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Sex-based difference in anticoagulated patients with mechanical prosthetic heart valves and long-term mortality risk.

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Sex-based difference in anticoagulated patients with mechanical prosthetic heart valves and long-term mortality risk.

Running title: mechanical heart valves and mortality in women

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Abstract

Background. Vitamin K antagonists (VKAs) reduces thromboembolism in patients with mechanical prosthetic heart valves (MPHV). It is unclear whether a sex-based difference in MPHV patients regarding valve site, anticoagulation quality and mortality risk do exist.

Methods. We analysed 2,111 MPHV patients from the nationwide PLECTRUM study promoted by the Italian Federation of Anticoagulation Clinics (FCSA). We analysed the site of MPHV, anticoagulation quality, as assessed by the time in therapeutic range (TiTR) and mortality risk in women and men.

Results. The mean age of the patients was 56.8±12.3 years. Women were older with a lower prevalence of ischemic heart disease and smokers and a higher prevalence of atrial fibrillation at baseline. Aortic MPHV was more frequent in men (74.7% vs. 43.3%, p<0.001), whereas mitral (41.1% vs 17.6%, p<0.001) and mitro-aortic (15.6% vs. 7.7%, p<0.001) MPVH in women. The association between **female sex and mitral/mitro-aortic site remained at multivariable logistic regression analysis (Odds Ratio 3.623, 95% Confidence Interval [CI] 2.947- 4.455, p<0.001). Regarding anticoagulation quality, women showed lower mean TiTR (63.0±19.4 vs. 57.5±19.2, p<0.001), and a higher proportion of TiTR <60% (54.9% vs. 43.3%, p<0.001).**

During a mean follow-up of 123 months (21,665 pt-years), 152 deaths occurred (0.7%/year); 83 in the aortic (0.63%/year) and 69 in the mitral/mitro-aortic (0.81%/year) group. At multivariable Cox proportional hazard regression analysis, female sex was not associated with mortality (HR 0.953, 95%CI 0.678 1.340, p=0.783).

Conclusions. Female sex is independently associated with mitral/mitro-aortic MPHV. **Despite a lower TiTR in women, mortality risk did not differ between the two groups.**

Key words. Women, anticoagulation, time in therapeutic range, mechanical heart valve prosthesis, mortality.

Introduction

Valve replacement with biological or mechanical prosthetic heart valves (MPHV) represent a therapeutic option which allowed a marked improvement in long-term prognosis of patients with valvular heart disease, with MPHV possibly being associated with a slightly better 10- and 15-year survival than biological valves in patients aged 50-70 years[1] and lower valve-related morbidity[2]. In a large study performed in the 90's including elderly high-risk patients undergoing valve replacement, the incidence rate of mortality in the group of MPHV receivers was 9.6%/year[3]. However, the types of MPHV have changed over the last decades with the new bi-leaflet MPHV having less thrombogenicity[4], and no data on antithrombotic treatments, in particular on oral anticoagulation, were reported in those studies. This last point is particularly important as MPHV patients require long-term oral anticoagulation therapy with vitamin K antagonists (VKAs) to reduce the risk of valve thrombosis, thromboembolism and mortality[5,6]. The efficacy of VKAs therapy depends on the quality of oral anticoagulation, as assessed by the Time in Therapeutic Range (TiTR), which may modify the risk of clinical outcomes, including thromboembolism, myocardial infarction, major bleeding and mortality[7-10]. One previous analysis from the PLECTRUM cohort showed however a consistently suboptimal TiTR in this patient population, with international normalized ratio (INR) ranges above 2.0-3.0 being consistently associated with poor anticoagulation quality[11].

Another unexplored issue is if a sex-based difference in MPHV site and outcomes does exist. Thus, in patients with non-valvular atrial fibrillation (AF), female sex has been associated with an increased risk of subtherapeutic anticoagulation[12], but data on MPHV population are not available. Furthermore, a retrospective cohort study including patients undergoing MPHV placement between 1976 and 2006 showed no survival difference between genders after aortic MPHV with a trend towards better survival for women after mitral MPHV replacement[13].

To investigate these aspects, we analysed data from the nationwide PLECTRUM registry which included anticoagulated patients who underwent MPHV regarding 1) the site of MPHV; 2) differences in the TiTR and 3) long-term mortality risk to see if a difference between women and men would exist.

Materials and methods.

The FCSA-START Valve study (PLECTRUM) is a retrospective multicenter observational study within the Italian Survey on Anticoagulation Patient Records (START register) **(NCT02219984)**[14] and conducted among 33 centers affiliated to the Italian Federation of Thrombosis Diagnosis Centers and Surveillance of antithrombotic therapies (FCSA)[15]. **The centers were asked to select from their databases patients with a mechanical or biological heart valve prosthesis was implanted after 1990 and who were on follow-up for the management of oral anticoagulant.** The patients followed by the FCSA centers for the management of oral anticoagulation receive an adequate education on the purpose of the treatment, the risk of complications, the INR values and the management of the dosage of the drugs.

Anticoagulation quality

The centers perform periodic INR measurements, prescribe daily VKAs dosage and schedule the date for subsequent visits; they also monitor and record changes in patient habits, diet, co-medications, intercurrent illness, bleeding and thrombotic complications during regular follow-up visits through patient interviews. All centers participate in the specially designed external laboratory quality control program, which is performed 3 times a year and uses lyophilized plasma samples obtained from anticoagulated patients. The quality of the anticoagulant control, calculated as TiTR using the linear interpolation method of Rosendaal et al.[16], was analyzed considering the INRs recorded in the last year of follow-up.

Definition of cardiovascular risk factors and disease

Demographic information and clinical data were collected. Patients were classified as having high blood pressure if they were taking medicines to lower their blood pressure. Diabetes mellitus was defined according to the criteria of the American Diabetes Association. Coronary artery disease has been defined on the basis of 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 that demonstrate objective evidence of cardiac dysfunction.

Ethical statement

The study protocol complies with the ethical guidelines of the 1975 Helsinki Declaration, as evidenced by the approval of the institution's human research committee and informed consent was obtained from each patient.

Statistical analysis

Continuous variables were reported as mean and standard deviation and compared by the Student t test. Categorical variables were reported as count and percentage and compared by Pearson chi squared test. A first descriptive analysis of clinical characteristics according to sex was performed.

Multivariable logistic regression analysis was used calculate the relative odds ratio (OR) the 95% confidence interval (95%CI) of factors associated with MPHV at mitral/mitro-aortic site.

Univariable and multivariable Cox proportional hazard regression analysis was used to calculate the relative Hazard Ratio (HR) with 95%CI of factors associated with the risk of mortality. We built three survival models 1) overall; 2) aortic MPHV and 3) mitral/mitro-aortic MPHV patients.

All available variables were inserted in the multivariable models; cardiovascular comorbidities were grouped under "number of comorbidities".

All p values <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS 25.0 software.

Results

The analysis included 2,111 patients with a mean age of 56.8 ± 12.3 years. Women were older with a lower prevalence of ischemic heart disease and less frequently smokers but with a higher prevalence of AF at baseline (**Table 1**). The number of cardiovascular comorbidities was similar between the two groups.

MPHV site and sex

The distribution of MPHV was significantly different between men and women. Thus, MPHV at aortic site was more frequently found in men than women (74.7% vs. 43.3%, p<0.001) (**Figure 1**). Conversely, mitral and mitro-aortic MPVH were more frequent in women than men (mitral 41.1% vs 17.6%, p<0.001; mitro-aortic 15.6% vs. 7.7%, p<0.001) (**Figure 1**).

Factors associated with MPHV at mitral/mitro-aortic site were female sex (OR 3.623, 95%CI 2.947-4.455, p<0.001), arterial hypertension (OR 0.744, 95%CI 0.600-0.923, p=0.007), ischemic heart disease (OR 0.564, 95%CI 0.402-0.791, p= 0.001), heart failure (OR 2.054, 95%CI 1.542-2.736, p<0.001), atrial fibrillation (OR 4.605, 95%CI 3.746-5.660, p<0.001) and previous thromboembolism (stroke/TIA/SE) (OR 2.567, 95%CI 1.765-3.734, p<0.001) (**Table 2**).

Anticoagulation quality

Women were more frequently kept at INR ranges above 2.0-3.0; in particular 67.6% and 13.7% of women were in the INR range 2.5-3.5 and 3.0-4.0 compared to 59.8% (p<0.001) and 5.6% (p<0.001) of men, respectively (**Table 1**).

When we analysed anticoagulation quality, we found that women showed a significantly lower mean TiTR than men (63.0±19.4 vs. 57.5±19.2, p<0.001). In particular, women disclosed a higher proportion of low-quality of anticoagulation: TiTR <60% 54.9% vs 43.3%, TiTR <65% 66.1% vs. 55.3%, TiTR <70% 72.7% vs. 62.3% (p<0.001 for all comparisons). (**Figure 1**)

We also found that patients with MPHV at mitral/mitro-aortic site had a lower TiTR range compared to aortic (55.4±18.6 vs. 64.0±19.3, p<0.001). In particular, the difference between men and women regarding TiTR was most evident in the aortic (TiTR 60.7±19.4 in women vs. 65.5±19.2 in men, p<0.001) but not in the mitral/mitro-aortic group, as in the latter group, the majority of patients had suboptimal anticoagulation (TiTR <70% in 78.3% of patients).

Mortality risk

During a mean follow-up of 123 months (21,665 pt-years), 152 deaths were recorded (incidence rate 0.7%/year); 83 in the aortic MPHV (0.63%/year) and 69 in the mitral/mitro-aortic MPHV (0.81%/year) group.

At multivariable Cox proportional hazard regression analysis we found that factors associated with an increased risk of mortality were the number of comorbidities (HR 1.280, 95%CI 1.130-1.449, p<0.001), age ≥65 years (HR 5.072, 95%CI 3.534-7.278, p<0.001), TiTR <60% (HR 2.645, 95%CI 1.745-4.009, p<0.001) and INR range above 2.0-3.0 (HR 1.968, 95%CI 1.115-3.472, p=0.019) (**Table 3, Model A**). Female sex was not associated with an increased mortality risk.

Similar results were obtained when patients with aortic and mitral/mitro-aortic MPHV were separately analysed (**Table 3, Model B and C**). Predictors of mortality were consistent in men and women (not shown).

Discussion

This analysis from the PLECTRUM study shows that women have more frequently a MPHV at mitral/mitro-aortic site together with a lower anticoagulation quality than men. The higher proportion of women in the mitral/mitro-aortic MPHV group is in keeping with a previous retrospective study including young patients (mean age of 40 years) undergoing both biological or mechanical prosthesis[17].

A new finding is that women with MPHV have lower quality of anticoagulation compared to men, regardless of the threshold used to define low TiTR. This evidence was previously reported in patients with non-valvular AF[18-20] and female sex is included as risk factor in the SAMe-TT_2R_2 score[21] for the prediction of low TiTR, but this association were not previously reported in patients carrying MPHV. This lower TiTR is probably explained by the fact that women are more frequently kept at INR ranges higher than 2.0-3.0, which have been previously shown to represent a risk factor for long-term low TiTR[11]. **Of note, a subanalysis showed that the difference in TiTR between women and men was evident in patients carrying a MPHV in the aortic site but not in the mitral/mitro-aortic position. This results may be explained by the fact that in the mitral group the TiTR was consistently suboptimal in the majority of patients with >75% of patients showing a TiTR <70%.**

Despite a higher mean age and a lower TiTR, long-term mortality risk was similar between men and women in this study. This finding is in contrast with a previous retrospective study including 2,727 patients undergoing aortic (n=950) mitral (n=1,255) or double (n=522) valve replacements[4]. During 34-year follow-up, mortality rate was 0.59%/year for cardiac death and 0.69%/year for valve-related death[4]. At multivariable analysis, the Authors found that male sex was associated with an increased risk of death (HR 1.25, 95%CI 1.11-1.42, p=0.0003), but the analysis was not apparently adjusted for comorbidities and antithrombotic treatments, including anticoagulation quality[4].

We found low anticoagulation quality, high INR range, aging and comorbidities as the most important factors associated with mortality, both in the aortic and mitral MPHV group. Our finding that low TiTR <60% is associated with an increased mortality risk supports and extends previous evidence that a high variability of INR was associated with poor survival in patients undergoing single valve replacement (HR 1.8 per 20% increase)[22].

A finding of particular interest is that MPHV site was not associated per se with the risk of death, but patients who were kept at INR ranges higher than 2.0-3.0 (i.e. 2.5-3.5 and 3.0-4.0) were at higher mortality risk. This finding raises concern on the benefit of using INR range higher than 2.0-

3.0 in patients with MPHV. In this context, the LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement showed that low intensity anticoagulation (i.e. INR range 2.0-3.0) would be as effective as higher INR ranges with less bleeding complications in patients with aortic MPHV[23].

Limitations

This study has various limitations that should be mentioned. The observational design of the study precludes the establishment of any cause-effect relationship between the variables of interest. Few patients were aged 75 or more, so these results need to be confirmed in elderly patients undergoing valve replacement. Furthermore, changes of TiTR over time as well as discontinuation of anticoagulation therapy may influence the risk of mortality, similarly to that reported in non-valvular AF patients[24,25].

Implications

Clinical implications from our study include that the quality and intensity of oral anticoagulation are the strongest factors associated with mortality risk in patients with MPHV. Much effort should be done to increase the TiTR in female patients as a low TiTR may predispose them also to other clinical adverse outcomes, such as thromboembolism, myocardial infarction and bleeding.

In conclusion, this analysis from the PLECTRUM registry shows significant differences regarding MPHV site and anticoagulation quality between men and women. However, mortality risk did not differ between the two groups.

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Table 1. Characteristics of patients according to MPHV site.

	Whole cohort (n= 2111)	Men (n= 1170)	Women (n= 941)	p value
Age (years)	56.8±12.3	55.4±15.5	58.5±11.8	<0.001*
Age ≥65 years (%)	29.1	24.9	34.3	<0.001#
Age ≥75 years (%)	4.0	2.4	6.1	<0.001
Arterial hypertension (%)	65.9	66.8	64.7	0.307#
Diabetes (%)	13.5	13.0	14.1	0.445#
Ischemic heart disease (%)	12.9	16.5	8.5	<0.001#
Heart failure (%)	14.9	14.0	16.0	0.193#
Previous thromboembolism* (%)	7.8	7.8	7.9	0.942#
Peripheral artery disease (%)**	4.9	5.7	3.9	0.058#
Current smoking (%)	6.7	9.1	3.6	<0.001
Atrial fibrillation (%)	38.4	32.3	46.0	< 0.001#
Number of comorbidities§	1.62±1.21	1.60±1.21	1.65±1.20	0.355*
MPHV site				< 0.001#
Aortic (%)	60.7	74.7	43.3	
Mitral (%)	28.1	17.6	41.1	
Mitro-aortic (%)	11.2	7.7	15.6	
INR ranges				< 0.001#
2.0-3.0 (%)	27.0	34.2	18.2	
2.5-3.5 (%)	63.3	59.8	67.6	
3.0-4.0 (%)	9.2	5.6	13.7	
TiTR (%)	60.6±19.5	63.0±19.4	57.5±19.2	<0.001*
Low-quality anticoagulation				
TiTR <60% (%)	48.5	43.3	54.9	<0.001#
TiTR <65% (%)	60.1	55.3	66.1	<0.001#
TiTR <70% (%)	66.9	62.3	72.7	<0.001#

* Student t test; #Chi squared test; *includes previous stroke/TIA/systemic embolism; ** includes lower limb and carotid disease.

§includes hypertension, diabetes, heart failure, previous stroke, vascular disease, previous ischemic heart disease, peripheral artery disease, atrial fibrillation.

MPHV: mechanical prosthetic heart valve; TiTR: time in therapeutic range

Table 2. Multivariable logistic regression analysis of factors associated with MPHV at mitral/mitro-aortic site.

	Odds ratio	95% Confidence Interval		p value
Female sex	3.623	2.947	4.455	<0.001
Age ≥65 years	0.864	0.689	1.083	0.205
Arterial hypertension	0.744	0.600	0.923	0.007
Diabetes	1.030	0.761	1.393	0.851
Smoking	0.904	0.783	1.043	0.166
Ischemic Heart Disease	0.564	0.402	0.791	0.001
Peripheral Artery Disease	0.750	0.513	1.097	0.138
Heart failure	2.054	1.542	2.736	<0.001
Atrial fibrillation	4.605	3.746	5.660	<0.001
Previous thromboembolism	2.567	1.765	3.734	<0.001

Table 3. Univariable and multivariable Cox proportional hazard regression analysis of factors associated with mortality. Model A: Overall; Model B: Aortic MPHV; Model C: Mitral/Mitro-aortic MPHV.

Model A. Whole cohort.	Hazard ratio	95% Confidence Interval		p value
Number of comorbidities	1.280	1.130	1.449	<0.001
Female sex	0.953	0.678	1.340	0.783
Age ≥65 years	5.072	3.534	7.278	<0.001
TiTR <60%	2.645	1.745	4.009	<0.001
Mitral (vs. aortic) MPHV	1.116	0.768	1.622	0.566
Mitro-aortic (vs. aortic) MPHV	0.796	0.452	1.400	0.428
INR range above 2.0-3.0	1.968	1.115	3.472	0.019
Model B. Aortic MPHV				
Number of comorbidities	1.268	1.075	1.497	0.005
Female sex	1.022	0.647	1.613	0.926
Age ≥65 years	5.311	3.256	8.664	<0.001
TiTR <60%	1.986	1.195	3.298	0.008
INR range above 2.0-3.0	2.570	1.296	5.095	0.007
Model C. Mitral/mitro-aortic MPHV				
Number of comorbidities	1.268	1.036	1.552	0.021
Female sex	0.870	0.519	1.459	0.597
Age ≥65 years	4.656	2.697	8.036	<0.001
TiTR <60%	4.404	1.993	9.732	<0.001
INR range above 2.0-3.0	0.921	0.331	2.561	0.875

TiTR: time in therapeutic range.

Figure Legend

Figure 1. Distribution of MPHV site (Panel A) and INR ranges (Panel B) and low TiTR (Panel C) according to sex.

Appendix

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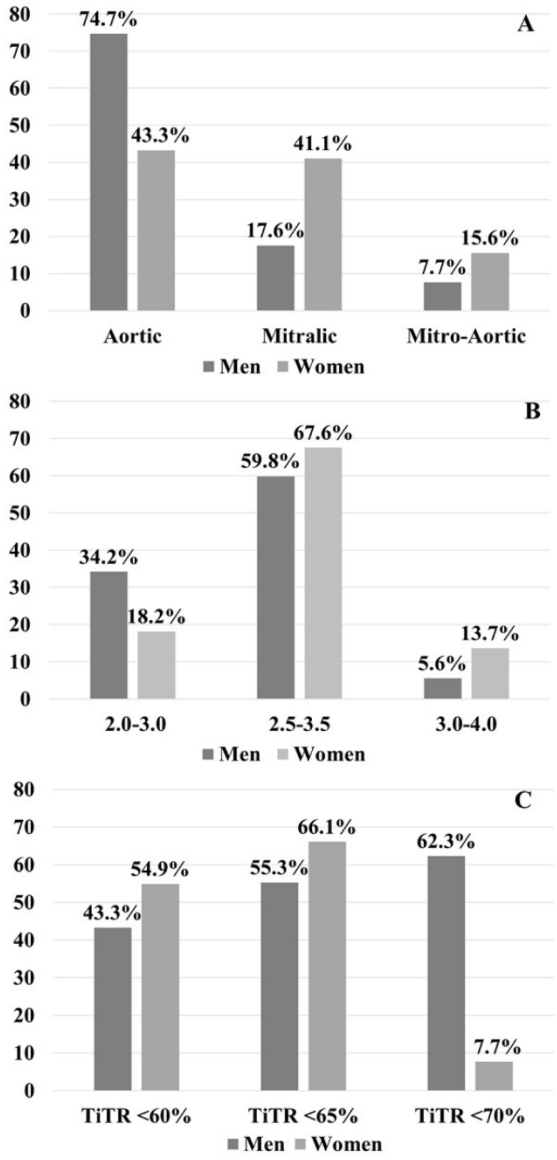

Figure 1

209x297mm (300 x 300 DPI)