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Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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ABSTRACT

Background: Anemia has an adverse impact on the outcome of patients with percutaneous coronary intervention (PCI). The aim of this study was to analyze the impact of anemia on the 12-month clinical outcome of patients with atrial fibrillation (AF) undergoing PCI and therefore requiring intense antithrombotic treatment.

Methods: Data from the prospective, multicenter AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry with AF patients undergoing PCI was analyzed. Anemia was defined as a hemoglobin concentration of <12 g/dl for women, and <13 g/dl for men. The primary endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE) or bleeding events.

Results: A total of 861/929 (92.7%) patients had available preprocedural hemoglobin concentration, of whom 258 (30%) had anemia. Anemic patients were older, had more often diabetes, higher CHA_2DS_2-VASc score, prior history of heart failure, chronic renal impairment, and acute coronary syndrome. Anemic patients had more MACCE than non-anemic (29.1% versus 19.4%, respectively, p=0.002), and minor bleeding events (7.0% versus 3.3%, respectively, p=0.028), with a trend toward more total bleeding events (25.2% versus 21.7%, respectively, p=0.059). No difference was observed in antithrombotic regimens at discharge. In multivariate analysis anemia was an

independent predictor of all-cause mortality at 12-months follow-up (HR 1.62, 95% CI 1.05 – 2.51, p=0.029).

Conclusions: Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients had a higher all-cause mortality, more thrombotic events, and minor bleeding events. Anemia seems to identify patients at risk for cardiovascular events and death.

Keywords: atrial fibrillation, percutaneous coronary intervention, anemia

Strengths and limitations of the study:

- The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.
- The study adds to our knowledge on the prevalence and impact of anemia in AF patients undergoing PCI and thus requiring combination antithrombotic medication. It shows that anemia is a frequent finding and that even mild anemia has an adverse impact on outcome.
- The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias. Another possible

confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines.

- The aetiology of anemia could not be systematically investigated and is therefore out of the scope of this study.

INTRODUCTION

It is estimated that around 5% of patients undergoing percutaneous coronary intervention (PCI) need long-term oral anticoagulation (OAC) due to atrial fibrillation (AF).[1,2] Yet, the current recommendations on the management of antithrombotic treatment in patients with AF undergoing PCI and stenting are mainly derived from small studies, amounting to a weak level of evidence.[3,4] Moreover, the real-world management of patients on OAC undergoing PCI is variable, and only partially adherent to the current recommendations.[5]

Defined according to the World Health Organization (WHO), anemia has been reported to affect nearly 25% of patients undergoing PCI and stenting. Anemic patients undergoing PCI are generally older with more comorbidities, and have higher rates of in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE), as well as 1-year mortality.[6,7] Furthermore, low admission hemoglobin level was found to be an independent predictor of in-hospital and long-term mortality, and was associated with higher rates of in-hospital minor and major bleeding events in patients undergoing primary PCI for ST-segment elevation myocardial infarction (MI).[8,9]

However, little is known about the effect of anemia on the outcome of patients with AF undergoing PCI and thus requiring intensive antithrombotic treatment. This population is at high bleeding risk, which could be aggravated by the underlying anemia and its cause. Therefore, we analyzed data from the

prospective AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry to explore the impact of anemia on the 12-month clinical outcome of patients with AF undergoing PCI.[10]

METHODS

Patients

The AFCAS registry (ClinicalTrials.gov number NCT00596570)
is a prospective, multicenter registry that enrolled patients with AF referred for PCI in 5 European countries. The study design has been described in detail previously.[11] Patients were enrolled if they had: 1) history of AF (paroxysmal, persistent, or permanent), or 2) on-going AF during the index PCI. Out of the 929 participants 861 (92.7%) had a preprocedural haemoglobin count available and were included in this analysis.

Coronary angiography and PCI were performed via either radial or femoral access, and hemostasis was achieved according to local practice. Coronary lesions were treated according to contemporary interventional techniques. Low-molecular-weight heparin (enoxaparin sodium, dalteparin), unfractionated heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion. The post-discharge medication was completely at the discretion of the treating physician.

The primary endpoints of the current study were 1) occurrence of MACCE defined as a composite of all-cause mortality, any non-fatal MI, any revascularization, definite/probable stent thrombosis, transient ischemic attack (TIA) or stroke, and peripheral arterial embolism; 2) bleeding events; and 3) total adverse events (a composite of MACCE plus bleeding events). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria as minor (BARC 2), and major (BARC 3a, 3b, 3c and 5) bleeding events; however, CABG-related bleeding was excluded.[12] (Online Table 1)

Anemia was defined as a hemoglobin concentration of <12 g/dl for women, and <13 g/dl for men, according to the definition of the WHO.[13] Chronic renal impairment was defined by an estimated glomerular filtration rate below 60 ml/min.

Ethical aspects

The study was initiated by the investigators and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002. Informed written consent was obtained from every patient after full explanation

of the study protocol. The study protocol was approved by the ethics committees of the participating centers.

Statistical analysis

For analysis patients with available preprocedural measurement of hemoglobin concentration were divided into two subgroups: anemic patients, and control patients without anemia. Continuous variables were reported as the mean ± standard deviation if normally distributed, and as median [inter-quartile range (IQR)] if they were skewed. Data were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two study subgroups were performed using the unpaired *t*-test or Mann-Whitney test for continuous variables, and Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up. Variables strongly correlated with the dependent variable by univariate analyses were entered in the model as covariates. Likewise, Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up in the subgroup of anemic patients. Finally we constructed Kaplan-Meier survival curves to display the time-to-event relationship for the occurrence of all-cause

mortality, MACCE, and all bleeding events. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA).

RESULTS

Baseline characteristics

Out of 929 patients enrolled in the AFCAS registry and followed up for 12 months, 861 (92.7%) had available preprocedural measurement of hemoglobin concentration, of whom 258 (30%) had anemia and 603 (70%) had normal hemoglobin concentration. Anemic patients were older, more likely to have diabetes mellitus, hypertension, history of heart failure and chronic renal impairment, HAS-BLED score ≥3, higher CHA_2DS_2VASC score, and more likely presented with acute coronary syndrome (ACS) as opposed to chronic stable angina, compared with those without anemia ($p<0.05$ for all), as shown in Table 1. Furthermore, anemic patients had more vessels treated during the index procedure, and a greater total stent length, compared with those without anemia ($p<0.05$ for both) (Table 2). At discharge, no significant differences were seen in the prescription of antithrombotic medications in the two study groups ($p=0.15$) (Table 3). The duration of clopidogrel treatment did not differ in anemic versus non-anemic patients on triple therapy (median [IQR]: 3 [11] versus 3 [5] months, $p=0.61$), on dual antiplatelet therapy (median [IQR]: 12 [11] versus 12 [11] months, $p=0.72$), or on vitamin K antagonist + clopidogrel

(median [IQR]: 12 [11] versus 3 [11] months, p=0.65). Proton pump inhibitors were more frequently prescribed to patients with anemia versus those without (47.7 versus 31.3%, respectively, p <0.001).

Table 1 Baseline clinical characteristics of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Age (yrs)	76 [9]	73 [11]	<0.001
Female gender	89 (34.5)	170 (28.2)	0.074
Diabetes mellitus	119 (46.1)	191 (31.7)	<0.001
Hypercholesterolemia	162 (62.8)	407 (67.5)	0.183
Current or ex-smoking	26 (10.1)	62 (10.3)	1.00
Hypertension	221 (85.7)	503 (83.4)	0.48
Paroxysmal atrial fibrillation	103 (39.9)	229 (38.0)	0.594
Persistent atrial fibrillation	22 (8.5)	78 (12.9)	0.081
Permanent atrial fibrillation	129 (50)	294 (48.8)	0.766
CHA_2DS_2-VASc score >4	148 (57.4)	235 (39.0)	<0.001
HAS BLED score ≥3	215 (83.3)	441 (73.1)	0.001
History of peptic ulcer	17 (6.6)	27 (4.5)	0.236

History of cerebral hemorrhage	4 (1.6)	6 (1.0)	0.497
History of GI hemorrhage	9 (3.5)	12 (2.0)	0.144
History of heart failure	69 (26.7)	113 (18.7)	0.011
eGFR below 60 ml/min	119 (52.2)	175 (31.9)	<0.001
Prior transient ischemic attacks	12 (4.7)	30 (5.0)	1.00
Prior stroke	36 (14.0)	67 (11.1)	0.252
Prior MI	76 (29.5)	146 (24.2)	0.126
Prior PCI	47 (18.2)	100 (16.6)	0.555
Prior coronary bypass surgery	47 (18.2)	78 (12.9)	0.057
Proton pump inhibitors	123 (47.7)	189 (31.3)	<0.001
Stable angina pectoris	81 (31.4)	289 (48.0)	<0.001
ACS	177 (68.6)	313 (52.0)	<0.001
Unstable angina pectoris	53 (20.5)	107 (17.7)	0.34
Non-ST-elevation MI	83 (32.2)	132 (21.9)	0.002
ST-elevation MI	41 (15.9)	74 (12.3)	0.156

Continuous variables are presented as median [interquartile range], whereas categorical variables are presented as frequency (percentage).

ACS indicates acute coronary syndrome; eGFR, estimated glomerular filtration rate; GI, gastrointestinal, IQR, inter-quartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Procedural data of the two study subgroups

Variable	Anemia (N=258)	Non-anemic (N=603)	*p* value
Femoral access	196 (76.0)	435 (72.1)	0.275
Number of treated vessels	1.22 ± 0.45	1.15 ± 0.41	0.04
DES	67 (27.0)	138 (23.6)	0.293
Peri-procedural INR	1.9 [1]	1.88 [1]	0.509
Stent diameter (mm)	3 [1]	3 [1]	0.965
Total stent length (mm)	20 [18]	19 [14]	0.014
Procedural success	252 (97.7)	582 (96.5)	0.085
Hemostasis			
Manual compression	112 (43.4)	249 (41.3)	0.765
Compression device[a]	49 (19.0)	155 (25.7)	0.083
Access-site closure device[b]	82 (31.8)	165 (27.4)	0.154

Continuous variables are presented as mean ± SD or median [interquartile range], whereas categorical variables are presented as frequency (percentage).

[a]FemoStop®, pneumatic compression device (Radi medical system, Sweden).

[b]Angioseal®, closure device (St. Jude medical, USA).

POBA indicates plain only balloon angioplasty, DES, drug-eluting stents; INR, international normalized ratio; IQR, inter-quartile range.

Table 3 Prescription of antithrombotic medications at discharge in the two study subgroups

Variable	Anemia (N=258)	Non-anemic (N=603)	*p* value
Triple therapy	181 (70.2)	442 (73.3)	0.15
DAPT	58 (22.5)	100 (16.6)	
VKA plus clopidogrel	15 (5.8)	51 (8.5)	
VKA plus aspirin	4 (1.6)	10 (1.7)	

Variables are presented as frequency (percentage).

*The number of patients available for follow-up of the duration of aspirin, clopidogrel, VKA was 258, 257, 159 in the group of anemia, and 600, 600, 402 in the control group, respectively.

VKA indicates vitamin K antagonist; DAPT, dual antiplatelet therapy.

Clinical outcome

Clinical outcomes at 12-month follow-up are presented in table 4 and figure 1. The primary endpoint of MACCE was significantly more frequent in anemic patients than those without anemia (29.1 versus 19.4%, respectively, p=0.002). This difference was driven by higher rates of all-cause mortality, non-fatal MI, and definite/probable ST (p<0.05 for all). Anemic patients had more BARC 3a bleeding events (7.0 versus 3.3%, respectively, p=0.028). No difference was seen in BARC 5 bleedings. There was a trend toward more total bleeding

events (25.2% in anemic versus 21.7% in controls, p=0.059). Total adverse events occurred more frequently in anemic versus non-anemic patients (43.0 versus 31.5%, respectively, p=0.001).

Table 4 Clinical outcome at 12-month follow-up in the two study subgroups

Endpoints	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
MACCE	75 (29.1)	117 (19.4)	0.002
All-cause mortality	48 (18.6)	50 (8.3)	<0.001
Stroke/TIA	6 (2.3)	17 (2.8)	0.819
Peripheral arterial embolism	2 (0.8)	5 (0.8)	1.00
Non-fatal myocardial infarction	24 (9.3)	27 (4.5)	0.011
Any revascularization	19 (7.4)	51 (8.5)	0.683
Definite/probable stent thrombosis	10 (3.9)	4 (0.7)	0.002
Total bleeding events	65 (25.2)	131 (21.7)	0.059
Minor bleeding (BARC 2)	22 (8.5)	48 (8.0)	0.786
Major bleeding (BARC 3a, 3b, 3c, 5)	33 (12.8)	56 (9.3)	0.142
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

MACCE indicates major adverse cardiac and cerebrovascular events; TIA, transient ischemic attacks; BARC, Bleeding Academic Research Consortium.

The incidence of definite/probable stent thrombosis was significantly higher in anemic versus non-anemic patients (3.9 versus 0.7%, respectively, *p*=0.002). Patients who developed stent thrombosis more often presented with ACS than those who did not (80.0 versus 56.6%, respectively, *p*=0.07); however, the use of triple therapy did not differ statistically between groups (60.0 versus 73.3%, respectively, *p*=0.25).

In univariate analysis age above 75, diabetes, congestive heart failure, anemia, chronic renal impairment, ACS at presentation, and total stent length were strongly correlated with both MACCE and all-cause mortality at 12-month follow-up. In the Cox regression model independent predictors of all-cause mortality were anemia (HR 1.62, 95% CI 1.05 – 2.51, p=0.029), ACS at presentation (HR 2.26, 95% CI 1.37 – 3.75, *p*=0.001), chronic renal impairment (HR 2.35, 95% CI 1.52 – 3.65, *p*<0.001), and diabetes (HR 1.76, 95% CI 1.15 – 2.70, p=0.009). In contrast, anemia was not an independent predictor of MACCE at 12-months follow-up unlike age above 75 years (HR 1.7, 95%-CI 1.2-2.4, p=0.004), diabetes (HR 1.7, 95%-CI 1.2-2.3, p=0.002), ACS at presentation (HR 1.7, 95%-CI 1.2-2.3, p=0.003), and congestive heart failure (HR 1.5, 95%-CI 1.0-2.1, p=0.03).

When the anemic patients were analysed separately in the Cox regression model, age over 75 years and ACS at presentation were identified as

independent predictors of MACCE at 12-months; and chronic renal impairment, age over 75 years and ACS at presentation as independent predictors of all-cause mortality

Among 861 patients with available preprocedural measurement of haemoglobin concentration, 26 (2.8%) had severe anemia (defined as haemoglobin below 10 g/dl). In this subgroup, MACCE occurred in 12 (46.2%) patients, 10 (38.5%) patients died, and 8 (30.8%) experienced a BARC 2-5 bleeding episode. At discharge, triple therapy was prescribed in 18 (69.2%) patients, dual anti-platelet therapy in 8 (30.8%), and no patient was prescribed vitamin K antagonists plus a single anti-platelet drug. Proton pump inhibitors were prescribed at discharge in 18 (69.2%) patients, and one (3.8%) patient had a history of gastrointestinal bleeding.

DISCUSSION

Our study is the first report on the impact of anemia on the long-term clinical outcome of patients with AF undergoing PCI. The AFCAS registry represent a real-life cohort of high-risk AF-patients requiring PCI. The results of the current study showing that 30% of the patients were anemic confirm the previous reports that anemia is a frequent finding in real-world patients with AF referred for PCI.[6-9,14] Anemic patients in the AFCAS registry were older

with more comorbidities, and presented more often with ACS, compared with non-anemic patients, as also reported in previous cohorts.[6,7,9,14].

Overall, the 12-month clinical outcome was worse in anemic patients. Anemia remained an independent predictor of all-cause mortality in multivariate analysis. The higher rate of all-cause mortality might be related to the higher-risk profile in anemic patients, as well as the underlying disease causing anemia. Furthermore, anemic patients had more frequent MACCE at 12 months, primarily driven by higher rates of all-cause mortality, and non-fatal MI. However, anemia was not an independent predictor of MACCE. The higher rate of non-fatal MI might be explained, at least in part, by the higher frequency of ACS at presentation in anemic patients.

The estimated thromboembolic risk of anemic patients according to $CHADS_2$ score was higher. However, no excess in TIA or stroke was seen during the follow-up and only a trend towards more bleeding was observed. This is contradictory to previous studies have reported a higher incidence of cardiac and cerebrovascular thrombotic events at long-term follow-up in anemic versus non-anemic patients in various patient cohorts referred for PCI.[7,9,14-18] The relatively small number of complications in our patient cohort might explain this difference.

The estimated bleeding risk according to the HAS-BLED score was higher in anemic patients, but there was only a trend towards increased risk of major bleeding. However, the results of the current study support the previous reports on the increased bleeding risk associated with anemia in various patient groups undergoing PCI.[8,9,19] Anemia may be a marker and consequence of an underlying condition such as bleeding diathesis, occult gastrointestinal bleeding, or malignancy that augments the bleeding risk. An interesting observation is that neither the presence of anemia nor higher estimated bleeding risk seemed to affect the clinician's choice of antithrombotic medications at discharge. In view of our results, patients with anemia tolerated triple therapy surprisingly well with only a trend towards increased bleeding.

We observed that the rate of definite or probable stent thrombosis was significantly higher in anemic versus non-anemic patients (p =0.002). ACS at presentation may have contributed to the higher rate of stent thrombosis in anemic patients, as patients with anemia more often presented with ACS versus those without anemia. Consistent with our results, Pilgrim and co-workers, observed a higher rate of definite stent thrombosis at 4-year follow-up in anemic patients who underwent PCI with unrestricted use of drug-eluting stents, compared with non-anemic ones.[14] Interestingly, in a recent study,

anemia was the only independent predictor of high residual platelet reactivity on clopidogrel in a series of patients undergoing PCI.[20] These observations warrant further studies to clarify the underlying mechanisms.

The effect of anemia on the clinical outcome of PCI appears early during hospitalization. Kaplan-Meier event-free survival curves in the current study revealed that most of the thrombotic as well as bleeding events occurred early (within 30 days) following the index PCI (Figure 1). This finding is in line with previous reports.[6,8,9,15] In patients with coronary artery disease, anemia may aggravate myocardial ischemia, and unveil significant coronary obstruction. Low hemoglobin levels might compromise myocardial oxygen supply, particularly when it exceeds the autoregulatory capacity of coronary flow reserve. Cardiac output increases in patients with anemia in order to maintain adequate oxygen delivery to the tissues. This increases heart rate and induces myocardial hypertrophy, which in turn, increases myocardial oxygen demand, and further exaggerates the myocardial oxygen demand/supply imbalance.[21] On the other hand, patients with severe anemia receive more frequent blood transfusion, which was reported to have an adverse impact on survival after PCI.[22] Unfortunately, information on blood transfusions was not available in our registry. More importantly, anemia is frequently associated with severe underlying chronic diseases which may compromise long-term

survival. Of note is a recent report suggesting that in patients who underwent PCI with drug-eluting stents, those in whom anemia improved at follow-up had less MACCE at a median follow-up of 25 months, compared with those with sustained anemia suggesting that a transient cause is less detrimental than a long-standing state causing anemia, e.g. malignancy.[16]

Limitations of the study

The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias, even though we did not observe any difference between the two study groups in the antithrombotic treatment prescribed at discharge. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines. Moreover, the aetiology of anemia was not systematically investigated; yet, it is beyond the scope of the current study. The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

Conclusion

Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients were older with more frequent comorbidities, and more often presented with ACS. Anemia seems to be an independent risk factor for all-cause mortality during 12-month follow-up. Anemia is also associated with more MACCE, and a trend toward a higher rate of bleeding.

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COMPETING INTERESTS

The authors declare no competing interests.

CONTRIBUTORSHIP STATEMENT

Marja Puurunen and Tuomas Kiviniemi participated in data collection and analysis and writing the manuscript; Wail Nammas contributed to data analysis and writing of the manuscript; Axel Schlitt, Andrea Rubboli, Kai Nyman, Pasi Karjalainen and Paulus Kirchhof contributed to data collection and critical revision of the manuscript; Gregory Lip contributed to study design, data collection and critical revision of the manuscript; Juhani Airaksinen acted as

the primary investigator of the AFCAS study and contributed to study design, data collection, data analysis and writing of the manuscript.

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Extra data is available by emailing Prof. Juhani Airaksinen at juhani.airaksinen@tyks.fi.

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FIGURE LEGENDS

Figure 1 Kaplan-Meier survival curves for the occurrence of adverse events in anemic (dotted lines) versus non-anemic (solid line) patients at 2-month follow-up: all-cause mortality (a), MACCE free survival (b) and bleeding event free survival (c)

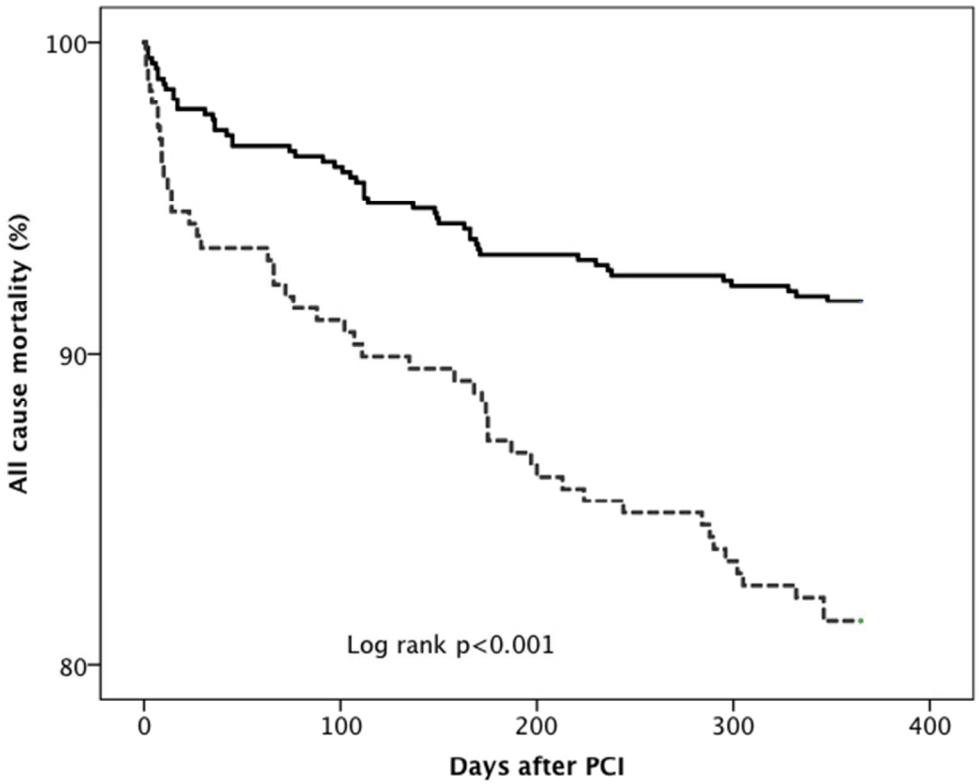

Figure 1 a
220x176mm (72 x 72 DPI)

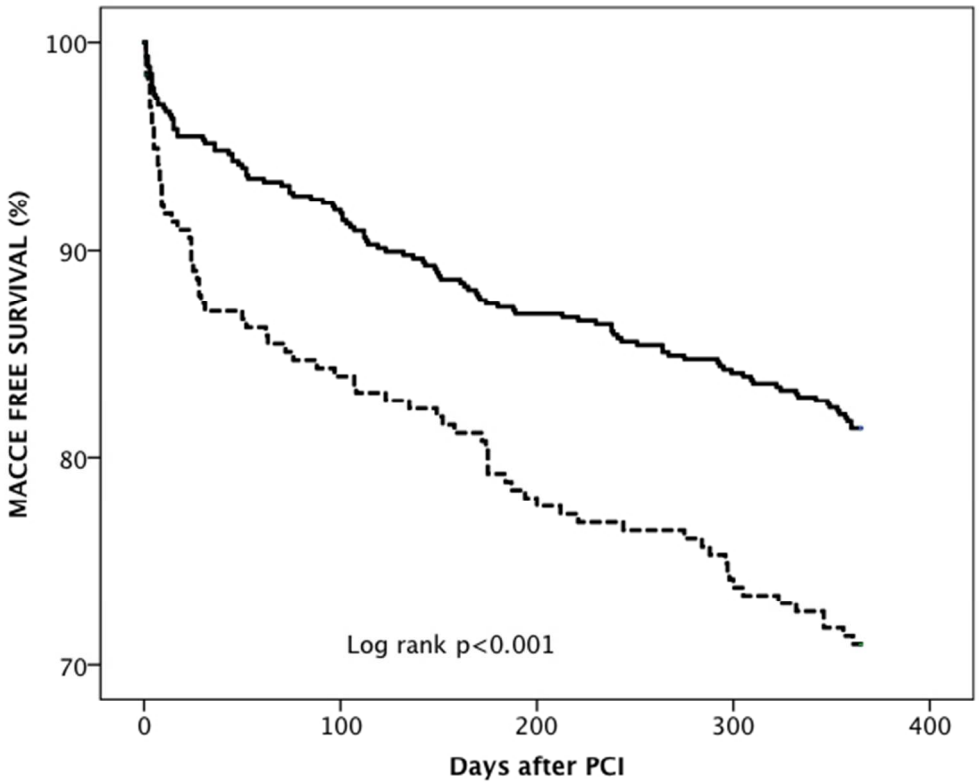

Figure 1 b
220x176mm (72 x 72 DPI)

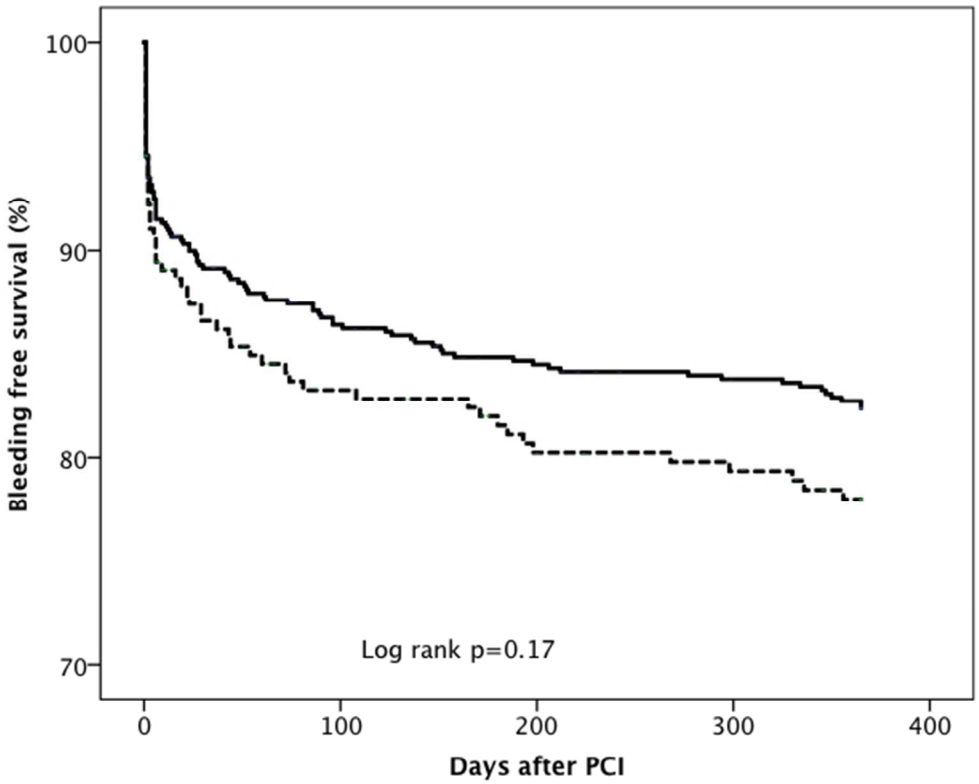

Figure 1 c
220x176mm (72 x 72 DPI)

Table 1. Bleeding Academic Research Consortium Definition for Bleeding.

Type 2	any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop >5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 5	fatal bleeding

Type 1 and type 4 (coronary bypass related) bleeding events were not included in the analysis.

Online Table 2 Bleeding events at 12-month follow-up in the two study subgroups

Endpoints	Anemia (N=258)	Non-anemic (N=603)	*p* value
BARC 2	22 (8.5)	48 (8.0)	0.786
BARC 3a bleeding	18 (7.0)	20 (3.3)	0.028
BARC 3b bleeding	10 (3.9)	22 (3.6)	0.846
BARC 3c bleeding	0 (0)	9 (1.5)	0.064
BARC 5 bleeding	4 (1.6)	5 (0.8)	0.464
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

BARC indicates Bleeding Academic Research Consortium.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ok
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ok
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ok
Objectives	3	State specific objectives, including any prespecified hypotheses ok
Methods		
Study design	4	Present key elements of study design early in the paper ok
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ok
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ok
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ok
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ok
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ok
		(*b*) Describe any methods used to examine subgroups and interactions ok
		(*c*) Explain how missing data were addressed ok
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ok
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ok
		(b) Indicate number of participants with missing data for each variable of interest ok
		(c) Summarise follow-up time (eg, average and total amount) ok
Outcome data	15*	Report numbers of outcome events or summary measures over time ok
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ok

		(*b*) Report category boundaries when continuous variables were categorized ok
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ok
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ok

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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Extra data is available by emailing Prof. Juhani Airaksinen at juhani.airaksinen@tyks.fi.

ABSTRACT

Objectives: Anemia has an adverse impact on the outcome in the general patient population undergoing percutaneous coronary intervention (PCI). The aim of this study was to analyze the impact of anemia on the 12-month clinical outcome of patients with atrial fibrillation (AF) undergoing PCI and therefore requiring intense antithrombotic treatment. We hypothesized that anemia might be associated with a worse outcome and more bleeding in these anticoagulated patients.

Setting: Data was collected from 17 secondary care centers in Europe.

Participants: Consecutive patients with AF undergoing PCI were enrolled in the prospective, multicenter AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry. Altogether 929 patients participated in the study. Preprocedural haemoglobin concentration was available for 861 (92.7%) (30% female). Only exclusion criteria were inability or unwillingness to give informed consent. Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men.

Outcome measures: The primary endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE) or bleeding events.

Results: 258/861 (30%) patients had anemia. Anemic patients were older, had more often diabetes, higher CHA_2DS_2-VASc score, prior history of heart

failure, chronic renal impairment, and acute coronary syndrome. Anemic patients had more MACCE than non-anemic (29.1% versus 19.4%, respectively, *p*=0.002), and minor bleeding events (7.0% versus 3.3%, respectively, *p*=0.028), with a trend toward more total bleeding events (25.2% versus 21.7%, respectively, *p*=0.059). No difference was observed in antithrombotic regimens at discharge. In multivariate analysis anemia was an independent predictor of all-cause mortality at 12-months follow-up (HR 1.62, 95% CI 1.05 – 2.51, p=0.029).

Conclusions: Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients had a higher all-cause mortality, more thrombotic events, and minor bleeding events. Anemia seems to identify patients at risk for cardiovascular events and death.

Trial registration: ClinicalTrials.gov number NCT00596570

Keywords: atrial fibrillation, percutaneous coronary intervention, anemia

Strengths and limitations of the study:

- The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

- The study adds to our knowledge on the prevalence and impact of anemia in AF patients undergoing PCI and thus requiring combination antithrombotic medication. It shows that anemia is a frequent finding and that even mild anemia has an adverse impact on outcome.
- The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines.
- The aetiology of anemia could not be systematically investigated and is therefore out of the scope of this study.

INTRODUCTION

It is estimated that around 5% of patients undergoing percutaneous coronary intervention (PCI) need long-term oral anticoagulation (OAC) due to atrial fibrillation (AF).[1,2] Yet, the current recommendations on the management of antithrombotic treatment in patients with AF undergoing PCI and stenting are mainly derived from small studies, amounting to a weak level of evidence.[3,4] Moreover, the real-world management of patients on OAC undergoing PCI is variable, and only partially adherent to the current recommendations.[5]

Defined according to the World Health Organization (WHO), anemia has been reported to affect nearly 25% of patients undergoing PCI and stenting. Anemic patients undergoing PCI are generally older with more comorbidities, and have higher rates of in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE), as well as 1-year mortality.[6,7] Furthermore, low admission haemoglobin level was found to be an independent predictor of in-hospital and long-term mortality, and was associated with higher rates of in-hospital minor and major bleeding events in patients undergoing primary PCI for ST-segment elevation myocardial infarction (MI).[8,9]

However, little is known about the effect of anemia on the outcome of patients with AF undergoing PCI and thus requiring intensive antithrombotic treatment. Anemia is possibly a marker of high bleeding risk, which could be aggravated by the underlying cause. Therefore, we analyzed data from the

prospective AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry to explore the impact of anemia on the 12-month clinical outcome of patients with AF undergoing PCI.[10]

METHODS

Patients

The AFCAS registry (ClinicalTrials.gov number NCT00596570) is a prospective, multicenter registry that enrolled patients with AF referred for PCI in 5 European countries. The study design has been described in detail previously.[11] Patients were enrolled if they had: 1) history of AF (paroxysmal, persistent, or permanent), or 2) on-going AF during the index PCI. Out of the 929 participants 861 (92.7%) had a preprocedural haemoglobin count available and were included in this analysis.

Coronary angiography and PCI were performed via either radial or femoral access, and hemostasis was achieved according to local practice. Coronary lesions were treated according to contemporary interventional techniques. Low-molecular-weight heparin (enoxaparin sodium, dalteparin), unfractionated heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion. The post-discharge medication was completely at the discretion of the treating physician.

The primary endpoints of the current study were 1) occurrence of MACCE defined as a composite of all-cause mortality, any non-fatal MI, any revascularization, definite/probable stent thrombosis, transient ischemic attack (TIA) or stroke, and peripheral arterial embolism; 2) bleeding events; and 3) total adverse events (a composite of MACCE plus bleeding events). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria as minor (BARC 2), and major (BARC 3a, 3b, 3c and 5) bleeding events; however, CABG-related bleeding was excluded.[12] (Online Table 1)

Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men, according to the definition of the WHO.[13] Chronic renal impairment was defined by an estimated glomerular filtration rate below 60 ml/min.

Ethical aspects

The study was initiated by the investigators and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002. Informed written consent was obtained from every patient after full explanation

of the study protocol. The study protocol was approved by the ethics committees of the participating centers.

Statistical analysis

For analysis patients with available preprocedural measurement of haemoglobin concentration were divided into two subgroups: anemic patients, and control patients without anemia. Continuous variables were reported as the mean ± standard deviation if normally distributed, and as median [inter-quartile range (IQR)] if they were skewed. Data were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two study subgroups were performed using the unpaired *t*-test or Mann-Whitney test for continuous variables, and Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up. Baseline variables correlating at $p<0.10$ level with the dependent variable in univariate analyses were entered in the Cox regression model as covariates. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up in the subgroup of anemic patients. Finally we constructed Kaplan-Meier survival curves to display the time-to-event relationship for the occurrence of

all-cause mortality, MACCE, and all bleeding events. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA).

RESULTS

Baseline characteristics

Out of 929 patients enrolled in the AFCAS registry and followed up for 12 months, 861 (92.7%) had available preprocedural measurement of haemoglobin concentration, of whom 258 (30%) had anemia and 603 (70%) had normal haemoglobin concentration. Anemic patients were older, more likely to have diabetes mellitus, hypertension, history of heart failure and chronic renal impairment, HAS-BLED score ≥3, higher CHA_2DS_2VASC score, and more likely presented with acute coronary syndrome (ACS) as opposed to chronic stable angina, compared with those without anemia ($p<0.05$ for all), as shown in Table 1. Furthermore, anemic patients had more vessels treated during the index procedure, and a greater total stent length, compared with those without anemia ($p<0.05$ for both) (Table 2). At discharge, no significant differences were seen in the prescription of antithrombotic medications in the two study groups ($p=0.15$) (Table 3). The duration of clopidogrel treatment did not differ in anemic versus non-anemic patients on triple therapy (median [IQR]: 3 [11] versus 3 [5] months, $p=0.61$), on dual antiplatelet therapy (median [IQR]: 12

[11] versus 12 [11] months, p=0.72), or on vitamin K antagonist + clopidogrel (median [IQR]: 12 [11] versus 3 [11] months, p=0.65). Proton pump inhibitors were more frequently prescribed to patients with anemia versus those without (47.7 versus 31.3%, respectively, p <0.001).

Table 1 Baseline clinical characteristics of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Age (yrs)	76 [9]	73 [11]	<0.001
Female gender	89 (34.5)	170 (28.2)	0.074
Diabetes mellitus	119 (46.1)	191 (31.7)	<0.001
Hypercholesterolemia	162 (62.8)	407 (67.5)	0.183
Current or ex-smoking	26 (10.1)	62 (10.3)	1.00
Hypertension	221 (85.7)	503 (83.4)	0.48
Paroxysmal atrial fibrillation	103 (39.9)	229 (38.0)	0.594
Persistent atrial fibrillation	22 (8.5)	78 (12.9)	0.081
Permanent atrial fibrillation	129 (50)	294 (48.8)	0.766

CHA_2DS_2-VASc score >4	148 (57.4)	235 (39.0)	<0.001
HAS BLED score ≥3	215 (83.3)	441 (73.1)	0.001
History of peptic ulcer	17 (6.6)	27 (4.5)	0.236
History of cerebral hemorrhage	4 (1.6)	6 (1.0)	0.497
History of GI hemorrhage	9 (3.5)	12 (2.0)	0.144
History of heart failure	69 (26.7)	113 (18.7)	0.011
eGFR below 60 ml/min	119 (52.2)	175 (31.9)	<0.001
Prior transient ischemic attacks	12 (4.7)	30 (5.0)	1.00
Prior stroke	36 (14.0)	67 (11.1)	0.252
Prior MI	76 (29.5)	146 (24.2)	0.126
Prior PCI	47 (18.2)	100 (16.6)	0.555
Prior coronary bypass surgery	47 (18.2)	78 (12.9)	0.057
Proton pump inhibitors	123 (47.7)	189 (31.3)	<0.001
Stable angina pectoris	81 (31.4)	289 (48.0)	<0.001
ACS	177 (68.6)	313 (52.0)	<0.001
Unstable angina pectoris	53 (20.5)	107 (17.7)	0.34
Non-ST-elevation MI	83 (32.2)	132 (21.9)	0.002
ST-elevation MI	41 (15.9)	74 (12.3)	0.156

Continuous variables are presented as median [interquartile range], whereas categorical variables are presented as frequency (percentage).

ACS indicates acute coronary syndrome; eGFR, estimated glomerular filtration rate; GI, gastrointestinal, IQR, inter-quartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Procedural data of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Femoral access	196 (76.0)	435 (72.1)	0.275
Number of treated vessels	1.22 ± 0.45	1.15 ± 0.41	0.04
DES	67 (27.0)	138 (23.6)	0.293
Peri-procedural INR	1.9 [1]	1.88 [1]	0.509
Stent diameter (mm)	3 [1]	3 [1]	0.965
Total stent length (mm)	20 [18]	19 [14]	0.014
Procedural success	252 (97.7)	582 (96.5)	0.085
Hemostasis			
Manual compression	112 (43.4)	249 (41.3)	0.765
Compression device[a]	49 (19.0)	155 (25.7)	0.083
Access-site closure device[b]	82 (31.8)	165 (27.4)	0.154

Continuous variables are presented as mean ± SD or median [interquartile range], whereas categorical variables are presented as frequency (percentage).

[a]FemoStop®, pneumatic compression device (Radi medical system, Sweden).

[b]Angioseal®, closure device (St. Jude medical, USA).

DES, drug-eluting stents; INR, international normalized ratio; IQR, inter-quartile range.

Table 3 Prescription of antithrombotic medications at discharge in the two study subgroups

Variable	Anemia (N=258)	Non-anemic (N=603)	*p* value
Triple therapy	181 (70.2)	442 (73.3)	0.15
DAPT	58 (22.5)	100 (16.6)	
VKA plus clopidogrel	15 (5.8)	51 (8.5)	
VKA plus aspirin	4 (1.6)	10 (1.7)	

Variables are presented as frequency (percentage).

VKA indicates vitamin K antagonist; DAPT, dual antiplatelet therapy.

Clinical outcome

Clinical outcomes at 12-month follow-up are presented in table 4 and figure 1. The primary endpoint of MACCE was significantly more frequent in anemic patients than those without anemia (29.1 versus 19.4%, respectively, p=0.002). This difference was driven by higher rates of all-cause mortality, non-fatal MI, and definite/probable ST (p<0.05 for all). Anemic patients had more BARC 3a bleeding events (7.0 versus 3.3%, respectively, p=0.028). No difference was

seen in BARC 5 bleedings. There was a trend toward more total bleeding events (25.2% in anemic versus 21.7% in controls, p=0.059). (For detailed information on bleeding events see Online Table 2.) Total adverse events occurred more frequently in anemic versus non-anemic patients (43.0 versus 31.5%, respectively, p=0.001).

Table 4 Clinical outcome at 12-month follow-up in the two study subgroups

Endpoints	Anemia (N=258)	Non-anemic (N=603)	*p* value
MACCE	75 (29.1)	117 (19.4)	0.002
All-cause mortality	48 (18.6)	50 (8.3)	<0.001
Stroke/TIA	6 (2.3)	17 (2.8)	0.819
Peripheral arterial embolism	2 (0.8)	5 (0.8)	1.00
Non-fatal myocardial infarction	24 (9.3)	27 (4.5)	0.011
Any revascularization	19 (7.4)	51 (8.5)	0.683
Definite/probable stent thrombosis	10 (3.9)	4 (0.7)	0.002
Total bleeding events	65 (25.2)	131 (21.7)	0.059
Minor bleeding (BARC 2)	22 (8.5)	48 (8.0)	0.786
Major bleeding (BARC 3a, 3b, 3c, 5)	33 (12.8)	56 (9.3)	0.142
Access site complications	25 (9.7)	49 (8.1)	0.51
Pseudoaneurysm	7 (2.7)	18 (3.0)	1.0
Red blood cell transfusion	10 (3.9)	5 (0.9)	0.002
Need for corrective surgery	5 (1.9)	8 (1.3)	0.25
Prolonged hospitalization	15 (5.8)	23 (3.8)	0.21
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

MACCE indicates major adverse cardiac and cerebrovascular events; TIA, transient ischemic attacks; BARC, Bleeding Academic Research Consortium.

The incidence of definite/probable stent thrombosis was significantly higher in anemic versus non-anemic patients (3.9 versus 0.7%, respectively, *p*=0.002). Patients who developed stent thrombosis more often presented with ACS than those who did not (80.0 versus 56.6%, respectively, *p*=0.07); however, the use of triple therapy did not differ statistically between groups (60.0 versus 73.3%, respectively, *p*=0.25). Overall, nearly half (46.7%) of ST events occurred early (<30 days). Acute (<24h after index PCI); early (<30 days) and late ST (>30 and < 365 days) were detected in 1 (0.4%) and 1 (0.2%) (p=0.51); 4 (1.6%) vs. 2 (0.3%) (p=0.07); and 6 (2.3%) vs. 2 (0.3%) (p=0.01) in patients with anemia vs. those without anemia, respectively.

In univariate analysis age above 75, diabetes, congestive heart failure, anemia, chronic renal impairment, ACS at presentation, and total stent length were strongly correlated with both MACCE and all-cause mortality at 12-month follow-up. In the Cox regression model including all the above variables, independent predictors of all-cause mortality were anemia (HR 1.62, 95% CI 1.05 – 2.51, p=0.029), ACS at presentation (HR 2.26, 95% CI 1.37 – 3.75, *p*=0.001), chronic renal impairment (HR 2.35, 95% CI 1.52 – 3.65, *p*<0.001), and diabetes (HR 1.76, 95% CI 1.15 – 2.70, p=0.009). In contrast, anemia as a categorical variable was not an independent predictor of MACCE at 12-months follow-up unlike age above 75 years (HR 1.7, 95%-CI 1.2-2.4, p=0.004),

diabetes (HR 1.7, 95%-CI 1.2-2.3, p=0.002), ACS at presentation (HR 1.7, 95%-CI 1.2-2.3, p=0.003), and congestive heart failure (HR 1.5, 95%-CI 1.0-2.1, p=0.03).

We performed the multivariate model also using haemoglobin as a continuous variable. Independent predictors of all-cause mortality were pre-procedural haemoglobin (HR 0.82, 95% CI 0.72 – 0.93, p=0.002), ACS at presentation (HR 2.07, 95% CI 1.25 – 3.45, p=0.005), chronic renal impairment (HR 2.06, 95% CI 1.31 – 3.24, p=0.002), and diabetes (HR 1.75, 95% CI 1.14 – 2.70, p=0.01) in a Cox regression model including age over 75 years, total stent length and number of treated vessels as covariates. On the contrary to what was found when assessing anemia as a categorical variable, haemoglobin as a continuous variable predicted also MACCE. Independent predictors of MACCE were pre-procedural haemoglobin (HR 0.89, 95% CI 0.81 – 0.98, p=0.016), ACS at presentation (HR 1.55, 95% CI 1.10 – 2.18, p=0.012), congestive heart failure (HR 1.45, 95% CI 1.03 – 2.04, p=0.035), age over 75 years (HR 1.77, 95%CI 1.27 – 2.45, p=0.001) and diabetes (HR 1.55, 95% CI 1.13 – 2.13, p=0.007) in a Cox regression model including also total stent length, chronic renal impairment and number of treated vessels as covariates.

When the anemic patients were analysed separately in the Cox regression model, age over 75 years and ACS at presentation were identified as independent predictors of MACCE at 12-months; and chronic renal

impairment, age over 75 years and ACS at presentation as independent predictors of all-cause mortality

Among 861 patients with available preprocedural measurement of haemoglobin concentration, 26 (2.8%) had severe anemia (defined as haemoglobin below 10 g/dl). In this subgroup, MACCE occurred in 12 (46.2%) patients, 10 (38.5%) patients died, and 8 (30.8%) experienced a BARC 2-5 bleeding episode. At discharge, triple therapy was prescribed in 18 (69.2%) patients, dual anti-platelet therapy in 8 (30.8%), and no patient was prescribed vitamin K antagonists plus a single anti-platelet drug. Proton pump inhibitors were prescribed at discharge in 18 (69.2%) patients, and one (3.8%) patient had a history of gastrointestinal bleeding.

DISCUSSION

Our study is the first report on the impact of anemia on the long-term clinical outcome of patients with AF undergoing PCI. The AFCAS registry represent a real-life cohort of high-risk AF-patients requiring PCI. The results of the current study showing that 30% of the patients were anemic confirm the previous reports that anemia is a frequent finding in real-world patients with AF referred for PCI.[6-9,14] Anemic patients in the AFCAS registry were older with more comorbidities, and presented more often with ACS, compared with non-anemic patients, as also reported in previous cohorts.[6,7,9,14].

Overall, the 12-month clinical outcome was worse in anemic patients. Anemia remained an independent predictor of all-cause mortality in multivariate analysis. The higher rate of all-cause mortality might be related to the higher-risk profile in anemic patients, as well as the underlying disease causing anemia. Furthermore, anemic patients had more frequent MACCE at 12 months, primarily driven by higher rates of all-cause mortality, and non-fatal MI. However, anemia was not an independent predictor of MACCE. The higher rate of non-fatal MI might be explained, at least in part, by the higher frequency of ACS at presentation in anemic patients.

The estimated thromboembolic risk of anemic patients according to $CHADS_2$ score was higher. However, no excess in TIA or stroke was seen during the follow-up and only a trend towards more bleeding was observed. This is contradictory to previous studies have reported a higher incidence of cardiac and cerebrovascular thrombotic events at long-term follow-up in anemic versus non-anemic patients in various patient cohorts referred for PCI.[7,9,14-18] The relatively small number of complications in our patient cohort might explain this difference.

The estimated bleeding risk according to the HAS-BLED score was higher in anemic patients, but there was only a trend towards increased risk of major bleeding. However, the results of the current study support the previous reports on the increased bleeding risk associated with anemia in various patient groups undergoing PCI.[8,9,19] Anemia may be a marker and consequence of an underlying condition such as bleeding diathesis, occult gastrointestinal bleeding, or malignancy that augments the bleeding risk. An interesting observation is that neither the presence of anemia nor higher estimated bleeding risk seemed to affect the clinician's choice of antithrombotic medications at discharge. In view of our results, patients with anemia tolerated triple therapy surprisingly well with only a trend towards increased bleeding.

We observed that the rate of definite or probable stent thrombosis was significantly higher in anemic versus non-anemic patients (p =0.002). ACS at presentation may have contributed to the higher rate of stent thrombosis in anemic patients, as patients with anemia more often presented with ACS versus those without anemia. Consistent with our results, Pilgrim and co-workers, observed a higher rate of definite stent thrombosis at 4-year follow-up in anemic patients who underwent PCI with unrestricted use of drug-eluting stents, compared with non-anemic ones.[14] Interestingly, in a recent study, anemia was the only independent predictor of high residual platelet reactivity

on clopidogrel in a series of patients undergoing PCI.[20] These observations warrant further studies to clarify the underlying mechanisms.

The effect of anemia on the clinical outcome of PCI appears early during hospitalization. Kaplan-Meier event-free survival curves in the current study revealed that most of the thrombotic as well as bleeding events occurred early (within 30 days) following the index PCI (Figure 1). This finding is in line with previous reports.[6,8,9,15] In patients with coronary artery disease, anemia may aggravate myocardial ischemia, and unveil significant coronary obstruction. Cardiac output increases in patients with anemia in order to maintain adequate oxygen delivery to the tissues. This increases heart rate and induces myocardial hypertrophy, which in turn, increases myocardial oxygen demand, and further exaggerates the myocardial oxygen demand/supply imbalance.[21] On the other hand, patients with severe anemia receive more frequent blood transfusion, which was reported to have an adverse impact on survival after PCI.[22] Unfortunately, information on blood transfusions was not available in our registry except for the in-hospital phase. More importantly, anemia is frequently associated with severe underlying chronic diseases which may compromise long-term survival. Of note is a recent report suggesting that in patients who underwent PCI with drug-eluting stents, those in whom anemia improved at follow-up had less MACCE at a median follow-up of 25 months,

compared with those with sustained anemia suggesting that a transient cause is less detrimental than a long-standing state causing anemia, e.g. malignancy.[16]

Limitations of the study

The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias, even though we did not observe any difference between the two study groups in the antithrombotic treatment prescribed at discharge. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines. Moreover, the aetiology of anemia was not systematically investigated; yet, it is beyond the scope of the current study. The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

Conclusion

Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients were older with more frequent comorbidities, and more often presented with ACS. Anemia seems to be an independent risk factor for all-cause

mortality during 12-month follow-up. Anemia is also associated with more MACCE, and a trend toward a higher rate of bleeding.

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COMPETING INTERESTS

The authors declare no competing interests.

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FIGURE LEGENDS

Figure 1 Kaplan-Meier survival curves for the occurrence of adverse events in anemic (dotted lines) versus non-anemic (solid line) patients at 2-month follow-up: all-cause mortality (a), MACCE free survival (b) and bleeding event free survival (c)

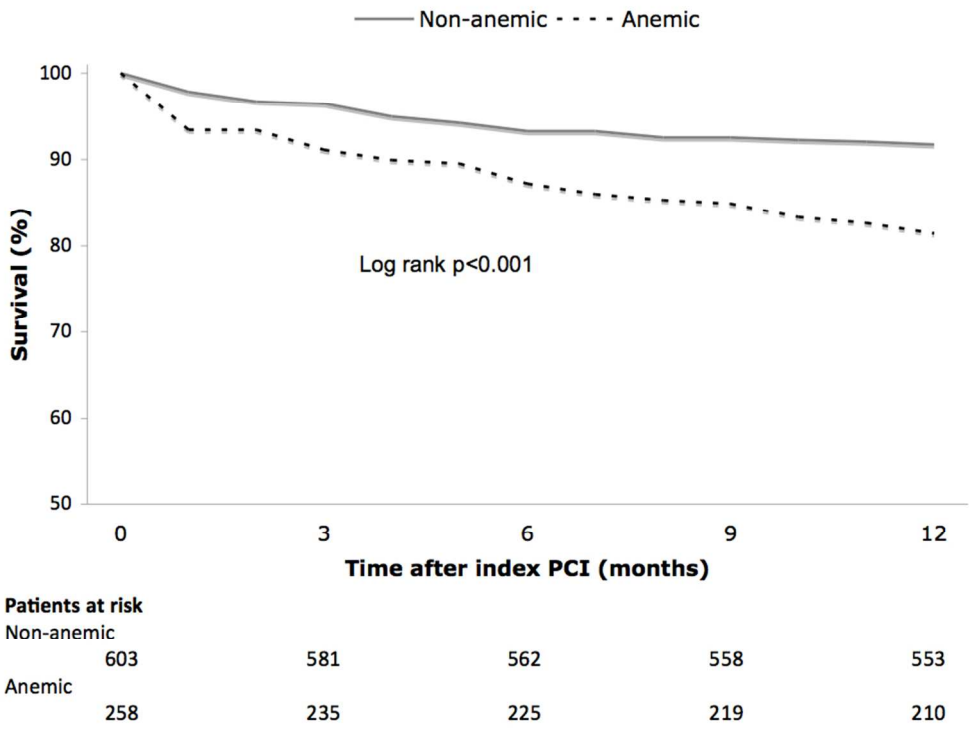

Figure 1a

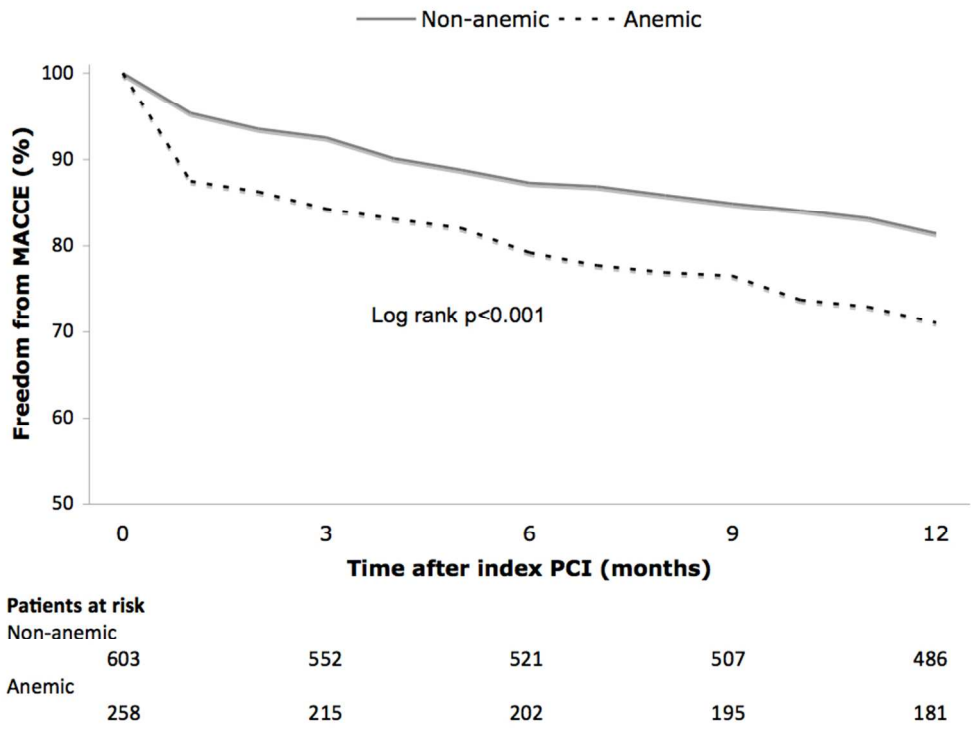

Figure 1b

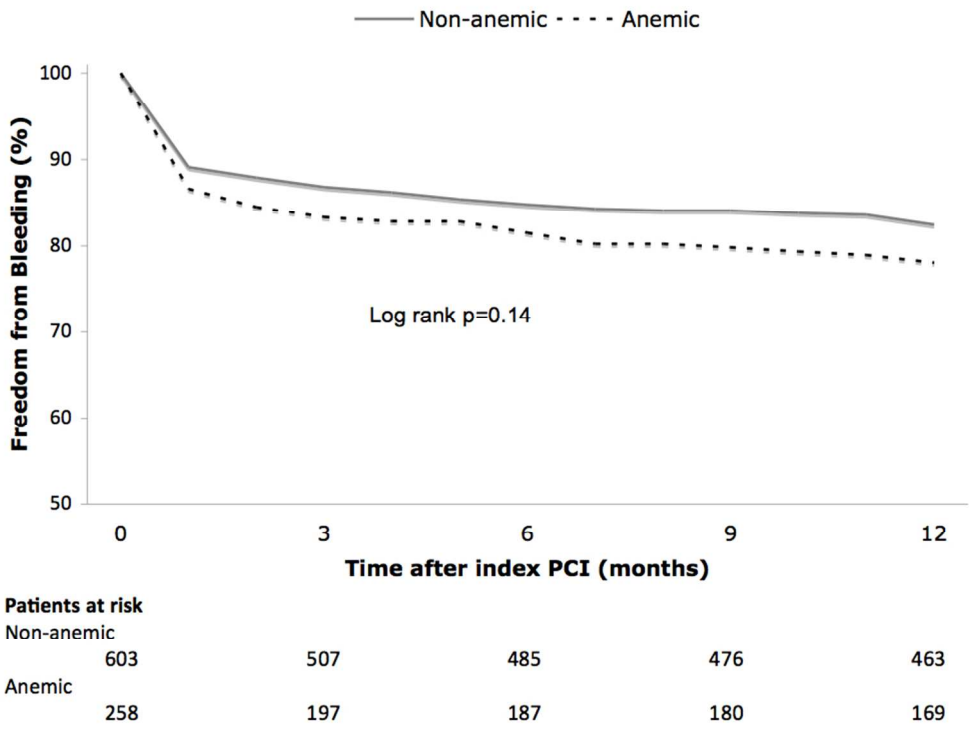

Figure 1c

Table 1. Bleeding Academic Research Consortium Definition for Bleeding.

Type 2	any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop >5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 5	fatal bleeding

Type 1 and type 4 (coronary bypass related) bleeding events were not included in the analysis.

Online Table 2 Bleeding events at 12-month follow-up in the two study subgroups

Endpoints	Anemia (N=258)	Non-anemic (N=603)	*p* value
BARC 2	22 (8.5)	48 (8.0)	0.786
BARC 3a bleeding	18 (7.0)	20 (3.3)	0.028
BARC 3b bleeding	10 (3.9)	22 (3.6)	0.846
BARC 3c bleeding	0 (0)	9 (1.5)	0.064
BARC 5 bleeding	4 (1.6)	5 (0.8)	0.464
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

BARC indicates Bleeding Academic Research Consortium.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ok
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ok
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ok
Objectives	3	State specific objectives, including any prespecified hypotheses ok
Methods		
Study design	4	Present key elements of study design early in the paper ok
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ok
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ok
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ok
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ok
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ok
		(*b*) Describe any methods used to examine subgroups and interactions ok
		(*c*) Explain how missing data were addressed ok
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ok
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ok
		(b) Indicate number of participants with missing data for each variable of interest ok
		(c) Summarise follow-up time (eg, average and total amount) ok
Outcome data	15*	Report numbers of outcome events or summary measures over time ok
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ok

		(*b*) Report category boundaries when continuous variables were categorized ok
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ok
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ok

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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ABSTRACT

Objectives: Anemia has an adverse impact on the outcome in the general patient population undergoing percutaneous coronary intervention (PCI). The aim of this study was to analyze the impact of anemia on the 12-month clinical outcome of patients with atrial fibrillation (AF) undergoing PCI and therefore requiring intense antithrombotic treatment. We hypothesized that anemia might be associated with a worse outcome and more bleeding in these anticoagulated patients.

Setting: Data was collected from 17 secondary care centers in Europe.

Participants: Consecutive patients with AF undergoing PCI were enrolled in the prospective, multicenter AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry. Altogether 929 patients participated in the study. Preprocedural haemoglobin concentration was available for 861 (92.7%) (30% female). Only exclusion criteria were inability or unwillingness to give informed consent. Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men.

Outcome measures: The primary endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE) or bleeding events.

Results: 258/861 (30%) patients had anemia. Anemic patients were older, had more often diabetes, higher CHA_2DS_2-VASc score, prior history of heart

failure, chronic renal impairment, and acute coronary syndrome. Anemic patients had more MACCE than non-anemic (29.1% versus 19.4%, respectively, *p*=0.002), and minor bleeding events (7.0% versus 3.3%, respectively, *p*=0.028), with a trend toward more total bleeding events (25.2% versus 21.7%, respectively, *p*=0.059). No difference was observed in antithrombotic regimens at discharge. In multivariate analysis anemia was an independent predictor of all-cause mortality at 12-months follow-up (HR 1.62, 95% CI 1.05 – 2.51, p=0.029).

Conclusions: Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients had a higher all-cause mortality, more thrombotic events, and minor bleeding events. Anemia seems to identify patients at risk for cardiovascular events and death.

Trial registration: ClinicalTrials.gov number NCT00596570

Keywords: atrial fibrillation, percutaneous coronary intervention, anemia

Strengths and limitations of the study:

- The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

- The study adds to our knowledge on the prevalence and impact of anemia in AF patients undergoing PCI and thus requiring combination antithrombotic medication. It shows that anemia is a frequent finding and that even mild anemia has an adverse impact on outcome.
- The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines.
- The aetiology of anemia could not be systematically investigated and is therefore out of the scope of this study.

INTRODUCTION

It is estimated that around 5% of patients undergoing percutaneous coronary intervention (PCI) need long-term oral anticoagulation (OAC) due to atrial fibrillation (AF).[1,2] Yet, the current recommendations on the management of antithrombotic treatment in patients with AF undergoing PCI and stenting are mainly derived from small studies, amounting to a weak level of evidence.[3,4] Moreover, the real-world management of patients on OAC undergoing PCI is variable, and only partially adherent to the current recommendations.[5]

Defined according to the World Health Organization (WHO), anemia has been reported to affect nearly 25% of patients undergoing PCI and stenting. Anemic patients undergoing PCI are generally older with more comorbidities, and have higher rates of in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE), as well as 1-year mortality.[6,7] Furthermore, low admission haemoglobin level was found to be an independent predictor of in-hospital and long-term mortality, and was associated with higher rates of in-hospital minor and major bleeding events in patients undergoing primary PCI for ST-segment elevation myocardial infarction (MI).[8,9]

However, little is known about the effect of anemia on the outcome of patients with AF undergoing PCI and thus requiring intensive antithrombotic treatment. Anemia is possibly a marker of high bleeding risk, which could be aggravated by the underlying cause. Therefore, we analyzed data from the

prospective AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry to explore the impact of anemia on the 12-month clinical outcome of patients with AF undergoing PCI.[10]

METHODS

Patients

The AFCAS registry (ClinicalTrials.gov number NCT00596570)
is a prospective, multicenter registry that enrolled patients with AF referred for PCI in 5 European countries. The study design has been described in detail previously.[11] Patients were enrolled if they had: 1) history of AF (paroxysmal, persistent, or permanent), or 2) on-going AF during the index PCI. Out of the 929 participants 861 (92.7%) had a preprocedural haemoglobin count available and were included in this analysis.

Coronary angiography and PCI were performed via either radial or femoral access, and hemostasis was achieved according to local practice. Coronary lesions were treated according to contemporary interventional techniques. Low-molecular-weight heparin (enoxaparin sodium, dalteparin), unfractionated heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion. The post-discharge medication was completely at the discretion of the treating physician.

The primary endpoints of the current study were 1) occurrence of MACCE defined as a composite of all-cause mortality, any non-fatal MI, any revascularization, definite/probable stent thrombosis, transient ischemic attack (TIA) or stroke, and peripheral arterial embolism; 2) bleeding events; and 3) total adverse events (a composite of MACCE plus bleeding events). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria as minor (BARC 2), and major (BARC 3a, 3b, 3c and 5) bleeding events; however, CABG-related bleeding was excluded.[12] (Web Table 1)

Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men, according to the definition of the WHO.[13] Chronic renal impairment was defined by an estimated glomerular filtration rate below 60 ml/min.

Ethical aspects

The study was initiated by the investigators and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002. Informed written consent was obtained from every patient after full explanation

of the study protocol. The study protocol was approved by the ethics committees of the participating centers.

Statistical analysis

For analysis patients with available preprocedural measurement of haemoglobin concentration were divided into two subgroups: anemic patients, and control patients without anemia. Continuous variables were reported as the mean ± standard deviation if normally distributed, and as median [inter-quartile range (IQR)] if they were skewed. Data were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two study subgroups were performed using the unpaired *t*-test or Mann-Whitney test for continuous variables, and Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up. Baseline variables correlating at $p<0.10$ level with the dependent variable in univariate analyses were entered in the Cox regression model as covariates. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up in the subgroup of anemic patients. Finally we constructed Kaplan-Meier survival curves to display the time-to-event relationship for the occurrence of

all-cause mortality, MACCE, and all bleeding events. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA).

RESULTS

Baseline characteristics

Out of 929 patients enrolled in the AFCAS registry and followed up for 12 months, 861 (92.7%) had available preprocedural measurement of haemoglobin concentration, of whom 258 (30%) had anemia and 603 (70%) had normal haemoglobin concentration. Anemic patients were older, more likely to have diabetes mellitus, hypertension, history of heart failure and chronic renal impairment, HAS-BLED score ≥3, higher CHA_2DS_2VASC score, and more likely presented with acute coronary syndrome (ACS) as opposed to chronic stable angina, compared with those without anemia ($p<0.05$ for all), as shown in Table 1. Furthermore, anemic patients had more vessels treated during the index procedure, and a greater total stent length, compared with those without anemia ($p<0.05$ for both) (Table 2). At discharge, no significant differences were seen in the prescription of antithrombotic medications in the two study groups ($p=0.15$) (Table 3). The duration of clopidogrel treatment did not differ in anemic versus non-anemic patients on triple therapy (median [IQR]: 3 [11] versus 3 [5] months, $p=0.61$), on dual antiplatelet therapy (median [IQR]: 12

[11] versus 12 [11] months, p=0.72), or on vitamin K antagonist + clopidogrel (median [IQR]: 12 [11] versus 3 [11] months, p=0.65). Proton pump inhibitors were more frequently prescribed to patients with anemia versus those without (47.7 versus 31.3%, respectively, p <0.001).

Table 1 Baseline clinical characteristics of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Age (yrs)	76 [9]	73 [11]	<0.001
Female gender	89 (34.5)	170 (28.2)	0.074
Diabetes mellitus	119 (46.1)	191 (31.7)	<0.001
Hypercholesterolemia	162 (62.8)	407 (67.5)	0.183
Current or ex-smoking	26 (10.1)	62 (10.3)	1.00
Hypertension	221 (85.7)	503 (83.4)	0.48
Paroxysmal atrial fibrillation	103 (39.9)	229 (38.0)	0.594
Persistent atrial fibrillation	22 (8.5)	78 (12.9)	0.081
Permanent atrial fibrillation	129 (50)	294 (48.8)	0.766

CHA_2DS_2-VASc score >4	148 (57.4)	235 (39.0)	<0.001
HAS BLED score ≥3	215 (83.3)	441 (73.1)	0.001
History of peptic ulcer	17 (6.6)	27 (4.5)	0.236
History of cerebral hemorrhage	4 (1.6)	6 (1.0)	0.497
History of GI hemorrhage	9 (3.5)	12 (2.0)	0.144
History of heart failure	69 (26.7)	113 (18.7)	0.011
eGFR below 60 ml/min	119 (52.2)	175 (31.9)	<0.001
Prior transient ischemic attacks	12 (4.7)	30 (5.0)	1.00
Prior stroke	36 (14.0)	67 (11.1)	0.252
Prior MI	76 (29.5)	146 (24.2)	0.126
Prior PCI	47 (18.2)	100 (16.6)	0.555
Prior coronary bypass surgery	47 (18.2)	78 (12.9)	0.057
Proton pump inhibitors	123 (47.7)	189 (31.3)	<0.001
Stable angina pectoris	81 (31.4)	289 (48.0)	<0.001
ACS	177 (68.6)	313 (52.0)	<0.001
Unstable angina pectoris	53 (20.5)	107 (17.7)	0.34
Non-ST-elevation MI	83 (32.2)	132 (21.9)	0.002
ST-elevation MI	41 (15.9)	74 (12.3)	0.156

Continuous variables are presented as median [interquartile range], whereas categorical variables are presented as frequency (percentage).

ACS indicates acute coronary syndrome; eGFR, estimated glomerular filtration rate; GI, gastrointestinal, IQR, inter-quartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Procedural data of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Femoral access	196 (76.0)	435 (72.1)	0.275
Number of treated vessels	1.22 ± 0.45	1.15 ± 0.41	0.04
DES	67 (27.0)	138 (23.6)	0.293
Peri-procedural INR	1.9 [1]	1.88 [1]	0.509
Stent diameter (mm)	3 [1]	3 [1]	0.965
Total stent length (mm)	20 [18]	19 [14]	0.014
Procedural success	252 (97.7)	582 (96.5)	0.085
Hemostasis			
Manual compression	112 (43.4)	249 (41.3)	0.765
Compression device[a]	49 (19.0)	155 (25.7)	0.083
Access-site closure device[b]	82 (31.8)	165 (27.4)	0.154

Continuous variables are presented as mean ± SD or median [interquartile range], whereas categorical variables are presented as frequency (percentage).

[a]FemoStop®, pneumatic compression device (Radi medical system, Sweden).

[b]Angioseal®, closure device (St. Jude medical, USA).

DES, drug-eluting stents; INR, international normalized ratio; IQR, inter-quartile range.

Table 3 Prescription of antithrombotic medications at discharge in the two study subgroups

Variable	Anemia (N=258)	Non-anemic (N=603)	*p* value
Triple therapy	181 (70.2)	442 (73.3)	0.15
DAPT	58 (22.5)	100 (16.6)	
VKA plus clopidogrel	15 (5.8)	51 (8.5)	
VKA plus aspirin	4 (1.6)	10 (1.7)	

Variables are presented as frequency (percentage).

VKA indicates vitamin K antagonist; DAPT, dual antiplatelet therapy.

Clinical outcome

Clinical outcomes at 12-month follow-up are presented in table 4 and figure 1. The primary endpoint of MACCE was significantly more frequent in anemic patients than those without anemia (29.1 versus 19.4%, respectively, p=0.002). This difference was driven by higher rates of all-cause mortality, non-fatal MI, and definite/probable ST (p<0.05 for all). Anemic patients had more BARC 3a bleeding events (7.0 versus 3.3%, respectively, p=0.028). No difference was

seen in BARC 5 bleedings. There was a trend toward more total bleeding events (25.2% in anemic versus 21.7% in controls, p=0.059). (For detailed information on bleeding events see Web Table 2.) Total adverse events occurred more frequently in anemic versus non-anemic patients (43.0 versus 31.5%, respectively, p=0.001).

Table 4 Clinical outcome at 12-month follow-up in the two study subgroups

Endpoints	Anemia (N=258)	Non-anemic (N=603)	*p* value
MACCE	75 (29.1)	117 (19.4)	0.002
All-cause mortality	48 (18.6)	50 (8.3)	<0.001
Stroke/TIA	6 (2.3)	17 (2.8)	0.819
Peripheral arterial embolism	2 (0.8)	5 (0.8)	1.00
Non-fatal myocardial infarction	24 (9.3)	27 (4.5)	0.011
Any revascularization	19 (7.4)	51 (8.5)	0.683
Definite/probable stent thrombosis	10 (3.9)	4 (0.7)	0.002
Total bleeding events	65 (25.2)	131 (21.7)	0.059
Minor bleeding (BARC 2)	22 (8.5)	48 (8.0)	0.786
Major bleeding (BARC 3a, 3b, 3c, 5)	33 (12.8)	56 (9.3)	0.142
Access site complications	25 (9.7)	49 (8.1)	0.51
Pseudoaneurysm	7 (2.7)	18 (3.0)	1.0
Red blood cell transfusion	10 (3.9)	5 (0.9)	0.002
Need for corrective surgery	5 (1.9)	8 (1.3)	0.25
Prolonged hospitalization	15 (5.8)	23 (3.8)	0.21
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

MACCE indicates major adverse cardiac and cerebrovascular events; TIA, transient ischemic attacks; BARC, Bleeding Academic Research Consortium.

The incidence of definite/probable stent thrombosis was significantly higher in anemic versus non-anemic patients (3.9 versus 0.7%, respectively, *p*=0.002). Patients who developed stent thrombosis more often presented with ACS than those who did not (80.0 versus 56.6%, respectively, *p*=0.07); however, the use of triple therapy did not differ statistically between groups (60.0 versus 73.3%, respectively, *p*=0.25). Overall, nearly half (46.7%) of ST events occurred early (<30 days). Acute (<24h after index PCI); early (<30 days) and late ST (>30 and < 365 days) were detected in 1 (0.4%) and 1 (0.2%) (p=0.51); 4 (1.6%) vs. 2 (0.3%) (p=0.07); and 6 (2.3%) vs. 2 (0.3%) (p=0.01) in patients with anemia vs. those without anemia, respectively.

In univariate analysis age above 75, diabetes, congestive heart failure, anemia, chronic renal impairment, ACS at presentation, and total stent length were strongly correlated with both MACCE and all-cause mortality at 12-month follow-up. In the Cox regression model including all the above variables, independent predictors of all-cause mortality were anemia (HR 1.62, 95% CI 1.05 – 2.51, p=0.029), ACS at presentation (HR 2.26, 95% CI 1.37 – 3.75, *p*=0.001), chronic renal impairment (HR 2.35, 95% CI 1.52 – 3.65, *p*<0.001), and diabetes (HR 1.76, 95% CI 1.15 – 2.70, p=0.009). In contrast, anemia as a categorical variable was not an independent predictor of MACCE at 12-months follow-up unlike age above 75 years (HR 1.7, 95%-CI 1.2-2.4, p=0.004),

diabetes (HR 1.7, 95%-CI 1.2-2.3, p=0.002), ACS at presentation (HR 1.7, 95%-CI 1.2-2.3, p=0.003), and congestive heart failure (HR 1.5, 95%-CI 1.0-2.1, p=0.03).

We performed the multivariate model also using haemoglobin as a continuous variable. Independent predictors of all-cause mortality were pre-procedural haemoglobin (HR 0.82, 95% CI 0.72 – 0.93, p=0.002), ACS at presentation (HR 2.07, 95% CI 1.25 – 3.45, p=0.005), chronic renal impairment (HR 2.06, 95% CI 1.31 – 3.24, p=0.002), and diabetes (HR 1.75, 95% CI 1.14 – 2.70, p=0.01) in a Cox regression model including age over 75 years, total stent length and number of treated vessels as covariates. On the contrary to what was found when assessing anemia as a categorical variable, haemoglobin as a continuous variable predicted also MACCE. Independent predictors of MACCE were pre-procedural haemoglobin (HR 0.89, 95% CI 0.81 – 0.98, p=0.016), ACS at presentation (HR 1.55, 95% CI 1.10 – 2.18, p=0.012), congestive heart failure (HR 1.45, 95% CI 1.03 – 2.04, p=0.035), age over 75 years (HR 1.77, 95%CI 1.27 – 2.45, p=0.001) and diabetes (HR 1.55, 95% CI 1.13 – 2.13, p=0.007) in a Cox regression model including also total stent length, chronic renal impairment and number of treated vessels as covariates.

When the anemic patients were analysed separately in the Cox regression model, age over 75 years and ACS at presentation were identified as independent predictors of MACCE at 12-months; and chronic renal

impairment, age over 75 years and ACS at presentation as independent predictors of all-cause mortality

Among 861 patients with available preprocedural measurement of haemoglobin concentration, 26 (2.8%) had severe anemia (defined as haemoglobin below 10 g/dl). In this subgroup, MACCE occurred in 12 (46.2%) patients, 10 (38.5%) patients died, and 8 (30.8%) experienced a BARC 2-5 bleeding episode. At discharge, triple therapy was prescribed in 18 (69.2%) patients, dual anti-platelet therapy in 8 (30.8%), and no patient was prescribed vitamin K antagonists plus a single anti-platelet drug. Proton pump inhibitors were prescribed at discharge in 18 (69.2%) patients, and one (3.8%) patient had a history of gastrointestinal bleeding.

DISCUSSION

Our study is the first report on the impact of anemia on the long-term clinical outcome of patients with AF undergoing PCI. The AFCAS registry represent a real-life cohort of high-risk AF-patients requiring PCI. The results of the current study showing that 30% of the patients were anemic confirm the previous reports that anemia is a frequent finding in real-world patients with AF referred for PCI.[6-9,14] Anemic patients in the AFCAS registry were older with more comorbidities, and presented more often with ACS, compared with non-anemic patients, as also reported in previous cohorts.[6,7,9,14].

Overall, the 12-month clinical outcome was worse in anemic patients. Anemia remained an independent predictor of all-cause mortality in multivariate analysis. The higher rate of all-cause mortality might be related to the higher-risk profile in anemic patients, as well as the underlying disease causing anemia. Furthermore, anemic patients had more frequent MACCE at 12 months, primarily driven by higher rates of all-cause mortality, and non-fatal MI. However, anemia was not an independent predictor of MACCE. The higher rate of non-fatal MI might be explained, at least in part, by the higher frequency of ACS at presentation in anemic patients.

The estimated thromboembolic risk of anemic patients according to $CHADS_2$ score was higher. However, no excess in TIA or stroke was seen during the follow-up and only a trend towards more bleeding was observed. This is contradictory to previous studies which have reported a higher incidence of cardiac and cerebrovascular thrombotic events at long-term follow-up in anemic versus non-anemic patients in various patient cohorts referred for PCI.[7,9,14-18] The relatively small number of complications in our patient cohort might explain this difference.

The estimated bleeding risk according to the HAS-BLED score was higher in anemic patients, but there was only a trend towards increased risk of major bleeding. However, the results of the current study support the previous reports on the increased bleeding risk associated with anemia in various patient groups undergoing PCI.[8,9,19] Anemia may be a marker and consequence of an underlying condition such as bleeding diathesis, occult gastrointestinal bleeding, or malignancy that augments the bleeding risk. An interesting observation is that neither the presence of anemia nor higher estimated bleeding risk seemed to affect the clinician's choice of antithrombotic medications at discharge. In view of our results, patients with anemia tolerated triple therapy surprisingly well with only a trend towards increased bleeding.

We observed that the rate of definite or probable stent thrombosis was significantly higher in anemic versus non-anemic patients (p =0.002). ACS at presentation may have contributed to the higher rate of stent thrombosis in anemic patients, as patients with anemia more often presented with ACS versus those without anemia. In addition, in individual cases the presence of anemia may have influenced the choice of antithrombotic medication. Also, a bleeding event could have lead to interruption of combination antithrombotic therapy and thus to a higher risk of stent thrombosis. Consistent with our results, Pilgrim and co-workers, observed a higher rate of definite stent thrombosis at

4-year follow-up in anemic patients who underwent PCI with unrestricted use of drug-eluting stents, compared with non-anemic ones.[14] Interestingly, in a recent study, anemia was the only independent predictor of high residual platelet reactivity on clopidogrel in a series of patients undergoing PCI.[20] These observations warrant further studies to clarify the underlying mechanisms.

The effect of anemia on the clinical outcome of PCI appears early during hospitalization. Kaplan-Meier event-free survival curves in the current study revealed that most of the thrombotic as well as bleeding events occurred early (within 30 days) following the index PCI (Figure 1). This finding is in line with previous reports.[6,8,9,15] In patients with coronary artery disease, anemia may aggravate myocardial ischemia, and unveil significant coronary obstruction. Cardiac output increases in patients with anemia in order to maintain adequate oxygen delivery to the tissues. This increases heart rate and induces myocardial hypertrophy, which in turn, increases myocardial oxygen demand, and further exaggerates the myocardial oxygen demand/supply imbalance.[21] On the other hand, patients with severe anemia receive more frequent blood transfusion, which was reported to have an adverse impact on survival after PCI.[22] Unfortunately, information on blood transfusions was not available in our registry except for the in-hospital phase. More importantly,

anemia is frequently associated with severe underlying chronic diseases which may compromise long-term survival. Of note is a recent report suggesting that in patients who underwent PCI with drug-eluting stents, those in whom anemia improved at follow-up had less MACCE at a median follow-up of 25 months, compared with those with sustained anemia suggesting that a transient cause is less detrimental than a long-standing state causing anemia, e.g. malignancy.[16]

Limitations of the study

The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias, even though we did not observe any difference between the two study groups in the antithrombotic treatment prescribed at discharge. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines. Moreover, the aetiology of anemia was not systematically investigated; yet, it is beyond the scope of the current study. The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

Conclusion

Anemia was a frequent finding in patients with AF referred for PCI. Anemia seems to be an independent risk factor for all-cause mortality during 12-month follow-up. Anemia is also associated with more MACCE, and a trend toward a higher rate of bleeding.

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COMPETING INTERESTS

The authors declare no competing interests.

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study and contributed to study design, data collection, data analysis and writing of the manuscript.

Data sharing The whole study data is available from the study coordinator Ms. Tuija Vasankari email: tuija.vasankari@tyks.fi or Dr. Tuomas Kiviniemi email: tuomas.kiviniemi@utu.fi in addition to corresponding author Prof. Juhani Airaksinen email: juhani.airaksinen@tyks.fi.

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FIGURE LEGENDS

Figure 1 Kaplan-Meier survival curves for the occurrence of adverse events in anemic (dotted lines) versus non-anemic (solid line) patients at 2-month follow-up: all-cause mortality (a), MACCE free survival (b) and bleeding event free survival (c)

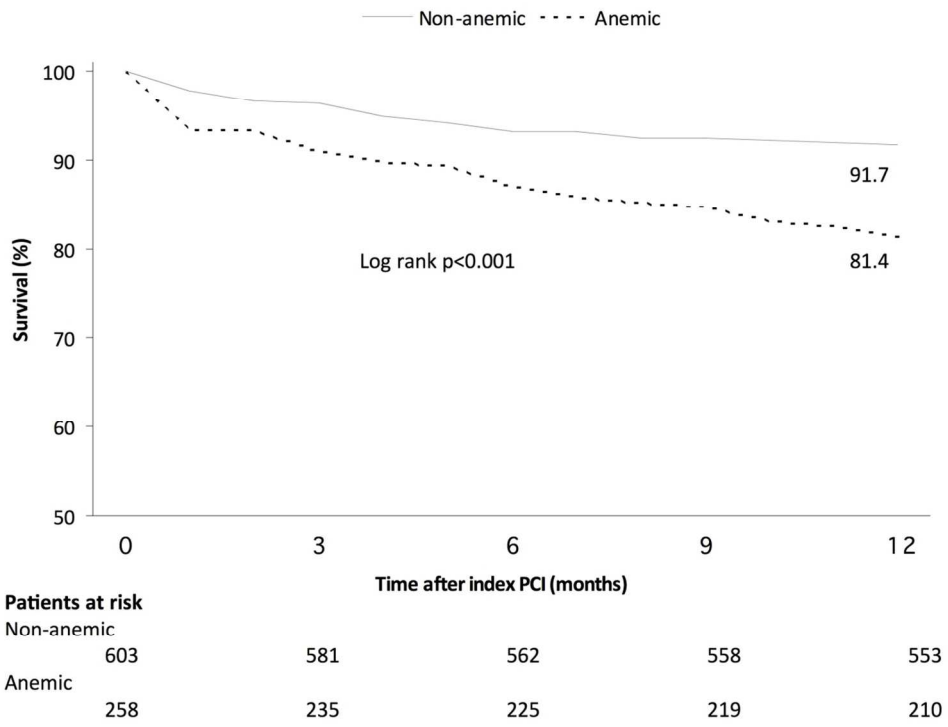

Figure 1a
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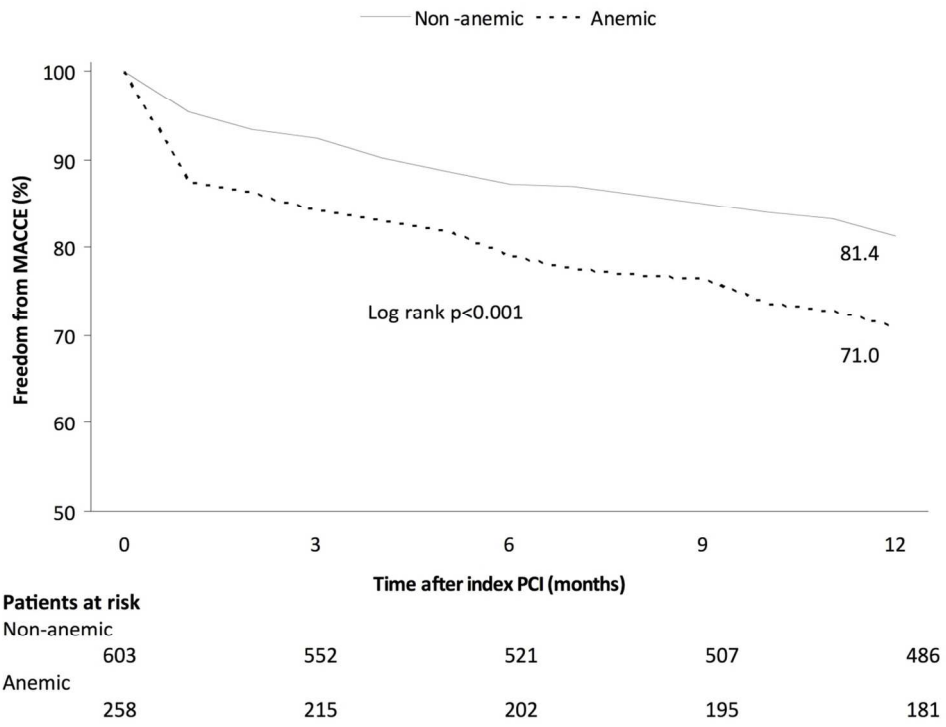

Figure 1b
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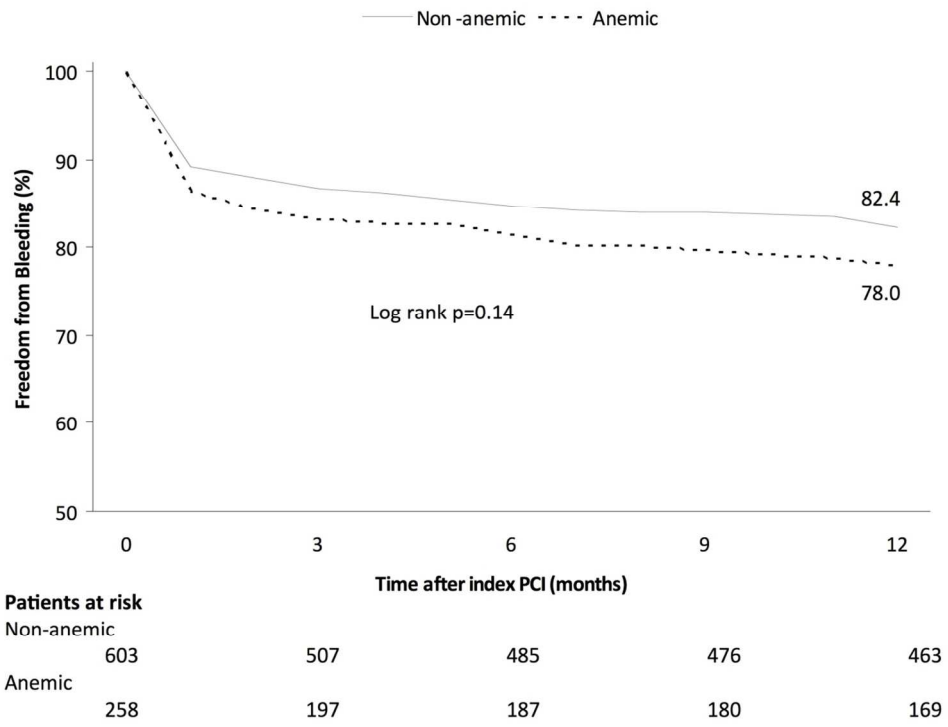

Figure 1c
119x90mm (300 x 300 DPI)

Table 1. Bleeding Academic Research Consortium Definition for Bleeding.

Type 2	any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop >5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 5	fatal bleeding

Type 1 and type 4 (coronary bypass related) bleeding events were not included in the analysis.

Online Table 2 Bleeding events at 12-month follow-up in the two study subgroups

Endpoints	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
BARC 2	22 (8.5)	48 (8.0)	0.786
BARC 3a bleeding	18 (7.0)	20 (3.3)	0.028
BARC 3b bleeding	10 (3.9)	22 (3.6)	0.846
BARC 3c bleeding	0 (0)	9 (1.5)	0.064
BARC 5 bleeding	4 (1.6)	5 (0.8)	0.464
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

BARC indicates Bleeding Academic Research Consortium.

Impact of anemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry

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Extra data is available by emailing Prof. Juhani Airaksinen at juhani.airaksinen@tyks.fi.

ABSTRACT

Objectives: Anemia has an adverse impact on the outcome in the general patient population undergoing percutaneous coronary intervention (PCI). The aim of this study was to analyze the impact of anemia on the 12-month clinical outcome of patients with atrial fibrillation (AF) undergoing PCI and therefore requiring intense antithrombotic treatment. We hypothesized that anemia might be associated with a worse outcome and more bleeding in these anticoagulated patients.

Setting: Data was collected from 17 secondary care centers in Europe.

Participants: Consecutive patients with AF undergoing PCI were enrolled in the prospective, multicenter AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry. Altogether 929 patients participated in the study. Preprocedural haemoglobin concentration was available for 861 (92.7%) (30% female). Only exclusion criteria were inability or unwillingness to give informed consent. Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men.

Outcome measures: The primary endpoint was occurrence of major adverse cardiac and cerebrovascular events (MACCE) or bleeding events.

Results: 258/861 (30%) patients had anemia. Anemic patients were older, had more often diabetes, higher CHA_2DS_2-VASc score, prior history of heart

failure, chronic renal impairment, and acute coronary syndrome. Anemic patients had more MACCE than non-anemic (29.1% versus 19.4%, respectively, *p*=0.002), and minor bleeding events (7.0% versus 3.3%, respectively, *p*=0.028), with a trend toward more total bleeding events (25.2% versus 21.7%, respectively, *p*=0.059). No difference was observed in antithrombotic regimens at discharge. In multivariate analysis anemia was an independent predictor of all-cause mortality at 12-months follow-up (HR 1.62, 95% CI 1.05 – 2.51, p=0.029).

Conclusions: Anemia was a frequent finding in patients with AF referred for PCI. Anemic patients had a higher all-cause mortality, more thrombotic events, and minor bleeding events. Anemia seems to identify patients at risk for cardiovascular events and death.

Trial registration: ClinicalTrials.gov number NCT00596570

Keywords: atrial fibrillation, percutaneous coronary intervention, anemia

Strengths and limitations of the study:

- The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

- The study adds to our knowledge on the prevalence and impact of anemia in AF patients undergoing PCI and thus requiring combination antithrombotic medication. It shows that anemia is a frequent finding and that even mild anemia has an adverse impact on outcome.
- The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines.
- The aetiology of anemia could not be systematically investigated and is therefore out of the scope of this study.

INTRODUCTION

It is estimated that around 5% of patients undergoing percutaneous coronary intervention (PCI) need long-term oral anticoagulation (OAC) due to atrial fibrillation (AF).[1,2] Yet, the current recommendations on the management of antithrombotic treatment in patients with AF undergoing PCI and stenting are mainly derived from small studies, amounting to a weak level of evidence.[3,4] Moreover, the real-world management of patients on OAC undergoing PCI is variable, and only partially adherent to the current recommendations.[5]

Defined according to the World Health Organization (WHO), anemia has been reported to affect nearly 25% of patients undergoing PCI and stenting. Anemic patients undergoing PCI are generally older with more comorbidities, and have higher rates of in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE), as well as 1-year mortality.[6,7] Furthermore, low admission haemoglobin level was found to be an independent predictor of in-hospital and long-term mortality, and was associated with higher rates of in-hospital minor and major bleeding events in patients undergoing primary PCI for ST-segment elevation myocardial infarction (MI).[8,9]

However, little is known about the effect of anemia on the outcome of patients with AF undergoing PCI and thus requiring intensive antithrombotic treatment. Anemia is possibly a marker of high bleeding risk, which could be aggravated by the underlying cause. Therefore, we analyzed data from the

prospective AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry to explore the impact of anemia on the 12-month clinical outcome of patients with AF undergoing PCI.[10]

METHODS

Patients

The AFCAS registry (ClinicalTrials.gov number NCT00596570)
is a prospective, multicenter registry that enrolled patients with AF referred for PCI in 5 European countries. The study design has been described in detail previously.[11] Patients were enrolled if they had: 1) history of AF (paroxysmal, persistent, or permanent), or 2) on-going AF during the index PCI. Out of the 929 participants 861 (92.7%) had a preprocedural haemoglobin count available and were included in this analysis.

Coronary angiography and PCI were performed via either radial or femoral access, and hemostasis was achieved according to local practice. Coronary lesions were treated according to contemporary interventional techniques. Low-molecular-weight heparin (enoxaparin sodium, dalteparin), unfractionated heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion. The post-discharge medication was completely at the discretion of the treating physician.

The primary endpoints of the current study were 1) occurrence of MACCE defined as a composite of all-cause mortality, any non-fatal MI, any revascularization, definite/probable stent thrombosis, transient ischemic attack (TIA) or stroke, and peripheral arterial embolism; 2) bleeding events; and 3) total adverse events (a composite of MACCE plus bleeding events). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria as minor (BARC 2), and major (BARC 3a, 3b, 3c and 5) bleeding events; however, CABG-related bleeding was excluded.[12] (Web~~Online~~ Table 1)

Anemia was defined as a haemoglobin concentration of <12 g/dl for women, and <13 g/dl for men, according to the definition of the WHO.[13] Chronic renal impairment was defined by an estimated glomerular filtration rate below 60 ml/min.

Ethical aspects

The study was initiated by the investigators and conducted according to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002. Informed written consent was obtained from every patient after full explanation

of the study protocol. The study protocol was approved by the ethics committees of the participating centers.

Statistical analysis

For analysis patients with available preprocedural measurement of haemoglobin concentration were divided into two subgroups: anemic patients, and control patients without anemia. Continuous variables were reported as the mean ± standard deviation if normally distributed, and as median [inter-quartile range (IQR)] if they were skewed. Data were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two study subgroups were performed using the unpaired *t*-test or Mann-Whitney test for continuous variables, and Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up. Baseline variables correlating at $p<0.10$ level with the dependent variable in univariate analyses were entered in the Cox regression model as covariates. Cox regression hazard model was used to identify the independent predictors of MACCE, and all-cause mortality at 12-month follow-up in the subgroup of anemic patients. Finally we constructed Kaplan-Meier survival curves to display the time-to-event relationship for the occurrence of

all-cause mortality, MACCE, and all bleeding events. Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1, SPSS Inc., Chicago, Ill., USA).

RESULTS

Baseline characteristics

Out of 929 patients enrolled in the AFCAS registry and followed up for 12 months, 861 (92.7%) had available preprocedural measurement of haemoglobin concentration, of whom 258 (30%) had anemia and 603 (70%) had normal haemoglobin concentration. Anemic patients were older, more likely to have diabetes mellitus, hypertension, history of heart failure and chronic renal impairment, HAS-BLED score ≥3, higher CHA_2DS_2VASC score, and more likely presented with acute coronary syndrome (ACS) as opposed to chronic stable angina, compared with those without anemia ($p<0.05$ for all), as shown in Table 1. Furthermore, anemic patients had more vessels treated during the index procedure, and a greater total stent length, compared with those without anemia ($p<0.05$ for both) (Table 2). At discharge, no significant differences were seen in the prescription of antithrombotic medications in the two study groups ($p=0.15$) (Table 3). The duration of clopidogrel treatment did not differ in anemic versus non-anemic patients on triple therapy (median [IQR]: 3 [11] versus 3 [5] months, $p=0.61$), on dual antiplatelet therapy (median [IQR]: 12

[11] versus 12 [11] months, p=0.72), or on vitamin K antagonist + clopidogrel (median [IQR]: 12 [11] versus 3 [11] months, p=0.65). Proton pump inhibitors were more frequently prescribed to patients with anemia versus those without (47.7 versus 31.3%, respectively, p <0.001).

Table 1 Baseline clinical characteristics of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Age (yrs)	76 [9]	73 [11]	<0.001
Female gender	89 (34.5)	170 (28.2)	0.074
Diabetes mellitus	119 (46.1)	191 (31.7)	<0.001
Hypercholesterolemia	162 (62.8)	407 (67.5)	0.183
Current or ex-smoking	26 (10.1)	62 (10.3)	1.00
Hypertension	221 (85.7)	503 (83.4)	0.48
Paroxysmal atrial fibrillation	103 (39.9)	229 (38.0)	0.594
Persistent atrial fibrillation	22 (8.5)	78 (12.9)	0.081
Permanent atrial fibrillation	129 (50)	294 (48.8)	0.766

CHA_2DS_2-VASc score >4	148 (57.4)	235 (39.0)	<0.001
HAS BLED score ≥3	215 (83.3)	441 (73.1)	0.001
History of peptic ulcer	17 (6.6)	27 (4.5)	0.236
History of cerebral hemorrhage	4 (1.6)	6 (1.0)	0.497
History of GI hemorrhage	9 (3.5)	12 (2.0)	0.144
History of heart failure	69 (26.7)	113 (18.7)	0.011
eGFR below 60 ml/min	119 (52.2)	175 (31.9)	<0.001
Prior transient ischemic attacks	12 (4.7)	30 (5.0)	1.00
Prior stroke	36 (14.0)	67 (11.1)	0.252
Prior MI	76 (29.5)	146 (24.2)	0.126
Prior PCI	47 (18.2)	100 (16.6)	0.555
Prior coronary bypass surgery	47 (18.2)	78 (12.9)	0.057
Proton pump inhibitors	123 (47.7)	189 (31.3)	<0.001
Stable angina pectoris	81 (31.4)	289 (48.0)	<0.001
ACS	177 (68.6)	313 (52.0)	<0.001
Unstable angina pectoris	53 (20.5)	107 (17.7)	0.34
Non-ST-elevation MI	83 (32.2)	132 (21.9)	0.002
ST-elevation MI	41 (15.9)	74 (12.3)	0.156

Continuous variables are presented as median [interquartile range], whereas categorical variables are presented as frequency (percentage).

ACS indicates acute coronary syndrome; eGFR, estimated glomerular filtration rate; GI, gastrointestinal, IQR, inter-quartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Procedural data of the two study subgroups

Variable	**Anemia (N=258)**	**Non-anemic (N=603)**	***p* value**
Femoral access	196 (76.0)	435 (72.1)	0.275
Number of treated vessels	1.22 ± 0.45	1.15 ± 0.41	0.04
DES	67 (27.0)	138 (23.6)	0.293
Peri-procedural INR	1.9 [1]	1.88 [1]	0.509
Stent diameter (mm)	3 [1]	3 [1]	0.965
Total stent length (mm)	20 [18]	19 [14]	0.014
Procedural success	252 (97.7)	582 (96.5)	0.085
Hemostasis			
Manual compression	112 (43.4)	249 (41.3)	0.765
Compression device[a]	49 (19.0)	155 (25.7)	0.083
Access-site closure device[b]	82 (31.8)	165 (27.4)	0.154

Continuous variables are presented as mean ± SD or median [interquartile range], whereas categorical variables are presented as frequency (percentage).

[a]FemoStop®, pneumatic compression device (Radi medical system, Sweden).

[b]Angioseal®, closure device (St. Jude medical, USA).

DES, drug-eluting stents; INR, international normalized ratio; IQR, inter-quartile range.

Table 3 Prescription of antithrombotic medications at discharge in the two study subgroups

Variable	Anemia (N=258)	Non-anemic (N=603)	*p* value
Triple therapy	181 (70.2)	442 (73.3)	0.15
DAPT	58 (22.5)	100 (16.6)	
VKA plus clopidogrel	15 (5.8)	51 (8.5)	
VKA plus aspirin	4 (1.6)	10 (1.7)	

Variables are presented as frequency (percentage).

VKA indicates vitamin K antagonist; DAPT, dual antiplatelet therapy.

Clinical outcome

Clinical outcomes at 12-month follow-up are presented in table 4 and figure 1. The primary endpoint of MACCE was significantly more frequent in anemic patients than those without anemia (29.1 versus 19.4%, respectively, p=0.002). This difference was driven by higher rates of all-cause mortality, non-fatal MI, and definite/probable ST (p<0.05 for all). Anemic patients had more BARC 3a bleeding events (7.0 versus 3.3%, respectively, p=0.028). No difference was

seen in BARC 5 bleedings. There was a trend toward more total bleeding events (25.2% in anemic versus 21.7% in controls, p=0.059). (For detailed information on bleeding events see Web~~Online~~ Table 2.) Total adverse events occurred more frequently in anemic versus non-anemic patients (43.0 versus 31.5%, respectively, p=0.001).

Table 4 Clinical outcome at 12-month follow-up in the two study subgroups

Endpoints	Anemia (N=258)	Non-anemic (N=603)	*p* value
MACCE	75 (29.1)	117 (19.4)	0.002
All-cause mortality	48 (18.6)	50 (8.3)	<0.001
Stroke/TIA	6 (2.3)	17 (2.8)	0.819
Peripheral arterial embolism	2 (0.8)	5 (0.8)	1.00
Non-fatal myocardial infarction	24 (9.3)	27 (4.5)	0.011
Any revascularization	19 (7.4)	51 (8.5)	0.683
Definite/probable stent thrombosis	10 (3.9)	4 (0.7)	0.002
Total bleeding events	65 (25.2)	131 (21.7)	0.059
Minor bleeding (BARC 2)	22 (8.5)	48 (8.0)	0.786
Major bleeding (BARC 3a, 3b, 3c, 5)	33 (12.8)	56 (9.3)	0.142
Access site complications	25 (9.7)	49 (8.1)	0.51
Pseudoaneurysm	7 (2.7)	18 (3.0)	1.0
Red blood cell transfusion	10 (3.9)	5 (0.9)	0.002
Need for corrective surgery	5 (1.9)	8 (1.3)	0.25
Prolonged hospitalization	15 (5.8)	23 (3.8)	0.21
Total adverse events	111 (43.0)	190 (31.5)	0.001

Variables are presented as frequency (percentage).

MACCE indicates major adverse cardiac and cerebrovascular events; TIA, transient ischemic attacks; BARC, Bleeding Academic Research Consortium.

The incidence of definite/probable stent thrombosis was significantly higher in anemic versus non-anemic patients (3.9 versus 0.7%, respectively, *p*=0.002). Patients who developed stent thrombosis more often presented with ACS than those who did not (80.0 versus 56.6%, respectively, *p*=0.07); however, the use of triple therapy did not differ statistically between groups (60.0 versus 73.3%, respectively, *p*=0.25). Overall, nearly half (46.7%) of ST events occurred early (<30 days). Acute (<24h after index PCI); early (<30 days) and late ST (>30 and < 365 days) were detected in 1 (0.4%) and 1 (0.2%) (p=0.51); 4 (1.6%) vs. 2 (0.3%) (p=0.07); and 6 (2.3%) vs. 2 (0.3%) (p=0.01) in patients with anemia vs. those without anemia, respectively.

In univariate analysis age above 75, diabetes, congestive heart failure, anemia, chronic renal impairment, ACS at presentation, and total stent length were strongly correlated with both MACCE and all-cause mortality at 12-month follow-up. In the Cox regression model including all the above variables, independent predictors of all-cause mortality were anemia (HR 1.62, 95% CI 1.05 – 2.51, p=0.029), ACS at presentation (HR 2.26, 95% CI 1.37 – 3.75, *p*=0.001), chronic renal impairment (HR 2.35, 95% CI 1.52 – 3.65, *p*<0.001), and diabetes (HR 1.76, 95% CI 1.15 – 2.70, p=0.009). In contrast, anemia as a categorical variable was not an independent predictor of MACCE at 12-months follow-up unlike age above 75 years (HR 1.7, 95%-CI 1.2-2.4, p=0.004),

diabetes (HR 1.7, 95%-CI 1.2-2.3, p=0.002), ACS at presentation (HR 1.7, 95%-CI 1.2-2.3, p=0.003), and congestive heart failure (HR 1.5, 95%-CI 1.0-2.1, p=0.03).

We performed the multivariate model also using haemoglobin as a continuous variable. Independent predictors of all-cause mortality were pre-procedural haemoglobin (HR 0.82, 95% CI 0.72 – 0.93, p=0.002), ACS at presentation (HR 2.07, 95% CI 1.25 – 3.45, p=0.005), chronic renal impairment (HR 2.06, 95% CI 1.31 – 3.24, p=0.002), and diabetes (HR 1.75, 95% CI 1.14 – 2.70, p=0.01) in a Cox regression model including age over 75 years, total stent length and number of treated vessels as covariates. On the contrary to what was found when assessing anemia as a categorical variable, haemoglobin as a continuous variable predicted also MACCE. Independent predictors of MACCE were pre-procedural haemoglobin (HR 0.89, 95% CI 0.81 – 0.98, p=0.016), ACS at presentation (HR 1.55, 95% CI 1.10 – 2.18, p=0.012), congestive heart failure (HR 1.45, 95% CI 1.03 – 2.04, p=0.035), age over 75 years (HR 1.77, 95%CI 1.27 – 2.45, p=0.001) and diabetes (HR 1.55, 95% CI 1.13 – 2.13, p=0.007) in a Cox regression model including also total stent length, chronic renal impairment and number of treated vessels as covariates.

When the anemic patients were analysed separately in the Cox regression model, age over 75 years and ACS at presentation were identified as independent predictors of MACCE at 12-months; and chronic renal

impairment, age over 75 years and ACS at presentation as independent predictors of all-cause mortality

Among 861 patients with available preprocedural measurement of haemoglobin concentration, 26 (2.8%) had severe anemia (defined as haemoglobin below 10 g/dl). In this subgroup, MACCE occurred in 12 (46.2%) patients, 10 (38.5%) patients died, and 8 (30.8%) experienced a BARC 2-5 bleeding episode. At discharge, triple therapy was prescribed in 18 (69.2%) patients, dual anti-platelet therapy in 8 (30.8%), and no patient was prescribed vitamin K antagonists plus a single anti-platelet drug. Proton pump inhibitors were prescribed at discharge in 18 (69.2%) patients, and one (3.8%) patient had a history of gastrointestinal bleeding.

DISCUSSION

Our study is the first report on the impact of anemia on the long-term clinical outcome of patients with AF undergoing PCI. The AFCAS registry represent a real-life cohort of high-risk AF-patients requiring PCI. The results of the current study showing that 30% of the patients were anemic confirm the previous reports that anemia is a frequent finding in real-world patients with AF referred for PCI.[6-9,14] Anemic patients in the AFCAS registry were older with more comorbidities, and presented more often with ACS, compared with non-anemic patients, as also reported in previous cohorts.[6,7,9,14].

Overall, the 12-month clinical outcome was worse in anemic patients. Anemia remained an independent predictor of all-cause mortality in multivariate analysis. The higher rate of all-cause mortality might be related to the higher-risk profile in anemic patients, as well as the underlying disease causing anemia. Furthermore, anemic patients had more frequent MACCE at 12 months, primarily driven by higher rates of all-cause mortality, and non-fatal MI. However, anemia was not an independent predictor of MACCE. The higher rate of non-fatal MI might be explained, at least in part, by the higher frequency of ACS at presentation in anemic patients.

The estimated thromboembolic risk of anemic patients according to $CHADS_2$ score was higher. However, no excess in TIA or stroke was seen during the follow-up and only a trend towards more bleeding was observed. This is contradictory to previous studies which have reported a higher incidence of cardiac and cerebrovascular thrombotic events at long-term follow-up in anemic versus non-anemic patients in various patient cohorts referred for PCI.[7,9,14-18] The relatively small number of complications in our patient cohort might explain this difference.

The estimated bleeding risk according to the HAS-BLED score was higher in anemic patients, but there was only a trend towards increased risk of major bleeding. However, the results of the current study support the previous reports on the increased bleeding risk associated with anemia in various patient groups undergoing PCI.[8,9,19] Anemia may be a marker and consequence of an underlying condition such as bleeding diathesis, occult gastrointestinal bleeding, or malignancy that augments the bleeding risk. An interesting observation is that neither the presence of anemia nor higher estimated bleeding risk seemed to affect the clinician's choice of antithrombotic medications at discharge. In view of our results, patients with anemia tolerated triple therapy surprisingly well with only a trend towards increased bleeding.

We observed that the rate of definite or probable stent thrombosis was significantly higher in anemic versus non-anemic patients (p =0.002). ACS at presentation may have contributed to the higher rate of stent thrombosis in anemic patients, as patients with anemia more often presented with ACS versus those without anemia. In addition, in individual cases the presence of anemia may have influenced the choice of antithrombotic medication. Also, a bleeding event could have lead to interruption of combination antithrombotic therapy and thus to a higher risk of stent thrombosis. Consistent with our results, Pilgrim and co-workers, observed a higher rate of definite stent thrombosis at

4-year follow-up in anemic patients who underwent PCI with unrestricted use of drug-eluting stents, compared with non-anemic ones.[14] Interestingly, in a recent study, anemia was the only independent predictor of high residual platelet reactivity on clopidogrel in a series of patients undergoing PCI.[20] These observations warrant further studies to clarify the underlying mechanisms.

The effect of anemia on the clinical outcome of PCI appears early during hospitalization. Kaplan-Meier event-free survival curves in the current study revealed that most of the thrombotic as well as bleeding events occurred early (within 30 days) following the index PCI (Figure 1). This finding is in line with previous reports.[6,8,9,15] In patients with coronary artery disease, anemia may aggravate myocardial ischemia, and unveil significant coronary obstruction. Cardiac output increases in patients with anemia in order to maintain adequate oxygen delivery to the tissues. This increases heart rate and induces myocardial hypertrophy, which in turn, increases myocardial oxygen demand, and further exaggerates the myocardial oxygen demand/supply imbalance.[21] On the other hand, patients with severe anemia receive more frequent blood transfusion, which was reported to have an adverse impact on survival after PCI.[22] Unfortunately, information on blood transfusions was not available in our registry except for the in-hospital phase. More importantly,

anemia is frequently associated with severe underlying chronic diseases which may compromise long-term survival. Of note is a recent report suggesting that in patients who underwent PCI with drug-eluting stents, those in whom anemia improved at follow-up had less MACCE at a median follow-up of 25 months, compared with those with sustained anemia suggesting that a transient cause is less detrimental than a long-standing state causing anemia, e.g. malignancy.[16]

Limitations of the study

The current study has the inherent limitations of the observational study design, including individual risk-based decision making in treatment choices, which may introduce selection bias, even though we did not observe any difference between the two study groups in the antithrombotic treatment prescribed at discharge. Another possible confounder is the heterogeneity of the AF population among the participating centers and some differences in the periprocedural routines. Moreover, the aetiology of anemia was not systematically investigated; yet, it is beyond the scope of the current study. The strength of the study is the enrolment of consecutive patients with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense the study population represents well real-world patients with AF referred for PCI.

Conclusion

Anemia was a frequent finding in patients with AF referred for PCI. ~~Anemic patients were older with more frequent comorbidities, and more often presented with ACS.~~ Anemia seems to be an independent risk factor for all-cause mortality during 12-month follow-up. Anemia is also associated with more MACCE, and a trend toward a higher rate of bleeding.

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COMPETING INTERESTS

The authors declare no competing interests.

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FIGURE LEGENDS

Figure 1 Kaplan-Meier survival curves for the occurrence of adverse events in anemic (dotted lines) versus non-anemic (solid line) patients at 2-month follow-up: all-cause mortality (a), MACCE free survival (b) and bleeding event free survival (c)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ok
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ok
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ok
Objectives	3	State specific objectives, including any prespecified hypotheses ok
Methods		
Study design	4	Present key elements of study design early in the paper ok
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ok
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ok
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ok
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ok
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ok
		(*b*) Describe any methods used to examine subgroups and interactions ok
		(*c*) Explain how missing data were addressed ok
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ok
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ok
		(b) Indicate number of participants with missing data for each variable of interest ok
		(c) Summarise follow-up time (eg, average and total amount) ok
Outcome data	15*	Report numbers of outcome events or summary measures over time ok
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ok

		(*b*) Report category boundaries when continuous variables were categorized ok
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ok
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ok

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.