Received: 22 July 2024 | Revised: 6 September 2024 | Accepted: 12 September 2024

https://doi.org/10.1016/j.rpth.2024.102575

ORIGINAL ARTICLE

Incident thrombocytopenia and bleeding risk in elderly patients with atrial fibrillation on direct oral anticoagulants: insights from the ATHEROsclerosis in Atrial Fibrillation study

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Handling Editor: Dr Michael Makris

Abstract

Background: The bleeding risk of patients with atrial fibrillation (AF) changes over time. Most studies thus far evaluated only the baseline bleeding risk with discordant results. The impact of incident thrombocytopenia during direct oral anticoagulant (DOAC) therapy and its relation to bleeding has not been previously investigated.

Objectives: To investigate the incidence rate of thrombocytopenia and major bleeding (MB) risk in AF patients on DOACs.

Methods: Prospective ongoing ATHEROsclerosis in Atrial Fibrillation study including patients with nonvalvular AF on DOACs. Incident thrombocytopenia was defined as a platelet count $<150 \times 10^9$/L. MB events were recorded at each follow-up visit. Gray estimator for competing risk data was used. Estimates are expressed in terms of sub-distributional hazard ratios (sHR) and relative 95% CI for MB.

Results: We enrolled 957 AF patients treated with DOACs (mean age, 77.3 ± 9.0 years; 49.1% women). During a follow-up (median time to censoring 1330 days; 95% CI, 1246-1443), 139 patients developed thrombocytopenia (3.08 per 100 person-years; 95% CI, 2.27-3.89) with no difference between direct thrombin and factor Xa inhibitors. Overall, 179 bleedings occurred, of which 80 were major (3.17 per 100 person-years; 95% CI, 2.34-3.99). Patients sustaining bleedings were more frequently affected by arterial hypertension, heart failure, anemia and had higher CHA_2DS_2-VASc and HAS-BLED scores. On multivariable Cox analysis, independent risk factors for MB were incident thrombocytopenia (sHR, 12.77; 95% CI, 8.880-18.360; $P < .001$), and age (sHR, 1.030 per year; 95% CI, 1.010-1.040; $P = .002$).

Conclusion: Patients developing thrombocytopenia have an increased risk of MB. Dynamic evaluation of platelet count during follow-up may provide better prognostic value than baseline assessment only.

Danilo Menichelli and Luca Crisanti contributed equally to this study.

KEYWORDS
aged, atrial fibrillation, direct oral anticoagulants, major bleeding, thrombocytopenia

Essentials

- The incidence of thrombocytopenia in atrial fibrillation is barely known.
- Patients with atrial fibrillation and thrombocytopenia may have an increased risk of bleeding.
- The incidence of thrombocytopenia during direct oral anticoagulants was 3.08 per 100 person-years.
- Incident thrombocytopenia was a risk factor for subsequent major bleeding.

1 | INTRODUCTION

Patients with atrial fibrillation (AF) at high thromboembolic risk require long-term anticoagulation with direct oral anticoagulants (DOACs) or vitamin K antagonists to reduce the risk of ischemic stroke [1,2]. Long-term anticoagulation may increase the bleeding risk, especially in patients with coexistent bleeding risk factors such as concomitant antiplatelet therapy, liver and kidney dysfunction, advanced age, history of bleeding, anemia, or thrombocytopenia [3,4]. When compared to vitamin K antagonists, DOACs reduce the incidence of major bleeding by about 31% [5] and the risk of intracranial hemorrhage (ICH) by 50% [6]. For example, in the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, the intracranial hemorrhage incidence rates were 0.76%, 0.31%, and 0.23% per year among patients assigned to warfarin, dabigatran 150 mg, and dabigatran 110 mg, respectively [7].

Despite a better safety profile compared to warfarin, the annual rate of major bleeding during DOAC therapy remains considerable at 2% to 4% per year [8]. This information is of concern considering that major bleeding is associated with worse clinical outcomes (eg, mortality) and with a higher risk of hospitalization and anticoagulation discontinuation [9].

Hence, it is crucial to evaluate the bleeding risk before and during treatment with oral anticoagulants. For this reason, several bleeding risk scores have been proposed in patients with AF [10]. In a Patient-Centered Outcomes Research Institute systematic review and evidence appraisal, the best-performing bleeding risk score is the HAS-BLED score [11]. HAS-BLED includes nonmodifiable and modifiable risk factors that may be addressed, hence allowing a reduction of bleeding risk over time [9]. As the risk of bleeding is dynamic, the monitoring of changes in the risk profile of patients during follow-up may provide more useful prognostic information than simply relying on the baseline bleeding risk assessment alone [3]. In the HAS-BLED score, the B criterion refers to bleeding tendency or predisposition (eg, anemia or thrombocytopenia), and the D criterion concomitant drug/alcohol use may be mitigated during follow-up.

Concerning thrombocytopenia, a platelet count less than 50×10^9/L is considered a contraindication to anticoagulant therapy [12]. Patients with this feature have been excluded from randomized clinical trials with DOACs, so very few safety and efficacy data on this population are available. In addition, severe thrombocytopenia has been associated with an increased risk of all-cause mortality in AF patients [13]. Nonetheless, the majority of patients develop mild to moderate thrombocytopenia, and their association with the risk of bleeding is not well defined.

On this basis, the aims of our study were to 1) estimate the annual incidence of thrombocytopenia in patients with AF while on treatment with DOACs, 2) evaluate the characteristics of patients developing thrombocytopenia, and 3) evaluate the risk of major bleeding in patients with thrombocytopenia.

2 | METHODS

2.1 | Study population

We analyzed patients from the observational single-center prospective ongoing cohort ATHEROsclerosis in Atrial Fibrillation (ATHERO-AF) study (ClinicalTrials.gov identifier: NCT01882114). The characteristics of the ATHERO-AF study have been previously described [14]. For this analysis, we included only patients treated with DOACs in the ATHERO-AF arm. During the first clinical examination, a complete personal medical history was collected, including drug therapy, baseline laboratory findings, and comorbidities. Definitions of cardiovascular risk factors have been previously reported [15].

Patients with mechanical prosthesis or the presence of any severe valvular disease; active neoplastic diseases; advanced liver cirrhosis; severe cognitive impairment; chronic infections such as HIV, hepatitis C virus, and hepatitis B virus infections; or autoimmune systemic disease were excluded. We also excluded patients with thrombocytopenia at baseline.

Thrombocytopenia was defined by a platelet count $<150 \times 10^9$/L [16]. Patients with ≥2 platelet count determinations during follow-up were included in this analysis. Thrombocytopenia was defined permanent if a platelet count $<150 \times 10^9$/L persisted during all available determinations during follow-up. Conversely, platelet count returning to a value $>150 \times 10^9$/L was defined as transient thrombocytopenia.

The CHA_2DS_2-VASc [1] (1 point for congestive heart failure, hypertension, age of 65-74 years, diabetes, female sex, and vascular disease and 2 points for age of ≥75 years and prior stroke) and HAS-BLED [1] (1

point for uncontrolled arterial hypertension, abnormal renal/liver function, previous stroke, bleeding history, or predisposition such as anemia or thrombocytopenia, age of >65 years, and drugs/alcohol concomitantly) scores were calculated. In the HAS-BLED, the "L" of labile international normalized ratio was scored 0, as all patients were in DOACs.

2.2 | Follow-up

Patients were regularly seen at the Atherothrombosis Outpatient Clinic of I Clinica Medica of the Sapienza University of Rome for the management of DOACs. Patients were re-evaluated at the outpatient clinic after 1, 3, 6, and 12 months during the first year of follow-up and then, every 6 to 12 months according to European Society of Cardiology recommendations [4]. Records about hospital admission and complications related to oral anticoagulation as bleeding events were collected during each visit. If patients missed 1 or more visits, follow-up was performed by telephone.

2.3 | Study outcomes

Clinical outcomes of our study were to estimate the incidence of thrombocytopenia in patients with nonvalvular AF treated with DOACs and potential clinical risk factors and assess the risk of major bleeding due to incident thrombocytopenia. Major bleeding events were classified according to the International Society on Thrombosis and Haemostasis [17].

2.4 | Sample size calculation

We calculated the sample size estimating a major bleeding cumulative incidence rate of 13.3% and 5.7% at 1 year in AF patients with and without thrombocytopenia, respectively. These 1-year major bleeding cumulative incidence rates were reported in a previous study [18] performed on 1070 AF patients with a sample size estimated with a power of 83%, α error of 5%, and a 1:3 ratio of assignment. The sample size was calculated estimating an α error of 5% and a power of 80% to detect a difference between our cohorts and assuming a 1:3 ratio of assignment (thrombocytopenia–to–no thrombocytopenia) and consisted in 568 patients.

2.5 | Statistical analysis

Continuous variables are expressed as mean and SD or median and IQR as appropriate, and categorical variables as numbers and percentages.

We evaluated the predictors of thrombocytopenia using a univariable Cox regression analysis; then, we performed a multivariable Cox analysis with significant clinical predictors of thrombocytopenia found at univariable Cox regression analysis.

For the analyses on major bleeding, time to death was recorded as a competing risk with respect to time to bleeding and/or time to thrombocytopenia. In order to evaluate cumulative incidence of both events, we thus used Gray estimator for competing risk data. Our main endpoint was major bleeding. At univariate analyses, major bleeding was associated with possible baseline predictors using Fine and Gray regression model for subdistribution functions in competing risk data. Estimates are expressed in terms of subdistributional hazard ratios (sHR). We also included time to thrombocytopenia as a time-dependent predictor which could be also possibly subject to censoring due to the competing risk of death using the methods described in a previous study [19]. Time was expressed as median time to censoring with 95% CI [20].

A similar strategy was used at multivariate analysis, where the final model was selected by minimizing the Akaike information criterion in a stepwise fashion.

All hypothesis testing was 2-tailed and P values of <.05 were considered statistically significant. All statistical analyses were performed using software package computers (SPSS-25.0, SPSS Inc) and R statistical software (version 4.2.2, R Core Team 2021).

3 | RESULTS

Twenty out of 977 AF patients were excluded from the analysis because they did not have ≥2 platelet count determinations during follow-up. We then included 957 patients on DOACs with a mean age of 77.3 ± 9.0 years and 49.1% of women. Median time to censoring was 1330 days (95% CI, 1246-1443). One hundred thirty-nine patients developed thrombocytopenia with an annual incidence of 3.08 (95% CI, 2.27-3.89) per 100 person-years (cumulative incidence at 1 year, 0.017; 95% CI, 0.008-0.025). Among patients with thrombocytopenia, 101 patients had transient thrombocytopenia and 38 had permanent thrombocytopenia. The median time to thrombocytopenia was 41.6 months (IQR, 23.9-64.4 months). The median platelet count of patients with thrombocytopenia was 133.0 × 10^3/μL (IQR, 122.0-141.0 × 10^3/μL; range, 12-149 × 10^3/μL).

AF patients who developed thrombocytopenia were older, more frequently men, and had a higher HAS-BLED score at baseline, a higher serum level of glutamic-oxaloacetic transaminase, and lower median platelet count at baseline (Table 1). No other differences were observed regarding clinical comorbidities, concomitant drug therapies, and laboratory findings. No patient discontinued oral anticoagulants during thrombocytopenia.

3.1 | Predictors of thrombocytopenia

At univariable Cox regression analysis, older age (hazard ratio [HR], 1.054; 95%CI, 1.031-1.077; P < .001), and concomitant heart failure (HR, 1.628; 95% CI, 1.044-2.539; P = .03) were potential risk factors for incident thrombocytopenia, while female sex (HR, 0.681;

TABLE 1 Baseline characteristics according to the development of thrombocytopenia.

Clinical characteristics	All patients (*N* = 957)	No thrombocytopenia (*n* = 818)	Incident thrombocytopenia (*n* = 139)	*P* value
Age (y), mean ± SD	77.3 ± 9.0	77.1 ± 9.2	78.8 ± 7.4	.04
Women (%)	49.1	51.3	36.0	.001
Diabetes (%)	21.2	21.1	21.2	.76
Arterial hypertension (%)	85.5	85.0	88.4	.54
Prior cardiovascular disease (%)	16.1	16.7	12.7	.24
Prior cerebrovascular disease (%)	18.1	18.6	15.7	.42
Heart failure (%)	15.9	15.5	17.9	.48
COPD (%)	14.9	15.2	12.7	.44
History of cancer (%)	13.9	13.4	16.5	.35
Baseline CHA_2DS_2-VASc, mean ± SD	3.8 ± 1.5	3.8 ± 1.6	3.7 ± 1.4	.55
Baseline HAS-BLED score, mean ± SD	1.3 ± 0.6	1.3 ± 0.7	1.4 ± 0.6	.03
Therapy				
Antiplatelets (%)	7.0	7.3	5.2	.38
ACEi/ARBs (%)	57.1	56.4	61.5	.266
Beta-blockers (%)	52.9	53.1	51.5	.72
Calcium channel blockers (%)	27.8	27.5	30.1	.517
Statin (%)	43.3	43.5	41.9	.72
Laboratory findings				
Creatinine (mg/dL), mean ± SD	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	.145
Clearance creatinine (mL/min), mean ± SD	66.2 ± 17.8	66.4 ± 17.8	64.9 ± 17.9	.35
Hemoglobin (g/dL), mean ± SD	13.4 ± 1.6	13.4 ± 1.6	13.4 ± 1.7	.978
Platelet count at baseline ($\times 10^3/\mu L$), median (25th-75th percentile IQR)	217 (185-262)	224 (192-266)	178 (162-205)	<.001
Anemia (%)	23.2	22.3	28.5	.117
GOT (U/L), median (25th-75th percentile IQR)	20.0 (17-25)	20.0 (16-25)	22.0 (17-26)	.04
GPT (U/L), median (25th-75th percentile IQR)	18.0 (14-25)	18.0 (14-25)	19.0 (14.26)	.347

ACEi, angiotensin converting enzyme inhibitor/; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

95% CI, 0.482-0.963; *P* = .03) was a potential protective factor (Table 2, panel A).

Multivariable Cox regression analysis confirmed older age (HR, 1.050; 95% CI, 1.026-1.074; *P* < .001) and female sex (HR, 0.675; 95% CI, 0.471-0.967; *P* = .03) as clinical factors associated with thrombocytopenia (Table 2, panel B).

3.2 | Bleeding events

During follow-up, 179 bleeding events occurred, of which, 80 were major bleedings (3.17 per 100 person-years; 95% CI, 2.34-3.99; cumulative incidence at 1 year, 0.030; 95% CI, 0.018-0.041). Patients with major bleeding were more frequently older and treated with antiplatelets and had lower hemoglobin levels and a higher CHA_2DS_2-VASc score (Table 3). The incidence of major bleeding was 3.17 (95% CI, 2.34-3.99) per 100 person-years (Figure).

We evaluated the platelet count in patients with thrombocytopenia with and without major bleeding. In patients with thrombocytopenia and major bleeding the median platelet count was 122.5 × $10^3/\mu L$ (IQR, 103.8-131.0), while in patients with thrombocytopenia without major bleeding, the median platelet count was 134.5 × $10^3/\mu L$ (IQR, 123.0-142.0; *P* = .04).

At univariate Cox regression analysis (Table 4, panel A), older age (sHR, 1.023; 95% CI, 1.004-1.042; *P* = .01), higher CHA_2DS_2-VASC (sHR, 1.096; 95% CI, 1.003-1.197; *P* = .04) and incident

TABLE 2 Univariable (panel A) and multivariable (panel B) Cox analysis of factors associated with incident thrombocytopenia.

Clinical variables	Hazard ratio	95% CI	*P* value
Panel A			
Age	1.054	1.031-1.077	<.001
Female sex	0.681	0.482-0.963	.03
Diabetes	1.058	0.703-1.592	.787
Arterial hypertension	1.270	0.742-2.173	.38
Prior cardiovascular disease	0.994	0.596-1.655	.98
Prior cerebrovascular disease	1.033	0.647-1.649	.89
Heart failure	1.628	1.044-2.539	.03
COPD	1.072	0.641-1.790	.79
History of cancer	1.503	0.896-2.520	.12
Therapy			
Antiplatelets	1.158	0.539-2.490	.707
ACEi/ARBs	1.034	0.726-1.471	.85
Beta-blockers	1.003	0.715-1.408	.986
Calcium channel blockers	1.230	0.851-1.777	.27
Statin	0.830	0.588-1.170	.287
DOAC (factor Xa vs factor IIa)	1.408	0.939-2.111	.098
Laboratory findings			
Creatinine	2.140	1.197-3.826	.01
Clearance creatinine	0.984	0.976-0.992	<.001
Hemoglobin	0.663	0.437-1.084	.05
Platelet count	0.984	0.980-0.989	<.001
GOT	1.031	1.017-1.045	<.001
GPT	1.008	0.995-1.021	.219
Panel B			
Age	1.050	1.026-1.074	<.001
Female sex	0.675	0.471-0.967	.03
Heart failure	1.501	0.960-2.346	.075
HAS-BLED score	1.099	0.830-1.455	.51

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

thrombocytopenia (sHR, 12.200; 95% CI, 8.130-18.200; $P < .001$), but not HAS-BLED (sHR, 1.149; 95% CI, 0.928-1.422; $P = .20$) were risk factors for major bleeding (Table 4, panel A).

Then, at multivariate analysis (Table 4, panel B), older age (sHR, 1.030; 95% CI, 1.010-1.040; $P = .002$) and incident thrombocytopenia (sHR, 12.77; 95% CI, 8.880-18.360; $P < .001$) were confirmed as potential risk factors for major bleeding (Table 4, panel B).

TABLE 3 Baseline characteristics of patients according to major bleeding.

Clinical characteristics	No major bleeding (n = 877)	Major bleeding (n = 80)	*P* value
Age (y), mean ± SD	77.1 ± 9.1	79.3 ± 7.9	.039
Women (%)	48.7	53.8	.386
Diabetes (%)	21.5	18.8	.57
Arterial hypertension (%)	84.9	92.5	.065
Previous cardiovascular disease (%)	15.8	20.3	.299
Previous cerebrovascular disease (%)	18.1	18.8	.88
Heart failure (%)	15.3	21.5	.15
COPD (%)	15.1	12.5	.53
History of cancer (%)	28.2	28.2	.996
CHA_2DS_2-VASc score, mean ± SD	3.7 ± 1.5	4.3 ± 1.8	.003
HAS-BLED score, mean ± SD	1.3 ± 0.6	1.4 ± 0.6	.12
Therapy			
Antiplatelets (%)	6.5	12.5	.04
ACEi/ARBs (%)	56.5	63.7	.209
Beta-blockers (%)	53.6	45.0	.14
Calcium channel blockers (%)	27.3	33.8	.218
Statin (%)	43.2	45.0	.75
Laboratory findings			
Platelet count baseline ($\times 10^3/\mu L$), median (25th-75th percentile IQR)	215 (186-261)	236 (188-295)	.01
Creatinine (mg/dL), mean ± SD	1.01 ± 0.3	0.98 ± 0.3	.44
Clearance creatinine (mL/min), mean ± SD	66.2 ± 17.8	65.9 ± 17.9	.877
Hemoglobin (g/dL), mean ± SD	13.4 ± 1.6	12.9 ± 1.8	.01
Anemia (%)	22.5	31.6	.06
GOT (U/L), median (25th-75th percentile IQR)	20 (17-25)	20 (17-25)	.977
GPT (U/L), median (25th-75th percentile IQR)	18 (14-25)	18 (13-27)	.787

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

4 | DISCUSSION

In this prospective cohort, we report the rate of incident thrombocytopenia in a prospective study of AF patients on DOACs, which has never been described previously. We reported an overall incidence rate of thrombocytopenia of 3.08 per 100 person-years. Second, we

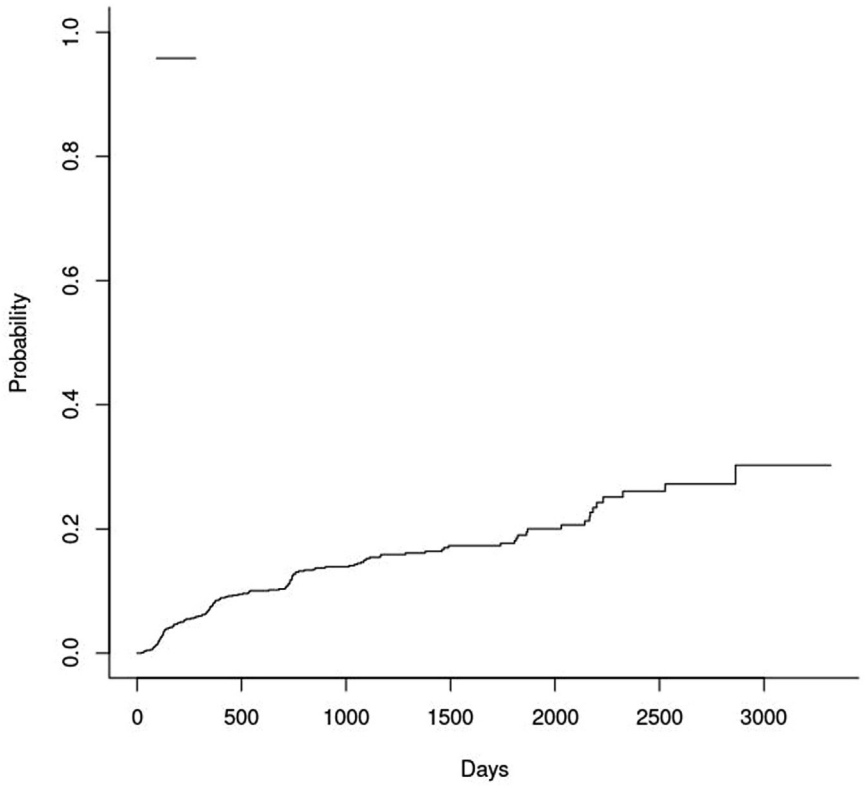

FIGURE Incidence of major bleeding in our cohort.

TABLE 4 Univariable (panel A) and multivariable (panel B) Fine and Gray regression model for major bleeding.

Clinical variables	sHR	95% CI	*P* value
Panel A			
Female sex	1.131	0.831-1.539	.43
Age	1.023	1.004-1.042	.01
Diabetes mellitus	0.854	0.571-1.277	.21
Smoking	0.658	0.343-1.260	.21
Alcohol	0.952	0.620-1.460	.82
COPD	1.150	0.743-1.778	.53
Heart failure	0.891	0.558-1.423	.63
CHA_2DS_2-VASc	1.10	1.003-1.197	.04
HAS-BLED	1.149	0.928-1.422	.20
BMI	1.002	0.967-1.39	.90
Platelets at baseline	1.000	0.998-1.002	.69
Incident thrombocytopenia	12.200	8.130-18.200	<.001
Panel B			
Incident thrombocytopenia	12.770	8.880-18.360	<.001
Age	1.030	1.010-1.040	.002

BMI, body mass index; COPD, chronic obstructive pulmonary disease; sHR, subdistributional hazard ratio.

found that incident thrombocytopenia is a risk factor for subsequent major bleeding.

Previous studies mainly focused on the relationship between baseline thrombocytopenia and bleeding risk with conflicting results. One retrospective study, performed on 1076 patients with comorbidities requiring anticoagulation and treated with warfarin, showed that patients with moderate thrombocytopenia at baseline ($<100 \times 10^9$/L) had a higher risk of major and minor bleeding compared with no thrombocytopenic ones (incidence rate ratios, 1.48; 95% CI, 0.44-3.98) [21]. This finding was confirmed by a retrospective study performed on 1070 AF patients with persistent thrombocytopenia ($<100 \times 10^9$/L), who experienced a higher 1-year cumulative incidence of major bleeding (13.3% vs 5.7%; $P < .0001$) compared to patients without [18].

Furthermore, a post hoc analysis of Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease trial [22], included 2063 AF patients treated with rivaroxaban, of which 70 with thrombocytopenia (defined as a platelet count, $<100.000/mm^3$), followed for 693.6 ± 268.3 days showed a higher risk of major bleeding (10.0% vs 4.1%; $P = .027$) [22]. Of note, about 50% of patients were treated with also antiplatelets that increased the risk of bleeding in these patients.

On the other hand, a retrospective Chinese AF study performed on 5469 AF patients on rivaroxaban or dabigatran [23] found no association between platelet count and bleeding events. However, this

study enrolled younger patients (mean age, 64.6 years), with less comorbidities such as diabetes (18.9%), arterial hypertension (54.6%), previous cardiovascular disease (8.7%), previous cerebrovascular disease (3.7%), heart failure (5.1%), chronic obstructive pulmonary disease (2.0%), and cancer (1.4%). Furthermore, no data were available about concomitant antiplatelet drug use and the majority of AF patients were on therapy with low dose dabigatran and rivaroxaban, including 14.4% of patients on a very low dose of rivaroxaban (10 mg), which is not approved in Europe to prevent thromboembolic stroke in patients with AF.

4.1 | Strengths and limitations

Our study has some strengths. First, to the best of our knowledge, no prospective data about incident thrombocytopenia are available in AF patients on DOACs. In addition, we found that also incident and transient thrombocytopenia were independent biomarkers associated with major bleeding. The results rely on clinical records meticulously collected during regular face-to-face visits with patients referring to a university hospital outpatient clinic. Therefore, patients have been closely monitored and data regularly registered, reducing the risk of missing information. Nevertheless, bleeding risk assessment should also be part of the current overall holistic approach to AF management [24,25].

Our study has also limitations to acknowledge. First, the observational design of our study did not allow establishment of a cause-effect relationship but only an association between incident thrombocytopenia as potential risk factor for major bleeding. In addition, we investigated only a Caucasian Italian population, and no data were available for other ethnicities. Also, patients with AF are clinically complex, being commonly associated with multimorbidity, polypharmacy, and frailty, with major implications for treatment and outcomes, including bleeding [26–28]. Finally, this study has potential risk of immortal time bias due to enrolment mechanisms. However, this bias is slightly mitigated by the treatment of thrombocytopenia as a time-varying exposure.

In conclusion, patients with AF on treatment of DOAC had a high incidence of thrombocytopenia, either permanent or transient. Developing thrombocytopenia during follow-up carries an increased risk of major bleeding.

APPENDICES

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FUNDING

The authors received no funding for this study.

AUTHOR CONTRIBUTIONS

D.M.: conceptualization, formal analysis, methodology, and writing (original draft). L.C.: formal analysis, writing (original draft), and methodology. T.B.: data curation, formal analysis, and methodology. G.Y.H.L.: writing (review and editing) and supervision. A.F.: formal analysis, methodology, writing (review and editing), and supervision. P.P.: writing (review and editing) and supervision. D.P.: conceptualization, writing (review and editing), and supervision. All authors read and approved the final version of the manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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