

Lowered bleeding rates for a mechanical valve



Can bleeding event rates be made the same for mechanical and tissue valves while still keeping thromboembolism rates equal?

Historic Bleeding Rates for Tissue Valves

A factor often overlooked in valve replacement decisions is that tissue valves recipients have a real risk of suffering bleeding events although it is generally considered to be lower than that of bileaflet mechanical valves. This is due to the need for warfarin in all mechanical valve patients as opposed to a portion of tissue valve patients.

In 1992 Grunkemeier¹ published a review of the long-term performance of prosthetic heart valves. At that time, bleeding event rates for tissue valves were as high as 1.3 %/pt.yr. in aortic valve replacement (AVR) and 2.4 %/pt.yr. in mitral replacement (MVR). The corresponding thromboembolism (TE) rates varied from 0.3 to 2.8 %/pt.yr. AVR and 0.3 to 3.8 %/pt.yr. MVR. In that same review, bileaflet mechanical valves had bleeding events as high as 3.0 %/pt.yr. in AVR and 0.0 to 2.1 %/pt.yr. in MVR with corresponding TE rates of 0.6 to 2.5 %/pt.yr. and 0.3 to 3.9 %/pt.yr.

Higher bleeding rates in MVR over AVR reflect two factors: 1) higher target anticoagulation for MVR over AVR, 2) larger percentages of tissue valve recipients on anticoagulation with MVR. Grunkemeier concludes that TE rates for these early valves are not related to valve design while bleeding rates are half as large for tissue valves versus mechanical valves due to anticoagulation requirements. This conclusion has been held as truth for over 15 years, but is it still true?

Table 1.

Valve Major Bleeding Event Rates from FDA Data (% per pt.yr.)		
Valve Type	AVR	MVR
Perimount Magna ²	0.4	Not Applicable
Prima Stentless ³	0.9	Not Applicable
SAV ⁴	2.05	Not Applicable
Mosaic ⁵	0.8	1.1
Hancock II ⁶	0.3	1.1
Biocor (Sweden) ⁷	0.77	0.95
Biocor (Italy) ⁷	0.69	.80
SJM Regent ⁸	2.2	Not Applicable
ATS ⁹	1.27	0.53
On-X ^{10, 11}	0.2	0.5

Based on data from FDA reviewed studies, current generation tissue valves continue to demonstrate bleeding event rates consistent with the Grunkemeier review as shown in Table 1—so too do most recent mechanical valves.

Current Bleeding Rates

AVR bleeding rates for tissue valves continue to be slightly less than those for MVR, most likely due to a lower percentage of patients maintained on anticoagulants and to lower target INR's. Tissue valve bleeding rates are half that of SJM and ATS mechanical valves at 0.8 versus 1.7 %/pt.yr. Adding the On-X valve rates into the mechanical average lowers it to 1.2 (still 50 % higher than tissue valves), but on its own **the On-X valve hemorrhage rate is equivalent to that for tissue valves.**

Thromboembolism rates are all consistent with the Grunkemeier review as shown in Table 2, but **On-X valve TE rates are on the lower end of the range.**

Table 2.

Valve Thromboembolic Rates from FDA Data (% per pt.yr.)		
Valve Type	AVR	MVR
Perimount Magna ²	2.4	Not Applicable
Prima Stentless ³	2.7	Not Applicable
SAV ⁴	2.64	Not Applicable
Mosaic ⁵	1.25	1.6
Hancock II ⁶	2.0	3.1
Biocor (Sweden) ⁷	1.96	2.52
Biocor (Italy) ⁷	1.30	1.40
SJM Regent ⁸	2.2	Not Applicable
ATS ⁹	2.08	4.00
On-X ^{10, 11}	1.7	1.7

Thromboembolism rates remain roughly equal between mechanical and tissue valves despite the passage of time and new designs. **If bleeding rates in mechanical valves could be reduced without increasing TE rates, then mechanical valve choice would be more favorable.**

Highlights of attempts to reduce bleeding complications:

- 1986 Review of efforts to reduce bleeding rates for previous generation mechanical valves by using antiplatelet therapy found them to be unsuccessful. *Hartz, et al.*¹²
- 1993 Published study showed that INR below 2.0 greatly increased the incidence of thromboembolism for the most widely implanted mechanical valve. *Horstkotte, et al.*¹³
- 1990-1997 Oden and Fahlen¹⁴ examined the risk of death in Sweden in all patients anticoagulated for any reason over the period of 1990 to 1997 using data from centralized clinics across the country. They found that death from all causes was lowest at an INR of 2.15; death from cerebral bleeding was lowest between an INR of 1.5 and 2.4. Based on this study, they proposed a lower INR with a narrower target range for all conditions, including implanted heart valves.
- 2001 ESCAT study demonstrated that bleeding rates can be reduced if tightly controlled with home monitoring. *Körtke, et al.*¹⁵
- 2006 PROACT study initiated with the first and only FDA approval of INR below recommended ranges and with antiplatelet therapy for low risk patients with the On-X mechanical valve.¹⁶
- 2006-2008 Three studies indicate lowered anticoagulation treatment for On-X valve patients lowers bleeding rates without increasing thromboembolic rates. *Williams et al.*,¹⁷ *Tsai et al.*,¹⁸ *Takanashi, et al.*¹⁹

PROACT Results

The PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial)¹⁶ trial is designed to determine the appropriate anticoagulation levels for the On-X valve. INR targets in the test group for AVR high risk patients (the largest portion of valve patients in the study) are lowered by 0.5 INR and are similarly narrowed. High risk AVR patients are tested at 1.5 to 2.0 against controls at 2.0 to 3.0. Currently in the high risk groups there are 122 patients in the control and 113 in the test arms with experience out to as much as 1.67 years of follow-up averaging 0.5 years. **Differences between the control and test groups have yet to reach statistical significance--bleeding event rates as of March 31, 2009, were 0.9 %/pt.yr. (test group) and 2.5 %/pt.yr. (control group).**

Further follow-up in PROACT may yet bear out the proposal of Oden and Fahlen.¹⁴ It may also show that the On-X South African trial¹⁷, where the INR targets were intuitively chosen to be 1.5-2.5 resulting in TE and bleeding rates of 1.4 %/pt.yr. and 0.9 %/pt.yr. respectively, correctly projected the success of lowered anticoagulation targets for the On-X valve in ongoing studies.^{18,19} **When a mechanical valve provides bleeding and TE rates equal to a tissue valve, where then would the choice of valve stand?**

Until the completion and analysis of study data, On-X Life Technologies, Inc., continues to recommend standard anticoagulation therapy as presently prescribed by various professional societies for the On-X valve.²⁰

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On-X aortic and mitral valves are FDA approved.

CAUTION: Federal law restricts this device to sale by or on the order of a physician. Refer to the Instructions for Use that accompany each valve for indications, contraindications, warnings, precautions and possible complications. For further information, visit www.onxlti.com. CAUTION: This investigational use of this device is limited by federal law to investigational sites.

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