Is Direct Endovascular Treatment as an Alternative of Bridging Therapy in Acute Stroke Patients with Large Vessel Occlusion?

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Background: Although endovascular treatment (EVT) is very effective for acute ischemia stroke (AIS) patients with proximal large vessels occlusion (LVO), whether bridging rPA before EVT in stroke patients of LVO is of any benefit and is currently one of the most urgent unanswered questions. We aim to comprehensively determine the efficacy and safety of direct EVT (DEVT) in AIS patients with LVO versus bridging therapy (BT). *Methods:* Clinical researches published in the Embase, PubMed, and Cochrane Library electronic databases up to May 2017 were identified for analysis. Two reviewers extracted data and conducted quality assessment independently. Statistical tests were performed to check for heterogeneity and publication bias. Subgroup and sensitivity analysis were also conducted to evaluate the robustness of the conclusions. *Results:* Overall, 13 studies involving 3302 patients met the inclusion criteria. The AIS patients with DEVT had a similar likelihood to achieve good functional outcome at 3 months (risk ratio [RR] = .93, 95% confidence interval [CI] = .85-1.01, P = .094), mortality at 3 months (RR = 1.10, 95% CI = .91-1.33, P = .33), and symptomatic intracranial hemorrhage (RR = 1.06, 95% CI = .74-1.51, P = .75) versus BT; furthermore, the risk of intracranial hemorrhage was lower in DEVT group (RR = .76, 95% CI = .60-.95, P = .02). No significant difference in recanalization rate existed between the 2 groups (RR = .97, 95% CI = .92-1.02, P = .22); however, in the subgroup analysis, it had a rise trend after DEVT than BT in IVT-eligible group (RR = 1.45, 95% CI = .95-2.22, P = .09). *Conclusions:* DEVT appears to have equally effectiveness to BT with a low risk of intracranial hemorrhage in AIS patients with LVO, especially for anterior circulation, which offered a practical information to select appropriate therapeutic strategies for patients with LVO, though the level of evidence seems to be quite shaky.

Key Words: Stroke—bridging therapy—direct endovascular treatment—outcome

Introduction

The aim of acute stroke treatment is to restore reperfusion and ultimately achieve patient recovery with the fact that the timeliness and extent of reperfusion is associated with better outcome.[1-4] But less 10% stroke patients receive the intravenous thrombolysis treatment (IVT),[5] the only approved therapy for almost 20 years,[6] due to the tight time window and contraindications to tissue-type plasminogen activator (t-PA). Furthermore, effectiveness is also limited by the low recanalization rate of large arterial occlusions (e.g., 32%-37% M1 middle cerebral artery, 6% carotid-T artery, and 4% basilar artery[2,7,8] as a result of the recanalization rate), with large clot burdens especially thrombus length exceeds 8 mm rarely occur for tPA.[9] However, bridging treatment (BT) for acute ischemic stroke (AIS), endovascular treatment (EVT) bridging with standard medical treatment, has been consistently demonstrated to be more effective in large vessel occlusion (LVO) versus IVT alone in 5 large, randomized trials,[10-14] and a published pooled meta-analysis of these 5 trials,[15] which was also confirmed by a recently finding of 12 months' follow-up that EVT reduced poststroke

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disability and improved health-related quality of life in the long term.[16] The main reason for the discrepancy in outcome might be EVT, because rate of patients with IVT did not differ between both groups[17] and subgroup analysis of 5 trials also did not find significant different effects between patients with or without bridging IVT; however, the number of patients received EVT alone was small in each trial, which makes it become extremely urgent to investigate the matter that whether treatment with IVT before EVT is still necessary, in other words, whether the effect of direct EVT (DEVT) is similar to bridging treatment for patients who are eligible to tPA. After all, IVT may increase the risk of systemic or intracerebral hemorrhage, limit the administration of antiplatelets or anticoagulants after EVT, and also increase the procedural cost.[18] Recent published studies specifically investigating the additional effects of IVT showed that prior t-PA facilitates EVT in LVO patients and prone to have higher recanalization rate or better outcome,[19-23] whereas other studies demonstrated that DEVT could achieve a functional outcome as favorable as bridging therapy.[24-29] As yet none of one randomized controlled trials (RCT) make a solo comparison in outcome between BT and DEVT.

In light of aforementioned uncertainty, we therefore pooled all results of studies available and conducted a substantial meta-analysis to evaluate the differences of effectiveness and safety between DEVT and BT in AIS patients of LVO.

Methods

Search Strategy

Potential relevant studies were identified by systematically searching PubMed, Embase, and the Cochrane Library from inception up to May 2017 without language restriction. The keywords such as “Bridging" or “endovascular treatment” and “thrombolysis” in combination with “stroke” were searched across all databases (details of search strategies are shown in Supplementary Table 1). Conference abstract and reference lists of available records identified in the initial publications were also manually searched to avoid omitting relevant researches.

Study Selection

The inclusion studies in present meta-analysis met all the following criteria: (1) original study focus on the comparison that good functional outcome at 3 months between bridging therapy and DEVT in AIS patients of LVO; (2) adults (>18 years) were diagnosed with ischemic stroke in original study; (3) IVT was initiated less than or equal to 4.5 hours of AIS symptom onset in bridging patients.

The following exclusion criteria were applied for subsequent analysis: (1) editorial, case report, systematic review, meta or pool analysis, letters to the editors, conference abstract, studies on animals model, and basic science studies; (2) repeated population or article with overlapping data; (3) unable to extract relevant data.

Outcomes Measure

The outcome was good functional outcome and mortality at 3 months, symptomatic intracranial hemorrhage (sICH), any intracranial hemorrhage (ICH), and recanalization. (1) Good functional outcome after 3 months was defined as a modified Rankin score (mRS) of 0-2 at 3 months after stroke onset. (2) Mortality at 3 months was defined as death during stroke onset to 3 months later. (3) sICH was defined as the definition in the original. (4) Recanalization was defined as patients with any thrombolysis had a TIMI in myocardial ischemic grades 2b or 3 by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography (DSA). For DEVT patients, the recanalization evaluation was conducted in the operation by the DSA. For BT patients, the same assessment was performed after IVT by the computed tomography angiography or magnetic resonance angiography and bridging EVT was started if recanalization failed, or bridging EVT was initiated directly after IVT regardless of recanalization and recanalization evaluation was performed in the operation by the DSA.

Data Extraction and Quality Assessment

Two authors (M.L. and G.L.) independently screened title and abstract of all studies so as to obtain potential literature that fulfilled the inclusion criteria. For the potential research, full text was then retrieved for the eligibility with all disagreements resolved by consensus. The extracted data consisted of the study general characteristics, baseline characteristics, time to treatment, treatment interval time, and occlusion-isolated anterior circulation, outcome. To maximize data requisition, we also contacted the authors whose articles contain insufficient information, where necessary. Quality of the included cohort studies was assessed respectively by the Newcastle-Ottawa Scale (NOS) with NOS scores of greater than or equal to 7 points considered as a high quality. The RCT research was assessed by the Risk of Bias Tool developed by Cochrane Collaboration separately in sequence generation, blinding, allocation concealment, outcome data, and selective outcome.

Statistical Analysis

All statistical analysis were conduct using the Stata (version 12 https://www.stata.com). Risk ratio (RR) and 95% confidence intervals (95% CI) were used to calculate dichotomous variables. The overall effect was tested using z scores calculated by Fisher’s z transformation with significance set at $P < .05$. The chi-squared (χ^2) and

I-squared (I^2) tests were used to evaluate statistical heterogeneity with significance set at $P < .10$. If an obvious heterogeneity existed ($I^2 > 50$ or $P < .10$), a random-effect model was used; otherwise, a fixed-effect was chosen. A sensitivity analysis was performed by changing the analysis model to random-effects model, sequentially removing individual studies and conducting subgroup analysis. Publication bias was evaluated by Egger's test and the funnel plot method.

Results

Search Results and Study Characteristics

After literature search, 502 citations were yielded and screened for retrieval from multiple databases. Thirteen original studies (Wang et al[25]; Maier et al[19]; Rai et al[30]; Abilleira et al[31]; Coutinho et al[32]; Broeg-Morvay et al[24]; Weber et al[26]; Goyal et al[33]; Mulder et al[34]; Guedin et al[21]; Leker et al[28]; Kass-Hont et al[27]; Sallustio et al[35]) involving 3302 subjects were ultimately deemed as suitable for the meta-analysis through careful selection based on the criteria above (Fig 1). Four of included researches were multicenter study[25,31-33] and the other 9 were single-center study. The country or region patients came from are different, while 9 studies from Europe,[19,21,24,26,31-35] 2 studies from Asia,[25,28] and the other 2 studies from North America.[27,30] The definition of sICH was mildly different, 1 study[35] was defined as a hemorrhage, which was not seen on a previous CT scan, there had subsequently been a decline in neurological functional status, 8 studies[19,21,24-27,32,34] were defined that an ICH on CT scan with a decrease in National Institutes of Health Stroke Scale score of 4 or more points, and the other 2[28,31] were not found the definition in original studies. In terms of comparability on the choice of therapy strategy, 4 studies[24-27] were comparable on account of the patients of DEVT and were also eligible for bridging therapy, whereas the patients of DEVT group from other 9 studies were ineligible for bridging IVT.[19,21,28,30-35] The detailed individual characteristics of the studies are tabulated in Supplementary Table 2, and the interesting outcomes included in the meta-analysis were shown in Supplementary Table 3.

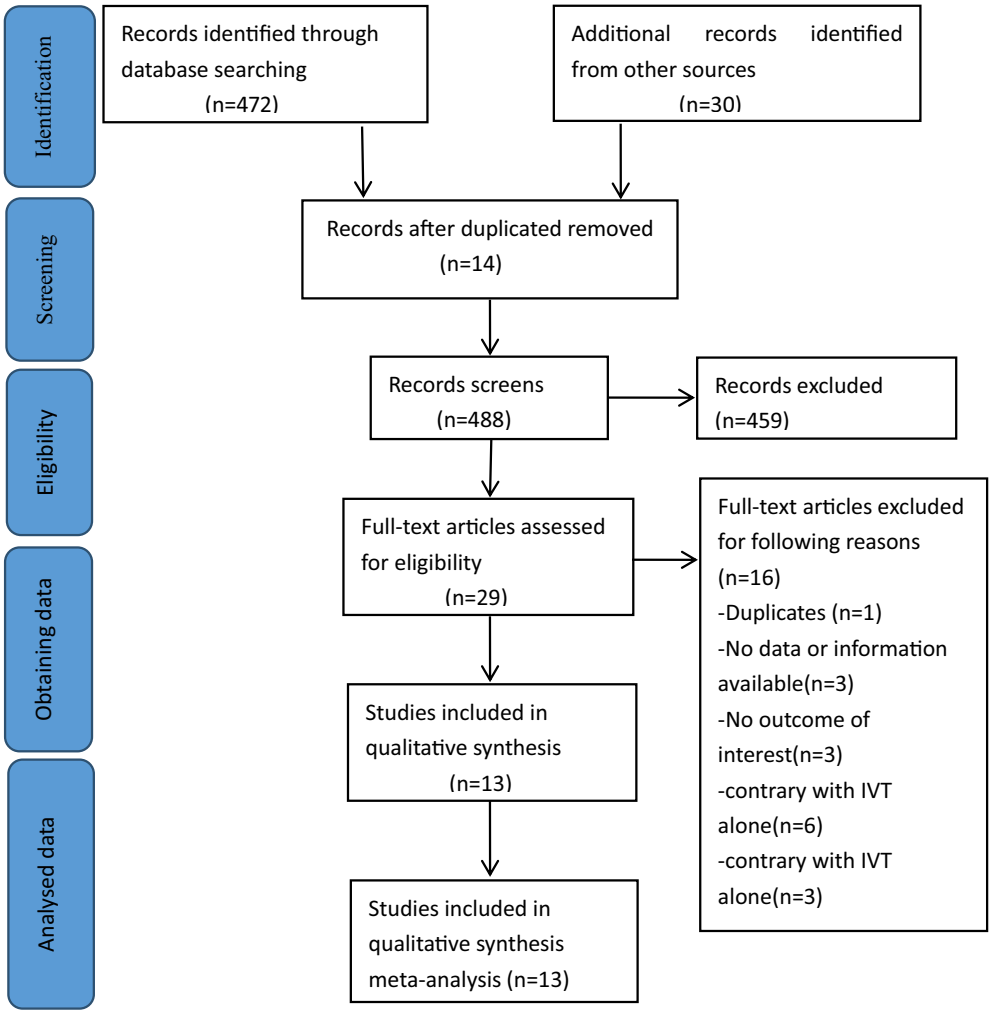

Figure 1. *Trails selection process.*

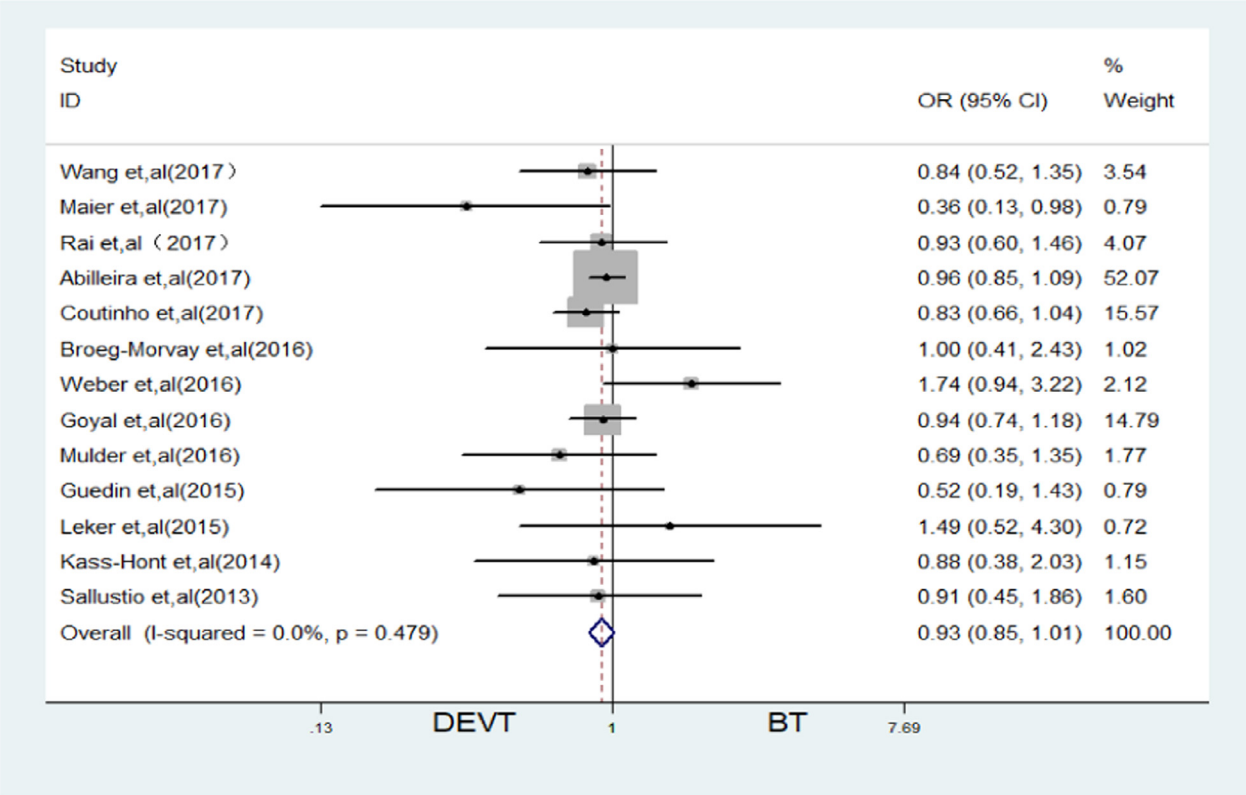

Figure 2. *Relative chance for achieving good functional outcome in AIS patients with LVO received DEVT versus bridging therapy applying fixed-effect model. Abbreviation: BT, bridging treatment.*

The NOS score was 9 points for 2 studies, 8 points for 5 studies, and 7 points for 3 studies (Supplementary Table 4). All of cohort studies were of high quality, and the other 3 RCT trials were also high quality according to the criteria above described, which indicated that the overall risk of bias among included studies is low.

Good Functional Outcome after Three Months

On the basis of 13 studies, patients of DEVT group have a similar chance to achieve a good functional outcome in LVO when contrary to these of bridging group (RR = .93, 95% CI = .85-1.01, *P* = .094; Fig 2) without significant heterogeneity (*P* = .48, $I^2 = 0.00\%$). The sensitivity analysis was performed in several aspects: (1) changing the analysis model to a random-effects model, which also predicted similar results (*P* = .094; seen in Supplementary Data as Fig 1); (2) sequentially removing individual studies, which produced minor changes (Fig 3); (3) in the subgroup analysis of patients in randomized or nonrandomized trial, no significant difference between BT and DEVT group existed in both subgroup (Fig 4). All of these indicated the robustness of the conclusions.

The likelihood to achieve a good functional outcome among subgroups sorted by whether patients of DEVT were also eligible for BT. The result still was of no significant difference not only in eligible group (RR = 1.05, 95% CI = .77-1.45, *P* = .75) but also in ineligible group (RR = .92, 95% CI = .83-1.00, *P* = .07; Fig 5).

Mortality at Three Months

The incidence of mortality was reported in 11 studies. There is no significant difference in mortality at 3 months between DEVT group and BT group (RR = 1.10, 95% CI = .91-1.33, *P* = .33; Fig 6) without significant heterogeneity (*P* = .29). In the subgroup analysis of whether patients of DEVT were also eligible for BT, the result still was of no significant difference in eligible group and ineligible group (seen in Supplementary Data as Fig 2).

Symptomatic ICH

On the basis of 11 studies, there is no significant difference in any sICH risk between DEVT group and BT group (RR = 1.06, 95% CI = .74-1.51, *P* = .75; Fig 7) without significant heterogeneity (*P* = .82, $I^2 = 0.0\%$).

Any ICH

Incidence of ICH was reported in 8 studies. The combined RR was calculated to be .76 (95% CI = .60-.95 *P* = .02; Fig 7), showing a decreased risk of ICH in DEVT

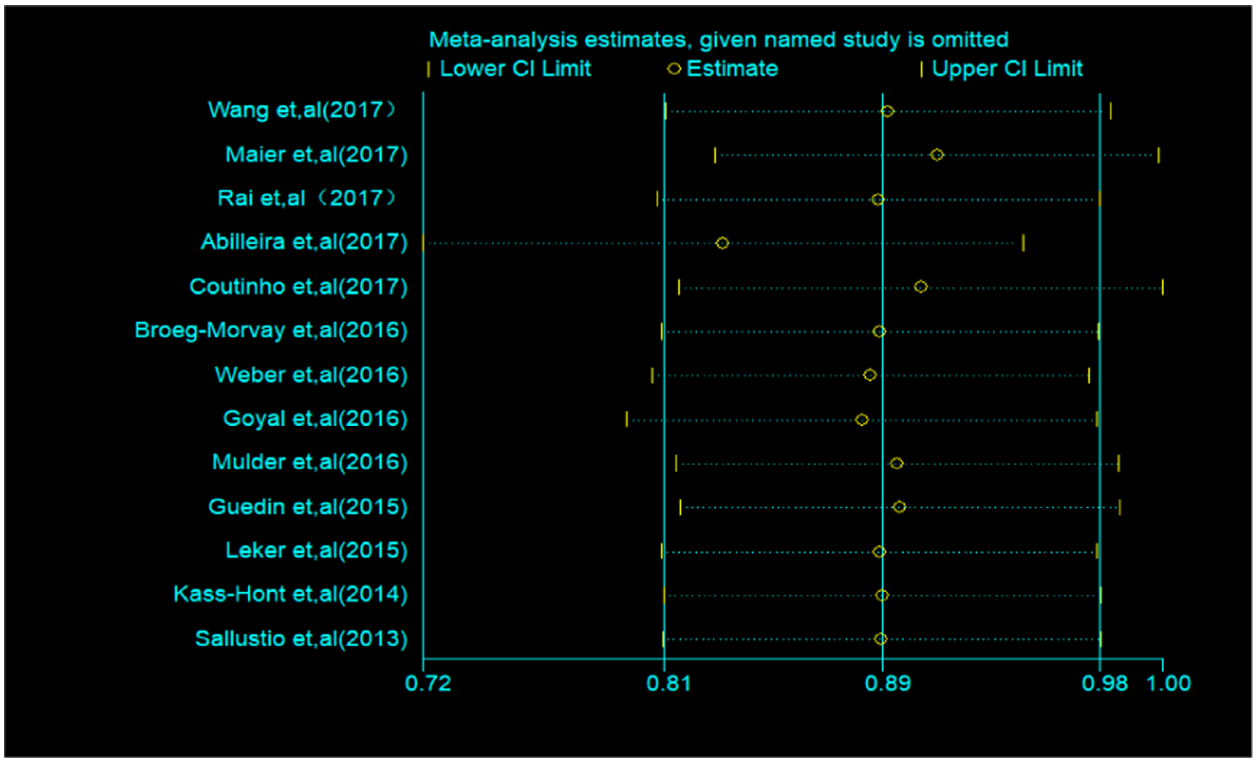

Figure 3. *The sensitivity analysis of good functional outcome by sequentially removing individual studies. Abbreviation: BT, bridging treatment.*

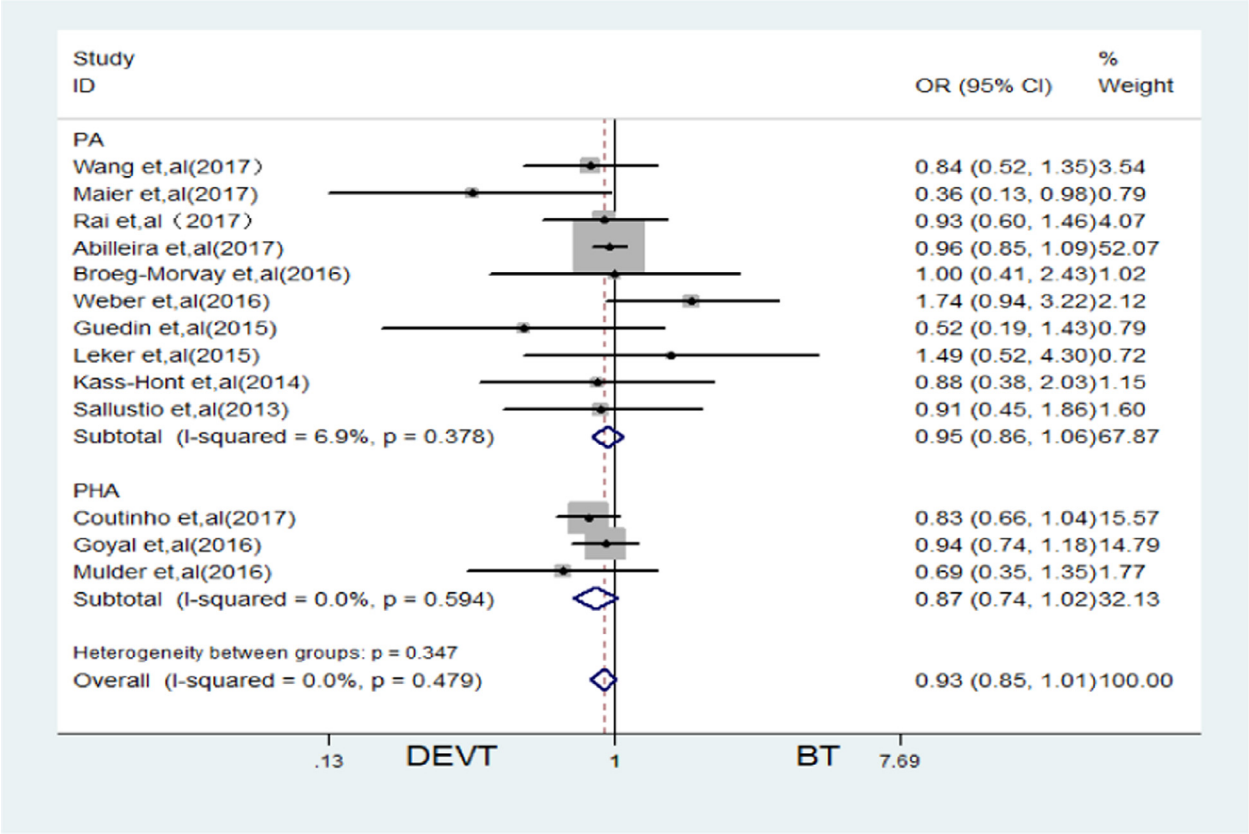

Figure 4. *The sensitivity analysis through subgroup analysis of patients in randomized or nonrandomized trial studies for the chance to achieve a good functional outcome in AIS patients with LVO received DEVT versus bridging therapy. Abbreviations: PHA, post hoc analysis; PR, prospective analysis.*

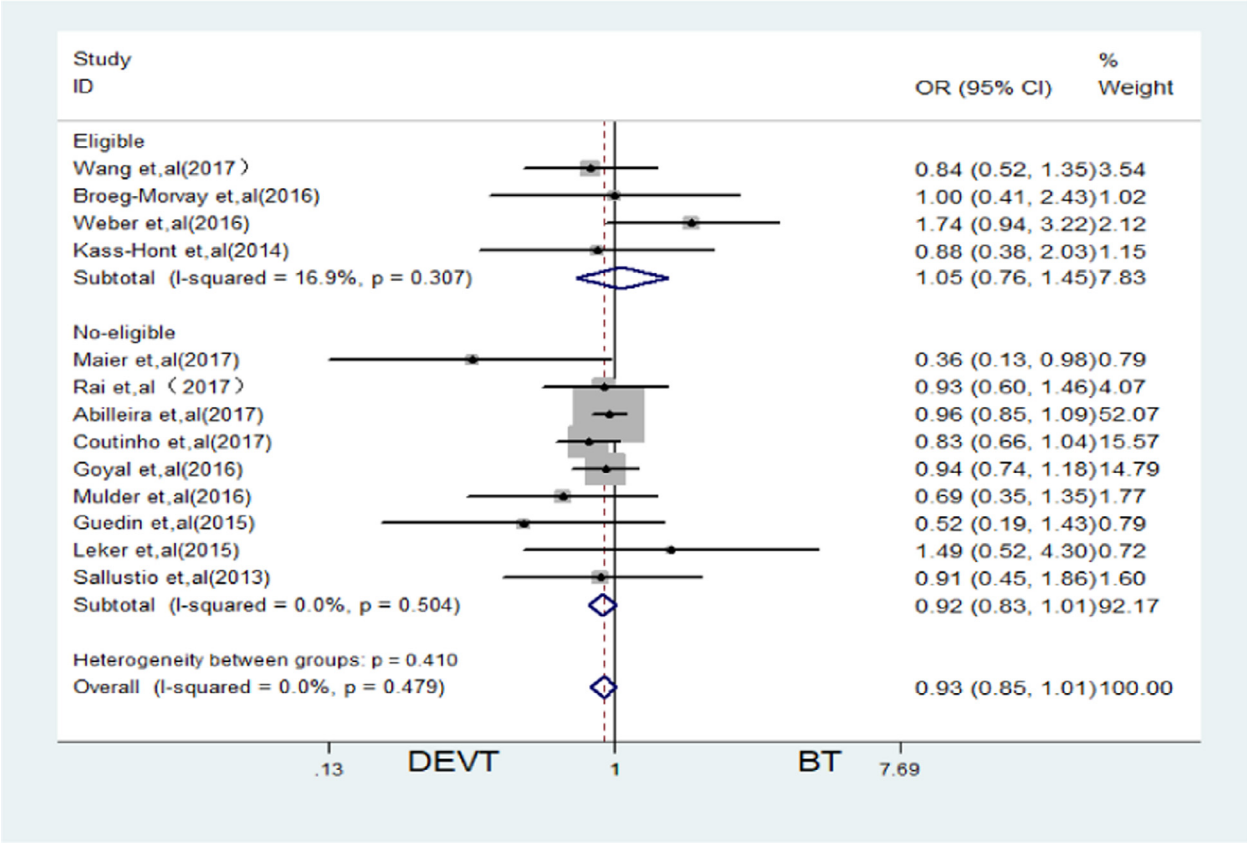

Figure 5. *Subgroup analysis by whether patients of DEVT were also eligible for bridging therapy for the chance to achieve a good functional outcome in AIS patients with LVO received DEVT versus bridging therapy.*

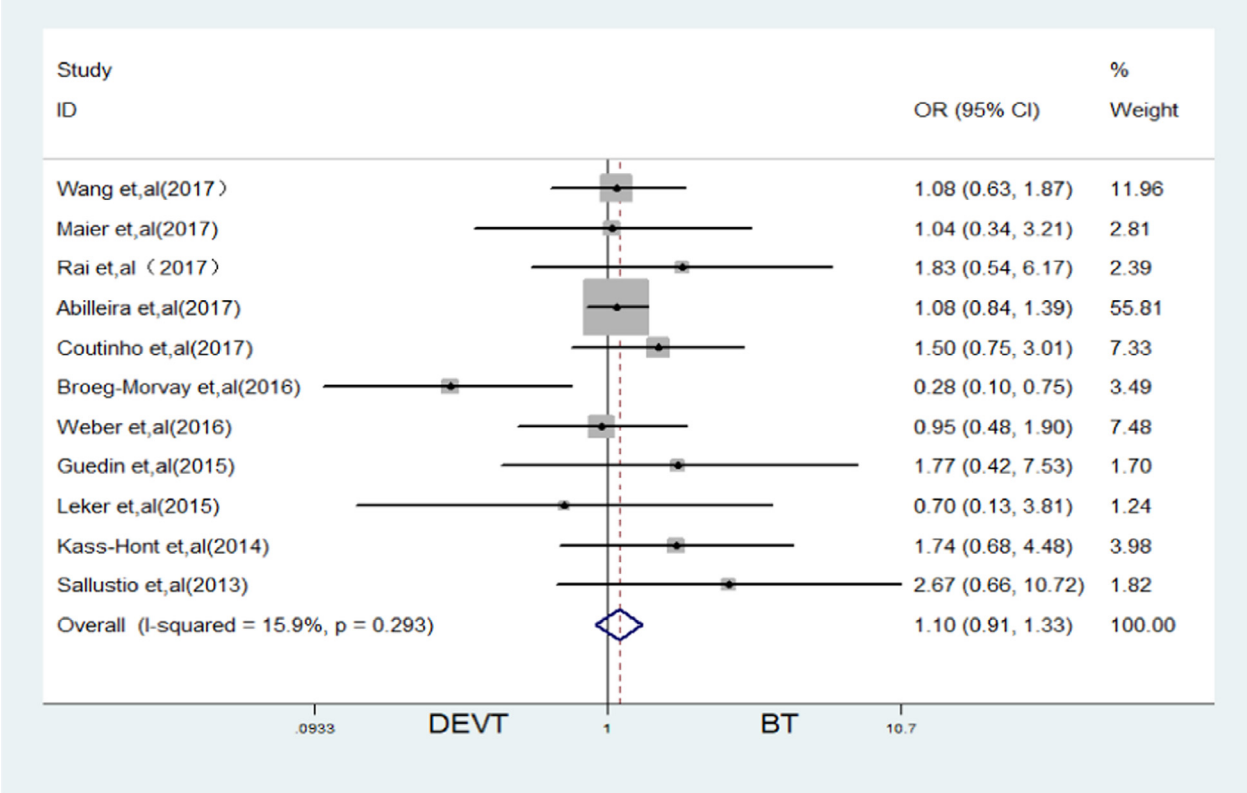

Figure 6. *Relative risk for mortality in AIS patients with LVO received DEVT versus bridging therapy applying fixed-effect model.*

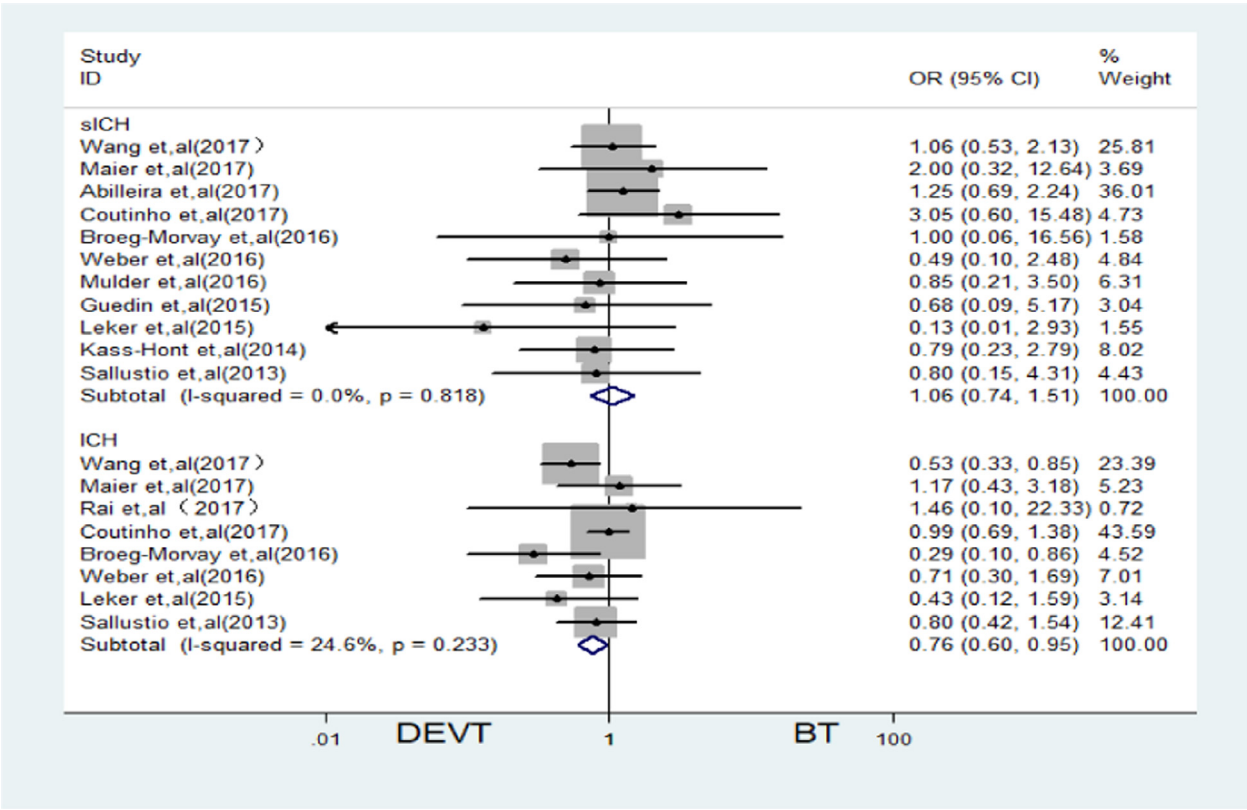

Figure 7. *Relative risk for achieving sICH and ICH in AIS with LVO patients received DEVT versus bridging therapy applying fixed-effect model.*

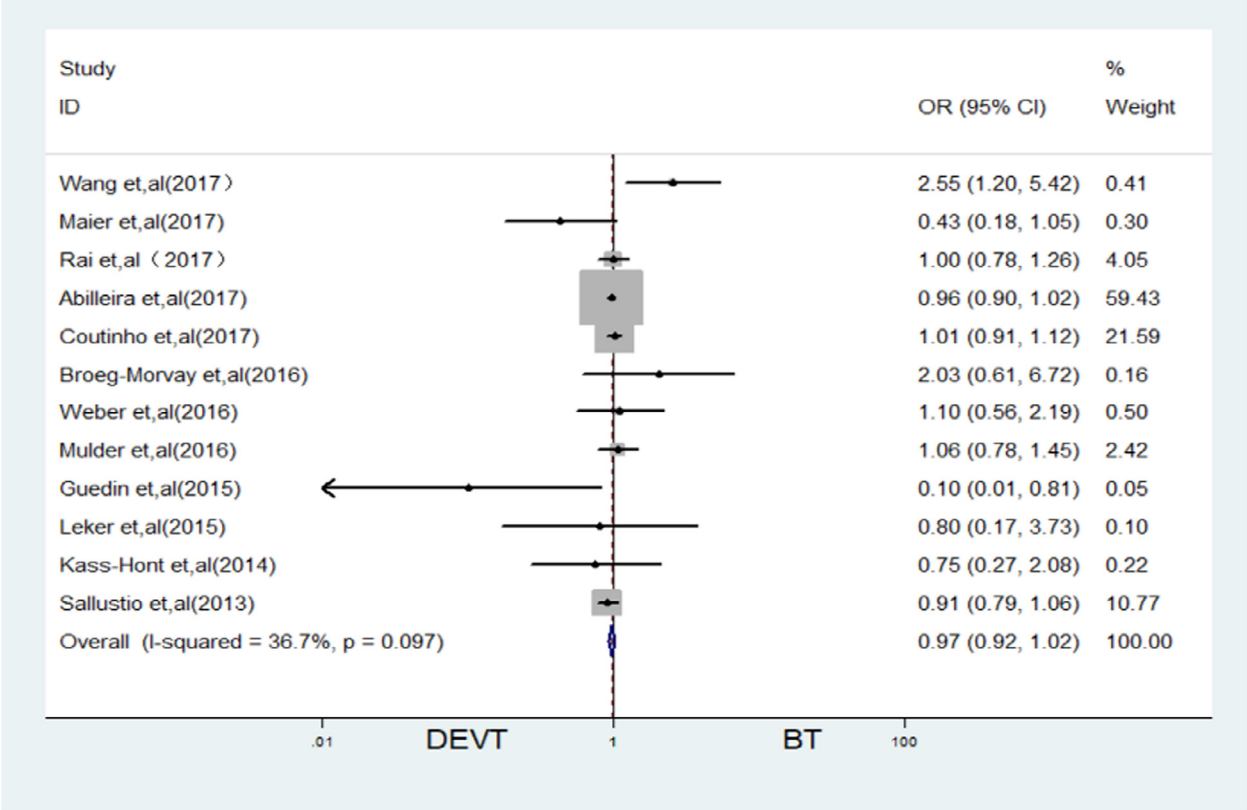

Figure 8. *Relative chance for the rate of recanalization in AIS patients with LVO received DEVT versus bridging therapy applying fixed-effect model.*

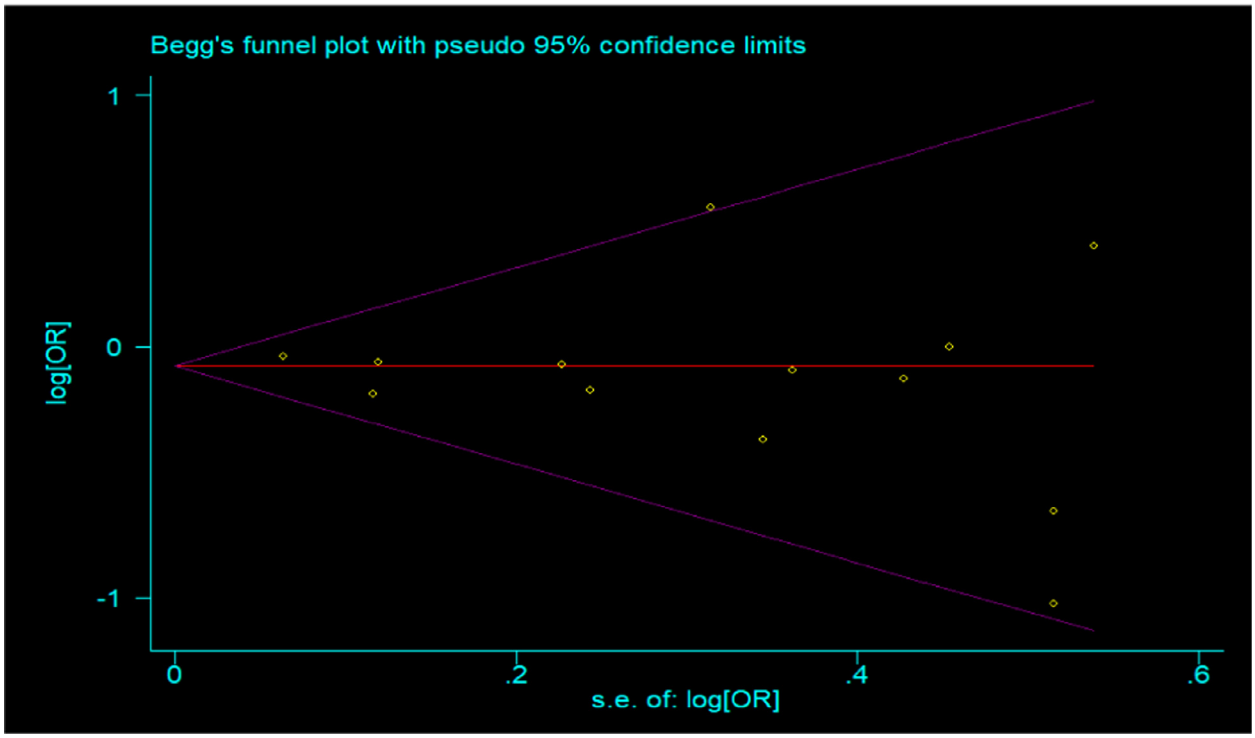

Figure 9. *Funnel plot for good functional outcome excellent.*

group bridging therapy group without significant heterogeneity (P = .23).

Recanalization

Recanalization was reported in 12 intra-arterial thrombolysis studies. No significant difference in recanalization rate existed between DEVT group and BT group (RR = .97, 95% CI = .92-1.02, P = .22; Fig 8) without significant heterogeneity (P = .10). The result still was of no significant difference not only in eligible group (RR = 1.45, 95% CI = .95-2.22, P = .09) but also in ineligible group (P = .16; seen in Supplementary Data as Fig 3) after conducting the subgroup analysis of whether patients of DEVT were also eligible for BT.

Publication Bias Evaluation

Overall, no significant publication bias was detected by Egger's test (P = .59) and Begger's test (P = .50) for good functional outcome. Moreover, the shape of funnel plot did not indicate any obvious asymmetry on visual inspection (Fig 9).

Discussion

The American Heart/Stroke Association in their latest guideline gave a class I recommendation for EVT in patients with LVO in anterior circulation as an adjunct to intravenous tPA.[36] However, whether the effect of EVT is so powerful in its own right that bridging tPA may not add to the efficacy of EVT even increase the risk of bleeding complication and thus whether bridging IVT before EVT in stroke patients of LVO is of any benefit is currently one of the most urgent unanswered questions. The present meta-analysis based on 7 higher quality cohort studies had the following main finding: First, functional outcome of DEVT is similar to these after bridging therapy. Second, the rates of mortality and sICH after EVT did not differ between patients with DEVT and those with BT, whereas patients with DEVT were less likely to achieve ICH than those with BT. Third, recanalization rate after DEVT is in the same order as after BT in pooled analysis; however, in the subgroup analysis, it had a rise trend after DEVT than BT in IVT-eligible group.

In line with previous studies,[24-29] good functional outcome and mortality at 3 months were not statistically different between DEVT and BT groups, which seemed to be inconsistent with the primary aim of bridging therapy proposed to combine the advantage of IVT (easy and rapid administration) with those of EVT (targeted therapy and high recanalization) therefore resulting in good outcome based on the setting that prior t-PA before EVT might contribute to recanalization in some patients, dissolve the small, peripheral thrombus impairing the penumbra-perfusion by collaterals, lower the rate of recurrent strokes occluded by cardiac thrombi during hospitalization,[19] and last can decrease thrombus volume and alter thrombus texture so that facilitated subsequent EVT.[22] But our analysis found no significant difference in the rate of

recanalization between DEVT and bridging therapy group even it had an obviously rise trend after DEVT in IVT-eligible group by subgroup analysis. And it has been widely accepted that recanalization is associated with good outcome, but time from symptom onset to recanalization is also a better predictor of good clinical outcome.[37-40] However, the bridging therapy significantly delayed the mean time from symptom onset to groin puncture when contrary to DEVT in almost all of the included studies and the time delay in bridging group mainly caused by obtaining consent for tPA, payment, drug preparation and administration, and evaluation of treatment effect,[25] which may diluted the actual advantage of bridging IVT in bridging group even reverse its benefit just as Weber et al showed that the highest rate of good outcome was seen in DEVT with no contraindications for IVT.[26] If the further large-scale random controlled trial also confirmed our finding that DEVT has equally effectiveness as bridging therapy in AIS patient of LVO. The rapidly initiated EVT might be a reasonable treatment strategy once LVO, especially anterior circulation, was diagnosed without contraindications for EVT within IVT time window just like treatment of ST-elevation-myocardial infraction has changed several years ago when facilitated percutaneous coronary intervention had no benefit over primary percutaneous coronary intervention.[41]

The present study showed no any difference in sICH but lower rates of ICH in DEVT than bridging manage. The discrepancy of these might result from significant difference in the asymptomatic ICH (aICH) between the 2 groups, consistent with the finding of previous studies.[24,25] The possible reason was that IVT increases the risk of aICH in bridging therapy group.[42] However, whether the aICH affect 3-month functional outcome still inconsistent.[43,44] The further studies address that the aforementioned disputes are warranted.

Our analysis also observed that recanalization rates after DEVT are in the same order as after bridging therapy in bulk analysis, which had a rise trend after DEVT in IVT-eligible group and significantly decreased chance after DEVT in IVT-ineligible group by subgroup analysis. The discrepancy of effect between IVT-eligible group and IVT-ineligible group may due to the patients received DEVT in IVT-ineligible group either exceed the time window of 4.5 or have relevant comorbidities with a possible impact on recanalization, such as oral anticoagulation or antiplatelet, increased bleeding risk, prior hemorrhage, or subacute stroke,[24] so as to these unbalances confounding the actual relevance between DEVT group and bridging group. A rise trend of recanalization rate after DEVT in IVT-eligible group seemed to contrary to the effect of bridging IVT to some extent. However, the bridging IVT was an important risk factor of periprocedural thrombus, and subsequent downstream embolism has been showed.[25,45,46] The role of preventing recanalization may partly account the rise trend of recanalization rate in DEVT.

As far as we are aware, a recently meta-analysis[47] has comprehensively determined the efficacy and safety in AIS patients after DEVT versus BT, and the different result was shown from our study. The most likely explanation is that DEVT of all included studies was not randomized to receive IVT (either exceed the time window of 4.5 or has relevant comorbidities for t-PA) except one[24] in Mistry et al's study; however, in our meta-analysis, 4 included studies[24-27] reported that patients with DEVT are also eligible to IVT. In addition, a subgroup analysis of whether patients with DEVT were also eligible for BT was conducted in the present study, and the equal effectiveness and recanalization between DEVT and BT are more remarkable in IVT-eligible group than that in IVT-ineligible group. Further, RCT studies with eliminating inherent difference are required to confirm our conclusions.

Our meta-analysis has several strengths. First, the baseline characteristics of stroke patients are comparable between 2 groups as an effort to minimize confounding effects. Furthermore, large sample size, sufficient observational outcomes, and none of heterogeneity and publication bias also represent considerable strengths of the present study. And subgroup and sensitivity analyses were also performed to ensure the robustness of the conclusions. Some limitations should also be mentioned before generalizing the present findings. First, all of the studies included were observational studies, which are particularly prone to lead to selection bias. Second, in some studies,[19,21,28] the unbalanced baseline between DEVT group and BT group could made the results unfully valid when the patients with DEVT are ineligible for bridging IVT. Third, although some variables (bleeding, recanalization, time from onset to prion) were carefully investigated, the factors likely having a relevant impact on outcome were not evaluated such as the thrombus length and collaterals due to the unavailable data of individual subjects. Last, the definition of sICH was mildly different; fortunately, the conclusion is seemingly robust when no statistical heterogeneity existed in pooled analysis of sICH.

Conclusion

In summary, DEVT appears to have equally effectiveness to BT with a low risk of ICH in AIS patients with LVO especially for anterior circulation; therefore, our data suggested that DEVT might be an alternative for BT. Given the limitation of currently available studies, further large-scale researches are urgently needed to confirm our conclusions with addressing some unsolved restriction.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Supplementary Materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.007.

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