Prognosis of anemic patients with atrial fibrillation undergoing percutaneous coronary intervention

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Prognosis of anemic patients with atrial fibrillation undergoing percutaneous coronary intervention

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Abstract

Background: There are limited data regarding whether anemia is an independent predictor for adverse clinical outcomes in patients with atrial fibrillation (AF) after percutaneous coronary intervention (PCI).

Methods: Patients with AF undergoing PCI at 15 institutions between January 2015 and March 2021 were included in this analysis. Based on the baseline hemoglobin levels, moderate to severe anemia was defined as hemoglobin levels <11 g/dL, and mild anemia was defined as hemoglobin levels 11-12.9 g/dL for men and 11-11.9 g/dL for women. Clinical outcomes within 1 year, including major adverse cardiovascular events (MACE: all-cause death, myocardial infarction, stent thrombosis, and stroke) and major bleeding events (BARC 3 or 5), were compared among patients with moderate/severe anemia, mild anemia, and no anemia.

Results: In a total of 746 enrolled patients, 119 (16.0%) and 168 (22.5%) patients presented with moderate/severe and mild anemia. The incidence of MACE (22.5%, 11.0%, and 9.1%, log-rank p<0.001) as well as major bleeding events (10.7%, 6.5%, and 2.7%, log-rank p<0.001) was the highest in the moderate/severe anemia group compared with the mild and no anemia groups. In multivariable Cox regression analyses, moderate/severe anemia (p=0.008), severe chronic kidney disease (p=0.019), and acute coronary syndrome (p=0.049) were independently associated with MACE. For major bleeding events, moderate/severe anemia (p=0.031) and platelet count (p=0.021) were independent predictors.

Conclusion: Moderate/severe anemia was significantly associated with the higher incidence of MACE as well as major bleeding events compared with mild and no anemia in AF patients undergoing PCI.

Keywords: anemia; percutaneous coronary intervention; atrial fibrillation

Introduction

In patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), it is well known that anemia is one of the important risk factors for bleeding events.(1-4) Recently, the standardized definition of high-bleeding risk (HBR) according to the Academic Research Consortium (ARC) has been widely used for risk stratification of bleeding complications in patients undergoing PCI.(5) In the ARC-HBR criteria, moderate to severe anemia (hemoglobin <11 g/dL) is categorized as a major criterion, and mild anemia (hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women) is a minor criterion for HBR. Concurrently, anemia has also been reported to increase the risk of thrombotic events after PCI.(6-8) Therefore, a multidisciplinary management approach is required to minimize both bleeding and thrombotic events in patients with coronary artery disease requiring PCI and concomitant anemia.

In patients with atrial fibrillation (AF), a similar relationship between anemia and the increased risks of bleeding, cardiovascular events, or mortality has been previously reported.(9-13) When patients with AF undergo PCI for coronary artery disease, the bleeding risk is clearly increased because of the need for strong antithrombotic therapy with a combination of anticoagulant and antiplatelet agents. Especially, triple antithrombotic therapy has significantly increased bleeding events.(14-18) Therefore, recent guidelines and expert consensus documents recommend against the routine use of triple antithrombotic therapy, and if required, the duration of triple antithrombotic therapy should be limited up to 1 week to 1 month, followed by dual antithrombotic therapy with an oral anticoagulant plus a P2Y12 inhibitor.(19-24) However, there are limited data on prognostic value of anemia in such a high-risk population. Thus, the purpose of this study was to evaluate the impact of anemia on clinical outcomes in patients with AF undergoing PCI using a multicenter registry database.

Methods

Study design and population

This was a prospective and retrospective, multicenter, observational cohort study at 15 institutions (CHIBA AF-PCI registry).(25) Patients with AF requiring oral anticoagulant (OAC) therapy undergoing PCI using drug-eluting stents (DES) for coronary artery disease between January 2015 and March 2021 were screened. Main exclusion criteria were as follows: PCI with two stent technique for bifurcation lesion, history of stent thrombosis, mechanical or bioprosthetic valve, cardiogenic shock, and severe liver dysfunction. Then, a total of 949 patients were registered in this study. The study flowchart of patient enrollment and final study sample is shown in Figure 1. Patients with OAC for any indications other than AF (n=11), no DES implantation (n=25), lack of PCI information (n=3), no OAC administration (n=134), and no follow-up data after discharge (n=30) were excluded. Consequently, 746 patients were eligible for analysis in the present study. The regimen and duration of antithrombotic therapies were at the discretion of attending physicians after assessment of each individual's thrombotic and bleeding risk profile. The study protocol was approved by the ethics committee of Chiba University Graduate School of Medicine (unique identifier: 3443), and also approved by the institutional review board or ethics committee at each participating institution. This study was performed in accordance with the principles of the Declaration of Helsinki and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000047503).

Definition of anemia

The hemoglobin values were obtained from the last blood tests prior to PCI. In patients requiring emergency cardiac catheterization, the blood tests were usually performed in the emergency department before transferring to the cardiac catheterization laboratory. In

accordance with the World Health Organization and the ARC-HBR criteria,(5, 26) moderate to severe anemia was defined as hemoglobin levels <11 g/dL, and mild anemia was defined as hemoglobin levels 11-12.9 g/dL for men and 11-11.9 g/dL for women, respectively, in the present study.

Clinical outcomes

The primary endpoint in the present study was the cumulative incidence of major adverse cardiovascular events (MACE), a composite of all-cause death, non-fatal myocardial infarction, stent thrombosis, and stroke within 1 year after PCI. The secondary safety endpoint was the cumulative incidence of major bleeding events, defined as Bleeding Academic Research Consortium (BARC) types 3 and 5, within 1 year after PCI.

Statistical analysis

Statistical analysis was performed using JMP® 14.0 (SAS Institute, Cary, NC, USA). Categorical variables are presented as percentages and compared among the 3 groups using Pearson's chi-squared test. Continuous variables are presented as mean ± SD. Comparisons of continuous variables among the 3 groups were conducted with analysis of variance (ANOVA). The incidence of MACE and major bleeding events were evaluated by the Kaplan-Meier curve analysis, and comparative studies were performed by log-rank quantification. Moderate/severe anemia, severe chronic kidney disease (CKD), acute coronary syndrome (ACS), prior PCI or coronary artery bypass graft surgery (CABG), peripheral artery disease, age ≥75 years, prior heart failure, and diabetes were the variables used in the multivariable Cox regression model to calculate hazard ratio to predict MACE. These variables were chosen based on the guidelines for antithrombotic therapy in patients with coronary artery disease.(22, 27) Furthermore, moderate/severe anemia, severe CKD, platelet level, age ≥75 years, and active cancer were the

variables used in the multivariable Cox regression model to calculate hazard ratio to predict major bleeding events. These variables were chosen based on the ARC-HBR criteria.(5) A $p<0.05$ was considered statistically significant.

Results

Baseline clinical characteristics

Of the 746 patients enrolled in this study, 119 (16.0%) and 168 (22.5%) patients presented with moderate/severe and mild anemia, respectively. Comparisons of baseline clinical characteristics among the 3 groups are summarized in Table 1. The average age was significantly higher ($p<0.001$), and body mass index (BMI) was significantly lower ($p<0.001$) in the anemia groups compared with the no anemia group. The proportion of female sex was significantly higher in the moderate/severe anemia group compared with the other 2 groups ($p<0.001$). The prevalence of hypertension ($p=0.034$), diabetes ($p=0.038$), current smoker ($p<0.001$), prior angina pectoris ($p<0.001$), prior PCI ($p<0.001$), prior CABG ($p=0.003$), prior heart failure ($p<0.001$), prior major bleeding events ($p<0.001$), severe CKD ($p<0.001$), hemodialysis ($p=0.004$), and active cancer ($p=0.012$) was significantly different among the 3 groups. CHADS2 score ($p<0.001$) and CHADS2-VASc score ($p<0.001$), as well as HAS-BLED score ($p<0.001$), were significantly higher in the moderate/severe anemia group, followed by the mild anemia group and no anemia group. The laboratory data demonstrated the lower levels of estimated glomerular filtration rate (eGFR) ($p<0.001$), total cholesterol ($p<0.001$), low-density lipoprotein cholesterol ($p<0.001$), and triglycerides ($p<0.001$) in the moderate/severe anemia group compared with the other 2 groups. In terms of lesion and procedural characteristics, there were no significant differences among the 3 groups, except for the rate of mechanical circulatory support ($p=0.031$).

Medications

Detailed information about medications is described in Table 2. At the time of discharge, the rate of vitamin K antagonist (VKA) use was significantly higher in the moderate/severe anemia group (28.6% vs. 13.7% vs. 11.6%, p<0.001), and conversely, the rate of DOAC use was lower in the moderate/severe anemia group (69.8% vs. 84.5% vs. 87.8%, p<0.001), compared with the other 2 groups. The percentage of P2Y12 inhibitor (88.2% vs. 96.4% vs. 95.2%, p<0.001), statin (73.1% vs. 86.3% vs. 86.5%, p=0.003), and steroid (0% vs. 4.8% vs. 2.2%, p=0.011) was significantly lower in the moderate/severe anemia group compared with the other 2 groups. At 6 months after PCI, the prevalence of P2Y12 inhibitor (53.4% vs. 68.8% vs. 68.1%, p=0.015) and triple therapy (8.7% vs. 19.5% vs. 18.0%, p=0.033) was significantly lower in the moderate/severe anemia group compared with the other 2 groups. The mean duration of triple therapy was 56.1±81.5 days in the moderate/severe anemia group, 83.4±106.2 days in the mild anemia group, and 81.6±81.6 days in the no anemia group (p=0.035).

Adverse clinical events

The incidence of adverse clinical events at 1 year is shown in Table 3. The crude incidence of MACE was significantly higher in the moderate/severe anemia group compared with the other 2 groups (21.0% vs. 10.7% vs. 8.3%, p=0.001). Among each component of MACE, the percentage of all-cause death (18.5% vs. 7.1% vs. 4.4%, p<0.001) and cardiac death (8.4% vs. 4.8% vs. 2.2%, p=0.009) was significantly higher in the moderate/severe anemia group compared with the other 2 groups. The incidence of major bleeding events was significantly higher in the moderate/severe anemia group (10.1% vs. 6.0% vs. 2.6%, p=0.003), whereas there was only a trend toward an increased incidence of all bleeding events in the moderate/severe anemia group compared with the other 2 groups (15.1% vs. 10.7% vs. 8.1%, p=0.076). Kaplan-Meier method was used to analyze time to event data of MACE and major bleeding events in comparison among the 3 groups (Figure 2). The incidence of MACE at 1 year was 22.5% in the moderate/severe anemia group, 11.0% in the mild anemia group, and

9.1% in the no anemia group (log-rank p<0.001). The incidence of major bleeding events at 1 year was 10.7% in the moderate/severe anemia group, 6.5% in the mild anemia group, and 2.7% in the no anemia group (log-rank p<0.001).

The multivariable Cox regression analysis was performed to determine predictors for MACE and major bleeding events at 1 year (Table 4 and 5). Moderate/severe anemia (adjusted HR 2.10, 95% CI 1.22-3.53, p=0.008), severe CKD (adjusted HR 2.08, 95% CI: 1.13-3.67, p=0.019), and ACS (adjusted HR 1.59, 95% CI: 1.00-2.53, p=0.049) were independently associated with occurrence of MACE at 1 year after PCI. In addition, moderate/severe anemia (adjusted HR 2.37, 95% CI: 1.09-5.13, p=0.031) and platelet count (adjusted HR 5.86, 95% CI: 1.70-20.25, p=0.021) were independent predictors for major bleeding events at 1 year after PCI.

Discussion

This observational cohort study investigated the impact of anemia on clinical outcomes in patients with AF undergoing PCI using DES. As a result, with the progression of anemia, the incidence of cardiovascular events as well as bleeding events increased incrementally. In particular, the moderate/severe anemia group demonstrated higher incidence of MACE, all-cause death, cardiovascular death, and major bleeding events compared with the mild and no anemia groups.

Anemia in patients undergoing PCI

It has been previously reported that the presence of anemia increases the risk of bleeding events in patients undergoing PCI.(1-4) In the ARC-HBR criteria, anemia is an important criterion to evaluate bleeding risk.(5) The PRECISE-DAPT score, which is a measure to predict bleeding risk during DAPT after PCI, includes hemoglobin level as one of the scoring factors.(4) In the

PARIS risk score for bleeding events, furthermore, the presence of anemia is one of the important clinical variables to predict the risk for bleeding events after PCI with DES.(3) In addition, anemia has also been reported to increase the risk of all-cause death and cardiovascular death after PCI, although inconsistent results have been reported in terms of myocardial infarction and stroke.(2, 6-8, 28) In the CREDO-Kyoto risk score, anemia is included in the risk scores for thrombotic events, whereas it is not included in the scores for bleeding events.(7) Based on these previous reports, anemia appears to be an important comorbidity for risk assessment of mortality as well as bleeding events in patients with coronary artery disease undergoing PCI.

Anemia in AF patients

In patients with AF, previous studies have revealed a similar association of anemia with the increased risks of bleeding events.(9-13, 29, 30) Furthermore, along with an increase in bleeding events, an increased risk of mortality has also been reported in AF patients with anemia.(9, 10, 12, 30) With regard to the risk of thromboembolic events, there are both reports demonstrating the relationship between anemia and thromboembolic events,(9, 13) and those demonstrating no relationship.(10, 30) A previous meta-analysis has shown an association of anemia with the increased risk of stroke or systemic thromboembolism.(12) Therefore, it appears that patients with AF should be treated with considerable caution for both bleeding and thromboembolic events when accompanied by anemia.

Mechanisms of the relationship between anemia and clinical events

There have been many possible reasons why anemia is a risk factor for bleeding events. The underlying conditions of anemia, such as bone marrow dysfunction, chronic kidney disease, vitamin deficiencies, and frailty, may be associated with bleeding events. Moreover, anemia

may indicate a potential source of bleeding, such as gastrointestinal malignancy. In fact, the results of the present study showed that the incrementally higher proportion of chronic kidney disease and dialysis, a history of bleeding events, and coexisting active cancer was observed in the anemia groups. Furthermore, there are several possible causes for the association between anemia and mortality. The limited oxygen supply to tissues and hypercoagulability caused by the reduced hemoglobin level might result in making patients more susceptible to cardiovascular events.(28, 31, 32) In addition, as with the risk of bleeding events, advanced age and more comorbidities in patients with anemia might increase the incidence of adverse cardiovascular events.

Anemia in patients with AF undergoing PCI

In patients with AF undergoing PCI for coronary artery disease, strong antithrombotic therapy with a combination of anticoagulant and antiplatelet agents can significantly increase the bleeding risk.(14-18) Therefore, recent guidelines and expert consensus documents recommend against the routine use of triple antithrombotic therapy, and if required, the duration of triple antithrombotic therapy should be limited up to 1 week to 1 month, followed by dual antithrombotic therapy with an oral anticoagulant plus a P2Y12 inhibitor.(19-24) In the present study, the incidence of major bleeding events was significantly higher in the moderate/severe anemia group, although the mean duration of triple therapy was significantly shorter, compared with the mild and no anemia groups. Even in recent clinical practice, in which the duration of triple antithrombotic therapy is becoming shorter, it may be necessary to be aware of the relationship between anemia and the increased risk of bleeding events. In a previous study conducted in Europe, the impact of anemia on clinical outcome in AF patients undergoing PCI was reported.(33) Anemic patients had more major adverse cardiac and cerebrovascular events and minor bleeding events compared with non-anemic patients, although there was no

significant difference in the incidence of total bleeding events. In that report, the main comparison was conducted between patients divided by the presence or absence of anemia. In the present study, on the other hand, there was the increased risk of major bleeding events as well as MACE by separating moderate/severe anemia. By focusing on the degree of anemia, it would be possible to identify patients at greater risk for bleeding events. There are several other differences between that study and mine. The previous study used data from an older era when DES was used in <30% of patients and only VKA was used as an anticoagulant. In my study, DES was used in all patients and DOAC was used in most patients, which suggest that my results are in line with current clinical practice.

Treatment of AF-PCI patients with anemia

In AF-PCI patients, medical management should focus very carefully regarding the bleeding risk, while reducing the risk of thromboembolic events and ischemic events, respectively. Long-term continuation of DOAC may be important to prevent thromboembolic events due to AF, since its efficacy and safety are well established. In terms of PCI, DAPT duration can be shorter than before because of improvements in DES technologies resulting in a decrease in stent thrombosis. Furthermore, it has become possible to use anticoagulants alone in the chronic phase,(34, 35) and the overall risk of bleeding events seems to be decreasing. To reduce ischemic and thromboembolic events, escalation of antithrombotic therapy is one of the options. However, it must be done with caution in patients at high risk for bleeding, such as anemic patients. Comprehensive treatment to improve anemia, such as adequate supplementation of iron and vitamins, preservation of renal function, scrutiny and treatment of comorbid hematological and gastrointestinal disorders, may be required in patients with AF undergoing PCI. Since it is unclear whether treatment of anemia improves clinical outcomes in AF-PCI patients, future studies would be warranted to address the issue.

Limitations

Several limitations should be noted in the present study. First, this was an observational study based on registry data, raising a possibility of confounding factors that could not be ruled out. Second, sample size was relatively small, especially in the moderate/severe anemia group. Third, the etiology of anemia, which was not systematically investigated, might have affected the results of the present study. Fourth, because of the limited number of clinical events, some baseline characteristics with different prevalence among the 3 groups could not be included in the multivariate analysis. Further prospective large-scale trials would be warranted to address this subject.

Conclusions

Moderate to severe anemia was significantly associated with the higher incidence of MACE as well as major bleeding events compared with mild and no anemia in AF patients undergoing PCI.

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Author contributions

Kaori Abe and Hideki Kitahara contributed to conception and design of the study, protocol development, acquisition and interpretation of the data, and revising the publication for important intellectual content. Takashi Hiraga and Tatsuro Yamazaki contributed to

acquisition, analysis and interpretation of the data, and revising the publication for important intellectual content. Sakuramaru Suzuki, Yuji Ohno, Junya Harada, Kenichi Fukushima, Tatsuhiko Asano, Naoki Ishio, Raita Uchiyama, Hirofumi Miyahara, Shinichi Okino, Masanori Sano, Nehiro Kuriyama, Masashi Yamamoto, and Naoya Sakamoto contributed to acquisition of the data, and revising the publication for important intellectual content. Junji Kanda and Yoshio Kobayashi contributed to interpretation of the data and revising the publication for important intellectual content.

Declaration of competing interest

All authors report no conflict of interest related to this study.

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References

1. Numasawa Y, Ueda I, Sawano M, Kuno T, Kodaira M, Noma S, et al. Relation of Baseline Hemoglobin Level to In-Hospital Outcomes in Patients Who Undergo Percutaneous Coronary Intervention (from a Japanese Multicenter Registry). Am J Cardiol. 2018;121(6):695-702. Epub 20171223. doi: 10.1016/j.amjcard.2017.12.007. PubMed PMID: 29361289.
2. Nagao K, Watanabe H, Morimoto T, Inada T, Hayashi F, Nakagawa Y, et al. Prognostic Impact of Baseline Hemoglobin Levels on Long-Term Thrombotic and Bleeding Events After Percutaneous Coronary Interventions. J Am Heart Assoc. 2019;8(22):e013703. Epub 20191108. doi: 10.1161/JAHA.119.013703. PubMed PMID: 31701786; PubMed Central PMCID: PMC6915278.
3. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. J Am Coll Cardiol. 2016;67(19):2224-34. Epub 20160411. doi: 10.1016/j.jacc.2016.02.064. PubMed PMID: 27079334.
4. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389(10073):1025-34. doi: 10.1016/S0140-6736(17)30397-5. PubMed PMID: 28290994.
5. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. Circulation. 2019;140(3):240-61. Epub 20190522. doi: 10.1161/CIRCULATIONAHA.119.040167. PubMed PMID: 31116032; PubMed Central PMCID: PMC6636810.
6. Faggioni M, Baber U, Sartori S, Chandrasekhar J, Cohen DJ, Henry TD, et al. Influence of Baseline Anemia on Dual Antiplatelet Therapy Cessation and Risk of Adverse Events After Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2019;12(4):e007133. doi: 10.1161/CIRCINTERVENTIONS.118.007133. PubMed PMID: 30998384.
7. Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, et al. Prediction of Thrombotic and Bleeding Events After Percutaneous Coronary Intervention: CREDO-Kyoto Thrombotic and Bleeding Risk Scores. J Am Heart Assoc. 2018;7(11). Epub 20180522. doi: 10.1161/JAHA.118.008708. PubMed PMID: 29789335; PubMed Central PMCID: PMC6015347.
8. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF, et al. Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol. 2016;118(4):610-20. Epub 20160529. doi: 10.1016/j.amjcard.2016.05.059. PubMed PMID: 27342283.
9. Westenbrink BD, Alings M, Connolly SJ, Eikelboom J, Ezekowitz MD, Oldgren J, et al. Anemia predicts thromboembolic events, bleeding complications and mortality in patients with atrial fibrillation: insights from the RE-LY trial. J Thromb Haemost. 2015;13(5):699-707. Epub 20150330. doi: 10.1111/jth.12874. PubMed PMID: 25683276.
10. Westenbrink BD, Alings M, Granger CB, Alexander JH, Lopes RD, Hylek EM, et al. Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: Insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J.

2017;185:140-9. Epub 20161222. doi: 10.1016/j.ahj.2016.12.008. PubMed PMID: 28267467.
11. Bonde AN, Blanche P, Staerk L, Gerds TA, Gundlund A, Gislason G, et al. Oral anticoagulation among atrial fibrillation patients with anaemia: an observational cohort study. Eur Heart J. 2019;40(46):3782-90. doi: 10.1093/eurheartj/ehz155. PubMed PMID: 30932145.
12. Tu SJ, Hanna-Rivero N, Elliott AD, Clarke N, Huang S, Pitman BM, et al. Associations of anemia with stroke, bleeding, and mortality in atrial fibrillation: A systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2021;32(3):686-94. Epub 20210202. doi: 10.1111/jce.14898. PubMed PMID: 33476452.
13. Helin TA, Raatikainen P, Lehto M, Haukka J, Lassila R. Associations of anaemia with bleeding and thrombotic complications in patients with atrial fibrillation treated with warfarin: a registry-based nested case-control study. BMJ Open. 2023;13(11):e071342. Epub 20231102. doi: 10.1136/bmjopen-2022-071342. PubMed PMID: 37918932; PubMed Central PMCID: PMC10626859.
14. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107-15. doi: 10.1016/S0140-6736(12)62177-1. PubMed PMID: 23415013.
15. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016;375(25):2423-34. doi: 10.1056/NEJMoa1611594. PubMed PMID: 27959713.
16. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377(16):1513-24. doi: 10.1056/NEJMoa1708454. PubMed PMID: 28844193.
17. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019;380(16):1509-24. Epub 20190317. doi: 10.1056/NEJMoa1817083. PubMed PMID: 30883055.
18. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019;394(10206):1335-43. Epub 20190903. doi: 10.1016/S0140-6736(19)31872-0. PubMed PMID: 31492505.
19. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612. PubMed PMID: 32860505.
20. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575. PubMed PMID: 32860058.
21. Kumbhani DJ, Cannon CP, Beavers CJ, Bhatt DL, Cuker A, Gluckman TJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing

Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(5):629-58. Epub 20201126. doi: 10.1016/j.jacc.2020.09.011. PubMed PMID: 33250267.
22. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, et al. JCS 2020 Guideline Focused Update on Antithrombotic Therapy in Patients With Coronary Artery Disease. Circ J. 2020;84(5):831-65. Epub 20200313. doi: 10.1253/circj.CJ-19-1109. PubMed PMID: 32173684.
23. Ozaki Y, Hara H, Onuma Y, Katagiri Y, Amano T, Kobayashi Y, et al. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) update 2022. Cardiovasc Interv Ther. 2022;37(1):1-34. Epub 20220112. doi: 10.1007/s12928-021-00829-9. PubMed PMID: 35018605; PubMed Central PMCID: PMC8789715.
24. Natsuaki M, Sonoda S, Yoshioka G, Hongo H, Kaneko T, Kashiyama K, et al. Antiplatelet therapy after percutaneous coronary intervention: current status and future perspectives. Cardiovasc Interv Ther. 2022;37(2):255-63. Epub 20220303. doi: 10.1007/s12928-022-00847-1. PubMed PMID: 35237927.
25. Kitahara H, Yamashita D, Sato T, Suzuki S, Hiraga T, Yamazaki T, et al. Dual antithrombotic therapy with oral anticoagulant and P2Y12 inhibitors in patients with atrial fibrillation after percutaneous coronary intervention. J Cardiol. 2023;82(3):207-14. Epub 20230617. doi: 10.1016/j.jjcc.2023.06.002. PubMed PMID: 37336423.
26. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968;405:5-37. PubMed PMID: 4975372.
27. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 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. 2018;39(3):213-60. doi: 10.1093/eurheartj/ehx419. PubMed PMID: 28886622.
28. 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(11):1710-6. Epub 20170316. doi: 10.1016/j.amjcard.2017.02.052. PubMed PMID: 28388994.
29. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol. 2014;63(9):891-900. Epub 20131204. doi: 10.1016/j.jacc.2013.11.013. PubMed PMID: 24315894; PubMed Central PMCID: PMC4206565.
30. An Y, Ogawa H, Esato M, Ishii M, Iguchi M, Masunaga N, et al. Cardiovascular Events and Mortality in Patients With Atrial Fibrillation and Anemia (from the Fushimi AF Registry). Am J Cardiol. 2020;134:74-82. Epub 20200815. doi: 10.1016/j.amjcard.2020.08.009. PubMed PMID: 32900468.
31. Wang X, Qiu M, Qi J, Li J, Wang H, Li Y, et al. Impact of anemia on long-term ischemic events and bleeding events in patients undergoing percutaneous coronary intervention: a system review and meta-analysis. J Thorac Dis. 2015;7(11):2041-52. doi: 10.3978/j.issn.2072-1439.2015.11.56. PubMed PMID: 26716044; PubMed Central PMCID: PMC4669281.

32. Lee SH, Kim HK, Ahn JH, Kang MG, Kim KH, Bae JS, et al. Prognostic impact of hypercoagulability and impaired fibrinolysis in acute myocardial infarction. Eur Heart J. 2023;44(19):1718-28. doi: 10.1093/eurheartj/ehad088. PubMed PMID: 36857519.
33. Puurunen M, Kiviniemi T, Nammas W, Schlitt A, Rubboli A, Nyman K, et al. Impact of anaemia on clinical outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention: insights from the AFCAS registry. BMJ Open. 2014;4(5):e004700. Epub 20140513. doi: 10.1136/bmjopen-2013-004700. PubMed PMID: 24823675; PubMed Central PMCID: PMC4025460.
34. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, et al. Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation. Circulation. 2019;139(5):604-16. doi: 10.1161/CIRCULATIONAHA.118.036768. PubMed PMID: 30586700.
35. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, et al. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. N Engl J Med. 2019;381(12):1103-13. Epub 20190902. doi: 10.1056/NEJMoa1904143. PubMed PMID: 31475793.

Table 1: Baseline clinical characteristics

	Moderate/severe anemia (n=119)	Mild anemia (n=168)	No anemia (n=459)	p value
Age (years)	77.2±7.5	77.5±7.7	72.0±9.3	<0.001
Age ≥75y	83(69.7)	113 (67.3)	199 (43.4)	<0.001
Male	71(59.7)	141(83.9)	384 (83.7)	<0.001
Body mass index (kg/m^2)	23.2±4.2	23.2±3.9	25.1±4.2	<0.001
Hypertension	108(90.8)	147 (87.5)	378 (82.4)	0.034
Dyslipidemia	95(79.8)	127 (75.6)	335 (73.0)	0.284
Diabetes	69 (58.0)	84 (50.0)	207 (45.1)	0.038
Current smoker	8 (6.7)	21 (12.6)	105 (23.1)	<0.001
Family history of CAD	22 (18.8)	20 (13.2)	56 (13.7)	0.356
Prior angina pectoris	46 (38.7)	62 (36.9)	103 (22.4)	<0.001
Prior myocardial infarction	32 (26.9)	48 (28.6)	110 (24.0)	0.470
Prior PCI	50 (42.0)	68 (40.5)	126 (27.5)	<0.001
Prior CABG	12 (10.2)	13 (7.7)	14 (3.1)	0.003
Persistent AF	55 (46.2)	88 (52.4)	242 (52.8)	0.427
Peripheral artery disease	10 (8.4)	14 (8.3)	33 (7.6)	0.843
Prior heart failure	51 (42.9)	46 (27.4)	93 (20.3)	<0.001
Prior major bleeding events	18 (15.1)	13 (7.7)	15 (3.3)	<0.001
Severe CKD	34 (28.6)	15 (8.9)	22 (4.8)	<0.001
Hemodialysis	10 (8.4)	5 (3.0)	5 (1.1)	<0.001
Liver cirrhosis	1 (0.9)	2 (1.2)	0 (0)	0.055
Active cancer	14 (11.8)	8 (4.8)	19 (4.1)	0.012
Prior bleeding stroke	4 (3.4)	3 (1.8)	15 (3.3)	0.570

Prior ischemic stroke	28 (23.5)	34 (20.2)	81 (17.7)	0.332
LVEF (%)	51.6±13.6	51.5±14.8	51.2±14.5	0.956
CHADS2 score	3.1±1.3	2.8±1.3	2.4±1.3	<0.001
CHA2DS2-VASc score	4.6±1.5	4.0±1.4	3.5±1.5	<0.001
HAS-BLED score	3.6±1.1	3.3±0.9	3.0±0.8	<0.001
Laboratory data				
Hemoglobin (g/dL)	9.6±1.1	12.0±0.6	14.5±1.3	<0.001
Platelet ($\times 10^4/\mu$L)	22.1±13.1	20.1±6.7	21.0±13.3	0.365
eGFR (mL/min/1.73cm^2)	42.2±18.8	49.9±17.6	58.9±17.3	<0.001
Total cholesterol (mg/dL)	152.7±37.2	160.3±33.7	175±39.0	<0.001
HDL cholesterol (mg/dL)	47.0±16.2	48.7±13.5	49.1±15.0	0.419
LDL cholesterol (mg/dL)	83.8±32.9	91.5±27.4	102.0±32.2	<0.001
Triglycerides (mg/dL)	103.5±62.4	110.2±95.6	142.6±94.5	<0.001
HbA1c (%)	7.0±0.8	6.2±1.0	6.4±1.1	0.118
Lesion and procedural characteristics				
Acute coronary syndrome	43 (36.1)	71 (42.3)	189 (41.2)	0.535
Multivessel disease	61 (51.3)	78 (46.4)	202 (44.1)	0.371
Bifurcation lesion	25 (21.0)	32 (19.1)	80 (17.5)	0.666
Femoral approach	22 (18.5)	27 (16.3)	69 (15.3)	0.700
Mechanical circulatory support	6 (5.0)	10 (6.0)	9 (2.0)	0.031
DES type				
Everolimus	81 (68.1)	100 (59.5)	276 (60.1)	
Zotarolimus	10 (8.4)	28 (16.7)	67 (14.6)	
Sirolimus	20 (8.4)	27 (16.7)	81 (17.7)	0.641
Biolimus	1 (0.8)	2 (1.2)	8 (1.7)	

Multiple	7 (5.8)	11 (6.6)	27 (5.9)	
Number of stents	1.5±0.7	1.5±0.9	1.5±0.8	0.980
Mean stent diameter (mm)	2.9±0.5	2.9±0.5	3.0±0.5	0.116
Total stent length (mm)	36.4±22.3	36.4±24.0	37.7±22.7	0.754

Values are mean±SD or n (%). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD; chronic kidney disease; DES, drug eluting stent; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention;.

Table 2: Medications

	Moderate/severe anemia (n=119)	Mild anemia (n=168)	No anemia (n=459)	p value
Medication at discharge				
Aspirin	95 (79.9)	141 (83.9)	364 (79.3)	0.414
P2Y12 inhibitor	105 (88.2)	162 (96.4)	437 (95.2)	0.013
VKA	34 (28.6)	23 (13.7)	53 (11.6)	<0.001
DOAC	83 (69.8)	142 (84.5)	403 (87.8)	<0.001
ACE-I/ARB	76 (63.9)	114 (67.9)	290 (63.2)	0.549
β-blocker	87 (73.1)	135 (80.8)	334 (72.8)	0.101
Statin	87 (73.1)	145 (86.3)	397 (86.5)	0.003
Oral antidiabetic agent	34 (28.6)	43 (25.6)	125 (27.2)	0.849
Insulin	16 (13.5)	15 (8.9)	33 (7.2)	0.115
PPI	104 (87.4)	151 (89.9)	398 (86.7)	0.554
Steroid	0 (0)	8 (4.8)	10 (2.2)	0.011
Medication at 6 months				
Aspirin	48 (46.6)	75 (48.7)	216 (49.9)	0.830
P2Y12 inhibitor	55 (53.4)	106 (68.8)	295 (68.1)	0.015
OAC	95 (92.2)	147 (95.5)	415 (95.8)	0.347
Triple therapy	9 (8.7)	30 (19.5)	78 (18.0)	0.033
Duration of triple therapy (days)	56.1±81.5	83.4±106.2	81.6±81.6	0.035

Values are mean±SD or n (%). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; PPI, proton pump inhibitor; VKA, vitamin K antagonist.

Table 3: Adverse clinical events at 1 year

	Moderate/severe anemia (n=119)	Mild anemia (n=168)	No anemia (n=459)	p value
MACE	25 (21.0)	18 (10.7)	38 (8.3)	0.001
All-cause death	22 (18.5)	12 (7.1)	20 (4.4)	<0.001
Cardiovascular death	10 (8.4)	8 (4.8)	10 (2.2)	0.009
Myocardial infarction	0 (0)	3 (1.8)	5 (1.1)	0.198
Stent thrombosis	1 (0.8)	2 (1.2)	2 (0.4)	0.596
Ischemic stroke	3 (2.5)	3 (1.8)	16 (3.5)	0.487
Unplanned revascularization	3 (2.5)	4 (2.4)	17 (3.7)	0.623
Major bleeding (BARC 3/5)	12 (10.1)	10 (6.0)	12 (2.6)	0.003
All bleeding	18 (15.1)	18 (10.7)	37 (8.1)	0.076

BARC, Bleeding Academic Research Consortium; MACE, major adverse cardiovascular events.

Table 4: Multivariable Cox regression model of predictors for MACE

	Hazard ratio	95% CI	p value
Moderate/severe anemia	2.10	1.22-3.53	0.008
Severe CKD	2.08	1.13-3.67	0.019
ACS	1.59	1.00-2.53	0.049
Prior PCI/CABG	1.06	0.66-1.70	0.803
Peripheral artery disease	1.81	0.90-3.30	0.088
Age ≥75	0.99	0.63-1.58	0.976
Prior heart failure	1.12	0.66-1.89	0.653
Diabetes	1.12	0.71-1.79	0.616

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

Table 5: Multivariable Cox regression model of predictors for major bleeding events

	Hazard ratio	95% CI	p value
Moderate/severe anemia	2.37	1.09-5.13	0.031
Severe CKD	1.43	0.54-3.78	0.567
Platelet ($\times 10^4/\mu$L)	5.86	1.70-20.25	0.021
Age ≥75	1.03	0.99-1.08	0.217
Active cancer	1.11	0.3-6.95	0.882

CKD, chronic kidney disease.

Table 6: Multivariable Cox regression model of predictors for all cause death

	Hazard ratio	95% CI	p value
Moderate/severe anemia	2.43	1.31-4.49	0.005
Severe CKD	3.57	1.91-6.66	<0.001
ACS	1.27	0.72-2.21	0.406
Prior PCI/CABG	1.30	0.75-2.27	0.350
Peripheral artery disease	1.65	0.76-3.57	0.205
Age ≥75	1.26	0.71-2.22	0.431
Active cancer	2.10	0.88-5.00	0.094

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; PCI, percutaneous coronary intervention.

Figure 1. Flowchart for patient selection in the present study.

AF, atrial fibrillation; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

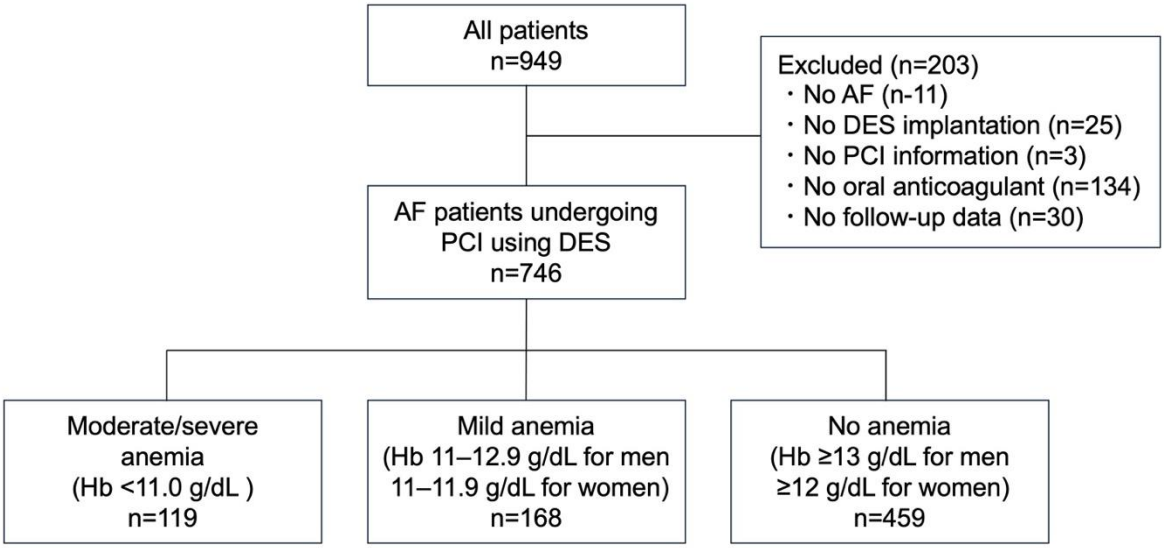
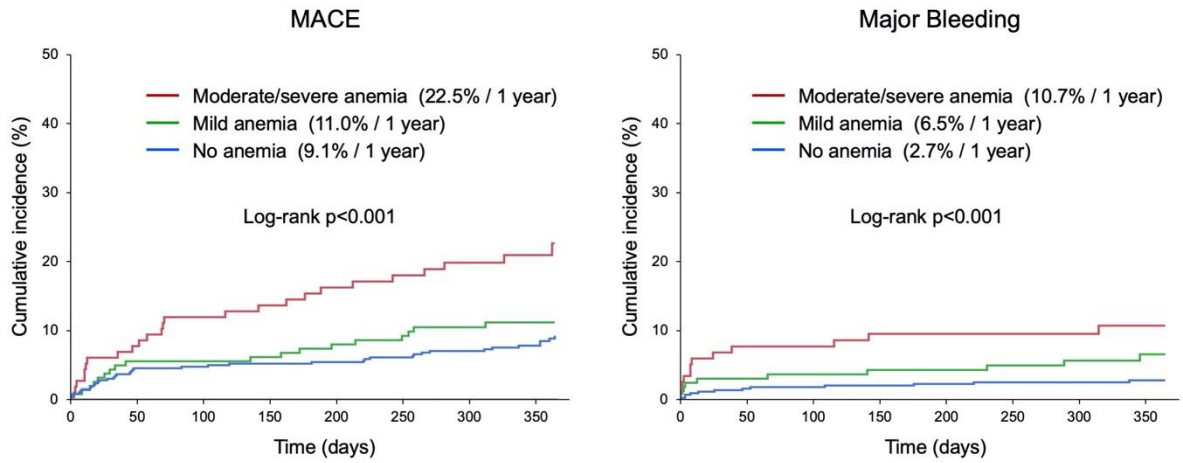


Figure 2. Kaplan-Meier curves for adverse clinical events at 1 year after PCI.

(A) MACE including all-cause death, non-fatal myocardial infarction, stent thrombosis, and stroke. (B) Major bleeding events (BARC types 3 and 5).

MACE, major adverse cardiovascular events; BARC, Bleeding Academic Research Consortium; PCI, percutaneous coronary intervention.



CLINICAL PERSPECTIVE

What Is New?

- In patients with atrial fibrillation (AF) on anticoagulation therapy and coronary artery disease requiring percutaneous coronary intervention (PCI), 38.5% of patients had anemia, and further, 16.0% had moderate to severe anemia.
- Patients with moderate to severe anemia demonstrated the higher incidence of MACE, all-cause death, cardiovascular death, and major bleeding events within 1 year after PCI, compared with those with mild and no anemia.

What Are the Clinical Implications?

- If patients with AF undergoing PCI have concomitant anemia, a multidisciplinary approach and careful follow-up are required to minimize adverse clinical events.
- Future studies would be warranted to address the optimal antithrombotic therapy in patients with anemia on both anticoagulation therapy for AF and antiplatelet therapy for coronary artery disease.

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