Efficacy of Medical Treatment Options for Reducing the Risk of Bleeding in Patients with Cerebral Cavernous Malformations: A Systematic Review and Network Meta-Analysis

Talha E Baser[1]; Eren Gulsahin[2]; Sam Elmuslimani[3]; Murat Durna[4], MD; Okyanus B Gulec[5]; Secil Yerci[6]; Irem Kaba[7]; Riza D Dogruer[8]; Omar Alomari[9]; Berkay Kilic[10]; Doga D Demir Yangi, MD[11]; Kivanc Yangi, MD[12]

[1]Biruni University, School of Medicine, Istanbul, Turkey; [2]Marmara University, School of Medicine, Istanbul, Turkey; [3]Aydin Adnan Menderes University, Aydin, Turkey, School of Medicine; [4]Kars Harakani Public Hospital, Kars, Turkey; [5]Akdeniz University, School of Medicine, Antalya, Turkey; [6]Ondokuz Mayis University, School of Medicine, Samsun, Turkey; [7]Pamukkale University, School of Medicine, Denizli, Turkey; [8]University of Health Sciences, Gulhane School of Medicine, Ankara, Turkey; [9]University of Health Sciences, Hamidiye International School of Medicine, Istanbul, Turkey; [10]Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Turkey; [11]Ivy Brain Tumor Center, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA; [12]Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Introduction

Cerebral cavernous malformations (CCMs) are low-flow vascular lesions of the central nervous system, characterized by abnormal clusters of capillaries lined with endothelial cells. [1, 2] The most critical clinical manifestation of CCMs is intracerebral hemorrhage (ICH), and its risk can increase with factors such as prior bleeding, lesion location, and associated developmental venous anomalies. [3, 4] Although surgery is the primary treatment option for CCMs, surgical intervention in deep-seated lesions may carry significant risks. Consequently, various medications have been proposed as potential pharmacological stabilizing agents; however, the relationship between bleeding risk and medication use remains unclear, and no consensus or standardized guidelines currently exist. This study aims to evaluate the potential roles of three commonly used medication groups in modifying hemorrhage risk in CCMs: statins, antithrombotics, and beta-blockers.

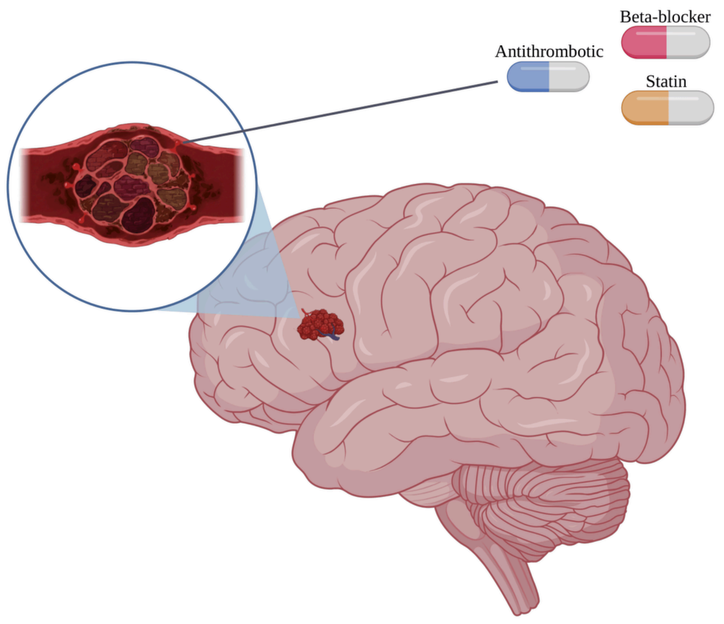

Figure 1. Potential medical therapies in CCMs.

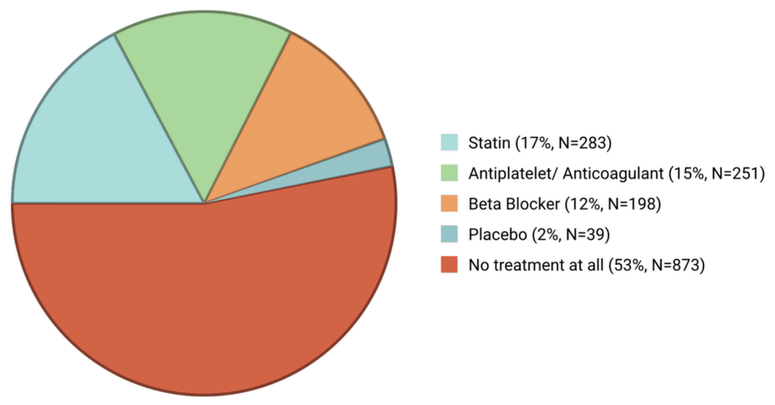

Figure 2. Reported patient distributions according to treatment strategies in the included studies.

Methods

This study followed PRISMA guidelines and was registered in PROSPERO (CRD420251069357). PubMed, Embase, Cochrane, and Scopus were searched from inception to July 9, 2025. Eligible studies included patients with sporadic or familial CCMs reporting ICH outcomes in those receiving statins, antithrombotics, or beta-blockers either as monotherapy or in combination, compared with no medical treatment. Studies involving surgical intervention were excluded. The primary outcome was prospective (re)bleeding during follow-up, and the secondary outcome was the association of prior medication use with hemorrhagic presentation at diagnosis. Odds ratios (ORs) were calculated for each medication group, and a multivariate meta-analysis with surface under the cumulative ranking curve (SUCRA) scores was performed to compare efficacy.

Results

Seven studies including 3,092 patients were included in the analysis. Females represented 54.9% of the cohort and the mean (SD) age at presentation was 45.1 ± 17.2 years. The multivariate meta-analysis showed that statin therapy significantly reduced the odds of (re)bleeding during follow-up compared with both beta-blockers [ln(OR)= –1.15, 95% CI: –2.24, –0.05] and no treatment [ln(OR)= –1.14, 95% CI: –1.96, –0.32]. Combination therapy with statins, antithrombotics, and beta-blockers also lowered the odds of (re)bleeding relative to no treatment [ln(OR)= –1.43, 95% CI: –2.82, –0.05], ranking highest in SUCRA analysis, followed by statin monotherapy. Furthermore, statin plus antithrombotic therapy significantly reduced the odds of (re)bleeding compared with beta-blockers [ln(OR)= –1.39, 95% CI: –2.46, –0.32]. Beta-blocker monotherapy showed a tendency toward increased risk compared with antithrombotic monotherapy [ln(OR)= 0.88, 95% CI: 0.12, 1.63], while patients receiving no treatment had higher odds of presenting with (re)bleeding relative to both statin plus antithrombotic therapy [ln(OR)= 1.13, 95% CI: 0.27, 2.00] and antithrombotic monotherapy [ln(OR)= 0.62, 95% CI: 0.09, 1.14]. In the SUCRA ranking, statin plus antithrombotic therapy was associated with the lowest risk of (re)bleeding at the time of diagnosis.

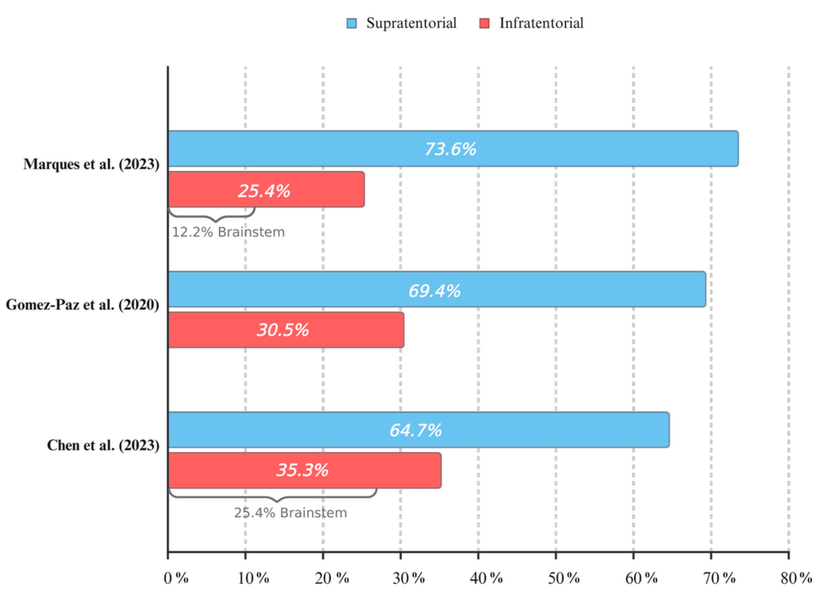

Figure 3. Reported distribution of lesion locations across the included studies.

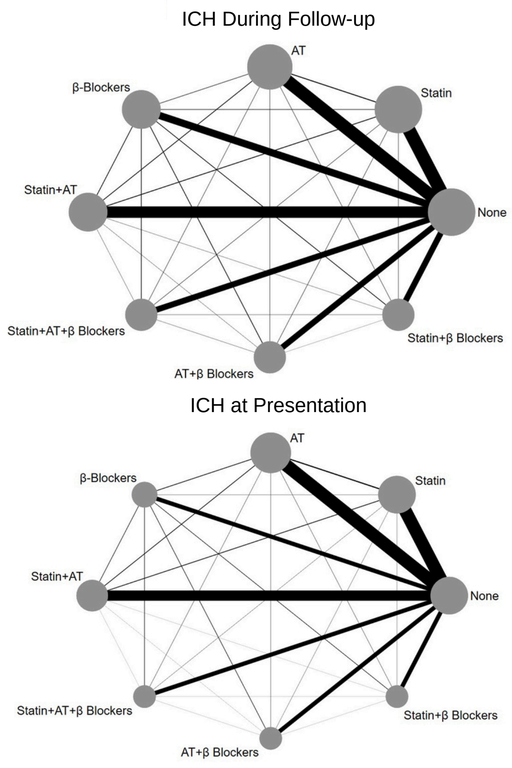

Figure 4. Network geometry of treatment comparisons for Intracerebral Hemorrhage (ICH) during follow-up and at Presentation.

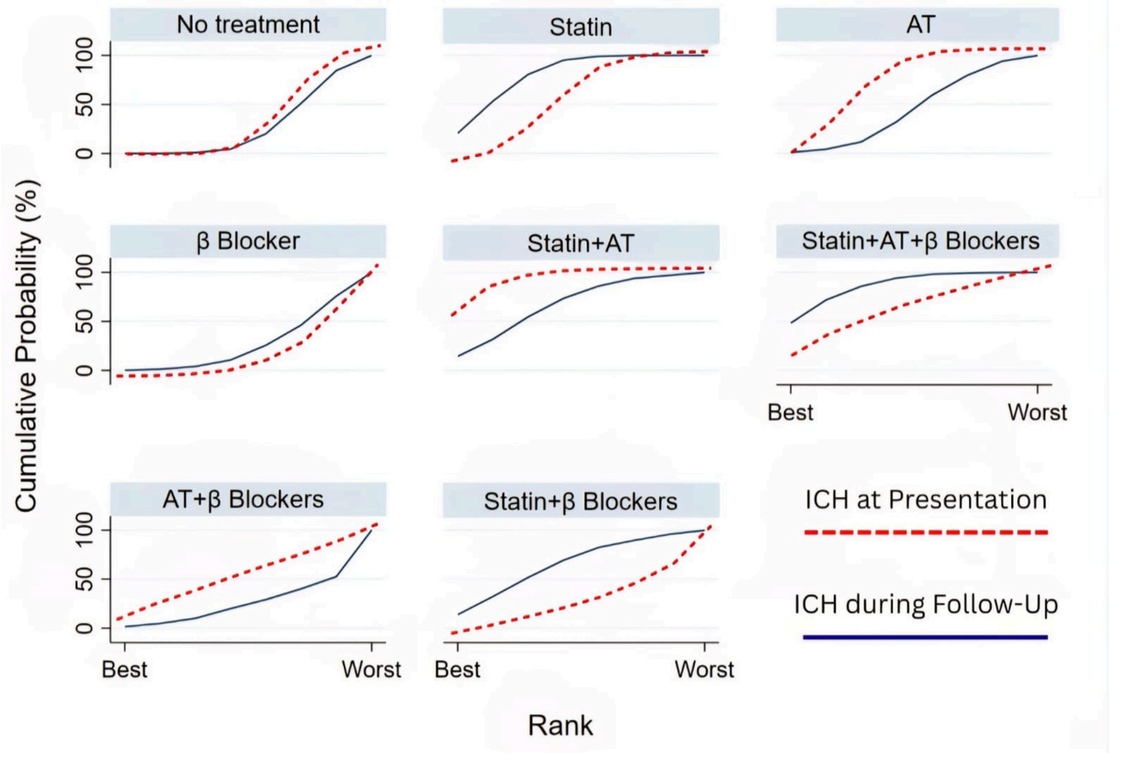

Figure 5. Cumulative ranking probability plots (rankograms) comparing treatment strategies for primary and secondary outcomes. (AT: Antithrombotics)

Conclusions

Our findings suggest the potential stabilizing role of statin-based therapies in CCMs, with combination therapy (statin+AT+beta-blocker) showing the most favorable risk profile, which warrants confirmation in future prospective randomized controlled trials, particularly for patients with lesions in eloquent regions or without a clear surgical indication, where medical therapy may serve as a valuable alternative.

References

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