Risk of Adverse Vascular Events in Patients with Malignant Glioma Treated with Bevacizumab Plus Irinotecan: A Systematic Review and Meta-Analysis

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■ BACKGROUND: **Bevacizumab plus irinotecan is a new beneficial chemotherapy strategy for patients with malignant glioma. The purpose of this systematic review and meta-analysis was to comprehensively assess the risk of adverse vascular events in adults with malignant glioma treated with bevacizumab plus irinotecan.**

■ METHODS: **The Cochrane Library, Embase and PubMed were searched, and relevant trials were identified up to June 2018. Two investigators screened all titles and abstracts for possible inclusion and extracted data independently. Six studies were included, and 5 of them in the control group using bevacizumab alone or bevacizumab with temozolomide. Three systems were used to assess the quality of evidence and the level of recommendation. The Oxford Centre for Evidence-Based Medicine Levels of Evidence (2009) system was used to classify the evidence into 5 levels (classes I–V). The star system from the Newcastle–Ottawa Scale was used to assess methodological quality. The GRADE profiler was used to evaluate the overall body of evidence.**

■ RESULTS: **Our data show that bevacizumab plus irinotecan therapy does not significantly affect the risk of systemic adverse events (odds ratio [OR], 1.17; 95% confidence interval [CI], 0.43–3.18). Patients treated with bevacizumab plus irinotecan had a similar risk of hematotoxicity (OR, 1.06; 95% CI, 0.26–4.38), thrombocytopenia (OR, 1.07; 95% CI, 0.25–4.63), and hypertension (OR, 1.34; 95% CI, 0.28–6.36) compared with the control group (those treated without irinotecan). Thrombosis occurred more frequently in patients treated with bevacizumab plus irinotecan compared with the control group (OR, 3.23; 95% CI, 1.47–7.12).**

■ CONCLUSIONS: **The risk of systemic adverse events was not significantly different between patients with malignant glioma treated with bevacizumab plus irinotecan and the control group. The risks of hematotoxicity, thrombocytopenia, and hypertension were similar in the 2 groups. The risk of thrombosis was higher in patients treated with bevacizumab plus irinotecan. Monitoring for thrombosis and administering anticoagulant therapy as necessary merit promotion for patients with malignant glioma receiving treatment with bevacizumab plus irinotecan.**

INTRODUCTION

Gliomas are the most common malignant tumor in central nervous system, accounting for approximately 50% of brain tumors.[1,2] Although the median life expectancy and 2-year survival rate of patients with glioblastoma or malignant glioma have been improving,[3,4] 5-year follow-up has shown an overall survival rate of only 9.8%, even under combined treatments of extent resection, adjuvant temozolomide, and radiotherapy.[5-8] Malignant glioma is a highly invasive and angiogenic tumor with prominent vascularization,[9] and vascular endothelial growth factor (VEGF) is an important factor in vascularization and

Key words
- Adverse vascular events
- Bevacizumab
- Irinotecan
- Malignant glioma

Abbreviations and Acronyms
CI: Confidence interval
GRADE: Grades of Recommendations, Assessment, Development and Evaluation
NOS: Newcastle–Ottawa Scale
OR: Odds ratio
PFS: Progression-free survival
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
VEGF: Vascular endothelial growth factor

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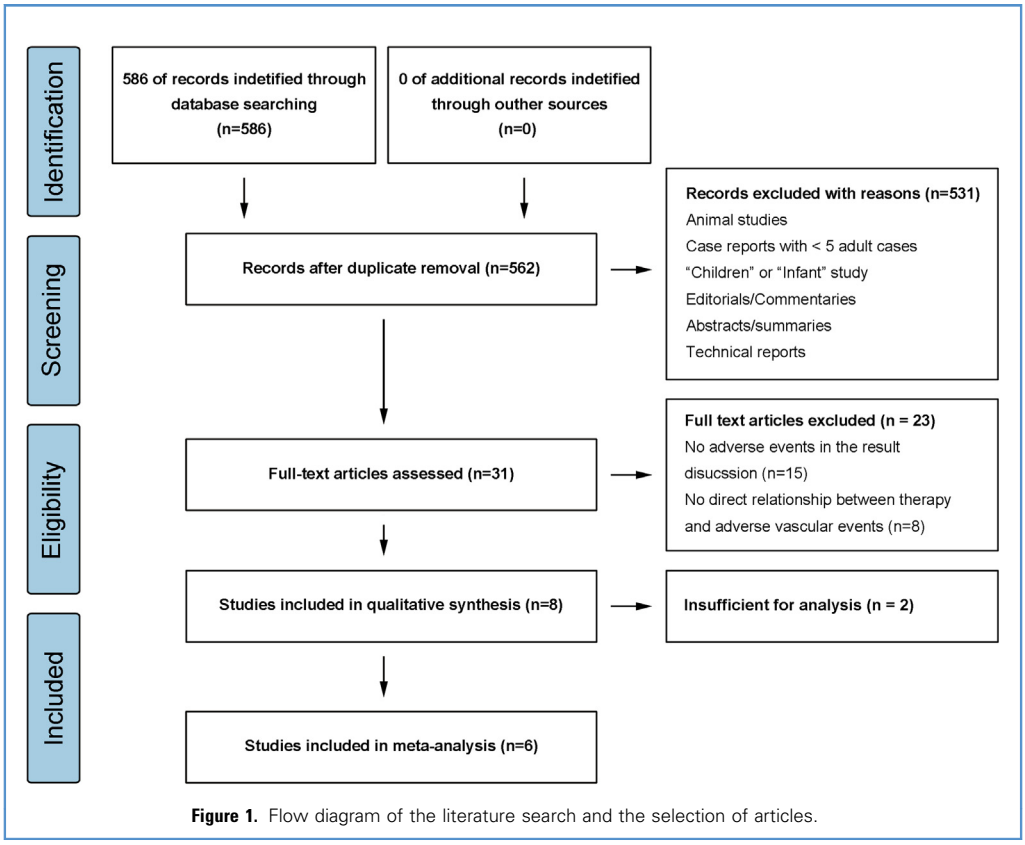

Figure 1. Flow diagram of the literature search and the selection of articles.

promotes the proliferation and migration of malignant glioma.[10] VEGF has served as a target for antiangiogenic therapy in malignant glioma, and clinical trials have shown encouraging results after antiangiogenic therapy.[11]

Bevacizumab is a recombinant, humanized monoclonal antibody against VEGF-A that inhibits the activity of VEGF through its interaction with the VEGF receptor and neuropilins.[12] It has been used as a salvage therapy in patients with malignant glioma since its approval in the United States in 2009.[13] In recent clinical trials, bevacizumab was added to the standard of care in patients with malignant glioma.[14,15] Owing to a combination of factors, patients with malignant glioma treated with bevacizumab are at increased risk for adverse vascular events, especially venous thromboembolism.[16] The addition of bevacizumab to the standard of care was found to prolong progression-free survival (PFS) but without improving overall survival.[17] Irinotecan, a topoisomerase inhibitor with a different mechanism than other alkylating agents such as temozolomide, has been used as a treatment for glioma and has demonstrated an improved response rate.[18-20] However, the individual differences in patient characteristics and the low number of cases included in the individual studies have made it difficult to assess any adverse vascular events in patients with malignant glioma treated with bevacizumab plus irinotecan. We performed a systematic review and meta-analysis of the available evidence to comprehensively determine the influence of bevacizumab plus irinotecan on adverse vascular events in adults with malignant glioma.

MATERIALS AND METHODS

Search Strategy

This systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines[21] and the Cochrane Handbook.[22] Relevant trials were identified from systematic searches of 3 major electronic databases—PubMed, Embase, and the Cochrane Library—from 2000 to June 2018 with different combinations of the following key words:)"glioma", "astrocytoma", "glioblastoma", "oligodendroglioma", "oligoastrocytoma" or "GBM") and ("bevacizumab" or "Avastin") and ("vascular", "hemorrhagic", "thromboembolic", "proteinuria", "stroke", "hypertension" or "gastrostomy") and ("irinotecan" or "CPT-11"). The reference lists of articles identified in the initial searches were scanned to obtain additional relevant articles. A literature search was performed by a group of investigators, and 2 other investigators independently reviewed and selected articles for further analysis. A group discussion with a third investigator was performed to resolve any disagreement between the 2 investigators.

Study Selection and Extraction

Exclusion criteria included animal studies, case reports with <5 adult cases of glioma, such words as "children" or "infant" in the title, editorials/commentaries, conference abstracts/summaries, and technical reports. For each study, we extracted the following information: first author's name, year of publication, country of

Table 1. Summary of Selected Studies

Study	Country	Number		Mean Age (years)		Sex (number)		Bevacizumab Dose, mg/kg* (+ Other Chemotherapy)		PFS	
		B	C	B	C	B (M/F)	C (M/F)	B	C	B	C
Jeck et al., 2018[31]	Germany	10	29	-	-	—	—	Bev 10 mg/kg q 2 wk + irinotecan (125/340) mg/m^2 2 wk	Bev 10 mg/kg q 2 wk	4.6	4.8
Gilbert et al., 2016[29]	USA	57	60	55	58	34/23	34/26	Bev 10 mg/kg q 2 wk + irinotecan 125 mg/m^2 2 wk	Bev 10 mg/kg q 2 wk + TMZ 75–100 mg/m^2	4.1	4.7
Herrlinger et al., 2016[30]	Germany	116	54	56	56	80/36	34/20	Bev 10 mg/kg q 2 wk + irinotecan (125/340) mg/m^2 2 wk	TMZ 75 mg/m^2/day →150–200 mg/m^2	—	—
Hofland et al., 2014[34]	Denmark	31	32	59	62	18/13	21/11	Bev 10 mg/kg q 2 wk + irinotecan (125/340) mg/m^2 2 wk	Bev 10 mg/kg q 2 wk + TMZ 75–100 mg/m^2	7.3	7.7
Seystahl et al., 2013[32]	Switzerland	12	27	29	38	8/4	16/11	Bev 10 mg/kg q 2 wk + irinotecan (125/340) mg/m^2 2 wk	Bev 10 mg/kg q 2 wk	4.7	4.2
Friedman et al., 2009[33]	USA	82	85	57	54	57/25	58/24	Bev 10 mg/kg q 2 wk + irinotecan (125/340) mg/m^2 2 wk	Bev 10 mg/kg q 2 wk	5.6	4.2

B, bevacizumab plus irinotecan therapy group; C, control group; Bev, bevacizumab; CPT, q 2 wk, twice weekly; 2 wk, every 2 weeks; TMZ, temozolomide.

publication, number of included patients, study arms, doses of bevacizumab and irinotecan, additional therapies and doses (if any), median duration of follow-up, proportion of protocol violations (%), and rates of adverse vascular events (%) including vascular, hemorrhagic, and thromboembolic events; proteinuria; stroke; hypertension; gastrostomy; and other adverse events.

Quality Assessment

According to the Oxford Centre for Evidence-Based Medicine—Level of Evidence (2009) (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/), evidence is classified into 5 levels (classes I–V). Class I represents the highest evidence level from homogenous randomized controlled trials, and class V represents the lowest level of evidence based on expert opinion. The methodological quality of all included studies was assessed using the star system of the Newcastle–Ottawa Scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).[23] The number of stars reflects the quality of an article; the maximum rating is 9 stars. Two investigators performed the evidence grading and quality assessment. Disagreements were resolved by consensus within the group. GRADE profiler (version 3.6) was used to evaluate the overall body of evidence after assessment of individual articles.[24] We divided the studies into different levels, assigning high, moderate, low, or very low overall quality of evidence based on 5 parameters: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Data Synthesis

The primary outcome measure was the risk of adverse vascular events between patients treated with bevacizumab plus irinotecan and the control group. Odds ratio (OR) and corresponding 95% CI

Table 2. Levels of Evidence and Quality Evaluation of Included Studies

Study	Adult Patients with Glioma (number)	Level of Evidence (Oxford Centre)	Quality Evaluation (Newcastle–Ottawa Scale)			
			Selection	Comparability	Outcome or Exposure	Score
Gilbert et al., 2017[29]	117	II	* *	*	* *	5
Herrlinger et al., 2016[30]	170	II	* * *	*	* *	6
Hofland et al., 2014[34]	63	II	* * * *	*	* * *	8
Seystahl et al, 2013[32]	39	IV	* *	*	* * *	6
Friedman et al., 2009[33]	167	II	* * *	*	* * *	7
Jeck et al., 2018[31]	39	IV	* *	*	* * *	6

Table 3. Evaluation of the Overall Body of Evidence for 4 Factors by the GRADE System

Outcome	Quality of Evidence*
Hematotoxicity	⊕⊕⊖⊖ low
Thrombosis	⊕⊕⊖⊖ low
Hypertension	⊕⊕⊖⊖ low
Thrombocytopenia	⊕⊕⊕⊖ moderate

*The quality of evidence is divided into 4 levels using the GRADEpro system. The symbols ⊕ and ⊖ represent different evidence levels; for example, ⊕⊕⊕⊕ means high quality, and ⊕⊖⊖⊖ means very low quality. Details of the assessment are provided in the GRADE profiler.

were used to assess the primary outcome measure.[25] The I^2 statistic, which estimates the percentage of total variation across studies attributable to heterogeneity over chance, was used to assess the heterogeneity of the included studies.[23] In the presence of significant heterogeneity ($I^2 > 50\%$; $P < 0.05$ for Cochran's Q test), a random-effects model was used to calculate data; otherwise, a fixed-effects model was used.[26] Meta-analysis was done using RevMan version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).[26,27] A P value < 0.05 was considered to indicate significant statistical publication bias.[28]

RESULTS

Search Hits

A total of 586 studies were identified from systematic searches of PubMed, Embase, and the Cochrane Library. No additional studies were identified from other sources. After eliminating duplicates, 562 articles remained. According to the exclusion criteria, the case reports and the articles with data that could not be extracted were removed. Five hundred and thirty-one studies were excluded, leaving 31 potentially eligible studies for further full-text assessment. After title and abstract screening, 15 studies with insufficient data for analysis and 8 studies without a control group were excluded. Finally, 2 of the 8 remaining studies were excluded owing to a lack of adverse vascular events data. Six studies met the inclusion criteria and were included in the full analysis (Figure 1). These 6 studies were published between 2009–2018 and included 2 from Germany, 2 from the United States, and 1 each from Denmark and Switzerland. Four were randomized phase II studies, and the other 2 were retrospective studies. The combined therapy was bevacizumab 10 mg/kg plus irinotecan 340 mg/m² or 125 mg/m² (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) once every 2 weeks, while the control group was treated without irinotecan (in 5 studies using bevacizumab alone or in combination with temozolomide). Among these studies, 4 were included in a meta-analysis of hematotoxicity,[29-32] 2 were included in a meta-analysis of thrombocytopenia,[31,32] 4 were included in a meta-analysis of hypertension,[30-33] and 5 were included in a meta-analysis of thrombosis.[29-31,33,34] These studies are described in Table 1.

Evidence Quality

The evidence quality was rated as class II for 4 of the studies and as class IV for the other 2 studies. None of the included studies was rated as class I. Based on the NOS evaluation,[35] 1 article was rated as 8 stars, 1 article as 7 stars, 3 articles as 6 stars, and 1 article as 5 stars (Table 2). According to the GRADE evaluation of the overall body of evidence pertaining to 4 variables,[24] the quality of evidence for thrombocytopenia was rated as moderate, and that for the other factors was rated as low (Table 3).

Meta-Analysis of Individual Factors

The studies included in the quantitative meta-analysis provided sufficient data for statistical control-based comparisons. These data were available for 4 meta-analytical comparisons of adverse vascular events between the patients treated with bevacizumab plus irinotecan and the control group. The risk of systemic adverse events was similar in the bevacizumab plus irinotecan group and the control group (OR, 1.17; 95% CI, 0.43–3.18; $P = 0.76$) (Figure 2). The risk of hematotoxicity, the main obstacle in high-dose chemotherapy,[36] was similar in the bevacizumab plus irinotecan group and the control group (OR, 1.06; 95% CI, 0.26–4.38; $P = 0.94$) (Figure 3A). The risk of thrombocytopenia was not significant different between the bevacizumab plus irinotecan group and the control group (OR, 1.07; 95% CI,

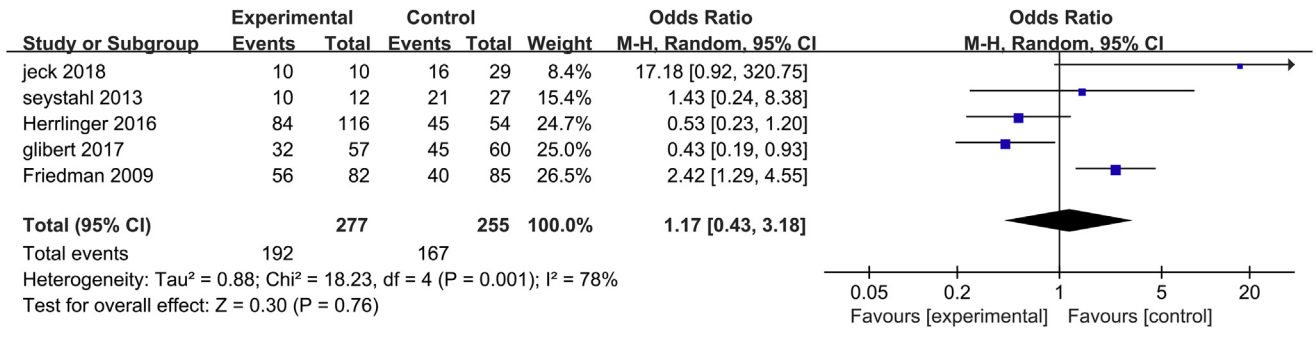

Figure 2. Forest plots of odds ratios for the risk of systemic adverse events in patients treated with bevacizumab plus irinotecan and in the control group.

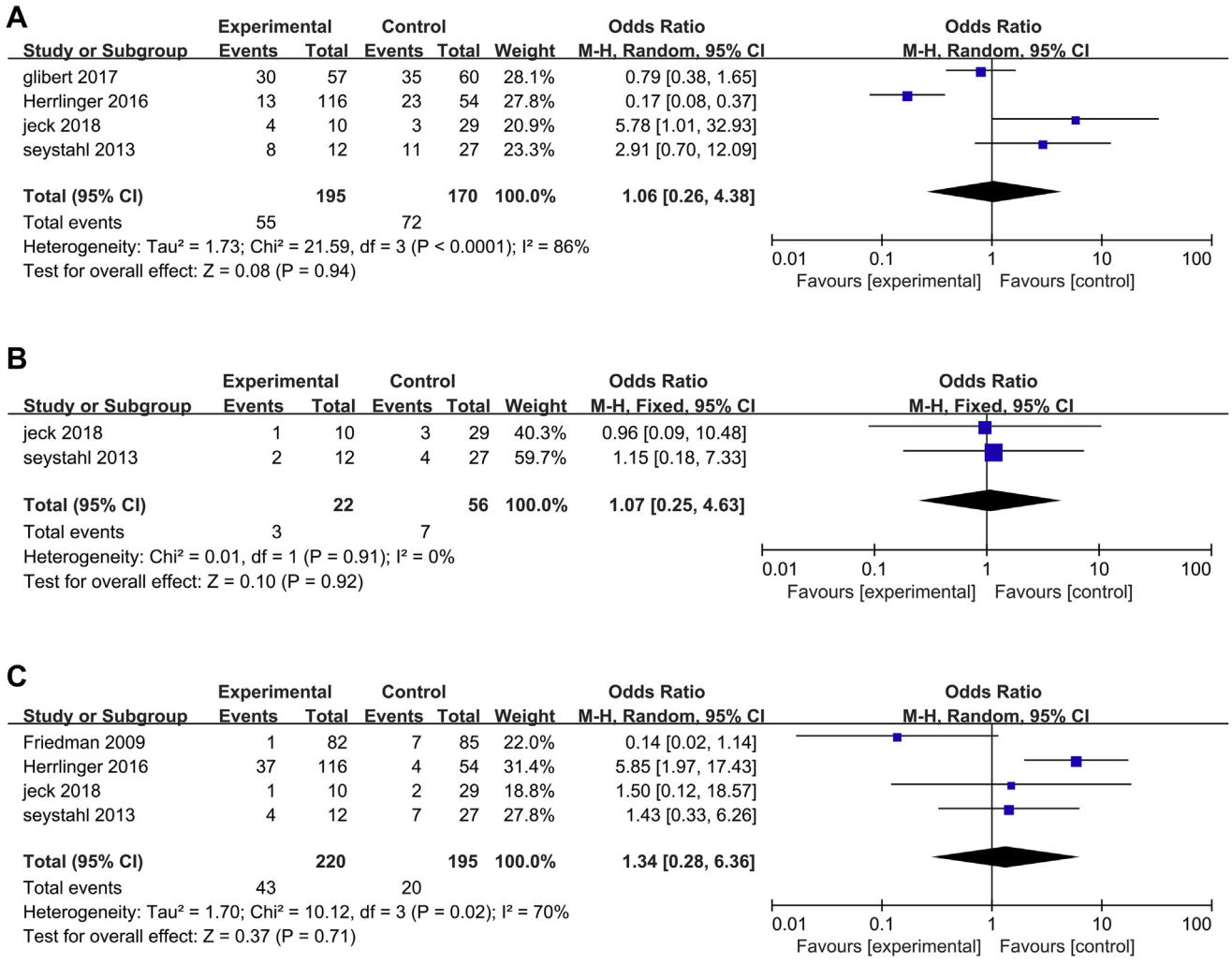

Figure 3. Forest plots of odds ratios for hematotoxicity, hypertension, and thrombocytopenia. (**A**) The risk of hematotoxicity in patients treated with bevacizumab plus irinotecan and the control group. (**B**) The risk of hypertension in patients treated with bevacizumab plus irinotecan and the control group. (**C**) The risk of thrombocytopenia in patients treated with bevacizumab plus irinotecan and the control group.

0.25–4.63; P = 0.92) (Figure 3B). In patients treated with bevacizumab alone, hypertension is one of the most frequent grade 3/4 toxicities.[37] However, there was no significant difference in the risk of hypertension between the patients treated with bevacizumab plus irinotecan and the control group (OR, 1.34; 95% CI, 0.28–6.36; P = 0.71) (Figure 3C). The risk of thrombosis, which is high throughout the course of disease in malignant glioma,[38] was greater in the bevacizumab plus irinotecan group compared with the control group (OR, 3.23; 95% CI, 1.47–7.12; P = 0.004) (Figure 4A).

There was significant heterogeneity (I^2 >50%) in the meta-analytical comparisons of hematotoxicity and hypertension between the bevacizumab plus irinotecan group and the control group (Figure 3A and C). The significant heterogeneity could not be eliminated by sensitivity analysis; however, the comparisons of thrombocytopenia (I^2 = 0%; P = 0.91 in Figure 3B) and thrombosis (I^2 = 0%; P = 0.74 in Figure 4A and B) showed no detectable heterogeneity.

DISCUSSION

Owing to therapeutic resistance and malignant glioma recurrence, efforts to identify the molecular alterations fundamental to regulation of tumor progression and provide novel approaches to patient treatment are ongoing.[39-42] Malignant gliomas are hypoxic and highly vascularized, and express relatively high VEGF levels that positively correlate with aggressiveness, making VEGF a promising therapeutic target.[43] Bevacizumab was developed to target VEGF with high affinity and specificity, and it serves to directly inhibit VEGF-associated angiogenic effects by blocking VEGF receptor activation.[44] Bevacizumab, a humanized IgG1 monoclonal antibody that binds to and inhibits the activity of

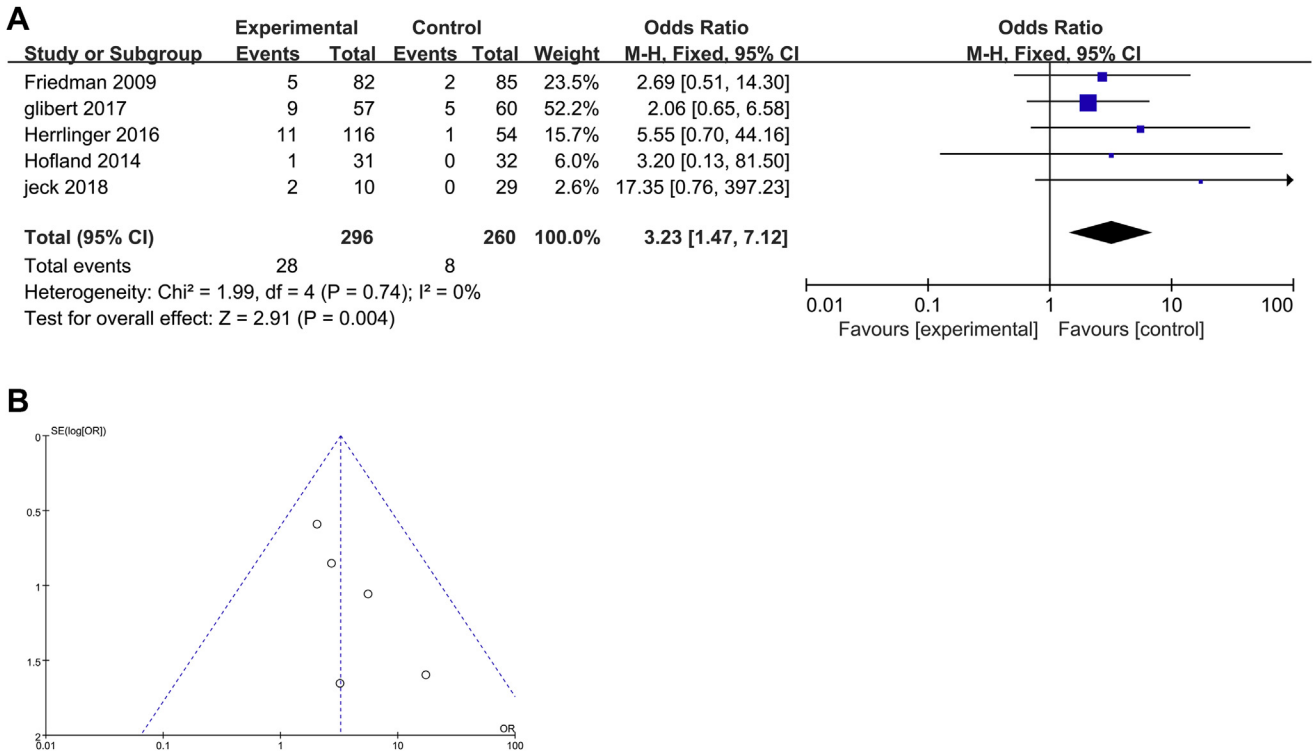

Figure 4. Forest plot and funnel plot of odds ratios for thrombosis. (**A**) Risk of thrombosis in patients treated with bevacizumab plus irinotecan and the control group. (**B**) Funnel plot showing no significant publication bias.

VEGF, prolongs the time to progression for patients through tumor starvation via insufficient blood supply, hypoxia, and undernutrition.[45-47]

Bevacizumab can decrease interstitial pressure, improve tissue oxygenation, and improve delivery of irinotecan to the tumor.[48] However, several adverse vascular events are associated with bevacizumab therapy, including hematotoxicity, thrombocytopenia, hypertension, and thrombosis. Severe hematotoxicity occurs in approximately 20%–50% of patients treated with bevacizumab and is especially prevalent in Asian patients.[49] Leal et al.[50] reported that patients may experience reversible and reproducible thrombocytopenia with multiple treatment cycles of bevacizumab. Hypertension is a characteristic adverse event of bevacizumab therapy, with a reported incidence of 17.9% in a clinical study.[51] The etiology of thrombosis in patients treated with bevacizumab is multifactorial, and in one study, the relative risk of thrombosis was 1.5-fold to 2-fold higher in patients who received bevacizumab compared with controls.[52]

Irinitoecan has been used both as a single-agent and together with other cytotoxic drugs to treat patients with glioma.[18,19] Irinotecan treatment has been associated with a reduced number of tumor vessels, decreased area of hypoxic lesions, and decreased expression of VEGF and hypoxia-inducible factor 1 subunit α.[53] Even in unresectable or subtotally resected gliomas, neoadjuvant treatment with irinotecan is tolerable and can provide disease control before radiotherapy.[54] Bevacizumab plus irinotecan is an effective adjuvant chemotherapy strategy with moderate toxicity[55] that has demonstrated a significant survival benefit in patients with malignant glioma postoperation[11,56]; however, the effect of bevacizumab plus irinotecan on the risk of these adverse vascular events remains unclear owing to relative lack of reports.

We performed a meta-analysis of the available evidence to determine the risk of adverse vascular events in patients with glioma treated with bevacizumab plus irinotecan. In brief, 586 studies identified from systematic searches were screened out, and 562 studies remained after duplicates were removed. After exclusion of 531 studies based on the exclusion criteria, leaving 31 potentially eligible studies for further full text assessment. Fifteen studies with insufficient data for analysis, 8 studies without a control group, and 2 studies lacking details of adverse vascular events were excluded. A total of 6 studies met the inclusion criteria and were subsequently included in the full analysis.

We found no significant difference in the risk of systemic adverse events between patients treated with bevacizumab plus irinotecan and the control group. An approximately equivalent risk of hematotoxicity was revealed between the patients treated with bevacizumab plus irinotecan and the control group. Thrombocytopenia, which was considerably prevalent during chemochemotherapy with bevacizumab alone,[57] showed no detectable difference the between patients treated with bevacizumab plus irinotecan and the control

group. The rate of hypertension, one of the most frequent adverse events occurring during bevacizumab treatment,[58] was not significantly different between the 2 groups. However, the risk of thrombosis was greater in the patients treated with bevacizumab plus irinotecan compared with the control group. Thus, monitoring thrombosis in patients treated with bevacizumab plus irinotecan might be a promising strategy. This may represent a new approach for patients to help avoid thrombosis that warrants investigations in further large-scale randomized, controlled trials.

The present study has some limitations. Although significant heterogeneity could be found in the meta-analyses of hematotoxicity and hypertension, we believe that that it is infeasible to eliminate all potential confounding factors, owing to the small number of included studies. Additional high-quality studies are needed for further verification.

In the present study, we conclude that patients with glioma treated with bevacizumab plus irinotecan did not show increased risks of hematotoxicity, thrombocytopenia, and hypertension. However, patients treated with bevacizumab plus irinotecan had a higher risk of thrombosis, and anticoagulation might still be advisable in patients with a history of thromboembolism.

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