Bleeding risk of cerebral cavernous malformations in patients on β -blocker medication: a cohort study

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OBJECTIVE Cerebral cavernous malformations (CCMs) are frequently diagnosed vascular malformations of the brain. Although most CCMs are asymptomatic, some can be responsible for intracerebral hemorrhage or seizures. In selected cases, microsurgical resection is the preferred treatment option. Treatment with the unselective β -blocker propranolol has been presumed to stabilize and eventually lead to CCM size regression in a limited number of published case series; however, the underlying mechanism and evidence for this effect remain unclear. The aim of this study was to investigate the risk for CCM-related hemorrhage in patients on long-term β -blocker medication.

METHODS A single-center database containing data on patients harboring CCMs was retrospectively interrogated for a time period of 35 years. The database included information about hemorrhage and antihypertensive medication. Descriptive and survival analyses were performed, focusing on the risk of hemorrhage at presentation and during follow-up (first or subsequent hemorrhage) in patients on long-term β -blocker medication versus those who were not. Follow-up was censored at the first occurrence of new hemorrhage, surgery, or the last clinical review. For purposes of this analysis, the β -blocker group was divided into the following main subgroups: any β -blocker, β 1-selective β -blocker, and any unselective β -blocker.

RESULTS Of 542 CCMs among 408 patients, 81 (14.9%) were under treatment with any β -blocker; 65 (12%) received β 1-selective β -blocker, and 16 (3%) received any unselective β -blocker. One hundred thirty-six (25.1%) CCMs presented with hemorrhage at diagnosis. None of the β -blocker groups was associated with a lower risk of hemorrhage at the time of diagnosis in a univariate descriptive analysis (any β -blocker: $p = 0.64$, β 1-selective: $p = 0.93$, any unselective β -blocker: $p = 0.25$). Four hundred ninety-six CCMs were followed up after diagnosis and included in the survival analysis, for a total of 1800 lesion-years. Follow-up hemorrhage occurred in 36 (7.3%) CCMs. Neither univariate descriptive nor univariate Cox proportional-hazards regression analysis showed a decreased risk for follow-up hemorrhage under treatment with β -blocker medication (any β -blocker: $p = 0.70$, HR 1.19, 95% CI 0.49–2.90; β 1-selective: $p = 0.78$, HR 1.15, 95% CI 0.44–3.00; any unselective β -blocker: $p = 0.76$, HR 1.37, 95% CI 0.19–10.08). Multivariate Cox proportional-hazards regression analysis including brainstem location, hemorrhage at diagnosis, age, and any β -blocker treatment showed no reduced risk for follow-up hemorrhage under any β -blocker treatment ($p = 0.53$, HR 1.36, 95% CI 0.52–3.56).

CONCLUSIONS In this retrospective cohort study, β -blocker medication does not seem to be associated with a decreased risk of CCM-related hemorrhage at presentation or during follow-up.

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KEYWORDS cerebral cavernous malformation; cavernous angioma; beta-blocker; β -blocker; propranolol; intracranial hemorrhage; vascular disorders

CEREBRAL cavernous malformations (CCMs) are the second most diagnosed vascular malformation of the brain after aneurysms.⁷ Most patients present with seizures, hemorrhage, and/or focal neurological deficits or are diagnosed incidentally. Overall annual hemorrhage rates from 0.7% to 6.2% per patient-year are

reported in pooled meta-analyses.^{6,8–10} In patients suffering from symptomatic CCMs with recurrent hemorrhages, microsurgical resection is one of the preferred treatment modalities.

Treatment of cutaneous hemangiomas in infants using the unselective β -blocker propranolol (β 1- and β 2-ad-

ABBREVIATIONS CCM = cerebral cavernous malformation.

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renoceptor antagonists) has shown great clinical success in reducing the size of hemangiomas and effecting a nearly normal appearance after several months of administration.^{12,14} Given the fact that CCMs and infantile hemangiomas are histopathologically similar lesions,^{5,21} propranolol has been discussed as a potential new treatment for patients with CCM. So far, a limited number of case series have suggested that propranolol can lead to size reduction or stabilization of CCMs in terms of the likelihood of hemorrhage.^{3,18,20,24,28} However, the underlying mechanisms of the treatment effect of propranolol in cutaneous hemangiomas have not been fully elucidated. Proposed mechanisms include vasoconstriction, inhibition of catecholamine-induced angiogenesis, apoptotic effects on hemangioma-derived endothelial cells, inhibition of the renin-angiotensin system, and the differentiation of endothelial cells.^{1,11,13,15,25,27} It is unclear whether the therapeutic effect of propranolol is mediated via β_1 or β_2 receptors.¹¹ Moreover, other β -blockers, such as the β_1 -selective drug atenolol, have also shown good clinical results in cutaneous hemangiomas.^{4,23} Since CCM-related hemorrhages are the main reason for focal neurological deficits and an important factor in clinical decision-making as regards potential resection, the aim of this study was to investigate whether long-term β -blocker medication leads to a lower bleeding risk for CCMs at presentation or during follow-up.

Methods

Data Collection

Data collection and study design were approved by the local institutional ethics committee. A retrospective database analysis of patients with a diagnosis of CCM in the period from January 1980 to September 2015 was performed. Diagnosis of CCM was confirmed by a neuroradiologist. The database contained demographic, clinical, radiological, and treatment-related information. Cases were included in the study regardless of the clinical management plan for the CCM. For the purposes of follow-up hemorrhage analysis, patients were excluded if they had only one clinical contact or had been surgically treated at the day of referral. Follow-up was started at the day of referral, first clinical consultation, or first radiological diagnosis of CCM. A CCM-related hemorrhage was defined as a new clinical event (focal deficit, seizure, or severe headache) in association with radiological evidence (CT or MRI) of acute hemorrhage or autopsy data suggesting acute hemorrhage. If follow-up hemorrhage did not occur, cases were censored at the first date of treatment (surgery) or the last available follow-up. Analyzed characteristics included 1) sex, 2) age (continuous variable), 3) history of hypertension, 4) antihypertensive medication, 5) family history of CCMs, 6) CCM location, 7) associated developmental venous anomalies, 8) hemorrhage at diagnosis, 9) surgical treatment, and 10) follow-up hemorrhage.

Statistical Analysis

A per-CCM analysis was chosen to stratify hemorrhage at diagnosis and during follow-up for each CCM. Descriptive statistics were used to report frequencies, means, ranges, and standard deviation. Continuous variables are

FIG. 1. Flowchart indicating the patient selection for study inclusion.

presented as the means $\pm$ standard deviation. For comparisons between any 2 groups, the Pearson chi-square test was performed. Univariate and multivariate Cox regression survival analyses were performed to estimate the hemorrhage risks and hazard ratio. Time (days of follow-up) was used as the continuous variable and hemorrhage during follow-up as the event. Statistical significance was established at the alpha level of $p = 0.05$. Statistical analyses were performed using the SPSS software package (version 21, IBM Corp.).

Results

Patient Cohort

Six hundred ninety-one patients were radiologically diagnosed with a CCM during the time period from January 1980 to September 2015 (Fig. 1). Ninety-six patients were excluded from our analysis because of missing medical records, and 187 patients were excluded because the diagnosis of CCM was one potential differential diagnosis that was not confirmed by further imaging. Four hundred eight patients harboring 542 CCMs were included in the data analysis. Follow-up was available for 496 (91.5%) CCMs, for a total of 1800 lesion-years over a mean follow-up of 44.2 ± 56.2 months. A summary of the characteristics of the cohorts is displayed in Table 1.

β -Blocker Medication

A total of 408 patients were screened for medication, 142 (34.8%) of whom had received long-term antihypertensive medication. For the purposes of this analysis, the following results are expressed as a factor per CCM. The β -blocker medication group was divided into the follow-

TABLE 1. Summary of characteristics among 408 patients with 542 CCMs

Variable	No. (%)		
	Total	Any β -Blocker	No β -Blocker
No. of patients	408 (100%)	67 (100%)	341 (100%)
Female sex	192 (47.1%)	27 (40.3%)	165 (48.4%)
Mean age in yrs	50.6 $\pm$ 18.9	62.5 $\pm$ 14.9	48.2 $\pm$ 18.7
History of hypertension	147 (36%)	62 (92.5%)	85 (24.9%)
Antihypertensive medication	142 (34.8%)	67 (100%)	75 (22%)
Family history of CCM	12 (2.9%)	0 (0%)	12 (3.5%)
No. of CCMs	542 (100%)	81 (100%)	461 (100%)
Location			
Frontal	135 (24.9%)	13 (16%)	122 (26.5%)
Parietal	46 (8.5%)	7 (8.6%)	39 (8.5%)
Temporal	95 (17.5%)	9 (11.1%)	86 (18.7%)
Occipital	29 (5.4%)	5 (6.2%)	24 (5.2%)
Basal ganglia	42 (7.7%)	9 (11.1%)	33 (7.2%)
Cerebellar	73 (13.5%)	12 (14.8%)	61 (13.2%)
Brainstem	65 (12%)	18 (22.2%)	47 (10.2%)
Centrum semiovale	57 (10.5%)	8 (9.9%)	49 (10.6%)
Associated DVA	94 (17.3%)	14 (17.3%)	80 (17.4%)
Hemorrhage at diagnosis	136 (25.1%)	22 (27.2%)	114 (24.7%)
Surgical treatment	86 (15.9%)	4 (4.9%)	82 (17.8%)
FU available	496 (91.5%)	69 (85.2%)	427 (92.6%)
Mean FU in months	44.2 $\pm$ 56.2	42 $\pm$ 54.6	44.5 $\pm$ 56.5
FU hemorrhage	36 (7.3%)	6 (8.7%)	30 (7%)

DVA = developmental venous anomaly; FU = follow-up.

ing main subgroups (Fig. 2): any β -blocker, β 1-selective β -blocker, and any unselective β -blocker. Further subgroups were α - and β -blocker and exclusive unselective β -blocker. Of the 542 CCMs, 81 (14.9%) were under long-term treatment with any β -blocker; 65 (12%) received β 1-selective β -blockers, and 16 (3%) received any unselective β -blockers. The latter group consisted of the α - and β -blockers (13 [2.4%]) and exclusive unselective β -blockers (3 [0.6%]) subgroups. For cumulative daily doses and distributions throughout the day see Table 2.

TABLE 2. Dosage of β -blockers in 67 patients

Drug (no. of patients)	Mean No. of Daily Doses (range)	Mean Total Daily Dose in mg (range)
α - & β -blocker		
Carvedilol (9)	1.44 $\pm$ 0.53 (1–2)	27.5 $\pm$ 15.7 (6.25–50)
Labetalol (1)	3	600
Exclusive unselective β -blocker		
Oxprenolol (1)	1	40
Propanolol (2)	2.5 $\pm$ 0.7 (2–3)	90 $\pm$ 42.43 (60–120)
β 1-selective β -blocker		
Atenolol (6)	1.33 $\pm$ 0.82 (1–3)	60.42 $\pm$ 45.01 (25–150)
Bisoprolol (4)	1.25 $\pm$ 0.5 (1–2)	3.13 $\pm$ 1.25 (2.5–5)
Metoprolol (38)	1.39 $\pm$ 0.5 (1–2)	66.12 $\pm$ 51.7 (12.5–200)
Nebivolol (6)	1.17 $\pm$ 0.41 (1–2)	3.96 $\pm$ 1.66 (1.25–5)

Hemorrhage at Diagnosis

One hundred thirty-six (25.1%) CCMs presented with hemorrhage at diagnosis. Descriptive analysis showed no reduced risk of hemorrhage at diagnosis under β -blocker medication (any β -blocker: $p = 0.64$, OR 1.14, 95% CI 0.67–1.94; β 1-selective β -blocker: $p = 0.93$, OR 0.97, 95% CI 0.53–1.77; any unselective β -blocker: $p = 0.25$, OR 1.83, 95% CI 0.65–5.13; α - and β -blockers: $p = 0.26$, OR 1.90, 95% CI 0.61–5.91; exclusive unselective β -blocker: $p = 0.74$, OR 1.50, 95% CI 0.14–16.63). In addition, no other antihypertensive drug showed a significant effect (Table 3).

Follow-Up Hemorrhage

Follow-up hemorrhage was observed in 36 (7.3%) of the 496 CCMs. Treatment with β -blockers did not lead to a reduced risk of follow-up hemorrhage in a descriptive analysis (any β -blocker: $p = 0.62$, OR 1.26, 95% CI 0.50–3.20; β 1-selective β -blocker: $p = 0.64$, OR 1.27, 95% CI 0.47–3.40; any unselective β -blocker: $p = 0.88$, OR 1.17, 95% CI 0.15–9.30; α - and β -blockers: $p = 0.65$, OR 1.61, 95% CI 0.20–13.28; exclusive unselective β -blocker: $p = 0.63$, OR not applicable; Table 4). No other antihypertensive drug showed a significant effect.

Additional survival analysis with univariate Cox proportional-hazards regression showed no risk reduction for

Group	Receptor antagonism	n of 542 CCMs (%)	Drugs	Classification, n of 542 CCMs (%)
α - and β -blocker	α 1 / β 1 / β 2	13 (2.4%)	Carvedilol, Labetalol	<div>any unselective β-blocker, 16 (3%)</div> <div>any β-blocker, 81 (14.9%)</div>
exclusive unselective β -blocker	β 1 / β 2	3 (0.6%)	Oxprenolol, Propanolol	
β 1-selective β -blocker	β 1	65 (12%)	Atenolol, Bisoprolol, Metoprolol, Nebivolol	

FIG. 2. β -blocker medication groups: main subgroups are indicated with solid black frames and other subgroups with dashed black frames.

TABLE 3. Univariate analysis of risk for hemorrhage at diagnosis among 542 CCMs

Drug	p Value* (OR, 95% CI)
β -blocker medication	
Any β -blocker	0.64 (1.14, 0.67–1.94)
β 1-selective β -blocker	0.93 (0.97, 0.53–1.77)
Any unselective β -blocker	0.25 (1.83, 0.65–5.13)
α - & β -blockers	0.26 (1.90, 0.61–5.91)
Exclusive unselective β -blocker	0.74 (1.50, 0.14–16.63)
Other antihypertensive drugs	
ACE inhibitor	0.99
α -blocker	0.19
α 2-adrenergic agonist	0.56
Angiotensin II receptor antagonist	0.95
Calcium channel blocker	0.63
Nitrates	0.32
Renin inhibitor	0.56

ACE = angiotensin-converting enzyme.

* Pearson chi-square.

follow-up hemorrhage under β -blocker medication (any β -blocker: $p = 0.70$, HR 1.19, 95% CI 0.49–2.90; β 1-selective β -blocker: $p = 0.78$, HR 1.15, 95% CI 0.44–3.00; any unselective β -blocker: $p = 0.76$, HR 1.37, 95% CI 0.19–10.08; α - and β -blockers: $p = 0.64$, HR 1.60, 95% CI 0.22–11.78; exclusive unselective β -blocker: $p = 0.83$, HR 0.49, 95% CI 0.00–34 $\times 10^9$; Table 4).

Multivariate Cox proportional-hazards regression analysis including brainstem location, hemorrhage at diagnosis (both factors described as being associated with an increased risk of CCM-related hemorrhage^{10,26}), age, and any β -blocker medication confirmed that brainstem loca-

TABLE 5. Multivariate analysis of factors that influence follow-up hemorrhage among 496 CCMs

Factor	p Value* (HR, 95% CI)
Any β -blocker	0.53 (1.36, 0.52–3.56)
Brainstem location	0.03 (2.40, 1.09–5.29)
Hemorrhage at diagnosis	0.69 (1.15, 0.57–2.34)
Younger age	0.01 (0.98, 0.96–0.99)

* Cox regression.

tion ($p = 0.03$, HR 2.40, 95% CI 1.09–5.29) and younger age ($p = 0.01$, HR 0.98, 95% CI 0.96–0.99) were significantly associated with follow-up hemorrhage. In the same analysis, any β -blocker medication was not associated with a reduced risk for follow-up hemorrhage ($p = 0.53$, HR 1.36, 95% CI 0.52–3.56; Table 5).

Discussion

Cerebral cavernous malformations are low-flow, low-pressure vascular lesions, and CCM-related hemorrhage usually leads to compression of the adjacent neural tissue rather than its destruction.²⁸ Depending on the single lesion location and patient characteristics, CCMs can be asymptomatic or present with headache, focal neurological deficits, and/or seizures. Hemorrhage at diagnosis has been reported as a significant risk factor for subsequent follow-up hemorrhage.^{8,10} In order to assess the possible role of β -blocker medication in the natural history of CCMs, we focused on CCM-related hemorrhage as the relevant clinical readout.

The results of our study showed no relation between β -blocker medication and the occurrence of hemorrhage at presentation or during follow-up. In addition, we could

TABLE 4. Univariate analysis of risk for follow-up hemorrhage among 496 CCMs

Drug	p Value* (OR, 95% CI)	p Value† (HR, 95% CI)
β -blocker medication		
Any β -blocker	0.62 (1.26, 0.50–3.20)	0.70 (1.19, 0.49–2.90)
β 1-selective β -blocker	0.64 (1.27, 0.47–3.40)	0.78 (1.15, 0.44–3.00)
Any unselective β -blocker	0.88 (1.17, 0.15–9.30)	0.76 (1.37, 0.19–10.08)
α - & β -blocker	0.65 (1.61, 0.20–13.28)	0.64 (1.60, 0.22–11.78)
Exclusive unselective β -blocker	0.63 (NA)	0.83 (0.49, 0.00–34 $\times 10^9$)
Other antihypertensive drugs		
ACE inhibitor	0.56	
α -blocker	0.53	
α 2-adrenergic agonist	0.78	
Angiotensin II receptor antagonist	0.66	
Calcium channel blocker	0.33	
Nitrates	0.69	
Renin inhibitor	0.78	

NA = not applicable.

* Pearson chi-square.

† Cox regression.

not find a relation with any other antihypertensive drug. To our knowledge, this is the largest consecutive patient cohort on the topic so far, including 408 patients harboring 542 CCMs, 81 (14.9%) of which were under β -blocker medication. Available case series on the topic have focused on treatment with the unselective β -blocker propranolol and have reported size reductions in CCMs or stabilization of the hemorrhage rate.^{3,18,20,28} The idea of propranolol treatment for CCM patients is driven by the reported effects in infants suffering from histopathologically similar cutaneous hemangiomas.⁹ The mechanisms underlying this therapeutic effect have not been elucidated as yet, and it is not known whether the effect is mediated via antagonism of β_1 or β_2 receptors or via any other pharmaceutical property of propranolol. In our cohort, only 3 (0.6%) CCMs were under treatment with the exclusive unselective β -blocker (β_1 and β_2 antagonism) propranolol ($n = 2$) or oxprenolol ($n = 1$). Exclusive unselective β -blockers have been grouped with α - and β -blockers (α_1 , β_1 , and β_2 antagonism) in the subgroup of any unselective β -blockers, containing every drug with β_1 and β_2 antagonism. Sixteen (3.0%) CCMs were under treatment with any unselective β -blockers, 13 (2.4%) of which received the α - and β -blockers carvedilol ($n = 12$) and labetalol ($n = 1$). Therefore, the statistical significance for the small subgroup of exclusive unselective β -blockers is limited in our study.

The β_1 -selective β -blocker atenolol has been shown to be effective for infantile cutaneous hemangiomas as well,^{4,23} suggesting that β_1 -selective β -blockers may also have an effect on CCMs. With this line of thinking, we investigated the influence of all types of β -blockers in our analysis. The majority, 65 (12%) CCMs, were under treatment with β_1 -selective β -blockers such as metoprolol. Like any other subgroup, β_1 -selective β -blockers were not associated with a lower risk of CCM-related hemorrhage. Multiple CCMs are more likely in patients with a family history of CCM.¹⁹ So far, we know of three gene defects (*CCM1–3*) that lead to the development of CCMs in an autosomal dominant fashion.¹⁷ A possible effect of β -blockers may be stronger in a subgroup of patients harboring a specific genetic predisposition and may be underrepresented in this study. However, a recent report has also shown an effect of propranolol in a patient with multiple CCMs who did not have a *CCM1–3* mutation.²⁴

In this study, brainstem location and younger age were predictors of follow-up hemorrhage in the multivariate Cox regression analysis, which is consistent with the literature and indicates similarity to other cohorts.^{2,9,10,16,22} In the same analysis, however, hemorrhage at diagnosis was not a predictor.

Overall, we could not find evidence for a reduced or an increased risk of CCM-related hemorrhage under β -blocker medication. This does not exclude the possibility that β -blockers may lead to size reductions or may have any other effect on CCMs that has not been measured in this trial.

Study Limitations

Due to the nature of our study, the results are subject to the well-known methodological limitations of retro-

spective and single-center cohorts. Brainstem location, which has been reported to be associated with a higher risk of CCM-related hemorrhage in the literature,^{10,26} was not equally distributed in the patient groups on any β -blocker or no β -blocker. Nevertheless, hemorrhage at diagnosis and on follow-up was equally distributed in these two groups. Multivariate survival analysis including brainstem location, age, and hemorrhage at diagnosis (known risk factors for follow-up hemorrhage) confirmed that β -blocker medication is not associated with CCM-related hemorrhage. Furthermore, the likelihood of older patients receiving β -blocker medication and undergoing regular medical examinations is higher, resulting in a possible selection bias regarding the detection rate of follow-up hemorrhage. However, in our cohort analysis, CCM-related hemorrhage during follow-up was associated with younger age.

The nature of the research question addressing whether CCM patients on β -blocker medication suffer from symptomatic hemorrhage, even in a large CCM cohort, leads to relatively small incidence rates, resulting in small effect sizes. Finally, the exclusive unselective β -blocker subgroup ($n = 3$) was too small to reach statistical significance, and the mean follow-up of 3.7 years is a limitation with regard to CCMs as a potential lifetime disease.

Conclusions

The results of our study showed no reduced risk of hemorrhage at presentation or during follow-up for CCMs under treatment with β -blocker medication.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Goldberg, Bervini. Acquisition of data: Goldberg, Jaeggi, Mordasini, Bervini. Analysis and interpretation of data: Goldberg, Jaeggi, Schoeni, Bervini. Drafting the article: Goldberg. Critically revising the article: Mordasini, Raabe, Bervini. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Goldberg. Statistical analysis: Goldberg, Bervini. Administrative/technical/material support: Raabe. Study supervision: Raabe, Bervini.

Supplemental Information

Previous Presentations

Portions of this work have been orally presented at the 4th Annual European Association of Neurosurgical Societies Vascular Neurosurgery Section Meeting held on September 8–9, 2017, in Nice, France.

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