Safety and efficacy of atorvastatin for rebleeding in cerebral cavernous malformations (AT CASH EPOC): a phase 1/2a, randomised placebo-controlled trial

Issam A Awad, Roberto J Alcazar-Felix*, Agnieszka Stadnik, Serena Kinkade, Aditya Jhaveri, Justine Lee, Stephanie Hage, Javed Iqbal, Sean P Polster, Robert Shenkar, Kevin Treine, Nichol McBee, Noeleen Ostapkovich, Karen Lane, James K Liao, Matthew Sorrentino, Cornelia Lee, Kelly D Flemming, Romuald Girard, Timothy J Carroll, Richard E Thompson, Daniel F Hanley*

Summary

Background Cerebral cavernous malformations (CCMs) carry a high risk of rebleeding after symptomatic haemorrhage, with serious clinical sequelae. Atorvastatin was shown to prevent CCM growth and bleeding in animal models. We aimed to assess the safety and efficacy of atorvastatin on rebleeding in patients with CCMs after a symptomatic haemorrhage.

Methods We did a phase 1/2a randomised trial at the University of Chicago's CCM Center of Excellence. Patients aged 18–80 years with untreated CCMs who had had symptomatic bleeding from a CCM lesion within the previous year were eligible. Patients were randomly allocated (1:1) to oral atorvastatin (80 mg daily for 2 years) or matching placebo. Investigators, clinical staff, and participants were masked to the assigned treatment. The primary efficacy outcome was the percentage change in mean lesional iron deposition per year, measured by quantitative susceptibility mapping (QSM) on MRI and averaged over 2 years; a decrease would signal potential benefit and an increase a safety concern. The primary efficacy outcome was analysed in the modified intention-to-treat cohort, including patients with at least one annual paired QSM assessment. Safety outcomes included rates of bleeds and serious adverse events necessitating drug discontinuation. This trial is registered at ClinicalTrials.gov (NCT02603328) and is completed.

Findings Between July 25, 2018, and July 22, 2022, 326 patients were assessed for eligibility, and 80 patients were allocated either atorvastatin (n=41) or placebo (n=39). 29 (36%) patients were male and 51 (64%) were female. 64 (80%) patients (33 in the atorvastatin group and 31 in the placebo group) had at least one annual paired QSM assessment and were included in the modified intention-to-treat analyses. The mean annual percentage change in lesional QSM was 10·88 (SE 7·29) with atorvastatin versus 12·09 (SE 7·54) with placebo (treatment effect –1·22, 95% CI –22·25 to 19·81; p=0·91). Symptomatic haemorrhage was reported in six patients assigned atorvastatin and seven patients assigned placebo (relative risk 0·81, 95% CI 0·31 to 2·13). No patients had a serious adverse event requiring drug discontinuation and no deaths were recorded.

Interpretation For people with symptomatic haemorrhage caused by CCMs, atorvastatin did not affect the mean change in lesional iron deposition on brain MRI over 2 years when compared with placebo. Atorvastatin was well tolerated and no safety concerns were noted. The study provides a useful framework for biomarker driven drug assessment in a rare disease.

Funding US National Institutes of Health.

Lancet Neurol 2025; 24: 295–304

See **Comment** page 276

*Contributed equally as first authors

Neurovascular Surgery Program, Department of Neurological Surgery, University of Chicago Medicine and Biological Sciences, Chicago, IL, USA (Prof I A Awad MD, R J Alcazar-Felix MD, A Stadnik MS, S Kinkade BS, A Jhaveri BS, J Lee BSN, S Hage MD, J Iqbal MBBS, S P Polster MD, R Shenkar PhD, R Girard PhD); **Department of Neurology, BIOS Clinical Trial Coordinating Center, Trial Innovation Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (K Treine BA, N McBee MPH, N Ostapkovich MS, K Lane CCRP, R E Thompson PhD, Prof D F Hanley MD); **Department of Medicine, University of Arizona, Tucson, AZ, USA** (Prof J K Liao MD); **Department of Medicine, University of Chicago Medicine and Biological Sciences, Chicago, IL, USA** (Prof M Sorrentino MD); **Alliance to Cure Cavernous Malformations, Charlottesville, VA, USA** (C Lee PsyD); **Department of Neurology, Mayo Clinic, Rochester, MN, USA** (Prof K D Flemming MD); **Department of Diagnostic Radiology, University of Chicago Medicine and Biological Sciences, Chicago, IL, USA** (Prof T J Carroll PhD)

Correspondence to: Prof Issam A Awad, Neurovascular Surgery Program, Department of Neurological Surgery, University of Chicago Medicine and Biological Sciences, Chicago, IL 60637, USA **iawad@uchicago.edu**

Introduction

Cerebral cavernous malformations (CCMs), also known as cavernous angiomas, are capillary-venous anomalies with dilated vascular spaces that affect about 1% of the population and are prone to repetitive bleeding.[1] CCMs manifesting symptomatic haemorrhage (ie, new bleeding on imaging studies and clinically attributable symptoms)[2] are rare, affecting fewer than 200 000 individuals in the USA, but they are much more likely to bleed again and to cause serious clinical sequelae than are CCMs without previous symptomatic haemorrhage. There is currently no treatment to prevent recurrent CCM bleeding, other than surgical resection or ablation, which could carry serious complications.[3,4] CCMs with symptomatic haemorrhage have thus been targeted for the development of novel therapies aimed at preventing rebleeding.[1,5]

Central to molecular mechanisms driving CCM development and bleeding[1] is Rho-associated protein kinase (ROCK) activation in endothelial cells, mediated by gene aberrations causing CCM genesis.[6] Sporadic and familial CCMs manifest endothelial ROCK activity not present in normal endothelium, and the inhibition of ROCK has been shown experimentally to restore

Research in context

Evidence before this study

Mechanistic and animal studies have suggested Rho-associated protein kinase (ROCK) inhibition could be a therapeutic target for cerebral cavernous malformations (CCMs), and atorvastatin at doses reaching pleotropic ROCK inhibition has been shown to decrease lesion growth and bleeding in mouse models of CCM. We searched PubMed for papers from database inception to Dec 2, 2024, with the terms ("statin" OR "atorvastatin") AND ("cavernous malformation" OR "CCM" OR "cavernoma" OR "cavernous angioma"). Human studies indicated clinical equipoise about whether this therapy effects CCM bleeding rate. In general, concerns have been raised about potentially increased brain bleeding with statins.

Added value of this study

To the best of our knowledge, our study is the first phase 1/2a randomised trial to assess ROCK inhibition with atorvastatin in people with CCMs and previous symptomatic haemorrhage. Our study incorporated a validated imaging biomarker of CCM haemorrhage, reflected by the mean change in lesional iron deposition per year, measured by quantitative susceptibility mapping (QSM) on MRI. A decrease in QSM change by a drug would signal potential benefit, and an increase would signal a safety concern.

Implications of all the available evidence

Our trial indicated no effect of atorvastatin compared with placebo on rebleeding in patients with CCMs who had had a symptomatic haemorrhage in the previous year. No safety concerns were noted. These results do not justify the use of atorvastatin to prevent CCM rebleeding. Drugs with stronger and more specific ROCK inhibition properties than atorvastatin might be needed to see a meaningful benefit.

endothelial integrity, which is disrupted in CCMs.[7] Atorvastatin at an oral daily dose of 80 mg causes ROCK inhibition in patients with atherosclerosis,[8] and equivalent doses in mice inhibited lesion growth and bleeding in CCM models, as did specific ROCK inhibitors.[9,10] Because atorvastatin is widely used and well tolerated clinically, its repurposing for the CCM indication is attractive. Yet, patients and clinicians continue to question whether atorvastatin is safe in patients after CCM bleeding, including concerns about pleiotropic effects;[11,12] a systematic review showed that there is equipoise around its clinical effectiveness (appendix pp 4, 17–19).

See Online for appendix

Designing a clinical trial in CCMs is challenging because of the number of participants who would be needed in such a rare disease to show an effect on symptomatic haemorrhage rates.[5] Lesional iron deposition (measured by quantitative susceptibility mapping [QSM] on MRI) and vascular permeability (measured by dynamic contrast enhanced quantitative perfusion [DCEQP]) have been shown to reflect new bleeding in previously stable CCMs.[13] A prospective multisite trial readiness study of CCMs with symptomatic haemorrhage in the previous year showed that two categorical threshold biomarker events (≥6% yearly increase in mean lesional QSM and ≥40% yearly increase in mean lesional DCEQP) were specific and more frequent than recurrent symptomatic haemorrhages.[14] Therefore, a drug effect on these imaging biomarkers can be observed with fewer patients than would be needed for an effect on the rate of symptomatic events.[1] Mean lesional QSM change per year has been accepted as a surrogate measure of potential drug effect on CCM bleeding by the US Food and Drug Administration.[15]

In view of the compelling biological rationale, clinical need, equipoise about the safety and potential efficacy of a commonly used drug, and the availability of mechanistically plausible and validated biomarkers, we designed an early-phase proof-of-concept trial (AT CASH EPOC). We aimed to investigate whether oral atorvastatin (80 mg daily for 2 years) might produce a difference compared with placebo in lesional iron deposition (as assessed by QSM) in CCMs with a documented symptomatic haemorrhage in the preceding year.[5] An increase in QSM change would signal a safety concern with the drug, and a decrease would signal potential benefit.

Methods

Study design

AT CASH EPOC was an investigator-initiated, single-centre, phase 1/2a, randomised, placebo-controlled, double-blinded, two-arm parallel assignment clinical trial done at the University of Chicago's CCM Center of Excellence. Ethics approval was granted by the University of Chicago Medicine Institutional Review Board (number 18-0445). Trial safety and data quality were monitored by the institutional review board, the Brain Injury Outcomes Section Clinical Trial Coordinating Center (BIOS CTCC) at Johns Hopkins Medical Institutions, and an independent medical safety monitor (appendix p 5). Data management was done by BIOS CTCC. The trial complied with US regulations and International Council for Harmonisation Good Clinical Practice guidelines. This trial is registered with ClinicalTrials.gov (NCT02603328).

Participants

Adults aged 18–80 years with untreated solitary or familial CCMs, who had experienced an adjudicated symptomatic haemorrhage from a CCM lesion within 1 year of trial enrolment, were eligible for the study. The symptomatic haemorrhage lesion must not have been resected or otherwise irradiated or ablated. Exclusion criteria included previous cranial irradiation or

radiosurgery and any statin use within the past year. A full list of inclusion and exclusion criteria is provided in the appendix (p 20). All participants gave written informed consent at the initial screening visit.

Randomisation and masking

Randomisation to active drug or placebo (1:1) was done at BIOS CTCC with a block algorithm, with stratification by sex. Allocation concealment was achieved using unlabelled indistinguishable capsules. Investigators, clinical staff, and participants were masked to the assigned treatment. The randomisation algorithm, treatment assignment process, and drug discontinuation criteria have been previously published,[5] and are detailed in the appendix (pp 4–5).

Procedures

Participants received either oral atorvastatin (80 mg per day) or matching placebo, to be taken once daily at a time of the patient's choosing. Drug or placebo were continued for 2 years or until a symptomatic haemorrhage or another safety event requiring drug discontinuation occurred.

Clinical, laboratory, and MRI evaluations were done at baseline, 12 months, and 24 months after randomisation; laboratory studies were also done 3 months after dose initiation. Functional status was assessed at each clinical visit with the Mini-Mental State Examination (MMSE), the National Institutes of Health Stroke Scale (NIHSS) score, and the modified Rankin scale (mRS) score. Quality of life was measured with Euro-QoL-5D, Euro-QoL visual analogue scale (VAS), and PROMIS-29 version 2.0. MRI was done with a 3T scanner with an eight-channel head coil. Details of imaging protocols have been published previously,[13,14] and are summarised in the appendix (p 6). Participants traveling more than 200 miles to the study centre for study evaluations received travel stipends.

Participants were contacted by telephone or electronic mail every 3 months to monitor drug compliance, adverse events, and to assess mRS. Drug compliance was also tracked with a mobile phone application that was completed by participants and monitored by the study team.

Outcomes

The primary outcome for both safety and efficacy was the percentage change in mean lesional QSM (change score) per year, as assessed on MRI. The MRI analysis was done on the index CCM lesion with qualifying symptomatic haemorrhage in the year before study enrolment. Secondary outcomes for potential efficacy were changes in vascular permeability, as measured by DCEQP in the index lesion and in brain white matter far from the lesion, and the proportion with QSM increase of 6% or greater, and with DCEQP increase of 40% or greater. Secondary outcomes for safety were rates of symptomatic haemorrhage (as per adjudicated criteria),[2] asymptomatic bleeding (ie, lesion expansion, defined as an increase in maximum lesion diameter on T2-weighted sequences of ≥3 mm or subclinical bleeding detected by MRI without attributable symptoms),[14,16] and any serious adverse events necessitating drug discontinuation. Other secondary outcomes were drug compliance (with a target of 90% or greater for protocol compliance, counted as number of days taking the drug per number of days in the study), changes in functional outcome measures (MMSE, mRS, and quality of life [Euro-QoL-5D, Euro-QoL VAS, and PROMIS-29]), and ROCK activity in peripheral blood leukocytes at each follow-up visit. For this report, we only present analyses of mRS scores and EuroQOL VAS, with plans to analyse the more extensive multiple domains of functional outcomes in a subsequent publication. Exploratory safety outcomes were serious adverse events and other adverse events. We also analysed non-fasting cholesterol levels (a known biological effect of atorvastatin) and vitamin D levels since these could affect CCM haemorrhage risk. We prespecified subgroup analyses of the primary outcome by sex, lesion location, and familial versus sporadic disease.

The safety assessment was prespecified to take place at the end of the first year, after 30 participants had completed 12 months of follow-up and again after 60 participants had completed 12 months of follow-up (appendix pp 5–6). The study's independent medical safety monitor had access to all adverse events as they occurred and to the treatment assignment of cases with adverse events (categorised as A or B without specifying which is placebo or atorvastatin). A protocol provision was made for pre-emptive suspension of trial enrolment for a full safety review if more than 40% of participants in a treatment group had a symptomatic brain haemorrhage from the index lesion or another source.

Statistical analysis

The trial was powered to detect a 20% relative difference in the percentage change of the mean lesional iron deposition (QSM change score) per year (two-tailed, power 0·9, alpha 0·05), with a sample size of 50 participants (which was expanded to 80 people to account for missing QSM data or patient attrition). The 20% effect size was proposed as a minimum to be clinically meaningful and mechanistically plausible (appendix pp 6–7). The initial sample size was calculated on the basis of a pilot study.[5] A futility analysis and sample size recalculation was done by the study's statistician when 50 paired biomarker assessments were successfully completed (ie, half the 100 assessments that were initially projected to be needed for testing the primary hypothesis). Futility criteria were not met, and the initial sample size was endorsed (appendix pp 8–9).

The primary outcome analysis was done as a time-averaged difference between two groups, using a

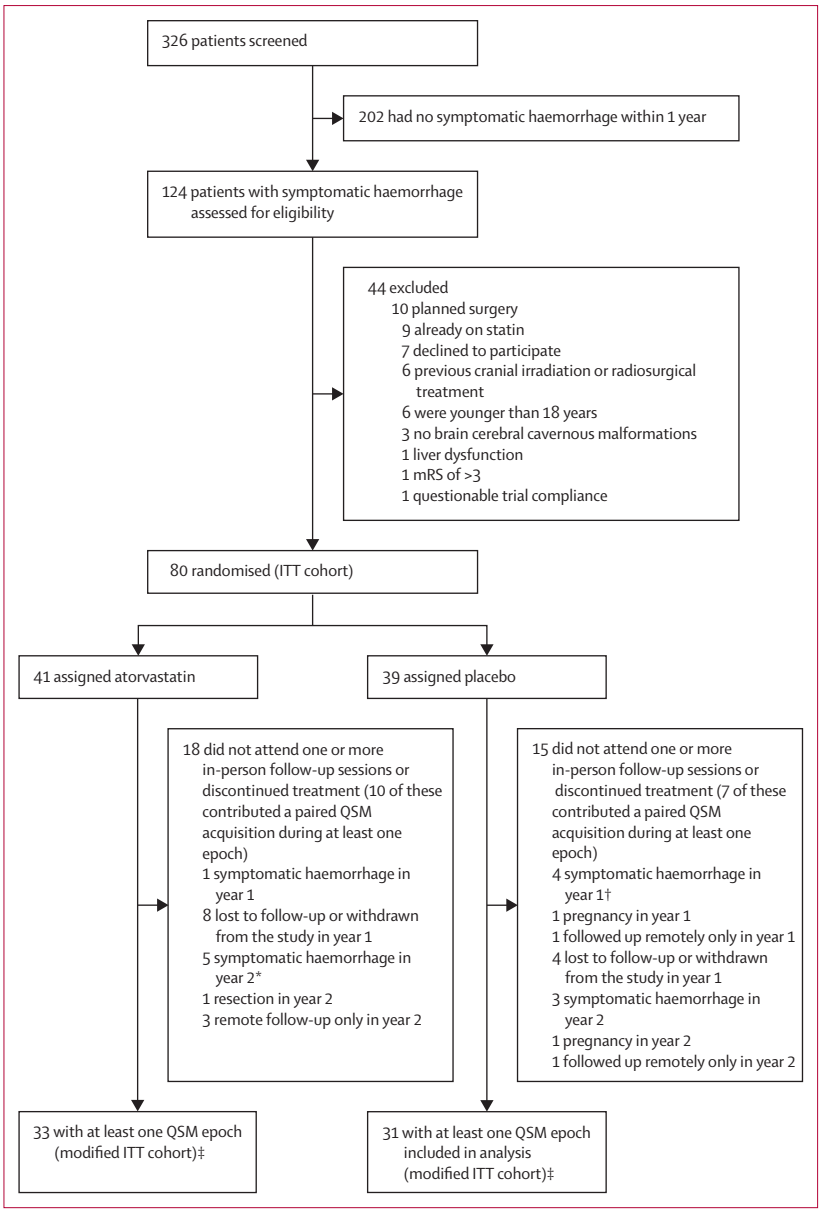

Figure 1: **Trial profile**
QSM=quantitative susceptibility mapping. mRS=modified Rankin score. ITT=intention to treat. *One patient had a symptomatic haemorrhage in year 2 after stopping the drug (atorvastatin) following a previous symptomatic haemorrhage in year 1. †One patient had a symptomatic haemorrhage before starting the study drug (placebo). ‡Modified ITT population met ≥90% active drug compliance.

repeated measures analysis implemented as a sex-adjusted linear mixed model, averaged over 2 years (appendix p 6).[17] Secondary analyses were done for QSM change during each year of follow-up. The same approach was used for the analysis of lesional vascular permeability change (measured by DCEQP) in the two study groups. Both the QSM change (primary outcome) and DCEQP change were analysed in the modified intention-to-treat (ITT) cohort, which comprised all participants who had paired biomarker assessments at the beginning and end of at least one annual epoch of follow-up. Safety outcomes (ie, bleeding rates and adverse events) and other secondary outcomes were evaluated in the overall trial cohort by the ITT principle. The time course of symptomatic haemorrhage was evaluated using Kaplan–Meier survival analysis, censoring cases who were lost to follow-up. An adjusted Poisson linear mixed model that controlled for sex was used to evaluate the difference in adverse event rates between the two treatment groups.

We compared, post-hoc, the features of participants who contributed at least one QSM paired annual data assessment (the modified ITT cohort) to those who did not. Because a few people with symptomatic haemorrhage did not contribute paired QSM assessments (ie, they either underwent surgery or declined follow-up), and these patients typically have a greater QSM change than do those without symptomatic haemorrhage, we implemented a secondary analysis with imputation of missing data for mean annual QSM change. The imputation approach was proposed as biologically and clinically relevant, after trial readiness analyses of the QSM biomarker in a similar CCM cohort.[14] Details of imputation method and analyses are reported in the appendix (pp 9, 25).

Point estimates and 95% CIs are reported for each analysis, with p values for the primary outcome. Continuous endpoints are presented by treatment groups as mean (SD) or median (IQR). Categorical endpoints are summarised by frequency in each category. Continuous variables are analysed using either the Student's *t* test for normally distributed data or the Mann–Whitney *U* test for non-normally distributed data. Categorical variables are assessed using the χ^2 test or Fisher's exact test, when appropriate. For the primary outcome, biased effects in prespecified subgroups by sex, lesion location, and solitary versus familial disease are queried using the χ^2 test. There was no allowance for multiplicity of variables queried. Statistical analyses were done with STATA-SE version 18.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 25, 2018, and July 22, 2022, 326 patients were assessed for eligibility, of whom 202 did not have a symptomatic haemorrhage in the previous year from the enrolment date and 44 met other exclusion criteria. 80 patients were randomly assigned to either atorvastatin (n=41) or placebo (n=39) and were included in ITT analyses of secondary and safety outcomes (figure 1). In year 1 of the study, five patients had a symptomatic haemorrhage, including one that occurred after randomisation but before starting the study (the patient was allowed to remain in the study). Furthermore,

one patient became pregnant and stopped the study drug, one patient participated in remote clinical follow-up without blood draws or imaging, and 12 patients withdrew from the study or contributed no follow-up. In year 2 of the study, eight patients had a symptomatic haemorrhage, one became pregnant, one withdrew from the study and underwent lesion resection, and four participated in remote clinical follow-up without blood draws or imaging. All these patients were excluded from the modified ITT analysis of the primary efficacy and safety outcome, because they did not have paired QSM measurements. Overall, 51 patients completed imaging biomarker acquisitions during two annual epochs (greater than the targeted number per sample size calculations to test the primary hypothesis), and 13 contributed a single annual epoch of paired biomarker acquisitions. Therefore, 64 patients were included in the primary (modified ITT) analysis, 33 who were assigned atorvastatin and 31 who were assigned placebo (figure 1).

Of the 80 patients enrolled in the trial, 54 (68%) were referred from further than 200 miles away from the study site. The median age of participants was 41 years (IQR 34–51), 51 (64%) were female, 13 (16%) were Hispanic or Latino, and eight (10%) were Black or African American. In 44 (55%) participants, the symptomatic haemorrhage lesion was in a brainstem location, 51 (64%) had a sporadic or solitary lesion, and 29 (36%) had familial or multifocal CCMs. Baseline demographic and clinical characteristics were well balanced between the two groups (table 1; appendix pp 21, 23–24), except for the mRS score, which appeared to be higher in patients assigned atorvastatin compared with placebo. Use of vitamin D, sex hormones, and propranolol at baseline did not differ between groups (appendix p 23).

Median follow-up of participants from trial enrolment until a safety endpoint, withdrawal from the study, or the final follow-up visit was 723 days (IQR 695–746). The last follow-up visit was logged on July 10, 2024. All but four trial participants had greater than 90% drug compliance. Four patients who did not meet this compliance threshold did not contribute to the biomarker assessments; one had symptomatic haemorrhage and three withdrew from the study in the first year (appendix p 10). One of these four patients had requested a dose reduction to 40 mg per day or placebo (while maintaining masked treatment assignment) before withdrawing from the study. All other patients in the trial, including the cases who contributed paired QSM assessments, continued per their assigned treatment and original dose with more than 90% compliance. Hence, there was no need for a separate analysis of the primary outcome per treatment received. No demographic or clinical differences were noted between patients who contributed paired QSM assessments and those who did not, except for a greater likelihood that men and active smokers would not attend follow-up (appendix pp 23–24).

	Total (n=80)	Atorvastatin (n=41)	Placebo (n=39)
Age, years	41 (34–51)	39 (34–54)	41 (34–49)
Sex			
Male	29 (36%)	15 (37%)	14 (36%)
Female	51 (64%)	26 (63%)	25 (64%)
Ethnicity, self-designated			
Hispanic or Latino	13 (16%)	6 (15%)	7 (18%)
Not Hispanic or Latino	65 (81%)	34 (83%)	31 (79%)
Unknown	2 (3%)	1 (2%)	1 (3%)
Race, self-designated			
Asian	2 (3%)	1 (2%)	1 (3%)
Black or African American	8 (10%)	6 (15%)	2 (5%)
White	63 (79%)	32 (78%)	31 (79%)
Other	5 (6%)	2 (5%)	3 (8%)
Unknown	2 (3%)	0	2 (5%)
Genotype			
Sporadic or solitary	51 (64%)	23 (56%)	28 (72%)
Familial or multifocal	29 (36%)	18 (44%)	11 (28%)
MRI characteristics			
Number of lesions on susceptibility weighted imaging in familial cases	1 (1–9)	1 (1–13)	1 (1–6)
Number of lesions on T2 ≥4 mm in familial cases	1 (1–3)	1 (1–5)	1 (1–1)
Size on T2, mm	14·80 (9·75–19·80)	14·70 (9·65–18)	16 (10–23·70)
Location of index CCM lesion with symptomatic haemorrhage			
Brainstem	44 (55%)	23 (56%)	21 (54%)
Cerebellum	4 (5%)	2 (5%)	2 (5%)
Frontal lobe	5 (6%)	3 (7%)	2 (5%)
Occipital lobe	4 (5%)	1 (2%)	3 (8%)
Parietal lobe	3 (4%)	1 (2%)	2 (5%)
Temporal lobe	8 (10%)	2 (5%)	6 (15%)
Thalamus	7 (9%)	5 (12%)	2 (5%)
Other location	5 (6%)	4 (10%)	1 (3%)
Time from most recent symptomatic haemorrhage to enrolment, days	104 (57–150)	103 (51–171)	104 (69–137)
Number of symptomatic haemorrhage before enrolment	1 (1–2)	1 (1–2·50)	1 (1–2)
Modified Rankin scale score			
0	14 (18%)	6 (15%)	8 (21%)
1	43 (54%)	18 (44%)	25 (64%)
2–3	23 (29%)	17 (42%)	6 (15%)
4	0	0	0
5–6	0	0	0
European quality of life index Visual Analog Scale	76·4 (14·7)	74·59 (16·29)	78·28 (12·67)

Data are median (IQR), n (%), or mean (SD). CCM=cerebral cavernous malformation.

Table 1: **Baseline demographic and clinical characteristics of the intention-to-treat cohort**

No difference was recorded between atorvastatin and placebo in the primary outcome of mean percentage change in lesional iron deposition per year (QSM change score, 10·88 [SE 7·29] *vs* 12·09 [7·54]; treatment effect –1·22, 95% CI –22·25 to 19·81; p=0·91; table 2). Furthermore, there was no difference in mean QSM change in years 1 or 2 (figure 2), or when analyses

	Atorvastatin (n=33)	Placebo (n=31)	Treatment effect (atorvastatin–placebo; 95% CI)
QSM change score averaged over both epochs	10·88 (7·29)	12·09 (7·54)	–1·22 (–22·25 to 19·81); –10%; p=0·91*
QSM change score by assigned treatment; year 1 minus baseline	7·35 (9·77)	0·24 (10·08)	7·12 (–20·38 to 34·62)
QSM change score by assigned treatment; year 2 minus year 1	15·18 (10·80)	26·80 (11·22)	–11·62 (–42·14 to 18·91)
Absolute QSM change by assigned treatment; year 1 minus baseline	0·00 (0·04)	–0·06 (0·04)	0·06 (–0·05 to 0·18)
Absolute QSM change by assigned treatment; year 2 minus year 1	0·06 (0·04)	0·08 (0·05)	–0·02 (–0·15 to 0·11)

Data are point estimate (SE), unless otherwise stated. All analyses are based on a mixed model, adjusted for sex. The treatment effect represents the difference in the percentage change or absolute change in reference to placebo (negative reflects smaller change than placebo, and positive reflects greater change than placebo). No differences were statistically significant. QSM=quantitative susceptibility mapping. *Relative effect and p value are presented for the prespecified primary outcome.

Table 2: **Percentage change in mean lesional iron deposition per year (QSM score) according to assigned treatment (modified intention-to-treat cohort)**

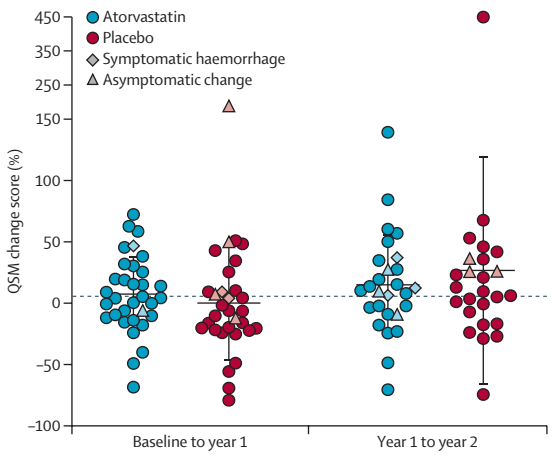

Figure 2: **Percentage change in mean lesional iron depossition per year (QSM score) during the first and second year, per assigned treatment (modified ITT cohort)**

Five of six symptomatic haemorrhages with paired QSM imaging had a QSM change score higher than 6%, which is the threshold associated with new bleeding. One statistical outlier value (>2 SD) was identified in the placebo group in each epoch, the first of which had an asymptomatic change identified at year 1 clinical MRI imaging, and subsequently had symptomatic haemorrhage in year 2. QSM=quantitative susceptibility mapping.

considered relative or absolute changes (table 2). Prespecified analyses of the QSM outcome in which missing QSM data were imputed also revealed no difference between atorvastatin and placebo (appendix p 25). Furthermore, no differences in the primary outcome were noted in prespecified subgroups (appendix pp 30–31).

No difference was recorded between atorvastatin and placebo in the secondary efficacy outcome of mean percentage change in vascular permeability per year (lesional DCEQP change score, 108·87 [SE 40·64] *vs* 59·09 [42·19]; treatment effect 49·77, 95% CI –71·41 to 170·96; appendix pp 11, 26). Furthermore, no difference was recorded in mean lesional DCEQP change in years 1 or 2 (appendix p 11), or when the analyses considered relative or absolute changes (appendix p 26). Vascular permeability of brain white matter far from lesions did not differ between groups (appendix pp 15–16). No differences in functional status (mRS score) or quality of life (Euro-QoL VAS) were noted at year 1 or 2 between atorvastatin and placebo (appendix p 27).

Prescribed safety reviews were done as planned (appendix p 5) and raised no concerns during the trial. Total bleed rates did not reach greater than 40% at any time, which would have suspended the trial, and no deaths were reported. Six patients assigned atorvastatin and seven assigned placebo had a symptomatic haemorrhage event, all of which occurred in the index CCM lesion (table 3). The time to symptomatic haemorrhage did not differ between patients allocated atorvastatin or placebo (figure 3). Furthermore, no differences were recorded between groups in rates of subclinical bleeds, assessed as asymptomatic change on MRI, mean lesional QSM change of 6% or more or mean lesional DCEQP of 40% or more (table 3). No serious adverse events necessitated discontinuation of treatment (table 4). Two serious adverse events were reported in patients receiving atorvastatin. One patient, a man aged 18 years, had elevated creatine kinase on laboratory tests, without overt symptoms. Per study protocol, he was given the option of stopping the drug temporarily then resuming a lower dose, but he decided to discontinue the drug. Another patient, a woman aged 59 years, was hospitalised after a fall, adjudicated as having a questionable relationship to the study drug. She continued taking the drug without further events and completed the trial. Adverse events were reported by 27 patients on atorvastatin and 21 patients on placebo, which were significantly more common in patients treated with atorvastatin by Poisson regression analysis. Adverse events per organ system class are reported in the appendix (pp 28–29).

Total cholesterol levels were significantly lower in patients receiving atorvastatin at years 1 and 2 of the study (appendix p 12). Vitamin D levels were not different in atorvastatin and placebo patients at years 1 and 2 (appendix p 22). Peripheral leukocyte ROCK activity and its change from baseline in individual patients in years 1 and 2 did not differ between groups (appendix pp 13–14).

Discussion

Our trial provides new evidence about the safety of atorvastatin in CCMs with recent symptomatic haemorrhage. Atorvastatin had no effect on biomarkers, rates of symptomatic haemorrhage, and subclinical bleeding rates, and there was no other suggestion of increased bleeding risk or serious adverse events requiring drug discontinuation, compared with placebo. This relevant clinical result addresses a knowledge gap

about the risk of atorvastatin in patients with CCMs, even after a recent bleed, and allays concerns previously raised in this regard.[11,12] Adverse events were no more frequent in participants taking atorvastatin than in those taking placebo, but the number of adverse events per patient were more common with atorvastatin. These events were mostly mild or non-specific. Two serious adverse events not requiring permanent drug discontinuation per protocol occurred in the atorvastatin group, and one patient withdrew from the trial after this event. The rate of adverse events in our study was greater than in clinical trials of patients with atherosclerosis, in whom events occurred almost equally with atorvastatin and placebo.[18] The more prevalent symptoms might represent a greater sensitivity of younger patients with CCMs to atorvastatin. As with other large clinical trials of patients with atherosclerosis, adverse events in our study had no lasting morbidity.

Our trial did not endorse a hypothesised benefit of atorvastatin with respect to lesional bleeding, as has been shown in animal studies. Studies in animal models showed decreased CCM lesion development as well as bleeding with atorvastatin,[9,10] but did not assess recurrent bleeding after a previous haemorrhage per se and, hence, might not have simulated recurrent bleeding in patients. Our trial did not examine a time course long enough to query lesion development, as was done in animal models. The lower rate of symptomatic haemorrhage in patients receiving atorvastatin in year 1 of our study (a quarter the rate in patients receiving atorvastatin than placebo) would have suggested a benefit based on the 80% CI method (80% CI 0·06–0·87)[19] advocated in another exploratory CCM trial of propranolol.[20] Yet, we had cautioned about the credulity of overinterpreting such results in the absence of sufficient statistical power.[21] With small event rates, a single symptomatic haemorrhage or its slightly different timing would eliminate the apparent difference, and such differences are virtually never replicated in studies with larger sample sizes. Analysis of the symptomatic haemorrhage-free survival curves, effect on biomarkers, and rates of subclinical bleeding did not endorse such benefit. It is possible that a bleeding benefit was merely too weak (a point estimate about half of the 20% postulated effect), but the clinical benefits of such weak effect would need further investigation. We also cannot exclude a potential synergistic benefit of atorvastatin in combination with other therapies.

The absence of postulated benefit of atorvastatin on recurrent bleeding in CCMs is consistent with evidence from previous cohort studies, suggesting a neutral effect (appendix pp 17–19). Several reasons could account for this absence of benefit of atorvastatin. The benefit of inhibition of ROCK activity by statins might be countered by pleiotropic depletion of other prenylation-dependent cellular processes that could increase bleeding.[12] In other research, lower cholesterol levels, as achieved with our patients on atorvastatin, were associated with greater

	Atorvastatin (n=41)	Placebo (n=39)	Absolute risk difference (95% CI)	Relative risk (95% CI)
Symptomatic haemorrhage, year 1	1 (2%)	4 (10%)*	0·08 (–0·07, 0·22)	0·24 (0·04, 1·50)
Symptomatic haemorrhage, year 2	5 (12%)†	3 (8%)	–0·05 (– 0·20, 0·12)	1·58 (0·45, 5·72)
Symptomatic haemorrhage total	6 (15%)	7 (18%)	0·03 (–0·15, 0·21)	0·81 (0·31 to 2·13)
Asymptomatic change, year 1	3 (7%)	4 (10%)	0·03 (–0·13 to 0·18)	0·71 (0·19 to 2·69)
Asymptomatic change, year 2	5 (12%)	3 (8%)	–0·05 (–0·20 to 0·12)	1·59 (0·45 to 5·73)
QSM ≥6%, year 1‡	15 (37%)	11 (28%)	–0·08 (–0·29 to 0·14)	1·30 (0·69 to 2·48)
QSM ≥6%, year 2‡	17 (41%)	14 (36%)	–0·06 (–0·27 to 0·17)	1·15 (0·67 to 2·02)
DCEQP ≥40%, year 1‡	15 (37%)	13 (33%)	–0·03 (–0·25 to 0·19)	1·10 (0·61 to 2·00)
DCEQP ≥40%, year 2‡	10 (24%)	7 (18%)	–0·06 (–0·25 to 0·13)	1·36 (0·59 to 3·17)
Symptomatic haemorrhage, asymptomatic change, QSM ≥6% or DCEQP ≥40%, year 1	24 (59%)	22 (56%)	–0·02 (–0·24 to 0·20)	1·04 (0·71 to 1·53)
Symptomatic haemorrhage, asymptomatic change, QSM ≥6% or DCEQP ≥40%, year 2	24 (59%)	20 (51%)	–0·07 (–0·29 to 0·16)	1·14 (0·77 to 1·73)

Data are n (%), unless otherwise stated. QSM used to measure mean lesional iron content. DCEQP used to measure mean lesional vascular permeability. QSM=quantitative susceptibility mapping. DCEQP=dynamic contrast quantitative perfusion. *One patient had symptomatic haemorrhage after being randomly assigned to the placebo group but before starting the drug. †One patient in the atorvastatin group who stopped the drug due to a symptomatic haemorrhage in year 1 and had a recurrent symptomatic haemorrhage from the same index lesion in year 2. ‡Cases with QSM or DCEQP change in index symptomatic lesion.

Table 3: **Clinical and subclinical bleeds and rate of biomarker changes during the study, according to assigned treatment (intention-to-treat cohort)**

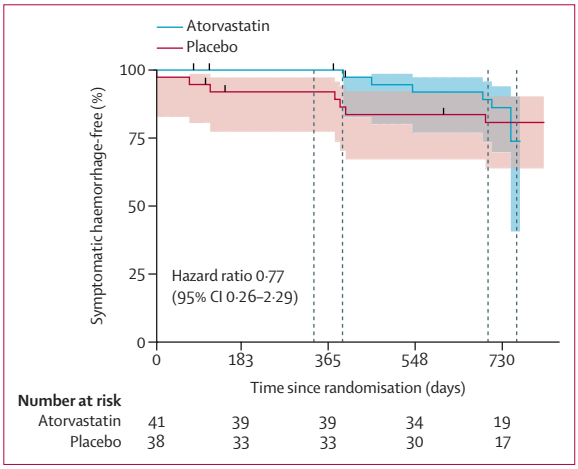

Figure 3: **Kaplan–Meier survival estimates showing time to symptomatic haemorrhage (ITT cohort)**

Six symptomatic haemorrhage events occurred in five patients assigned to the atorvastatin treatment versus seven symptomatic haemorrhage events in seven patients assigned to the placebo group. One patient in the placebo group had a symptomatic haemorrhage after enrolment but before starting the drug, with the bleed counted as day zero in the ITT cohort. Another patient in the atorvastatin group had a symptomatic haemorrhage identified at the year 1 clinic visit and stopped the drug, and who had a recurrent symptomatic haemorrhage from the same index lesion 2 months after; this was counted in the atorvastatin group for the ITT analysis. There were seven censored observations due to patients lost to follow-up, noted as vertical dashes, with the censored date as the last date of logged follow-up. Years 1 and 2 follow-up visits were planned at 360 and 730 days (plus or minus 30 days), respectively, from the date of enrolment (patients completed the study as early as 700 days after enrolment, hence fewer numbers of patients at risk after 730 days). The log-rank test revealed non-significant differences between the treatment groups in the rate and time to symptomatic haemorrhage. ITT=intention to treat.

	Atorvastatin (n=41)	Placebo (n=39)	Absolute risk difference (95% CI)	Relative risk (95% CI)
Deaths	0	0	0	0
Serious adverse events requiring discontinuation of drug	0	0	0	0
Patients with other serious adverse events	2	0	−0·05 (−0·18 to 0·07)	Not calculable
Patients with adverse events	27	21	−0·12 (−0·33 to 0·11)	1·22 (0·85 to 1·80)
Patient adverse events by Poisson regression*	27	21	0·79 (0·30 to 1·28)†	0·53 (0·35 to 0·80)‡

Data are n, unless otherwise stated. NA=not applicable. *Poisson regression considered the number of adverse events as well as the number of patients reporting them. †Absolute risk difference was obtained using a generalised linear model with a Poisson distribution and an identity link. ‡Placebo *vs* atorvastatin.

Table 4: **Serious adverse events and adverse events, according to assigned treatment (intention-to-treat cohort)**

clinical aggressiveness of CCMs, including greater haemorrhagic events.[22] A more targeted ROCK inhibitor, several of which are in development, might have a greater benefit in the absence of such pleiotropic effects.[23]

When considering the subgroup analyses by sex, lesion location, and lesion type (familial or sporadic), no significant effect was noted on the primary outcome. However, any observations would have been merely hypothesis-generating, because our trial was not powered to detect significance in these subgroups. Future trials might consider stratifying for these subgroups and the use of adaptive designs to drop subgroups without benefit.

In the subgroup analysis by sex, a non-significant decrease in the point estimate of the primary outcome was noted with atorvastatin in men, but not women. Although this finding should be interpreted cautiously, it is consistent with observations in other studies, which postulated there could be sex-related differences in endothelial inflammation, and other mechanisms, with atorvastatin.[24,25] With more women enrolled in our study than men, it is possible that the fewer men had more aggressive lesions, and the more aggressive lesions could have been more responsive to atorvastatin, creating a preselection bias. Another preselection bias for more aggressive lesions could have accounted for a non-significant decrease in the primary outcome point estimate for lesions at the brainstem, but no other locations. Patients with CCM lesions with symptomatic haemorrhage at non-brainstem locations might have been more likely to opt for resection of their lesion, rather than enrol in the trial. Thus, patients with more aggressive lesions at the brainstem (for whom surgery would be more prohibitive) could have been more likely to enrol. The non-significant decrease in the primary outcome point estimate in sporadic, but not familial cases, could also have been biased by the greater prevalence of men among these cases.

Most participants in our study took vitamin D supplements, thereby preventing low systemic levels, and they avoided sex hormone therapy. These measures have been suggested to prevent CCM bleeding.[22,26,27] Lower rates of symptomatic haemorrhage in our trial than reported in previous studies[16] could imply that the medical care of our patients might have diluted potential added benefits of atorvastatin. If true, this would imply that simpler medical measures per good current clinical practice might by themselves lessen CCM rebleeding, and novel experimental therapies would need to do better.

Despite excellent treatment compliance, and low cholesterol levels, atorvastatin did not inhibit peripheral leukocyte ROCK activity, as had been shown in patients with atherosclerosis.[8] We used the same ROCK activity assay in our trial as had been used in the atherosclerosis trials, and the assays were conducted by the same principal investigator of those earlier studies. It is possible that older patients with atherosclerosis have a higher baseline ROCK activity in peripheral leukocytes, or are more prone to its inhibition by atorvastatin, than are patients without atherosclerosis, who are typically young.

In patients with familial CCM, who have systemic haploinsufficiency of genes that would be expected to increase vascular permeability, we could not replicate findings of cohort studies in which higher baseline permeability was noted in brain white matter.[28] However, a non-significant reduction in brain white matter vascular permeability from baseline in years 1 and 2 was shown in patients who received atorvastatin compared with placebo. This is consistent with mild ROCK inhibition by the drug in brain vasculature. ROCK activity within resected lesions receiving placebo or atorvastatin would have been interesting to explore, but there were too few resected lesions in study participants to test this hypothesis.

Our study was based on extensive mechanistic and preclinical investigations and benefited from previous characterisation of the clinical features of trial participants, event rate estimations, and biomarker validations in a trial readiness project.[14,16] We did not see an effect of atorvastatin on lesional vascular permeability (as measured by DCEQP) in our trial, which was not unexpected in view of the predicted poor performance of the DCEQP measure in trial simulations,[14] and we observed great variance of these measurements in our trial. Notwithstanding the negative results with atorvastatin, our study provides a conceptual framework for deploying a surrogate biomarker to increase the sensitivity of detecting therapeutic effects in a rare disease. The absence of effect on biomarkers also adds confidence, endorsing the lack of difference in clinical event rates. This approach can also be applied in comparing different doses and drug effects in platform trials.

Our study had some limitations. First, we enrolled patients who had had symptomatic haemorrhage in the previous year. A significant treatment effect would

probably not have been observed in patients with longer intervals since the most recent symptomatic haemorrhage, or those with non-symptomatic haemorrhage, because these patients would most likely have had lower rebleed rates. Second, our study was done at a single site, without multisite validation of imaging biomarkers. However, we instituted a nationwide outreach effort to enrol patients, through patient support organisations, and we provided a stipend to more than two-thirds of patients traveling for enrolment. More recently, the biomarkers deployed have been validated as reflecting CCM bleeding in multisite studies,[14] so future trials using them can be done at multiple sites. It is unclear if the results would have been different in a multisite trial and with different patient referral patterns. Third, the sample size was small, limiting the statistical power for secondary and exploratory outcomes. Fourth, we assessed the treatment effect over 2 years, but the persistent bleed risks (in the second year of our study and in recent trial readiness results) justify testing over that period.[14,16] We cannot speculate if a 1-year study with near double the number of patients would have yielded different results. Fifth, 64% of enrolled patients were women, and they were more likely to contribute complete biomarker data in the study, but we cannot speculate about any implications of this limitation. Finally, up to now, the imaging biomarker QSM has never been shown to be affected by a drug, and this finding will need to be explored with other pharmacotherapies. Novel plasma biomarkers might also reflect CCM haemorrhage.[29,30] Such biomarkers might enhance the assessment of drug effects in future trials, as dual criteria, in conjunction with imaging biomarkers.[31]

In conclusion, our results endorse no safety concerns with atorvastatin in patients with CCMs after recent symptomatic haemorrhage. However, we cannot recommend its use with the aim of preventing CCM rebleeding.

Contributors

IAA conceptualised the study, secured funding, and oversaw the project as principal investigator and trial co-chair. RJA-F did the trial results analyses, created data tables and figures, and wrote the first manuscript draft. AS, JL, KT, NM, NO, and KL participated in or oversaw clinical coordination, data collection, or monitoring. SK did the imaging biomarker analyses, and TJC and RG developed and oversaw the imaging biomarker analyses. AJ, SH, and JI assisted in data acquisition and analyses. JKL assisted in trial design and oversaw ROCK assays in peripheral leukocytes. MS oversaw drug adverse event interpretation and management. CL assisted in trial design and engagement of patient community. KDF served as an independent medical safety monitor and oversaw safety monitoring. RS, RG, and SPP assisted in protocol development, data analyses, and manuscript preparation. RET participated in study design, developed the statistical analysis plan, and did the interim analyses and final statistical analyses. DFH conceptualised the study design, oversaw the data management, participated in data analyses and interpretation, and served as trial co-chair. IAA, RJA-F, RET, and DFH directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the manuscript, and reviewed and provided input on the final manuscript, and they take responsibility for the decision to submit it for publication.

Declaration of interests

All authors reported receiving research funding from US federal government agencies, which presents no conflict of interests with this study. IAA is a consultant to Neurelis and Ovid, and has done medicolegal consulting. KDF has done consulting work for Ovid, Blue Orphan, and Recursion. SPP is a consultant to Guidepoint and Gerson Lehrman Group. DFH is a consultant to Neurelis, Synaptogenix–Neurotrop; is a board member and has stock options in Epiwatch; and has done medicolegal consulting.

Data sharing

As required by the National Institute for Neurological Disorders and Stroke for phase 2 studies, a complete de-identified dataset containing all variables collected in the trial and a data dictionary will be submitted to https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research/archived-clinical-research-datasets for data sharing within a timeframe to be agreed upon with National Institute for Neurological Disorders and Stroke Program Officer, ideally within 1 year of publication of the primary outcome paper.

Acknowledgments

This study was funded by the US National Institutes of Health's National Institute for Neurological Disorders and Stroke (R01NS107887). We thank Leslie Morrison and Kevin Whitehead for their work as external medical safety consultants; Nicholas Hobson for QSM and DCEQP protocol development; Kristina Piedad for assistance in clinical coordination; and Ying Wang for assistance in data management.

References

1 Snellings DA, Hong CC, Ren AA, et al. Cerebral cavernous malformation: from mechanism to therapy. *Circ Res* 2021; **129:** 195–215.
2 Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. *Stroke* 2008; **39:** 3222–30.
3 Moultrie F, Horne MA, Josephson CB, et al. Outcome after surgical or conservative management of cerebral cavernous malformations. *Neurology* 2014; **83:** 582–89.
4 Akers A, Al-Shahi Salman R, A Awad I, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. *Neurosurgery* 2017; **80:** 665–80.
5 Polster SP, Stadnik A, Akers AL, et al. Atorvastatin treatment of cavernous angiomas with symptomatic hemorrhage exploratory proof of concept (AT CASH EPOC) trial. *Neurosurgery* 2019; **85:** 843–53.
6 Ayata C, Kim H, Morrison L, et al. Role of Rho-associated kinase in the pathophysiology of cerebral cavernous malformations. *Neurol Genet* 2024; **10:** e200121.
7 Stockton RA, Shenkar R, Awad IA, Ginsberg MH. Cerebral cavernous malformations proteins inhibit Rho kinase to stabilize vascular integrity. *J Exp Med* 2010; **207:** 881–96.
8 Nohria A, Prsic A, Liu P-Y, et al. Statins inhibit Rho kinase activity in patients with atherosclerosis. *Atherosclerosis* 2009; **205:** 517–21.
9 Shenkar R, Shi C, Austin C, et al. RhoA kinase inhibition with fasudil versus simvastatin in murine models of cerebral cavernous malformations. *Stroke* 2017; **48:** 187–94.
10 Shenkar R, Peiper A, Pardo H, et al. Rho kinase inhibition blunts lesion development and hemorrhage in murine models of aggressive Pdcd10/Ccm3 disease. *Stroke* 2019; **50:** 738–44.
11 Gonzalez-Castellon MA, Marshall RS. Statin use and brain hemorrhage: real risk or unfounded fear? *JAMA Neurol* 2014; **71:** 1353–54.
12 Eisa-Beygi S, Wen X-Y, Macdonald RL. A call for rigorous study of statins in resolution of cerebral cavernous malformation pathology. *Stroke* 2014; **45:** 1859–61.
13 Girard R, Fam MD, Zeineddine HA, et al. Vascular permeability and iron deposition biomarkers in longitudinal follow-up of cerebral cavernous malformations. *J Neurosurg* 2017; **127:** 102–10.
14 Hage S, Kinkade S, Girard R, et al. Trial readiness of cavernous malformations with symptomatic hemorrhage, part II: biomarkers and trial modeling. *Stroke* 2024; **55:** 31–39.

15 US Food and Drug Administration. Drug development tool letter of intent determination letter DDT-BMQ-000127. Oct 20, 2023. https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=174 (accessed Feb 25, 2025).

16 Flemming KD, Kim H, Hage S, et al. Trial readiness of cavernous malformations with symptomatic hemorrhage, part I: event rates and clinical outcome. *Stroke* 2024; **55:** 22–30.

17 Varosanec M, Uher T, Horakova D, et al. Longitudinal mixed-effect model analysis of the association between global and tissue-specific brain atrophy and lesion accumulation in patients with clinically isolated syndrome. *AJNR Am J Neuroradiol* 2015; **36:** 1457–64.

18 Howard JP, Wood FA, Finegold JA, et al. Side effect patterns in a crossover trial of statin, placebo, and no treatment. *J Am Coll Cardiol* 2021; **78:** 1210–22.

19 Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *J Clin Epidemiol* 2013; **66:** 197–201.

20 Lanfranconi S, Scola E, Meessen JMTA, et al. Safety and efficacy of propranolol for treatment of familial cerebral cavernous malformations (Treat_CCM): a randomised, open-label, blinded-endpoint, phase 2 pilot trial. *Lancet Neurol* 2023; **22:** 35–44.

21 Shenkar R, Awad IA. Credulity of exploratory trials for cerebral cavernous malformations. *Lancet Neurol* 2023; **22:** 2–3.

22 Girard R, Khanna O, Shenkar R, et al. Peripheral plasma vitamin D and non-HDL cholesterol reflect the severity of cerebral cavernous malformation disease. *Biomark Med* 2016; **10:** 255–64.

23 McKerracher L, Shenkar R, Abbinanti M, et al. A brain-targeted orally available ROCK2 inhibitor benefits mild and aggressive cavernous angioma disease. *Transl Stroke Res* 2020; **11:** 365–76.

24 Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacol Res* 2007; **55:** 81–95.

25 Cangemi R, Romiti GF, Campolongo G, et al. Gender related differences in treatment and response to statins in primary and secondary cardiovascular prevention: the never-ending debate. *Pharmacol Res* 2017; **117:** 148–55.

26 Zuurbier SM, Santos AN, Flemming KD, et al. Female hormone therapy and risk of intracranial hemorrhage from cerebral cavernous malformations: a multicenter observational cohort study. *Neurology* 2023; **100:** e1673–79.

27 Previch L, Lanzino G, Brown RDJ Jr, Flemming KD. The influence of select medications on prospective hemorrhage risk in patients with spinal or cerebral cavernous malformations. *World Neurosurg* 2022; **163:** e678–83.

28 Mikati AG, Khanna O, Zhang L, et al. Vascular permeability in cerebral cavernous malformations. *J Cereb Blood Flow Metab* 2015; **35:** 1632–39.

29 Girard R, Li Y, Stadnik A, et al. A roadmap for developing plasma diagnostic and prognostic biomarkers of cerebral cavernous angioma with symptomatic hemorrhage (CASH). *Neurosurgery* 2021; **88:** 686–97.

30 Hage SF, Bi DE, Kinkade S, et al. Circulating molecules reflect imaging biomarkers of hemorrhage in cerebral cavernous malformations. *J Cereb Blood Flow Metab* 2025; published online Jan 20. https://doi.org/10.1177/0271678x251314366.

31 Zhao Y, Li D, Liu R, Yuan Y. Bayesian optimal phase II designs with dual-criterion decision making. *Pharm Stat* 2023; **22:** 605–18.