Safety and efficacy of propranolol for treatment of familial cerebral cavernous malformations (Treat_CCM): a randomised, open-label, blinded-endpoint, phase 2 pilot trial

*Silvia Lanfranconi, Elisa Scola, Jennifer M T A Meessen, Roberto Pallini, Giulio A Bertani, Rustam Al-Shahi Salman, Elisabetta Dejana, Roberto Latini, on behalf of the Treat_CCM Investigators**

Summary

Background Observations in people with cerebral cavernous malformations, and in preclinical models of this disorder, suggest that the β-blocker propranolol might reduce the risk of intracerebral haemorrhage. We aimed to evaluate the safety and efficacy of prolonged treatment with propranolol to reduce the incidence of symptomatic intracerebral haemorrhage or focal neurological deficit in people with familial cerebral cavernous malformations.

Methods We conducted a randomised, open-label, blinded-endpoint, phase 2 pilot trial (Treat_CCM) at six national reference centres for rare diseases in Italy. People aged 18 years or older with symptomatic familial cerebral cavernous malformation were eligible for enrolment. Participants were randomly assigned (2:1) to receive either oral propranolol (20–320 mg daily) plus standard care (intervention group), or standard care alone (control group), for 24 months. Participants, caregivers, and investigators were aware of treatment group assignment. Participants had clinical assessments and 3 T brain MRI at baseline and at 12 and 24 months. The primary outcome was new occurrence of symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation over 24 months. Outcome assessors were masked to treatment group assignment. The primary analysis was done in the intention-to-treat population. Because of the pilot study design, we chose a one-sided 80% CI, which could either exclude a clinically meaningful effect or show a signal of efficacy. This trial is registered with EudraCT, 2017-003595-30, and ClinicalTrials.gov, NCT03589014, and is closed to recruitment.

Findings Between April 11, 2018, and Dec 5, 2019, 95 people were assessed for eligibility and 83 were enrolled, of whom 57 were assigned to the propranolol plus standard care group and 26 to the standard care alone group. The mean age of participants was 46 years (SD 15); 48 (58%) were female and 35 (42%) were male. The incidence of symptomatic intracerebral haemorrhage or focal neurological deficit was 1·7 (95% CI 1·4–2·0) cases per 100 person-years (two [4%] of 57 participants) in the propranolol plus standard care group and 3·9 (3·1–4·7) per 100 person-years (two [8%] of 26) in the standard care alone group (univariable hazard ratio [HR] 0·43, 80% CI 0·18–0·98). The univariable HR showed a signal of efficacy, according to predefined criteria. The incidence of hospitalisation did not differ between groups (8·2 cases [95% CI 7·5–8·9] per 100 person-years in the propranolol plus standard care group *vs* 8·2 [95% CI 7·1–9·3] per 100 person-years in the standard care alone group). One participant in the standard care alone group died of sepsis. Three participants in the propranolol plus standard care group discontinued propranolol due to side-effects (two reported hypotension and one reported weakness).

Interpretation Propranolol was safe and well tolerated in this population. Propranolol might be beneficial for reducing the incidence of clinical events in people with symptomatic familial cerebral cavernous malformations, although this trial was not designed to be adequately powered to investigate efficacy. A definitive phase 3 trial of propranolol in people with symptomatic familial cerebral cavernous malformations is justified.

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*Treat_CCM Writing and Steering Committee members are listed at the end of the manuscript and Treat_CCM collaborators and participating centres are listed in the appendix (p 7)

Department of Neurology (S Lanfranconi MD), **Department of Neurosurgery** (G A Bertani MD), **and Department of Neuroradiology** (E Scola MD), **Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Cardiovascular Medicine, Institute for Pharmacological Research Mario Negri IRCCS, Milan, Italy** (J M T A Meessen PhD, R Latini MD); **Department of Neurosurgery, Università Cattolica del Sacro Cuore, Rome, Italy** (Prof R Pallini MD); **Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK** (Prof R Al-Shahi Salman PhD); **Laboratory of Vascular Biology, IFOM, Firc Institute for Molecular Oncology, Milan, Italy** (Prof E Dejana PhD)

Correspondence to: Dr Roberto Latini, Department of Cardiovascular Medicine, Institute for Pharmacological Research Mario Negri IRCCS, Milan 20156, Italy **roberto.latini@marionegri.it**

See Online for appendix

Introduction

Cerebral cavernous malformations are vascular malformations characterised by clusters of enlarged leaky capillaries mainly affecting the CNS. They represent the second most common type of intracranial vascular malformation, with a reported prevalence ranging from 0·1% to 0·8% in the general population in the USA.[1] Most cerebral cavernous malformations are solitary and sporadic, and of unknown cause, whereas multiple cerebral cavernous malformations are usually familial. Familial cerebral cavernous malformation is a rare genetic disease, with an estimated population prevalence of one case per 5000–10 000 population (Orphanet), arising from autosomal dominant inheritance of loss-of-function mutations in genes encoding one of three proteins—*KRIT1* (*CCM1*), *CCM2* (Malcavernin), or *PDCD10* (*CCM3*).[2]

For more on **Orphanet** see https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=18935

Research in context

Evidence before this study

We searched PubMed on May 30, 2022, from database inception to May 30, 2022, using the terms "cerebral cavernous malformation" and "propranolol", with no language restrictions. We found seven case reports (five in infants or children) reporting benefits of propranolol for cerebral cavernous malformation in humans. We found four cohort studies investigating outcomes for patients with sporadic or familial cerebral cavernous malformation associated with β-blocker use: three retrospective cohort studies did not find any associations between β-blocker use and outcomes; although one prospective, population-based study found an association between β-blocker use and a lower risk of intracerebral haemorrhage or new persistent or progressive focal neurological deficit adjusted for known predictors of these outcomes (adjusted hazard ratio 0·09, 95% CI 0·01–0·66; p=0·018). We searched ClinicalTrials.gov on May 30, 2022, using the terms "cerebral cavernous malformation" and "propranolol" and found, excluding the present study, two randomised clinical trials: one for patients with surgically inaccessible cerebral cavernous malformation (NCT03523650) and another for people undergoing surgery for cerebral cavernous malformation (NCT03474614); both clinical trials were of unknown status and had not yet been published.

Added value of this study

To our knowledge, this study is the first phase 2, randomised, controlled trial to assess the safety and efficacy of propranolol for people with familial cerebral cavernous malformation. Compared with previous studies, the prospective design of this multicentre study, together with randomisation of included participants, allows for reduction of potential bias and increases the generalisability of the findings.

Implications of all the available evidence

We found that propranolol was safe and well tolerated for the treatment of familial cerebral cavernous malformation. The effects on clinical outcomes and new occurrence of cerebral cavernous malformation on MRI were not significant, but their direction and magnitude suggest that propranolol might be beneficial. Altogether, the findings from preclinical work in animal models, case reports and observational studies in humans, and the present study justify a definitive phase 3 clinical trial of propranolol for preventing intracerebral haemorrhage and focal neurological deficit from cerebral cavernous malformation.

Cerebral cavernous malformations can cause intracerebral haemorrhage, non-haemorrhagic focal neurological deficit, or epileptic seizure, and can lead to severe disability. The 5-year risk of intracerebral haemorrhage in people with cerebral cavernous malformation ranges from 3·8% to 30·8%.[3] Without effective medical treatment to prevent intracerebral haemorrhage, the main therapeutic option is neurosurgical excision of solitary cerebral cavernous malformation, which is offered to a minority of patients with symptomatic cerebral cavernous malformation located in safely accessible locations,[4] or stereotactic radiosurgery, which is reserved for patients for whom surgery is unsuitable. Patients with familial cerebral cavernous malformation remain at risk from other cerebral cavernous malformations even after treatment. Drug treatment of familial cerebral cavernous malformation could reduce the burden of disease and avoid the need for invasive treatment.

To our knowledge, other than a pilot clinical trial of simvastatin in 12 participants with familial cerebral cavernous malformation,[5] and an ongoing phase 1/2 clinical trial of atorvastatin in 80 participants with cerebral cavernous malformation (NCT02603328), no clinical trials have assessed potential disease-modifying treatments for familial cerebral cavernous malformation.[4] Propranolol, a non-selective β-adrenergic receptor blocker, is effective for soft-tissue infantile haemangioma,[6–11] a condition that is similar to cerebral cavernous malformation. Animal models have suggested that propranolol could also stabilise cerebral cavernous malformation via effects on inflammation, angiogenesis, and the pericyte–endothelial cell interaction.[12,13] In humans with cerebral cavernous malformation, several case reports have reported disease regression or stabilisation with propranolol.[14–16] One non-randomised cohort study of humans with sporadic cerebral cavernous malformation and familial cerebral cavernous malformation showed an association between any β-blocker and a lower risk of intracerebral haemorrhage from cerebral cavernous malformation after adjusting for known predictors of intracerebral haemorrhage,[17] although other previous cohort studies had not shown such an association.[18–20]

We aimed to evaluate the safety and efficacy of prolonged treatment with propranolol to reduce the incidence of symptomatic intracerebral haemorrhage or focal neurological deficit in people with familial cerebral cavernous malformation.

Methods

Study design and participants

We conducted a randomised, open-label, blinded-endpoint, phase 2 pilot trial (Treat_CCM) at six national reference centres for rare diseases in Italy (appendix p 7). The study protocol has been published.[21]

Eligible patients were adults aged 18 years or older with familial cerebral cavernous malformation and a history of clinical symptoms of intracerebral haemorrhage, seizures, stroke, permanent or transient focal neurological deficit, intellectual disability, or any other neurological symptoms supposedly related to cerebral cavernous malformation.

Patients unable to provide informed consent and to adhere to the study procedures were not eligible for inclusion. Exclusion criteria were implanted pacemaker or any other condition contraindicating MRI; bradycardia (heart rate <50 beats per min); 2nd or 3rd degree atrioventricular block; symptomatic hypotension; unstable diabetes of any type; severe asthma; renal or liver failure; current use of verapamil or diltiazem; brain surgery within the past 6 months; known hypersensitivity to study drug (propranolol or any of the ingredients); women who were pregnant or lactating, or women of childbearing potential who were not protected from pregnancy by an accepted method of contraception; and participation in another clinical trial.

The study was approved by local research ethics committees for each study site and all participants provided written informed consent at the first study visit before any procedures or assessments occurred. The trial was conducted according to all the stipulations of the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Guideline for Good Clinical Practice requirements, and the applicable regulatory requirements.

Randomisation and masking

Participants were randomly assigned (2:1) to receive either propranolol plus standard care (intervention group) or standard care alone (control group). A randomised blocks list was generated through a C language programme to define the randomisation list. A block size of six was used, and blocks were assigned in equal number to the participating centres to stratify randomisation by centre. The web-based randomisation system (REDCap electronic data capture tools hosted at Mario Negri) gave the code number and study group assignment to the investigators, after correct introduction of data documenting the presence of eligibility criteria and the absence of any exclusion criterion. Participants, caregivers, and study investigators were aware of treatment group assignment. The investigators involved in event adjudication and MRI analysis were masked to treatment group assignment, adhering to a PROBE (prospective, randomised, open-label, blinded-endpoint) design. Masking of all event documentation and of MRI recordings was performed by trained personnel at the Study Secretariat at Mario Negri Institute for Pharmacological Research.

Procedures

Participants had blood analyses to check liver and renal function, electrolytes, and blood glucose at baseline and at 12 and 24 months. We performed *CCM1*, *CCM2*, and *CCM3* mutation analysis on all participants during follow-up, for those who did not have it done before randomisation.

In the propranolol plus standard care group, oral propranolol was administered immediately after randomisation, alongside standard care, at a recommended initial dose of 40 mg twice daily, to be up-titrated to 80 mg twice daily. However, we amended the study protocol on Nov 30, 2018, to allow for doses as low as 10 mg twice daily and up to 160 mg twice daily, for a total dose of 20–320 mg daily, according to tolerability. Clinical monitors checked participants' adherence during monitoring throughout the study by comparing the amount of propranolol prescribed versus the amount returned used or unused. The analysis of propranolol in plasma was performed using high performance liquid chromatography mass spectrometry (appendix p 2).

Except for brain surgery, which was a criterion for exclusion, any intervention deemed necessary for patients was allowed as part of standard care, including non-steroidal anti-inflammatory drugs, anticonvulsants, and antithrombotic agents.

We performed follow-up clinical visits at weeks 2 and 4 to adjust the dose of propranolol, then every 6 months until study end at month 24. The clinical follow-up visits at baseline and at 12 and 24 months included a clinical examination, blood pressure and heart rate measurement, a full neurological examination, modified Rankin Scale (mRS) assessment, electrocardiogram (ECG), and blood sampling. We performed the 6-month and 18-month follow-up visits either in person or by telephone to check for drug tolerability and occurrence of adverse events. Blood chemistry analyses, including vitamin D and high-sensitivity C-reactive protein, were performed using conventional methods in a clinical chemistry laboratory (Desio Hospital, Desio, Italy).

Participants had 3 T cerebral MRI according to a dedicated protocol in five site-specific MRI scanners at baseline and at 12 and 24 months. The MRI protocol included: sagittal 3D T1-weighted turbo field echo, sagittal 3D T2-weighted turbo spin echo, sagittal 3D fluid-attenuated inversion recovery, axial diffusion-weighted imaging, axial susceptibility-weighted imaging, and axial T2-weighted gradient echo. We did multiplanar reconstruction for 3D sequences. MRIs were assessed centrally by masked personnel.

Outcomes

The primary outcome was the occurrence of new clinically symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation over 24 months.[22] Prespecified secondary outcomes were microvascular haemorrhages (assessed by quantitative susceptibility mapping); patient-reported clinical outcomes other than intracerebral haemorrhage and focal neurological deficit (global cognitive function, global disability assessed by mRS, health-related quality of life [assessed with the 36-item short form survey]); epileptic seizures; and cerebral cavernous malformation characteristics, as assessed by MRI (including number, diameter, and length of cerebral cavernous malformations, location [cerebellum, brainstem, basal ganglia, and hemispheric white matter], volume of the largest cerebral cavernous malformation, and appearance of

de novo cerebral cavernous malformation); and signs of new bleeding at 12 and 24 months. MRI signal of cerebral cavernous malformations was reported according to the Zabramski classification.[23] The analysis of some secondary outcomes—ie, microvascular haemorrhages and patient-reported outcomes—will be the subject of separate publications.

Safety outcomes comprised assessment of serious adverse events—defined as hospitalisation for any reason—and adverse events. Severity of adverse events was evaluated using the Common Terminology Criteria for Adverse Events (version 5.0). Serious adverse events were adjudicated by the Event Committee. We also assessed the causal relation between adverse events and the use of propranolol or the study procedures.

Statistical analysis

We estimated a 10·1% 2-year risk of the primary outcome in patients with familial cerebral cavernous malformation who received standard care.[3] Assuming a 50% reduction of clinical events with propranolol, at least 834 patients (556 in the propranolol plus standard care group and 278 in the standard care alone group) would have been needed to achieve a study power of 80% at a significance level of one-tail α=0·05,[24] which was an unrealistic scenario. Thus, for this trial, a pilot study, we adopted a CI approach,[25] and a one-sided 80% CI was chosen, because we were interested in proceeding towards a phase 3 trial only if some evidence of efficacy was observed. We defined a clinically meaningful effect as at least a 50% reduction of the 2-year risk of the primary outcome. If the 80% CI did not include 1·0 (equivalence), the results would be considered as showing a signal of efficacy. 60 patients randomly assigned (2:1) to either propranolol or control were considered a feasible number to show a signal of efficacy.

Baseline characteristics are presented by treatment groups, as mean (SD), median (IQR), or n (%), as appropriate. We performed the main analyses of the safety and primary efficacy outcomes according to an intention-to-treat approach, including all participants who were

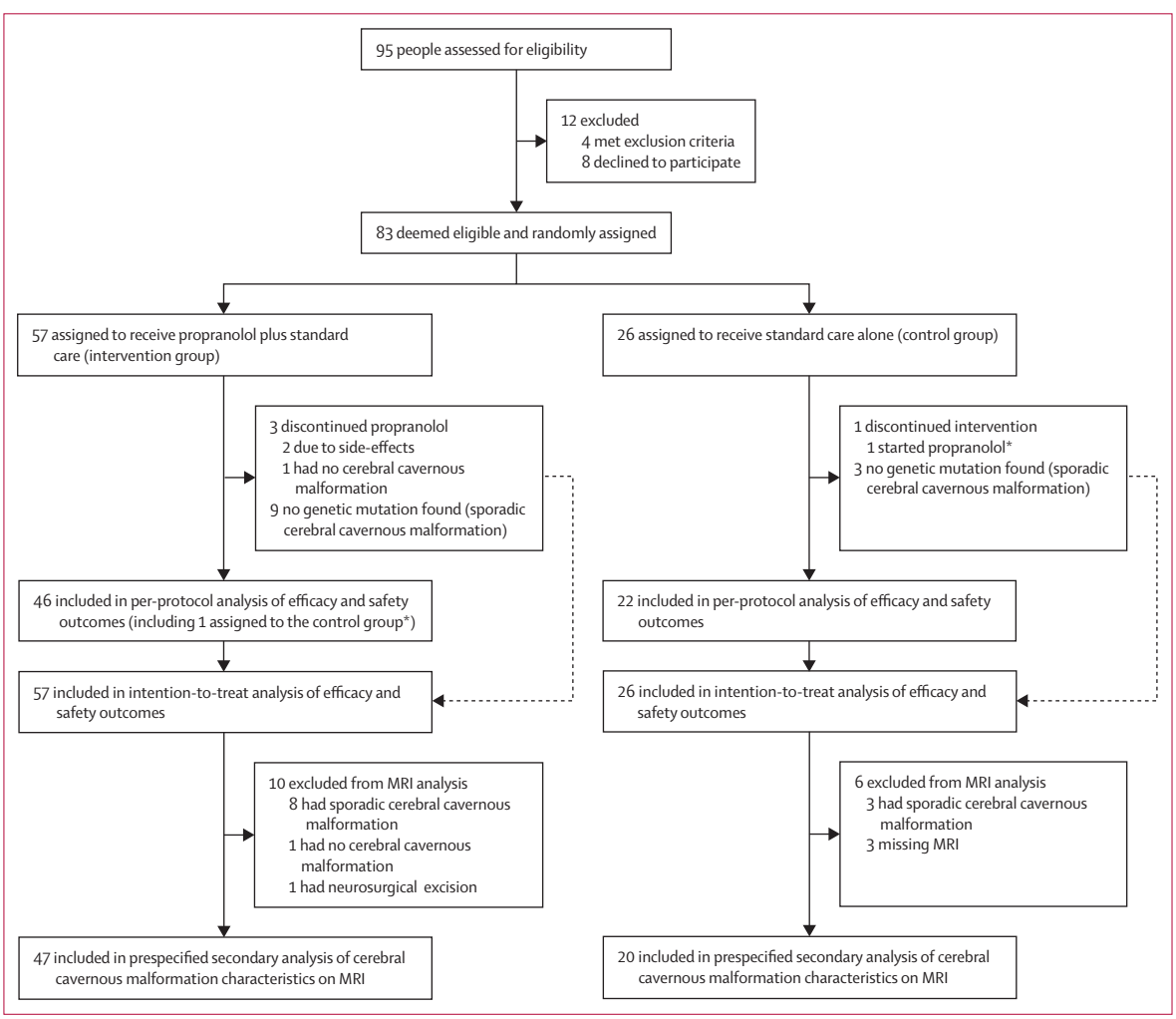

Figure 1: **Trial profile**
*Included in the propanol per-protocol population.

randomly assigned to a treatment group. We conducted secondary per-protocol analyses, restricted to participants with confirmed genetic mutation and excluding participants who did not adhere to the assigned treatment. Serious adverse events and primary outcome events (ie, intracerebral haemorrhage or focal neurological deficit) are reported per treatment group as incident rate per 100 person-years (including Poisson exact 95% CI). Univariable unadjusted Cox regression analysis was performed with an 80% CI for the primary outcome, including all available follow-up, to assess whether the results of the trial could be considered encouraging. For the radiological secondary outcomes, we excluded participants who had neurosurgical excision of cerebral cavernous malformation, those without genetically confirmed familial cerebral cavernous malformation, and those without baseline MRI.

Analyses were performed using IBM SPSS Statistics for Windows (version 27).

This trial is registered with EudraCT, 2017-003595-30, and ClinicalTrials.gov, NCT03589014, and is closed to recruitment.

Role of the funding source

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

Results

Between April 11, 2018, and Dec 5, 2019, 95 people were assessed for eligibility, of whom four met exclusion criteria and eight did not provide consent. Thus, 83 patients were enrolled and randomly assigned to receive propranolol plus standard care (n=57; intervention group) or standard care alone (n=26; control group; figure 1). 12 participants with no genetic mutation (nine in the propranolol plus standard care group and three in the standard care alone group) were deemed ineligible after review of baseline MRI due to normal MRI (n=1), leukoencephalopathy with microbleeds (n=1), radiation-induced cerebral cavernous malformation (n=1), and sporadic cerebral cavernous malformation without genetic mutation (n=9), and four other participants discontinued their assigned intervention (figure 1).

Baseline characteristics were generally balanced between treatment groups (table 1). The mean age of participants was 45·8 years (SD 14·8), 48 (58%) were female and 35 (42%) were male, and all participants were White. The most common previous symptom related to cerebral cavernous malformation was recurrent headache (59 [71%] of 83 participants), followed by intracerebral haemorrhage (48 [58%]), focal neurological deficit (40 [48%]), and epileptic seizures (31 [37%]). A greater proportion of participants in the propranolol plus standard care group had a history of focal neurological deficit than in the standard care alone group (31 [54%] *vs* nine [35%]). 71 (86%) of 83 participants had familial cerebral cavernous malformation with a known genetic mutation (48 in the propranolol plus standard care group *vs* 23 in the standard care alone group; table 1). 13 patients were prescribed a statin, four in the standard care alone group and nine in the propranolol plus standard care group. Furthermore, ten patients were on vitamin D supplementation, two in the standard care alone group and eight in the propranolol plus standard care group (table 1).

79 (95%) of 83 participants adhered to the treatment assigned by randomisation. Three (5%) participants in the propranolol plus standard care group discontinued propranolol at 10 weeks, 6 months, and 18 months after randomisation due to side-effects (two reported hypotension and one reported weakness). One (4%) participant in the standard care alone group started propranolol 20 mg twice daily on their own initiative at 6 months. Propranolol was not detectable in blood samples at 2 years in nine participants assigned to the propranolol plus standard care group (five participants at one study site had sporadic cerebral cavernous malformation), and was detectable in two participants

	Propranolol plus standard care group (n=57)	Standard care alone group (n=26)
Age, years	45·4 (14·2)	46·8 (16·3)
Sex		
Female	34 (60%)	14 (54%)
Male	23 (40%)	12 (46%)
BMI, kg/m²	24·3 (3·6)	23·9 (4·1)
Systolic blood pressure, mm Hg	122 (14)	123 (13)
Diastolic blood pressure, mm Hg	79 (9)	77 (8)
Heart rate, beats per min	71 (11)	71 (13)
Previous intracerebral haemorrhage	33 (58%)	15 (58%)
Previous focal neurological deficit	31 (54%)	9 (35%)
Previous epileptic seizures	21 (37%)	10 (38%)
Previous headache	41 (72%)	18 (69%)
Genetic mutations		
KRIT1	37 (65%)	17 (65%)
MGC4607	7 (12%)	5 (19%)
PDCD10	4 (7%)	1 (4%)
No mutation found	9 (16%)	3 (12%)
Hypertension	13 (23%)	6 (23%)
Diabetes	1 (2%)	1 (4%)
Hypercholesterolaemia	7 (12%)	4 (15%)
Ischaemic heart disease	0	1 (4%)
Antiepileptic drug treatment	24 (42%)	11 (42%)
Non-steroidal anti-inflammatory drugs	1 (2%)	1 (4%)
Antihypertensive treatment	14 (25%)	6 (23%)
Antidepressant treatment	9 (16%)	2 (8%)
Vitamin D supplementation	8 (14%)	2 (8%)
Statin	9 (16%)	4 (15%)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics of the intention-to-treat population**

assigned to the standard care alone group. Daily doses of propranolol ranged from 20 mg to 160 mg during 2-year follow-up; a dose of propranolol of at least 40 mg per day was prescribed for 40 (70%) of 57 participants in the propranolol plus standard care group and the median prescribed daily dose over 24 months was 50 mg. Low daily doses ranged from 20 mg to 40 mg, and appropriate daily doses ranged from 40 mg to 160 mg. At the 2-year follow-up visit, the median plasma propranolol concentration was 27·5 ng/mL (IQR 9·8–61·0) in participants assigned to the propra nolol plus standard care group. Participants who were prescribed a daily dose of propranolol 50 mg or less (n=33) had a median plasma propranolol concentration of 15·8 ng/mL (IQR 7·3–35·8), whereas participants who were prescribed a daily dose of 60 mg or greater (n=24) had a median concentration of 54·9 ng/mL (21·8–89·0).

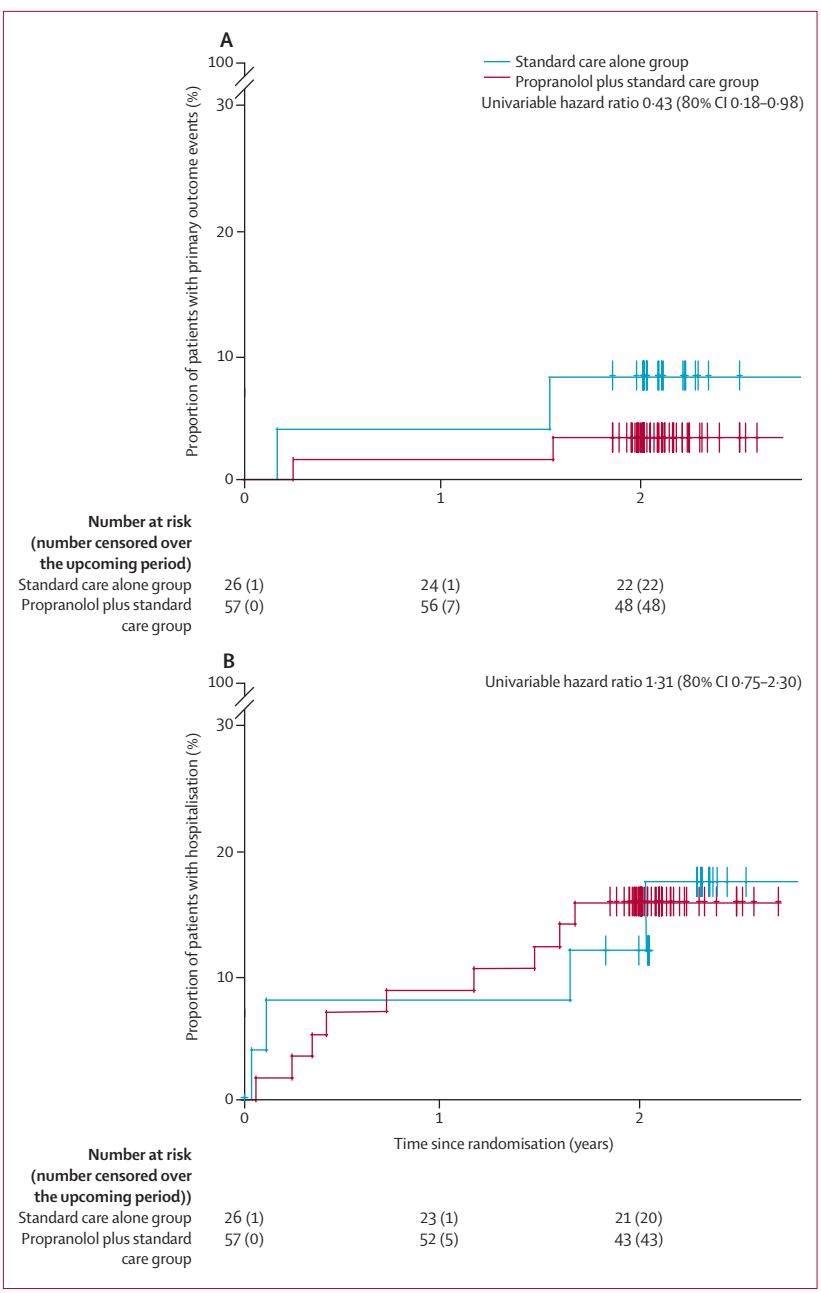

Figure 2: **Survival analysis of primary and secondary outcomes**
(A) Time to new symptomatic intracerebral haemorrhage or focal neurological deficits (primary outcome). (B) Hospitalisations during follow-up (secondary outcome).

Only one (1%) participant who was assigned to the standard care alone group was lost to follow-up immediately after the baseline visit. The median duration of follow-up was 764 days (IQR 736–808).

Among 83 participants in the intention-to-treat population, the primary clinical outcome of new symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation occurred in two (4%) of 57 participants in the propranolol plus standard care group (incidence 1·7 cases [95% CI 1·4–2·0] per 100 person-years) and two (8%) of 26 in the standard care alone group (3·9 [3·1–4·7] per 100 person-years; univariable hazard ratio [HR] 0·43 [80% CI 0·18–0·98]; figure 2A). The 80% CI excluded 1 (equivalence) and therefore showed a signal of efficacy, as determined in the protocol. The two intracerebral haemorrhages caused transient neurological deficit in one participant and permanent neurological deficit in the other; the two focal neurological deficits were not disabling, and the symptoms were transient in one participant (appendix p 3). The four participants who had at least one primary outcome all had familial cerebral cavernous malformation with a confirmed genetic mutation.

The secondary clinical outcome of epileptic seizures during follow-up occurred in two (4%) participants in the propranolol plus standard care group (incidence 1·7 cases [95% CI 1·3–2·0] per 100 person-years) and one (4%) in the standard care alone group (1·9 [1·4–2·5] per 100 person-years; HR 0·92 [95% CI 0·08–10·12]). Cerebral cavernous malformation characteristics, as assessed by MRI, at baseline and 1 and 2 years of follow-up were available for 68 participants with familial cerebral cavernous malformation. After exclusion of one participant who had neurosurgical excision of cerebral cavernous malformation before completing the 2-year follow-up, MRI appearances (prespecified secondary outcomes) were rated and analysed for 67 participants (table 2). The median numbers of supratentorial and infratentorial cerebral cavernous malformations were balanced between groups at baseline. The median total number of cerebral cavernous malformations increased over 2 years of follow-up in both groups overall and in supratentorial and infratentorial locations. During 2-year follow-up, the median number of de novo cerebral cavernous malformation was four (IQR 2–9) in the propranolol plus standard care group versus five (1–11) in the standard care alone group (appendix p 6). The formation of five or more new cerebral cavernous

malformations was found in five (71%) of seven participants taking low-dose propranolol and in 16 (40%) of 40 taking an appropriate dose (appendix p 6), while in the standard care alone group the incidence was 11 (55%) of 20 participants.

The frequency of hospitalisation for any reason (ie, the definition of serious adverse events) was similar in both groups. 11 hospitalisations were recorded in nine (16%) of 57 participants in the propranolol plus standard care group and six hospitalisations were recorded in four (15%) of 26 participants in the standard care alone group (incidence 8·2 cases [95% CI 7·5–8·9] per 100 person-years *vs* 8·2 [7·1–9·3] per 100 person-years; HR 1·31 [80% CI 0·75–2·30]; figure 2B). We adjudicated nine hospitalisations as unrelated to cerebral cavernous malformation and none was deemed related to propranolol (table 3). One participant died, in the standard care alone group, due to sepsis. Adverse events are shown in table 3.

Propranolol was well tolerated. 11 (19%) of 57 participants in the propranolol plus standard care group had transient symptomatic episodes of hypotension (ie, systolic blood pressure <90 mm Hg and diastolic blood pressure <60 mm Hg) or bradycardia (ie, heart rate <50 beats per min). 35 participants reported 78 transient side-effects, the most common being fatigue (34 episodes in 19 participants), hypotension (19 episodes in 16 participants), and bradycardia (17 episodes in 13 participants). No ECG abnormalities attributable to propranolol were found during the trial. Systolic blood pressure fell by a mean of 6·1 mm Hg, diastolic blood pressure fell by a mean of 4·9 mm Hg, and heart rate fell by a mean of 7·8 beats per min after 1 year in the propranolol plus standard care group (appendix p 4).

Of 71 participants with familial cerebral cavernous malformation and evidence of a genetic mutation, 48 were assigned to the propranolol plus standard care group and 23 to the standard care alone group; baseline characteristics were similar between the groups (appendix p 5). In this population, the incidence of the primary clinical outcome of new symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation was 2·0 cases (95% CI 1·6–2·4) per 100 person-years in 48 participants assigned to the propranolol plus standard care group versus 4·3 (3·4–5·1) per 100 person-years in 23 assigned to the standard care alone group. The incidence of hospitalisation was 7·5 cases (95% CI 6·7–8·3) per 100 person-years in participants assigned to the propranolol plus standard care group versus 9·0 (7·8–10·2) per 100 person-years in those assigned to the standard care alone group.

The per-protocol analysis (excluding patients who did not adhere to study treatment and those with sporadic cerebral cavernous malformation) included 68 patients, of whom 46 were assigned to the propranolol plus standard care group and 22 were assigned to the standard care alone group (figure 1). The primary clinical outcome of new symptomatic intracerebral haemorrhage or focal neurological deficit attributable to cerebral cavernous malformation occurred in two (4%) of 46 participants in the propranolol plus standard care group (incidence 2·1 cases [95% CI 1·7–2·5] per 100 person-years) versus two (9%) of 22 in the standard care alone group (incidence 4·5 [3·6-5·4] per 100 person-years; HR 0·46 [80% CI 0·13–1·66]). The incidence of hospitalisation was 7·9 cases (95% CI 7·1–8·7) per 100 person-years in participants assigned to the propranolol plus standard care group versus 6·7 (5·7–7·8) per 100 person-years in those assigned to the standard care alone group.

	Propranolol plus standard care group (n=47)			Standard care alone group (n=20)		
	Baseline	1 year	2 years	Baseline	1 year	2 years
Volume of largest cerebral cavernous malformation*, mm³	551 (157–1621)	616 (155–1671)	616 (174–1678)	455 (94–1033)	423 (106–1060)	423 (102–1048)
Total number of supratentorial cerebral cavernous malformations per participant†	41 (16–101)	46 (16–103)	47 (18–106)	42 (20–96)	45 (20–102)	49 (21–103)
Total number of infratentorial cerebral cavernous malformations per participant‡	13 (4–31)	13 (4–35)	13 (5–35)	14 (5–32)	14 (5–32)	15 (5–34)
Total number of cerebral cavernous malformations per participant	56 (21–145)	58 (21–149)	64 (23–154)	57 (24–129)	60 (24–133)	65 (25–139)
At least one Zabramski 1A cerebral cavernous malformation (extralesional bleeding)	5 (11%)	8 (17%)	7 (15%)	1 (5%)	4 (20%)	4 (20%)
At least one Zabramski 1B cerebral cavernous malformation (intralesional bleeding)	33 (70%)	37 (79%)	38 (81%)	9 (45%)	10 (50%)	12 (60%)
At least one haemorrhagic cerebral cavernous malformation (Zabramski 1A or 1B)	34 (72%)	39 (83%)	38 (81%)	9 (45%)	10 (50%)	12 (60%)
Signs of new cerebral cavernous malformation haemorrhage compared with previous MRI	..	24 (51%)	28 (60%)	..	8 (40%)	9 (45%)

Data are n (%) or median (IQR). Data are shown only for participants who had brain MRI available. *One patient excluded from analysis for outlier for volume. †Supratentorial includes the basal ganglia and cerebral hemispheres. ‡Infratentorial includes cerebellum and brainstem.

Table 2: **Cerebral cavernous malformation characteristics, as assessed by MRI, during 2-year follow-up in participants with familial cerebral cavernous malformation who did not have neurosurgical resection**

	Propranolol plus standard care group (n=57)	Standard care alone group (n=26)
Adverse events	15 (26%)	4 (15%)
Serious adverse events	6 (11%)	3 (11%)
Treatment-related serious adverse events	0	0
Nervous system disorders		
Epileptic seizure	2 (4%)	1 (4%)
Spinal haemorrhage	0	1 (4%)
Intracerebral haemorrhage	1 (2%)	0
Headache	4 (7%)	0
Paraesthesia	2 (4%)	0
Infections and infestations		
Sepsis	0	1 (4%)
Endocarditis	0	1 (4%)
Cardiac disorders		
Tachycardia	1 (2%)	0
Atrial fibrillation	1 (2%)	0
Myocardial infarction	1 (2%)	0
Eye disorders		
Diplopia	1 (2%)	0
Scotoma	1 (2%)	0
Injury, poisoning, and procedural complications		
Post-traumatic subarachnoid haemorrhage	1 (2%)	0
Renal and urinary disorders		
Kidney stones	1 (2%)	0
Reproductive system and breast disorders		
Squamous intraepithelial lesion on uterine cervix	0	1 (4%)
Skin and subcutaneous tissue disorders		
Phlegmon	1 (2%)	0
Musculoskeletal and connective tissue disorders		
Tibia fracture	1 (2%)	0
Metabolism and nutrition disorders		
Iatrogenic hyponatraemia	0	1 (4%)

Data are number of participants (%). Participants could have more than one adverse event, or the same adverse events more than once. Adverse events are categorised according to Medical Dictionary for Regulatory Activities terminology.

Table 3: **Adverse events**

Discussion

To our knowledge, Treat_CCM is the first completed pilot-phase randomised trial of propranolol for familial cerebral cavernous malformation and the largest published randomised trial for any form of cerebral cavernous malformation. We found that propranolol was safe, well tolerated, and showed a signal of efficacy for preventing symptomatic intracerebral haemorrhage and focal neurological deficit attributable to familial cerebral cavernous malformation, although this trial was not designed to be adequately powered to investigate efficacy. The magnitudes and directions of the estimated effects on efficacy and safety clinical outcomes were consistent in the intention-to-treat analysis and the per-protocol analysis restricted to participants with familial cerebral cavernous malformation with a genetic mutation. The observed event rate for the primary outcome was similar to the estimate that informed the design of this trial.[3]

The MRI substudy suggested that propranolol might not affect pre-existing cerebral cavernous malformation size but might reduce the number of new cerebral cavernous malformations over 2 years, consistent with one possible mechanism of action of propranolol observed in preclinical studies.[12,13] However, the mechanism of action of propranolol for cerebral cavernous malformation remains poorly understood. This molecule has a pleiotropic effect on vascular permeability and angiogenesis and was found to rescue the function of the endothelium and to reduce de novo cerebral cavernous malformation formation in preclinical models,[12,13] although propranolol did not significantly reduce the incidence of intracerebral haemorrhage in murine models.[12] Different mechanisms have been proposed, such as β-1 adrenergic receptor blockade,[12] or a morphological or functional improvement of pericyte–endothelial cell association, which is altered in cerebral cavernous malformation.[13]

This study has several strengths. Our methods reduced selection bias by random sequence generation using computerised blocks and allocation concealment. We reduced detection bias by masking outcome assessment to assigned treatment, although we could not reduce performance bias by masking participants and study personnel to the intervention and comparator (although many of our outcomes were objective and most might not have been affected by performance bias). Completeness of follow-up was excellent, thereby minimising attrition bias. We have reported most of the outcomes prespecified in the protocol, and will publish the remainder separately to avoid selective outcome reporting, and analysed the data according to our prespecified statistical analysis plan.

This study has some limitations. The trial recruited more than its target sample size. The steering committee decided to include as many patients as possible within the 18-month inclusion period, because of the expected low incidence of clinical outcome events. Additionally, this over-recruitment allowed us to compensate for unplanned enrolment of patients with sporadic cerebral cavernous malformation, due mostly to a single centre at which the study protocol was incorrectly applied. 83 participants were recruited and randomly assigned, although only 71 (86%) had familial cerebral cavernous malformation confirmed by genetic testing (nine participants had sporadic cerebral cavernous malformation and three had normal brain MRI). Nine of the 12 participants without familial cerebral cavernous malformation were recruited at one site, and propranolol was found to be undetectable in the plasma of the participants at this site, leaving concern about trial integrity at this site. However, because of the over-recruitment, we could correct this

unexpected recruitment of patients with sporadic cerebral cavernous malformation. Although headache is a relatively weak criterion for inclusion as cerebral cavernous malformation, qualifying clinical signs and symptoms (ie, epilepsy, focal neurological deficit, intracerebral haemorrhage) were equally distributed among patients who were later identified as not having familial cerebral cavernous malformation mutation.

Another limitation is that half of the participants assigned to the propranolol plus standard care group did not reach 80 mg per day propranolol, a dose that is conventionally considered as pharmacologically effective. Moreover, we did not implement a standardised dosing approach for propranolol. The minimum therapeutic dose of propranolol for familial cerebral cavernous malformation in humans, as reported in animal models,[26] is unknown. In this exploratory pilot-phase trial, variable doses of propranolol were allowed. Many patients did not tolerate (according to the investigator's judgement) 40 mg twice a day, so we introduced a protocol amendment (on Nov 30, 2018) to allow for lower doses to be given, thereby avoiding loss to follow-up of patients. Also, propranolol has a bioavailability of greater than 90% but 30–70% is metabolised on first passage though the liver, with large interindividual variability.[27] In a pharmacokinetics and pharmacodynamics study in healthy volunteers, average trough plasma concentrations of 20–30 ng/mL at steady state were associated with a significant decrease in heart rate.[28] The median concentration of 27·5 ng/mL found in the participants in Treat_CCM suggests that the dose was within a pharmacologically effective range. This finding is reassuring, assuming that β-blockade is the mechanism of action in cerebral cavernous malformation, although this mechanism has not been consistently shown.[12,13] In any future phase 3 trial, the minimum dose of 40 mg twice daily should be adhered to, with online monitoring of prescribed dose regimens.

Another potential limitation was our choice of a one-sided 80% CI in the sample size calculation. We took this approach because we were conducting a pilot-phase trial, and it allowed us to identify a sample size that would give us reasonable confidence in the result while not requiring too large a sample size (which increases the cost, time taken to conduct the study, and leads to the potential for more patients to be exposed to an ineffective treatment). An 80% CI satisfies the need for reasonable certainty for trial decision making but is small enough to deliver a study within a reasonable budget and timeframe, although we acknowledge some people might feel more comfortable using a 90% CI. Furthermore, we used a one-sided 80% CI because we were only interested in proceeding towards a main trial if there was some evidence of efficacy. If the intervention appeared to be harmful, it would not be reasonable to proceed, even if the finding was not significant.

Although our findings do not have immediate implications for clinical practice, they have implications for future clinical research. Our estimates of event rates and effect size show promise and are informative for the design of definitive clinical trials of propranolol for cerebral cavernous malformation. We have shown that a multicentre clinical trial for cerebral cavernous malformation is possible in Italy, and that adherence to protocol and target doses of propranolol will require careful attention in a main-phase trial. Our study has shown that a large proportion of participants can undergo serial brain MRI to monitor cerebral cavernous malformation progression as a response to treatment, which makes this a useful biomarker for future clinical trials in familial cerebral cavernous malformation. The choice of an open-label design was dictated mainly by the need to perform an investigator-driven trial with limited funding. It is conceivable that performance bias could be an issue with, for example, mild focal neurological deficit, so placebo would be ideal; the phase 2/3 Treat2_CCM trial, which has been submitted to Horizon EU for funding (not yet registered), will be double-blinded. Another important task would be to include the much more frequent sporadic cerebral cavernous malformation, and children with familial cerebral cavernous malformation.

Treat_CCM Writing Committee
Silvia Lanfranconi, Elisa Scola, Jennifer M T A Meessen, Roberto Pallini, Giulio A Bertani, Rustam Al-Shahi Salman, Elisabetta Dejana, Roberto Latini.

Treat_CCM Steering Committee
Elisabetta Dejana (Chair), Roberto Latini (co-Chair), Silvia Lanfranconi, Silvia Marino, Maria R Carriero, Laura Tassi, Roberto Pallini, Rustam Al-Shahi Salman, Marco Castori, Rita Treglia.

Contributors
ED and RL had the idea for the study and acquired funding. SL was the principal investigator of the trial, wrote the original draft, and edited the manuscript. ES, JMTAM, RA-SS, ED, and RL reviewed and edited the manuscript. ES analysed and cured all MRI data and validated MRI examinations. JMTAM (Treat_CCM statistician) and Enrico B Nicolis (Treat_CCM data manager; appendix p 7) verified the raw data before analyses. JMTAM made the statistical plan and did the statistical analyses. RP, GAB, and SL, in addition to the rest of the steering committee members, enrolled and followed up patients and acquired data. RL supervised the study and had final responsibility for the decision to submit for publication. All authors had full access to all the data and accept responsibility for the decision to submit for publication.

Declaration of interests
RASS has received a National Institute of Health Research Health Technology Assessment trial grant for the Cavernomas A Randomised Effectiveness (CARE) pilot trial (NIHR128694), paid to the University of Edinburgh; consultancy fees from Recursion Pharmaceuticals, paid to the University of Edinburgh; is on the Scientific Advisory Board for Angioma Alliance (unfunded); and is Medical Advisor and Patron for Cavernoma Alliance UK (unfunded). RL has received speaker fees from Neurelis. All other authors declare no competing interests.

Data sharing
The data are stored at the Department of Cardiovascular Medicine, Mario Negri Institute for Pharmacological Research in Milan, Italy. Deidentified individual participant data and the data dictionary, study protocol, and informed consent form will be made available for scientific purposes upon formal request and consequent approval of the proposal by the Steering Committee after publication. Requests should be sent to the corresponding author.

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