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Mechanical heart valve prosthesis and warfarin – Treatment quality and prognosis

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ABSTRACT

Introduction: Every year about 2500 patients in Sweden undergo surgery due to heart valve disease. A mechanical heart valve prosthesis causes risk of thromboembolic stroke or thrombus formation in the valve while anticoagulant treatment increases the risk of bleeding. Treatment quality with warfarin is crucial for patients with mechanical valve prostheses. It has previously been shown that poorly controlled warfarin treatment increases mortality in this patient group.
TTR (Time in Therapeutic Range) on warfarin has been shown to affect the risk of complications in atrial fibrillation, but has not been studied in patients with mechanical heart valves. Our aim is to evaluate the impact of TTR on the risk of complications in this patient group.
Materials and Methods: A non-randomized, prospective study of 534 adults with mechanical heart valve prostheses from Malmö and Sundsvall registered in the Swedish National Quality Registry Auricula between 01.01.2008 and 31.12.2011. Quartiles regarding individual TTR levels were compared regarding risk of complications.
Results: The risk of complications was significantly higher at lower TTR levels for all complications ($p = 0.005$), bleeding ($p = 0.01$) and death ($p = 0.018$) but not for thromboembolism. In multivariate analysis the risk was significantly increased at lower TTR levels for bleeding and all complications but not for death or thromboembolism.
Conclusion: Patients with a lower warfarin treatment quality measured by TTR have a higher risk of complications such as severe bleeding or death. A TTR of 83% or higher at the individual level should be obtained for best outcome.

Introduction

Each year about 2500 heart valve surgeries are performed in Sweden. In 75% of the cases this is due to disease of the aortic valve, which usually needs to be replaced with a prosthesis. The mitral valve can, however, in 70% of cases be repaired with valve plasty [1]. The majority of implanted valves are biological, whereas 40% of mitral valve and 25% of aortic valve prostheses are mechanical.

A prosthetic heart valve involves a risk of thromboembolic stroke or thrombus formation in the valve with mechanical heart valve prostheses conferring the highest risk.

While the need for anticoagulation with biological heart valve prostheses is controversial and still discussed [2], a mechanical heart valve prosthesis demands a life – long treatment with vitamin K – antagonists, mainly warfarin.

The risk of valve thrombosis in patients with mechanical prosthetic heart valves has been reported in a meta-analysis from 1994 at 0.2% per year with anticoagulation and 1.8% per year without treatment. Total risk of thrombosis with anticoagulation was 1.8% per year, as compared to 8.6% without oral anticoagulant treatment. At the same time the risk of serious bleeding during anticoagulant therapy was 1.4% [3]. Treatment quality with warfarin is of great importance for patients with a mechanical heart valve prosthesis. A study of Butchart et al. showed that mortality was significantly increased among patients with poorly controlled warfarin treatment [4]. The risk was highest for patients with a mechanical heart valve prosthesis in the mitral position.

In atrial fibrillation the quality of warfarin therapy measured by TTR (Time in Therapeutic Range) has been shown to affect the risk of complications such as thromboembolism or severe bleeding at center level [5].

A retrospective study from an anticoagulation clinic recruiting patients with several indications for warfarin treatment was done in a high TTR setting (92.1%) with a wide INR target range of 2.5 – 4.2 [6].

Abbreviations: TTR, Time in Therapeutic Range; AF, Atrial fibrillation; OR, Odds ratio; CI, Confidence interval; TIA, Transient ischemic attack; SD, Standard deviation; INR, International Normalized Ratio.

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An association between the number of complications and warfarin treatment quality as measured by TTR in patients with mechanical heart valve prostheses have previously not been investigated. Our aim of this study is to evaluate the impact of TTR on the risk of complications in this patient group.

Materials

Auricula is a national quality registry funded by grants from the Swedish Association of Local Authorities and Regions (SKL). The registry was established in 2006, and today over 200 affiliated centers manage their daily dosing activity of oral anticoagulants, mainly warfarin, through the system. The program is web-based and includes decision support for dosing of warfarin. When using the dosing system, quality parameters are automatically registered. The primary endpoints, major bleeding and thromboembolic events, are recorded prospectively and are requested at the end of each dosing period or annually. The system currently consists of over 110,000 patients and more than 4 million doses of warfarin corresponding to approximately 50% of all patients treated with oral anticoagulation in Sweden.

Method

A prospective, non-randomized study including all adult patients with mechanical prosthetic heart valves in Malmö and Sundsvall who were registered in Auricula between 01.01.2008 and 31.12.2011. Information letters about the study's purpose and procedures were sent to all patients. One patient with tricuspid valve and one, which after reading the information letter declined participation, were excluded.

The material consisted primarily of 543 patients. Nine were excluded due to insufficient data on INR, which made calculation of TTR impossible. The analysis was made on the remaining 534 patients, 132 from Sundsvall and 402 from Malmö with a total of 1,814 patient-years of warfarin treatment (Table 1).

Data on complications were collected prospectively in Auricula during everyday work with the dosing program. Concurrent diseases and complications have been validated by reviewing medical records from the medical, surgery, ophthalmology, laryngology, gynecology clinic, and primary care. Thromboembolic events (valve thrombosis, stroke/TIA, and other – among those myocardial infarctions) and bleeding according to ISTH (International Society of Thrombosis and Hemostasis) definition, ie, fatal bleeding, and / or equivalent blood loss greater than 20 g hemoglobin/L, demanding transfusion of at least 2 units of blood and/or bleeding that were verified by diagnostic radiology, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome were defined as complications [7].

Information on the individual's quality of treatment with warfarin as measured by TTR with target INR 2 – 3 was calculated according to Rosendaals method [8].

Statistics

With help of T – test a connection between TTR and risk of bleeding, thrombosis or death in the whole study group was investigated. The patients were then grouped into four quartiles depending on their individual TTR: TTR < 61.6, 61.6 to 71.9, 71.9 to 82.9 and > 82.9%. The groups were compared regarding risk of serious complications such as thromboembolism, bleeding or death per treatment year (Tables 1, 2 and 3). A 95% confidence interval of person-time incidence rate with normal approximation was done for rates of complications [9].

Data were analyzed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA), with Chi 2 test with and without Linear by Linear Association, ANOVA, multivariate analysis with logistic regression and T - test.

Results

Mean TTR was 71.3% (median 71.9%) in the whole group, 68.2% in women and 73.1% in men. Mean time interval between INR tests was 24.1 days, mean INR 2.8 regardless of gender. Heart valve prosthesis in the aortic position was most common (n = 388), followed by mitral (n = 119) and aortic and mitral position combined (n = 26). Among those who had received an aortic heart valve prosthesis 31.7% were women, while they counted for 52.9% of those who received a prosthetic valve in mitral position ($p < 0.001$). Atrial fibrillation and heart failure were significantly more common in the mitral valve group ($p = 0.003$). 58 patients had 64 thromboembolic events, 77 a total number of 79 serious bleeding while 85 patients died during the study period. Mean age varied significantly between the TTR quartiles ($p = 0.033$), although with no apparent trend. Mitral heart prostethic heart valves were overrepresented in lower TTR levels, and had a slightly increased risk of bleeding as compared to prostheses in the aortic position (4.8 vs 4.4% per person year).Presence of other diseases including mean $CHADS_2$ did not differ significantly between the TTR quartiles (Table 1). 12 patients had concurrent antiplatlet therapy with clopidogrel/ASA.

T- test performed on the whole study group (before dividing into quartiles) showed a difference in mean TTR between patients with and without a bleeding event (mean 67.7 vs 71.9, $p = 0.017$), death (mean 66.6 vs 72.2, $p = 0.001$) and all complications (68.3 vs 72.5, $p = 0,002$) but not for thromboembolic events (69.4 vs 71.4).

Table 1
Comorbidity and age in relation to TTR (%) divided into quartiles.

	Quartile 4 (>82.9) n = 134	Quartile 3 (82.9 – 71.9) n = 133	Quartile 2 (71.9 – 61.6) n = 133	Quartile 1 (<61.6) n = 134	Sign. (p)
Mean age (years), mean ± SD	63.5 ± 12.1	64.4 ± 14.8	68.3 ± 13.3	65.3 ± 15.4	0.033
Comorbidity, n (%)					
AF	47 (35.1)	47 (35.3)	57 (42.9)	57 (42.5)	NS
Diabetes	14 (10.4)	16 (12.0)	24 (18.0)	21 (15.7)	NS
Hypertension	93 (69.4)	77 (57.9)	89 (66.9)	82 (61.2)	NS
Previous Stroke/TIA	17 (12.7)	17 (12.8)	14 (10.5)	15 (11.2)	NS
Heart failure	52 (38.8)	61 (45.9)	65 (48.9)	67 (50.0)	NS
$CHADS_2$, mean ± SD	1.6 ± 1.3	1.7 ± 1.4	1.9 ± 1.4	1.8 ± 1.4	NS
Valve position, n (%)					
Aortic	113 (84.4)	108 (81.2)	94 (70.8)	74 (55.2)	
Mitral	16 (11.9)	19 (14.3)	34 (25.5)	50 (37.3)	
Aortic and Mitral	5 (3.7)	6 (4.5)	5 (3.7)	10 (7.5)	

Comorbidity and age in relation to TTR (%) divided into quartiles. Mean age varied significantly between the TTR quartiles ($p = 0.033$), without an apparent trend. No significant difference in presence of other diseases including mean CHADS2 was found between the TTR quartiles. Mitral valve prostheses were more common in patients with lower TTR levels.