European Journal of Internal Medicine 61 (2019) 48–53

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Impact of anemia as risk factor for major bleeding and mortality in patients with acute coronary syndrome

Nuria Vicente-Ibarra[a], Francisco Marín[b], Vicente Pernías-Escrig[a], Miriam Sandín-Rollán[c], Laura Núñez-Martínez[a], Teresa Lozano[c], Manuel Jesús Macías-Villaniego[c], Luna Carrillo-Alemán[c], Elena Candela-Sánchez[c], Elena Guzmán[c], María Asunción Esteve-Pastor[b], Esteban Orenes-Piñero[b], Mariano Valdés[b], José Miguel Rivera-Caravaca[b], Juan M. Ruiz-Nodar[c,*]

[a] Department of Cardiology, University Hospital of Elche, Alicante, Spain
[b] Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBERCV, Murcia, Spain
[c] Department of Cardiology, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

ARTICLE INFO

Keywords:
Anemia
Acute coronary syndrome
Hemorrhage
Ischemia
Mortality
Platelet aggregation inhibitors

ABSTRACT

Background: Anemia is frequent in acute coronary syndrome (ACS) patients and is associated with worse clinical outcomes. We aimed to investigate the therapeutic strategies, the use of novel $P2Y_{12}$ inhibitors, and the prognostic implication of anemia in a "real world" cohort of ACS patients.

Methods: This is an observational and prospective registry including 1717 ACS patients from three tertiary hospitals. During hospitalization we recorded the clinical management and the antiplatelet therapy at discharge. Patients were divided into 2 groups according to the baseline hemoglobin level, i.e. anemic (hemoglobin < 13 g/dL in men and < 12 g/dL in women) and non-anemic patients. Bleeding events, mortality and major adverse cardiovascular events (MACEs) were recorded during 1-year of follow-up.

Results: Anemia was present in 445 (25.9%) patients. Cardiac catheterization (83.8% vs. 94.5%, p < .001), and revascularization by percutaneous coronary intervention (53.5% vs. 70.5%, p < .001) were less frequent in these patients. Excluding anticoagulated patients, novel $P2Y_{12}$ inhibitors were less prescribed in anemic patients (OR 2.80 [95% CI 2.13–3.67], p < .001). Anemia was independently associated with major bleeding (HR 2.26 [95% CI 1.07–4.78], p = .033) and all-cause mortality (HR 1.62 [95% CI 1.03–2.56], p = .038), but not with MACE. At 1-year of follow-up, the risk of mortality in anemic patients taking clopidogrel was higher (HR 2.38 [95% CI 1.01–5.67]; p = .049).

Conclusions: In this registry involving ACS patients, anemia had influence on clinical management and antiplatelet therapy. Patients suffering from anemia had higher risk for major bleeding and mortality. In particular, anemic patients treated with clopidogrel had even more mortality events.

1. Background

Anemia is a frequent comorbidity in patients admitted for an acute coronary syndrome (ACS) and it is also strongly associated with an increased risk of hemorrhagic complications and worse in-hospital and long-term clinical outcomes [1–5]. However, novel $P2Y_{12}$ inhibitors have improved the prognosis of patients with ACS, and thus the European Society of Cardiology (ESC) has recommend the use of prasugrel and ticagrelor over clopidogrel for the management of ACS patients, in both non-ST-elevation and ST-elevation [6,7]. Nevertheless, the higher antiplatelet potency of these drugs has been associated with increased risk of bleeding [8,9].

Randomized clinical trials (RCTs) and particularly antithrombotic RCTs, often exclude patients with anemia and do not offer accurate evidence about the effect of some interventions and treatments on this population. By this reason, current clinical practice guidelines cannot provide recommendations regarding which antithrombotic therapy should be used in anemic patients, balancing ischaemic and bleeding risk in each individual case [6]. So far, there are no studies exploring the prognosis of patients with anemia treated with novel $P2Y_{12}$ inhibitors, such as ticagrelor and prasugrel, after presenting an ACS.

The aim of this study was to investigate the impact of anemia in a "real world" cohort of patients discharged after an ACS, and to analyze

* Corresponding author at: Department of Cardiology, Hospital General Universitario de Alicante, C/Maestro Alonso s/n, 03010 Alicante, Spain.
E-mail address: ruiz_jmi@gva.es (J.M. Ruiz-Nodar).

https://doi.org/10.1016/j.ejim.2018.12.004
Received 28 May 2018; Received in revised form 13 November 2018; Accepted 17 December 2018
Available online 20 December 2018

Table 1
Baseline characteristics.

	Anemic patients (n = 445)	Non-anemic patients (n = 1272)	p
Age (years), median (IQR)	75 (66–81)	64 (54–74)	< 0.001
Female sex, n (%)	151 (33.9)	341 (26.8)	0.004
BMI (kg/m^2), median (IQR)	27.2 (24.9–30.4)	27.7 (25.3–31.0)	0.061
Clinical presentation, n (%)			
ST-elevation ACS	115 (25.8)	459 (36.1)	
Non-ST elevation ACS	330 (74.2)	813 (63.9)	
Killip ≥ 2	158 (35.5)	201 (15.8)	< 0.001
GRACE, median (IQR)			
GRACE (in-hospital)	155 (129.3–186.8)	128 (103.0–155.0)	< 0.001
GRACE (6-month)	132 (109.0–155.5)	103 (84.0–128.0)	< 0.001
CRUSADE, median (IQR)	42 (31–54)	24 (16.0–33.3)	< 0.001
Ejection fraction (%), median	58 (49–62)	60 (51–64)	0.009
Comorbidities, n (%)			
Hypertension	361 (81.6)	796 (62.6)	< 0.001
Diabetes mellitus	251 (56.4)	402 (31.6)	< 0.001
Dyslipidemia	294 (66.1)	731 (57.5)	0.001
Current smoking habit	98 (22.1)	536 (42.1)	< 0.001
Previous coronary artery disease	198 (44.5)	343 (27.0)	< 0.001
Previous revascularization			
PCI	133 (29.9)	237 (18.6)	< 0.001
CABG	19 (4.3)	36 (2.8)	
Previous Stroke/TIA	56 (12.6)	93 (7.3)	0.001
Hemoglobin (g/dL)	11.4 (10.4–12.0)	14.4 (13.6–15.3)	< 0.001
eGFR (mL/min/1.73 m^2)	62.2 (42.7–87.9)	85.1 (69.7–100.1)	< 0.001
Previous antithrombotic therapy, n (%)			
Aspirin	208 (46.7)	388 (30.5)	< 0.001
Clopidogrel	101 (22.7)	127 (10.0)	< 0.001
Oral anticoagulants	64 (14.4)	77 (6.1)	< 0.001

ACS = acute coronary syndrome; BMI = body mass index; CABG = coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; IQR = interquartile range; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack.

the therapeutic strategies, the use of novel $P2Y_{12}$ inhibitors, and the prognostic implication of the anemia in the mid-term follow-up.

2. Methods

The rationale and design of this study have been reported elsewhere [10,11]. Briefly, this is an observational, prospective and multicenter registry involving three tertiary hospitals that analyzes the prescription and influence on clinical outcomes of different antiplatelet agents in patients discharged after an ACS. Patients older than 18 years discharged with a definitive diagnosis of ACS either with or without elevation of the ST segment (chest pain with ischemic and unstable characteristics, with or without electrocardiographic and/or enzymatic biomarkers) were consecutively included from February, 2014 to December, 2015. Only patients admitted with an ACS in the context of other extracardiac pathology such as stroke or sepsis and those who died during admission were excluded. The management strategy (invasive versus conservative therapy) and the pharmacological treatment were both established at the discretion of the responsible physician.

The MDRD-4 equation was used to estimate glomerular filtration rate (eGFR) and mortality risk and bleeding risk were assessed by the GRACE and CRUSADE scores, respectively. Baseline anemia was defined according to World Health Organization criteria as a hemoglobin (Hb) level < 13 g/dL in men and < 12 g/dL in women. Of note, no patient was excluded depending on the Hb level. For the present analysis, patients were divided into 2 groups according to the baseline Hb level. Then, a comparative study was performed between anemic patients (Hb < 13 g/dL in men and < 12 g/dL in women) and non-anemic patients.

2.1. Study endpoints and follow-up

The primary endpoint for this study was the major adverse cardiovascular events (MACE, the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke). Secondary endpoints included all-cause mortality and any bleeding episode according to the Bleeding Academic Research Consortium (BARC) classification [12]. Follow-up was performed by telephone contact and through medical records review, and was completed in the 98% of the overall cohort.

2.2. Ethical considerations

The research protocol agrees with the Declaration of Helsinki and was approved by the Ethical Research Committee of the three hospitals involved. The Department of Medicines for Human Use of the National Agency for Medicines and Medical Devices also approved this study with reference: JRN-NAG-2014-01.

An external independent audit of the registry was performed in order to evaluate the correct inclusion of patients, the analyzed data, and the possible existence of patients not included during the recruitment period in all participating hospitals.

2.3. Statistical analyses

Categorical variables were expressed as absolute frequencies and percentages, whereas continuous variables were tested for normality using the Kolmogorov Smirnov test and expressed as mean (± standard deviation) if appropriate.

Comparison of variables was performed with the χ^2 test for categorical variables, with the Student *t*-test for normal distributed continuous variables, and with the Mann Whitney *U* test for non-normally distributed continuous variables.

Multivariate Cox proportional hazards regression models were performed, using potential confounders (with p < .15 in the univariate analysis) to adjust these analyses. Kaplan-Meier survival analyses were

Table 2
Clinical management and type of revascularization during hospitalization.

	Anemic patients (n = 445)	Non-anemic patients (n = 1272)	p
Cardiac catheterization, n (%)			
Cardiac catheterization performed	373 (83.8)	1202 (94.5)	< 0.001
Complete revascularization	101 (64.5)	762 (77.2)	< 0.001
At least one drug-eluting stent	185 (76.0)	695 (78.5)	0.400
Result of the cardiac catheterization, n (%)			
No significant disease	24 (8.3)	101 (10.5)	< 0.001
1 vessel disease	110 (29.5)	504 (42.0)	
2 vessels disease	82 (22.0)	299 (24.8)	
3 vessels disease	124 (33.2)	228 (18.9)	
Left main coronary artery disease	26 (7.0)	46 (3.8)	
Therapeutic management, n (%)			
Conservative medical treatment	85 (19.1)	213 (16.7)	< 0.001
PCI	238 (53.5)	897 (70.5)	
Cardiovascular surgery	50 (11.2)	92 (7.2)	

PCI = percutaneous coronary intervention.

used to estimate time-related events and the log-rank test were applied to compare the survival experiences of patients with anemia versus non-anemic patients.

Receiver operating characteristic (ROC) curves were carried out to investigate the predictive ability. The Youden index was used to determine the Hb level with the best combination of sensitivity and specificity, in order to establish a cut-off value.

In all tests, p values < .05 were considered statistically significant. Statistical analysis was performed using the statistical software package SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

Of the 1717 ACS patients included, 445 (25.9%) had baseline anemia with a mean Hb level of 11.4 (IQR 10.4–12.0) g/dL. In overall, these patients were older and more frequently women with higher prevalence of several comorbidities. Anemic patients also presented lower eGFR and higher thrombotic risk according to the GRACE score, as well as higher bleeding risk according to the CRUSADE score. A summary of baseline characteristics is shown in Table 1.

Regarding the clinical management during hospitalization, patients with anemia were less likely to undergo cardiac catheterization in comparison with patients without anemia (83.8% vs. 94.5%, p < .001). Additionally, these patients had more vessels affected (33.2% of anemic patients with 3 vessels disease vs. 18.9% in non-anemic groups, p < .001) and more frequently left main coronary artery disease (7.0% vs. 3.8%, p < .001). Although revascularization by percutaneous coronary intervention was the most common strategy in anemic patients, it was less frequent compared to non-anemic (53.5 vs. 70.5%, p < .001). Of note, conservative medical treatment (19.1% vs. 16.7%, p < .001) and cardiovascular surgery (11.2% vs. 7.2%%, p < .001) were both selected with higher frequency in the anemic population (Table 2).

After exclude patients discharged under oral anticoagulation, 1493 ACS patients remained in the study. Of them, 358 (24%) were anemic and 1135 (76%) were not. Focusing on patients with anemia, 211 (58.9%) were discharged with clopidogrel and only 84 (23.5%) patients were prescribed novel $P2Y_{12}$ inhibitors (65 [18.2%] ticagrelor and 19 [5.3%] prasugrel), a proportion significantly lower compared with non-anemic patients (23.5% vs. 46.2%; OR 2.80 [95% CI 2.13–3.67], p < .001). At 1 year of follow-up, there was not different risk of MACE or bleeding in anemic patients depending on the $P2Y_{12}$ inhibitor prescribed. Thus, the risk of MACE in anemic patients was not significantly higher when clopidogrel was prescribed (HR 1.49 [95% CI 0.71–3.12]; p = .287). Similarly, the risk of all-severity bleeding (i.e. BARC 1–5) was not significantly lower in anemic patients taking clopidogrel (HR 0.80 [95% CI 0.41–1.55]; p = .503), whereas the risk of major bleeding (BARC 3–5) was not significantly higher (HR 1.40 [95% CI 0.39–5.02]; p = .606). On contrary, anemic patients under clopidogrel therapy suffered more mortality events (16.1% vs. 7.1%, p = .043) and therefore, the risk of mortality was 2.38-fold increased (HR 2.38 [95% CI 1.01–5.67]; p = .049) (Table 3).

During the follow-up, there were 146 (9.8%) MACEs, 31 (2.1%) major bleeding (BARC 3–5) and 88 (5.9%) deaths in the overall population excluding patients who were prescribed oral anticoagulants. Proportionally, anemic patients suffered more MACEs (14.9% vs. 8.4%, p < .001), more major bleeding (4.5% vs. 1.3%, p < .001) and more deaths (13.2% vs. 3.7%, p < .001). Multivariate Cox proportional regression models adjusted by comorbidities showed that anemia was an independent risk factor for major bleeding (HR 2.26 [95% CI 1.07–4.78], p = .033) and all-cause mortality (HR 1.62 [95% CI 1.03–2.56], p = .038) but not for MACE (HR 1.09 [95% CI 0.75–1.59], p = .636) (Table 4, Fig. 1). When we investigated the association of several variables with the risk of adverse events by excluding patients on monotherapy (34 patients, final cohort of 1459 patients), anemia still showed to be an independent risk factor for major bleeding (HR 2.15 [95% CI 1.01–4.60], p = .048) and all-cause mortality (HR 1.64 [95% CI 1.01–2.67], p = .045) (Supplementary Table 1). Additional analyses using Hb as independent variable demonstrated similar results (HR 1.22 [95% CI 1.08–1.35], p = .004 for major bleeding; HR 1.19 [95% CI 1.10–1.27], p < .001 for all-cause mortality and every g/dL decrease) (Supplementary Table 2). Therefore, we also tested the predictive ability of Hb for these events. For both, Hb demonstrated a moderate (but significant) predictive performance (c-index: 0.655 [95% CI 0.629–0.679], p = .007 for major bleeding; c-index: 0.728 [95% CI 0.728–0.751], p < .001 for all-cause mortality). An Hb level of 11.1 g/dL had the best combination of sensitivity (36.7 [19.9–56.1]) and specificity (90.6 [88.9–92.1]) for major bleeding whereas an Hb level of

Table 3
Adverse events during follow-up in anemic ACS patients according to the $P2Y_{12}$ prescribed at discharge.

	Clopidogrel (n = 211)	Novel $P2Y_{12}$ (n = 84)	p	Non-adjusted HR (95% CI); p
Mace, n (%)	33 (15.6)	9 (10.7)	0.277	1.49 (0.71–3.12); 0.287
Non-fatal myocardial infarction	16 (7.6)	5 (5.9)	0.623	1.30 (0.48–3.56); 0.605
Ischemic stroke	0 (0.0)	0 (0.0)	–	–
Cardiovascular death	17 (8.0)	4 (4.8)	0.321	1.73 (0.58–5.14); 0.325
Bleeding events, n (%)				
BARC type 1–5	27 (12.8)	13 (15.5)	0.544	0.80 (0.41–1.55); 0.503
BARC type 2–5	24 (11.4)	12 (14.3)	0.486	0.77 (0.38–1.54); 0.456
BARC type 3–5	11 (5.2)	3 (3.6)	0.552	1.40 (0.39–5.02); 0.606
All-cause mortality, n (%)	34 (16.1)	6 (7.1)	0.043	2.38 (1.01–5.67); 0.049

BARC = Bleeding Academic Research Consortium; HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event.

Table 4
Independent predictors of adverse events during follow-up by Cox regression analysis.

Risk factors	Univariate analysis	Multivariate analysis
	HR (95% CI); p	HR (95% CI); p
MACE		
Age	1.04 (1.03–1.05); < 0.001	1.03 (1.01–1.05); < 0.001
Male sex	0.80 (0.56–1.13); 0.198	–
Hypertension	1.89 (1.28–2.80); 0.001	1.05 (0.68–1.62); 0.820
Smoking habit	0.75 (0.53–1.06); 0.108	1.38 (0.93–2.03); 0.108
Dyslipidemia	1.23 (0.88–1.73); 0.231	–
Previous stroke/TIA	2.67 (1.73–4.10); < 0.001	1.89 (1.21–2.94); 0.005
Diabetes mellitus	1.93 (1.40–2.67); < 0.001	1.34 (0.95–1.90); 0.098
Previous coronary artery disease	1.40 (1.18–1.63); < 0.001	1.74 (1.24–2.46); 0.002
Renal impairment	2.31 (1.64–3.24); < 0.001	1.41 (0.96–2.07); 0.079
Anemia	1.86 (1.32–2.60); < 0.001	1.09 (0.75–1.59); 0.636
Major Bleeding (BARC 3–5)		
Age	1.06 (1.02–1.09); < 0.001	1.04 (1.01–1.07); 0.026
Male sex	0.59 (0.29–1.23); 0.158	–
Hypertension	2.73 (1.05–7.11); 0.040	1.58 (0.58–4.28); 0.368
Smoking habit	0.57 (0.25–1.28); 0.176	–
Dyslipidemia	0.84 (0.41–1.70); 0.618	–
Previous stroke/TIA	2.43 (0.93–6.34); 0.069	1.58 (0.60–4.18); 0.354
Diabetes mellitus	0.70 (0.32–1.52); 0.371	–
Previous coronary artery disease	1.06 (0.50–2.25); 0.879	–
Renal impairment	1.01 (0.89–1.15); 0.861	–
Anemia	3.49 (1.72–7.05); 0.001	2.26 (1.07–4.78); 0.033
All-cause mortality		
Age	1.09 (1.07–1.12); < 0.001	1.07 (1.04–1.09); < 0.001
Male sex	0.60 (0.40–0.92); 0.019	0.94 (0.60–1.49); 0.803
Hypertension	3.37 (1.84–6.20); < 0.001	1.37 (0.73–2.60); 0.329
Smoking habit	0.39 (0.23–0.66); < 0.001	1.16 (0.66–2.03); 0.608
Dyslipidemia	1.31 (0.84–2.04); 0.228	–
Previous stroke/TIA	3.54 (2.13–5.87); < 0.001	2.19 (1.30–3.70); 0.003
Diabetes mellitus	1.68 (1.10–2.55); 0.015	0.96 (0.62–1.50); 0.867
Previous coronary artery disease	1.92 (1.27–2.93); 0.002	1.25 (0.81–1.94); 0.319
Renal impairment	5.11 (3.36–7.77); < 0.001	2.11 (1.32–3.37); 0.002
Anemia	3.78 (2.49–5.74); < 0.001	1.62 (1.03–2.56); 0.038

BARC = Bleeding Academic Research Consortium; HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event; TIA = transient ischemic attack.

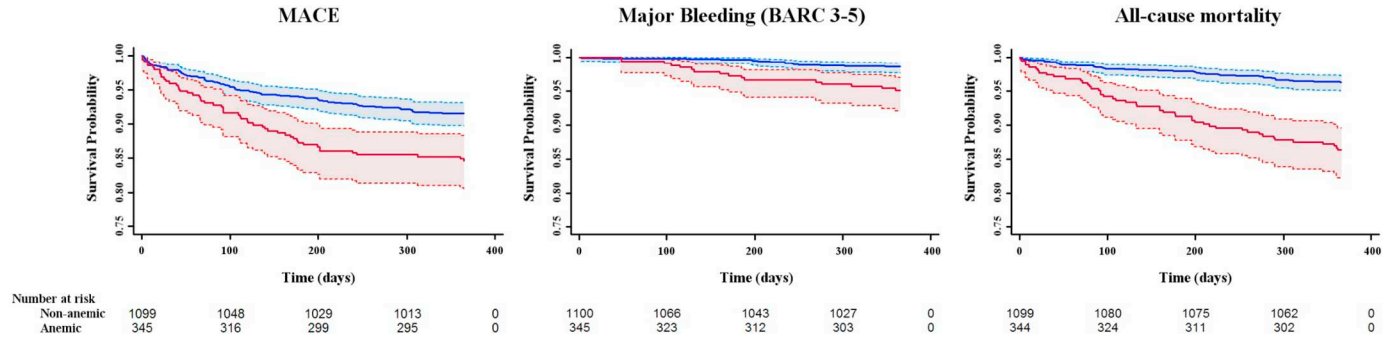

Fig. 1. Kaplan-Meier survival curves for MACE, major bleeding (BARC 3–5) and all-cause mortality depending on the presence of anemia. Red line = anemic acute coronary syndrome patients; Blue line = Non-anemic acute coronary syndrome patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

12.9 g/dL had the best combination of sensitivity (61.9 [50.7–72.3]) and specificity (73.3 [70.9–75.7]) for all-cause mortality. Hence, these values could be considered as cut-off for predicting major bleeding and all-cause mortality in our cohort.

4. Discussion

The results of this contemporary registry show that anemia is a frequent comorbidity in ACS patients that has important clinical implications in the management and prognosis of these patients. Indeed, anemia was an independent risk factor for major bleeding (BARC 3–5) and mortality, and those anemic patients treated with clopidogrel had even higher risk for mortality compared with those treated with new $P2Y_{12}$ inhibitors.

The prevalence of anemia in the present study was ≈26%, similar to that reported in previous studies [1–4,13]. These patients were older, had more comorbidities and an increased ischemic and bleeding risk at admission according to the GRACE and CRUSADE scores. Although in the majority of anemic patients a cardiac catheterization was performed, they were managed in a more conservative manner and revascularization by PCI was less performed. Nevertheless, baseline clinical characteristics of patients with anemia could also play an independent role and act as a limitation or even a contraindication to some interventional or therapeutic procedures.

This apparently higher frailty could explain why anemic patients were less likely to be invasively treated. However, Sudarsky et al. [14] observed that anemic patients who underwent revascularization therapy had better long-term prognosis than those managed conservatively.

On the other hand, anemia has demonstrated to be, in the view of our results, an independent risk factor for major bleeding and mortality. In fact, major bleeding events and all-cause deaths were four times higher in the anemic population. This goes on the same line with recent evidence suggesting that anemia increase the risk of bleeding and mortality in the medium- and long-term follow-up [5,15–17]. However, the clinical characteristics of this population (i.e. elderly patients with more comorbidities) could also be involved in a higher baseline ischemic risk. This is a possible reason why anemia did not independently increase the risk of MACE on multivariate analysis.

However, not only anemia as categorical variable demonstrated risk association with bleeding and mortality since we performed additional analyses with Hb levels and the results were similar. In this regard, a recent study proves that baseline Hb carries important prognostic information and demonstrates an association with major bleeding and mortality in patients with ACS [18], whereas Ennezat et al. [2] showed suggesting that Hb could be incorporated to improve the GRACE score to improve risk stratification in ACS.

Besides patients with anemia had a poor prognosis, they were also less prescribed new $P2Y_{12}$ agents (i.e. ticagrelor or prasugrel). However, this could be motivated by the low inclusion rate of such patients in RCTs. For example, the TRITON-TIMI 38 excluded patients with baseline anemia [8]. In addition, anemic patients have higher estimated bleeding risk, and recent guidelines recommends not using new antiplatelet agents in patients at high-risk of bleeding [19]. Indeed, anemia has been found as an independent predictor of clopidogrel prescription [20]. However, the subgroup of anemic patients treated with new $P2Y_{12}$ inhibitors in the present study reported less rates of MACE, mortality and even major bleeding (BARC 3–5). We did not find significant differences in bleeding and MACE risks between both groups, but a higher risk of mortality has been shown in patients treated with clopidogrel. In fact, previous studies showed that anemia reduces platelet inhibition to the loading dose of clopidogrel, contributing to a consequent increase in ischaemic and mortality risks [16,21]. All these factors lead to think that poor prognosis associated with anemia could be also related to a suboptimal therapy in this population in addition to related comorbidities or anemia per se, as suggested by previous studies [22]. Our results demonstrate the need for further investigations to analyze new and more powerful treatments in this particular ACS population in order to improve survival and prevention of cardiovascular events.

4.1. Limitations

Our study has several potential limitations. First, the etiology of anemia in the studied population was not assessed, so the impact of anemia according to etiology could be variable. In relation to this, we did not record other biochemical parameters such as platelet count data, iron level, unsaturated iron binding capacity, vitamin B12 or folic acid concentration that might provide some additional information. Additionally, we aimed to investigate the implication of baseline anemia on the clinical management, the use of novel $P2Y_{12}$ inhibitors, and outcomes during follow-up. For that reason, we did not analyzed Hb value at discharge. Second, we acknowledge that blood transfusions requirements were not registered, which may have clinical implications in ACS patients. However, the prospective nature of this study allowed us to assess all adverse events, even early ones. Third, although a registry often represents better the clinical practice than a clinical trial, patients included are usually heterogeneous and have diverse clinical characteristics that make difficult generalized conclusions about a particular therapeutic approach. Thus, we recognize that clinical practice of the participant hospitals may not reflect the general clinical practice clinic other hospitals. For this reason, clinical outcomes in anemic ACS patients receiving novel $P2Y_{12}$ inhibitors should be interpreted with caution in order to recommend a possible clinical benefit of this treatment in such population, given the small sample size and the study design. On the other hand, the participant hospitals had hemodynamics rooms, which may be related with more invasive hospital management and in this context the study results should be interpreted.

Finally, inclusion criteria of this study were based on ACS diagnosis at discharge and thus, a potential selection bias could be occurred, taken into account that patients who died during admission were not included.

As this was a voluntary registry, investigators only collected data at discharge, so the patient decision did not influenced the clinical manage or clinical decisions taken by responsible physicians. This voluntariness of the registry guarantees a high quality of the data that has been corroborated by an external and independent audit.

5. Conclusions

In the present study, the prevalence of anemia in patients discharged after an ACS was high, and this comorbidity had influence in the selection of clinical management during hospitalization and antiplatelet therapy at discharge. ACS patients who also suffered from anemia had significantly higher risk for major bleeding and mortality, and anemic patients who were treated with clopidogrel had even more mortality events.

Funding

This work has been supported by the Spanish Society of Cardiology (Project of Clinical Research in Cardiology Dr. Pedro Zarco 2016).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.12.004.

References

[1] Wang H, Yang Y, Ma L, Wang X, Zhang J, Fu J, et al. Impact of anemia and dual antiplatelet therapy on mortality in patients undergoing percutaneous coronary intervention with drug-eluting stents. Sci Rep 2015;5:17213.
[2] Ennezat PV, Marechaux S, Pincon C, Finzi J, Barrailler S, Bouabdallaoui N, et al. Anaemia to predict outcome in patients with acute coronary syndromes. Arch Cardiovasc Dis 2013;106:357–65.
[3] Kunadian V, Mehran R, Lincoff AM, Feit F, Manoukian SV, Hamon M, et al. Effect of anemia on frequency of short- and long-term clinical events in acute coronary syndromes (from the acute catheterization and urgent intervention triage strategy trial). Am J Cardiol 2014;114:1823–9.
[4] Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, Eisenberg MJ. Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis. Am Heart J 2013;165. 143-53.e5.
[5] Uscinska E, Sobkowicz B, Sawicki R, Kiluk I, Baranicz M, Stepek T, et al. Parameters influencing in-hospital mortality in patients hospitalized in intensive cardiac care unit: is there an influence of anemia and iron deficiency? Intern Emerg Med 2015;10:337–44.
[6] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). Eur Heart J 2015;37:267–315.
[7] Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
[8] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

[9] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
[10] Esteve-Pastor MA, Ruiz-Nodar JM, Orenes-Pinero E, Rivera-Caravaca JM, Quintana-Giner M, Veliz-Martinez A, et al. Temporal trends in the use of antiplatelet therapy in patients with acute coronary syndromes. J Cardiovasc Pharmacol Ther 2017;23:57–65.
[11] Rivera-Caravaca JM, Ruiz-Nodar JM, Tello-Montoliu A, Esteve-Pastor MA, Veliz-Martinez A, Orenes-Pinero E, et al. Low body weight and clinical outcomes in acute coronary syndrome patients: results of the ACHILLES Registry. Eur J Cardiovasc Nurs 2017;16:696–703.
[12] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736–47.
[13] Merono O, Cladellas M, Recasens L, Garcia-Garcia C, Ribas N, Bazan V, et al. In-hospital acquired anemia in acute coronary syndrome. Predictors, in-hospital prognosis and one-year mortality. Rev Esp Cardiol (Engl Ed) 2012;65:742–8.
[14] Sudarsky D, Sudarsky M, Matezky S, Goldenberg I, Farcas A, Nikolsky E. Impact of early invasive approach on outcomes of patients with acute coronary syndrome and baseline anemia: analysis from the ACSIS registry. J Interv Cardiol 2015;28:315–25.
[15] Mamas MA, Kwok CS, Kontopantelis E, Fryer AA, Buchan I, Bachmann MO, et al. Relationship between anemia and mortality outcomes in a national acute coronary syndrome cohort: insights from the UK myocardial ischemia national audit project registry. J Am Heart Assoc 2016;5.
[16] Giustino G, Kirtane AJ, Baber U, Genereux P, Witzenbichler B, Neumann FJ, et al. Impact of anemia on platelet reactivity and ischemic and bleeding risk: from the assessment of dual antiplatelet therapy with drug-eluting stents study. Am J Cardiol 2016;117:1877–83.
[17] Yazji K, Abdul F, Elangovan S, Ul Haq MZ, Ossei-Gerning N, Morris K, et al. Baseline anemia in patients undergoing percutaneous coronary intervention after an acute coronary syndrome-a paradox of high bleeding risk, high ischemic risk, and complex coronary disease. J Interv Cardiol 2017;30:491–9.
[18] Brener SJ, Mehran R, Dangas GD, Ohman EM, Witzenbichler B, Zhang Y, et al. Relation of baseline hemoglobin levels and adverse events in patients with acute coronary syndromes (from the Acute Catheterization and Urgent intervention Triage strategY and Harmonizing Outcomes with RevasculariZatiON and stents in acute myocardial infarction trials). Am J Cardiol 2017;119:1710–6.
[19] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology (ESC) and of the European association for cardio-thoracic surgery (EACTS). Eur Heart J 2017;39:213–60.
[20] Castini D, Persampieri S, Cazzaniga S, Ferrante G, Centola M, Lucreziotti S, et al. Real-world clopidogrel utilization in acute coronary syndromes: patients selection and outcomes in a single-center experience. Ther Adv Cardiovasc Dis 2017;11:323–31.
[21] Toma C, Zahr F, Moguilanski D, Grate S, Semaan RW, Lemieux N, et al. Impact of anemia on platelet response to clopidogrel in patients undergoing percutaneous coronary stenting. Am J Cardiol 2012;109:1148–53.
[22] Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Anaemia and prognosis in acute coronary syndromes: a systematic review and meta-analysis. J Int Med Res 2012;40:43–55.