Review Article
Comparative effect of pecutaneous transtuminl angioplasty and stenting (PTAS) plus medical therapy treatment versus medical therapy treatment for intracranial atherosclerotic stenosis: evidence from a meta-analysis involving ten studies

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Abstract: The aim of our study was to define the rates of stroke or death, survival, and restenosis after enrolment among patients with intracranial atherosclerotic stenosis events, who underwent PTAS plus medical therapy and medical therapy only. Databases, including PubMed, EMBASE, and Web of Science, were comprehensively searched. RevMan software was used to analyze the outcome measures. Outcome measures included primary endpoints which were stroke or death within 30 days after enrolment, primary endpoint which were stroke or death within one year after enrolment, survival rate within one year after enrolment, and restenosis rate. PTAS plus medical therapy group had a higher rate of stroke or death within 30 days (RR=1.451, 95% CI=(1.011-2.084), P=0.044) and restenosis (RR=2.830, 95% CI=(1.351-5.927), P=0.006). PTAS plus medical therapy group and medical therapy group had similar rates of stroke or death within one year (RR=0.987, 95% CI=(0.634-1.539), P=0.956) and survival within one year (RR=0.877, 95% CI=(0.616-1.248), P=0.466). The present meta-analysis indicated that the outcomes of PTAS plus medical therapy were not obviously better compared to the outcomes of medical therapy on patients with intracranial atherosclerotic stenosis.

Keywords: Intracranial atherosclerotic stenosis, pecutaneous transtuminl angioplasty, stenting, medical therapy, stroke

Introduction

Intracranial atherosclerotic stenosis, the third leading cause to death and adult disability among Europeans, Asians and Americans, is the most common etiologies of ischaemic attack and stroke [1, 2]. For example, in Asian population, nearly half of the stroke cases were induced by intracranial atherosclerotic stenosis [3]. The prognosis of intracranial atherosclerotic stenosis was mainly associated with the status of cerebral blood flow [4]. After the initial stroke event, there would still be existent of a high risk of recurrent stoke [5, 6].

Medical treatments based on antithrombotic and endovascular interventional therapies are the two major options for the therapy of intra-cranial atherosclerotic stenosis [7, 8]. Patients who accepted medical intervention would still have an elevating risk of re-stroke, especially those who were composited with cardiovascular risk factor [9-12]. For high-dose medical therapy group, annual risk of ischemic stroke in a symptomatic stenotic intracranial artery was previously reported to be about 11%-12% [5, 10]. Moreover, an increasing risk of severe bleeding was reported as the side effect for medical treatment [9, 10]. Endovascular therapies, including angioplasty, stenting and the combination of both, had originally emerged as alternative approaches because of the poor prognosis of pharmacotherapy [8]. Self-expanding Wingspan stent had been demonstrated to have a better outcomes than medical treatment for severe intracranial atherosclerot-

ic stenosis [13], while the result was opposite in balloon-expandable stent [8]. Percutaneous transluminal angioplasty and stenting (PTAS) was, as the name implied, the combination of the technique of percutaneous transluminal angioplasty which was the procedure that can open up a blocked blood vessel using a small, flexible plastic tube, or catheter, with a sausage-shaped balloon at the end of it and the technique of stenting which was the procedure that a stent is placed into an artery or blood vessel to hold it open. PTAS, as one of endovascular techniques which had a success rate over 90% was originally available in 2005 [14]. According to a meta-analysis published in 2009, PTAS provided a better prognosis in symptomatic intracranial atherosclerosis patients than those were treated with angioplasty only [15]. However there was no existent of significant difference between the PTAS group and aggressive medical treatment group in a retrospective meta-analysis of China [16]. Moreover, from the result of Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial for high-risk patients, both short-term and long-term follow-up indicated the use of aggressive medical management had benefit over PTAS with the Wingspan stent [17, 18]. In addition, variable complications of periprocedural were also need to be carefully concerned. Therefore, whether medical treatment alone or medical treatment plus PTAS would be a preferred strategy for intracranial atherosclerotic stenosis still remains uncertain.

In the current study, global-related literature were collected to conduct a systematic review and meta-analysis, and the rates of stroke or death, survival, and restenosis after enrolment among patients with intracranial atherosclerotic stenosis events, who underwent PTAS plus medical therapy and medical therapy only was successfully assessed.

Materials and methods

Search strategy

PubMed, Web of science and Embase were the electron databases used for literature search. We identified relevant articles with no language restriction by using the keywords which are "intracranial stenosis" AND "stenting" AND "medical" (up to Mar. 23th, 2016) combined with a complete set of same expression words.

Later, a manual search will be conduct as well to identify additional articles by scanning meta-analysis of similar research topic for the purpose of increasing the completeness of the selection process.

Inclusion criteria

We screened title and abstract of all identified article. Studies satisfied following selection criteria were included in the present meta-analysis. 1) Studies were relevant to intracranial stenosis; 2) Studies should specifically evaluate the outcome measure in both PTAS plus medical therapy group and medical therapy only group.

Exclusion criteria

Studies were excluded from analysis if they met the exclusion criteria as follow. 1) Studies were animal or simulation test; 2) studies were review, book or non-peer reviewed literature; 3) Details on treatment and outcome could not be assessed.

Data extraction

Two investigators independently screened the titles and abstracts of studies to exclude articles that conflicted with one of the inclusion criteria or fulfilled one of the exclusion criteria and then did full text review of studies that were finally selected. When discrepancy occurred, a third investigator was required to resolve it. The information was extract from the studies. First author, year of publication, study population characteristics, study design, intracranial stenosis type, methods of case and control group, primary endpoint, number of participating subjects for two groups. For each outcome, we separately recorded or calculated study population and number of events within one study. When missing data occurred in selected studies, email will be used to connect with author.

Outcome measures included primary end point which was the rate of stroke or death within 30 days after enrolment, primary endpoint which was the rate of stroke or death within one year after enrolment, survival rate within one year after enrolment, and restenosis rate.

Statistical methods

We performed statistical analyses through following recommendations of the Cochrane
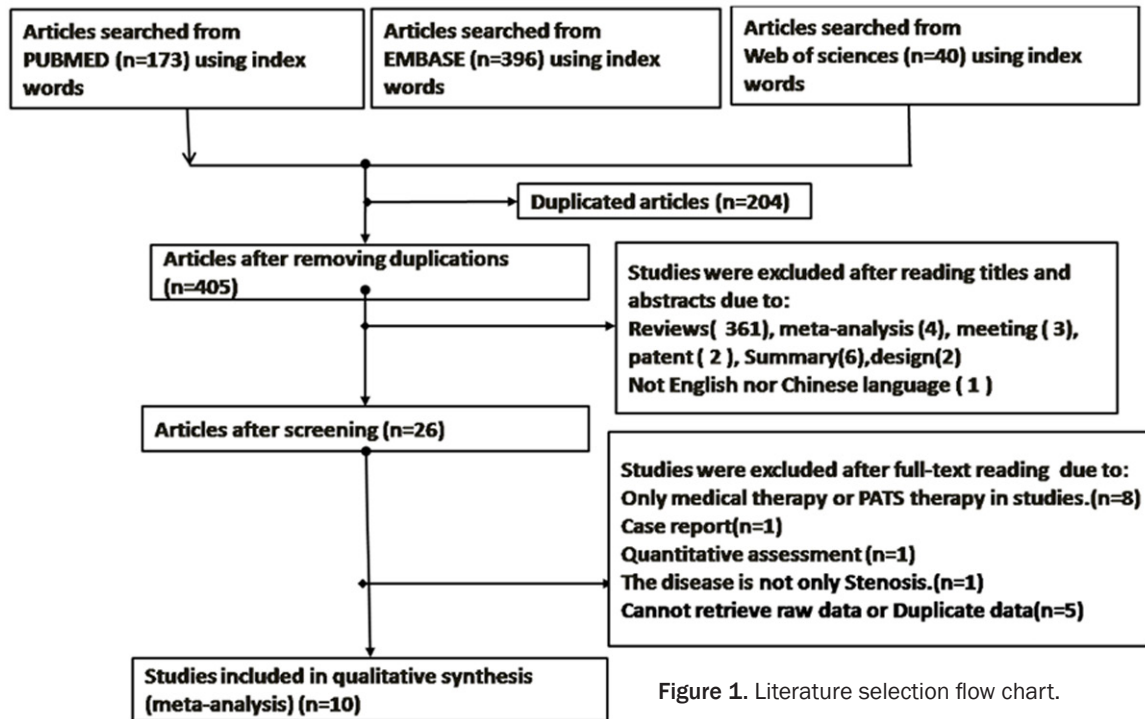
Figure 1. Literature selection flow chart.

Collaboration and Quality of Reporting of Meta-analyses guidelines [19]. When a study reported 0 events in one of two groups, a correction of 0.5 was introduced to allow for estimation. However trials with 0 events in both groups were excluded from meta-analysis. Review Manager (RevMan 5.3; Cochrane Collaboration, Copenhagen, Denmark) was used to analyze the pooled data. Since all the outcomes mentioned above were dichotomous data. Risk ratios (RRs) were used to present as the overall effect. The probable size of interval for each outcome was shown by 95% confidence intervals (CIs) calculation. A P-value that was < 0.05 indicated significant difference. Forest plots were also displayed along with numeric results.

The statistical heterogeneity across studies was assessed by chi-square test of Higgins and Thompson and quantified by the I^2 value. A fixed-effect was adopted when no heterogeneity was considered (I^2 < 50%). Otherwise, in the light of significant heterogeneity, a random-effects model was adopted to provide a relatively conservative estimate. Sensitivity analysis and subgroups analysis were carried out to investigate the consistency of the result and the potential sources of heterogeneity. The risk of publication bias for each outcome was identified by an inverted funnel plot.

Results

Literature search

A total of 609 articles were identified by search strategy from electronic database. The abstracts and keywords of 405 non-duplicated articles (204 duplicated publications excluded) were further reviewed. After screening, 15 studies meeting the inclusion criteria were included while 390 articles were excluded according to the selection criteria listed above. Only 10 full text review of the selected 15 article could be retrieved by us for data assessment [8, 13, 16, 18, 20-25]. The other 5 articles were excluded for because of insufficient or duplicate data. **Figure 1** summarized the whole process of literature search, from article identification to the final stage of inclusion.

Main characteristics of the included studies

The including studies were published between 2010 and 2015. The meta-analysis consisted of 1501 patients with intracranial atherosclerotic stenosis, of whom 690 cases were in the PTAS plus medical therapy group and 811 cases were in the medical therapy group. **Table 1** indicated the main characteristics of the selected studies.

Table 1. Summary of eligible articles

Study	Randomized	The design of study	The patient who was enrolment	The method of established stenosis	The method of case group	The method of control group	The method of control potential risk factors	Primary endpoint	M/P	Age (mean year)	Male	Follow-up time
Liu (2012) [20]	N	Retrospective	Intracranial stenosis	DSA angiographically	PTA and Wingspan-expandable stenting plus medical therapy	Medical therapy (100/d aspirin and 75 mg/d clopidogrel for 3 months therapy, then long time 100-300/d aspirin and/or 75 mg/d clopidogrel as anticoagulation)	Atorvastatin	NHISS	20/19	59	77%	12 months
Povedano (2010) [21]	N	Retrospective	Atherosclerotic intracranial vessel stenosis	Noninvasive methods OR angiographically	Percutaneous transluminal balloon angioplasty and stent placement (AVE INX and AVE GFX; Cypher, Sonic, and Velocity; Express and Neuroform; Taxus Express; Herculink and MultiLink Pixel; and Wingspan stenting) plus medical therapy	Medical therapy (antiplatelet therapy or anticoagulation)	Statins, antihypertensive agents, and other prevention strategies	TIA, stroke, or major bleeding, death	38/25	65	86%	12 months
Mohammadian (2012) [13]	N	Prospective	Symptomatic intracranial arterial stenosis	Angiographically	PTAS (SES and BMS) plus medical therapy	Medical therapy (antiplatelet therapy or anticoagulation: clopidogrel 75 mg/day and ASA 100 mg/day at least 3 days previous to the procedure and full heparinization)	Antiplatelet, statin, and daily physiotherapy	AEs, and mortality rate	29/34	68	60%	12 months
Zaidat (2015) [8]	Y	Prospective	Symptomatic intracranial stenosis	Cerebral angiogram	Percutaneous transluminal balloon angioplasty with stenting stent plus medical therapy	Clopidogrel (75 mg daily) for the first 3 months after enrollment and aspirin (81-325 mg daily) for the study duration	Statin, antihypertensive	TIA, Store, NIHSS	53/59	62	66%	12 months
Hou (2014) [23]	N	Retrospective	Intracranial stenosis	Angiography	PTA and stenting (Gateway PTA Balloon Catheter and Wingspan Stent System) plus medical therapy	Medical therapy (clopidogrel 75 mg per day and aspirin 100 mg per day for the first 1 month after enrollment, clopidogrel 75 mg per day or aspirin 100 mg per day for the study duration)	Atorvastatin	TIA, stroke	73/72	58	64%	12 months
Jiao (2013) [24]	N	Retrospective	Intracranial stenosis	DSA angiographically	PTA and Wingspan-expandable stenting plus medical therapy	Medical therapy (clopidogrel 75 mg per day and aspirin 100-300 mg per day for the first 3 months after enrollment, aspirin 100 mg per day for the study duration)	Atorvastatin	NHISS, mRs, stroke, and death	86/122	56	66%	> 24 months
Yin (2015) [16]	N	Retrospective	Severe intracranial artery stenosis	Angiographically	PTAS plus medical therapy	Medical therapy (Antiplatelet drugs: 100-300 mg/d aspirin and/or 75 mg/d clopidogrel, as dual-antiplatelets for at least 6 months in the medical treatment group, then either one was selected for lifetime use)	Atorvastatin, antihypertensives and anti-diabetic medications	Stroke or death	172/48	59	67%	12 months
Derdeyn (2014) [18]	Y	Prospective	Atherosclerotic intracranial arterial stenosis	Angiographically	Gateway PTA Balloon Catheter and Wingspan Stent System (both manufactured by Boston Scientific Corporation) AND medical therapy	Medical therapy (aspirin 325 mg per day and clopidogrel, 75 mg per day for 3 months after enrollment)	Rosuvastatin,	TIA, Store and NHISS	227/224	60	60%	36 months
Pan (2013) [25]	N	Retrospective	Symptomatic intracranial stenosis	DSA angiographically	PTA and Wingspan-expandable stenting or Apollo plus medical therapy	Medical therapy (Antiplatelet drugs: 300 mg/d aspirin and 75 mg/d clopidogrel, as dual-antiplatelets for 1-3 months)	Atorvastatin	TIA, Store and NHISS	52/34	62	67%	48 months
Tang (2011) [22]	N	Retrospective	Symptomatic intracranial stenosis	Angiographically	PTAS plus medical therapy	Double antiplatelet (aspirin and clopidogrel) therapy was given as standard treatment, if tolerated, from 1-3 days before to at least 3 months after the procedure	-	TIA, Store and death	61/53	66	83%	36 months

PTAS: percutaneous transluminal angioplasty and stenting; PTA: percutaneous transluminal angioplasty; BMS: bare metal stent; SES: self-expandable stent; TIA: transient ischemic attacks; ISR: symptomatic in-stent restenosis.
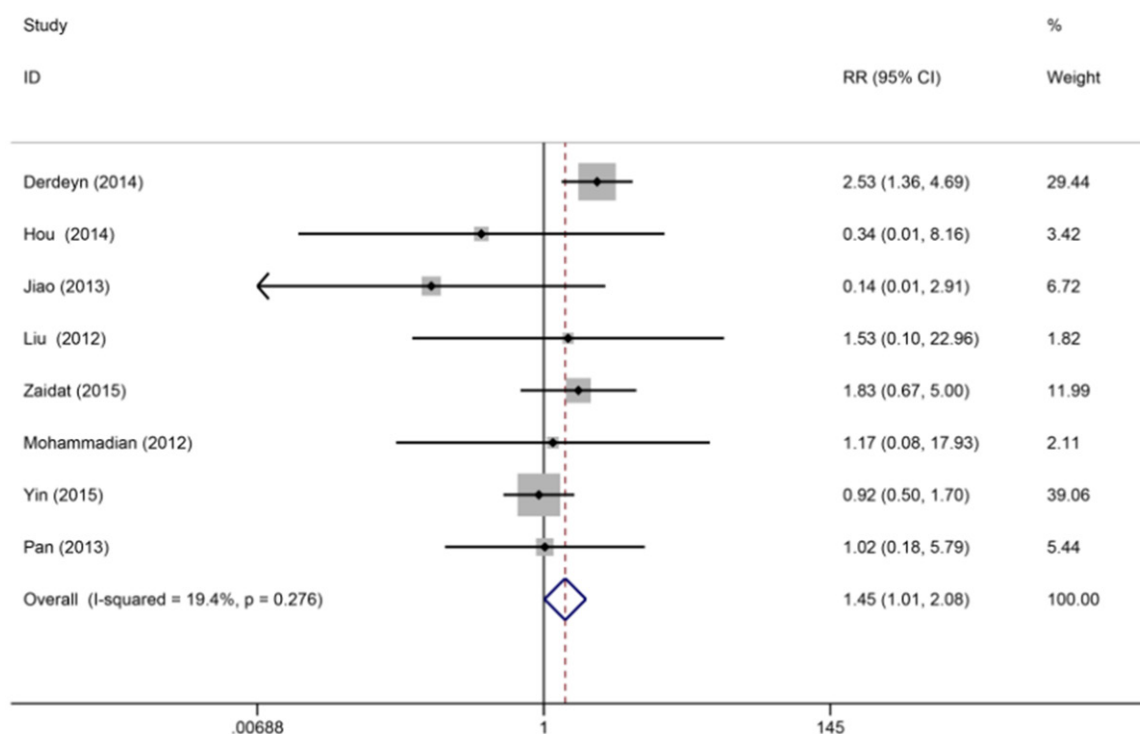
Figure 2. The forest plot of risk ratios for 30 days primary endpoint. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.

Table 2. Meta-analysis of the clinic outcome between medical therapy and stenting therapy in intracranial stenosis therapy

Study	OR	Lower Limit	Upper Limit	P (OR)	I^2	P (Heterogeneity)	P (Begg's Test)	P (Egger's test)
30 day primary outcome	1.451	1.011	2.084	0.044	19.40%	0.276	0.386	0.277
1 year primary outcome	0.987	0.634	1.539	0.956	73.50%	< 0.001	0.371	0.272
1 year survival rate	0.877	0.616	1.248	0.466	< 0.01%	0.627	0.060	0.182
Restenosis rate	2.83	1.351	5.927	0.006	35.10%	0.173	0.707	0.006

Stroke or death within 30 days

The forest plot and the chi-square test for heterogeneity of 30 days primary endpoint (I^2 < 50%) displayed in **Figure 2** visually and statistically suggested no heterogeneity among included studies. In this case, we chose a fixed-effects model to do the calculation of RRs for 30 days primary endpoint which was indicated in **Table 2**. Based on the data in **Table 2**, PTAS plus medical therapy group had a higher rate of stroke or death within 30 days than medical therapy group and difference between two group was statistically significant (RR=1.451, 95% CI=(1.011-2.084), P=0.044).

Stroke or death within one year

The forest plot and the chi-square test for heterogeneity of one year primary endpoint (I^2 > 50%) displayed in **Figure 3** visually and statistically suggested a heterogeneity among included studies. In this case, we chose a random-effects model to conduct the calculation of RRs for one year primary endpoint which was indicated in **Table 2**. Based on the data in **Table 2**, PTAS plus medical therapy group had a slightly lower rate of stroke or death within one year than medical therapy group but difference between two group was not statistically significant (RR=0.987, 95% CI=(0.634-1.539), P=0.956).
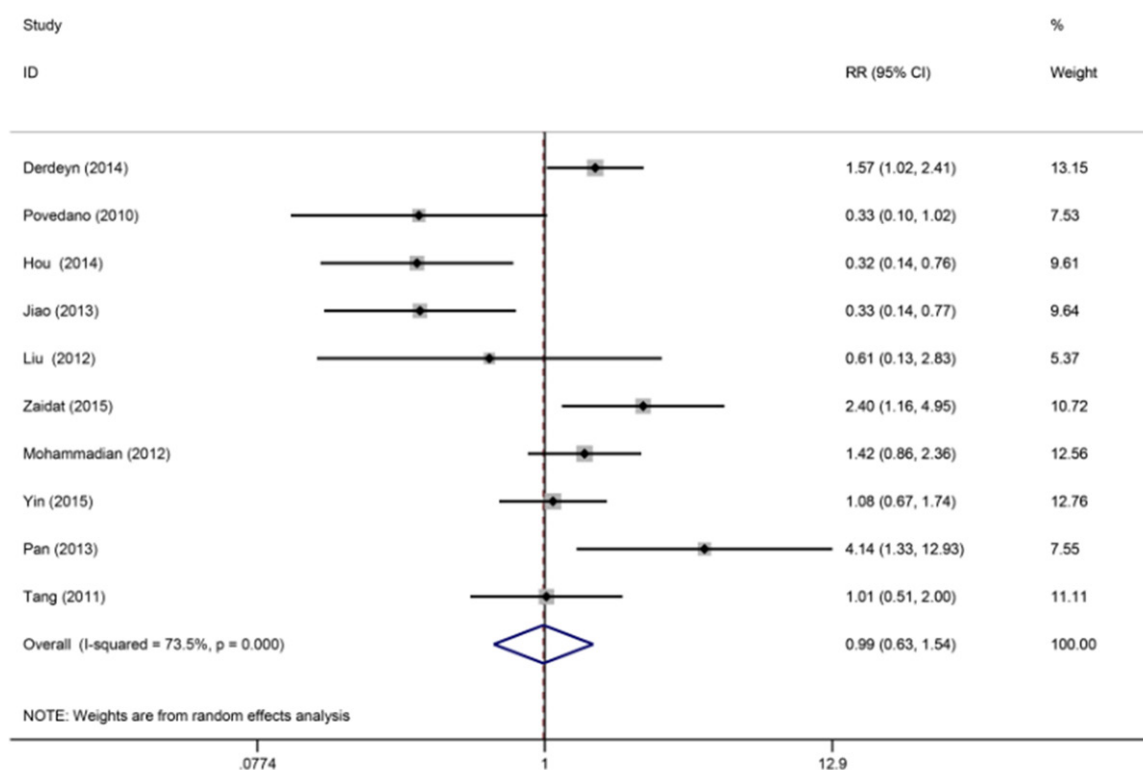
Figure 3. The forest plot of risk ratios for one year primary endpoint. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.
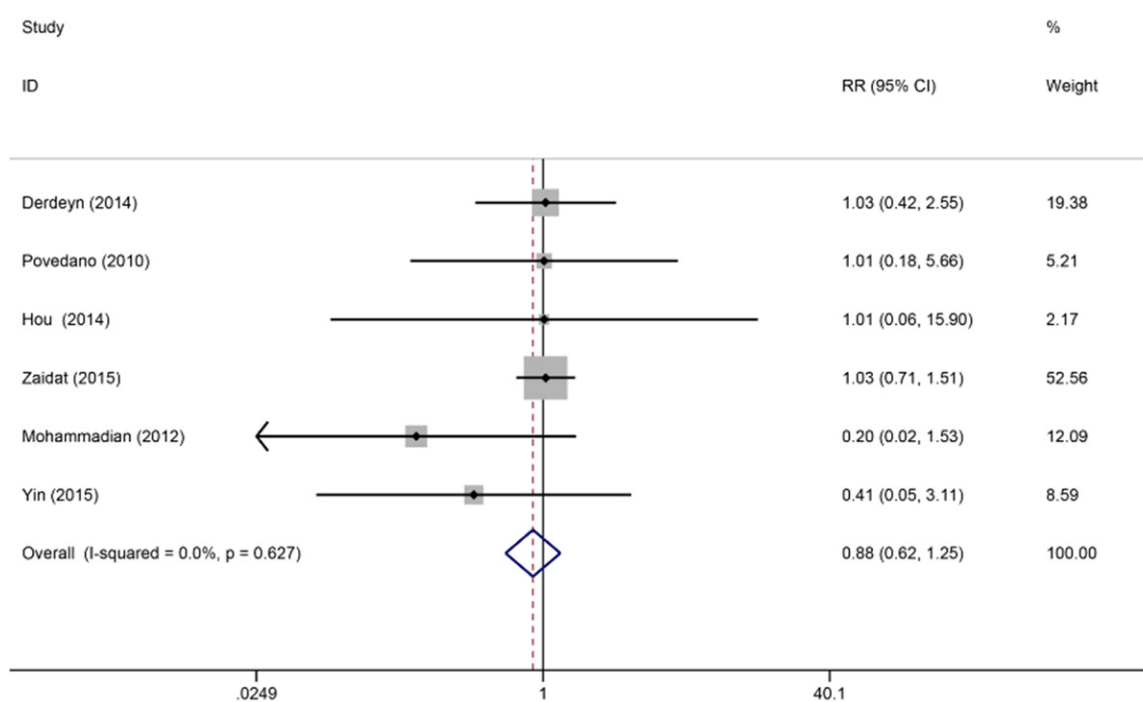

Figure 4. The forest plot of risk ratios for one year survival rate. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.
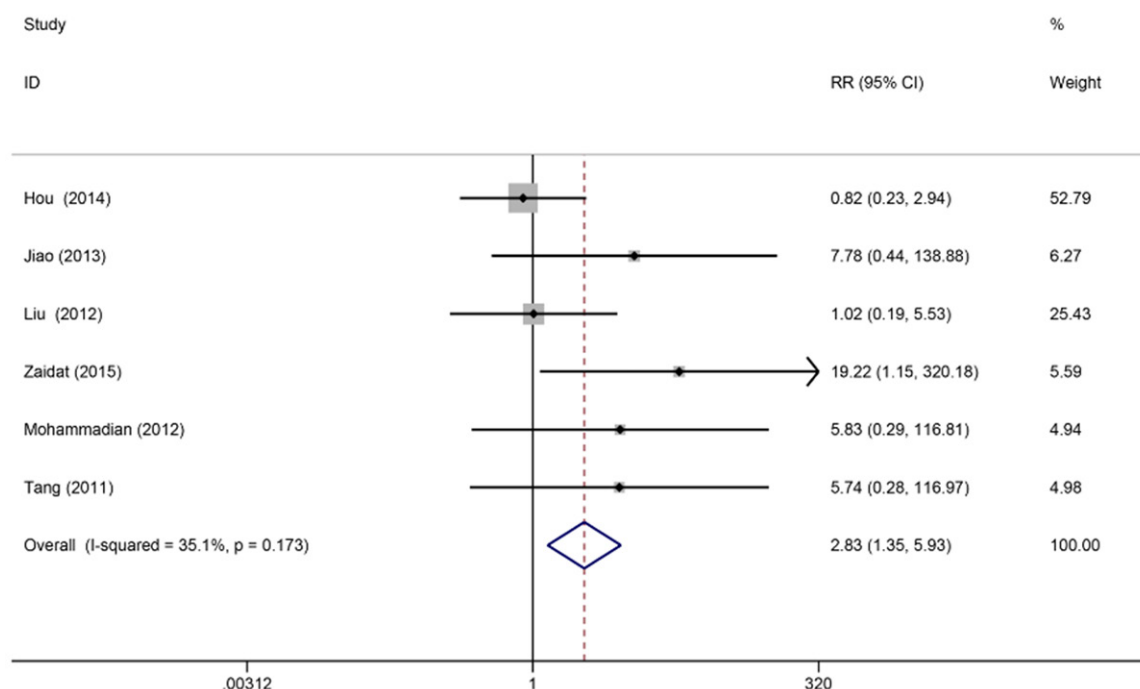
Figure 5. The forest plot of risk ratios for restenosis rate. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.
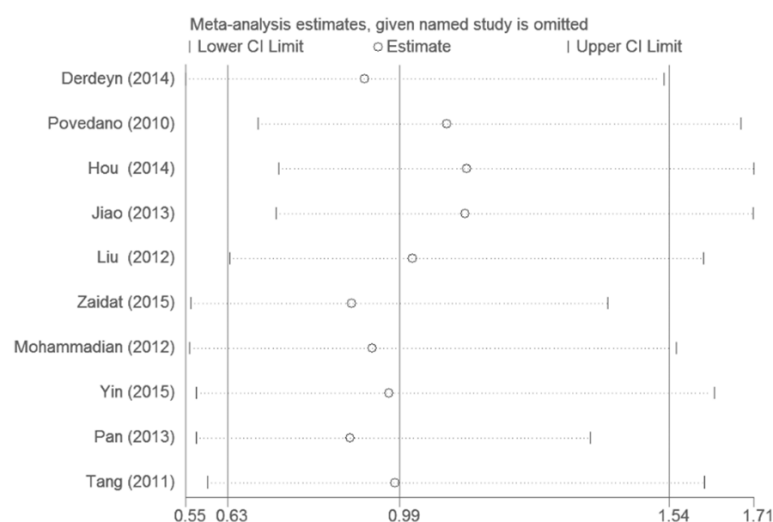

Figure 6. Sensitivity analysis for the effect of one year stroke or death rate. CI, confidence interval.

Survival within one year

The forest plot and the chi-square test for heterogeneity of one year survival rate ($I^2 < 50\%$) displayed in **Figure 4** visually and statistically suggested no heterogeneity among included studies. In this case, we chose a fixed-effects model to do the calculation of RRs for one year survival rate which was indicated in **Table 2**. Based on the data in **Table 2**, PTAS plus medical therapy group had a slightly lower rate of survival within one year than medical therapy group but difference between two group was not statistically significant (RR= 0.877, 95% CI=(0.616-1.248), P=0.466).

Restenosis rate

The forest plot and the chi-square test for heterogeneity of restenosis rate ($I^2 < 50\%$) displayed in **Figure 5** visually and statistically suggested no heterogeneity among included studies. In this case, we chose a fixed-effects model to do the calculation of RRs for restenosis rate which was indicated in **Table 2**. Based on the data in **Table 2**, PTAS plus medical therapy group had a quite higher rate of restenosis than medical therapy group and difference between two
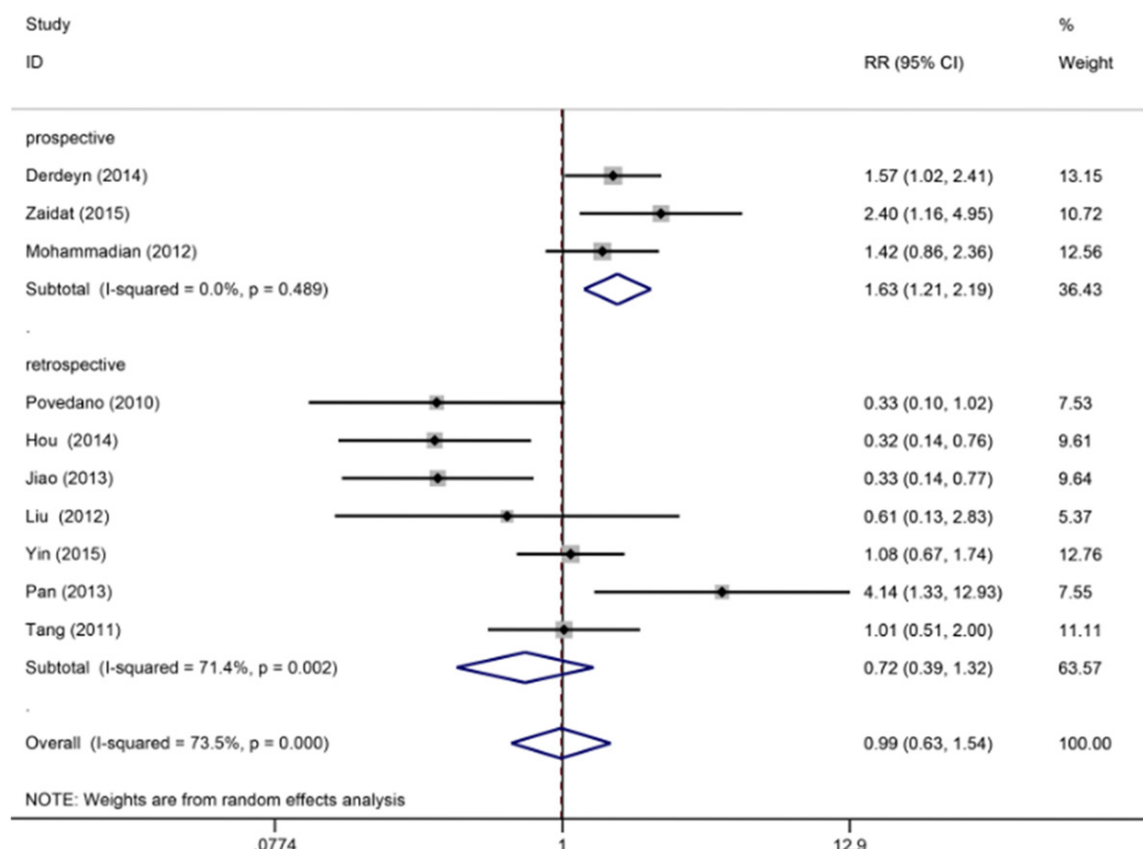
Figure 7. The forest plot of subgroup analysis according to the design of study. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.

Table 3. Subgroup analysis of the 1 year primary outcome between medical therapy and stenting therapy in intracranial stenosis therapy

Study		OR	Lower Limit	Upper Limit	P (OR)	I^2	P (Heterogeneity)
Randomized	Yes	1.750	1.209	2.534	0.003	< 0.01%	0.321
	No	0.802	0.472	1.364	0.416	72.20%	0.001
The design of study	Prospective	1.628	1.208	2.195	0.001	< 0.01%	0.489
	Retrospective	0.717	0.390	1.320	0.286	71.40%	0.002

group was statistically significant (RR= 2.830, 95% CI=(1.351-5.927), P=0.006).

Sensitivity and subgroup analysis

Leave-one-out approach was used to performed sensitivity. The meta-analysis of the one year stroke or death rate was performed with each study removed in turn. Based on the result of sensitivity analysis displayed in **Figure 6**, the direction and magnitude of combined estimates did not vary markedly with the removal of the studies which visually indicated that data of the one year stroke or death rate was not overly affected by any one study and that the meta-analysis has a good reliability.

In order to investigate the potential sources of heterogeneity of one year stroke or death rate, two subgroup analyses were carried out. The forest plot and the chi-square test for heterogeneity of subgroup analysis according to the design of study displayed in **Figure 7** visually and statistically suggested no heterogeneity among prospective studies (I^2 < 0.01%) but among retrospective studies (I^2=71.4%). Compared to medical therapy, PTAS plus medical therapy induced a higher incidence of one year stroke or death in prospective studies (RR= 1.628, 95% CI=(1.208-2.195), P=0.001), while no significant differences were found in retrospective studies (RR=0.717, 95% CI=(0.390-1.320), P=0.286), as shown in **Table 3**.
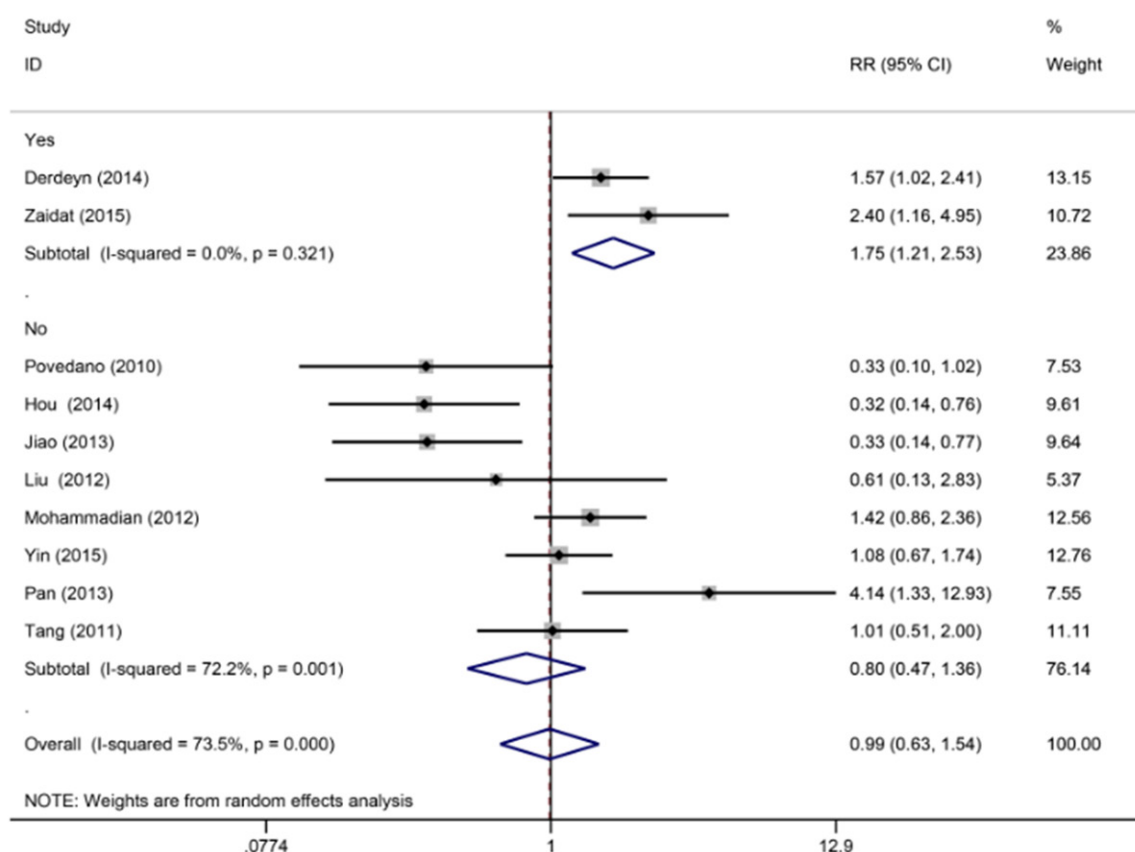
Figure 8. The forest plot of subgroup analysis according to whether randomize or not. The risk ratio from each study are represented by rhombus, and the confidence interval (CI) is indicated by error bars.
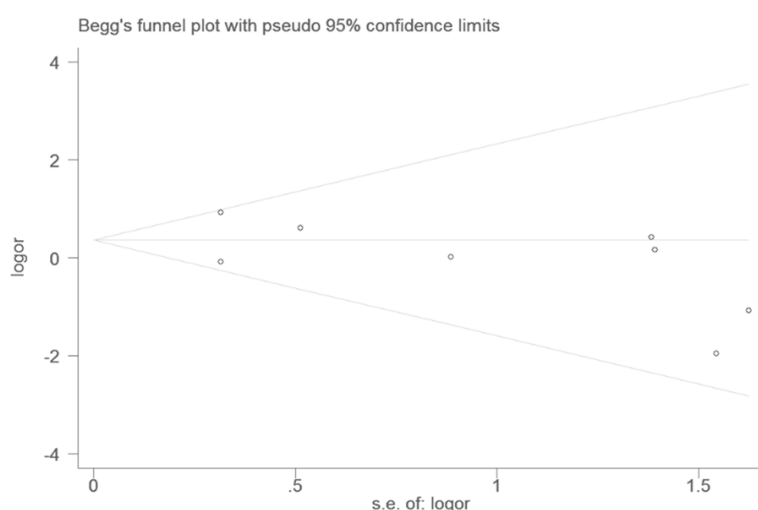

Figure 9. Funnel plot investigating publication bias for 30 days primary endpoint.

The forest plot and the chi-square test for heterogeneity of subgroup analysis according to whether randomize or not displayed in **Figure 8** visually and statistically suggested no hetero-

geneity among randomized studies ($I^2 < 0.01\%$) but among non-randomized studies ($I^2 = 72.2\%$). Compared to medical therapy, PTAS plus medical therapy induced a higher incidence of one year stroke or death in randomized studies (RR=1.750, 95% CI=(1.209-2.534), P=0.003), while no significant differences were found in non-randomized studies (RR=0.802, 95% CI= (0.472-1.364), P=0.416), as shown in **Table 3**.

Publication bias

Funnel plots displayed in **Figures 9-12** were used to visually reflect the potential publication bias of four outcomes. Egger method and Begg method were additionally applied because of the low number of enrolled studies, as shown in **Table**
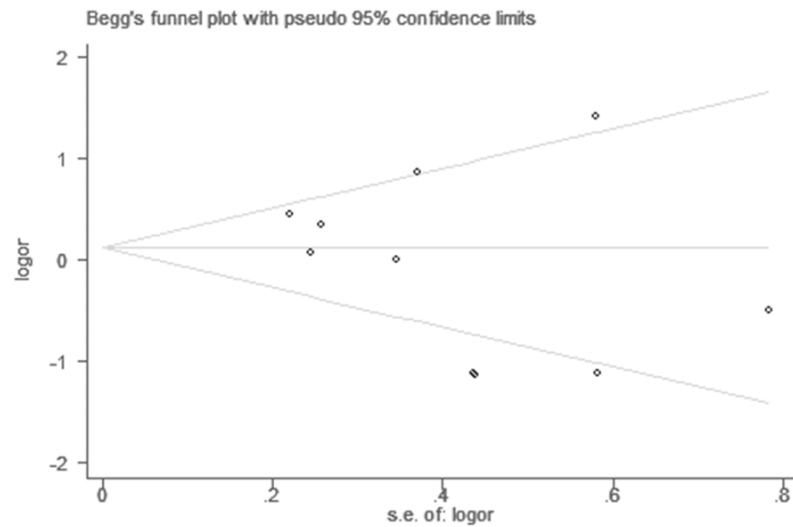
Figure 10. Funnel plot investigating publication bias for one year primary endpoint.
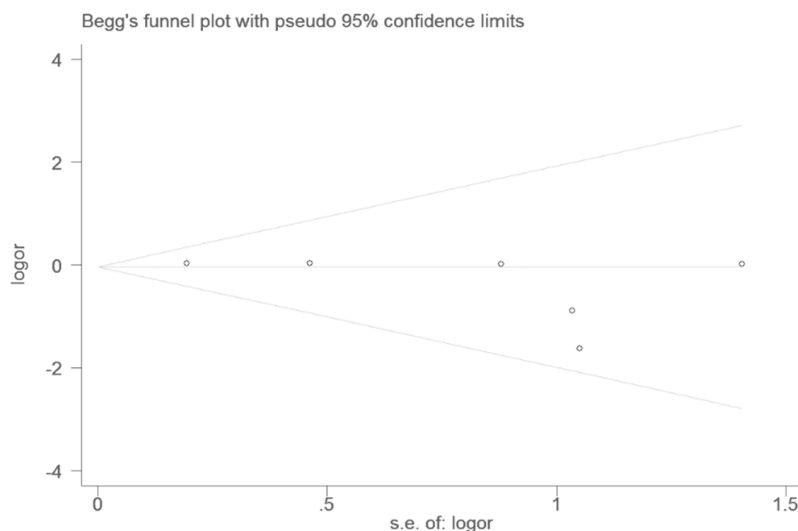

Figure 11. Funnel plot investigating publication bias for one year survival rate.

2. No obvious evidence of publication bias was found for primary endpoint with 30 days, primary endpoint with one year, and survival rate within one year. However Egger method show a risk of publication bias for restenosis rate (Egger method: P=0.006, Begg method: P= 0.707).

Discussion

With the rapid development of people's lifestyle, not only did people enjoy the benefits of modern technology, but also suffered from novel and severe health problems. According to accumulating reports, cardiovascular disease has become one of the major health burdens worldwide over the past several decades [26, 27]. Intracranial atherosclerotic stenosis, regarded as the most common etiology of ischemia stroke, has been reported to be the third leading cause on adults [1, 28, 29]. Moreover, it was reported that patients underlying intracranial atherosclerotic stenosis were susceptible to acute middle cerebral artery occlusion [30]. Kim et al. found that intracranial atherosclerotic stenosis is independently correlated to progressively greater white matter hyperintensities burden in Korean stroke population [31]. The results of studies suggested various major vascular risk factors including sex, hypertension, diabetes, dyslipidemia, smoking, age and metabolic syndrome were contributed to intracranial atherosclerotic stenosis in Asian population [32, 33]. In addition, it was found the occurrence of intracranial artery stenosis was more frequent than that of extracranial artery in the Chinese population [34]. Therefore, the effective and safe therapy for intracranial atherosclerotic stenosis was urgently needed. Although lots of different treatments for intracranial atherosclerotic stenosis were performed, these regimens could be classified into medical treatment based on antithrombotic therapy and endovascular therapy such as angioplasty and stenting [35, 36]. Intensive statin therapy, such as long term use of low-dose atorvastatin therapy, was demonstrated as a safe and effective treatment for Chinese patients with intracranial ath-
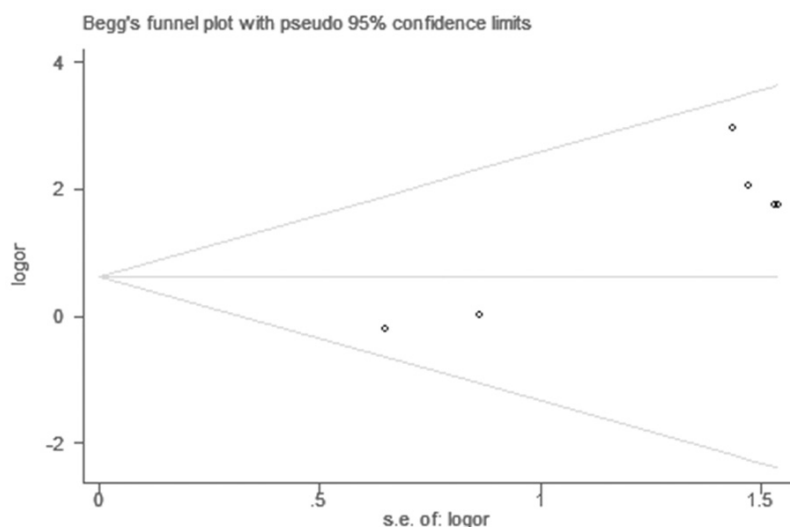
Begg's funnel plot with pseudo 95% confidence limits

Figure 12. Funnel plot investigating publication bias for restenosis rate.

lower than that in medical therapy group, it did not show significant difference between two groups (RR= 0.987, 95% CI: 0.634-1.539, P=0.956; and RR= 0.877, 95% CI: 0.616-1.248, P=0.466; respectively). Furthermore, the rate of restenosis in PTAS plus medical therapy group was quite higher than that in medical therapy group (RR=2.830, 95% CI: 1.351-5.927, P=0.006). The sensitivity analysis showed the results were quite robust. These results indicated PTAS plus medical therapy did not own greater benefit

erosclerotic stenosis [37]. Angioplasty and stenting was also an effective method to treat intracranial atherosclerotic stenosis [38]. PTAS (percutaneous transluminal angioplasty and stenting) was revealed to play an important role in treating intracranial atherosclerotic stenosis [39, 40]. Patients underlying intracranial atherosclerotic stenosis have less severe infarctions at presentation and higher successful revascularization after multimodal endovascular therapy in the setting of hyperacute stroke than those with other stroke subtypes, indicating that combined therapy might be a potential treatment for intracranial atherosclerotic stenosis [41]. Hence, these unclear conclusions lead us to conduct this meta-analysis to compare the efficacy and safety of PTAS plus medical treatment versus medical treatment only on intracranial atherosclerotic stenosis, which to our knowledge, has not been investigated before.

In this meta-analysis, 10 articles published between 2010 and 2015 were included, consisting of 1501 patients with intracranial atherosclerotic stenosis, of whom 690 cases were in the PTAS plus medical therapy group and 811 cases were in the medical therapy group. We found that the rate of stroke or death within 30 days in PTAS plus medical therapy was significantly higher than that in medical therapy (RR=1.451, 95% CI: 1.011-2.084, P=0.044). However, although the rate of stroke or death within one year and one year survival rate in PTAS plus medical therapy group was slightly

for patients underlying intracranial atherosclerotic stenosis than medical therapy. Nevertheless, as some studies suggested angioplasty and stenting might be a last resort for patients with high grade of intracranial atherosclerotic stenosis who were not responsible to medical therapy, it may explain the poorer outcomes of PTAS plus medical therapy group [40, 42]. What's more, the symptomatic intracranial atherosclerotic disease evolves with current medical therapy [43]. The slight difference of medical therapy in the included studies may have impacts on the results as well. For example, in Derdeyn (2014) study, aspirin was used for the duration of follow-up in a dose of 325 mg per day, while 100 mg aspirin per day was adopted in Yin (2015) study [16, 18].

If the I^2 from forest plot and the chi-square test for heterogeneity was over 50%, meaning the heterogeneity exited. The I^2=73.50% in 1 year primary outcome, which suggested the heterogeneity exited in the studies on 1 year stroke or death rate. Subgroup analysis was performed to find the source of heterogeneity, revealing the heterogeneity occurred from the design of study. It showed no heterogeneity among prospective studies (I^2 < 0.01%), while among retrospective studies (I^2=71.4%). These may be influenced by the characteristics of study design, for retrospective study has specific difficulty to ensure the data included criteria. There are still some limitations in our analysis. The Egger method showed the risk of publication bias for restenosis rate (Egger method:

P=0.006, Begg method: P=0.707). It may be resulted from the limited number of included studies, and we speculated the good efficacy of medical therapy was more easily to be published. Besides, although relevant studies were searched under our best attempt, the articles not published online would be neglected. Finally, the effects of study design needed to be considered in future investigation.

In conclusion, our study showed that PTAS plus medical therapy did not demonstrate obvious advantages compared to medical therapy on patients with intracranial atherosclerotic stenosis. More studies were expected to evaluate the efficacy of PTAS on intracranial atherosclerotic stenosis in the future.

Disclosure of conflict of interest

None.

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