Rho-Associated Kinase Inhibitors in Cerebral Cavernous Malformations
A Preclinical Systematic Review

Irem Uslu[1]; Ecem Senturk[2]; Bilge Kara, MD[3]; Merve G. Turkmenel[4]; Zeynep E. Celikkiran[5]; Berkay Kilic[6]
Doga D. Demir Yangi, MD[7]; **Kivanc Yangi, MD**[8]

1: Pamukkale University, School of Medicine, Denizli, Turkiye 2: Lobachevsky University, School of Medicine, Nizhny Novgorod, Russia 3: Manavgat State Hospital, Antalya, Turkiye 4: Atilim University, School of Medicine, Ankara, Turkiye 5: Biruni University, School of Medicine, Istanbul, Turkiye 6: Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Turkiye
7-Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, AZ, USA 8-Dept. of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ, USA

Introduction

Cerebral cavernous malformations (CCMs) are vascular lesions of the central nervous system characterized by clusters of dilated, thin-walled capillaries. Clinically, they may manifest with seizures, focal neurological deficits, or remain asymptomatic until detected incidentally. Hemorrhagic events, ranging from microhemorrhages to clinically significant bleeding, are a key determinant of symptom onset, disease progression, and overall severity, and they play a central role in lesion instability and long-term neurological outcomes.

CCM management is influenced by multiple factors, including lesion location (supratentorial vs. infratentorial), prior hemorrhage history, and patient-specific clinical features. Treatment strategies are individualized, with conservative monitoring or surgical resection representing the main approaches. However, surgery for deep-seated lesions requires advanced technical expertise and carries substantial risk, highlighting the growing interest in medical management strategies for CCMs. Among the pharmacologic candidates under investigation are Rho kinase (ROCK) inhibitors.

At the molecular level, CCM pathogenesis is driven by loss-of-function mutations in three genes: KRIT1 (CCM1), CCM2, and PDCD10 (CCM3). Loss of these genes has been shown to increase Ras homolog family member A (RhoA) activity, a small GTPase that regulates endothelial cytoskeletal organization and junctional integrity, leading to activation of downstream ROCK signaling in capillary endothelial cells. Enhanced RhoA–ROCK signaling promotes stress fiber formation, intercellular gap development, endothelial barrier dysfunction, lesion maturation, and accumulation of non-heme iron, an indicator of chronic microhemorrhage and lesion instability.

Accordingly, this study aims to comprehensively review the effects of ROCK-targeting agents on lesion burden, lesion maturation, and non-heme iron deposition in CCM.

Methods

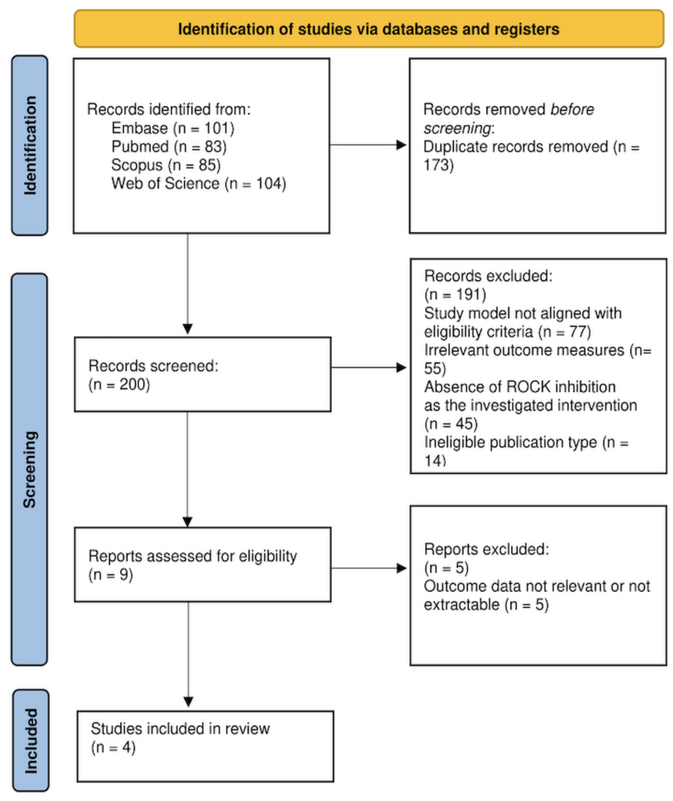

Figure 1: PRISMA Flowchart depicting study selection process.

This study followed PRISMA 2020 guidelines and was registered in PROSPERO (CRD420251048073). A comprehensive literature search was conducted in PubMed, Embase, Scopus, and Web of Science from database inception through January 20, 2026.

Eligible studies included CCM mouse models harboring mutations in CCM1, CCM2, or PDCD10 (CCM3), including heterozygous, homozygous, conditional knockout, or transgenic models; in vitro studies were included when relevant. Studies were required to evaluate pharmacologic ROCK inhibitors, regardless of dose, route, or treatment duration, and to provide molecular evidence of altered RhoA/ROCK pathway activity.

The primary outcome was lesion burden. Secondary outcomes included lesion maturation, hemorrhage, non-heme iron deposition, and markers reflecting ROCK pathway activity.

Results

Among 373 screened records, four preclinical studies demonstrated that fasudil consistently reduced both lesion burden and non-heme iron deposition in CCM mouse models.

In $CCM1^{+/-}$ $MSH2^{-/-}$ mice, fasudil significantly decreased non-heme iron levels ($P<0.01$) and reduced mature stage-2 lesions by 74% compared with placebo (0.68 ± 0.30 vs. 0.18 ± 0.24 lesions/mouse, $P=0.02$) [2]. Similarly, in $CCM2^{+/-}$ $MSH2^{-/-}$ mice, fasudil lowered non-heme iron deposition ($P=0.028$) and reduced lesion burden ($P=0.039$).

Another study reported complete absence of extravascular iron deposits in fasudil-treated animals (3/4 vs. 0/6, $P=0.03$) along with fewer lesions ($P=0.049$) [3]. The related ROCK inhibitor BA-1049 also produced dose-dependent reductions in non-heme iron deposition ($P\leq0.037$) and lesion burden ($P=0.022$) compared with placebo [4].

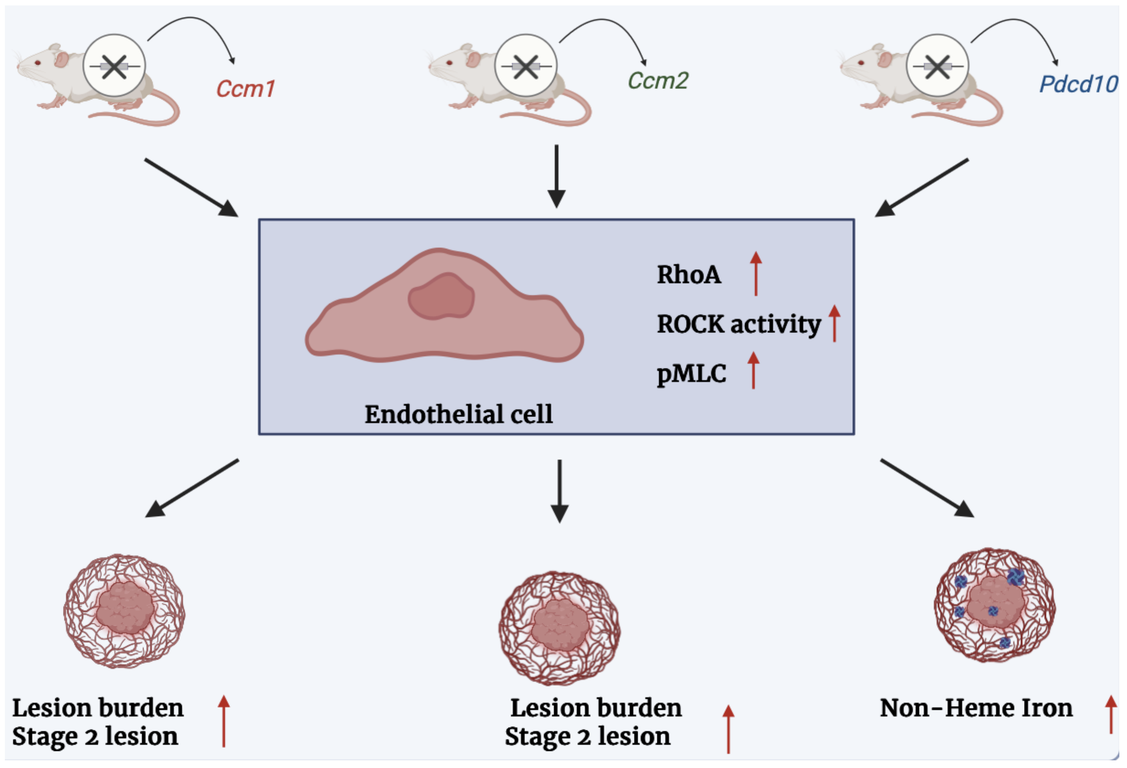

Figure 2: Loss of CCM1, CCM2, or PDCD10 activates the RhoA–ROCK pathway, leading to endothelial dysfunction that drives lesion progression, microhemorrhage, and vascular instability.

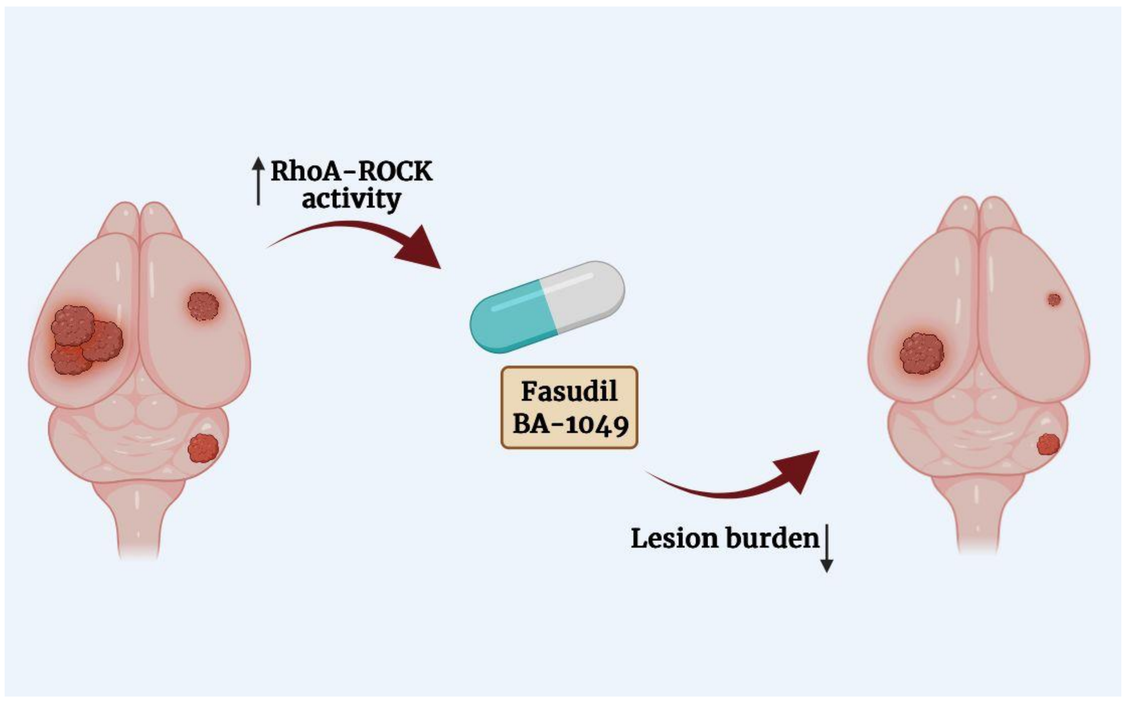

Figure 3: Therapeutic rationale for ROCK inhibition in CCMs. Elevated RhoA/ROCK signaling contributes to increased lesion burden and vascular instability. Treatment with ROCK inhibitors, such as fasudil (FA) or BA-1049, suppresses downstream signaling, leading to a significant reduction in lesion burden in CCM murine models.

Conclusions

Fasudil and other ROCK inhibitors consistently reduced lesion burden and decreased non-heme iron deposition in CCM mouse models. These findings suggest that inhibition of Rho-associated kinase may represent a therapeutic strategy to mitigate hemorrhagic activity in CCMs. However, further clinical studies are required to confirm translational efficacy, and future investigations with larger sample sizes are needed to better define optimal dosing regimens, treatment duration, and long-term safety profiles of these agents.

Contact

Kivanc Yangi, M.D.
Dept. of Neurosurgery, Barrow Neurological Institute
St. Joseph's Hospital and Medical Center
2910 N 3rd Ave, 85013, Phoenix, Arizona, USA
kivancyangi@gmail.com
602-767-9802

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