

Multiple international studies with lowered INR and the On-X valve



Three studies support the protocol of the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT).

In the past two years, there have been three publications/presentations of studies supporting lowered anticoagulation with the On-X® Prosthetic Heart Valve. These three studies that incorporated reduced INR levels are from South Africa, Taiwan and Japan.¹⁻³

Chief Director Takanashi and associates reported results for aortic patients with an INR of 1.3-1.8 in October of 2008 in Fukuoka, Japan, at the Japanese Association of Thoracic Surgery.¹ In this study, 81 aortic patients accrued a mean follow-up of 12 months. Patients were divided in two groups (high risk and low risk) at three postoperative months according to presence of risk factors which included chronic atrial fibrillation, EF<30%, LAD>50mm diameter, left or right ventricular aneurysm and neurological events. There was no thrombosis in either group. One early thromboembolic event occurred in one high risk patient (standard anticoagulant therapy) and one cerebral bleeding event occurred in the low risk group at 8 months postoperatively (reduced anticoagulant therapy).

Professor Tsai and associates of Taiwan reported results for 573 patients with the On-X valve and an INR of 1.5 - 2.5 for aortic replacement and 2.0 - 3.0 for mitral replacement.² These results were reported in a poster presentation at the Society of Heart Valve Disease 4th Biennial meeting in New York City in June of 2007. The thromboembolic rate at this tertiary care center was 0.7%/pt.yr., bleeding was 1.6%/pt.yr. and there were no thromboses in the ten year study span. This is a similar finding to the FDA study of the On-X valve in which there were no thromboses during the first seven years.³

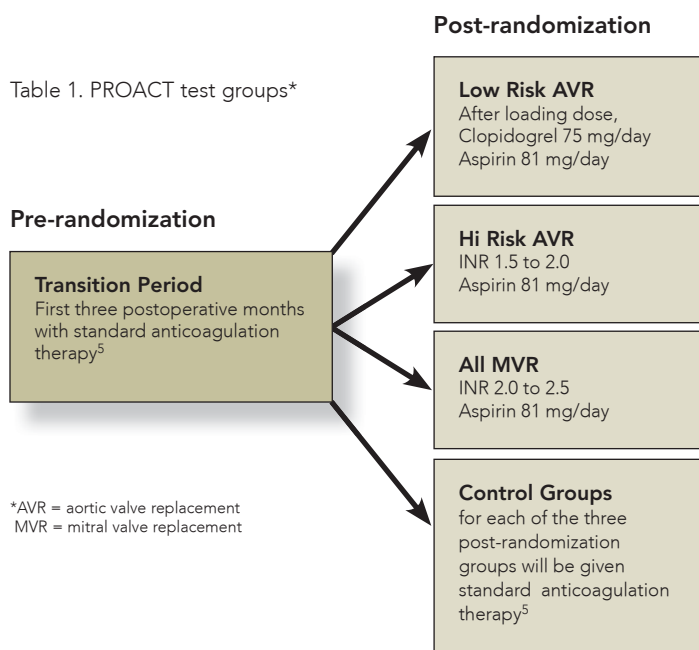
Mervyn Williams and Sonia van Riet of Port Elizabeth, South Africa, published their results for 438 patients implanted with an On-X valve with an INR of 1.5-2.5 in a highly non-compliant population (42% not properly anticoagulated).⁴ Even so, at 1.7 years mean follow-up (>95% complete follow-up), the thromboembolism rate for aortic and mitral valves was 1.4 %/pt.yr., the thrombosis rate was 0.17 %/pt.yr. and hemorrhage was 0.9 %/pt.yr.—actually lower event rates than seen in most conventional valves studies in Western society. Moreover, a majority of these implants were mitral valves (55%) and double valves (21%).

These three studies support the hypothesis for the PROACT study—the On-X valve will provide an equally low incidence of complications with standard therapy and with lowered anticoagulation. This study is now almost three years old. Forty centers have been recruited. The patient population has more

than doubled in the past year. Randomization of patients to the different test groups (Table 1) occurs at three months postoperatively according to the Clinical Trial Investigation Plan. Enrollment in the AVR high risk group is expected to close in 2009, with the other groups to follow in 2010. Statistics are reviewed annually by the PROACT Data and Safety Monitoring Committee.

The six study groups are low risk aortic, high risk aortic and mitral valve implants each with a control group. These groups are defined in Table 1.

Table 1. PROACT test groups*



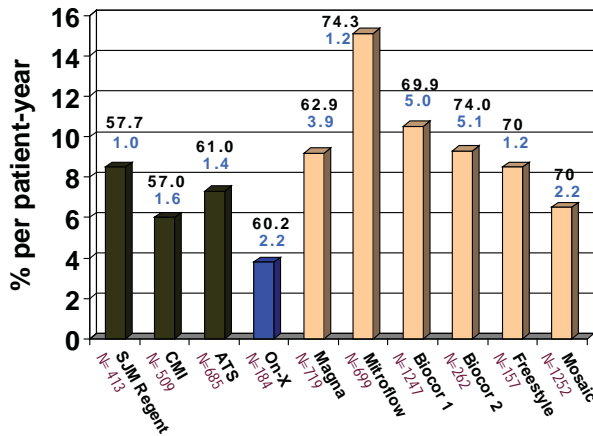
Exclusion criteria from the low risk group of aortic patients who will receive non-warfarin treatment after three months postoperatively are seen in Table 2. Non-warfarin treatment consists of aspirin 81 mg every day along with clopidogrel (300 mg loading dose followed by 75 mg every day) IF the patient has tested positive for response to both drugs.

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.⁵

Table 2. Exclusion criteria from low risk aortic valve patient group

Chronic atrial fibrillation
 Left ventricular ejection fraction < 30 %
 Enlarged left atrium >50mm diameter
 Spontaneous echo contrasts in the left atrium
 Vascular pathology
 Neurological events
 Hypercoagulability
 Left or right ventricular aneurysm
 Lack of platelet response to aspirin or clopidogrel
 Women receiving estrogen replacement therapy

Figure 1. Aortic Valves



Aortic valves: Aggregates of linearized rates (% per patient-year) provided in FDA submission data in the past 15 years. Aggregate = thromboembolism + hemorrhage + thrombosis + reoperation + mortality. Data is available in each product's *Instructions for Use* or *Summary of Safety and Effectiveness*. Numbers at top of or near aggregate bars are mean age in years (value in black) and mean follow-up in years (value in blue). Some age data are estimates.^{3,6-13}

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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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Updates on the PROACT study will be posted as available on the On-X Life Technologies, Inc., website at www.onxlti.com. Further information may be obtained by calling 1 (888) 339-8000 in the USA and Canada and + 1 (512) 339-8000 internationally.

Risks associated with other mechanical and tissue valve designs

Older design "low profile" mechanical valves have higher incidences of thrombus, thromboembolism, hemorrhage, reoperation and mortality as evident in a comparison of morbid event rates from the Summary of Safety and Effectiveness or the Instructions for Use. These multi-center, mostly international studies were conducted under similar protocols and were closely scrutinized by the USA Food and Drug Administration. Figure 1 reflects the cumulative morbid event rates from these studies of currently implanted valves on the market.^{3,6-13}

Trials of the On-X valve from diverse healthcare and ethnic environments at reduced anticoagulation levels provide continuing evidence that this valve consistently demonstrates excellent clinical performance in all aspects. This evidence in combination with the results of the PROACT trial may one day permit present and future patients to choose life without warfarin or reoperation!

