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Trial Readiness of Cavernous Malformations with Symptomatic Hemorrhage. Part I: Event Rates and Clinical Outcome

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Abstract

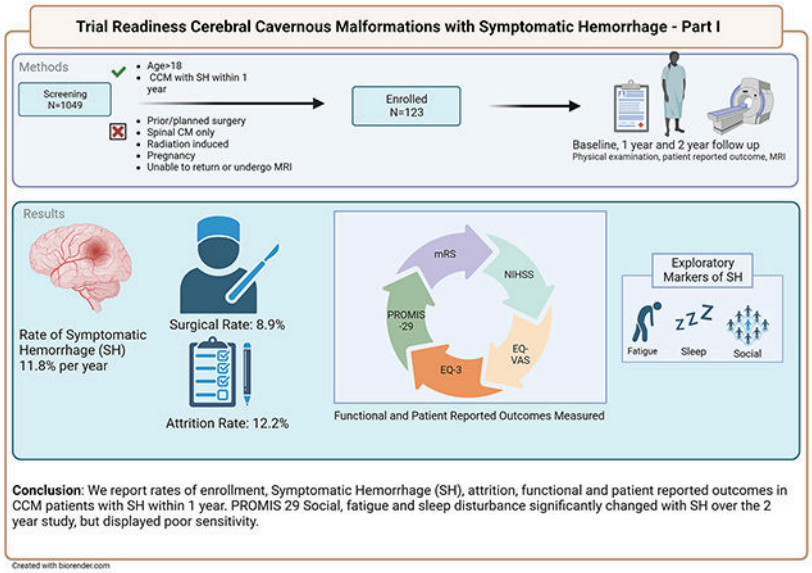
Background: Cerebral cavernous malformation (CCM) with symptomatic hemorrhage (SH) are targets for novel therapies. A multisite trial-readiness project (clinicaltrials.gov NCT03652181) aimed to identify clinical, imaging, and functional changes in these patients.

Methods: We enrolled adult CCM patients from 5 high-volume centers with SH within the prior year and no planned surgery. In addition to clinical and imaging review, we assessed baseline, 1-year and 2-year NIH-stroke scale (NIHSS), modified Rankin scale (mRS), Euro-QOL 5D-3L (EQ-5D-3L), and PROMIS-29. SH and asymptomatic change (AC) rates were adjudicated. Changes in functional scores were assessed as a marker for hemorrhage.

Results: 123, 102 and 69 patients completed baseline, 1- and 2-year clinical assessments respectively. There were 21 SH during 178.3 patient-years of follow-up (11.8% per patient year). At baseline, 62.6% and 95.1% of patients had a mRS 0-1 and NIHSS 0-4, respectively, which improved to 75.4 % (p=0.03) and 100% (p=0.06) at 2 years. At baseline, 74.8% had at least one abnormal PROMIS-29 domain compared to 61.2% at 2 years (p=0.004). The most common abnormal EQ-5D-3L domains were pain (48.7%), anxiety (41.5%), and participation in usual activities (41.4%). Patients with prospective SH were more likely than those without SH to display functional decline in sleep, fatigue, and social-function PROMIS-29 domains at 2 years. Other score changes did not differ significantly between groups at 2 years. The sensitivity of scores as an SH marker remained poor at the time interval assessed.

Conclusions: We report SH rate, functional and patient-reported outcomes (PRO) in trial-eligible CCM with SH patients. Functional outcomes and PRO generally improved over 2 years. No score change was highly sensitive or specific for SH and could not be used as a primary endpoint in a trial.

Graphical Abstract



Keywords

Trial Readiness; Cavernous Angioma; Cerebral Cavernous Malformation (CCM); Symptomatic Hemorrhage; patient-reported outcome; quality of life

Introduction

Cerebral cavernous malformations (CCM) are angiographically occult lesions formed by endothelial-lined caverns. They may occur sporadically, characterized by a solitary lesion often associated with a developmental venous anomaly (DVA) or be familial, characterized by multiple non-contiguous lesions without a DVA.[1]

CCMs may be detected incidentally, or patients may present with seizures, headache, or focal neurologic deficit with or without associated hemorrhage. Once a patient has symptomatic hemorrhage (SH), the risk of recurrence may reach 30% over 5 years and is associated with increasing morbidity.[1–3] Several candidate therapeutics have emerged target signaling aberrations related to loss of CCM gene function and associated vascular permeability, angiogenic activity, or inflammatory response.[4] There is clinical equipoise for testing novel therapies to prevent re-bleeding in CCM patients not undergoing surgical resection. While it clinically makes sense to use SH as a primary endpoint in such clinical trials, powering such a study would require ~800 patients per arm.[5] Given the low prevalence of SH, alternative endpoints are needed. Further knowledge of event outcomes in CCM patients with SH (CCM-SH) could also affect clinical-trial design.

The Trial Readiness project (clinicaltrials.gov NCT03652181) aimed to characterize CCM-SH patients who might participate in therapeutic clinical trials. The first major aim was quantifying prevalence, enrollment rates, and baseline characteristics of CCM-SH patients at multiple sites using a standard protocol (previously published[6]). The second aim was to evaluate utility of MRI biomarkers, an aim presented in the companion article. The third aim is to 1) assess eligibility, enrollment, and surgical cross-over rates in CCM-SH-eligible patients during ≤2-year follow-up; 2) determine prospective SH and asymptomatic change (AC) rates; 3) assess 2-year change in functional and patient-reported outcomes (PRO). Herein, we describe the methods and results for Aim 3.

Methods

Overview

This trial is an observational cohort study of adult CCM patients with SH in prior 1 year without planned intervention between 2017 and 2022 at 7 sites. All 7 sites contributed to screening and clinical assessment (SCA), which characterized baseline features of trial-eligible patients as previously reported.[6] Three sites enrolled patients in the follow-up biomarker-validation (FUBV) part of the study (Mayo Clinic, University of Chicago, University of New Mexico). Patients in the parallel Atorvastatin Treatment in Cavernous Angioma Symptomatic Hemorrhage-Exploratory Proof of Concept (AT-CASH-EPOC) Trial were enrolled at the University of Chicago.[7] Due to slow enrollment and the pandemic, 2 sites initially enrolling baseline-only patients started enrolling FUBV patients during years

3 and 4 (Johns Hopkins University, University of California-San Francisco). De-identified data from this trial will be made available to qualified investigators upon request to the BIOS Clinical Trials Coordinating Center at the Johns Hopkins University School of Medicine Department of Neurology.

Inclusion/Exclusion Criteria

Eligible patients were (1) ≥18 years of age, (2) diagnosed with a brain CCM (single or multiple), and (3) SH within the past year.

Excluded patients had (1) SH of spinal CM, (2) prior brain irradiation, (3) prior or planned surgical treatment, or if (4) SH imaging-review verification could not be accomplished. Additional exclusion criteria included 1) contraindication to MRI contrast or unwillingness/unable to undergo MRI, (2) pregnancy or breastfeeding, (3) homelessness or incarceration, or (4) unlikely to return for follow-up.

Screening and Enrollment

Five sites screened and enrolled FUBV patients. Enrolled cases underwent baseline in-person visits and follow-up visits at 1 year±1 month and 2 years±1 month. Due to the pandemic, virtual follow-up visits were allowed.

Baseline Clinical, MRI, Functional and Patient-reported Outcome

Baseline demographics and type of CCM (familial versus sporadic) were recorded. Patients were regarded as having familial form if they had a suggestive MRI, a known genotype, or a family history.[1] Qualifying SH events were verified and history of previous SH noted. Relevant medical history ascertained included hypertension, diabetes, tobacco, alcohol use, obstructive sleep apnea at diagnosis. We recorded all medications and specifically assessed vitamin D-supplement use, contraceptives, statin, and propranolol. We also recorded blood pressure, height, and weight.

A credentialed provider administered the modified Rankin scale (mRS) and National Institutes of Health Stroke Scale (NIHSS). PRO included PROMIS-29 (patient-reported outcome-measurement information system, version 2.0), EuroQOL-5D-3L, and EuroQol VAS (visual analogue scale). These scores were selected based on ease of administration and prior studies of stroke and/or cavernous malformation outcome.[6] The mRS is a simple global measure of functional disability. Scores range from 0 (no symptoms) to 6 (death). An mRS score of 0-1 is considered minimal clinical disability and 0-2 as independent.[8] NIHSS values range from 0 to 42, with stroke severity categorized as mild (0–4), moderate (5–14), severe (15–24), and very severe (≥25).[9] A 4-point decline in ischemic-stroke clinical trials typically measures functional decline.[10] EQ-5D-3L includes 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[11] There are 3 questions per domain where patients respond if they have no problems, mild, or severe problems. In a visual-analogue scale, patients select how they perceive their current health on a 0-100 scale. PROMIS-29 (version 2.0) is a generic health-related quality-of-life measure including 7 domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities).[12] Each domain contains

questions ranked using a 5-point Likert scale. PROMIS-29 domain scores are converted to T scores and have been standardized to a reference population (mean 50, SD 10). Clinically meaningful change is considered to be at least half the standard deviation (5 points).

The qualifying SH was verified on clinical MRI and the location and pattern (familial vs. sporadic) recorded. Patients underwent a baseline MRI scan (3 Tesla field strength with eight-channel head coil) with standard T1, T2, FLAIR sequences in addition to quantitative-susceptibility mapping (QSM) and dynamic, contrast-enhanced quantitative permeability (DCEQP).[5] The baseline maximum diameter was measured on axial, T2 sequences. The companion article discusses results of the MRI biomarker study (QSM and DCEQP).

Follow-up Clinical, MRI, and Functional and Patient-reported Outcome

Patients at 1- and 2-year follow-up underwent reassessment of clinical symptoms, medical history, and medications. Blood pressure, height, and weight were repeated. MRI brain, NIHSS, mRS, PROMIS-29 and Euro-QOL measures were also repeated. The University of Chicago adjudicated SH based on standard guidelines [13] and asymptomatic change (AC; growth ≥3mm or hemorrhage without symptoms).[14]

Patients were removed from the study if they completed 2-year final follow-up, underwent surgery of SH lesion, were lost to follow-up or withdrew, or by November 1, 2022 (end of 5-year grant). Patients with SH during an epoch and failing to complete follow-up visit at the end of the epoch were considered SH, within a fraction year of follow-up when calculating SH rates.

Oversight and Compliance

A Central Institutional Review Board provided oversight and approval. Research staff at Johns Hopkins performed data-monitoring and quality reviews; the University of Chicago research staff provided outcome adjudication. Patients provided written informed consent for the use of their medical information.

Statistical Analysis

Frequencies, means, and medians were used to report demographic, clinical, and MRI variables. The prospective-hemorrhage rate was calculated by the number of hemorrhages divided by the patient years of follow-up, and Kaplan-Meier survival curve analysis assessed hemorrhage-free survival. Patients were censored at last follow-up, 2-year visit, or surgical removal of the CASH lesion. Predictors of prospective hemorrhage were evaluated by Cox proportional hazards-regression analysis. We report hazard ratios (HRs), 95% confidence intervals (CIs), and likelihood ratio *P* values. *P* values <0.05 were considered statistically significant.

Frequencies, means, medians and proportions were used to report NIHSS, mRS, and Euro-QOL VAS, PROMIS 29 and Euro-QOL domains. The change in baseline year 1 (Epoch 1), year 1 to year 2 (Epoch 2) and baseline to 2 years was calculated with one sample t-test with $p<0.05$ considered significant.

We compared the proportions of patients with functional decline in each scale or score in Epochs 1 and 2 and baseline to 2 years in those with and without SH during the same epoch with Chi-square or Fisher's exact test as appropriate (p value <0.05 statistically significant). Patients with missing data were not imputed into the calculation. The sensitivity and specificity of each score as an SH marker were calculated. The same calculations were repeated comparing those with any hemorrhage (symptomatic or asymptomatic) versus no hemorrhage. Decline was considered a 4-point functional decline of NIHSS, a 1-point functional decline in EQ-5 domains, a 10-point functional decline in EQ-VAS, and a 5-point functional decline in PROMIS-29 . For mRS, we compared those with and without SH who had mRS 2 or higher using Chi square or Fisher's exact test as appropriate (p value <0.05 statistically significant).

Reporting Guidelines

This study followed the STROBE reporting guidelines.[15]

Results

Screening and Enrollment

Of 1049 patients screened, 144 were eligible and 123 enrolled (63 concomitantly enrolled in AT-CASH-EPOC trial) **(**Figure 1**).** The overall proportion of eligible screened patients was 13.7%. The most common reason for exclusion was no SH in the preceding year. The proportion of enrolled, eligible patients was 85.4%. Patients were enrolled an average of 114.0 days post-qualifying SH event.

Baseline FUBV characteristics

Average enrollment age was 43.9 +/−15.3 years with a slight predominance of females (61.0%). Most had sporadic CCM, but 48 (39.0%) had familial form (*CCM 1* = 21, *CCM2*=7, *CCM3*=6; Unknown=14). Table 1 displays the baseline characteristics of this cohort**.** Brainstem was the most common location in patients enrolled (40.7%).

Follow-up, Outcomes, and Attrition

Supplemental Figure 1 and Supplemental Table 1 display baseline, year-1, and year-2 completion rates of the clinical visit, MRI, functional, PRO, and reasons for attrition. At baseline, 123 patients completed clinical, functional, and PRO, and 122 completed a baseline MRI. A total of 102 patients completed year-1 visit. In Epoch 1, 5 patients underwent surgery, 12 withdrew or were lost to follow-up, 1 became pregnant, 1 skipped year 1 but completed baseline and year-2 visits, and 2 did not reach year 1 before the grant ended. In Epoch 1, 10 patients had SH and 10 had AC for a total of 20 individual patients with either SH or AC.

A total of 69 patients completed year-2 (Supplemental Figure 1 and Supplemental Table 1). In Epoch 2, 6 patients underwent surgery, 2 withdrew or were lost to follow-up, 1 became pregnant , and 24 did not reach year 2 before the grant ended. Epoch 2 had 11 SH and 4 AC. No SH patients in Epoch 2 had SH in Epoch 1. Two patients with SH in Epoch 2 had AC in Epoch 1. Therefore, a total of 15 individual patients had either SH *or* AC in Epoch 2,

and 33 individual patients had either SH or AC over 2 years. Supplemental Table 2 shows characteristics of those completing the trial versus those lost to follow up or withdrew from the study.

Symptomatic Hemorrhage Rate, Surgical Cross over, and Predictors of Hemorrhage

There were 10 SH in Epoch 1 over 110.2 patient-years (9.1%) and 11 SH in Epoch 2 over 68.1 patient years (16.1%). The overall SH rate during the entire study was 11.8% per patient year. The average time from baseline visit to prospective SH was 501 days (Range 6-764). Supplemental Figure 2 shows a Kaplan-Meier curve of hemorrhage-free survival by brainstem location versus non-brainstem location (log rank; p=0.8). Thirty-three individuals had either AC or SH during the entire study (18.5% per patient year).

Females accounted for 12 (57.1%) of prospective SH (Supplemental Table 3). Most experienced SH in the same location as the initial SH-qualifying event, but two had a prospective SH in a second lesion.

Supplemental Table 4 displays the Cox proportional-hazard analysis assessing baseline characteristics as predictors of prospective SH. Brainstem location did not predict prospective SH (42.8% SH vs 40.2% no SH; p=0.8). No baseline clinical feature predicted prospective SH.

Eleven patients underwent surgery during the study (7 female; 4 male). All patients with surgery in Epoch 1 had SH in epoch 1. In Epoch 2, 6 patients underwent surgery (3 patients with SH in Epoch 2,1 patient with SH in Epoch 1, 1 patient with AC on 1 year MRI and 1 patient with worsening seizure without MRI change).

Provider-administrated scales/scores

Modified Rankin Scale (mRS).—Figure 2a and Supplemental Table 5 show the proportions of patients with mRS 0-1, 2, 3, 4-5. Most were minimally affected by SH at enrollment (62.6% mRS 0-1). Over 2 years, the proportion of patients with mRS 0-1 improved to 72.6% at year 1 and 75.4% at year 2.

National Institutes of Health Stroke Scale (NIHSS).—The proportion of patients with NIHSS 0-4, 5-14 , 15-24 and 25 or more are displayed in Figure 2a and Supplemental Table 5. Median NIHSS was 0 at baseline (range: 0-15). At baseline, 95.1% had NIHSS 0-4. Median NIHSS remained 0 at year-1 (range 0-9) and year-2 (range 0-6); the proportion with NIHSS 0-4 was 100% at year 2 without significant change over time.

Patient-reported Outcomes

EQ-VAS Score.—Median EQ-VAS at baseline was 80 (range 9-100). Over half (52.9%) reported scores ≥80. Median score remained at 80 at 1 (range 30-100) and 2 years (range 35-100) with significant improvement in the EQ-VAS score during Epoch 1 (p=0.02).

EQ-3D-5L.—Figure 2b and Supplemental Table 5 display the proportion of patients in each domain with no, mild, or severe problems. The most affected (mild or severe) domains at baseline included pain (48.8%), usual activities (41.4%), and anxiety/depression (41.5%).

Each domain showed overall improvements from baseline to year-2 visit; pain-score changes reached statistical significance (p=0.02). EQ mobility and self-care remained stable across time.

PROMIS-29.—48.8 % of patients had at least 1 abnormal PROMIS 29 domain (1.0 SD) at baseline compared to 48.1% and 29.8% at 1- and 2-year visits, respectively (Year 2–baseline visit; p=0.04). Figure 3 shows the median T scores and proportion of patients with mild (0.5 SD or worse) and moderate-severe (1 SD or worse) PROMIS-29 domain at baseline, year 1, and year 2. Compared to baseline, social function, anxiety, and pain domains showed significant improvement over 2 years (p=0.004, p=0.03; p=0.04), and fatigue showed a trend (p=0.05).

Functional Scales/Scores as a Marker for Symptomatic Hemorrhage

We assessed a functional decline in scores as a marker for SH in each epoch and over the 2 year study. Table 2 show comparison data, p values, sensitivities, and specificities for each measure There was no significant differences in mRS in those with or without SH. The sensitivity of mRS as an SH marker was poor (20.0-28.6%) and specificity poor (72.6-75.8%). When assessing the combined endpoint of SH *or* AC, mRS also demonstrated poor sensitivity and specificity (Supplemental Table 6**)**.

No patient had a 4-point decline in NIHSS at the 1- or 2-year visit with or without SH. A 10-point decline on EQ-VAS occurred more frequently in patients with SH than without in the first epoch (80.0% SH versus 15.9% without SH, p=0.004). However, no significant change appeared in epoch 2 or the overall study. A 10-point decline on EQ-VAS demonstrated poor sensitivity (22.2-80.0%) and moderate specificity (82.8-84.0%) as a marker for SH.

During the first epoch, a 1-point functional decline in EQ-activity and anxiety/depression scores were more commonly seen in those with SH than without (Table 2). No significant changes appeared in these domains in Epoch 2 nor in the overall study. Overall, EQ domains had very poor sensitivity for SH or the combined SH/AC endpoint (Supplemental Table 6). Specificity was >90% for ≥1 epochs in each domain. However, this was because very few patients in either group experienced a functional decline in EQ domains.

A ≥5-point changed score in an unfavorable direction in each PROMIS-29 domain at 1 and 2 years was compared in those with and without SH and presented in Table 3. Functional declines in fatigue (55.6% SH vs 17.2% without SH; p0.02), sleep (55.6% SH vs. 5.2% without SH; p=0.0006), and social function (44.4% SH vs. 12.1% without SH, p=0.03) were more commonly and significantly associated with SH but only over the entire timeframe of the study (year 2 to baseline visit). Sensitivity was poor for all PROMIS domains. Specificity was highest for functional decline in the sleep-disturbance domain (94.8%).

Combining SH and AC as an endpoint, the PROMIS-29 fatigue, sleep, and social domains continue to demonstrate more patients with reduced scores (≥5 points) in the hemorrhage group than in the non-hemorrhage group but only over the course of 2 years **(**Supplemental Table 7**).** In addition, more patients with any hemorrhage demonstrate a decline in physical domain (47.1% hemorrhage group vs. 10.0% non-hemorrhage group; p=0.002).

Discussion

This is the first study to prospectively assesses hemorrhage rates in CCM-SH patients, compare functional and PRO, and assesses their utility as markers for SH. For future trial planning, we also provide the proportion of trial-eligible patients, surgical crossover and lost to follow up rates**.**

Fortunately, SH is rare in CCM patients. Due to a 13.7% eligibility rate at 7 high-volume centers, future clinical trials need multiple sites and secondary markers for SH to be feasible. In this study, 11 (8.9%) patients crossed over to surgery primarily due to recurrent SH, and 12.2% were lost to follow-up. Future trials should factor in these data when estimating numbers for screening and enrollment.

Recurrent SH risk in this study is similar to published natural-history studies,[2,16,17] although the risk did not plateau or decline. Natural-history studies often show declining hemorrhage risk after ≤3 years.[2] Natural-history studies generally use an inception point of CCM diagnosis, whereas this study used an inception point of any SH event, which may have been a second or third SH event. Thus, rates of recurrent hemorrhage from initial diagnosis versus from any CCM-SH may differ. Indeed, Santos and colleagues[3] suggest the risk of a third hemorrhage increases after a second with increasing morbidity. Patients in this study were enrolled an average of 114 days after qualifying event. Therefore, patients with CCM-SH and early (≤1 month) recurrent hemorrhage may have had surgery and were thus not enrolled in this study. Despite most patients having a brainstem CCM, brainstem location did not predict future hemorrhage in this cohort. This study may have been too small to see the effect of location, or brainstem location may have predisposed to the initial SH but not rebleeding.

Some have suggested using functional outcome or PRO for CCM drug trials. Only limited data exist on functional outcome and PRO after CCM-SH without surgery in patients with mRS most commonly used. However, many studies retrospectively assign the score and/or are assigned by untrained personnel with limited longitudinal data. PRO data are even more limited; most studies report on surgical patients only[18,19] or cross-sectional evaluations viewing patients at single points in time.[6,20] Our study demonstrates that CCM-SH and no further bleeding improve functionally and in many PRO domains over 2 years. While changes in PROMIS-29 sleep, fatigue, and social function domains were significantly more common in those with SH than those without over the duration of the study, the sensitivity and specificity of these outcomes are insufficient to substitute as an endpoint for SH.

This study aimed to assess the utility of functional and PRO scores within a clinical-trial setting, not to validate these scores as clinical-outcome measures. Our data show an average mRS of 1 approximately114 days after a SH-qualifying event. This indicates improvement from initial symptoms, often within the first several months of a clinical event. Thus, measuring annual functional and PRO may miss the effects of a SH occurring midyear. Additionally, patients with seizure or isolated headaches as symptomatic presentations can limit the ability of functional and PRO to detect changes at the time interval assessed.

All data considered, PROMIS-29 may add additional information beyond mRS and could be a secondary endpoint in clinical trials. It is not recommended as a primary endpoint due to its low sensitivity as an SH marker at the time intervals measured in this study. The mRS could remain a secondary outcome in trials for direct comparison to prior studies, but is poorly sensitive and specific as a marker of SH. The NIHSS, EQ-5D-3L and EQ-VAS offered little added value.

This study has several limitations. First, the numbers remain small for comparisons despite enrolling patients from high-volume centers, due, in part, to the prevalence of SH in patients with CCM. The pandemic also affected the attrition rate (12.2%) and patients' ability to return for follow-up within the preferred time frame of 1 year±1 month. These small numbers limit our ability to adjust for multiple comparisons. We feel this exploratory study of PRO in CCM-SH patients adds important data, but larger studies may be necessary to assess the value. We further acknowledge that specific triggers (e.g., contraceptive use) or blinded exposure to statin in the AT-CASH-EPOC cohort may have influenced some outcome events. These will be addressed upon completion of that trial.

We report for the first time SH rates, functional and patient-reported outcome at baseline and 2-year change rates in trial-eligible CCM -SH. Functional and PRO improve over 2 years but had poor sensitivity for outcome events at the time frame measured.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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Non-standard Abbreviations and Acronyms

AC	Asymptomatic Change

AT-CASH-EPOC	Atorvastatin Cavernous Angioma Symptomatic Hemorrhage Exploratory Proof of Concept
CCM	Cerebral Cavernous Malformation
CCM-SH	Cerebral Cavernous Malformation Symptomatic Hemorrhage
DCEQP	Dynamic contrast enhanced quantitative permeability
DVA	Developmental venous anomaly
Euro-QOL	European Quality of Life
FUBV	Follow up biomarker validation
mRS	Modified Rankin Score
NIHSS	National Institutes of Health Stroke Scale
PROMIS-29	Patient reported outcome mesasurement information system
PRO	Patient reported outcome
QSM	Quantitative Susceptibility Mapping
SH	Symptomatic Hemorrhage

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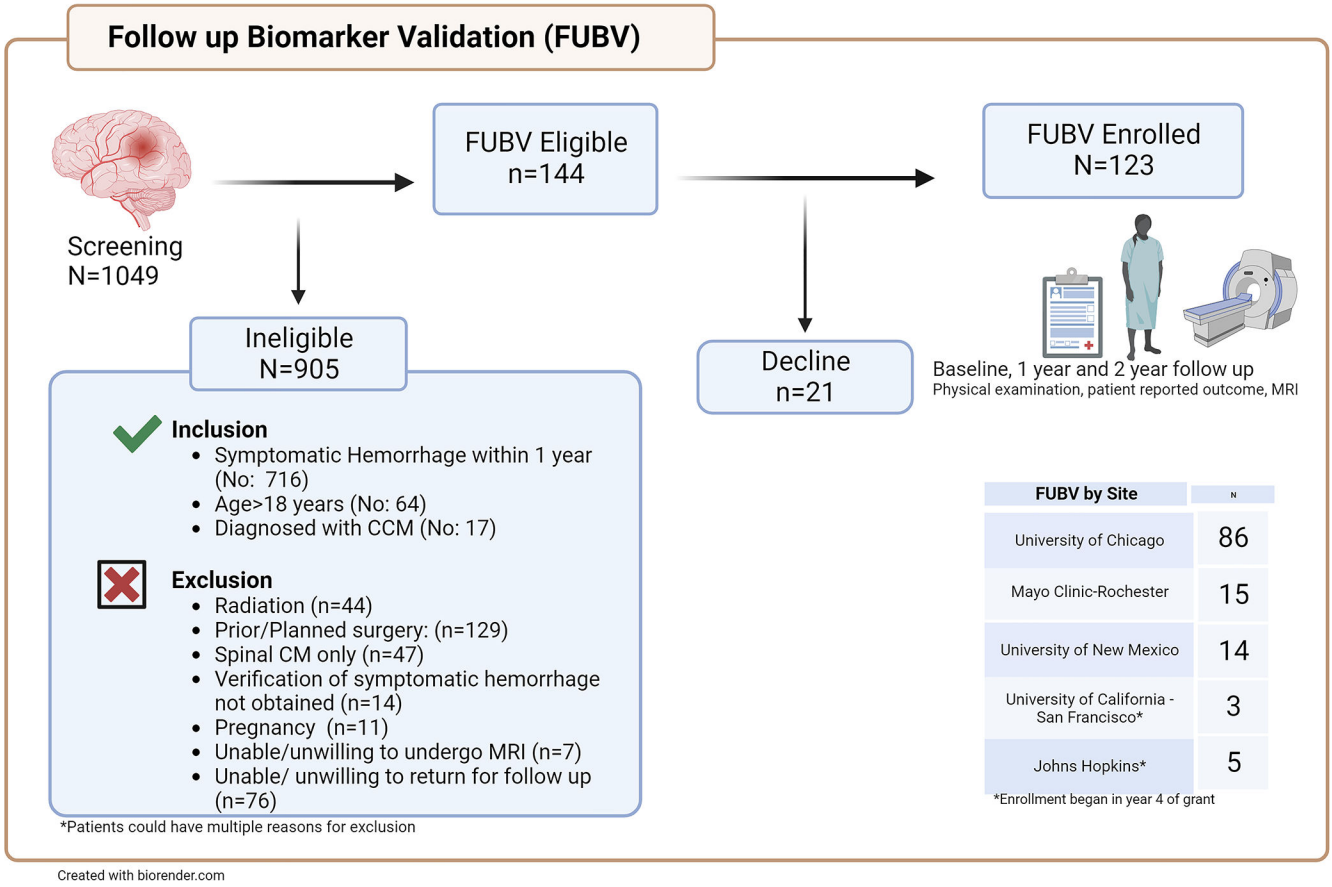

Figure 1:
Screening, Enrollment.

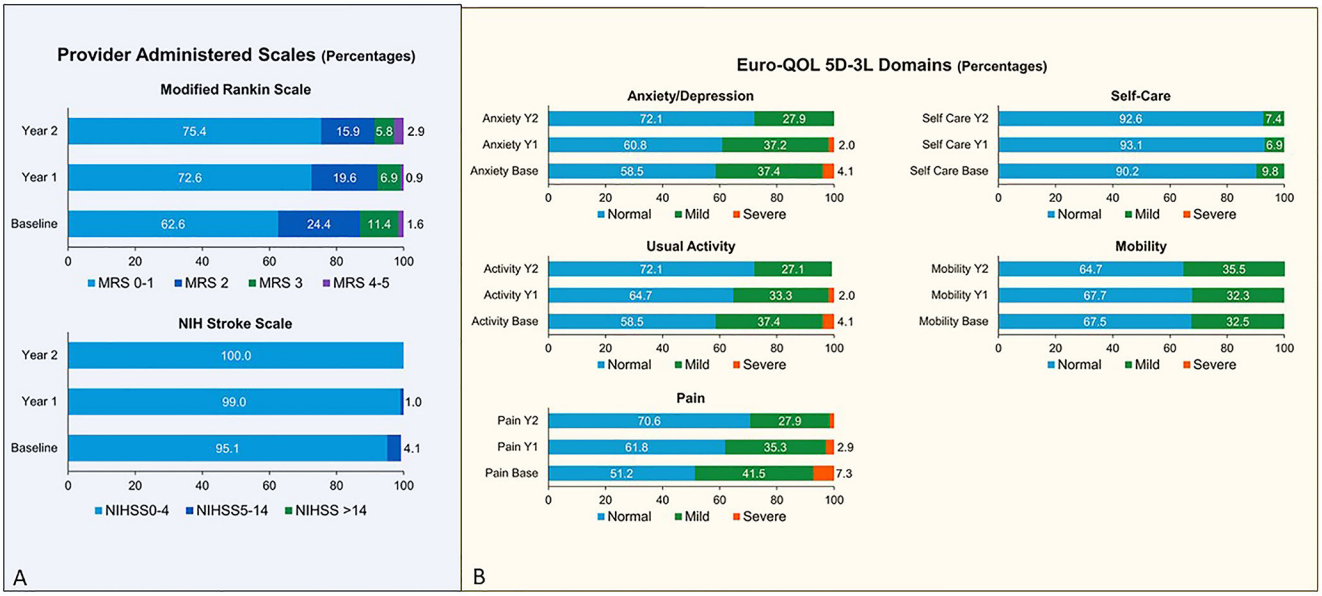

Figure 2.

A: Provider-administered Scales: The proportion of patients with a) Modified Rankin Scale 0-1 (Teal), 2 (Navy), 3 (Green), 4-5 (Purple) at baseline, year-1 and year-2; b) NIH Stroke Scale 0-4 (Teal), 5-14 (Navy) at baseline, year 1 and year 2. **2B:** Euro-QOL 5D-3L Domains. Patients with normal (blue), mild (green), severe (red) symptoms per domain at baseline, year 1 and 2.

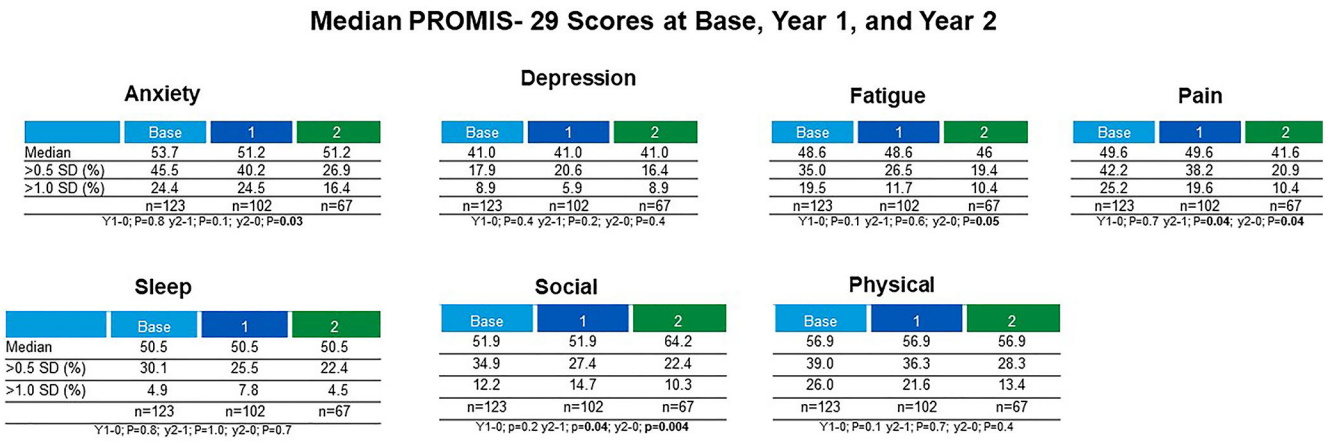

Figure 3:

PROMIS-29 median T scores and proportion of abnormal scores at baseline (teal), 1 (navy) and 2 years (green). T scores of 50 are considered standard for the population. For anxiety, depression, fatigue, pain and sleep disturbance, higher scores are unfavorable. For physical function and social domains, lower scores are unfavorable. Whether change in individual epochs (Year 1 minus baseline [Y1-0]; Year 2 minus year 1 [Y2-Y1]) or over the course of the study (Year 2 minus baseline [Y2-0]) were statistically significant are also noted (T test).

Table 1:

Characteristics of the Cohort (n=123)

Baseline Characteristics	N (%) or Mean +/−SD
Age at Enrollment (years)	43.9 +/−15.3
Female Sex	75 (61.0%)
White Race	99 (80.5%)
Hispanic Ethnicity	28 (22.8%)
Familial Cavernous Malformation Syndrome	48 (39.0%) 2 missing
History of hypertension	35 (28.4%)
History of diabetes	6 (4.9%)
Tobacco use	11 (8.9%)
Obstructive Sleep Apnea	10 (9.0%) 12 missing
Alcohol use	56 (45.9%)
Statin **	25 (20.3%)
Vitamin D supplementation	68 (55.3%)
Propranolol	7 (5.7%)
Birth control	2/75 Female (2.7%)
Systolic blood pressure (mmHg)	122.7 +/− 14.7 8 missing
Diastolic blood pressure (mmHg)	78.3 +/−10 8 missing
Body Mass Index	26.7 +/− 5.1
Qualifying SH Location	
Brainstem	50 (40.7%)
Thalamus	13 (10.5%)
Lobar	35 (28.4%)
Cerebellum	12 (9.8%)
Other	13 (10.6%)

SH= symptomatic hemorrhage

** This number does not reflect the patients randomized to atorvastatin 80mg versus placebo in the CASH-EPOC study.

Table 2:

The significance, sensitivity and specificity of a functional decline in each score as a marker of symptomatic hemorrhage

	Symptomatic Hemorrhage^	No Symptomatic Hemorrhage^	P value	Sensitivity	Specificity
Modified Rankin Scale (mRS score 2 or higher at indicated year))					
Year 1	1 (20.0%) N=5	27 (27.8%) N=97	1.0	20.0%	72.6%
Year 2	2 (28.6%) N=7	15 (24.2%) N=62	1.0	28.6%	75.8%
EQ VAS (Decrease by 10 point^)					
Epoch 1 Y1-Base Visit	4 (80.0%) N=5	15 (15.9%) N=94	**0.004**	80.0%	84.0%
Epoch 2 Y2-Y1 Visit	2 (33.3%) N=6	10 (16.4%) N=61	0.3	33.3%	83.6%
Y2 – Base Visit	2 (22.2%) N=9	10 (17.2%) N=58	0.7	22.2%	82.8%
EQ-5D-3L (decline by 1 point ^)					
EQ Activity					
Epoch 1 Y1-Base Visit	3 (60.0%) N=5	8 (8.2%) N=97	**0.008**	60.0%	91.7%
Epoch2 Y2-Y1 Visit	0 N=6	6 (9.8%) N=61	1.0	0	90.1%
Y2 -Base Visit	1 (10.0%) N=10	5 (8.8%) N=58	1.0	10.0%	91.4%
EQ Mobility					
Epoch 1 Y1-Base visit	1 (20.0%) N=5	6 (6.2%) N=97	0.3	20.0%	93.8%
Epoch2 Y2-Y1 visit	2 (33.3%) N=6	6 (9.8%) N=61	0.1	33.3%	90.2%
Y2-Base visit	2 (20.0%) N=10	5 (8.6%) N=58	0.3	20.0%	91.4%
EQ Pain					
Epoch1 Y1-Base visit	1 (20.0%) N=5	6 (6.2%) N=97	0.3	20.0%	93.8%
Epoch2 Y2-Y1 Visit	1 (16.7%) N=6	7 (11.4%) N=61	0.5	16.7%	88.5%
Y2-Base visit	1 (10.0%) N=10	5 (8.6%) N=58	1.0	10.0%	91.4%
EQ Anxiety/Depression					
Epoch1 Y1-Base visit	4 (80.0%) N=5	16 (16.5%) N=97	**0.04**	80.0%	83.5%
Epoch2 Y2-Y1 Visit	1 (16.7%) N=6	2 (3.3%) N=61	0.2	16.7%	96.7%
Y2-Base Visit	2 (20.0%) N=10	5 (8.6%) N=58	0.3	20.0%	91.4%
EQ Self-Care					

	Symptomatic Hemorrhage^	**No Symptomatic Hemorrhage^**	**P value**	**Sensitivity**	**Specificity**
Epoch1 Y1-Base Visit	0 N=5	4 (4.1%) N=97	1.0	0	96.0%
Epoch2 Y2-Y1 Visit	0 N=6	4 (6.6%) N=61	1.0	0	93.4%
Y 2-Base Visit	2 (20.0%) N=10	2 (3.4%) N=58	0.1	20.0%	96.5%

^In epoch specified; Y1=Year 1 Visit Score; Y2=Year 2 visit score; EQ=Euro-QOL

TABLE 3:

Significance, sensitivity and specificity of PROMIS-29 Domains as a marker for symptomatic hemorrhage

	Symptomatic Hemorrhage^	**No Symptomatic Hemorrhage^**	**P value**	**Sensitivity**	**Specificity**
PROMIS-29 (functional decline by 5 in Domain specified)					
Anxiety					
Epoch 1 Y1-Base Visit	3 (60.0%) N=5	24 (24.7%) N=97	0.1	60.0%	75.3%
Epoch 2 Y2-Y1 Visit	0 N=5	1 (18.0%) N=61	0.6	0	98.3%
Y2-Base Visit	2 (22.2%) N=9	11 (19.0%) N=58	1.0	22.2%	81.0%
Depression					
Epoch 1 Y1- Base Visit	2 (40.0%) N=5	20 (20.6%) N=97	0.3	40.0%	79.4%
Epoch 2 Y2-Y1 Visit	1 (20.0%) N=5	13 (21.3%) N=61	1.0	20.0%	78.7%
Y2-Base Visit	3 (33.3%) N-9	13 (22.4%) N=58	0.4	33.3%	77.6%
Pain					
Epoch 1 Y1-Base Visit	1 (20.0%) N=5	21 (21.6%) N=97	0.8	20.0%	78.3%
Epoch 2 Y2-Y1 Visit	0 N=5	8 (13.1%) N=61	1.0	0	86.9%
Y2-Base Visit	2 (22.2%) N=9	6 (10.3%) N=58	0.3	22.2%	89.6%
Fatigue					
Epoch 1 Y1-Base Visit	1 (20.0%) N=5	24 (24.7%) N=97	1.0	20.0%	75.3%
Epoch 2 Y2-Y1 Visit	0 N=5	15 (24.6%) N=61	0.6	0	75.4%
Y2-Base Visit	5 (55.6%) N=9	10 (17.2%) N=58	**0.02**	55.6%	82.8%
Sleep Disturbance					
Epoch 1 Y1-Base Visit	3 (50.0%) N=5	18 (18.4%) N=97	0.2	60.0%	81.4%
Epoch 2 Y2-Y1 Visit	2 (40.0%) N=5	7 (11.5%) N=61	0.1	40.0%	88.5%
Y2-Base Visit	5 (55.6%) N=9	3 (5.2%) N=58	**0.0006**	55.6%	94.8%
Social					
Epoch 1 Y1-Base Visit	2 (40.0%) N=5	21 (21.6%) N=97	0.3	40.0%	78.3%
Epoch 2 Y2-Y1 Visit	1 (20.0%) N=5	8 (13.1%) N=61	0.5	20.0%	86.9%
Y2-Base Visit	4 (44.4%) N=9	7 (12.1%) N=58	**0.03**	44.4%	87.9%
Physical					

	Symptomatic Hemorrhage^	**No Symptomatic Hemorrhage^**	**P value**	**Sensitivity**	**Specificity**
Epoch 1 Y1-Base Visit	1 (20.0%) N=5	9 (9.3%) N=97	0.4	20.0%	90.7%
Epoch 2 Y2-Y1 Visit	0 N=5	8 (13.1%) N=61	1.0	0%	86.9%
Y2-Base Visit	3 (33.3%) N=9	10 (17.2%) N=58	0.4	33.3%	82.8%

^In epoch specified; Y1=Year 1 Visit Score; Y2=Year 2 visit score