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Review

Risk of Intracranial Hemorrhage after Endovascular Treatment for Acute Ischemic Stroke: Systematic Review and Meta-Analysis

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Keywords
Endovascular treatment · Intracranial hemorrhage · Recanalization · Stroke

Abstract
Background: Intracranial hemorrhage is a major complication of endovascular treatment in patients with acute ischemic stroke. Controlled clinical trials reported varied incidences of intracranial hemorrhage after endovascular treatment. This meta-analysis aimed to estimate whether endovascular treatment, compared with medical treatment, increases the risk of intracranial hemorrhage in patients with acute ischemic stroke. ***Methods:*** The current publications on endovascular treatment for acute ischemic stroke were systematically reviewed. Rates of intracranial hemorrhage after endovascular treatment for acute ischemic stroke reported in controlled clinical trials were pooled and analyzed. Random and fixed-effect models were used to pool the outcomes. For analyzing their individual risks, intracranial hemorrhages after endovascular treatment were classified as symptomatic and asymptomatic. ***Results:*** Eleven studies involving 1,499 patients with endovascular treatment and 1,320 patients with medical treatment were included. After pooling the data, the risk of any intracranial hemorrhage was significantly higher in patients with endovascular treatment than in patients with medical treatment (35.0 vs. 19.0%, OR = 2.55, 95% CI: 1.64–3.97, $p < 0.00001$). The risk of asymptomatic intracranial hemorrhage was also significantly higher in patients with endovascular treatment than in those with medical treatment (28 vs. 12%, OR = 3.16, 95% CI: 1.62–6.16, $p < 0.001$). However, the risks of symptomatic intracranial hemorrhage were similar in patients

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with endovascular treatment and in those with medical treatment (5.6 vs. 5.2%, OR = 1.09, 95% CI: 0.79–1.50, p = 0.61). ***Conclusion:*** Although the risk of any intracranial hemorrhage may increase after endovascular treatment, the risk of symptomatic intracranial hemorrhage may remain similar as compared with medical treatment.

Introduction

As a major complication of endovascular treatment in patients with acute ischemic stroke, intracranial hemorrhage may neutralize or even invert the benefit-risk ratio of the treatments [1]. Several carefully designed clinical trials have validated the efficacy of endovascular treatment over medical treatment in patients with acute ischemic stroke, but these trials reported varied rates of intracranial hemorrhage [2–7]. The higher incidences of intracranial hemorrhage have been attributed to cases with asymptomatic intracranial hemorrhage after endovascular treatment. Given the limited cases with intracranial hemorrhage in individual studies, this interpretation may be less convincing. Although the efficacy of endovascular treatment over medical treatment has been reviewed in recent meta-analyses [8–10], the risk of intracranial hemorrhage after these 2 treatment strategies has not been systematically evaluated.

After the endovascular treatment recommended by the AHA/ASA guidelines for acute ischemic stroke [11], the number of patients treated with this new strategy is expected to increase considerably. Therefore, evaluating the risk of intracranial hemorrhage becomes an important issue for continuously improving the efficacy of this new treatment strategy. Based on the current evidence, this meta-analysis assessed whether endovascular treatment, compared with medical treatment, increases the risk of intracranial hemorrhage in patients with acute ischemic stroke.

Methods

Search Strategy and Selection Criteria

This meta-analysis follows the guidelines introduced by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched PubMed, Web of Science, and Cochrane Library for publications in English from 1995 to 2015. The following search formula was used: (ischemic stroke OR cerebral infarct OR brain infarct) AND (intra-arterial thrombolysis OR intra-arterial therapy OR endovascular therapy OR endovascular treatment OR interventional therapy OR thrombectomy OR embolectomy).

All returned publications were evaluated by 2 authors (Z.Y. and H.Z.) independently. Studies meeting all following criteria were included: controlled clinical trials comparing endovascular treatment with medical treatment in patients with acute ischemic stroke; at least 20 patients enrolled for endovascular approach; involved functional follow-up of 3 months or longer, and reported incidences of symptomatic intracranial hemorrhage. Animal and experimental studies were not included. Data of multiple publications from 1 study were combined. Considering the less application in current clinical practice, trials with urokinase as the main thrombolytic agent were excluded.

Data Extraction and Quality Assessment

Two authors (Y.H. and H.Z.) extracted data from the included studies independently. Any disagreements were resolved by discussion. The primary outcome was the rates of symptomatic intracranial hemorrhage. The secondary outcomes included any intracranial hemorrhage, asymptomatic intracranial hemorrhage, parenchymal hemorrhage, and subarachnoid hemorrhage (SAH). The methodological quality of randomized controlled trials (RCTs) was assessed with the Cochrane risk of bias tool [12]. Retrospective studies were assessed with the modified Newcastle-Ottawa scale (≥6 indicates high quality) [13].

Table 1. Baseline characteristics of the clinical trials included

Trials (year of publication)	Design	Treatment in intervention	Treatment in controls	Intervention/ controls, *n*	Time window of ET/IVT, h	Time of follow-up, days	Quality score
IMS [18], 2004	RP	IAT	IVT	80/182	5/3	90	7
IMS II [19], 2007	RP	IAT	IVT	81/182	5/3	90	7
Synthesis [17], 2010	PROBE	IAT/ME	IVT	25/29	6/3	90	RCT
Synthesis Exp [16], 2013	PROBE	IAT/ME	IVT	181/181	6/4.5	90	RCT
IMS III [15], 2013	PROBE	IAT/ME/IVT	IVT	434/222	5/3	90	RCT
MR-RESCUE [14], 2013	PROBE	IAT/ME/IVT	IVT/BM	64/54	8/4.5	90	RCT
MR CLEAN [2], 2015	PROBE	IAT/ME/IVT	IVT/BM	233/267	6/4.5	90	RCT
Escape [4], 2015	PROBE	ME/IVT	IVT/BM	120/118	12/4.5	90	RCT
EXTEND-IA [5], 2015	PROBE	ME/IVT	IVT	35/35	6/4.5	90	RCT
SWIFT PRIME [6], 2015	PROBE	ME/IVT	IVT	98/98	6/4.5	90	RCT
Revascat [3], 2015	PROBE	ME/IVT	IVT/BM	103/103	8/4.5	90	RCT

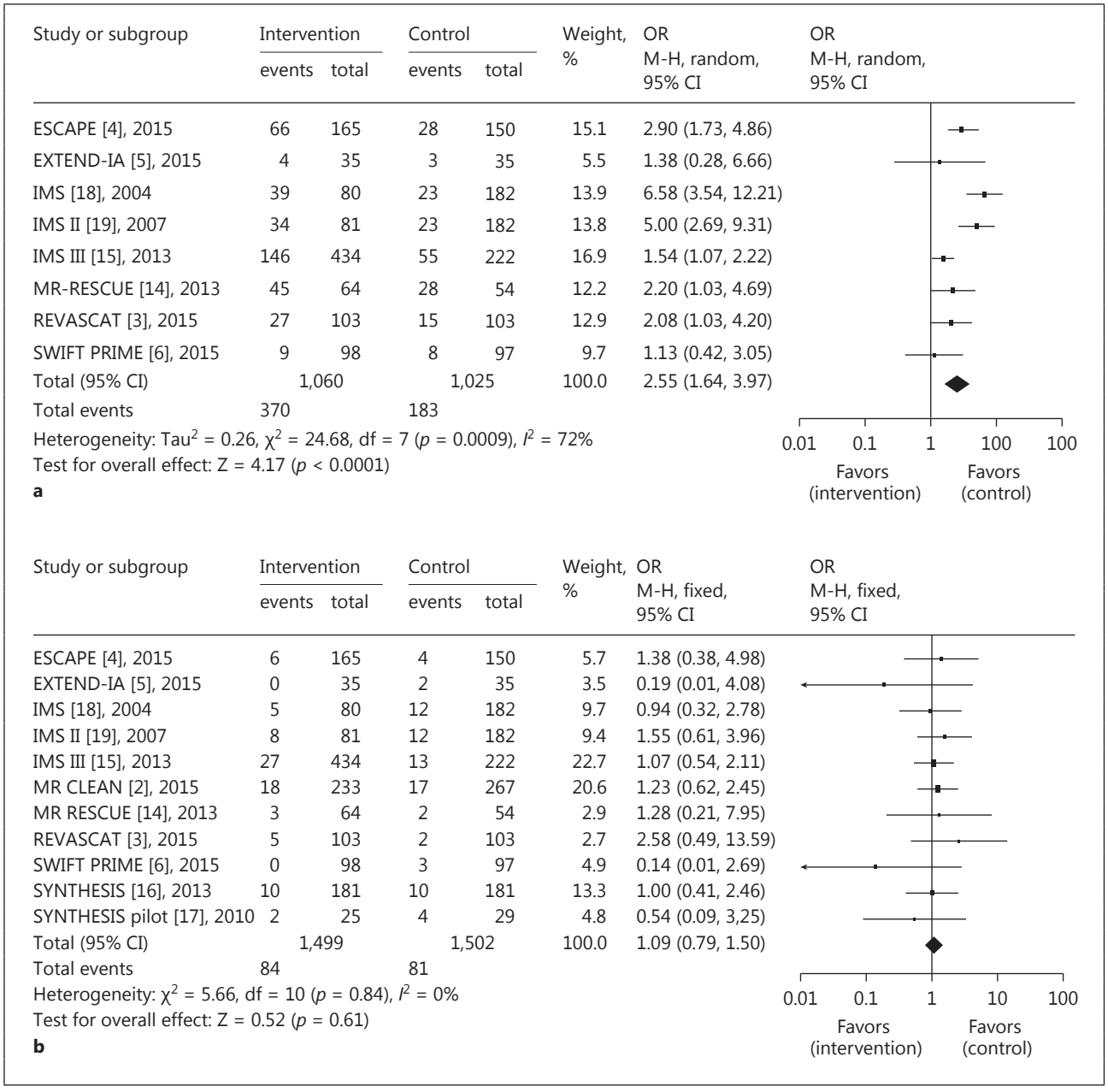
RP, retrospective design, prospective data collection; PROBE, prospective randomized open-label blinded-endpoint design; ET, endovascular treatments; IAT, intra-arterial thrombolysis; ME, mechanical embolectomy; IVT, intravenous t-PA only; BM, best medical management; RCT, randomized controlled trail.

Statistical Analysis and Evidence Synthesis

Statistical analyses were performed using the Review Manager 5.3 (Cochrane Collaborane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corp LP, College Station, TX, USA) software. The odds ratio (OR) and associated 95% confidence interval (CI) were used to compare dichotomous variables. Heterogeneity among studies was assessed with the Cochran Q test and the Higgins I^2 test. A Cochran's Q of $p < 0.10$ and $I^2 > 50\%$ were considered as significant heterogeneity. The fixed-effect model was used if there was no significant heterogeneity among studies. Otherwise, the random-effect model was used. Sensitivity analyses were implemented for high-quality studies. The funnel plots, Egger test, and Begg test were used to evaluate publication bias. Meta-regression analysis was conducted to explore the potential for sources of heterogeneity.

Results

Eleven studies meeting the inclusion criteria were identified (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000454721), which involved 1,499 patients with endovascular treatment and 1,320 patients with medical treatment. The characteristics of the included studies are shown in Table 1. There were 9 RCTs [2–6, 14–17] and 2 single-arm studies [18, 19] which used historical series as controls. The reported endovascular procedures included intra-arterial thrombolysis, balloon angioplasty, stent implantation, and mechanical embolectomy with different devices. Some endovascular treatments were bridged with intravenous thrombolysis, others were not. The 2 arms, with and without ischemic penumbra, stratified in the endovascular treatment group in the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) trial were combined for data analysis [14]. Since the same patient series with intravenous thrombolysis was used as historical control in the Interventional Management of Stroke (IMS) I and II studies [18, 19], these patients were counted only once when pooling the sample size. These studies were estimated for risks of bias. All enrolled RCTs were identified to have a high risk for performance bias as the patients and stroke teams could not be blinded to treatment allocations, which may generate biases during outcome reporting.



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Eight of the 11 enrolled studies reported rates of any intracranial hemorrhage. After pooling these data, the risk of any intracranial hemorrhage was significantly higher in patients with endovascular treatment than in patients with medical treatment (35.0 vs. 19.0%, OR = 2.55, 95% CI: 1.64–3.97, $p < 0.00001$), with a high heterogeneity among studies ($I^2 = 72\%$, $p < 0.001$; Fig. 1a). After excluding 2 nonrandomized control trials (IMS I and IMS II), the risk of any intracranial hemorrhage was still significantly higher in the endovascular arm (OR = 1.88, 95% CI: 1.47–2.40, $p < 0.00001$), with a relatively low heterogeneity among studies ($I^2 = 6\%$, $p = 0.38$).

All 11 enrolled studies reported rates of symptomatic intracranial hemorrhage. The risk of symptomatic intracranial hemorrhage was much similar in patients treated with endovas-

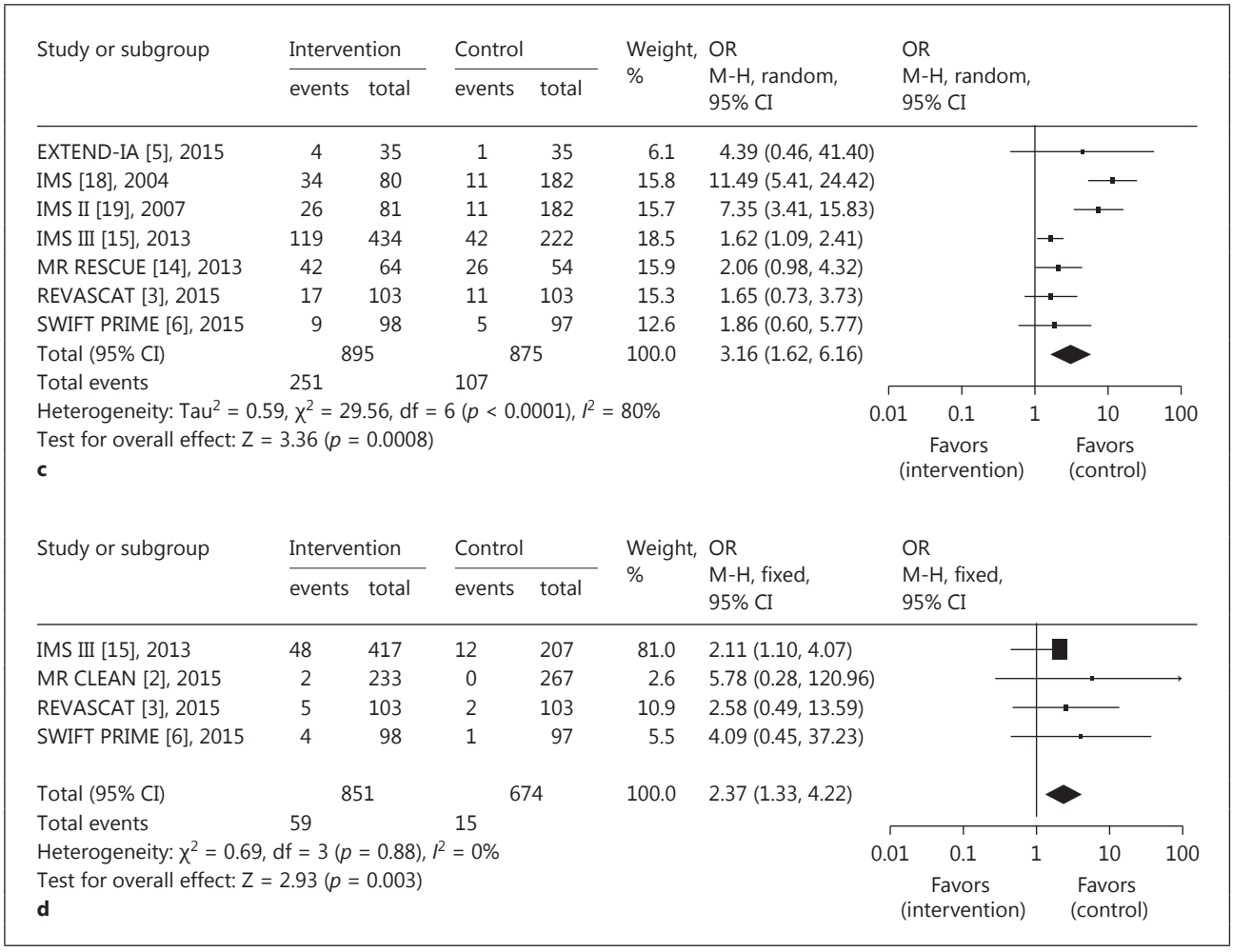

Fig. 1. Forest plot of hazard ratio by patient subgroups.

cular procedures and with medicines (5.6 vs. 5.2%, OR = 1.09, 95% CI: 0.79–1.50, $p = 0.61$; Fig. 1b), with a very low heterogeneity among studies ($I^2 = 0\%$, $p = 0.89$). Seven of the 11 enrolled studies provided valid data of asymptomatic intracranial hemorrhage. The risk of asymptomatic intracranial hemorrhage was significantly higher in patients with endovascular treatment than in patients with medical treatment (28.0 vs. 13.9%, OR = 3.16, 95% CI: 1.62–6.16, $p < 0.001$; Fig. 1c), with a relatively high heterogeneity among studies ($I^2 = 80\%$, $p < 0.0001$). After excluding 2 nonrandomized control trials (IMS I and IMS II), the risk of asymptomatic intracranial hemorrhage was still significantly higher in the endovascular arm (OR = 1.74, 95% CI: 1.28–2.37, $p < 0.001$), but the heterogeneity among studies decreased considerably ($I^2 = 0$, $p = 0.91$).

Seven of the 11 enrolled studies reported rates of parenchymal hemorrhage. When the data were pooled, no significant differences concerning the risk of parenchymal hemorrhage were detected between patients with endovascular treatment and those with medical treatment (7.7 vs. 5.7%, OR = 1.23, 95% CI: 0.86–1.75, $p = 0.25$; online suppl. Fig. 2). Four studies provided valid data on SAH. The reported SAH incidence was higher in patients with endovascular treatment than in patients with medical treatment (6.9 vs. 2.2%, OR = 2.37, 95% CI: 1.33–4.22, $p < 0.01$; Fig. 1d).

When data from randomized control trails were pooled for sensitivity analysis, there was no change concerning the difference level of the outcomes (online suppl. Table 1). Fixed-effect and random-effect models induced consistent results in sensitivity analyses. Univariate meta-regression analyses showed that nonrandomized control trials were more heterogeneous when evaluating the risk of asymptomatic intracranial hemorrhage ($p = 0.003$). No significant publication biases were detected by the funnel plots, the Egger test, and the Begg test when evaluating the risk of symptomatic intracranial hemorrhage (online suppl. Table 2, Fig. 3).

Discussion

This meta-analysis showed that endovascular treatments increased the risk of any intracranial hemorrhage compared with medical treatment. This increased risk was mainly due to extra cases with asymptomatic intracranial hemorrhage after endovascular treatment. Although the risk of SAH increased in patients with endovascular treatment, the risk of symptomatic hemorrhage remained much similar as compared with that in patients with medical treatment.

During or after endovascular treatment for acute ischemic stroke, intracranial hemorrhage may result from mechanical lesion of the vessel wall, reperfusion lesion, increased blood-brain barrier permeability [20], hemorrhagic tendency related to thrombolysis agents or heparinization [21, 22], and hemodynamic lesion due to fluctuation of blood pressure [23]. Intracranial hemorrhage resulting from mechanical lesions of vessels is limited to patients with endovascular treatment, which is not possible in patients with medical treatment. Mechanical penetration of the vessel wall usually occurs during or shortly after the guidewire crosses the target occlusion, a circumstance that arises when the artery is not visualized under X-ray fluoroscopy. Retrieving the stent-like devices may displace the target artery and break small perforate arteries. Most of these occasions may result in SAH or intracerebral hemorrhage. These complications related to endovascular procedures are largely responsible for the increased risk of endovascular treatment [24]. This meta-analysis confirmed that the risk of SAH was increased in patients with endovascular treatment. Since complications related to endovascular procedures are highly skill dependent, the risk of SAH was lower in centers with a large patient volume, in the hands of experienced operators, and in recent studies with more advanced devices [2, 4, 5].

A reperfusion lesion may occur after the recanalization of the target occluded the artery [25]. Hemorrhage may result from rapture of the necrotic vessel wall and increased blood-brain barrier permeability due to prolonged ischemia [20]. Therefore, hemorrhage due to a reperfusion lesion is relevant to the degree and tempo of the reperfusion flow, the pretreatment infarct volume, and the time of recanalization. More recent studies reported higher rates of recanalization (58.7–88.0%), but also higher rates of intracranial hemorrhage (9.2–40.0%) after endovascular treatment [3–6]. Minor or asymptomatic intracranial hemorrhage in CT has been suggested as an indicator of successful reperfusion.

Imaging examinations may influence the rates of symptomatic intracranial hemorrhage. The incidences of symptomatic intracranial hemorrhage in MR CLEAN [2] and THERAPY [26] were higher than those reported in SWIFT PRIME [6] and EXTEND-IA [5] which excluded patients with large ischemic core. Infarct volume was negatively related to baseline collateral status [27] and time delay from symptoms onset to recanalization [28]. As in the EXTEND-IA trial, CTA and CTP were used to exclude patients with large infarct cores for endovascular treatment. Favorable outcomes were observed in patients with moderate-to-good collateral circulation and in those with small infarct core. The incidence of symptomatic intracranial hemorrhage did not increase despite the time window for endovascular treatment was ex-

tended to 12 h after stroke onset [4, 5]. These results suggested that recanalization treatment initiated even 12 h after stroke onset may result in favorable outcomes in selected patients.

Several limitations should be emphasized when interpreting the results of this meta-analysis. Some potential confounders which may influence the risk of intracranial hemorrhage were not analyzed in this study. Different thrombectomy devices were used in these trials. The types of endovascular device may influence the risk of intracranial hemorrhage. One study showed that stent-like thrombus retrievers may decrease intracranial hemorrhage compared with previously developed devices [29]. The time window for endovascular treatment varied considerably in the 11 included studies. The incidence of intracranial hemorrhage may increase with the delay of recanalization treatment. Another potential confounder is the varied definitions of symptomatic intracranial hemorrhage [30]. At least 4 different definitions were used in these 11 studies [31–34]. One major concern for these definitions lies in that different time intervals between treatment and CT scan were proposed (online suppl. Table 3). Since small intracranial hemorrhage may be absorbed in time, the longer interval between symptom onset and CT scan may indicate a decreased detection rate. The criteria for symptomatic intracranial hemorrhage were also discrepant, which may lead to different reported incidences of the symptomatic intracranial hemorrhage. The recently published Heidelberg Bleeding Classification may provide a reasonable solution for this issue [35]. Furthermore, some trials were terminated prematurely due to a significantly futile or beneficial effect in interim analysis [3–6, 15], which may have attenuated the power when evaluating the risk of hemorrhage.

Summary

Compared with medical treatment, endovascular treatment may increase the risk of asymptomatic intracranial hemorrhage, but not the risk of symptomatic intracranial hemorrhage in patients with ischemic stroke due to large vessel occlusion. Imaging-based patient selection for endovascular treatment may reduce the risk of symptomatic intracranial hemorrhage after recanalization. Future studies should consider using uniformed definitions and standardized procedures in diagnosing intracranial hemorrhage.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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