



## Thrombo-embolic and bleeding complications in patients with mechanical valve replacements – a prospective observational study

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**Background and objectives.** Long-term anticoagulation therapy is essential to prevent thrombo-embolic events in patients with mechanical valve replacements. In order to offer indigent patients mechanical heart valve replacement surgery, dedicated anticoagulation clinics are necessary for follow-up. This study assessed the safety and efficacy of lifelong oral anticoagulation therapy in Johannesburg General Hospital mechanical heart valve replacement recipients. The incidence of bleeding and thrombo-embolic complications was documented in three groups of patients with mechanical valve replacements. The groups included patients with aortic valve replacements (AVRs), mitral valve replacements (MVRs) and double (aortic and mitral) valve replacements (DVRs).

**Materials and methods.** A prospective observational study was conducted over a 4-month period. Data on 306 patients attending the Johannesburg General Hospital anticoagulation clinic between 2000 and 2005 were analysed. Of the total patients selected, 205 were assigned to the mechanical valve replacement group (which included 63 patients with AVRs, 93 with MVRs and 49 with DVRs); a control group of 101 non-mechanical valve replacement patients were also included. At each visit the level of anticoagulation was assessed from the international normalised ratio (INR) values, and the presence of bleeding and/or thrombo-embolic complications was documented.

**Results.** There were a total of 51 bleeding and thrombo-embolic complications in the study population. Patients with DVRs had a higher proportion of combined complications (30.61%) than patients with single valve replacements (14.29% in the AVR group and 18.05% in the MVR group) and patients in the control group (12.87%). There were 38 bleeding complications, 30 minor and 8 major. Twelve thrombo-embolic events were documented. Individually, there was no significant difference in thrombo-embolic and bleeding complications between the subgroups. Eighty-two per cent of patients in the mechanical valve replacement group were within the therapeutic range for anticoagulant control (INR 2.5 - 3.5) v. 54% in the control group (INR 2.0 - 3.0). Anticoagulant control was of a high quality and was not a contributing factor to the incidence of bleeding and/or thrombo-embolic complications.

**Conclusion.** The finding of a low incidence of bleeding and thrombo-embolic complications in patients with mechanical valve replacements supports the continued placement of mechanical valves in our setting and use of oral anticoagulation therapy at an INR of 2.5 - 3.5. However the increased risk of both bleeding and thrombo-embolic complications in the DVR group is cause for great concern and warrants further investigation.

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Long-term antithrombotic prophylaxis is essential for the prevention of thrombo-embolic events in patients with mechanical valve replacements.<sup>1</sup> Factors influencing the risk of arterial thrombo-embolism include the valve type (caged ball, caged disk, tilting disk or bileaflet), valve site (aortic or mitral) and number of valves replaced.<sup>2</sup> Higher rates of thrombo-embolic complications have been reported with valves in the mitral valve position. This can be attributed to left atrial enlargement, which predisposes to an increased incidence of

atrial fibrillation.<sup>3</sup> In our South African setting where First- and Third-World areas co-exist, predisposing factors for rheumatic fever still persist in developing areas leading to a high incidence of rheumatic heart disease (RHD).<sup>4</sup> Rheumatic mitral valve disease leads to endocardial damage, which is another strongly contributing factor to the high incidence of systemic embolism with valves in the mitral position.<sup>3</sup> Thrombo-embolism has been reported to occur at an incidence of 1.5% per annum in patients with rheumatic mitral valve disease.<sup>5</sup>

The aim of anticoagulation is to balance the lowest risk of bleeding with the lowest risk of thrombo-embolic complications. In the past an international normalised ratio (INR) of 3.0 - 4.5 was recommended for patients with mechanical valve replacements.<sup>6</sup> This range is associated with an increased risk of bleeding complications. In a randomised trial, Saour *et al.*<sup>7</sup> compared low-dose (INR 1.9 - 3.6) and high-dose (INR 7.4 - 10.8) warfarin anticoagulation therapy. Their analysis revealed no increase in thrombo-embolic events with low-dose anticoagulation. An INR of > 3.6 was associated

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with an increased risk of bleeding.<sup>7</sup> A less intensive oral anticoagulation regimen is associated with a lower incidence of bleeding complications, without a significant increase in thrombo-embolic events. A target INR of 2.5 - 3.5 is now the current recommendation for patients with mechanical valve replacements.<sup>2</sup>

In the developing world the question still remains whether it is safe to perform mechanical valve replacements, as patients will require lifelong anticoagulation therapy. Factors that may contribute to poor anticoagulant control include patient compliance, diet and drug interactions, as well as irregular access to anticoagulation clinics.

An average of 1 500 patients attend the dedicated anticoagulation clinic at the Johannesburg General Hospital every month. Twenty-five per cent are patients with mechanical valve replacements on lifelong anticoagulation therapy. Patients are assessed at a maximum of 1-month intervals and followed up by nursing sisters who staff the clinic.

This study focused primarily on the 25% of patients with mechanical valve replacements. In order to assess the safety and efficacy of lifelong oral anticoagulation therapy in this patient group we: (i) monitored the incidence of bleeding and thrombo-embolic complications in three groups of mechanical valve replacement patients, namely patients with aortic valve replacements (AVRs), mitral valve replacements (MVRs) and double valve (aortic and mitral) replacements (DVRs); and (ii) assessed the level of INR control in patients in the mechanical valve groups compared with patients in the non-mechanical valve replacement group.

## Materials and methods

A prospective observational study was conducted over a 4-month period. Data on 205 patients attending the Johannesburg General Hospital anticoagulation clinic between 2000 and 2005 were analysed. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (protocol number M050703). Patients were assessed at 4 consecutive visits. At each visit the level of anticoagulation was assessed from the INR values, and the presence of bleeding and/or thrombo-embolic complications was documented. Of the total 306 patients selected, 205 were assigned to the mechanical valve replacement group (which included 63 patients with AVRs, 93 with MVRs and 49 with DVRs). A control group comprised 101 patients without valve replacements on lifelong oral anticoagulation therapy for conditions such as atrial fibrillation and dilated cardiomyopathy. The level of anticoagulation control was assessed by assigning patients to 1 of 4 classes (Table I). The target therapeutic INR range (as currently aimed for in South Africa) for patients with mechanical valve replacements was taken at 2.5 - 3.5, and for the control group at an INR value

**Table I. Classes of anticoagulant control**

Class	Mechanical valve replacement group (INR value)	Control group (INR value)
I	2.5 - 3.5	2 - 3
II	> 3.6	> 3.1
III	< 2.4	< 1.9
IV	< 2.4 or > 3.6 In range < 30% of time	< 1.9 or > 3.1 In range < 30% of time

of 2 - 3. Patients who maintained a target INR at 80% of their recorded visits were assigned to class I. Patients who had INR values above or below the target range 80% of the time were assigned to classes II and III respectively. Class IV represented patients with poor, fluctuating anticoagulant control in the target range only 30% of the time.

## Data analysis

The Medical Research Council in Pretoria performed the data analysis. The incidence of bleeding and thrombo-embolic complications in the 4 groups was analysed using Pearson's correlation.

## Results

Level of oral anticoagulation control was high, with 71.5% of patients in the therapeutic range. Details are given in Table II. The level of anticoagulant control in the 3 mechanical valve replacement groups was similarly distributed within the 4 classes but differed from the control group.

A total of 51 thrombo-embolic and bleeding complications were documented in the study population (Table III). Patients with DVRs had a higher proportion of complications (30.61%). However the control group (12.87%), AVR group (14.29%) and MVR group (18.05%) did not differ with regard to the proportion of complications. The odds of complications in the DVR group were 2.7-fold higher ( $p$ -value > 0.024) than in the control group. There was no increased risk of complications in the MVR and AVR groups relative to the control group.

Thirty-eight bleeding complications were reported, of which 30 were minor and 8 major (Table IV). Bleeding was defined as major if the patient required hospitalisation, surgery or transfusion. All other bleeding events were defined as minor. Total bleeding incidence was 9.52% in the AVR group, 9.68% in the MVR group, and 22.45% in the DVR group. There was no significant difference in the overall bleeding complication rate between the mechanical valve replacement subgroups and the control group.

A total of 12 thrombo-embolic events were documented (Table V). Thrombo-embolism was defined as a temporary or permanent neurological, limb or visceral deficit. The incidence of thrombo-emboli in the AVR group was 4.76%, in the MVR

**Table II. Level of anticoagulant control (N (%))**

Class	Study groups				Total
	Control	AVR	MVR	DVR	
Class I	54 (55)	55 (87)	68 (73)	42 (86)	219 (75)
Class II	15 (4)	4 (6)	11 (12)	3 (6)	33 (11)
Class III	5 (5)	1 (2)	7 (8)	1 (2)	14 (6)
Class IV	27 (27)	3 (5)	7 (8)	3 (6)	40 (13)

Pearson's chi-square (3) = 8.3401 Pr = 0.039.

AVR = aortic valve replacement; MVR = mitral valve replacement; DVR = double valve replacement.

**Table III. Bleeding and thrombo-embolic complications (N (%))**

Pool complications	Study groups				Total
	Control	AVR	MVR	DVR	
Absent	88 (87)	54 (86)	79 (85)	34 (69)	255 (83)
Present	13 (13)	9 (14)	14 (15)	15 (31)	51 (17)

Pearson's chi-square (3) = 8.3401 Pr = 0.039.

AVR = aortic valve replacement; MVR = mitral valve replacement; DVR = double valve replacement.

**Table IV. Bleeding complications (N (%))**

Bleeding complications	Study groups				Total
	Control	AVR	MVR	DVR	
Absent	89 (88)	57 (91)	84 (90)	38 (78)	268 (88)
Present	12 (12)	6 (10)	9 (10)	11 (23)	38 (13)

AVR = aortic valve replacement; MVR = mitral valve replacement; DVR = double valve replacement.

**Table V. Thrombo-embolic complications (N (%))**

Thrombo-embolic complications	Study groups				Total
	Control	AVR	MVR	DVR	
Absent	100 (99)	60 (95)	88 (95)	46 (94)	294 (96)
Present	1 (1)	3 (5)	5 (5)	3 (6)	12 (4)

AVR = aortic valve replacement; MVR = mitral valve replacement; DVR = double valve replacement.

group 5.38%, and in the DVR group 6.12%. There was no significant difference in thrombo-embolic complications between the patient subgroups.

## Discussion

This prospective observational study compared the incidence of bleeding and thrombo-embolic complications in three groups of patients with mechanical valve replacements and on warfarin, with patients in a control group. The three groups were divided into patients with MVRs, AVRs and DVRs. Various studies<sup>1,8-10</sup> have reported low incidences of complications at the current recommended levels of oral anticoagulation.

Cannegieter *et al.*<sup>10</sup> reported an incidence of thrombo-emboli

of 0.5% per year in patients with AVRs, 0.9% per year in those with MVRs, and 1.2% per year in patients with DVRs. Similarly Pengo *et al.*<sup>9</sup> found an overall incidence of complications of 1.2% per year in patients with MVRs, AVRs and DVRs at a target INR of 2.5 - 3.5. These studies do not seem to indicate any significant differences among the groups and highlight the low incidence of complications.

These results correlate with our findings. It was found that patients with single valve replacements had no significant increase in complications compared with the control group.

However, a statistically significant increase in all complications in the DVR group when compared with the control and single valve replacement groups was found in this study (for the same intensity of anticoagulation control).



The reason for this interesting finding of an increased risk of bleeding and thrombosis in the DVR group is unclear. While it may be a pure chance finding in view of the relatively small numbers in the study, it certainly cannot be ignored. Closer monitoring and follow-up visits are definitely warranted in this group of patients.

The current guidelines, produced by the 7th American College of Chest Physicians conference on the use of anticoagulation in patients with valve replacements, recommend a target INR in the range of 2.5 - 3.5.<sup>2</sup> Exact values are dependent on valve type but all fall within this range.

Eighty-two per cent of the mechanical valve replacement group were within this therapeutic range for anticoagulation (class I). This indicates that the anticoagulant control was of a high quality and not a contributing factor to the incidence of bleeding and/or thrombo-embolic complications in the study group. Only 54% of the control group were in their therapeutic range (class I). The reason for the better control in the mechanical valve replacement group is unknown. Patient education on compliance and the nature of the underlying disease process may be contributing factors.

The level of anticoagulant control in mechanical valve replacement recipients in this study is higher than that reported in other prospective studies performed in South African centres. A recent study conducted by Buchanan-Lee *et al.*<sup>11</sup> in the Cape Town centre found that only 63 - 64% of their mechanical valve replacement group were in the therapeutic range (2 - 4.5) for INR control. The higher standard of anticoagulant control at the Johannesburg General Hospital can be attributed to regular patient follow-up at a dedicated anticoagulation centre. The improved control in these patients can be attributed either to chance or to the fact that they were well informed about the potential dangers of not being in the therapeutic range. Another possible reason is that the Johannesburg General Hospital anticoagulation clinic is staffed

by dedicated nursing staff. Studies have demonstrated that anticoagulation clinics staffed by nurses are safe and effective.<sup>12</sup>

In conclusion, the findings of a low risk of bleeding and thrombo-embolic complications in patients with single valve replacements support the performance of mechanical valve replacement surgery requiring lifelong oral anticoagulation in a developing setting such as South Africa. This is on condition that patients have regular access to dedicated anticoagulation clinics such as offered at Johannesburg General Hospital. A target INR of 2.5 - 3.5 should be maintained. However the increased risk of both bleeding and thrombo-embolic complications in the DVR group is of great concern and warrants further investigation.

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