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Thrombocytopenia and Mortality Risk in Patients With Atrial Fibrillation: An Analysis From the START Registry

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***Background*—**Thrombocytopenia is associated with increased mortality in the general population, but few data exist in patients with atrial fibrillation (AF) taking oral anticoagulants. We investigated factor determinants of thrombocytopenia in a large cohort of patients affected by AF and its association with total mortality.

***Methods and Results*—**Multicenter prospective cohort study, including 5215 patients with AF from the START (Survey on Anticoagulated Patients Register) registry, 3877 (74.3%) and 1338 (25.7%) on vitamin K or non–vitamin K antagonist oral anticoagulants, respectively. Thrombocytopenia was defined by a platelet count $<150\times10^9$/L. Determinants of thrombocytopenia were investigated, and all-cause mortality was the primary survival end point of the study. Thrombocytopenia was present in 592 patients (11.4%). At multivariable logistic regression analysis, chronic kidney disease (odds ratio [OR], 1.257; P=0.030), active cancer (OR, 2.065; P=0.001), liver cirrhosis (OR, 7.635; P<0.001), and the use of diuretics (OR, 1.234; P=0.046) were positively associated with thrombocytopenia, whereas female sex (OR, 0.387; P<0.001) and the use of calcium channel blockers (OR, 0.787; P=0.032) were negatively associated. During a median follow-up of 19.2 months (9942 patient-years), 391 deaths occurred (rate, 3.93%/year). Mortality rate increased from 3.8%/year to 9.9%/year in patients with normal platelet count and in those with moderate-severe thrombocytopenia, respectively (log-rank test, P=0.009). The association between moderate-severe thrombocytopenia and mortality persisted after adjustment for CHA_2DS_2 VASc score (hazard ratio, 2.431; 95% CI, 1.254–4.713; P=0.009), but not in the fully adjusted multivariable Cox regression analysis model.

***Conclusions*—**Thrombocytopenia is common in patients with AF. Despite an increased incidence of mortality, thrombocytopenia was not associated with mortality at multivariable analysis. Thrombocytopenia may reflect the presence of comorbidities associated with poor survival in AF. **(*J Am Heart Assoc*. 2019;8:e012596. DOI: 10.1161/JAHA.119.012596.)**

Key Words: atrial fibrillation • mortality • thrombocytopenia

The most common causes of thrombocytopenia in adults include acute and chronic infectious diseases, liver cirrhosis, cancer, and use of drugs like heparin, chemotherapies, antibiotics, and antidiabetic medications.[1] In addition, platelet count may be reduced in patients with myelofibrosis or hematologic diseases.

Thrombocytopenia is usually defined as a platelet count $<150\times10^9$/L, and in the general population, it is associated with an increased risk of mortality.[2] Furthermore, the presence of a low platelet count was associated with worse short- and long-term outcomes in patients with acute coronary syndrome or cancer.[3,4]

The management of patients with thrombocytopenia requiring oral anticoagulation, such as those with venous thromboembolism or atrial fibrillation (AF), is particularly challenging for the potential risk of bleeding.[3,5] Indeed, anticoagulation is generally contraindicated if platelet count is $<50\times10^9$/L,[6] and patients with platelet count $<100\times10^9$/L were excluded from recent clinical trials with non–vitamin K antagonist (VKA) oral anticoagulants (NOACs).[7–10] Prevalence and determinants of thrombocytopenia in AF patients are still unclear. In 2 recent studies, the prevalence of thrombocytopenia was highly variable, as it ranged from 6% to 24%.[4,5] Furthermore, follow-up data about the relationship between thrombocytopenia and mortality in patients with AF were not reported.

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Clinical Perspective

What Is New?

- Thrombocytopenia is common in patients experiencing atrial fibrillation and taking oral anticoagulants.
- Platelet count was lower in men than women and decreased by aging, and the presence of chronic kidney disease, active cancer, and liver cirrhosis was associated with thrombocytopenia.
- We observed a significant association between moderate-severe thrombocytopenia and mortality, which persisted after adjustment for CHA_2DS_2 VASc score.

What Are the Clinical Implications?

- Thrombocytopenia may identify a subgroup of patients with atrial fibrillation at higher risk of mortality.
- When thrombocytopenia is detected, the presence of comorbidities potentially affecting survival should be investigated.

On the basis of this, the aim of the present study was to assess prevalence and determinants of thrombocytopenia and its relationship with mortality in a large population of the multicenter cohort START (Survey on Anticoagulated Patients Register) registry.

Methods

Study Population

The authors declare that all supporting data are available within the article. Details of the START registry have been previously described.[11] Briefly, the START registry is an observational, multicenter, ongoing cohort study that includes patients (aged ≥18 years) who start anticoagulation therapy (ClinicalTrials.gov NCT02219984). The study protocol was accepted by the Institutional Review Board of each participating center, and informed consent was obtained from patients at enrollment. The present analysis is limited to patients with nonvalvular AF starting oral anticoagulants, either VKAs (warfarin or acenocoumarol) or NOACs. Patients treated with low-molecular-weight heparin were excluded.

Patients with a life expectancy <6 months, not residents in the participant region, or planning on leaving in the next 6 months were not included in the registry, as well as patients already enrolled in phase 2 or 3 clinical studies. Patients enrolled in other observational or phase 4 studies were considered eligible for the study.

Thrombocytopenia was defined by a platelet count $<150\times10^9$/L.[12] Primary end point of the study was the occurrence of all-cause mortality. Data on death were obtained from relatives of patients or from general practitioners. CHA_2DS_2 VASc [congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), prior stroke (2 points), age 65–74 years (1 point), female sex (1 point), and vascular disease (1 point)] and HAS BLED (hypertension i.e. uncontrolled, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years, drugs/alcohol concomitantly) scores were also calculated. In the HAS BLED, the "L" of labile international normalized ratio was scored 0.

Statistical Analysis

Data are expressed as mean and SD or median and interquartile range, depending on variable distribution. Group comparisons were performed by unpaired Student *t* test. Proportions and categorical variables were tested by the χ^2 test.

We divided patients' cohort according to the presence of thrombocytopenia (ie, platelet count $<150\times10^9$/L) and performed a descriptive analysis of characteristics of patients with and without low platelet count.

Multivariable logistic regression analysis was used to investigate factors associated with thrombocytopenia and to estimate the adjusted odds ratio (OR) of each variable.

Variables were categorized or dichotomized for the multivariable model, which included the following covariates: persistent/permanent AF (versus paroxysmal AF), female sex, aged ≥75 years, obesity (body mass index ≥30 kg/m^2), chronic kidney disease (creatinine clearance <60 mL/min), active cancer, diabetes mellitus, previous cerebrovascular events, previous cardiovascular disease, heart failure, peripheral artery disease, pulmonary disease, liver cirrhosis, smoking, NOACs use (versus VKAs), antiplatelet drugs, lipid-lowering drugs, antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, β blockers, calcium channel blockers, diuretics, nitrate, angiotensin receptor blockers, digoxin, proton pump inhibitors, and xanthine oxidase inhibitors.

Survival analysis was performed to investigate the relationship between thrombocytopenia and all-cause mortality. For this analysis, patients were divided in 3 groups: normal ($>150\times10^9$/L), mildly reduced ($150–100\times10^9$/L), and moderately severely reduced ($<100\times10^9$/L) platelet count.

The cumulative incidence of all-cause mortality was estimated using a Kaplan-Meier product-limit estimator, and survival curves were formally compared using the log-rank test. Univariate and multivariate stepwise Cox proportional hazards regression analysis was used to calculate the adjusted relative hazard ratios (HRs) of death by each clinical variable. Three models of survival analysis were built: model A, adjusted for age and sex; model B, adjusted for CHA_2DS_2 VASc score; and model C, fully adjusted.

All tests were 2 tailed, and $P<0.05$ was considered statistically significant. Analyses were performed using computer software (IBM SPSS 23 Inc).

Results

The cohort was composed of 5236 patients with AF; 4 patients had missing data, and 17 patients taking low-molecular-weight heparin were excluded. Thus, the analysis was performed in 5215 patients. Of these patients, 3877 (74.3%) were taking VKAs, and 1338 (25.7%) NOACs: 469 taking dabigatran, 478 taking apixaban, 379 taking rivaroxaban, and 12 taking edoxaban.

Characteristics of patients are reported in Table 1. The mean age was 75.0±9.6 years, and 2368 (45.4%) were women. Overall, thrombocytopenia was present in 592 patients (11.4%) (Table 1). Of these patients, 10.4% had mild and 0.96% had moderate-severe thrombocytopenia. Patients with thrombocytopenia were older; they were more likely to have persistent/permanent AF, active cancer, and liver cirrhosis; and more of them were treated with calcium channel blockers, nitrate, diuretics, and xanthine oxidase inhibitors. A trend for higher use of lipid-lowering drugs and proton pump inhibitors and diabetes mellitus was also found (Table 1). Among antiarrhythmic drugs, 147 were treated with propafenone, 258 were treated with flecainide, 674 were treated with amiodarone, and 229 were treated with other drugs (dronedarone/unknown).

The CHA_2DS_2 VASc score was similar between the 2 groups, whereas the HAS BLED score was significantly higher in patients with thrombocytopenia (Table 1).

Women were less likely to have thrombocytopenia compared with men (Table 1). Thus, median platelet count was significantly lower in men than women, independently from aging (Table 2). In particular, in male but not female patients, a significant decrease in platelet count was found according to age group (Table 2).

At multivariable logistic regression analysis, chronic kidney disease (OR, 1.257; $P=0.030$), active cancer (OR, 2.065; $P=0.001$), liver cirrhosis (OR, 7.635; $P<0.001$), and the use of diuretics (OR, 1.234; $P=0.046$) were positively associated with thrombocytopenia, whereas female sex (OR, 0.387; $P<0.001$) and calcium channel blockers (OR, 0.787; $P=0.032$) were negatively associated (Table 3).

Survival Analysis

Median follow-up was 19.2 (interquartile range, 8.8–35.4) months, yielding 9942 patient-years of observation; 391 deaths were registered with an annual incidence rate of 3.93% (95% CI, 3.6%–4.3%). Incidence of mortality increased from 3.8%/year in patients with normal platelet count to 9.9%/year in those with moderate-severe thrombocytopenia (Table 4).

Kaplan-Meier curves showed a significant decrease of survival across the 3 groups of thrombocytopenia (log-rank test, $P=0.009$; Figure). Univariate Cox regression analysis showed that moderate-severe, but not mild, thrombocytopenia was associated with mortality (Table 4). Among antiarrhythmic drugs, we found that propafenone (univariate HR, 0.339; 95% CI, 0.126–0.908; $P=0.031$) and flecainide (n=258; univariate HR, 0.370; 95% CI, 0.183–0.747; $P=0.006$), but not amiodarone (n=674; univariate HR, 0.865; 95% CI, 0.640–1.169; $P=0.344$) or other antiarrhythmic drugs (n=229 dronedarone/unknown; univariate HR, 0.692; 95% CI, 0.412–1.162; $P=0.164$), were associated with mortality. However, given the low number of deaths in each group (4 in the propafenone group, 8 in the flecainide group, 49 in the amiodarone group, and 15 in the other group), antiarrhythmic drugs were grouped for multivariable analysis.

The association between moderate-severe thrombocytopenia and mortality persisted after adjustment for age and sex (Table 5, model A) and CHA_2DS_2 VASc score (Table 5, model B). However, it was no longer significant at fully adjusted multivariable Cox regression analysis (Table 5, model C): HR, 1.147 (95% CI, 0.840–1.566; $P=0.390$) for platelet count 150 to 100×10^9/L; and HR, 1.712 (95% CI, 0.873–3.3354; $P=0.117$) for platelet count $<100\times10^9$/L versus normal platelet count. All significant predictors of mortality are reported in Table 5.

Thrombocytopenia and Bleeding

During follow-up, 133 major bleeding events were reported. Univariate Cox regression analysis found that moderate-severe thrombocytopenia resulted in a significant association with major bleeding (HR, 3.699; 95% CI, 1.170–11.692; $P=0.026$). This association was not evident for mild thrombocytopenia (HR, 1.218; 95% CI, 0.700–2.118; $P=0.486$).

Discussion

The study shows a relatively high prevalence of thrombocytopenia in AF patients on treatment with oral anticoagulants. The incidence of mortality increased with the severity of thrombocytopenia and persisted after adjustment for CHA_2DS_2 VASc score.

The present study reports a prevalence of thrombocytopenia of 11.4%, which is in between the prevalence reported in previous studies.[4,5] For the study that reported a prevalence of 5.7% of white patients, it is possible that the difference in age of the population could account for the different results; thus, the mean age of the cohort of Yadav et al. was lower than that of our study (mean, 65 versus 75 years, respectively).[4]

Table 1. Characteristics of Patients With AF, According to the Presence of Thrombocytopenia

Characteristics	All Cohort (n=5215)	Normal Platelet Count (n=4623)	Thrombocytopenia (n=592)	*P* Value
Persistent/permanent AF	3282 (62.9)	2883 (62.4)	399 (67.4)	0.017
Women	2368 (45.4)	2207 (47.7)	161 (27.2)	<0.001
Age, y	75.0±9.6	74.9±9.7	75.6±9.2	0.115
Aged ≥75 y	3051 (58.5)	2692 (58.2)	359 (60.6)	0.268
BMI, kg/m^2	26.8±4.7	26.8±4.7	27.0±4.6	0.505
Obesity (BMI ≥30 kg/m^2)	1101 (21.1)	974 (21.1)	127 (21.5)	0.831
Creatinine clearance, mL/min	66.8±28.3	66.9±28.2	65.9±29.0	0.420
CKD (creatinine clearance <60 mL/min)	2357 (45.2)	2075 (44.9)	282 (47.6)	0.219
Active cancer	134 (2.6)	104 (2.2)	30 (5.1)	<0.001
Hypertension	4182 (80.2)	3694 (79.9)	488 (82.4)	0.155
Diabetes mellitus	1048 (20.1)	911 (19.7)	137 (23.1)	0.056
Previous cerebrovascular events	857 (16.4)	765 (16.5)	92 (15.5)	0.556
Previous cardiovascular disease	966 (18.5)	817 (17.7)	149 (25.2)	<0.001
Heart failure	808 (15.5)	706 (15.3)	102 (17.2)	0.227
Peripheral artery disease	332 (6.4)	289 (6.3)	43 (7.3)	0.326
Pulmonary disease	655 (12.6)	580 (12.5)	75 (12.7)	0.947
Liver cirrhosis	27 (0.5)	13 (0.3)	14 (2.4)	<0.001
Smoking	688 (13.2)	609 (13.2)	79 (13.3)	0.897
CHA_2DS_2 VASc score	3.6±1.5	3.6±1.5	3.6±1.4	0.795
HAS BLED score	1.27±0.73	1.26±0.73	1.35±0.73	0.010
Anticoagulant drugs				0.294
VKAs	3877 (74.3)	3426 (74.1)	451 (76.2)	
NOACs	1338 (25.7)	1197 (25.9)	141 (23.8)	
Dabigatran	469 (9.0)	416 (9.0)	53 (9.0)	
Apixaban	478 (9.2)	424 (9.2)	54 (9.1)	
Rivaroxaban	379 (7.3)	345 (7.5)	34 (5.7)	
Edoxaban	12 (0.2)	12 (0.3)	0 (0.0)	
Antiplatelet drugs	646 (12.4)	560 (12.1)	86 (14.5)	0.098
Aspirin	507 (9.7)	444 (9.6)	63 (10.6)	0.418
Others	205 (3.9)	175 (3.8)	30 (5.1)	0.143
Lipid-lowering drugs	1803 (34.6)	1580 (34.2)	223 (37.7)	0.098
Antiarrhythmic drugs	1308 (25.1)	1162 (25.1)	146 (24.7)	0.840
ACE inhibitors	1501 (28.8)	1318 (28.5)	183 (30.9)	0.228
β Blockers	2745 (52.6)	2421 (52.4)	324 (54.7)	0.294
Calcium channel blockers	1197 (23.0)	1075 (23.3)	122 (20.6)	0.161
Diuretics	1880 (36.0)	1634 (35.3)	246 (41.6)	0.004
Nitrate	260 (5.0)	219 (4.7)	41 (6.9)	0.027
Angiotensin receptor blockers	1191 (22.8)	1051 (22.7)	140 (23.6)	0.640
Digoxin	480 (9.2)	427 (9.2)	53 (9.0)	0.880
Proton pump inhibitors	2384 (45.7)	2093 (45.3)	291 (49.2)	0.080
Xanthine oxidase inhibitors (allopurinol and febuxostat)	386 (7.4)	329 (7.1)	57 (9.6)	0.037

Data are given as number (percentage) or mean±SD. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; NOAC, non-VKA oral anticoagulant; VKA, vitamin K antagonist.

Table 2. Median (Interquartile Range) Platelet Count, According to Age and Sex Groups

Variable	Men	Women	*P* Value (Between Sex Groups)
Age below median (≤75 y)	206 (173–246)	229 (195–276)	<0.001
Age above median (>75 y)	196 (163–240)	225 (188–272)	<0.001
P value (between age groups)	<0.001	0.201	. . .

Platelet count is given as number $\times 10^9$/L.

Conversely, a significantly higher prevalence of thrombocytopenia of 24.2% has been reported in the Korean population,[5] despite a significantly lower prevalence of comorbidities, such as hypertension, chronic kidney disease, and previous cerebrovascular events, compared with the present cohort. Another large nationwide study, including 8478 middle-aged participants without cardiovascular risk factors, reported a prevalence of thrombocytopenia of 16.5%.[13]

We found that chronic kidney disease, active cancer, and liver cirrhosis, which are frequent features of patients with

Table 3. Multivariable Logistic Regression Analysis of Factors Associated With Thrombocytopenia (Platelet Count $<150\times 10^9$/L)

Variable	Odds Ratio	95% CI		*P* Value
		Lower	Upper	
Persistent/permanent AF (vs paroxysmal)	1.156	0.956	1.398	0.135
Female sex	0.387	0.316	0.475	<0.001
Aged ≥75 y	1.077	0.879	1.319	0.476
Obesity (BMI ≥30 kg/m^2)	1.090	0.869	1.368	0.456
CKD (creatinine clearance <60 mL/min)	1.257	1.022	1.547	0.030
Active cancer	2.065	1.341	3.177	0.001
Diabetes mellitus	1.080	0.868	1.344	0.492
Previous cerebrovascular events	0.930	0.728	1.187	0.559
Previous cardiovascular disease	1.235	0.965	1.580	0.093
Heart failure	0.924	0.714	1.196	0.550
Peripheral artery disease	0.994	0.703	1.407	0.975
Pulmonary disease	0.864	0.658	1.136	0.295
Liver cirrhosis	7.635	3.458	16.854	<0.001
Smoking	0.829	0.638	1.078	0.162
NOAC use (vs VKAs)	0.897	0.728	1.106	0.309
Antiplatelet drugs	0.934	0.710	1.229	0.626
Lipid-lowering drugs	1.014	0.825	1.248	0.892
Antiarrhythmic drugs	1.035	0.840	1.275	0.747
ACE inhibitors	1.056	0.860	1.298	0.601
β Blockers	1.023	0.850	1.231	0.808
Calcium channel blockers	0.787	0.632	0.979	0.032
Diuretics	1.234	1.004	1.517	0.046
Nitrate	1.191	0.819	1.732	0.359
Angiotensin receptor blockers	1.090	0.873	1.361	0.446
Digoxin	1.022	0.745	1.403	0.893
Proton pump inhibitors	1.057	0.877	1.274	0.562
Xanthine oxidase inhibitors	1.076	0.788	1.468	0.645

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; NOAC, non-VKA oral anticoagulant; VKA, vitamin K antagonist.

Table 4. Annual Incidence Rates of Mortality and Univariate HR, According to Thrombocytopenia Groups

Variable	No. of Deaths/No. of Patients	Annual Incidence Rate (95% CI)	*P* Value	Univariate HR (95% CI)	*P* Value
Normal platelet count (>150×10^9/L)	334/4623	3.8 (3.4–4.2)	Reference	Reference	Reference
Mild thrombocytopenia (150–100×10^9/L)	48/542	4.6 (3.4–6.1)	0.230	1.201 (0.888–1.626)	0.235
Moderate-severe thrombocytopenia (<100×10^9/L)	9/50	9.9 (4.5–18.8)	0.003* 0.029†	2.558 (1.320–4.961)	0.005

HR indicates hazard ratio.
*vs normal platelet count.
†vs mild thrombocytopenia.

AF,[14] were significantly associated with thrombocytopenia; this is in accordance with previous reports in different clinical settings.[15] In addition, we found a sex-based difference in platelet count, with women having mean higher platelet count than men. This difference was evident both in younger (aged ≤75 years) and elderly (aged >75 years) patients. This finding is in keeping with a previous study on a large sample of the Italian general population,[16] showing higher platelet count in women than men. In the same study, a decrease in platelet count by aging was present both in men and women, whereas

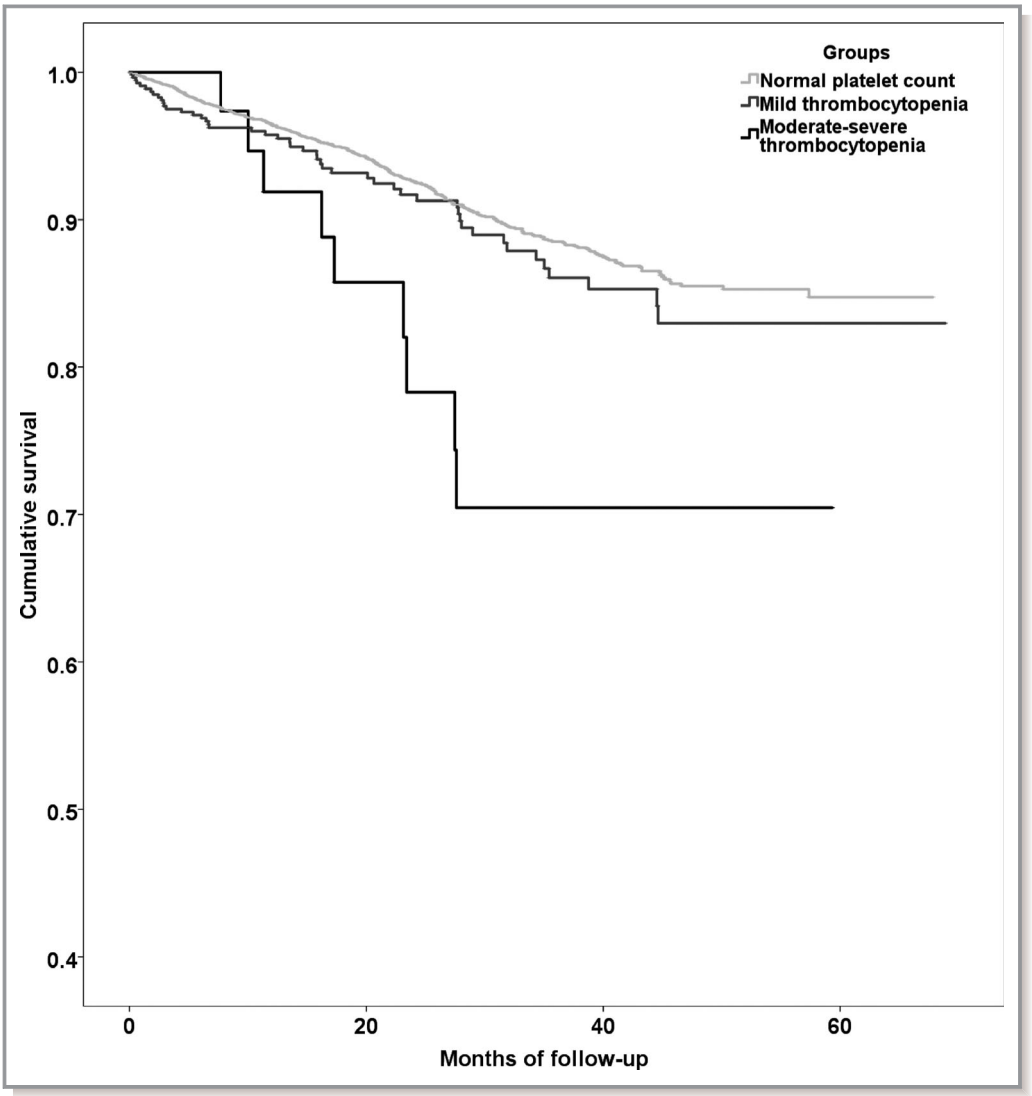

Figure. Kaplan-Meier curves for risk of mortality, according to the presence of thrombocytopenia.

Table 5. Cox Proportional Hazards Regression Analysis of Factors Associated With All-Cause Mortality

Variable	HR	95% Confidence Interval		*P* Value
		Lower	Upper	
Model A (adjusted for age and sex)				
Mild thrombocytopenia	1.169	0.859	1.591	0.320
Moderate-severe thrombocytopenia	2.232	1.147	4.342	0.018
Sex	0.841	0.686	1.032	0.097
Age	1.134	1.116	1.152	<0.001
Model B (adjusted for CHA_2DS_2 VASc score)				
Mild thrombocytopenia	1.259	0.930	1.704	0.136
Moderate-severe thrombocytopenia	2.431	1.254	4.713	0.009
CHA_2DS_2 VASc score	1.342	1.257	1.433	<0.001
Model C (stepwise fully adjusted)				
Aged ≥75 y	2.339	1.730	3.163	<0.001
Chronic kidney disease (Cr Cl <60 mL/min)	2.372	1.854	3.035	<0.001
Active cancer	2.855	1.869	4.360	<0.001
Diabetes mellitus	1.315	1.035	1.671	0.025
Heart failure	1.382	1.072	1.781	0.013
Pulmonary disease	1.513	1.180	1.941	0.001
Previous cardiovascular disease	1.351	1.047	1.744	0.021
Peripheral artery disease	1.845	1.345	2.531	<0.001
Antiarrhythmic drugs	0.764	0.593	0.984	0.037
Lipid-lowering drugs	0.608	0.477	0.774	<0.001
Diuretics	1.521	1.222	1.894	<0.001
Angiotensin receptor blockers	0.769	0.598	0.989	0.041

Cr Cl indicates creatinine clearance.

we found a decrease of platelet count according to age in men but not in women.

A mortality rate of 3.93%/year was registered in the present study, which is substantially in line with previous studies reporting an incidence of mortality ranging from 2.19%[17] to 5.15%.[18–20] At survival analysis, we found a progressive increase of mortality rate from 3.8%/year in patients with normal platelet count to 4.6% and 9.9% in patients with mild and moderate-severe thrombocytopenia, respectively. This association persisted after adjustment for CHA_2DS_2 VASc score but was lost at fully adjusted multivariable hazard Cox regression analysis. This suggests that some risk factors not currently used for thromboembolic risk stratification, such as chronic liver and kidney disease or active cancer, may be associated with thrombocytopenia. These factors should be evaluated in patients presenting with thrombocytopenia.

Thrombocytopenia has also been proposed as a risk factor for mortality in other clinical cardiovascular settings, such as patients experiencing an acute ischemic stroke,[21] a myocardial infarction,[22] or undergoing percutaneous coronary intervention.[23] However, mechanisms underlying this association have not been explored. Beyond platelet count, an important factor to be considered is platelet function, which may be increased by aging and cardiovascular risk factors.[24] Thus, in a previous study, patients with AF presenting with an increased urinary excretion of thromboxane B_2, a marker of systemic platelet activation, experienced a higher rate of cardiovascular events, independently from platelet count.[25]

Another interesting finding of the study is the inverse association between antiarrhythmic drugs and mortality. In particular, univariate analysis showed that propafenone and flecainide, but not amiodarone, were associated with a lower mortality rate. However, the low number of deaths in each group of antiarrhythmic users did not allow us to explore the association between mortality and single drugs. The association between antiarrhythmic drugs and relevant clinical outcomes, such as thromboembolism, heart failure, ischemic heart disease, and cardiovascular mortality, needs further research, mostly considering the potential adverse effects related to the use of these drugs.[26,27]

The studys has implications and limitations. The presence of thrombocytopenia in AF should be regarded as a marker of coexistence of comorbidities associated with poor survival. The reasons for men having less platelet count with a decline according to age should be further investigated. Another limitation of the study is the lack of information on the quality of anticoagulation in patients treated with VKAs. Finally, data reflect a cohort representative of the Italian population and cannot be transferred to another population. Furthermore, to better understand the role of thrombocytopenia in patients with AF taking oral anticoagulants, the association between thrombocytopenia and other end points, such as cardiovascular events and bleeding, should be further explored.

In conclusion, thrombocytopenia is frequent in patients with AF receiving treatment with oral anticoagulants. Despite an increased risk of mortality, thrombocytopenia may not represent *per se* a risk factor for mortality but may rather mirror the presence of comorbidities associated with poor survival.

Appendix

START2 Registry Investigators

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Disclosures

None.

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