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Antithrombotic Therapy in Cerebral Cavernous Malformations: A Systematic Review, Meta-Analysis, and Network Meta-Analysis

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ORIGINAL RESEARCH

Antithrombotic Therapy in Cerebral Cavernous Malformations: A Systematic Review, Meta-Analysis, and Network Meta-Analysis

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BACKGROUND: Cerebral cavernous malformations are complex vascular anomalies in the central nervous system associated with a risk of intracranial hemorrhage. Traditional guidelines have been cautious about the use of antithrombotic therapy in this patient group, citing concerns about potential bleeding risk. However, recent research posits that antithrombotic therapy may actually be beneficial. This study aims to clarify the association between antithrombotic therapy, including antiplatelet and anticoagulant medications, and the risk of intracranial hemorrhage in patients with cerebral cavernous malformations.

METHODS AND RESULTS: A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus databases, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Nine single-center, nonrandomized cohort studies involving 2709 patients were included. Outcomes were analyzed using random-effects model, and a network meta-analysis was conducted for further insight. Of the 2709 patients studied, 388 were on antithrombotic therapy. Patients on antithrombotic therapy had a lower risk of presenting with intracranial hemorrhage (odds ratio [OR], 0.56 [95% CI, 0.45–0.7]; $P<0.0001$). In addition, the use of antithrombotic therapy was associated with lower risk of intracranial hemorrhage from a cerebral cavernous malformation on follow-up (OR, 0.21 [95% CI, 0.13–0.35]; $P<0.0001$). A network meta-analysis revealed a nonsignificant OR of 0.73 (95% CI, 0.23–2.56) when antiplatelet therapy was compared with anticoagulant therapy.

CONCLUSIONS: Our study explores the potential benefits of antithrombotic therapy in cerebral cavernous malformations. Although the analysis suggests a possible role for antithrombotic agents, it is critical to note that the evidence remains preliminary. Fundamental biases in study design, such as ascertainment and assignment bias, limit the weight of our conclusions. Therefore, our findings should be considered hypothesis-generating and not definitive for clinical practice change.

Key Words: antithrombotic ■ CCM ■ cerebral cavernous malformation ■ intracranial hemorrhage

Cerebral cavernous malformations (CCMs) are complex vascular pathologies of the brain, often encountered as the second most common incidental finding on brain magnetic resonance imaging.[1] These low-flow, low-pressure malformations occur within the central nervous system and have been found in 0.1% to 0.8% of the general population.[2,3]

CCMs can lead to hemorrhagic or nonhemorrhagic focal neurologic deficits, with risks heightened for those with prior hemorrhage or brainstem CCMs.[4] The estimated annual risk for symptomatic hemorrhage ranges

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CLINICAL PERSPECTIVE

What Is New?

- This systematic review, meta-analysis, and network meta-analysis indicates that antithrombotic therapy may be associated with a decreased risk of intracranial hemorrhage in patients with cerebral cavernous malformations.

What Are the Clinical Implications?

- Contrary to traditional guidelines, antithrombotic agents might have potential benefits in patients with cerebral cavernous malformation; however, due to inherent biases in the included studies, these findings should be considered hypothesis-generating, and randomized clinical trials are needed to ascertain their clinical significance.

Nonstandard Abbreviations and Acronyms

CCM	cerebral cavernous malformation

from 2.5% to 3.2%, and the condition can become a source of severe disability, especially in patients with eloquently located CCMs.[5–7]

Microsurgical resection is often the first-line treatment; other treatment modalities, such as radiosurgery, are controversial due to higher postradiosurgical bleeding risk.[8] Consequently, the need for medical treatment options has been identified as a priority in CCM research.[9]

Around a quarter of patients with CCMs could have an indication for antithrombotic therapy, encompassing either anticoagulant or antiplatelet agents, for the prevention of occlusive vascular disease.[10–13] Anticoagulant therapy can be deployed to prevent systemic embolism in conditions like atrial fibrillation or venous thromboembolism, while antiplatelet therapy may be used for secondary prevention after ischemic cerebrovascular and cardiovascular diseases.[14]

Some cohort studies have found nonsignificant associations between the long-term use of antithrombotic therapy and a lower risk of intracranial hemorrhage from a CCM.[10–13] However, the data on the effect of antithrombotic therapy on the risk of intracranial hemorrhage in patients with CCMs remains sparse and ambiguous.

In this systematic review, meta-analysis, and network meta-analysis, we aim to fill this gap by investigating the association between antithrombotic therapy and intracranial hemorrhage in patients with CCMs.

METHODS

The authors declare that all supporting data are available within the article.

Literature Search

This study was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] A systematic search was performed on August 22, 2023, using the PubMed (National Library of Medicine), Web of Science, and Scopus databases from inception to present. The following Boolean search terms: *aspirin* OR '*acetylsalicylic acid* OR *ASA* OR *antiplatelet* OR *anti-platelet agents* OR *platelet aggregation inhibitors* OR *antithrombotic agents* OR *thrombosis prevention* OR *anticoagulant agents* OR *blood thinners* OR *anticoagulant* OR *antithrombotic*) AND (*cerebral cavernous malformation* OR *CCM* OR *cavernoma* OR *cerebral cavernous angioma*) were used to identify the most relevant studies describing antithrombotics and CCMs. Only publications on human subjects and those published or professionally translated to the English language were included.

Because of the study design, no institutional review board approval or patients' informed consents were obtained.

Study Selection Process

After completion of the search in 3 databases, the results were screened against title and abstract by 2 reviewers according to prespecified inclusion and exclusion criteria. Points of disagreement were resolved by consultation with a third author until consensus among the 3 authors was reached. Full texts were then screened to determine suitability for final inclusion. References of all included studies were searched to identify any additional studies that may have been missed during initial screening for inclusion. Inclusion criteria were studies published in English between the dates of inception of each database and August 2023 and studies comparing patients using antithrombotic medications (antiplatelets or anticoagulants) to those who are not. Cadaveric, animal, in vitro studies, case reports and case series consisting of <10 patients were excluded.

Data Extraction

The variables extracted from each study included sample size, age, sex, study design, period of inclusion, comorbidities (ischemic heart disease, transient ischemic attack or ischemic stroke, hypertension), atrial fibrillation, family history of CCM, presentation with intracranial hemorrhage, multiple CCM, brainstem CCM location, and intracranial hemorrhage during follow-up and person-years follow-up.

Patients were prescribed an antithrombotic before the diagnosis of CCM due to other indications (cardiovascular, hematological, etc) with the exception of the study by Zuurbier et al,[14] where 29 patients were started on antithrombotic upon CCM diagnosis. Our primary end points were patients presenting with intracranial hemorrhage and those who had intracranial hemorrhage during follow-up.

Quality Assessment

We assessed the quality of the included observational studies using the Cochrane risk-of-bias tool, Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I).[16] All bias assessments were performed and validated among authors.

Statistical Analysis

Forest plots were constructed to illustrate the odds ratio (OR) and 95% CI for each outcome variable. For the traditional meta-analysis, we employed a random-effects model using the DerSimonian and Laird method. This approach was selected to account for variation both within and across the included studies. Statistical analyses and forest plot generation were completed using R studio version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). A P value of <0.05 was considered statistically significant.

The heterogeneity among studies was assessed using chi-square, I^2, and τ^2 tests. When heterogeneity was substantial ($I^2 \geq 50\%$), we used a random-effects model, acknowledging the variability among study results. Conversely, in cases in which heterogeneity was relatively low ($I^2 < 50\%$), suggesting more homogeneity across studies, a fixed-effects model was used.

For the network meta-analysis, we evaluated the efficacy of anticoagulants and antiplatelets compared with no antithrombotic therapy. This analysis, which incorporated 8 studies comprising 2362 observations

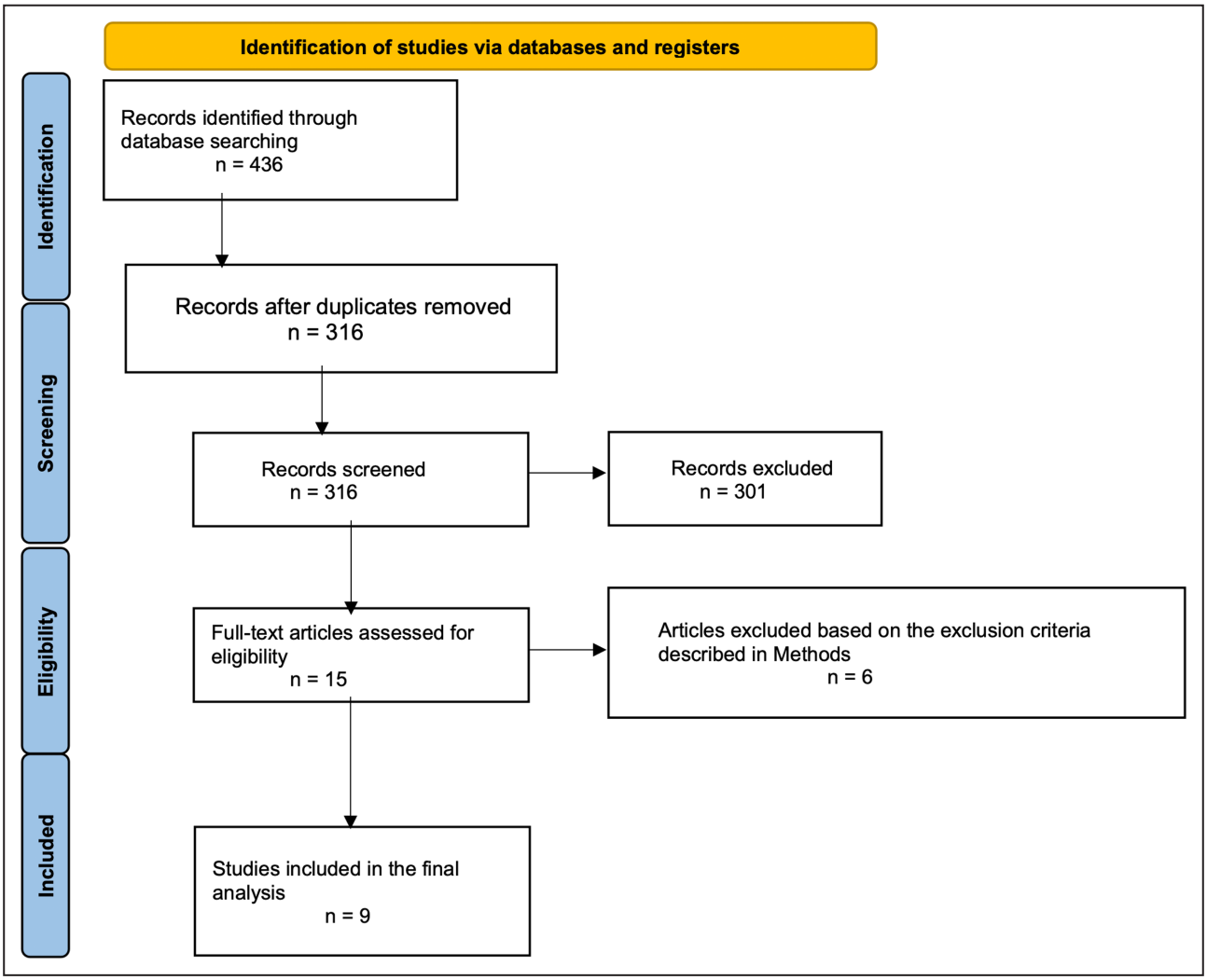

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Table. Characteristics of Studies Included

	Schneble et al, 2012[12]		Flemming et al, 2013[11]		Wityk et al, 2014[13]		Bervini et al, 2018[10]		Flemming et al, 2018[18]		Zuurbier et al, 2019[14]		Gomez-Paz et al, 2020[19]		Marques et al, 2023[20]		Wildi et al, 2023[21]	
	Prospective cohort study		Retrospective cohort study		Retrospective cohort study		Prospective cohort study		Prospective cohort study		Prospective cohort study		Retrospective cohort study		Retrospective cohort study		Retrospective cohort study	
	2008–2010		1989–1999		1987–2009		1980–2015		2015–2018		1999–2003 or 2006–2010		1990–2018		1980–2021		2006–2018	
Variables	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT	No ATT	ATT
N (%)	71 (82)	16 (18)	252 (86)	40 (14)	74 (77)	22 (23)	294 (81)	71 (19)	160 (79)	42 (21)	238 (79)	62 (21)	328 (73.5)	20 (4.5)	545 (79.2)	46 (6.6)	359 (83.8)	69 (16.1)
Sex, male, n (%)	27 (38)	10 (62)	117 (46)	21 (52)	25 (34)	13 (59)	144 (49)	52 (73)	66 (41)	19 (45)	107 (45)	34 (55)	140 (42.6)	8 (40)	269 (49.3)	32 (69.5)	184 (51.2)	43 (62.3)
Mean age, y, mean (SD)	54.0 (16.5)	68.4 (16.1)	43.2 (18.6)	62.4 (13.2)	38.2 (15.9)	53.0 (15.5)	46.8 (18.2)	62.4 (15.8)	41.9 (15.7)	51.4 (16.2)	42.2 (15.1)	54.5 (14.9)	44 (36–54)*	68.5 (56–77.5)*	47.3 (17.7)	63.5 (13.8)	41.3 (16.9)	61.2 (16.6)
Family history of CCM, n	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10	1	12	0	8	1
Hypertension, n	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	28	32	59	15	NR	NR	83	50
Ischemic heart disease, n	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6	24	NR	NR	NR	NR	7	19
Atrial fibrillation, n	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	7	NR	NR	NR	NR	8	12
TIA/ischemic stroke, n	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4	21	NR	NR	NR	NR	10	25
Presentatation with hemorrhage, n (%)	11 (15)	0	69 (27)	5 (13)	23 (31)	5 (23)	102 (35)	14 (20)	64 (40)	6 (14)	47 (20)	5 (8)	104 (31.7)	4 (20)	189 (24.7)	6 (12.5)	236 (65.7)	31 (44.9)
Multiple CCMs, n (%)	27 (38)	5 (31)	51 (20)	4 (10)	17 (23)	8 (36)	48 (16)	7 (10)	45 (28)	11 (26)	81 (34)	16 (26)	NR	NR	80 (14.7)	3 (6.5)	60 (16.7)	18 (26.1)
Brainstem CCM location, n (%)	20 (28)	3 (19)	21 (8)	7 (18)	21 (28)	9 (41)	57 (19)	8 (11)	52 (33)	9 (21)	25 (11)	9 (15)	NR	NR	95 (12.4)	5 (10.4)	73 (20.3)	8 (11.6)
Hemorrhage during follow-up, n (%)	9 (13)	0	31 (12)	1 (3)	14 (19)	1 (5)	33 (11)	1 (1)	47 (29)	4 (10)	18 (8)	1 (2)	NR	NR	67 (9.5)	2 (4.7)	180 (50.1)	4 (5.7)
Person-years follow-up	205	82	1776	247	468	122	813	134	609	170	2342	726	NR	NR	22144.50	911.6	1563.28	321.98
Quality assessment	Serious		Serious		Serious		Serious		Moderate		Moderate		Serious		Serious		Serious	

ATT indicates antithrombotic therapy; CCM, cerebral cavernous malformation; NR, not reported; and TIA, transient ischemic attack.
*Median (interquartile range).

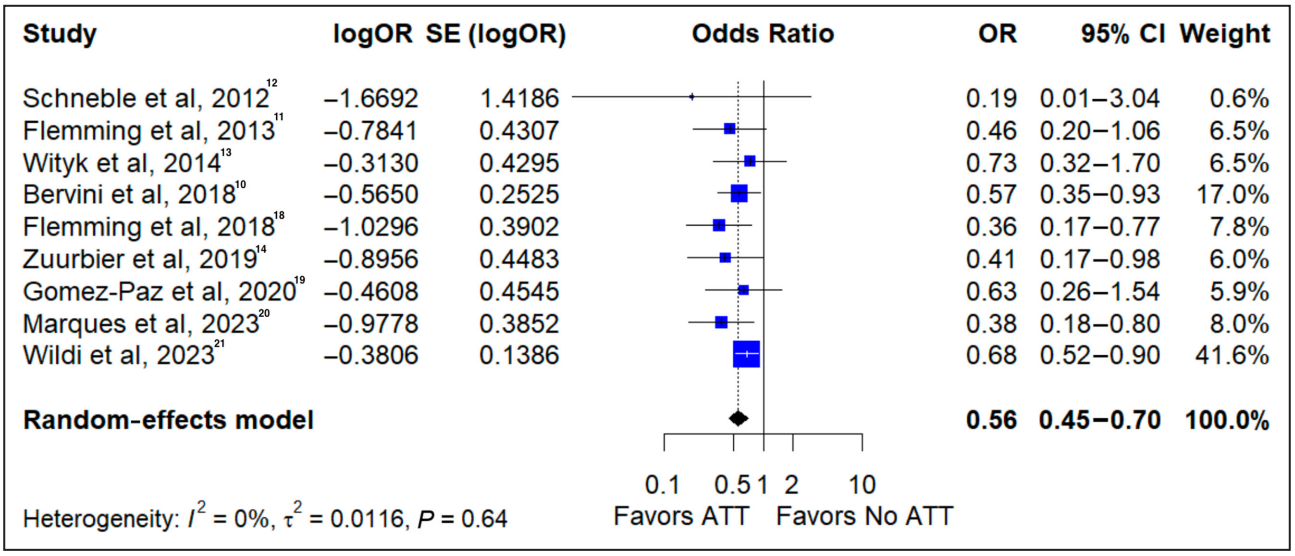

Figure 2. Forest plot for first presentation hemorrhage.
ATT indicates antithrombotic therapy; and OR, odds ratio.

across 22 pairwise comparisons, was performed using a fixed-effects model when I^2 was below 50%. The Mantel–Haenszel method was applied under this fixed-effects framework to derive treatment estimates. This method was chosen for its efficacy in handling sparse data and low heterogeneity scenarios. To assess publication bias, funnel plots and rank correlation tests were used.

A univariate meta-regression was also done including 4 variables: age, brainstem CCMs, sex, and multiple CCMs. Other variables, including family history of CCM and other comorbidities, were not included due to the limited studies reporting data on these. This was followed by multivariable meta-regression, which included variables that had an R^2 value indicating a meaningful explanatory power. The Sidik–Jonkman estimator method was used to estimate the variance of the error term in our meta-regression model.[17]

RESULTS

Study Identification

The study resulted in 436 articles, of which 120 were duplicates. Of the 316 screened articles, 15 articles were assessed in full text, and 9 studies were included in the final analysis (Figure 1).[10–14,18–21] All studies were single-center, nonrandomized cohort studies at moderate to high risk of bias (Table). A total of 2709 patients were

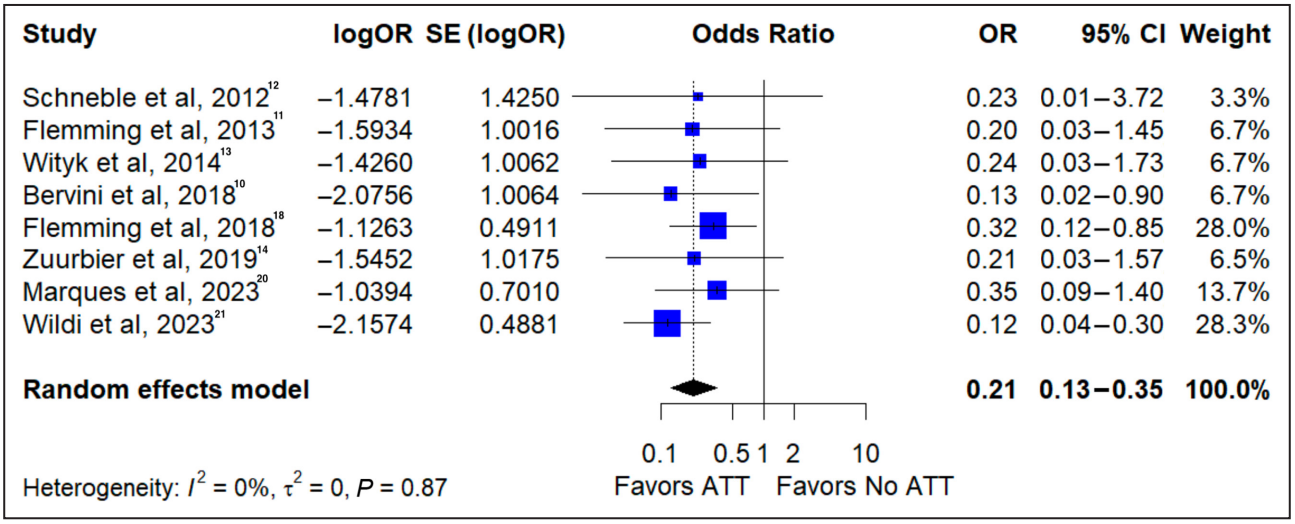

Figure 3. Forest plot for last follow-up hemorrhage.
ATT indicates antithrombotic therapy; and OR, odds ratio.

included in the analysis. Antithrombotic (anticoagulant or antiplatelet) therapy was used in 388 patients. Of these, 322 (11.8%) used antiplatelet therapy alone, and 66 (2.4%) used anticoagulant therapy. Antithrombotic therapy was not used in 2321 patients (Table).

Quantitative Synthesis and Meta-Analysis

Of the 316 records identified in the systematic review, 15 were selected as potentially relevant studies, of which 9 met our inclusion criteria in the meta-analysis. A total of 2709 patients were included in the meta-analysis. Of these, 2321 (85.6%) did not use antithrombotic therapy, and 388 (14.4%) used antithrombotic therapy. Patients who did not use antithrombotic therapy experienced 399 intracranial hemorrhages during 29 920 person-years. On the other hand, 14 patients had intracranial hemorrhages among those who used antithrombotic therapy during 2714 person-years. A meta-analysis was done to compare the baseline characteristics between the 2 groups. A statistically significant difference was found in terms of age (mean difference, 16.19 [95% CI, 13.45–18.93]; $P<0.001$), male sex (OR, 1.73 [95% CI, 1.35–2.22]; $P<0.01$), ischemic heart disease (OR, 21.48 [95% CI, 11.08–41.65]; $P<0.01$), transient ischemic attack or ischemic stroke (OR, 22.79 [95% CI, 11.9–43.63]; $P<0.01$), atrial fibrillation (OR, 11.24 [95% CI, 4.74–26.62]; $P<0.01$), and hypertension (OR, 9.01 [95% CI, 6.05–13.4]; $P<0.01$) (Figure S1).

Patients who used antithrombotic therapy presented less often with intracranial hemorrhage (76

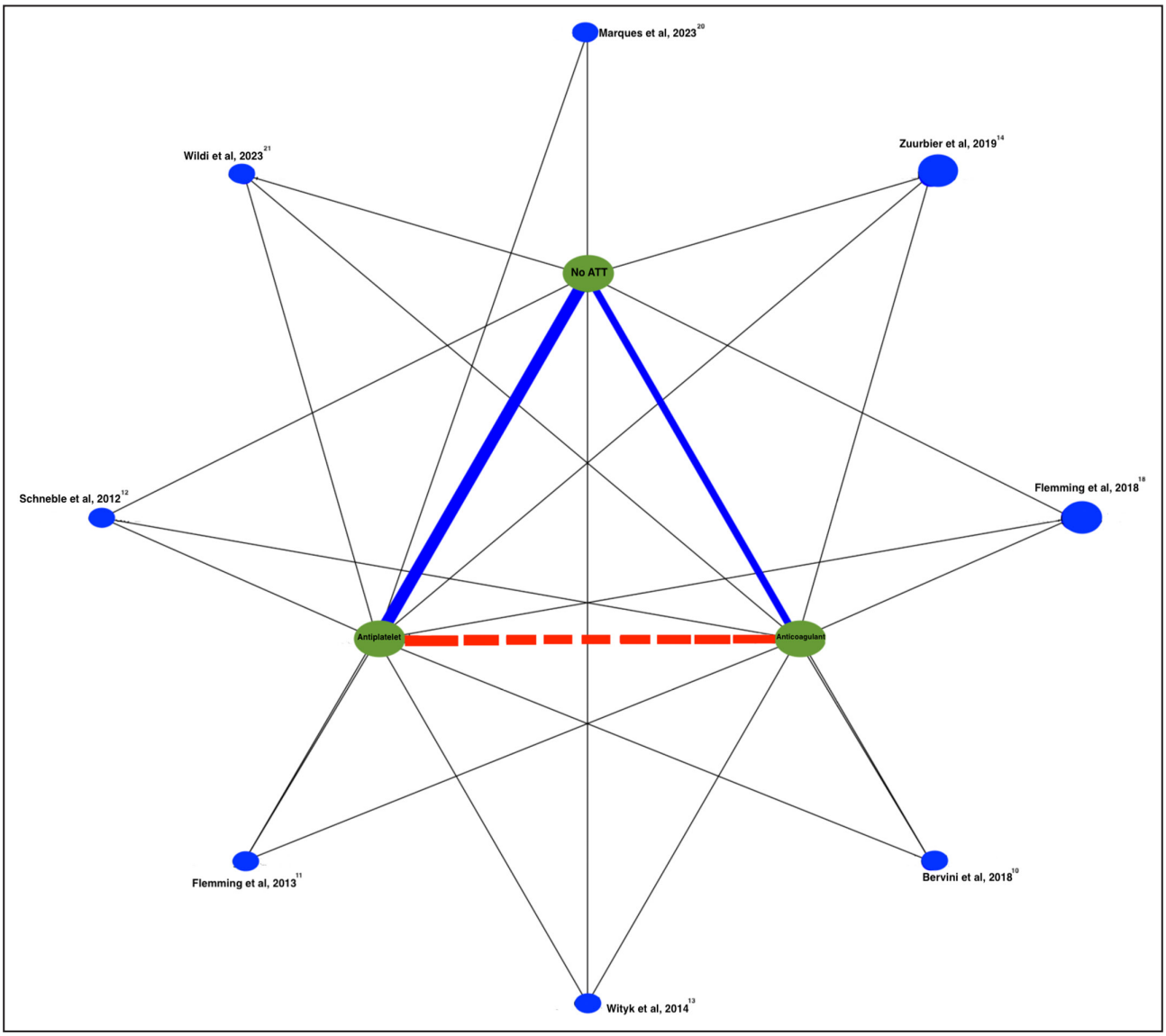

Figure 4. Geometry of the network presenting how each treatment is connected to the others.
ATT indicates antithrombotic therapy.

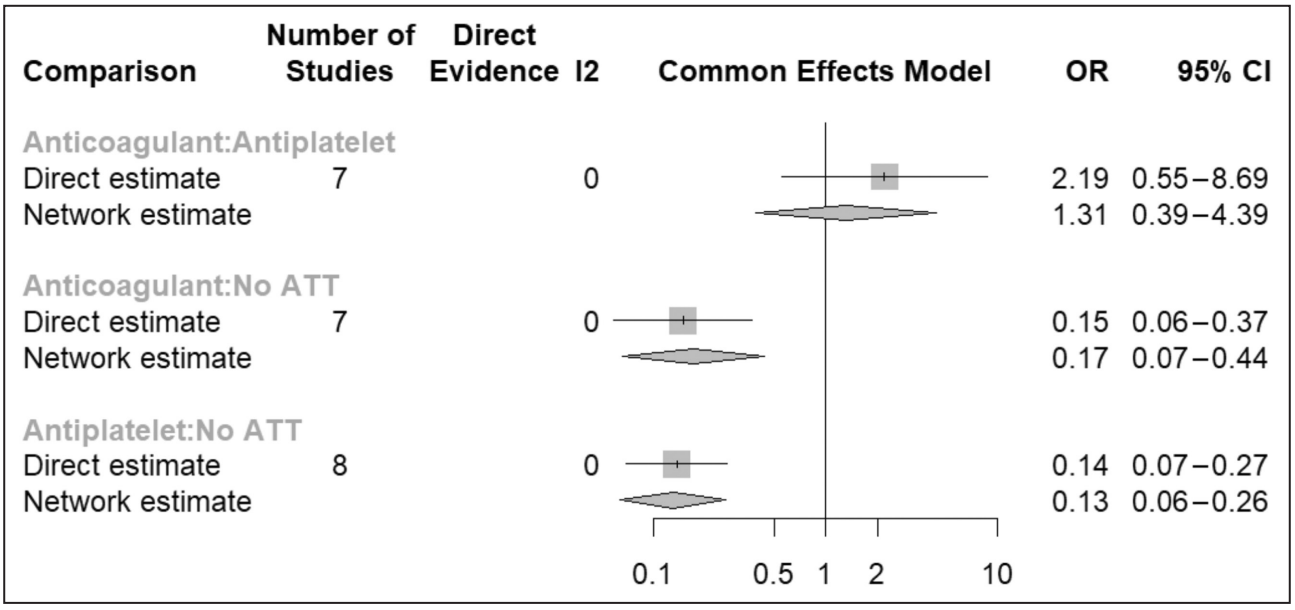

Figure 5. Forest plot for network meta-analysis.
ATT indicates antithrombotic therapy; and OR, odds ratio.

[19.5%] of 388 versus 845 [36.4%] of 2321) than patients who did not use antithrombotic therapy, a result that was statistically significant on meta-analysis (OR, 0.56 [95% CI, 0.45–0.70]; $P<0.0001$; $I^2=0\%$, $P=0.64$) (Figure 2). A rank correlation test for funnel plot asymmetry was conducted, and the results were statistically nonsignificant ($P=0.904$; Figure S2). In addition, the use of antithrombotic therapy was associated with a lower risk of intracranial hemorrhage from a CCM (14 [3.8%] of 368 versus 399 [20%] of 1993; OR, 0.21 [95% CI, 0.13–0.35]; $P<0.0001$) with no statistically significant inconsistency between the studies ($I^2=0\%$, $P=0.87$; Figure 3). A rank correlation test was also conducted for funnel plot asymmetry, and the results were also statistically nonsignificant ($P=0.612$; Figure S3).

A network meta-analysis was performed for the outcome of intracranial hemorrhage at follow-up. A network diagram of included studies is shown in Figure 4. The analysis encompassed 8 studies with 22 pairwise comparisons involving 2362 observations. The pooled network estimate comparing anticoagulant therapy with no antithrombotic therapy revealed a statistically significant OR of 0.17 (95% CI, 0.07–0.44; $P<0.001$). Similarly, the pooled effect of antiplatelet therapy compared with no antithrombotic therapy was also statistically significant (OR, 0.13 [95% CI, 0.06–0.26]; $P<0.001$; Figure 5).

In addition, a comparison between anticoagulant and antiplatelet was performed. The pooled network estimate comparing antiplatelet therapy to anticoagulant therapy revealed a statistically nonsignificant OR of 1.31 (95% CI, 0.39–4.39) (Figure 5). A test of inconsistency was performed showing a nonsignificant result ($P=0.15$).

Univariate and Multivariable Meta-Regression

A univariate meta-regression was done to assess the effect of age, brainstem CCMs, sex, and multiple CCMs on the outcome of hemorrhage. No significant association between any of the variables and the hemorrhage outcome was noted. After this, a multivariable meta-regression was done including variables that had an R^2 value with a meaningful explanatory power. The model's overall explanatory capacity, as shown by the R^2 coefficient, was found to be moderate, with an R^2 value of 55%. However, there were no statistically significant relationships found between any of the factors and the incidence of bleeding. (Figure S4 and Table S1).

DISCUSSION

This systematic review, meta-analysis, and network meta-analysis aimed to explore the association between the use of antithrombotic therapy and the risk of intracranial hemorrhage in patients with CCMs. The study's significant findings associate antithrombotic therapy with a lower risk of intracranial hemorrhage in patients with CCMs.

Recent research has prompted a significant shift in our understanding of the pathophysiology of CCM hemorrhages.[12] The prevailing view of the causes of hemorrhage and specific neurological impairments in

patients with CCMs is being challenged, with growing evidence pointing to thrombosis within the CCM or a related venous anomaly as likely triggers.[22] CCMs consist of endothelial-lined spaces filled with blood of varying ages.[22,23] The enlargement of these caverns can lead to slow blood flow, increasing their vulnerability to clotting.[22,23] This, in turn, can lead to new or worsening neurological deficits or hemorrhages.[24,25] This observation has led to the suggestion that treatment with antithrombotic agents may be helpful in these cases, as they prevent venous clot formation.[21] The findings of this analysis are consistent with this hypothesis.

These results challenge conventional wisdom and prior recommendations that anticoagulation was contraindicated for people with CCM.[14] Instead, they query the potential benefits of antithrombotic therapy in this patient population.

So far, however, the effect of antithrombotic therapy on CCM-related hemorrhage has not been well studied.[12] In a prospective series of 746 patients receiving prophylactic low-molecular-weight heparin injections after surgery, none of the 9 patients with CCM in the cohort experienced postoperative bleeding.[26] Another case report describes a patient with a known asymptomatic CCM who was treated intravenously with recombinant tissue-type plasminogen activator for acute ischemic stroke without hemorrhagic complications.[27] These findings align with this meta-analysis and offers insight into the potential broader application of antithrombotic therapy in patients with CCMs. This was further supported by a systematic review by Bianconi et al, which suggested the safety of antithrombotic medications in patients with CCM.[28]

While this meta-analysis offers valuable insights into the role of antithrombotic therapy in CCMs, there are several noteworthy limitations. The studies included are primarily single-center, nonrandomized designs, contributing to selection bias and confounding by indication. This restricts the generalizability of our findings across different health care settings and populations. One of the most significant limitations of our analysis and the studies it includes is the potential for ascertainment and assignment bias. Patients with symptomatic hemorrhage are often taken off blood-thinning medications, which skews the data toward nonhemorrhagic lesions in patients on antithrombotics. This fundamental limitation cannot be corrected retrospectively and poses a challenge for interpreting prospective data. Additionally, the lack of control for statin and vitamin D exposure, commonly used for cardiovascular risk modification, could influence CCM outcomes.[29,30] The data on the effect of antithrombotic therapy on intracranial hemorrhage in patients with CCMs are often conflicting, casting further uncertainty on our conclusions. Furthermore, the possibility of publication bias cannot be ignored. Studies with nonsignificant effects may not have been published, potentially skewing the results in favor of antithrombotic therapy. Finally, we acknowledge a notable concern regarding the wide CIs observed in some comparisons of our network meta-analysis, particularly in the OR for antiplatelet versus anticoagulant therapies. These wide intervals, ranging from 0.23 to 2.56, introduce a significant degree of uncertainty in our findings. The broad range of these CIs implies that while our analysis suggests a direction of effect, the exact magnitude of this effect remains highly uncertain. Consequently, these results should be interpreted with caution. Given these limitations, our findings should be considered hypothesis-generating and should not advocate for a change in clinical practice.

CONCLUSIONS

In conclusion, this study suggests that antithrombotic therapy is associated with decreased risk of intracranial hemorrhage. Further studies, including randomized clinical trials, are warranted to validate and further investigate these results.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S4

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