

Major bleedings in mechanical prosthetic heart valves patients on Vitamin K antagonist treatment. Data from the PLECTRUM Study

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ABSTRACT

Patients with mechanical prosthetic heart valves (MHV) need vitamin K antagonist (VKA) treatment, due to the high thrombotic risk. The need to evaluate the bleeding risk of these patients is of great clinical relevance. This is an observational retrospective multicenter study among Centers affiliated to the Italian Federation of Anticoagulation Clinics on MHV patients, with the aim to evaluate the risk of major bleeding (MB) and associated risk factors. 2357 patients with MHV were included in the study, patients were followed for 24.081 pt-years; 246 patients had MB (rate 1.0×100 pt-yrs), 54 were intracranial hemorrhage (rate 0.22×100 pt-yrs). Patients with MB were significantly older, more affected by peripheral obstructive arterial disease (POAD) and atrial fibrillation (AF), and presented a history of previous MB, with respect to patients who did not bleed. Patients with MB showed a trend for lower time in therapeutic range (TTR), and a significant number of patients had a TTR in the lower quartile. Patients with MB had a higher mortality rate with respect to patients who did not bleed ($p=0.001$). The history of previous bleeding, the presence of POAD or of AF, and a TTR in the lowest quartile, were significantly associated with MB. MHV patients treated with VKAs followed by Anticoagulation Clinics, showed a low bleeding risk. Risk factors associated with major bleeding are older age, the presence of POAD or AF, the history of previous bleeding, and poor quality of anticoagulation. Patients who experienced MB during anticoagulation are at high risk of death.

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INTRODUCTION

Patients with mechanical heart valves (MHV) require long-term oral anticoagulant therapy with vitamin K antagonists (VKAs) for the high risk of valve thrombosis and systemic embolism.^{1,2} The number of implantations of MHV is dramatically reduced in the recent years in western countries, where widespread antibiotic treatment has reduced the incidence of rheumatic heart disease among young people. In these countries, the need for cardiac surgery is mainly due to degenerative valve disease occurring in elderly patients, in whom the use of biological valves is preferred.³⁻⁶ Instead, the need for heart valve prosthesis implantation is still a serious problem in low-income countries.⁷ Notwithstanding the reduction of MHV implantation in western countries, patients who carry a MHV need long-life anticoagulation and therefore a not negligible number of MHV patients are still on an-

ticoagulant treatment. Moreover, an increasing number of patients coming from low-income countries are now living in the west, due to the widespread immigration. After the premature stopping of the RE-ALING trial, where dabigatran was compared with warfarin in patients with prosthetic heart valves, due to the excess of bleeding and thrombotic events in the group of patients treated with dabigatran, VKAs are nowadays the unique treatment available for these patients.⁸ Therefore, the need to evaluate the bleeding risk of long-term anticoagulation is of great clinical relevance. For this reason, we performed the observational, retrospective, multicenter PLECTRUM study, whose results have been previously published.⁹

In this sub-study we aimed to evaluate the risk of bleeding in anticoagulated MHV patients and the associated risk factors.

MATERIALS AND METHODS

The FCSA-START Valve Study (PLECTRUM) is an observational retrospective multicenter study performed within the Italian Survey on anticoagulated patients Register (START Register),¹⁰ and conducted among 33 Centers affiliated to the Italian Federation of Anticoagulation Clinics (FCSA). Centers were asked to select from their databases patients in whom a mechanical heart valve prosthesis or a bio-prosthesis was implanted after 1990 and who were followed for the management of anticoagulation; 3029 patients were enrolled in the study, of whom 2357 patients received MHV implantation. Methods have been previously described.⁹ Briefly, participating Centers followed patients for the management of anticoagulation after hospital discharge. All Centers adhere to FCSA and participate in the specifically designed laboratory external quality control program, which is run 3 times per year and uses lyophilized plasma samples obtained from anticoagulated patients.¹¹ At enrollment, patients' demographic information and clinical data were collected. The center provides regular INR measurements, prescribes the daily VKA dosages and schedules the date for the subsequent visits. According to the routine practice of the participating centers, follow-up visits were scheduled every 2 to 4 weeks for INR monitoring. Patients who missed check-ups for >2 months were contacted (personally or through their family or general practitioner), and the reason for interrupting treatment monitoring was recorded. The occurrence of bleeding or thrombotic complications during follow-up is recorded. Major Bleeding (MB) was defined accordingly with the definition reported by Palareti *et al.*, in use in Italian centers during the study period:¹² fatal (death due to hemorrhage); intracranial (documented by imaging), ocular (with blindness), articular, or retroperitoneal; if surgery or angiographic intervention was required to stop bleeding; and if bleeding led to hemoglobin

reduction of 2 g/dL or more and/or need for transfusion of two or more blood units. Follow-up started at enrollment and was stopped at patient's death, at the occurrence of the first adverse event or when a patient was no longer monitored by the participating Center.

The quality of anticoagulation control was calculated as Time in Therapeutic Range (TTR) by using the linear interpolation method by Rosendaal *et al.*¹³ TTR was analyzed considering the INRs recorded in the last year of follow-up, and the intended anticoagulation ranges referred to the last year of follow-up for the examined patients.

The present study was approved by the local Institutional Committees on Human Experimentation.

Statistical analysis

Baseline characteristics were summarized with descriptive statistics. Categorical variables were reported as counts and percentages and continuous variables were expressed as median and interquartile range (IQR). Incidence rates of adverse events were calculated as the number of events per 100 patient-years of observation, and rate ratios were given with their 95% confidence intervals (CI). For this calculation, observation started at the beginning of the follow-up and ended when patients experienced either death, a major outcome or stopped regular monitoring at the participating Center. Analyses were performed with the Fisher exact test (for categorical data), the unpaired t test (for normally distributed data), and the Mann-Whitney test (for non-normally distributed data). All variables found to be significant at univariable analysis were subsequently entered into a multivariable analysis. Risk was expressed as odds ratio (OR) with 95% CI. A 2-sided value of $p < 0.05$ was chosen for statistical significance. Kaplan-Meier survival curves for bleeding events were also provided.

We used the SPSS version 25 software (SPSS Inc, Chicago, IL, USA) and the Stata version 14 software (Stata Corp, College Station, TX) for Windows for data processing.

RESULTS

A total of 2357 patients with MHV were included in the PLECTRUM study, for a total of 24,081 patient-years of observation. Clinical characteristics of this cohort are reported in Table 1. Among these patients, 246 MBs were recorded during the observation period, with a rate of 1.0×100 patient-years (pt-yrs). As detailed in Table 2, 54 of these events were intracranial hemorrhage (ICH) (rate 0.22×100 pt-yrs). Among patients who experienced MB, 40 died during follow-up: 12 patients for MB, 18 for heart failure, 1 for stroke, 2 for cancer, 2 for respiratory failure

and 3 for sudden death; in 2 patients in whom MB was excluded, the cause of death was not reported.

Co-morbidities and risk factors for bleeding in patients who experienced MB and who did not, are reported in Table 3. Patients with MB were significantly older, more frequently affected by peripheral obstructive arterial disease (POAD) and atrial fibrillation (AF), and more often presented a history of previous MB with respect to patients who did not bleed (Figure 1A). Moreover, among patients with MB a trend for lower time in therapeutic range (TTR) was present, and a higher number of patients, even if not statistically significant had a TTR in the lower quartile (Figure 1B). Patients with MB showed a higher mortality rate with respect to patients who did not bleed (rate 1.35×100 pt-yrs and 0.6×100 pt-yrs, respectively; Relative Risk 2.1, 95% CI 1.4-3.0; $p=0.000$).

We performed a univariate and multivariate analysis for risk factors associated with MB (Table 4), and found that history of previous bleeding, presence of POAD or AF, and TTR in the lowest quartile were significantly associated with MB.

Table 1. Characteristics of the whole cohort.

	Number (%)
All patients	2357
Males, n (%)	1301 (55.2)
Median age at implantation (years) (IQR)	59.0 (49.7-65.7)
Site of prosthesis valve, n (%)	
Aortic	1408 (59.7)
Mitral	682 (28.8)
Mitral-aortic	267 (11.5)
Vitamin K antagonist, n (%)	
Warfarin	1929 (81.8)
Acenocoumarol	428 (18.2)
Follow-up	
Median follow-up (years) (IQR)	9.7 (5.0-14.1)
Total follow-up (pt-yrs)	24,081
Adverse events during follow-up, (rate $\times 100$ pt-yrs)	
Major bleeding	246 (1.0)
Stroke/TIA/peripheral embolism	164 (0.7)

IQR, interquartile range.

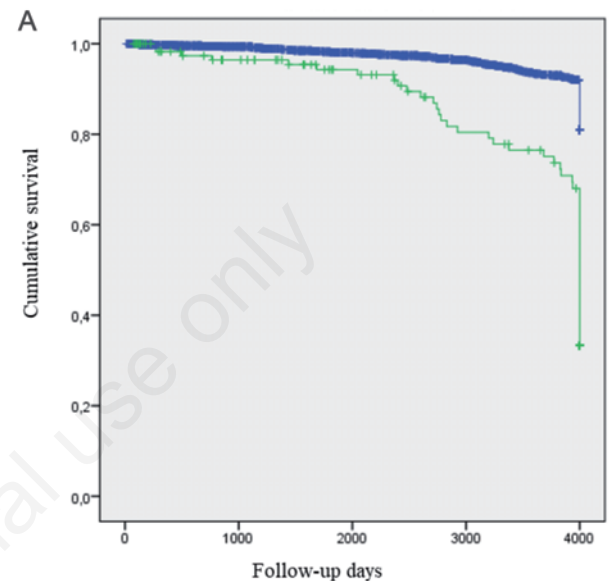
Table 2. Type of major bleedings.

	Number (%)
Total bleedings	246
Fatal	12 (4.9)
Gastrointestinal bleeding	78 (31.7)
Intracranial hemorrhage	54 (22.0)
Muscular hematoma	36 (14.6)
Hb drop >2 g/dL and/or transfusion ≥ 2 RBC units	29 (11.8)
Other Bleeding	49 (19.9)

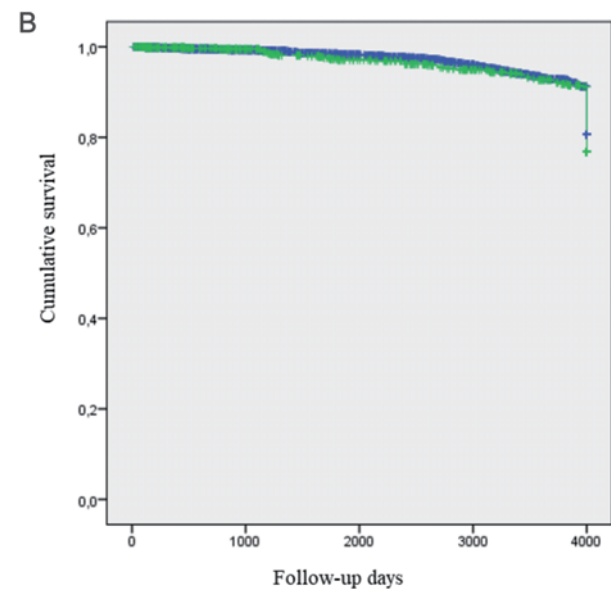
Hb, hemoglobin; RBC, red blood cell.

DISCUSSION

The principal finding of this observational study is the low rate of bleeding in patients with MHV on long-term anticoagulation with VKA followed by Anticoagulation



Green line = patients with history of bleeding event
Blue line = patients without history of bleeding event



Green line = patients on lower TTR quartile
Blue line = patients on normal TTR

Figure 1. Cumulative survival of major bleeding A) in relation to the history of bleeding event, B) in relation to lower quartile of INR (TTR $<47\%$).

Clinics. Among patients who experienced MB, one fifth had intracerebral bleedings, and the overall mortality rate of MBs was 4.9%, so confirming the low rate of serious bleeding complications. Cannegiter *et al.* in 1994 found

a rate of major bleeding of 1.9 per 100 patient-years (95% CI, 1.7 to 2.0), with a rate of intracerebral bleeding of 0.5 per 100 patient-years. The wide-ranged target INR-levels with older generation MHV may have contributed to these

Table 3. Characteristics of patients with and without major bleedings.

	Major bleeding N, 246 (%)	No major bleeding N, 2111 (%)	p value
Age years (IQR)	60.7 (52.3-67.0)	58.8 (49.6-65.6)	0.03
Females	117 (47.6)	941 (44.5)	0.5
Hypertension	168 (68.3)	1284 (60.8)	0.2
Diabetes mellitus	37 (15.0)	260 (12.3)	0.6
Coronary artery disease	36 (14.6)	254 (12.0)	0.6
Peripheral obstructive arterial disease	25 (10.2)	86 (4.1)	0.000
Heart failure	13 (5.3)	152 (7.2)	0.2
Atrial fibrillation	115 (46.7)	793 (37.6)	0.006
Previous ischemic stroke/TIA	25 (10.2)	152 (7.2)	0.3
Previous major bleed	42 (17.1)	44 (2.1)	0.000
Aspirin treatment	31 (12.6)	206 (9.8)	0.3
Target INR \geq 3.0	168 (69.1)	1518 (71.8)	0.3
Mitralic or mitro-aortic valve	99 (40.2)	850 (40.3)	1.0
Renal failure (eGFR <30mL/min)	1 (0.4)	25 (1.2)	0.3
eGFR <60 mL/min	44 (17.9)	352 (16.7)	0.6
TTR in the lowest quartile	77 (31.3)	490 (23.2)	0.01
TTR median (IQR)	56 (44-73)	61 (8-74)	0.07
Anemia (Hb <10 g/dL)	15 (6.1)	105 (5.0)	0.4
Platelet count <100,000/mL	5 (2.0)	21 (1.0)	0.2

Hb, hemoglobin; IQR, interquartile range.

Table 4. Univariate and multivariate analysis of risk factors associated with major bleeding.

	Univariate analysis		Multivariate analysis,
	OR (95%CI)	p value	p value
Females	1.1 (0.8-1.4)	0.5	
Age >59 years	1.4 (1.0-1.8)	0.02	0.2
Hypertension	1.2 (0.9-1.7)	0.2	
Diabetes mellitus	1.1 (0.8-1.6)	0.6	
Coronary artery disease	1.1 (0.7-1.6)	0.6	
Peripheral obstructive arterial disease	2.5 (1.6-4.0)	0.000	0.001
Heart failure	0.7 (0.4-1.2)	0.2	
Atrial fibrillation	1.5 (1.1-1.9)	0.004	0.04
Previous ischemic stroke/TIA	1.3 (0.8-2.1)	0.3	
Previous major bleeding	8.7 (5.6-13.6)	0.000	0.000
Renal failure (eGFR <30 mL/min)*	0.3 (0.5-2.5)	0.3	
eGFR <60 mL/min	1.1 (0.8-1.7)	0.6	
Mitral valve	1.0 (0.8-1.3)	0.9	
INR range 2.5-3.5	1.2 (0.6-2.3)	0.6	
TTR <47%	1.5 (1.1-2.0)	0.009	0.05
Aspirin treatment	1.2 (0.8-1.8)	0.3	
Anemia (hemoglobin <10 g/dL)	1.3 (0.7-2.3)	0.4	
Platelet count <100,000/mL	2.0 (0.7-5.4)	0.2	

*Calculated with Cockcroft-Gault formula.

findings. More recently, several studies have demonstrated that the risk of bleeding outweighs the risk of thromboembolism when standard target INR are maintained,^{14,15} while it is more balanced when lower INR target are indicated. A recent Sweden study reported a bleeding risk of 2.6 per 100 patient-years in patients with aortic MHV and 3.9 per 100 patient-years in patients with mitral MHV, despite the optimal anticoagulation levels obtained (TTR >70%).¹⁶ However, previous data reported from the same group, showed elevated median TTR with intense anticoagulant treatment among Swedish patients.¹⁷ As a matter of fact, in this study the Authors reported a high median INR and high percentage of time spent above the therapeutic range, both these conditions could be associated with the high bleeding risk found in the study.

The risk factors significantly associated with bleeding were the presence of POAD, of AF, a suboptimal anticoagulation control expressed by a TTR in the lowest quartile, and a history of previous bleeding. In particular, history of previous bleeding and POAD are the factors showing the highest ORs for the occurrence of MB. The history of previous bleeding is a well-known risk factor for bleeding and it is included in most of the published bleeding scores.¹⁹⁻²¹ Therefore, patients who suffered previous bleeding should be carefully studied to identify and correct clinical conditions associated with the risk of bleeding. This observation reinforces the indication to make any effort to identify and correct modifiable bleeding risk factors, such as uncontrolled hypertension.²² Moreover, particular attention should be paid to patients who experienced gastro-intestinal bleeding, who need periodic hemoglobin levels control and occult blood testing, in addition to a careful use of proton-pump inhibitors.^{23,24}

The high bleeding risk of patients with POAD was previously reported in the ISCOAT study.¹² This was confirmed later in the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial among patients randomized to oral anticoagulation and antiplatelet therapy versus antiplatelet therapy alone, where there was an increase in bleeding endpoints including life-threatening and intracranial bleeding.²⁵ The *AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease* recommend that anticoagulation should not be used in patients with POAD²⁶. Enhanced bleeding risk was also associated with a suboptimal quality of anticoagulation, in particular in patients with a TTR in the lowest quartile, whereas only a trend for lower median TTR was found in bleeding patients. This finding is not surprising because the high instability of patients with low TTR has been reported⁹. Finally, the presence of AF was associated with a higher bleeding risk. The use of antiarrhythmic drugs, such as amiodarone, and/or the occurrence of acute heart failure episodes associated with the arrhythmia, may possibly enhance anticoagulation instability and favor

bleeding.²⁷ Moreover, patients of our cohort who experienced MB also showed a trend (not statistically significant) to a higher incidence of several cardiovascular risk factors, such as hypertension, diabetes mellitus, coronary artery disease, ischemic cerebrovascular disease. These associations could explain, at least in part, the higher mortality recorded in these patients.

In our cohort, among patients with MB, one fifth had intracerebral bleedings with a rate of 1/500 patient-years, and the overall mortality rate of MB was 4.9%. These data regarding severe events are in contrast with the widespread trend to avoid the use of MHV due to the fear of long-term anticoagulation, in favor of the use of biological valves, that could lead to an elevated risk of re-intervention in particular among patients aged < 65 years.^{3,5,28} Patients with biological heart valves frequently develop atrial fibrillation, therefore they require long-term anticoagulation. It is interesting to note that, among patients with biological heart valves enrolled in the PLECTRUM study, we found a bleeding risk similar to that of MHV patients.²⁸

Study limitations

We are aware of the limitations of our study. Firstly, this is an observational retrospective cohort study, and therefore we could not adjust for clinical information that were not recorded. Secondly, the observational nature of the study could have enhanced the risk of underreporting adverse events. However, patients included in the study were followed by the Anticoagulation Clinics for many years, suggesting a stable patient-doctor relation and careful adverse event reporting. Moreover, participating Centers routinely carry out periodic checks with patients who miss the planned controls.

CONCLUSIONS

In conclusion, patients with MHV on long-term oral anticoagulation with VKAs followed by Anticoagulation Clinics, showed a low bleeding risk. Risk factors associated with major bleeding are the presence of POAD, of AF, the history of previous bleeding, and a poor quality of anticoagulation. Patients who experienced MB during anticoagulation are at high risk for death.

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