 50    | NA  | 138 | 50       | NA             | NA            | NA                   | NA        |
| Kim BM et al 2018 51         | NA  | EVT | 468:86   | mRS 90 days    | NA            | TICI 2b-3            | NA        |
| Wang F et al 2018 52         | IVT | EVT | 185:85   | mRS 90 days    | NA            | Mortality at 90 days | NA        |
| Park JS et al 2018 53        | IVT | EVT | 33:57    | TICI 2b-3      | NA            | sICH                 | NA        |
| Havenon DA et al 2019 54     | 8   | 130 | 97:33    | Infarct volume | >90% reduction in the region of perfusion delay (Tmax of >6 seconds) | Mortality at 90 days | ≥4 point worsening of immediate pre deterioration NIH |

- Infarct growth
- mRS at 90 days
- Mortality at 90 days
- TICI 2b-3
- sICH
- INH Stroke Scale neurological status versus post deterioration and associated with brain hemorrhage
resonance angiogram.

Abbreviations: EVT: Endovascular Thrombolysis; IVT: Intravenous thrombolysis; mRS: modified rankin scale; NA: Not applicable; NCCT: Non contrast CT scan; NIHSS: National Institute of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; sICH: symptomatic intracerebral hemorrhage

TABLE 3: RESULTS OF ALL STUDIES
| Trial or Study     | Modified Rankin Scale (0-2) | TICI 2b-3 Good v/s Poor Collaterals | Infarct Volume Expansion (ml) Good v/s Poor Collaterals | Mortality Good v/s Poor Collaterals | sICH Good v/s Poor Collaterals |
|-------------------|-----------------------------|-------------------------------------|--------------------------------------------------------|-------------------------------------|--------------------------------|
| Lee 2000          | 9/9: 1/4                    | NA                                  | NA                                                     | NA                                  | 1/13: 0/4                     |
| Kim et al 2008    | 4/6: 2/3                    | NA                                  | NA                                                     | NA                                  | 1/6: 0/3                      |
| Miteff F et al 2009 | 24/51: 3/41                 | N/A                                 | 4:42                                                   | NA                                  | NA                             |
| Lee 2009          | NA                          | 15/20: 10/14                       | NA                                                     | NA                                  | NA                             |
| Lima F et al 2010 | IVT:25/82                   | NA                                  | 7/55:14/45                                            | NA                                  | NA                             |
|                   | IA thrombolysis             | 7/82                                | 72/82:10/82                                           | NA                                  | NA                             |
| Angermaier et al 2011 | NA                          | NA                                  | NA                                                     | NA                                  | 2/15: 0/10                    |
| Park et al 2011   | NA                          | 30/35: 7/23                        | NA                                                     | NA                                  | 0/37: 3/21                    |
| Bang et al 2011   | NA                          | 20/78:120                          | NA                                                     | NA                                  | 22/144: 20/78                |
| Choi et al 2011   | 20/29: 5/26                 | NA                                  | NA                                                     | NA                                  | 3/29: 12/26                  |
| Gallimanis et al 2012 | 163/316                     | NA                                  | 45/175:11/22                                          | NA                                  | 5/190: 28/420                |
| Souza et al 2012  | No Treatment: 45/175:8/22   | NA                                  | 45/175:11/22                                          | NA                                  | NA                             |
|                   | IVT:30/175:1                | 3/22                                | 3/22                                                   | NA                                  | NA                             |
|                   | IAT±IV: 75/175:1            | 22/144:120                         | 22/144:120                                            | NA                                  | NA                             |
| Rai et al 2012    | 38/62: 6/27                 | NA                                  | 9/62: 14/27                                           | NA                                  | NA                             |
| Ramaiah et al 2014 | 24/34:23/53                 | 25/34:35/53                         | 2/34:11/53                                            | 4/34:13/53                          | NA                             |
| Study                          | IAT:2/34:11/5 3 | 24/37: 2/17 | 22/37: 5/15 | NA | NA | 1/37: 1/17 |
|-------------------------------|-----------------|-------------|-------------|----|----|------------|
| Calleja et al 2013            |                 |             |             |    |    |            |
| Ichijo et al 2013              | 15/20: 11/30    | 12/12: 7/14 | NA          | NA | NA | NA         |
| Nambiar V et al. 2013          | N/A             | 23/53: 9/31 | 42.1:37.6:90.9 | 8/53:24/31 | N/A |
| Saarien et al 2014             | 41/57: 13/47    | NA          | NA          | NA | NA | NA         |
| Brunner et al 2014             | NA              | NA          | NA          | NA | NA | 10/205: 6/41 |
| Al-Ali et al 2014              | 8/13: 1/15      | NA          | NA          | NA | NA | NA         |
| Marks MP et al. 2014           | NA              | 10/15: 5/7  | NA          | NA | NA | NA         |
| Sung SM et al 2014             | 9/30            | 7/11:11/19  | N/A         | N/A | 2/30 |
| Liebeskind IMS-III et al 2014  | 50/96: 54/180   | NA          | NA          | 11/96: 40/180  | 6/96: 11/180 |
| Liebeskind SWIFT et al 2014    | 20/35: 14/71    | NA          | NA          | 3/35: 27/71  | NA |
| Mangiafico et al 2014          | 22/65: 4/37     | NA          | NA          | 12/65: 13/37  | 7/66: 6/37 |
| Chen et al 2015                | 21/25: 9/50     | NA          | NA          | 3/25: 8/50  | 3/25: 12/50 |
| Fanou et al 2015               | NA              | 19/310:26/85 | NA          | NA | NA | NA         |
| Menon BK et al 2015            | IVT             | NA          | NA          | NA | NA | NA         |

**Note:** CCS1: 42/59:17/59
CCS 2: 52/59:7/59
CCS 3: 43/59:16/59
### EVT

| Study                  | CCS1         | CCS2         | CCS3         |
|------------------------|--------------|--------------|--------------|
| Kufner 2015            | NA           | 16/30: 23/31 | NA           |
| Hwang et al 2015       | 82/131: 35/76| NA           | 13/131: 11/76| 6/131: 4/76 |
| Singer et al 2015      | 20/41: 25/83 | NA           | NA           | NA          |
| **ENDOSTROKE**         |              |              |              |
| Singer et al 2015      | 38/78: 24/82 | NA           | NA           | NA          |
| **ENDOSTROKE**         |              |              |              |
| Zhang S et al 2016 (Zhang S) | 15/23: 4/41 | 11/23: 16/41 | 16.1/52.8    | 0/23: 10/41 | 0/23: 6/41 |
| Van Seeters T et al 2016 | 194/342:39/142 | NA         | NA           | NA          |
| Tan BYQ et al 2016     | 77/143: 24/97 | 65/99: 49/73 | NA           | 15/143:25/97 | 12/143: 18/97 |
| Sheth sa ET AL 2016   | NA           | 27/51:27/66  | 73:13        | NA          | 20/51:41/66 |
| Garcia-Tome A et al 2016 | 40/65:12/27 | 49/63:32/45  | 17:98        | NA          | 2/3:4/9    |
| Sallustio F et al 2016 | N/A          | 55/75:33/60  | N/A          | 6/75:27/60  | 5/75:22/60 |
| Gersing AS et al 2017 (Gersing AS) | 53/75: 23/40 | 34/75: 21/40 | NA          | NA          | NA         |
| Son JP et al 2017 (Son) | NA          | 10/23: 5/14  | 4.5/52       | NA          | NA         |
| Study                                      | N1/N2 | N3/N4 | N5/N6 | N7/N8 | N9/N10 |
|-------------------------------------------|-------|-------|-------|-------|--------|
| Nordmeyer H et al 2017 (Nordmeyer H)      | 19/37: 2/14 | 34/37: 12/14 | NA | 0/37: 12/14 | NA |
| Madelung CF et al 2017 (Madelung CF)      | 40/55: 10/44 | NA | NA | NA | NA |
| Rebello LC et al 2017 (Rebello LC)        | 49/87: 7/24 | 81: 19 | 30.1±49.4: 34.7±62.8 | 13/87: 4/24 | NA |
| Dankbaar JW et al 2018 (Dankbaar JW)      | 65/138:10/50 | NA | NA | NA | NA |
| Kim BM et al 2018 (Kim BM)                | 303/468: 5/86 | NA | NA | 20/468: 31/86 | 25/468: 20/86 |
| Wang F et al 2018 (Wang F)                | 112/185: 27/85 | NA | NA | 17/185: 30/85 | 29/185: 27/85 |
| Park JS et al 2018 (Park JS)              | 21/33: 7/57 | 24/33: 34/57 | NA | 2/33: 16/57 | 2/33: 14/57 |
| Havenon DA et al 2019 (Havenon AD)        | 29/97: 13/33 | 42/97: 12/33 | 26.9: 65.7 | 18/97: 8/33 | 5/97: 12/33 |

Figures
Figure 1

Pooled analysis of all included studies. A. Patients with acute ischemic stroke with good CBF had a more than 2-fold higher likelihood of having good outcome (mRS 0-2 at 90 days) in comparison to patients with stroke having poor CBF (RR: 2.27; 95% CI: 1.94-2.65; p<0.00001). B. Patients with good pretreatment collaterals receiving intra venous thrombolysis showed around 3-fold higher risk of better outcome as compared to patients with poor collaterals (RR: 2.90; 95% CI: 2.14-3.94; p<0.00001). C. Patients with good collaterals who received thrombolysis either intrarterial or mechanical had approximately 2-fold higher risk of favorable outcome compared to patients with pre-treatment poor collaterals (RR: 1.99; 95% CI: 1.55-2.55; p<0.00001)
Figure 2

Patients with good collaterals showed 1-fold higher likelihood of complete recanalization as compared to poor collaterals RR of Recanalization: 1.31; 95% CI: 1.15-1.49; p<0.00001

Figure 3

Compared to poor collateral status, good pretreatment collaterals had 54% less relative risk of sICH at 90 days. The RR of sICH: 0.46; 95% CI: 0.35-0.60; p<0.00001
Patients with good collateral status has 64% less risk of mortality at 3-months compared to patients with poor collateral status irrespective of the type of thrombolysis. The RR of mortality: 0.36; 95%CI: 0.27-0.48; p<0.00001