ORIGINAL ARTICLE

Anaemia at admission is associated with poor clinical outcome in cerebral venous thrombosis

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Background and purpose: Anaemia is associated with poor clinical outcome after ischaemic and haemorrhagic stroke. The association between anaemia and outcome in patients with cerebral venous thrombosis (CVT) was examined.

Methods: Consecutive adult patients with CVT were included from seven centres. Anaemia at admission was scored according to World Health Organization definitions. Poor clinical outcome was defined as a modified Rankin Scale score 3–6 at last follow-up. A multiple imputation procedure was applied for handling missing data in the multivariable analysis. Using binary logistic regression analysis, adjustments were made for age, sex, cancer and centre of recruitment (model 1). In a secondary analysis, adjustments were additionally made for coma, intracerebral haemorrhage, non-haemorrhagic lesion and deep venous system thrombosis (model 2). In a sensitivity analysis, patients with cancer were excluded.

Results: Data for 952 patients with CVT were included, 22% of whom had anaemia at admission. Patients with anaemia more often had a history of cancer (17% vs. 7%, $P < 0.001$) than patients without anaemia. Poor clinical outcome (21% vs. 11%, $P < 0.001$) and mortality (11% vs. 6%, $P = 0.07$) were more common amongst patients with anaemia. After adjustment, anaemia at admission increased the risk of poor outcome [adjusted odds ratio (aOR) 2.4, 95% confidence interval (CI) 1.5–3.7, model 1]. Model 2 revealed comparable results (aOR 1.9, 95% CI 1.2–3.2), as did the sensitivity analysis excluding patients with cancer (aOR 2.3, 95% CI 1.3–3.8, model 1).

Conclusion: The risk of poor clinical outcome is doubled in CVT patients presenting with anaemia at admission.

Introduction

Cerebral venous thrombosis (CVT) is a rare thrombotic disorder and an infrequent cause of stroke that mainly affects young adults and children [1]. Approximately 9%–27% of patients with CVT have anaemia at presentation, and the presence of anaemia has been shown to increase the risk of CVT [2,3]. In adults, the most common cause of microcytic anaemia is iron deficiency. The latter has been associated with thrombocytosis and increased concentrations of factor VIII, which are risk factors for venous thrombosis [4,5].

In patients with ischaemic and haemorrhagic stroke, the presence of anaemia has been found to be

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associated with poor clinical outcome [6,7]. One proposed mechanism is that low haemoglobin levels impair oxygen delivery to the damaged brain and induce an inflammatory response [8]. Data from a recent single-centre study suggest that an association between anaemia and poor clinical outcome also exists in CVT, but this study had a limited sample size [9]. The aim of our study was to assess the association between anaemia and poor clinical outcome in CVT, using data from a large international CVT consortium.

Methods

Study design and patient inclusion

Data were derived from seven hospital-based CVT registries from the international CVT consortium: Amsterdam UMC (The Netherlands), Helsinki University Hospital (Finland), Sahlgrenska University Hospital (Sweden), Inselspital Bern University Hospital (Switzerland), National Institute Manuel Velasco Suarez (Mexico), Hamadan University of Medical Science (Iran) and Hospital Dr Calderón Guardia (Costa Rica). Detailed information on consecutive patients with CVT has been collected prospectively since January 2006 (Amsterdam), January 2010 (Helsinki), January 2000 (Bern), January 2008 (Mexico City), April 2012 (Hamadan) and May 2015 (San José). Data were collected retrospectively from January 1987 until January 2010 (Helsinki) and January 1997 (Gothenburg). Since only observational data were collected in each of the CVT registries, written informed consent was not required under applicable national laws. All data that were collected were part of routine patient care. According to local regulations, in this specific situation no formal ethical approval is required.

All adult patients diagnosed with CVT until 1 March 2018 were included. To increase the generalizability of the results, no exclusion criteria were applied. Data were recorded using a standardized case record form. Diagnosis of CVT had to be confirmed with computed tomography venography, magnetic resonance imaging with magnetic resonance venography, catheter angiography or autopsy [10]. Poor clinical outcome was defined as a score of 3–6 on the modified Rankin Scale (mRS), assessed at the last available follow-up contact. Mortality and mRS 0–1 were also analysed separately.

Measurement of haemoglobin and definition of anaemia

Haemoglobin concentration was measured in venous blood samples as part of routine medical care, and the first haemoglobin measurement that was performed at arrival at the hospital was used for analysis, with a maximum of 48 h after admission. The World Health Organization definitions for anaemia were used: men, haemoglobin <130 g/l; non-pregnant women, haemoglobin <120 g/l; and pregnant women, haemoglobin <110 g/l [11]. Patients with hyperhaemoglobinaemia (men >175 g/l, women >155 g/l) were categorized in the 'no anaemia' group. Anaemia subgroups were defined as mild anaemia (men 110–129 g/l, non-pregnant women 110–119 g/l, pregnant women 100–109 g/l) and moderate to severe anaemia (men/non-pregnant women <110 g/l, pregnant women <100 g/l). Anaemia was further categorized as microcytic [mean corpuscular volume (MCV) <80 fL], normocytic (MCV 80–100 fL) or macrocytic (MCV >100 fL).

Statistical analysis

Patients with anaemia were compared to those without anaemia. Differences between groups were analysed with a chi-squared test, Fisher's exact test or the Mann–Whitney U test, as appropriate. A multiple imputation procedure was used to account for handling missing data in the multivariable analysis. The following variables were imputed: haemoglobin concentration, MCV, thrombocytes, baseline coma, intracerebral haemorrhage, non-haemorrhagic lesion (cerebral oedema/infarction), deep venous system thrombosis and mRS at follow-up. The proportion of patients with missing data prior to imputation is reported and for baseline characteristics only non-imputed data are shown. In total, five datasets were imputed, and results were pooled according to Rubin's rules. Multivariable binary logistic regression analysis was applied to study the association between admission anaemia and clinical outcome (mRS 0–2 vs. 3–6, mRS 0–1 vs. 2–6, and mortality), using two different models. In the first model, potential confounders that were considered to have a causal relation both with anaemia and with outcome were adjusted for age, sex and cancer, and for centre of recruitment. In the second model, all variables of model 1 were used and additionally known predictors of poor outcome in CVT were adjusted for coma, intracerebral haemorrhage, non-haemorrhagic lesion and deep venous system thrombosis [3]. A sensitivity analysis excluding patients with cancer was performed. Multivariable ordinal logistic regression analysis was also used to calculate the adjusted common odds ratio for a shift in the direction of poor clinical outcome on the mRS in the presence of anaemia. In a separate analysis, haemoglobin was analysed as a continuous

Table 1 Baseline characteristics and treatment

	Anaemia $N = 196$	No anaemia $N = 678$	P value
Demographics			
Women, *n*, %	144/196 (74%)	464/678 (68%)	0.17
Median age (IQR)	38 (27–49)	42 (29–54)	0.02
Onset to diagnosis [median (IQR) in days]	4 (2–9)	5 (2–10)	0.25
Risk factors, *n*/*N* (%)			
Oral contraceptive use[a]	57/142 (40%)	236/461 (51%)	0.02
Pregnancy, puerperium[a]	25/144 (17%)	46/464 (10%)	0.02
Previous thrombosis	15/196 (8%)	63/671 (9%)	0.46
Cancer	33/196 (17%)	50/677 (7%)	<0.001
Characteristics at presentation			
Headache	158/192 (82%)	587/672 (87%)	0.07
Focal neurological deficits	126/193 (65%)	391/676 (58%)	0.06
Seizure (s)	74/195 (38%)	202/673 (30%)	0.04
Coma (GCS < 9)	21/196 (11%)	31/677 (5%)	0.001
Laboratory findings[b]			
Glucose (mmol/l)	6.3 ± 1.7	6.5 ± 2.4	0.57
Mean corpuscular volume (fl)	81 ± 12	89 ± 5	<0.001
Thrombocyte count (10^9/l)	283 ± 117	260 ± 83	0.28
Radiological characteristics			
Any parenchymal lesion	118/194 (61%)	348/677 (51%)	0.02
Non-haemorrhagic lesion	85/194 (44%)	205/677 (30%)	<0.001
Intracranial haemorrhage	69/193 (36%)	213/677 (32%)	0.26
Superior sagittal sinus thrombosis	95/195 (49%)	361/678 (53%)	0.27
Deep venous system thrombosis	20/195 (10%)	72/678 (11%)	0.88
Thrombosis in multiple veins or sinus (≥3)	32/195 (16%)	165/178 (24%)	0.02
Treatment			
Anticoagulation	186/196 (95%)	654/677 (97%)	0.27
Endovascular treatment	15/196 (8%)	37/678 (6%)	0.25
Decompressive hemicraniectomy	17/196 (9%)	33/678 (5%)	0.04

GCS, Glasgow Coma Scale; IQR, interquartile range. [a]Percentage of women. [b]mean (±SD).

variable, and in subgroup analyses mild versus moderate or severe anaemia was stratified. Further, subgroup analysis was performed in men and women, women who were pregnant or postpartum, women using oral contraceptives, and in CVT patients with cancer. All data were analysed with SPSS statistical software, version 24 (IBM, Armonk, NY, USA).

Results

There were 952 patients diagnosed with CVT within the study period ($n = 225$ Amsterdam cohort, $n = 246$ Helsinki cohort, $n = 127$ Gothenburg cohort, $n = 182$ Bern cohort, $n = 77$ Mexico City cohort, $n = 70$ Hamadan cohort, $n = 25$ San José cohort). Numbers of patients with imputed data were as follows: haemoglobin $n = 78$, MCV $n = 238$, thrombocytes $n = 88$, baseline coma $n = 4$, intracerebral haemorrhage $n = 6$, non-haemorrhagic lesion $n = 5$, deep venous system thrombosis $n = 1$, mRS at last follow-up $n = 2$. After exclusion of the 78 patients with missing haemoglobin, 874 patients were included in the baseline comparison (Table 1). There were no significant differences in the baseline characteristics between the included and excluded patients (data not shown).

Of the 874 included patients, 196 (22%) had anaemia [median haemoglobin 109 g/l, interquartile range (IQR) 94–117]. Of the patients with anaemia, 102 patients (52%) had mild anaemia and 94 (48%) had moderate to severe anaemia. There were 56 patients (29%) with microcytic anaemia, 98 patients (50%) with normocytic anaemia and two patients (1%) with macrocytic anaemia. Hyperhaemoglobinaemia was present in 42 patients. Causes of anaemia are reported in Table 2. Haemoglobin values normalized in 10 patients during admission, one of whom received a blood transfusion. In total, 26/196 patients (13%) received a blood transfusion during admission. Patients with admission anaemia were younger (median age 37 vs. 42 years, $P = 0.02$), more often had a history of cancer (17% vs. 7%, $P < 0.001$), more often presented with coma (11% vs. 5%, $P = 0.001$) and more often had non-haemorrhagic parenchymal lesions (44% vs. 30%, $P < 0.001$, Table 1).

Table 2 Cause of anaemia

Suspected cause	Frequency *n*/*N* (%)
Iron deficiency	43/196 (22)
Cancer	28/196 (14)
Haematological condition other than cancer	16/196 (8)
Inflammatory bowel disease or related gastrointestinal condition	15/196 (8)
Pregnancy/puerperium	20/196 (10)
Infection	10/196 (5)
Other	15/196 (8)
Unknown	49/196 (25)

Median duration of follow-up was 6 months in patients with anaemia (IQR 5–13 months) and 7 months in patients without anaemia (IQR 6–12 months, $P = 0.276$). Poor clinical outcome was more common in patients with anaemia (mRS 3–6: 21% vs. 11%, $P < 0.001$). Mortality was also increased in anaemic patients (11% vs. 6%; $P = 0.07$). After adjustment, anaemia at baseline was associated with an increased risk of poor clinical outcome (adjusted odds ratio [aOR] mRS 3–6: 2.4, 95% CI 1.5–3.7, model 1; Table 3). There was also a trend towards an increased risk of mortality (aOR 1.7, 95% CI 0.9–3.1) and a lower chance of mRS 0–1 (aOR 0.7, 95% CI 0.5–1.0). Additional adjustment for coma, intracerebral haemorrhage, non-haemorrhagic lesion and deep venous system thrombosis revealed similar results (aOR 1.9, 95% CI 1.2–3.2, model 2). The results of the sensitivity analysis excluding patients with cancer were comparable to the main analysis (aOR 2.3, 95% CI 1.3–3.8).

The full distribution of the mRS is shown in Fig. 1. Ordinal logistic regression analysis demonstrated a shift in the distribution of the mRS towards poor clinical outcome in the presence of anaemia (adjusted common odds ratio 1.4, 95% CI 1.0–1.9). When haemoglobin was analysed as a continuous variable, there was an inverse association between haemoglobin and poor clinical outcome (aOR for mRS 3–6 per 10 g/l increase in haemoglobin concentration: 0.83, 95% CI 0.72–0.95).

Stratification by severity of anaemia revealed that the risk of poor clinical outcome was increased in both patients with mild and patients with moderate to severe anaemia (aOR mild anaemia 1.8, 95% CI 1.0–3.3; aOR moderate to severe anaemia 3.1, 95% CI 1.8–5.5; Table 4). Subgroup analyses demonstrated an increased risk of poor clinical outcome in both male and female anaemic patients with CVT (Table 5).

Discussion

In this large international observational study, anaemia was found to be an independent predictor of poor clinical outcome in patients with CVT. The risk of death or dependency (mRS 3–6) was approximately doubled in patients with anaemia. Furthermore, a meaningful sign of the exposure–response relationship was observed.

The strength of the association between anaemia and poor clinical outcome in our CVT cohort is similar to results of studies on arterial ischaemic stroke and haemorrhagic stroke [6]. Our study may have been underpowered to detect an association with mortality. Studies on ischaemic stroke had data of thousands of patients available and the rate of mortality is also higher is this condition. Only one other study was identified that examined the association between outcome and anaemia in CVT [9]. This study found a more pronounced association between anaemia and both poor clinical outcome (aOR 3.6) and mortality (aOR 5.5) than the current study. However, this was a retrospective, single-centre study and thus the estimate of the strength of the association may be less accurate. Interestingly, in this study, mortality was twice as high compared to our study (14% vs. 7%). This rate of mortality is also higher than that generally reported in the literature on CVT [12]. There were differences in baseline characteristics that may partly explain the difference in mortality. Most notably, the proportion of anaemic patients who were comatose at admission was substantially higher (25% vs. 11%) and coma is one of the strongest predictors of poor outcome in CVT [3]. Also, a very large proportion of patients in the study by Liu *et al.* [9] received endovascular treatment, which may also indicate a generally more severe clinical condition of their population.

Table 3 Association between anaemia and clinical outcome

	Anaemia	No anaemia	Unadjusted OR, 95% CI	Adjusted OR,[a] 95% CI	Adjusted OR,[b] 95% CI
mRS 3–6	47/219 (21%)	82/733 (11%)	2.2 (1.4–3.4)	2.4 (1.5–3.7)	1.9 (1.2–3.2)
Mortality	23/219 (11%)	44/733 (6%)	1.9 (1.0–3.5)	1.7 (0.9–3.1)	1.4 (0.7–2.9)
mRS 0–1	124/219 (57%)	476/733 (65%)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.8 (0.6–1.2)

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio. Binary logistic regression analysis is based on the pooled estimate after multiple imputation to account for missing variables. [a]Adjusted for age, sex, cancer and centre of recruitment; [b]adjusted for sex, age, cancer, coma, intracerebral haemorrhage, non-haemorrhagic lesion, thrombosis deep venous system and centre of recruitment.

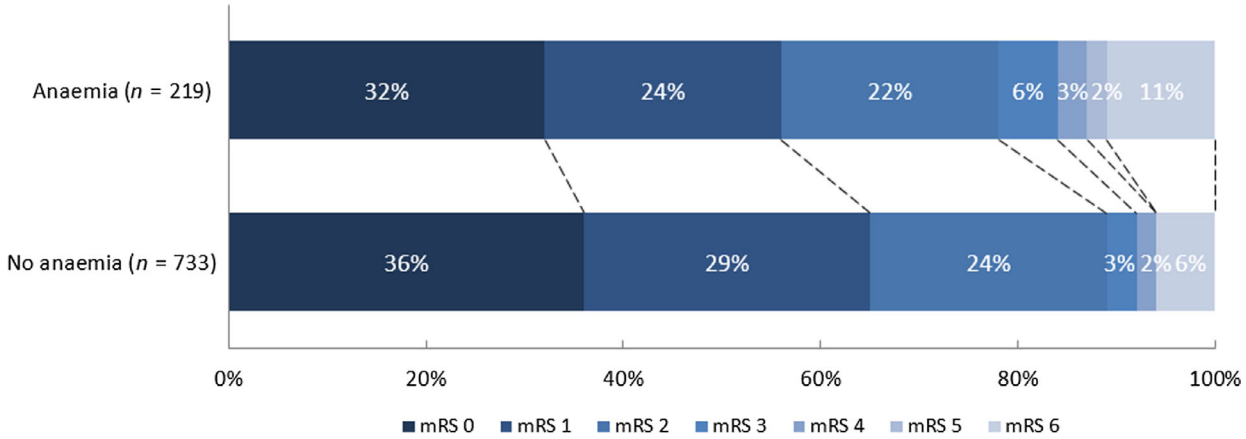

Figure 1 Distribution of modified Rankin Scale (mRS) scores. Scores on the mRS at last follow-up are shown for patients with and without admission anaemia. For each score, the percentage is shown in the bars. No patient in the non-anaemia group had an mRS score of 5. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 4 Stratification by severity of anaemia

	No. of patients		Unadjusted OR, 95% CI	Adjusted OR,[a] 95% CI	Adjusted OR,[b] 95% CI
Functional status	mRS, 0–2	mRS, 3–6			
Mild	95/823 (12%)	21/129 (16%)	1.8 (1.0–3.2)	1.8 (1.0–3.3)	1.5 (0.8–2.8)
Moderate to severe	77/823 (9%)	27/129 (21%)	2.6 (1.5–4.7)	3.1 (1.8–5.5)	2.4 (1.2–4.7)
Mortality	Alive	Dead			
Mild	106/885 (12%)	10/67 (15%)	1.6 (0.7–3.6)	1.4 (0.6–3.1)	1.3 (0.5–3.1)
Moderate to severe	91/885 (10%)	13/67 (19%)	2.1 (1.0–4.4)	2.2 (1.0–4.7)	1.6 (0.6–4.0)

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio. Binary logistic regression analysis based on the pooled estimate after multiple imputation to account for missing variables. [a]Adjusted for age, sex, cancer and centre of recruitment; [b]adjusted for sex, age, cancer, coma, intracerebral haemorrhage, non-haemorrhagic lesion, thrombosis deep venous system and centre of recruitment.

Table 5 Outcome (mRS 3–6) in specific subgroups in the presence of anaemia

	Anaemia mRS 3–6	No anaemia mRS 3–6	Unadjusted OR, 95% CI	Adjusted OR 95% CI
Men	15/58 (26%)	27/236 (11%)	2.5 (1.2–5.0)	2.7 (1.2–5.7)[a]
Women	32/158 (20%)	54/498 (11%)	2.1 (1.2–3.6)	2.3 (1.3–4.1)[a]
Pregnancy/puerperium	6/26 (23%)	4/49 (8%)	2.6 (0.7–9.6)	2.5 (0.6–10.3)[a]
Oral contraceptive use	11/65 (17%)	12/253 (5%)	4.2 (1.6–10.8)	2.6 (0.9–7.8)[a]
Cancer	14/36 (39%)	15/54 (28%)	1.8 (0.6–5.0)	2.8 (0.9–9.4)[b]

CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio. Binary logistic regression analysis based on the pooled estimate after multiple imputation to account for missing variables. [a]Adjusted for age, cancer and centre of recruitment; [b]adjusted for age, sex and centre of recruitment.

There are several hypotheses that may explain the association between anaemia and poor clinical outcome in patients with arterial ischaemic stroke, and some of these may also apply to CVT. Anaemia is thought to induce a hyperdynamic circulation that triggers an inflammatory response, consequently leading to increased thrombus formation [8]. In the presence of a parenchymal lesion, lower oxygen carrying capacity of the blood in anaemic patients may induce increased hypoxia in the affected tissue [6,13,14]. Further, there is evidence from experimental studies that hypoxic anaemia can lead to secondary ischaemic brain tissue due to upregulation of inflammatory mediators [15,16]. The higher rate of baseline parenchymal lesions in anaemic patients provides support to this hypothesis.

Despite the above-mentioned hypotheses, the observation of an association obviously does not prove the

presence of a causal relationship between anaemia and outcome in CVT. However, if such a causal relationship existed, treatment to raise haemoglobin levels in anaemic patients might improve outcome. The efficacy of red blood cell transfusion has been evaluated in one observational study in anaemic patients with intracerebral haemorrhage. The results were promising, but until these results have been confirmed in a randomized trial a more liberal transfusion practice outside the current transfusion guidelines in anaemic CVT patients is not justified [17,18].

The strengths of our study are the large sample size and the multi-centre design with data from both middle- and high-income countries. Our study also has several limitations. First, 78 cases (8%) had to be excluded from baseline analysis because of missing baseline haemoglobin. In order to minimize the risk of bias, a multiple imputation procedure was used to account for the missing data in multivariable analysis. Secondly, although data from consecutive cases were included, some of our data were collected retrospectively. Thirdly, there was no pre-defined follow-up time point. Centres followed local protocols regarding follow-up intervals, and last available mRS was used in analysis. However, median duration of follow-up was not different between patients with and without anaemia, and the analysis was adjusted for centre of recruitment, which negates this potential bias. Fourthly, analysis by red blood cell morphology to evaluate anaemia was not possible because these ancillary investigations were not routinely performed. Finally, our study was underpowered to reliably investigate the risk of poor clinical outcome in specific CVT subgroups.

In conclusion, our study shows that admission anaemia occurs in about one-fifth of patients with CVT and that anaemia is an independent predictor of poor clinical outcome in these patients. Whether a causal relationship underlies this association and whether increasing haemoglobin levels improve clinical outcome require further study.

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J.P. reports personal fees from Boehringer-Ingelheim during the conduct of the study. T.T. reports grants from Helsinki University Central Hospital, grants from University of Gothenburg, grants from Sahlgrenska University Hospital, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, personal fees from Lumosa Pharm, grants and personal fees from Bayer, personal fees from BMS, outside the submitted work. In addition, T.T. has a patent use of a mast cell activation or degranulation blocking agent in the manufacture of a medicament for the treatment of a patient subjected to thrombolyses. Patent no: US8163734. Filed: 13 February 2004. Issued: 24 April 2012. J.M.C. has received research grants for CVT from two non-profit organizations, i.e. the Dutch Thrombosis Society and the Netherlands Brain Foundation, and reports fees from Boehringer Ingelheim and Bayer. All fees were paid to the institute and used to fund scientific research. The other authors declare no financial or other conflicts of interest.

References

1. Silvis SM, de Sousa DA, Ferro JM, Coutinho JM. Cerebral venous thrombosis. *Nat Rev Neurol* 2017; **13:** 555–565.
2. Coutinho JM, Zuurbier SM, Gaartman AE, *et al*. Association between anemia and cerebral venous thrombosis: case–control study. *Stroke* 2015; **46:** 2735–2740.
3. Ferro JM, Canhao P, Stam J, *et al*. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004; **35:** 664–670.
4. Ho KM, Yip CB, Duff O. Reactive thrombocytosis and risk of subsequent venous thromboembolism: a cohort study. *J Thromb Haemost*. 2012; **10:** 1768–1774.
5. Livesey JA, Manning RA, Meek JH, *et al*. Low serum iron levels are associated with elevated plasma levels of coagulation factor VIII and pulmonary emboli/deep venous thromboses in replicate cohorts of patients with hereditary haemorrhagic telangiectasia. *Thorax* 2012; **67:** 328–333.
6. Barlas RS, Honney K, Loke YK, *et al*. Impact of hemoglobin levels and anemia on mortality in acute stroke: analysis of uk regional registry data. Systematic review, and meta-analysis. *J Am Heart Assoc* 2016; **5**. https**:**//doi.org/10.1161/JAHA.115.003019
7. Faller N, Limacher A, Mean M, *et al*. Predictors and causes of long-term mortality in elderly patients with acute venous thromboembolism: a prospective cohort study. *Am J Med* 2017; **130:** 198–206.
8. Kaiafa G, Savopoulos C, Kanellos I, *et al*. Anemia and stroke: where do we stand? *Acta Neurol Scand*. 2017; **135:** 596–602.
9. Liu K, Song B, Gao Y, *et al*. Long-term outcomes in patients with anemia and cerebral venous thrombosis. *Neurocrit Care*. 2018; **29:** 463–468. https://doi.org/10.1007/s12028-018-0544-6.
10. Saposnik G, Barinagarrementeria F, Brown RD Jr, *et al*. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; **42:** 1158–1192.
11. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011 [Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf]

12. Coutinho JM, Zuurbier SM, Stam J. Declining mortality in cerebral venous thrombosis: a systematic review. *Stroke* 2014; **45:** 1338–1341.
13. Shao J, Xi G, Hua Y, Schallert T, Felt B. Intracerebral hemorrhage in the iron-deficient rat. *Stroke* 2005; **36:** 660–664.
14. Bellwald S, Balasubramaniam R, Nagler M, *et al*. Association of anemia and hemoglobin decrease during acute stroke treatment with infarct growth and clinical outcome. *PLoS One* 2018; **13:** e0203535.
15. McLaren AT, Marsden PA, Mazer CD, *et al*. Increased expression of HIF-1alpha, nNOS, and VEGF in the cerebral cortex of anemic rats. *Am J Physiol Regul Integr Comp Physiol* 2007; **292:** R403–14.
16. Moro MA, Cardenas A, Hurtado O, Leza JC, Lizasoain I. Role of nitric oxide after brain ischaemia. *Cell Calcium* 2004; **36:** 265–275.
17. Sheth KN, Gilson AJ, Chang Y, *et al*. Packed red blood cell transfusion and decreased mortality in intracerebral hemorrhage. *Neurosurgery* 2011; **68:** 1286–1292.
18. Carson JL, Stanworth SJ, Roubinian N, *et al*. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2016; **10:** CD002042.