

openheart Risk of reoperation in bioprosthetic valve patients with indication for long-term anticoagulation. Results from the observational retrospective multicentre PLECTRUM study

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ABSTRACT

Objective Several factors should be considered when a prosthetic heart valve, bioprosthetic valve (BV) or mechanical valve is to be implanted: thrombogenicity, life expectancy and the risk of reoperation.

Methods We conducted an observational retrospective multicentre study among Italian Thrombosis Centers on patients with BV on long-term vitamin K antagonist (VKA) treatment to evaluate the risk of reoperation and the rate of bleeding and thrombotic events.

Results We analysed 612 patients (median age 71.8 years) with BV on long-term VKA treatment for the presence of atrial fibrillation (AF) (78.4%) or other indications (21.6%). Thirty-four major bleeding events (rate 1.1×100 patient-years) and 29 thromboembolic events (rate 0.9×100 patient-years) were recorded, and 46 patients (rate 1.5×100 patient-years) underwent reoperation. The rate of reoperation was higher among younger patients: 32.9% in patients <60 years and 3.9% in patients ≥60 years (relative risk (RR) 3.8, 95% CI 2.1 to 7.2; p=0.0001). When patients were analysed according to age <65 or ≥65 years and <75 or ≥70 years, younger patients still were at higher risk for reoperation (RR 3.1, 95% CI 1.7 to 6.0 and 3.7, 95% CI 1.7 to 8.6, respectively). **Conclusions** Our findings suggest that the threshold of 65 years for implanting a BV should be carefully evaluated, considering the high risk for reoperation and the high risk of AF occurrence with persisting need for long-term anticoagulation. The high risk for reoperation of young patients implanted with BV and the availability of a safer and easier way to conduct VKA treatment, such as the use of point-of-care devices, should be considered when the type of valve must be chosen.

INTRODUCTION

The selection of the type of valve, bioprosthetic valve (BV) or mechanical valve (MV), in patients who need valve replacement is an important decision that seriously influences

Key questions

What is already known about this subject?

- ▶ Bioprosthetic valve duration is considered on average 15 years when implanted in elderly patients; however, the lifespan of these valves is shorter among younger patients.
- ▶ Clinical guidelines recommend the use of mechanic prosthesis in young patients.

What does this study add?

- ▶ Reoperation in young patients who have received bioprosthetic valve implantation is a frequent event.
- ▶ In our cohort the relative risk of reoperation among patients aged 60–70 years was more than three times higher with respect to older patients.

How might this impact on clinical practice?

- ▶ Bioprosthetic valves are implanted to avoid the burden due to long-term anticoagulation, but the frequent occurrence of atrial fibrillation may nullify this advantage.
- ▶ These patients need to be anticoagulated with vitamin K antagonists.
- ▶ Self-monitoring and self-management is a safe option that should be offered to these patients.

the quality of life of patients, who should be actively involved in this choice.¹ Several factors should be considered for this decision, mainly thrombogenicity, life expectancy and the risk of reoperation. Because of thrombogenicity, mechanical prostheses require lifelong anticoagulation and expose the patient to both bleeding risk and thrombus formation, particularly when anticoagulation is not well managed. On the other hand, mechanical prostheses have a longer lifespan, reducing the risk of reoperation that is the main limitation to BV implantation. BV



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duration is considered to be on average 15 years when implanted in elderly patients; however, the lifespan of these valves is shorter among younger patients who show accelerated valve deterioration.² For this reason, clinical guidelines recommend the use of MV prosthesis in young patients, indicating the age of less than 60 years as the optimal age for the implantation of this kind of valve. However, uncertainty still exists for the choice of the type of valve for patients in the lifespan between 60 and 70 years, and recommendations differ from European and American guidelines.^{1,3} European guidelines recommend to use BV after the age of 65 years,¹ with uncertainty for patients aged 60–65 years. Instead, American guidelines recommend the use of BV after the age of 70 years, with an interval of uncertainty for patients between 60 and 70 years.³ The use of BV has significantly increased over the last years. In the UK the number of BV implantations grows from 65.4% to 77.8% between 2004 and 2009.⁴ Similarly, the rate of BV implantation increased in the Netherlands between 1995 and 2010⁵ and in the USA between 1999 and 2011⁶ even among patients aged 55–64 years, despite the different guideline recommendations.^{1,3}

Moreover, with respect to the need for long-life anticoagulant treatment, it should be noted that a large number of elderly patients develop other indications to anticoagulation, mainly atrial fibrillation (AF), so losing the advantages of carrying a BV.² According to the longer life expectancy that has been recorded in Western countries in the recent years, the incidence of AF is progressively growing particularly among patients with heart valve diseases, leading to an increasing need for anticoagulation to prevent thromboembolic stroke. Therefore, a growing number of patients who received BV implantation did not stop anticoagulation after the first few months after surgery, but are maintained on long-term treatment. We have conducted an observational, retrospective, multicentre study among Italian Thrombosis Centers on patients on long-term anticoagulation for the presence of prosthetic heart valves to obtain information on the adverse events occurring during follow-up. In this study, we report data on patients with BV on long-term vitamin K antagonist (VKA) treatment for the presence of AF or other indications, with the aim of evaluating the risk of undergoing reoperation and the rate of bleeding and thrombotic events during anticoagulation.

METHODS

The FCSA-START Valve Study (PLECTRUM) is an observational retrospective multicentre study performed in the frame of the START Register (Italian Survey on Anticoagulated Patients Register) (NCT02219984)⁷ conducted among 33 centres affiliated to the Italian Federation of Anticoagulation Clinics (FCSA). Centres were asked to select from their database patients in whom a mechanical or biological heart valve prosthesis was implanted after 1990 and who were followed for the management

of anticoagulation treatment. Six hundred and twelve patients who received BV implantation and who have indication to maintain anticoagulation after the standard course of 3 months were enrolled. Patients followed by FCSA centres for anticoagulant management receive adequate education on the purpose of the treatment, the risk of complications, international normalised ratio (INR) values and drug dosage management. The centres perform periodic INR measurements, prescribe the daily VKA dosages and schedule the date for the subsequent visits; they monitor and record changes in patients' habits, diet, comedications, intercurrent illnesses, bleeding and thrombotic complications during follow-up through patient interviews. All centres take part in the specifically designed laboratory external quality control programme, which runs three times yearly and uses lyophilised plasma samples obtained from anticoagulated patients.⁸

Patients

Patients' demographic information and clinical data were collected. Patients were classified as hypertensive if they were taking medications to lower blood pressure. Diabetes mellitus was defined according to American Diabetes Association criteria.⁹ Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Heart failure was defined as the presence of signs and symptoms of right or left ventricular failure or both and confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction.

Follow-up and endpoints

In the routine practice of the participating centres follow-up visits were scheduled every 2–4 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. In the case of death, further information about its cause was requested. Deaths for all causes were recorded. The major endpoint of the study was the occurrence of reoperation. The characteristics of these patients, the cause of reoperation and the time intercourse from the first prosthetic valve implant were recorded. Secondary endpoints were thrombotic event (stroke, transient ischaemic attack (TIA), peripheral emboli, valve thrombosis) and major bleeding. Stroke was defined as a syndrome characterised by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, lasting >24 hours, and with no apparent cause other than vascular. Ischaemic stroke was defined as a stroke with either a normal brain CT or evidence of a recent infarction in the clinically relevant area of the brain on a CT or MR scan within 3 weeks of the event, while TIA was diagnosed when neurological defects lasted <24 hours. Peripheral embolism was diagnosed when proved with angiography or thrombectomy. Major bleeding was defined accordingly with the definition reported by Palareti *et al.*,¹⁰ taking into account

the definition in use in Italian centres in the study period. Follow-up was stopped after the first adverse event occurred or when a patient was no longer monitored by the participating centre.

Statistical analysis

Baseline characteristics were summarised with descriptive statistics. Categorical variables were reported as counts and percentages and continuous variables were expressed as median and 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% CIs. For this calculation, observation started at the beginning of follow-up and ended when patients experienced a major outcome or were censored. Analyses were performed with the Fisher's exact test (categorical data), unpaired t-test (normally distributed data) and Mann-Whitney test (non-normally distributed data). All variables found to be significant at univariate analysis were subsequently entered in a multivariate analysis. Risk was expressed as OR with its 95% CI. A two-sided value of $p < 0.05$ was chosen for statistical significance.

The SPSS software for Windows V.20 (SPSS) and Stata V.14 statistical software package (StataCorp, College Station, TX) were used for data processing.

RESULTS

We analysed 612 patients (52.9% men, median age 71.8 years) with BV who were on long-term VKA treatment for the presence of AF (78.4%) or other indications to anticoagulation (21.6%). Patients were followed up for a median time of 2.4 years. The characteristics of patients are listed in table 1. During follow-up 38 patients died: 6 for major bleeding, 1 acute myocardial infarction, 1 for sudden death, 6 for sepsis, 5 for cancer, 6 for unknown reasons and 13 for heart failure. Among the patients who died of heart failure, two underwent reoperation for structural valve deterioration and died a few months later, two were implanted at 51 and 59 years, and nine after 70 years of age. For these 11 patients no information on valve deterioration is available. Thirty-four major bleeding events (rate 1.1×100 patient-years) and 29 thromboembolic events (rate 0.9×100 patient-years) were recorded. Forty-six patients (7.5%, rate 1.5×100 patient-years) undergo reoperation: 11 (24%) for endocarditis and 35 (76%) for structural valve deterioration (table 2). Reoperation occurred a median time of 84 months after prosthesis implantation. This interval was shorter (median time 14 months) for patients who needed reoperation for infections with respect to patients with structural valve deterioration (median time 9.2 years). The percentage of reoperation was higher among younger patients: 32.9% among patients < 60 years and 3.9% among patients ≥ 60 years (relative risk RR 3.8, 95% CI 2.1 to 7.2, $p = 0.0001$). When patients were analysed according to age < 65 or ≥ 65 years and < 70 or ≥ 70 years, younger patients still were at higher risk for reoperation (RR 3.1, 95% CI 1.7 to 6.0,

Table 1 Characteristics of patients with biological heart prosthesis and adverse events during anticoagulant treatment

n	612
Male (%)	324 (52.9)
Median age (range)	71.8 (24–89)
Total follow-up (patient-years)	3085
Median follow-up (range)	2.4 (0.5–7.5)
Indications for long-term anticoagulation, n (%)	
Atrial fibrillation	480 (78.4)
History of stroke/TIA	13 (2.1)
Cardiac diseases	22 (3.6)
Other indications for VKA	6 (1.0)
Unknown	91 (14.8)
Clinical characteristics, n (%)	
Hypertension	438 (71.6)
Diabetes mellitus	121 (19.8)
Coronary artery disease-peripheral arteriopathy	246 (40.2)
Heart failure	124 (20.3)
Previous stroke/TIA	77 (12.6)
Antiplatelet treatment	195 (31.9)
Adverse events, n (rate)	
Major bleeding	34 (1.1)
Stroke/TIA	29 (0.9)
Death	36 (1.2)

TIA, transient ischaemic attack; VKA, vitamin k antagonist.

$p = 0.0001$ and 3.7, 95% CI 1.7 to 8.6, $p = 0.0001$, respectively). Patients who needed reoperation were similar to patients who did not for associated comorbidities, except for age and the presence of AF (table 3).

DISCUSSION

Choosing the optimal heart valve prosthesis is a challenging decision, in particular to middle-aged patients, due to the limited duration of BVs and to the increased life expectancy of the population, with a prolonged active life. The principal finding of this multicentre retrospective observational study is the confirmation that reoperation among young patients who have received BV implantation is a frequent event. In our cohort, the RR of reoperation among patients aged 60–70 years was more than three times higher with respect to older patients. The need for reoperation after BV implantation is the consequence of infective endocarditis or of structural valve deterioration. Endocarditis affects similarly patients with BV and patients with MV, with a reported risk ranging from 0.24 to 0.54×100 patient-years.¹¹ Instead, structural valve deterioration is a rare complication among patients with MV and a frequent event among patients with BV.

Table 2 Characteristics of patients undergoing valve prosthesis reimplantation

n (%)	46 (7.5)
Median age (range)	59.9 (24–79)
Male, n (%)	24 (52.2)
Median time interval to reimplant (months)	84 (1–312)
Site of first implantation, n (%)	
Aortic	30 (65.2)
Mitral	14 (30.4)
Mitroaortic	2 (4.3)
Median time interval to reoperation (months)	84 (1–312)
Cause of reoperation, n (%)	
Infection	11 (23.9)
Prosthetic valve deterioration	35 (76.1)
Median time interval to reimplant, months (range)	
Due to infection	14 (2–72)
Due to valve deterioration	114 (1–312)
Median age of patients, years (range)	
With infections	69.8 (31–78)
With structural valve deterioration	55.8 (24–79)

BVs have an expected life of average 15 years.² A rate of reoperation due to structural valve deterioration has been reported in 1.9% of patients after 10 years and in 15% at 20 years.¹² Accordingly, a study from Chiang *et al*¹³

Table 3 Clinical characteristics of patients with and without reoperation

	Patients without reoperation (n=567)	Patients with reoperation (n=45)	P values
Median age (range)	72.6 (27–89)	56.7 (24–79)	0.0001
Valve position, n (%)			
Aortic	335 (59.1)	29 (64.4)	
Mitralic	157 (27.7)	14 (31.1)	
Both	75 (13.2)	2 (4.5)	0.2
Comorbidity, n (%)			
Hypertension	402 (70.9)	36 (80.0)	0.4
Diabetes mellitus	110 (19.4)	11 (24.4)	0.6
Coronary artery disease	131 (23.1)	13 (28.9)	0.5
Atrial fibrillation	450 (79.4)	30 (66.7)	0.05
Previous stroke/TIA	69 (12.2)	8 (17.8)	0.3
Heart failure	113 (19.9)	11 (24.4)	0.7
eGFR <30 mL/min	12/273 (4.4)	1/26 (3.8)	1.0
Smoking habitus	118 (20.8)	12 (26.7)	0.4
Antiplatelet treatment	185 (32.6)	10 (22.2)	0.2

eGFR, estimated glomerular filtration rate; TIA, transient ischaemic attack.

reported a rate of reoperation of 12.1% after 15 years. More recently, Goldstone *et al*¹⁴ reported a percentage of reoperation of 14.8% among patients aged <70 years, similarly to the percentage recorded in our study. Reoperation carries a high mortality rate,^{13 15 16} even if the use of minimal access approaches may reduce this risk. Similarly, the recent availability of the technique of valve-in-valve procedure in patients with structural valve deterioration is an option to be considered to lower the risk of reoperation.^{17 18} However, there is limited experience with this procedures and long-term follow-up is limited.¹⁹

When an MV is implanted the need for reoperation is rare^{14 20}; however, long-term anticoagulation is required to avoid thrombus formation. The bleeding risk associated with anticoagulation is a limitation to use of MVs, influencing patients and physicians' choice. Bleeding risk is reduced when anticoagulation intensity is lower²¹ and when adequate INR monitoring is achieved.^{22 23} With the introduction of direct oral anticoagulants (DOAC), which showed to be non-inferior to VKAs for stroke prevention with a significant lower bleeding risk in patients with AF, it was expected a similar improvement even in patients with prosthetic heart valves. However, the results of RE-ALIGN trial²⁴ demonstrated an increase of both bleeding and thrombotic risks among patients with MV, leading to the premature stopping of the trial. At the moment, no large randomised trials on the use of DOACs in patients with MV are ongoing and these patients need to be anticoagulated with VKAs. Therefore, with increased frequency BVs are implanted to avoid the burden due to long-term anticoagulation. The frequent occurrence of AF may nullify this advantage. AF is a frequent cardiac arrhythmia at high embolic risk and there is strong evidence of the advantage of anticoagulation for stroke prevention.²⁵ Its incidence is growing with age and there are no studies that evaluate the outcomes of patients with BV already on anticoagulation because of AF,² even if it should be noted that these patients, although different from MV patients, can be treated also with DOACs.²⁵ VKAs have been demonstrated to be highly effective in the prevention of thromboembolism among patients with MVs and are still used by millions of patients worldwide.²⁶ It has been well defined that a strong association exists between the quality of anticoagulation control, evaluated as time in therapeutic range (TTR),²⁷ and the occurrence of adverse events.²⁸ Among patients with MV on long-term VKA treatment the direct involvement of the patient itself in the management of the anticoagulation has been successfully reported. The availability of accurate point-of-care devices allows the self-testing by the patients, who can have the INR results managed by the responsible physician (self-testing) or can be trained to adjust the drug dosage according to the INR results (self-management). This modality has been widely used in Germany due to the availability of reimbursement for these devices in this country. A higher TTR was obtained among patients on self-management compared with patients on routine care monitoring.²⁹ Moreover, it has

been reported that self-monitoring was superior to usual care with 49% (HR 0.51, 95% CI 0.31 to 0.85) risk reduction of thromboembolic events.³⁰ The advantage over the routine care was higher mainly among younger patients and particularly in those with MVs.³⁰ Patients with MV are younger than patients on VKAs for other indications, and are highly aware of thromboembolic risks, with particular willingness to simplify their treatment and have a better quality of life. It should be noted that bleeding rates are not reduced among patients on self-monitoring, and no major effect on mortality has been reported.²² Several studies show that self-monitoring and self-management is a safe option for suitable patients and this is an option that should be offered to all patients who need long-term VKA treatment.²²

LIMITATIONS

We are aware of the limitations of our study. First, this is an observational retrospective cohort study, and therefore we could not adjust for clinical information that was not recorded. Second, our observation excluded patients without indication to long-term anticoagulation. Therefore, we cannot evaluate the outcome of these patients. Third, for 11 patients no information on valve deterioration was available.

The strengths of our study are the multicentre design, and the prospective recording of the adverse events and of anticoagulation history routinely done by participating centres in electronic databases.

In conclusion, our findings suggest that the threshold of 65 years for implanting a BV should be carefully evaluated, considering the high risk for reoperation and the high risk of AF occurrence with persisting need for long-term anticoagulation. The high risk for reoperation of young patients implanted with BV and the availability of a safe and easy way to conduct VKA treatment should be considered when the type of valve must be chosen.

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Contributors DP designed the study, collected the data, analysed and interpreted the data, and drafted the manuscript. EA collected the data, analysed and interpreted the data, and drafted the manuscript. EG, NM, ST, CL, DB, AI, FM, CP, EB and PP contributed to the data collection. VP and GP revised the draft of the manuscript critically for important intellectual content and finally approved the submitted manuscript.

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