

North American Multicenter Experience with the On-X[®] Prosthetic Heart Valve

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Background and aim of the study: This ongoing, longitudinal, multi-center, North American study was designed to evaluate the safety and effectiveness of the On-X[®] valve.

Methods: The On-X valve was implanted in isolated aortic (AVR) and mitral (MVR) valve replacement patients at nine North American centers. Follow up was 98.6% complete. Anticoagulation compliance was evaluated by collection of international normalized ratio (INR) results in all patients throughout their postoperative follow up. Adverse events were recorded according to the AATS/STS guidance criteria. Hematologic studies were conducted postoperatively to evaluate hemodynamics and hemolysis.

Results: In total, 142 AVR and 142 MVR implants were performed; the mean follow up was 4.5 years; total follow up was 1,273 patient-years (pt-yr). At implant, the mean patient age was 59.2 years (range: 28 to 85 years); 71.8% of patients who underwent AVR and 33.1% who underwent MVR were males. Preoperatively, 89.4% of AVR patients and 56.3% of MVR patients were in sinus rhythm. The cardiac dis-

ease etiology was primarily stenotic, calcific degeneration in AVR and rheumatic or degenerative regurgitation in MVR. Hemolysis represented by postoperative elevation of serum lactate dehydrogenase was very low (median 217 IU after AVR and 251 IU after MVR at one year (82% AVR and 98% MVR of upper normal). Late adverse event rates were low, most notably thromboembolism (0.9%/pt-yr after AVR; 1.6%/pt-yr after MVR) and thrombosis. Kaplan-Meier event-free rates at five years were correspondingly high. Anticoagulation compliance analysis showed only about 40% of INR readings to be within target ranges postoperatively; thus, the control range achieved was much greater than the desired target, as might generally be expected for clinic-controlled INR.

Conclusion: The On-X valve performed well in this study, confirming the original design intent of minimal hemolysis and low adverse event rates.

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The On-X[®] prosthetic heart valve was introduced internationally in 1996, and clinical experience with the valve has been reported in the literature on several occasions. Both, Laczkovics et al. (1) and Moidl et al. (2) provided general reports on the valve demonstrating its early clinical performance in a multicenter European trial designed in identical fashion to the present study. Birnbaum et al. (3) first reported on the low levels of blood damage created by the valve, while Chambers et al. (4) identified the valve's improved hemodynamics.

As with all mechanical valves, design considerations for the On-X included goals to reduce turbulence, to improve flow through the critical pivot area, improve the overall flow dynamics, and to reduce the chance for pannus overgrowth causing malfunction. The ultimate goal for a mechanical valve is to mimic the natural valve enough to allow the reduction or elimination of anticoagulant therapy to the levels used with tissue valves, while maintaining a level of durability that even the latest-generation tissue valves cannot match.

The particular features of the On-X valve that combine to create a potential for reduced anticoagulation include a flared, elongated orifice, pure pyrolytic carbon with ultrasmooth and ultrapure surfaces, a pivot mechanism that allows full 90° opening and has no stasis points during any phase of the cardiac cycle, and highly controlled dimensional matching that creates consistent mechanical performance. The valve has supra-annularly positioned sewing rings and also

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complete intra-annular support for full protection against late pannus overgrowth in both the aortic and mitral positions.

Clinical material and methods

Patients

A prospective, non-randomized, multicenter clinical trial in North America was conducted at nine centers. The first implant was conducted on March 13, 1998 and patients were enrolled through May 2002. All data were current to May 31, 2005. The total patient population in the present study was 284 (142 aortic valve replacement (AVR), 142 mitral valve replacement (MVR)). Follow up was conducted in the physicians' offices, in the outpatient clinic or by telephone, and included a total of 1,273 patient-years (pt-yr) (659 pt-yr after AVR, 614 pt-yr after MVR) with a maximum follow up of 5.7 years and a mean of 4.5 years. Follow up was complete in 97.9% of AVR patients and in 99.3% of MVR patients. The study included adult patients requiring isolated AVR or MVR according to the standard valve replacement criteria of each center; concomitant cardiovascular procedures were permitted. Exclusions were women of childbearing age, patients with active endocarditis, intravenous drug abusers, and patients with existing major non-cardiac disease that would limit survival to less than the five-year planned course of the study.

The mean patient age at the time of surgery was 58.6 ± 9.9 years (range: 59 to 85 years) after AVR, and 59.9 ± 10.6 years (range: 61 to 78 years) after MVR. AVR patients included 71.8% males, and MVR patients 33.1% males. Preoperatively, the majority of patients were in NYHA classes II or III; the distribution of NYHA class among all patients is shown graphically in Figure 1. AVR patients were in sinus rhythm on 89.4% of occasions, and atrial fibrillation occurred in 7.8% of patients. In contrast, sinus rhythm was present in 56.3% of MVR patients, and atrial fibrillation in 39.4%. The predominant valve pathology in AVR patients was calcific (56.3%), congenital bicuspid (35.2%) or degenerative (15.5%), whilst among MVR patients it was rheumatic (36.6%), degenerative (33.1%) or calcific (12.7%). The aortic valve lesion was stenotic (45.1%),

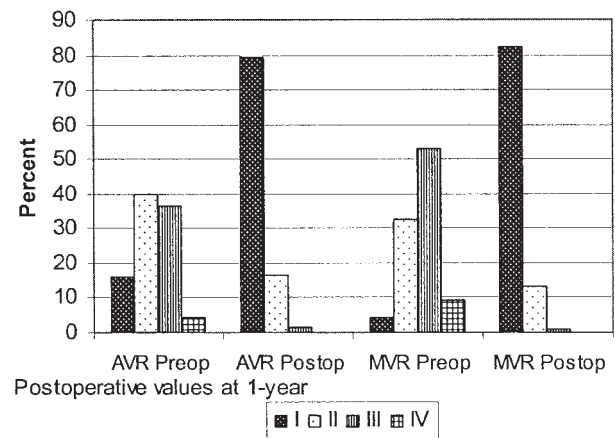


Figure 1: NYHA classification at preoperative and one-year postoperative intervals.

mixed (41.5%) and regurgitant (13.4%), while the mitral lesion was regurgitant (48.6%), mixed (43.0%) or stenotic (5.6%).

Anticoagulation

From the start of the study in 1998, patients were maintained on permanent warfarin anticoagulation therapy as per the protocol requirements based on the 1993 recommendations of Gohlke-Barwolf et al. (5); this was the situation for all of the AVR patients (International Normalized Ratio (INR) target 2.5-3.5) and for 99.2% of MVR patients (INR target 3.0-4.5). INR histories for all patients were collected at each follow up visit wherever possible in order to allow an assessment of anticoagulant compliance.

Hematologic studies

For blood damage studies all samples were shipped to a central laboratory (Quest Diagnostics) according to a precise handling protocol for analysis, thus assuring consistent and comparable results across all centers. Parameters measured included the elements of a complete blood count plus serum lactate dehydrogenase (LDH) activity and serum haptoglobin levels.

Valve implants

The size distribution of the valves implanted is

Table I: Size distribution for aortic and mitral valve implants.

Valve type	Valve size (mm)						Total
	19	21	23	25	27/29	31/33	
AVR	23 (16.2)	46 (32.4)	50 (35.2)	10 (9.2)	10 (7.0)	-	142 (100)
MVR	-	-	-	26 (18.3)	77 (54.2)	39 (27.5)	142 (100)

Values in parentheses are percentages.

detailed in Table I. This was an expected normal distribution, the largest size group being 23 mm among AVR patients and 27/29 mm among MVR patients. Concomitant procedures were performed in 46.5% of AVR patients and in 54.2% of MVR patients; coronary artery bypass grafting was the most frequently performed procedure (40.1% during AVR, and 23.9% during MVR). The predominant suturing method chosen for AVR was interrupted, non-everting mattress sutures; that for MVR was interrupted, everting mattress sutures. No preferred valve orientation was seen for AVR, but for MVR an anti-anatomical placement was preferred.

Statistical analysis

Standard statistical techniques were used during these studies. Normal descriptive statistics were used to calculate mean (\pm SD), median and range, where appropriate. Early event rates were expressed as percentages against numbers of implants or patients, whereas late event rates were linearized to follow up time as percent per pt-yr of follow up. Some late event rates were calculated using the life-table methods of Kaplan-Meier and presented as percentage freedom from the event. All events were recorded and classified according to American Association of Thoracic Surgeons/Society of Thoracic Surgeons guidelines (6).

Results

Adverse events

Details of early events are listed in Table II, and those of late events in Table III.

Aortic valve replacement

Among AVR patients there were 10 thromboembolisms (TE) (four early and six late). Seven of the TEs were transient and three were reversible ischemic neurological deficits (RINDs). None of these resulted in permanent impairment. At the time of the event, six patients had an INR within the target range, two were below target, none exceeded the target value, and two had an unknown anticoagulant status. The five-year event-free rate for TE was $94.2 \pm 2.0\%$. There were no cases of valve thrombosis.

Twenty-four bleeding events occurred (six early, 18 late), and of these events 17 (four early, 13 late) were classified as major bleeding. Only one bleeding event was neurological, whereas 15 involved the gastrointestinal (GI) tract. The remaining eight were a mixture of nosebleeds, hematomas and post-surgical bleeds after non-cardiac reoperations. Two patients each had three separate GI bleeding events. Two of these led to death; one after an inguinal hernia repair and one GI bleed. The INR value at the time of the event exceeded the target on 10 occasions, was below target once, was within target range seven times, and was unknown six times. The five-year event-free rate for bleeding was $87.7 \pm 2.8\%$.

Other late valve-related adverse events included one major paravalvular leak which was repaired on reoperation, one case of endocarditis, and one unexplained high gradient two weeks after hernia repair surgery that resolved without treatment. There was no early mortality. The late mortality rate was 1.37% per pt-yr (nine events) of which five were valve-related, including the two bleeding events noted above and three

Table II: Early (<30 days) adverse event rates after aortic valve replacement (AVR) and mitral valve replacement (MVR).*

Event	AVR	MVR
Thromboembolism	2.8 (0.8-7.2)	1.4 (0.2-5.1)
Thrombosis	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Bleeding event	4.2 (1.9-9.2)	2.8 (0.8-7.2)
Major bleed	2.8 (0.8-7.2)	2.8 (0.8-7.2)
Paravalvular leak	0.7 (0.02-4.0)	0.7 (0.02-4.0)
Major paravalvular leak	0.7 (0.02-4.0)	0.0 (0.0-2.6)
Prosthetic endocarditis	0.7 (0.02-4.0)	0.0 (0.0-2.6)
Hemolysis	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Structural dysfunction	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Non-structural dysfunction	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Valve-related reoperations	0.7 (0.02-4.0)	1.4 (0.2-5.1)
Explants	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Sudden death	0.0 (0.0-2.6)	0.0 (0.0-2.6)
Valve-related mortality (including sudden death)	0.0 (0.0-2.6)	0.7 (0.02-4.0)
Total valve-related morbidity and mortality	8.4 (4.4-14.6)	4.9 (2.0-10.2)
Overall mortality	0.0 (0.0-2.6)	2.1 (0.4-6.2)

*Values are percentages with Poisson distribution; values in parentheses are 95% confidence limits.

cases of sudden death, The five-year event-free rate for valve-related mortality was $96.3 \pm 1.6\%$, and for overall mortality was $93.4 \pm 2.1\%$.

Mitral valve replacement

Twelve TEs occurred after MVR (two early, 10 late). Eight of these TEs were transient, one was a RIND, and three led to permanent deficits (including one death from a stroke). At the time of the event, five INR-values were low, four were in range, none was high, and three had unknown anticoagulant status. The five-year event-free rate for TE was $92.5 \pm 2.3\%$. There were no cases of valve thrombosis.

Twenty-three bleeding events occurred (four early, 19 late), and of these events 16 (four early, 12 late) were classified as a major bleeding. Only one of the bleeding events was neurological, nine were gastrointestinal, and 13 were a mixture of nosebleeds, hematomas and post-surgical bleeding after non-cardiac reoperations. One early GI bleed and two late GI bleeding events led to death. Bleeding events occurred nine times when the INR-value exceeded target, five times with the INR in target range, four times with below INR target, and in five cases the INR status was unknown. The five-year event-free rate for bleeding was $88.0 \pm 3.0\%$.

The early mortality rate was 2.1% (n = 3), with one GI bleeding event being valve-related. Other late valve-related adverse events included three paravalvular leaks (one major leak that was repaired surgically and two minor leaks seen on echocardiography). The late mortality rate was 2.28% per pt-yr (14 events) of which six were valve-related, including the stroke and two bleeding events listed above and three sudden deaths.

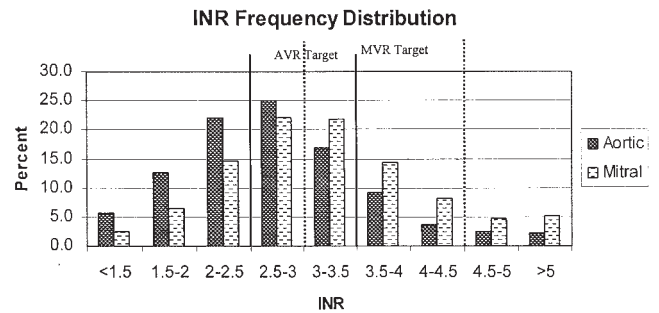


Figure 2: Frequency distributions for International Normalized Ratio (INR) within the study.

The five-year event-free rate for valve-related mortality was $95.6 \pm 1.8\%$, and for overall mortality was $89.9 \pm 2.6\%$.

Anticoagulant compliance

Patients were asked to record all their INR measurements and to bring their records to the follow up examination for at least the first year after implantation. These measurements were collected and analyzed to assess and confirm anticoagulant compliance. A total of 10,488 INR values was collected from 282 patients over the entire study. The frequency distribution of INR, expressed as percentage by position, is illustrated in Figure 2. Target INR ranges were met in 41.8% of AVR readings, and in 44.2% of MVR readings. The span of the MVR target range was 1.5, whilst that for AVR was 1.0. Readings exceeded target in 17.6% of AVR cases and in 9.8% of MVR cases, but were below target in 40.5% of AVR and 46.0% of MVR patients. The

Table III: Late (>30 days) adverse event rates after aortic valve replacement (AVR) and mitral valve replacement (MVR).*

Event	AVR	MVR
Thromboembolism	0.9 (0.3-2.0)	1.63 (0.8-3.0)
Thrombosis	0.0 (0.0-0.6)	0.0 (0.0-0.6)
Bleeding event	2.7 (1.6-4.3)	3.1 (1.9-4.8)
Major bleed	2.0 (1.0-3.4)	1.9 (1.0-3.4)
Paravalvular leak	0.1 (0.04-0.8)	0.5 (0.1-1.4)
Major paravalvular leak	0.1 (0.04-0.8)	0.2 (0.04-0.9)
Prosthetic endocarditis	0.1 (0.04-0.8)	0.0 (0.0-0.6)
Hemolysis	0.0 (0.0-0.6)	0.0 (0.0-0.6)
Structural dysfunction	0.0 (0.0-0.6)	0.0 (0.0-0.6)
Non-structural dysfunction	0.1 (0.04-0.8)	0.0 (0.0-0.6)
Valve-related reoperations	0.5 (0.09-1.3)	0.5 (0.1-1.4)
Explants	0.0 (0.0-0.6)	0.0 (0.0-0.6)
Sudden death	0.5 (0.09-0.6)	0.5 (0.1-1.4)
Valve-related mortality (including sudden death)	0.8 (0.2-1.8)	1.0 (0.4-2.1)
Total valve-related morbidity and mortality	4.6 (3.1-6.5)	6.0 (4.2-8.3)
Overall mortality	1.4 (0.6/2.6)	2.3 (1.2/3.8)

*Values are percentages with Poisson distribution; values in parentheses are 95% confidence limits.

mean INR value was within target, but skewed to the low end of target in both positions: 2.7 ± 1.0 after AVR and 3.2 ± 1.2 after MVR. The number of readings exceeding the target range might have resulted in the slightly elevated bleeding rates. In contrast, the very large number of readings below the target range did not seem to affect the thrombotic event rates.

NYHA functional class

The NYHA classification for patients at the one-year postoperative interval is shown in Figure 2. The improvement from preoperative status was significant: 76.2% of AVR patients showed improvement, with 16.7% in class I. Likewise, 90.2% of MVR patients improved, with 4.3% in class I. Only one patient in each group (0.8%) had a higher postoperative NYHA classification.

Hematologic findings

The mean results of one-year postoperative blood tests for LDH by position were 221 ± 47 IU after AVR, and 254 ± 58 IU after MVR (each with a sample size of 61). The upper normal LDH value was 250 IU for females and 270 IU for males in this study, giving a weighted average upper normal for LDH of 264 IU after AVR and 257 IU after MVR. Unlike most valves, where the postoperative LDH is routinely above normal, LDH remained in the normal range: median 217 (82% of upper normal for AVR) and 251 (98% for MVR) with this valve for most patients. Haptoglobin levels were typically reduced postoperatively in most patients, although 32% of AVR patients and 11% of MVR patients remained in the normal range at one year after surgery. Postoperatively, all elements of the complete blood count remained within the normal range for both valve groups.

Discussion

It is recommended that all patients with mechanical valve implants require permanent warfarin-based anticoagulant therapy, with current INR target recommendations for bileaflet valves of 2.0-3.0 after AVR and 2.5-3.5 after MVR (7,8). Due to the timing of the start of the present study, the targets were 2.5-3.5 for AVR and 3.0-4.5 for MVR. Despite these higher targets, patients tended to have INR values below 3.0. Thromboembolism occurred with either low or targeted INRs, particularly in MVR patients, while bleeding events occurred most often with INR values exceeding the target range. Thromboembolisms were also predominantly transient in the study, whilst bleeding events were frequently major. Almost twice as many bleeding events occurred as TEs. Bearing these data in mind, it is clear that an improved performance could

be achieved by reducing the number of bleeding events with better INR control, or with lower levels of anticoagulation.

Studies of mechanical valves focus on the rates of thrombotic and bleeding events, either separately or as a composite index, due to the general requirement for anticoagulation and the generally accepted long-term durability of bileaflet mechanical valves. In a complete review of the literature on mechanical valves Akins (9) reported the composite sum of thrombotic and bleeding events for the St. Jude Medical (SJM) valve of 4.28% per pt-yr (range: 0.87 to 10.67%/pt-yr) after AVR, and 4.16% per pt-yr (range: 0.35 to 10.81%/pt-yr) after MVR. The composite rates in the present study were comparable at 3.64 after AVR and 4.72 after MVR. However, rates for thrombosis of zero in both positions and thromboembolism (0.91 after AVR, 1.63 after MVR) were lower than the SJM composite indices of 0.2 for thrombosis in both positions and 2.0 after AVR and 2.5 after MVR for TE, indicating a potential for reduced thrombotic event rates for the On-X valve.

Because the reporting of minor or transient events is often inconsistent, it is interesting also to examine the occurrence only of major events. Koertke and Koerfer (10) reported on a study of three current-generation mechanical valves using conventional clinic monitoring or home monitoring of anticoagulation control. In this report, only major bleeding and thrombotic events (termed grade III events) were considered. The sum of both early and late events was also used. Home monitoring was found to increase the percentage of within-range (2.5-4.5) INR measurements from 60.5 to 78.3% and to reduce event rates by about 40% compared to clinic monitoring. The patient population and follow up were roughly equivalent to those of the present study, including the percentage of within-range INR values (61.5% using the Koertke range) in the clinic-monitored group. The Koertke clinic-controlled group had a bleeding event rate of 2.1% per pt-yr and a thrombotic event rate of 2.6% per pt-yr, compared to rates in the present study of 2.3% per pt-yr and 0.6% per pt-yr when analyzed by the Koertke criteria. As would be expected with similar INR control, the bleeding rates were similar despite the higher proportion (9.8% versus 3.7%) of high readings in the present study. However, the thrombotic event rate for the On-X valve was about 20% that of the Koertke report, again indicating a potential for better thromboresistance with the On-X valve.

The results presented by Laczkovics et al. (1) and Moidl et al. (2) at different points in the same European study also showed TE rates below 2.0% per pt-yr, and no thrombosis in both positions. A study of 438 patients by Williams and Van Riet (11) in a poorly, anticoagulated population with approximately 40% of

patients not under proper control and an INR target of 1.5-2.5 in all patients also had TE rates below 2.0% per pt-yr and, remarkably, only one thrombosis in the mitral position at up to six years of follow up. Another multicenter study in Europe (12) produced one-year event-free rates for TE of 98.9% after AVR and 100% after MVR, and with no thrombosis. This cumulative experience would suggest that the On-X valve has increased thromboresistance that might allow for reduced anticoagulation.

Low levels of postoperative LDH activity in patients receiving the On-X valve in both the aortic and mitral positions provided evidence of minimal blood damage caused by this valve, and confirmed the findings reported by Birnbaum et al. (3). A correlation between the presence of elevated LDH activity and adverse events such as TE and bleeding is suggested. A typical bileaflet valve elevates LDH to levels of around 120-150% of upper normal (13-15), while tissue valves produce postoperative LDH values within the upper normal range (14). In behaving more like a tissue valve, the On-X valve suggested a clear improvement in performance that will most likely benefit patients by providing fewer complications. This may also support the notion of a potential for reducing anticoagulation with the On-X valve.

In conclusion, the On-X valve performed very well through an average follow up of 4.5 years, and a maximum follow up of 5.7 years, in patients with isolated valve replacement. The findings of a longer-term follow up are awaited to confirm the performance of the valve beyond 10 years. During the intermediate term, however, the On-X valve has performed well in all aspects evaluated, in particular showing low levels of hemolysis and low thrombotic event rates with high degrees of freedom from TE and thrombosis. As a result of these findings, the On-X valve is an ideal candidate device for studies exploring reduced anticoagulation in mechanical valves.

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Meeting discussion

DR. PAUL KURLANSKY (Miami, Florida, USA): There are significant theoretical reasons to suspect that this valve may have less thromboembolic potential than other valves, yet the target INRs used were on the high side - 2.5 to 3.5 in the aortic position, and 3 and upward in the mitral position. This may relate to the relatively higher incidence of bleeding than expected. I have two questions. First, why were the target INRs chosen to be so high? Second, did you correlate the bleeding episodes with actual INR rates rather than whether they were above or below the target range? Was there was a discernable cut-off level for bleeding relative to INR with this valve?

DR. KATHLEEN W. McNICHOLAS (Newark, Delaware, USA): The INR rates were set high because of FDA recommendations, but they have now been adjusted downwards. The On-X is our preferred valve, and we have been very favorably impressed. In fact, we have some patients with much lower INRs, but we can't recommend that because of FDA constraints. The bleeding rates were also higher in patients, as could be expected. We can improve the thromboembolic events

with the design of the valve, but the inherent problems of warfarin still plague us. Some other current studies using the On-X have lower anticoagulation - in Germany for example there may be aspirin-only studies.

MR. JOHN PEPPER (London, UK): Your gradients were excellent, but did you consider exercise? Were any of your patients subjected to stress echocardiography? Also, what happens to hemolysis on exercise?

DR. McNICHOLAS: We did not check hemolysis on exercise, but we have used stress echocardiography. There is an amazing lack of turbulence and lack of significant gradient, even with exercise. This is particularly the case in very large patients.

DR. W. R. ERIC JAMIESON (Vancouver, Canada): I have two questions. First, the mitral prostheses were all size 25 mm, and that relates to Dr. Pepper's question about exercise. Second, there is an ongoing control trial between On-X and another conventional valve. Based on your current experience, what anticoagulant targets would you set for the aortic and mitral valves?

DR. McNICHOLAS: For the aortic valve we use an INR value of 2 to 3, and for the mitral valve a value of 2.5 to 3.5.