

Low-dose warfarin with a novel mechanical aortic valve: Interim registry results at 5-year follow-up



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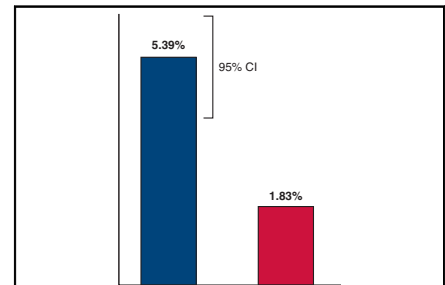
ABSTRACT

Objectives: To evaluate whether warfarin targeted at an international normalized ratio of 1.8 (range, 1.5-2.0) after On-X mechanical aortic valve implant is safe for all patients.

Methods: This prospective, observational clinical registry assessed adverse event rates in adult patients receiving low-dose warfarin (target international normalized ratio, 1.8; range, 1.5-2.0) plus daily aspirin (75-100 mg) during a 5-year period after On-X aortic valve implant. The primary end point is the combined rate of major bleeding, valve thrombosis, and thromboembolism overall and in 4 subgroups. The comparator is the Prospective Randomized On-X Anticoagulation Trial control group patients on standard-dose warfarin (international normalized ratio, 2.0-3.0) plus aspirin 81 milligrams daily.

Results: A total of 510 patients were recruited at 23 centers in the United States, United Kingdom, and Canada between November 2015 and January 2022. This interim analysis includes 229 patients scheduled to complete 5-year follow-up by August 16, 2023. The linearized occurrence rate (in percent per patient-year) of the primary composite end point of major bleeding, valve thrombosis, and thromboembolism is 1.83% compared with 5.39% (95% confidence interval, 4.12%-6.93%) in the comparator group. Results are consistent in clinic-monitored and home-monitored patients and in those at high risk for thromboembolism. Major bleeding and total bleeding were reduced by 87% and 71%, respectively, versus the comparator group, without an increase in thromboembolic events.

Conclusions: Interim results support the continued safety of the On-X aortic mechanical valve with a target international normalized ratio of 1.8 plus low-dose aspirin through 5 years after implant, with or without home monitoring. (*J Thorac Cardiovasc Surg* 2024;168:1645-55)



The primary end point rate of 1.83% was better than the 95% CI in the control group.

CENTRAL MESSAGE

Interim registry results support the safety of the On-X aortic mechanical valve with warfarin targeted at an INR of 1.8 (range, 1.5-2.0) plus aspirin, with or without home INR monitoring.

PERSPECTIVE

The On-X aortic valve is the only mechanical valve proven safe and approved for use with INR targeted to 1.5 to 2.0. Approval was based on the PRO-ACT trial, which used warfarin, low-dose ASA, and home INR monitoring. Interim results from this registry support the continued safety of the On-X aortic valve with target INR 1.8 (range, 1.5-2.0) plus aspirin, with or without home INR monitoring.

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interpret the data and to analyze and report the results independent from the sponsor. They also had sole authority to make the final decision to submit the material for publication.

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Abbreviations and Acronyms

AE	= adverse event
ASA	= aspirin
CI	= confidence interval
FDA	= U.S. Food and Drug Administration
INR	= international normalized ratio
MB	= major bleeding
PROACT	= Prospective Randomized On-X Valve Anticoagulation Clinical Trial
pt-yr(s)	= patient-year(s)
TE	= thromboembolism
TIA	= transient ischemic attack
VT	= valve thrombosis

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Lifelong anticoagulation with a vitamin K antagonist remains the current standard of treatment to minimize risks of thromboembolism (TE) and valve thrombosis (VT) in patients with a mechanical heart valve.^{1,2} Clinical trials using other antithrombotic agents, such as apixaban, dabigatran, or dual antiplatelet therapy with clopidogrel and aspirin (ASA), have failed to demonstrate efficacy in preventing thromboembolic events among patients with mechanical heart valves.³⁻⁵ Target international normalized ratio (INR) in all patients with mechanical valves should be individualized depending on valve type and patient risk factors for TE.^{2,6} Except for the On-X aortic mechanical valve (Artivion), guidelines currently recommend an INR target of not less than 2.5 for patients with a bileaflet aortic mechanical valve.^{2,6}

The On-X mechanical aortic valve, designed to minimize thrombogenic potential, has received U.S. Food and Drug Administration (FDA), Health Canada, and Conformité Européenne Mark approval for use with anticoagulation targeted to INR range 1.5 to 2.0 in combination with low-dose ASA, starting at least 3 months after On-X aortic valve implantation.^{4,7,8} Approval was based on results of the Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT).^{4,9}

In the PROACT high-risk arm, patients with 1 or more TE risk factors were randomized to either low-dose warfarin (INR, 1.5-2.0) plus daily ASA 81 mg or standard-dose warfarin (INR, 2.0-3.0) plus daily ASA 81 mg (consistent with guidelines when the trial started in 2006), starting at least 3 months after On-X aortic valve

implant.^{4,9,10} All patients received a home INR monitor at time of randomization and were encouraged to use home INR monitoring.⁴ Those randomized to low-dose warfarin experienced markedly reduced rates of bleeding compared with those randomized to standard-dose warfarin, without a significant increase in thromboembolic events.

This study attempts to answer the following questions:

- Is low-dose warfarin safe for all patients with an On-X aortic valve, without regard to TE risk level or INR monitoring method?
- Are the PROACT results reproducible in a clinical setting, as opposed to a randomized controlled trial?

To address these questions, our study (NCT02677974) assesses major bleeding (MB), VT, and TE rates in all-comer patients receiving low-dose warfarin (target INR, 1.8; range, 1.5-2.0) and low-dose ASA through 5 years of follow-up after On-X aortic valve implantation. The principal objective is to compare rates of adverse events (AEs) among patients in specified subgroups to those in the PROACT trial. The secondary objective is to further assess the long-term safety of the On-X aortic valve. Our prespecified study hypothesis states that the composite incidence rate of MB, VT, and TE in the clinical registry study will be better than the 95% confidence bound of the rate among patients in the PROACT trial who received standard-dose warfarin (INR range, 2.0-3.0). In this interim report, we describe results from 229 patients who were scheduled to complete 5 years of follow-up by August 16, 2023. We will report final results once all patients have completed 5 years of follow-up, anticipated to occur in May 2027.

METHODS**Ethical Statement**

The study was conducted in accordance with principles of the Declaration of Helsinki or under the rules of the local country, whichever provides more patient protection. The institutional review board or ethics committee granted approval of the study at each site. Institutional review board approval numbers and dates are listed in [Table E1](#). All patients provided written informed consent.

Study Design

This prospective, observational, multicenter single-arm registry study (NCT02677974) evaluates AE rates in patients receiving warfarin targeted at INR 1.8 (range, 1.5-2.0) along with low-dose ASA after On-X aortic valve implantation, after at least 3 months of standard-dose warfarin (target INR, 2.5; range, 2.0-3.0) with low-dose ASA postimplant. Each patient is to be followed for 5 years. All-comer patients were enrolled regardless of TE risk status or INR monitoring method. Patients were to be recruited from 15 to 35 centers with appropriate expertise in the United States, United Kingdom, Canada, and Europe starting in November 2015, and continuing until enrollment target was met.

Risk Classification for TE

Patients classified as high risk for TE have 1 or more of these risk factors: chronic atrial fibrillation, enlarged left atrium >50 mm diameter, estrogen-replacement therapy in female patients, hypercoagulability, lack of platelet response to ASA or clopidogrel, left or right ventricular

aneurysm, left ventricular ejection fraction <30%, neurologic events, vascular pathology (history of significant peripheral, carotid, or coronary disease), or spontaneous echo contrast in the left atrium. Patients without these risk factors are classified as low risk for TE.

Inclusion and Exclusion Criteria

Eligible patients include adults 18 years or older who agree to participate and meet the following:

- whose life expectancy is at least 5 years;
- with On-X aortic valve surgery within 12 months before recruitment; and
- have only an On-X aortic prosthetic heart valve (ONXA, ONXAE, ONXAC, ONXACE, ONXAN, and ONXANE) implant with or without concomitant procedures (Table E2).

The study excludes the following patients:

- those with history of arterial thromboembolic event(s) before valve surgery or recruitment;

- those with develop valvular thrombosis after valve implant and before recruitment;
- those with died before recruitment or before hospital discharge after On-X valve surgery; and
- those with any other type of prosthetic valve implant, either isolated or in combination with another valve(s), or any On-X mitral valve.

To minimize bias, all patients who meet inclusion/exclusion criteria are offered enrollment.

Intervention

After On-X aortic valve implant, all registry patients receive low-dose warfarin (target INR, 1.8; range, 1.5-2.0) plus daily ASA (75-100 mg), unless ASA is contraindicated, after a minimum of 3 months of standard-dose anticoagulation. INR monitoring site, ie, at home or in clinic, is decided by each patient, in conjunction with their following and investigating physician(s), at 3 months' postoperatively or at enrollment if later than 3 months after implant. For registry purposes, a clinic is defined as an anticoagulation clinic, hospital laboratory, or physician's office. All home-monitoring

TABLE 1. Baseline characteristics

Characteristic	Clinical registry study		PROACT composite control	
	Value	Subjects assessed	Value	Subjects assessed
Age, y		229		292
Mean \pm SD	53.2 \pm 10.70		54.6	
Median (min, max)	56.0 (23.0, 73.0)			
Sex, n (%)		229		292
Male	165 (72.1%)		230 (78.8%)	
Female	64 (27.9%)		62 (21.2%)	
NYHA class, n (%)		170		271
Class I	45 (26.5%)		57 (21.1%)	
Class II	87 (51.2%)		127 (46.9%)	
Class III	34 (20.0%)		70 (25.8%)	
Class IV	4 (2.4%)		17 (6.3%)	
Lesion, n (%)		229		292
Stenosis	129 (56.3%)		152 (52.1%)	
Regurgitation	58 (25.3%)		57 (19.5%)	
Mixed	40 (17.5%)		77 (26.4%)	
Other	2 (0.9%)		6 (2.1%)	
TE risk group, n (%)		229		292
Low	170 (74.2%)		102 (34.9%)	
High	59 (25.8%)		190 (65.1%)	
Ejection fraction, %		190		
Mean \pm SD	56.8 \pm 10.65			
Median (min, max)	60.0 (6.0, 90.0)			
INR monitoring method, n (%)		229		
Clinic	192 (83.8%)			
Home	37 (16.2%)			
Cardiac rhythm, n (%)		229		
Sinus	219 (95.6%)			
Atrial fibrillation	2 (0.9%)			
Paced	2 (0.9%)			
Other	6 (2.6%)			
Previous cardiac surgery, n (%)		228		
No	203 (89.0%)			
Yes	25 (11.0%)			

PROACT, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; SD, standard deviation; min, minimum; max, maximum; NYHA, New York Heart Association; TE, thromboembolism; INR, international normalized ratio.

arrangements, including insurance coverage if applicable, are coordinated by the patient and physician. Any registry participant experiencing a thrombotic event during the study is returned to standard-dose warfarin. Those who experience a bleeding event may be continued or discontinued from low-dose warfarin, based on the discretion of the clinician and principal investigator. All patients will remain in the registry for analysis purposes, consistent with the intent-to-treat principle.

Control

We compared AE rates in the registry study with those from the historical PROACT control group receiving standard-dose warfarin (target INR, 2.0-3.0) plus ASA 81 mg daily after isolated On-X aortic valve replacement, with or without concomitant procedures. AE rates from this historical control group were predefined when the clinical registry study was designed, from data then available in 2015. For the low-risk control group, data were obtained from the 2014 annual PROACT trial report (G050208). For the high-risk control group, data were obtained from P000037/S030, a supplement to the FDA’s premarket approval of the On-X valve. Data from both high- and low-risk control groups were combined for the “composite” control group. AE rates for this composite group were calculated using a weighted average. These predefined historical control rates are listed in Table E3 (and incorporated into Tables 2-4). The data differ slightly from 2014 and 2018 published reports of the PROACT trial due to the time frame.^{4,9}

End Points

The primary end point is the composite rate of MB, VT, and TE overall and in 4 subgroups: INR monitored at home, INR monitored in clinic, high TE risk, and low TE risk.

Secondary end points include the following:

- individual components of the primary end point;

- TE plus VT rate; and
- the primary end point rate in 4 patient subsets: high-risk home-monitored, high-risk clinic-monitored, low-risk home-monitored, and low-risk clinic-monitored.

Statistical comparisons between subsets were not performed because the subsets were not randomized.

Secondary events also include (1) death, explant, or reoperation associated with a primary end point; (2) sudden death; (3) minor bleeding requiring medical care; and (4) the number and proportion of patients with INR readings below 1.5 or greater than 3.0.

Additional (tertiary) end points include the following: (1) peripheral TE; (2) transient ischemic attack (TIA); (3) ischemic stroke; (4) hemorrhagic stroke; (5) minor bleeding; and (6) all bleeding (major and minor). These events are reported overall, stratified by INR monitoring site, and stratified by TE risk status. Death, explant, and reoperation associated with valve-related bleeding, VT, or TE are tertiary end points.

Definitions of all study end points are shown in Table E4.¹¹

Data and Follow-up

Study participants must agree to the proposed INR therapy, to visit their following physician 6 months after valve implant and annually for 5 years, and to follow-up contact by the registry. Patients must agree the registry site may contact their following physician for information.

Information from the 6-month postoperative visit may be obtained prospectively or retrospectively. Other data are collected prospectively for each patient over a period of 5 years. The study center will contact each patient at 6 months postoperatively if enrolled, and then annually by telephone, text messaging, e-mail survey, or other accepted means of electronic communication. The patient’s anticoagulant status, including current target INR range and most recent INR value, are reviewed at each postoperative visit or electronic interaction. Any valve-related

TABLE 2. Clinical registry study event rates versus PROACT control, all patients*

Event	Clinical registry study all INR 1.5-2.0		PROACT composite control INR 2.0-3.0	P value
	LOR, %/pt-yr (95% CI), no. events		LOR, %/pt-yr (95% CI)	
Number of subjects	229		292	
pt-yr†	981.3		1131.2	
Primary end point				
MB, VT, TE	1.83% (1.09%-2.90%)	18	5.39% (4.12%-6.93%)	<.0001
Secondary and other end points				
MB	0.51% (0.17%-1.19%)	5	3.80% (2.75%-5.12%)	<.0001
TE‡	1.32% (0.71%-2.27%)	13	1.41% (0.81%-2.30%)	
VT	0.00% (0.00%-0.38%)	0	0.18% (0.02%-0.64%)	
All bleeding	2.04% (1.24%-3.15%)	20	7.07% (5.61%-8.80%)	
TE and VT	1.32%	13		
Minor bleeding	1.53%	15		
Hemorrhagic stroke	0.10%	1		
Ischemic stroke	0.82%	8		
Nonthrombotic ischemic stroke	0.10%	1		
TIA	0.51%	5		
Peripheral TE	0.0%	0		
Valve-related reoperation	0.31%	3		
Sudden death	0.0%	0		
Valve-related mortality	0.0%	0		
Total mortality	0.92% (0.42%-1.74%)	9	1.63% (1.08%-2.73%)	.1993

PROACT, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; INR, international normalized ratio; LOR, linearized occurrence rate; pt-yr(s), patient-year(s); CI, confidence interval; MB, major bleeding; VT, valve thrombosis; TE, thromboembolism; TIA, transient ischemic attack. *LORs are calculated based on late patient-years; end points occurring before low INR initiation are excluded. †Patient-years in late follow-up, ie, once low-dose anticoagulation initiated. ‡Ischemic stroke, TIA, plus peripheral TE.

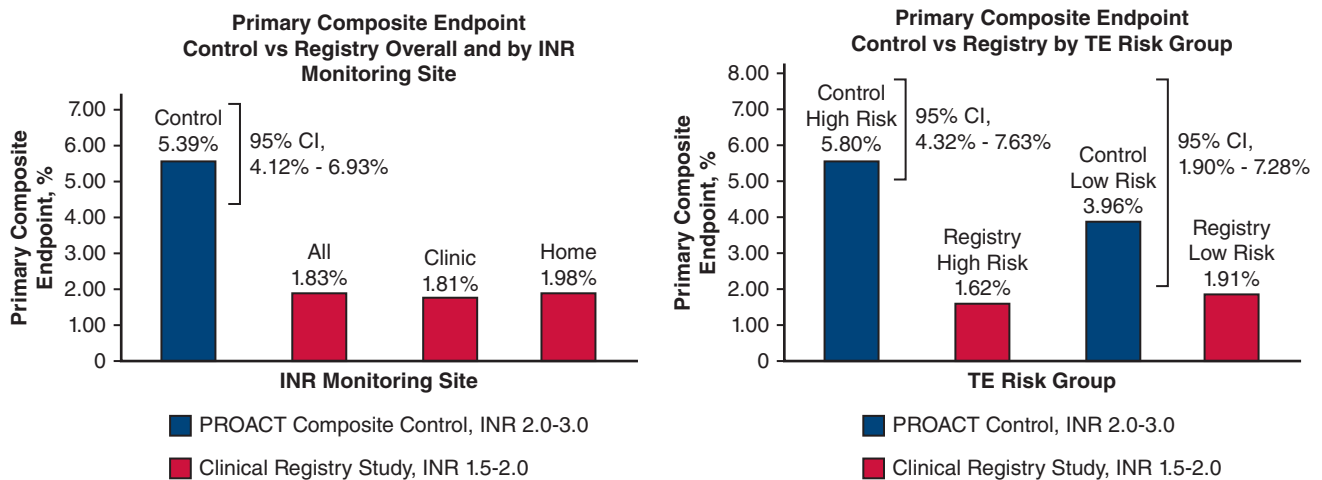


FIGURE 1. Primary composite endpoint. A, Among 229 patients receiving low-dose warfarin, the combined rate (%/pt-yr) of MB, VT, and TE was 1.83% overall, 1.81% in clinic-monitored patients, and 1.98% in home-monitored patients. All were better than the 95% confidence bound in the historical PROACT composite control group on standard warfarin. B, Among high-risk patients, the rate (%/pt-yr) of MB, VT, and TE with low-dose warfarin was 1.62% and better than the 95% confidence bound in the high-risk historical PROACT control group on standard warfarin. Among low-risk patients, the 1.91% rate was within the 95% confidence bound of the low-risk historical PROACT control group. *INR*, International normalized ratio; *CI*, confidence interval; *PROACT*, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; *TE*, thromboembolism; *pt-yr(s)*, patient-year(s); *MB*, major bleeding; *VT*, valve thrombosis

complications will be documented with each contact. Clinical records of any patient experiencing a primary end point event(s) will be obtained and uploaded to the study database for adjudication and classification.

Statistical Analyses

The sample size calculation assumed a 5% significance level, a one-sided test comparing the composite outcome to the reference value, at least 80% power, follow-up of 5 years per subject with 20% loss to follow-up over 5 years, and greater than 800 patient-years (pt-yr) of follow-up in the high-risk group. A Poisson regression estimated the composite outcome incidence. The anticipated overall composite rate of 4.57% per pt-yr was based on results from the high-risk treatment (low-dose warfarin) arm of the PROACT trial. The reference value of 6.93% per pt-yr was based on the upper 95% confidence bound of the rate in the PROACT composite control group (high-risk and low-risk patients on standard-dose warfarin) (Table E3). The sample size calculation generated a target enrollment of 510 subjects with approximately 816 pt-yr in the high-risk group, if a minimum of 40% of enrolled patients were high-risk.

Analyses were performed using SAS, version 9.4.¹² All available data were analyzed overall and by subgroups based on INR method and TE risk category, allowing accurate comparison with the PROACT trial, which was stratified by TE risk and in which all patients were assigned to home INR monitoring.

Early events, ie, those occurring before initiation of low-dose warfarin, are summarized with proportions. If the date of initiation of low-dose warfarin is unknown, early events are defined as those occurring up to 90 days postimplant.

Late events, defined as those occurring after initiation of low-dose warfarin (or after 90 days postimplant if date of initiation of low-dose warfarin was unknown), are summarized with linearized occurrence rates and Kaplan-Meier estimates. Poisson regression was used to analyze the incidence rate of the primary composite end point and its components. Kaplan-Meier estimates are based on the time from initiation of low-dose warfarin to first occurrence of the specified event, and subjects who had not experienced the event as of their date of last contact were censored at this date.

RESULTS

Between November 2015 and January 2022, the registry enrolled 525 patients at 23 centers across the United States, United Kingdom, and Canada. However, 15 patients were deemed ineligible after enrollment and were subsequently exited: (1) one had received aortic and mitral prosthetic valves, (2) one had experienced a previous thrombotic event, and (3) 13 had been implanted with an excluded On-X valve model (AAP, or ascending aortic prosthesis). Of the 510 included patients, 229 were scheduled to complete 5 years of follow-up on or before August 16, 2023. This 5-year interim report analyzes data for these 229 patients.

In this cohort, 59 (25.8%) were high risk for TE, 170 (74.2%) were low risk for TE, 37 (16.2%) were home-monitored, and 192 (83.8%) were clinic-monitored. Median duration of follow-up was 4.7 years since implementation of lower INR target and 5.0 years since valve implant. Since implementation of lower INR target, 981.3 pt-yr were accumulated with 247.1 pt-yr in the high-risk subgroup. Median achieved INR was 1.9. Overall follow-up was 96% complete. Surgery dates spanned from November 2014 through August 2018.

Of these 229 subjects, 24 discontinued study participation before the 5-year follow-up: 9 died, 3 underwent valve explant, 6 were lost to follow-up, 5 chose to withdraw, and 1 discontinued to participate in another study (Figure E1).

Baseline Characteristics

Table 1 shows baseline demographic and clinical data. Mean patient age was 53.2 ± 10.7 years, and 72.1% of

patients were male. Mean preoperative left ventricular ejection fraction was $56.8 \pm 10.65\%$, and 95.6% were in sinus rhythm preoperatively.

Early Events

Early AEs, ie, those occurring before lower INR implementation, occurred in 29 (12.7%) patients. Bleeding events occurred in 15 (6.6%), with 5 (2.2%) MBs, 2 (0.9%) minor bleeds, 6 (2.6%) postoperative bleeds, and 2 (0.9%) traumatic bleeds. Postoperative and traumatic bleeds were not classified as major or minor. Cardiac events occurred in 6 (2.6%). Noncardiac events occurred in 11 (4.8%). An early death, TE, or VT excluded a patient from the study.

Primary End Point

Overall. The primary composite end point (MB, VT, and TE) rate was 1.83% (95% confidence interval [CI], 1.09%-2.90%) per pt-yr versus 5.4% (95% CI, 4.1%-6.9%) in the composite PROACT control group (high- and low-risk patients on standard-dose warfarin); [Table 2](#) and [Figure 1, A](#). [Figure 2](#) displays the Kaplan-Meier time-to-first event curve for freedom from the primary end point. At 5 years after implant, the minimum

estimated freedom from a primary end point event was 91.5% (standard error, 2.3%).

Home-monitored and clinic-monitored subgroups. Among home-monitored patients, the primary end point rate (%/pt-yr) was 2.0% versus 1.8% among clinic-monitored patients. Both were less than the 95% CI (4.1%-6.9%) of the rate in the composite PROACT control group ([Table 3](#) and [Figure 1, A](#)).

High-risk and low-risk subgroups. The primary end point rate (%/pt-y) was 1.6% in the high-risk subgroup versus 5.8% (95% CI, 4.3%-7.6%) in the PROACT high-risk control group, and below the 95% CI ([Table 4](#), [Figure 1, B](#)). The primary end point rate was 1.9% in the low-risk subgroup versus 4.0% (95% CI, 1.9%-7.3%) in the PROACT low-risk control group and was within the 95% CI ([Table 4](#), [Figure 1, B](#)).

Secondary End Points

Individual components of the primary end point. The rate (%/pt-y) of MB was 0.5% versus 3.8% (95% CI, 2.8%-5.1%) in the PROACT composite control group and was better than the 95% CI. The rate of TE (stroke, TIA, and peripheral TE) was 1.3% and similar to the

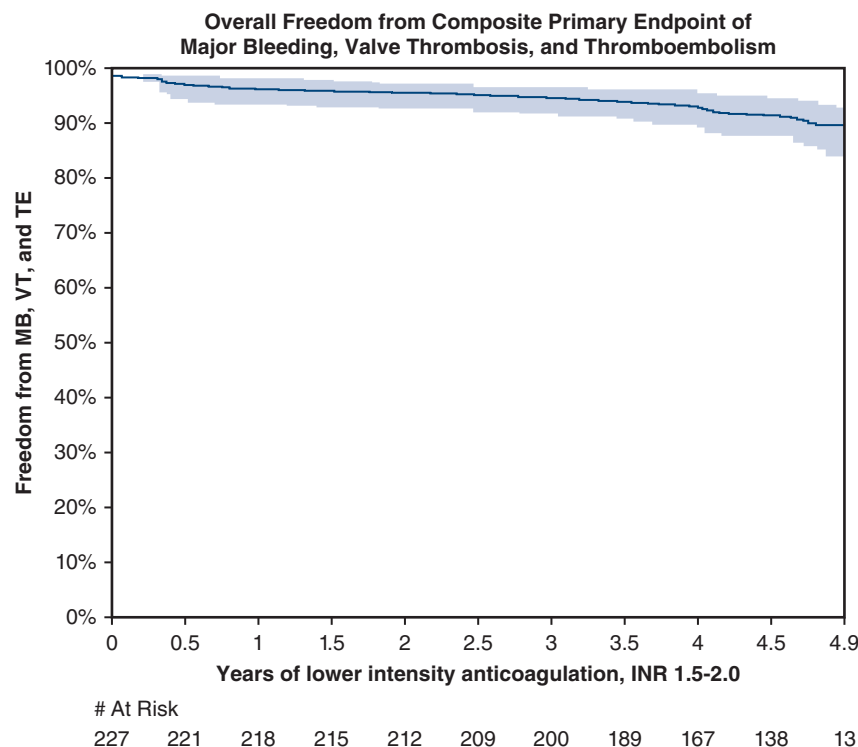


FIGURE 2. Freedom from composite primary end point. The latest Kaplan-Meier estimate for freedom from a primary composite end point is 91.5% (SE 2.3%). The shaded area represents the 95% confidence interval. Kaplan-Meier estimates were based on the time from initiation of low-dose warfarin to first occurrence of the specified event, and subjects who had not experienced the event as of their date of last contact were censored at this date. Patients who did not complete the study were censored upon first occurrence of a primary end point event, or if no event occurred, as of the date of last contact. At any given point in time, the number at risk may not correspond to the number of subjects followed because follow-up visits may have taken place before the exact corresponding anniversary date. MB, Major bleeding; VT, valve thrombosis; TE, thromboembolism; INR, international normalized ratio; SE, standard error.

TABLE 3. Clinical registry study event rates versus PROACT control by INR method*

Event	Linearized occurrence rate, %/pt-yr (number of events)			
	Clinical registry study	Clinical registry study	PROACT composite	PROACT composite
	home INR INR 1.5-2.0	clinic INR INR 1.5-2.0	control INR 2.0-3.0	control 95% CI
Number of subjects	37	192	292	
Pt-yrs†	151.8	829.5	1131.2	
Primary end point MB, VT, TE	1.98% (3)	1.81% (15)	5.39%	4.12%-6.93%
Secondary and other end points				
MB	0.00% (0)	0.60% (5)	3.80%	2.75%-5.12%
TE‡	1.98% (3)	1.21% (10)	1.41%	0.81%-2.30%
VT	0.00% (0)	0.00% (0)	0.18%	0.02%-0.64%
All bleeding	2.63% (4)	1.93 (16)	7.07%	5.61%-8.80%
TE and VT	1.98% (3)	1.21% (10)		
Minor bleeding	2.63% (4)	1.33% (11)		
Hemorrhagic stroke	0.00% (0)	0.12% (1)		
Ischemic stroke	1.98% (3)	0.60% (5)		
Nonthrombotic ischemic stroke	0.00% (0)	0.12% (1)		
TIA	0.00% (0)	0.60% (5)		
Peripheral TE	0.00% (0)	0.00% (0)		
Valve-related reoperation	0.00% (0)	0.36% (3)		
Sudden death	0.00% (0)	0.00% (0)		
Valve-related mortality	0.00% (0)	0.00% (0)		
Total mortality	0.66% (1)	0.96% (8)		

pt-yr(s), Patient-year(s); PROACT, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; INR, international normalized ratio; CI, confidence interval; MB, major bleeding; VT, valve thrombosis; TE, thromboembolism; TIA, transient ischemic attack. *Linearized occurrence rates are calculated based on late pt-yrs; end points occurring before low INR initiation date are excluded. †Pt-yrs in late follow-up, ie, once low-dose anticoagulation initiated. ‡Ischemic stroke, TIA, plus peripheral TE.

1.4% (95% CI, 0.8%-2.3%) rate per pt-yr in the PROACT composite control group (Table 2). The rate of VT events was 0.0% versus 0.2% (95% CI, 0.02%-0.6%) per pt-yr in the PROACT composite control group. The rate of TE plus VT overall was 1.3% versus 1.6% (TE 1.4% plus VT 0.2%) in the PROACT composite control group (Table 2).

Patient subsets. Rates of the primary end point, bleeding, and TE for the 4 subsets of home-monitored high-risk, clinic-monitored high-risk, home-monitored low-risk, and clinic-monitored low-risk patients are displayed in Table 5. There were no MBs in the 2 subsets of home-monitored patients.

Other. No deaths, explants, or reoperations were associated with a primary end point event. No sudden deaths occurred. There were 9 deaths (0.92%/pt-yr) total. Of deaths with known causes, all were noncardiac, and none were related to stroke. Death was related to cancer in 6 patients, sepsis with multiorgan failure in 1 patient, and of unknown cause in 2 patients. All but 1 death occurred in clinic-monitored patients; 1 death occurred in high-risk patients and 8 occurred in low-risk patients. No autopsies were performed. Valve explant was needed in 3 patients (all clinic-monitored), with 2 caused by prosthetic valve endocarditis and 1 caused by major paravalvular leak.

INR less than 1.5 or greater than 3.0. INR was less than 1.5 with 7.5% (92 of 1221) of follow-up visits, 27.0% (40 of 148) of complications, and 9.6% (132 of 1369) of all readings (follow-up visits and complications). INR was greater than 3.0 with 4.3% (52 of 1221) of follow-up visits, 15.5% (23 of 148) of complications, and 5.5% (75 of 1369) of all readings.

INR was between 1.5 and 2.0 at 54.9% (670 of 1221) of follow-up visits, with 29.1% (43 of 148) of complications, and at 52.1% (713 of 1369) of all readings. Thus, INR was outside the target range of 1.5 to 2.0 at 70.9% (105 of 148) of times when complications occurred.

INR less than 1.5 was associated with 3 of 3 TE events in home monitored patients and 3 of 10 TE events in clinic-monitored patients. It was associated with 5 of 9 TE events in low-risk patients, and 1 of 4 TE events in high-risk patients.

Tertiary End Points

Minor bleeding, all bleeding, hemorrhagic stroke, ischemic stroke, TIA, and peripheral TE rates are displayed in Tables 2 to 5. No reoperations, explants, or deaths were associated with valve-related MB, VT, or TE.

Total bleeding. Notably, the overall rate (%/pt-yr) was 2.0% versus 7.1% (95% CI, 5.6%-8.8%) in the PROACT composite control group (Table 2).

TABLE 4. Clinical registry study event rates versus PROACT control by TE risk category*, †

Event	Clinical registry high risk‡ INR 1.5-2.0		PROACT high risk INR 2.0-3.0
	LOR, %/pt-yr (95% CI)	No. events	LOR, %/pt-yr (95% CI)
Number of subjects	59		190
Pt-yr§	247.1		878.6
Primary: MB, VT, TE	1.62% (0.44%-4.14%)	4	5.80% (4.32%-7.63%)
MB	0.00% (0.00%-1.49%)	0	3.87% (2.68%-5.41%)
TE	1.62% (0.44%-4.14%)	4	1.70% (0.96%-2.82%)
VT	0.00% (0.00%-1.49%)	0	0.23% (0.03%-0.82%)
All bleeding	1.21% (0.25%-3.55%)	3	7.85% (6.11%-9.94%)
TE and VT	1.62%	4	
Minor bleeding	1.21%	3	
Hemorrhagic stroke	0.00%	0	
Ischemic stroke	0.81%	2	
Nonthrombotic ischemic stroke	0.00%	0	
TIA	0.81%	2	
Total mortality	0.40% (0.01%-2.25%)	1	
Event	Clinical registry low risk INR 1.5-2.0		PROACT low risk INR 2.0-3.0
	LOR, %/pt-yr (95% CI)	No. events	LOR, %/pt-yr (95% CI)
Number of subjects	170		102
Pt-yrs§	734.3		252.6
Primary: MB, VT, TE	1.91% (1.04%-3.20%)	14	3.96% (1.90%-7.28%)
MB	0.68% (0.22%-1.59%)	5	3.56% (1.63%-6.76%)
TE	1.23% (0.56%-2.33%)	9	0.40% (0.01%-2.21%)
VT	0.00% (0.00%-0.50%)	0	0.00% (0.00%-1.46%)
All bleeding	2.32% (1.34%-3.70%)	17	4.53% (2.17%-7.79%)
TE and VT	1.23%	9	
Minor bleeding	1.63%	12	
Hemorrhagic stroke	0.14%	1	
Ischemic stroke	0.82%	6	
Non-thrombotic ischemic stroke	0.14%	1	
TIA	0.41%	3	
Total mortality	1.09% (0.47%-2.15%)	8	

INR, International normalized ratio; PROACT, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; LOR, linearized occurrence rate; pt-yr(s), patient-year(s); CI, confidence interval; MB, major bleeding; VT, valve thrombosis; TE, thromboembolism; TIA, transient ischemic attack. *Linearized occurrence rates are calculated based on late pt-yrs; end points occurring before low INR initiation date are excluded. †There were no peripheral TE, sudden death, or valve-related mortality events in either the high-risk or low-risk groups of the clinical registry study. ‡See "Study Design" section for criteria for high-risk classification. §Patient-years in late follow-up, ie, once low-dose anticoagulation initiated. ||Ischemic stroke, TIA, plus peripheral TE.

Summary of end points. Key study outcomes, plus all-cause mortality, are summarized in Table E5. Table E6 shows key end point events with INR levels.

DISCUSSION

The FDA approved an expanded labeling indication for the On-X aortic valve with INR 1.5 to 2.0 based on the PROACT results. The clinical registry, initiated to validate results of the PROACT trial, assesses whether low-dose warfarin is safe for all patients with an On-X aortic valve regardless of INR monitoring method. The PROACT trial

assessed safety of low-dose warfarin with low-dose ASA in patients at high TE risk on home INR monitoring; the clinical registry includes patients at high or low risk of TE on home or clinic INR monitoring. Results will inform decisions by patients and clinicians regarding anticoagulation with an On-X aortic valve.

Enrollment was offered to all eligible patients at 23 centers. Follow-up to 5 years was planned for each patient. This interim report includes data for 229 patients scheduled to complete 5 years of follow-up as of August 16, 2023. The primary composite end point rate of 1.83% was lower than the 5.39% rate in the composite control

TABLE 5. Clinical registry study event rates by subsets*

Event	Linearized occurrence rate, %/pt-yr			
	Number of events			
	High risk Home INR	High risk Clinic INR	Low risk Home INR	Low risk Clinic INR
Number of subjects	9	50	28	142
Pt-yrs†	31.2	215.9	120.6	613.6
Primary end point MB, VT, TE	0.00% (0)	1.85% (4)	2.49% (3)	1.79% (11)
Secondary and other end points				
MB	0.00% (0)	0.00% (0)	0.00% (0)	0.81% (5)
TE‡	0.00% (0)	1.85% (4)	2.49% (3)	0.98% (6)
VT	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)
TE and VT	0.00% (0)	1.85% (4)	2.49% (3)	0.98% (6)
Minor bleeding	3.21% (1)	0.93% (2)	2.49% (3)	1.47% (9)
All bleeding	3.21% (1)	0.93% (2)	2.49% (3)	2.28% (14)
Hemorrhagic stroke	0.00% (0)	0.00% (0)	0.00% (0)	0.16% (1)
Ischemic stroke	0.00% (0)	0.93% (2)	2.49% (3)	0.49% (3)
Nonthrombotic ischemic stroke	0.00% (0)	0.00% (0)	0.00% (0)	0.16% (1)
TIA	0.00% (0)	0.93% (2)	0.00% (0)	0.49% (3)
Peripheral TE	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)
Sudden death	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)
Valve-related mortality	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)
Total mortality	0.00% (0)	0.46% (1)	0.83% (1)	1.14% (7)

pt-yr(s), Patient-year(s); INR, international normalized ratio; MB, major bleeding; VT, valve thrombosis; TE, thromboembolism; TIA, transient ischemic attack. *Linearized occurrence rate are calculated based on late patient-years; end points occurring before low INR initiation date are excluded. †Patient-years in late follow-up, ie, once low-dose anticoagulation initiated. ‡Ischemic stroke, TIA, and peripheral TE.

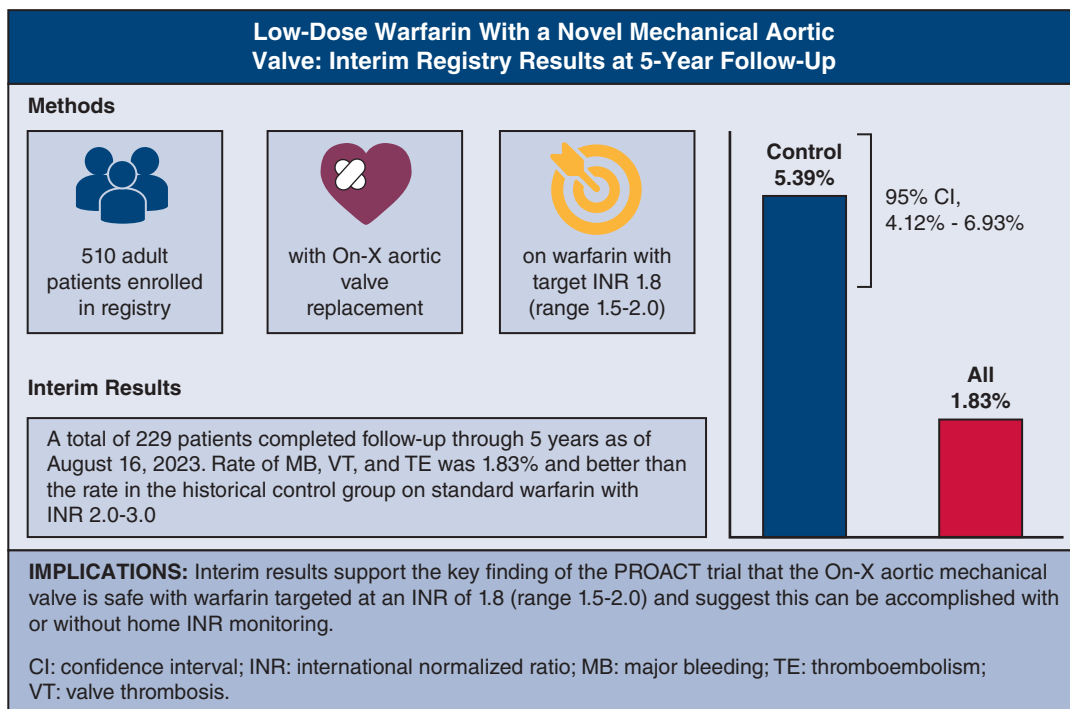
group; the difference was driven by the reduction in major bleeding (0.51% vs 3.80%). The primary composite end point (MB, VT, and TE) rate is better (less) than the 95% confidence bound of the comparable rate in the PROACT composite control group. Findings are consistent among subgroups of home-monitored, clinic-monitored, and high-risk patients. Individual rates of MB and total bleeding overall were better (less) than the 95% confidence bound in the PROACT composite control group. The rate of TE was similar to that in the PROACT composite control group. There were no VT events. The VT rate in the PROACT composite control group was low at 0.2% per pt-yr (95% CI, 0.02%-0.64%). Our results are similar to the PROACT results, which showed decreased bleeding rates with low-dose warfarin and ASA (81 mg/d) and similar TE rates. The LOWERING IT (LOWERING the INTensity of oral anticoGulant Therapy) and ESCAT III (Early Self-Controlled Anticoagulation Trial III) randomized controlled trials also showed reduced bleeding and similar TE rates with low-dose anticoagulation versus standard-dose anticoagulation.^{13,14} Those trials were conducted using other mechanical valves, no ASA, and different target INR ranges. The LOWERING IT trial used a target INR of 1.5 to 2.5, and the ESCAT III trial used a target INR of 1.6 to 2.1.

Previous studies have demonstrated the benefit of home INR monitoring.¹⁵ We observed no MB events among home-monitored patients. Only 37 (16.2%) patients used home INR monitoring, suggesting actual or perceived barriers to its use. Barriers might be logistical, financial, or insurance-related, or attributed to physician or patient preference.

A systematic review of home INR monitoring suggested that decreased TE rates among home-monitored patients are likely the result of increased time in therapeutic range.¹⁵ However, we observed numerically greater rates of TE and ischemic stroke in home-monitored patients and numerically greater TIA rates among clinic-monitored patients. In home-monitored patients, however, all of these TE and ischemic stroke events occurred with INR less than 1.5.

Unexpectedly, rates of most AEs in the low-risk group were numerically greater than or equal to rates in the high-risk group; only TE, TE plus VT, and TIA were greater in the high-risk group than the low-risk group. Absolute numbers of AEs were low in both groups. However, more than one half (5 of 9) of the TE events that occurred in the low-risk group were associated with INR less than 1.5, and almost all (8 of 9) occurred with INR 1.6 or below.

Study limitations are its observational design and lack of randomization to INR monitoring location. Patients who



@AATSHQ

FIGURE 3. Graphical summary of the study. The clinical registry enrolled 510 patients with On-X aortic valve replacement. Patients received low-dose warfarin (target INR, 1.8; range, 1.5-2.0) after at least 3 months of standard warfarin. A total of 229 patients were scheduled to complete 5 years of follow-up as of August 16, 2023. In the cohort of 229 patients, the combined rate of MB, VT, and TE was 1.83% per patient-year, which was better than in the historical PROACT control group on standard warfarin (INR 2.0-3.0). *CI*, Confidence interval; *MB*, major bleeding; *VT*, valve thrombosis; *TE*, thromboembolism; *INR*, international normalized ratio; *PROACT*, Prospective Randomized On-X Valve Anticoagulation Clinical Trial.

chose to enroll may differ from those who did not. Not all INR readings were obtained. INR values were documented at each annual visit with the following physician and whenever a complication (such as hospitalization) occurred. As such, we were unable to calculate time in therapeutic range. Although the overall study included 229 patients, 2 of the subsets included fewer than 30 patients. Study merits are its prospective methodology, inclusion of all willing and eligible patients, and its multicenter international design.

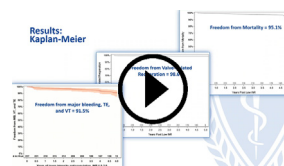
CONCLUSIONS

Interim results among patients completing 5 years of follow-up in the clinical registry (with target INR, 1.8; range, 1.5-2.0) support the study hypothesis that the rate of the primary composite end point of MB, VT, and TE will be better than the comparable rate in the historical PROACT composite control group (target INR range, 2.0-3.0). The findings are consistent across subgroups of clinic-monitored, home-monitored, and high-risk patients. The rates of major bleeding and total bleeding were reduced by 87% and 71%, respectively. TE rates were similar. Interim results from this study support the main conclusion of the original PROACT trial that the On-X aortic valve is

safe and effective with an INR target range of 1.5 to 2.0 with low-dose ASA and furthermore suggest this can be achieved with or without home INR monitoring (Figure 3).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: <https://www.aats.org/resources/registry-results-of-low-dose-w-7574>



Conflict of Interest Statement

M.W.G., M.J.P., M.J., A.Y.O., M.L., G.M.T., J.Z., and M.S. hold a consulting agreement with Artivion. R.C.H. reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict

of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: anticoagulation, aortic valve replacement, low-dose warfarin, mechanical heart valve, prosthetic valve

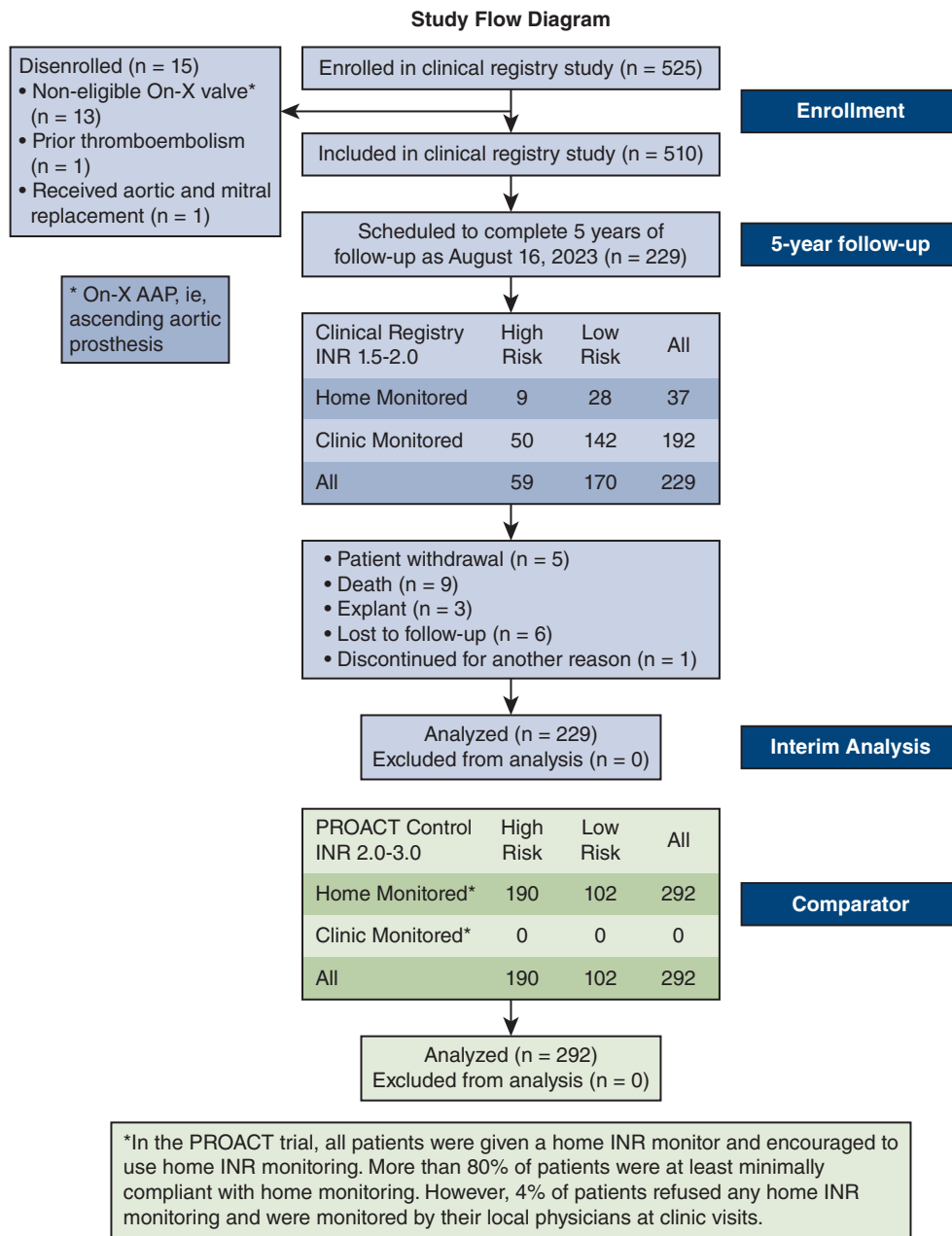


FIGURE E1. Study flow diagram. The diagram shows patient flow in the clinical registry study through 5 years of follow-up. The comparison group is the control group on standard-dose warfarin in the PROACT randomized controlled trial. *INR*, International normalized ratio; *PROACT*, Prospective Randomized On-X Valve Anticoagulation Clinical Trial.

TABLE E1. Institutional review board approvals

Institution	IRB approval date	IRB approval ID#
Baylor Scott & White Plano, Tex	July 27, 2018	018-210
Blackpool Victoria Hospital Blackpool, Lancashire, England, United Kingdom	September 8, 2017	17/SC/0191
Carilion Clinic Cardiothoracic Surgery Roanoke, Va	August 7, 2018	20151431
Cleveland Clinic Cleveland, Ohio	June 23, 2016	16-722
Franciscan St. Francis Health Indianapolis, Ind	April 21, 2016	20151431
Hartford Healthcare Hartford, Conn	August 6, 2015	HHC-2015-0186
Hull and East Yorkshire Hospitals Hull, England, United Kingdom	September 8, 2017	17/SC/0191
MaineHealth Portland, Maine	December 8, 2016	20151431
MultiCare Health Tacoma, Wash	February 11, 2016	20151431
Ottawa Heart Institute Ottawa, Ontario, Canada	October 30, 2018	20180501-01H
Oxford Heart Centre, John Radcliffe Hospital Oxford, England, United Kingdom	September 8, 2017	17/SC/0191
Providence St. Vincent Medical Center Portland, Ore	August 1, 2018	STUDY2018000294
Sanford Medical Center Fargo, ND	November 3, 2015	20151431
Sentara Norfolk General Hospital Norfolk, Va	December 8, 2015	20151431
St Bartholomew's Hospital London, England, United Kingdom	September 8, 2017	17/SC/0191
Southampton University Hospital Southampton, England, United Kingdom	September 8, 2017	17/SC/0191
Swedish Medical Center Seattle, Wash	October 11, 2015	20151431
The Christ Hospital, Lindner Center Cincinnati, Ohio	September 21, 2015	TCH#15-41
University Hospital Southampton Southampton, England, United Kingdom	September 8, 2017	17/SC/0191
University of Calgary Foothills Calgary, Alberta, Canada	May 4, 2018	REB18-0458
UT Health Science Center at Houston Houston, Tex	December 2, 2016	HSC-MS-16-0471
UT Southwestern Dallas, Tex	November 7, 2016	STU 092015-071
Victoria Heart Institute Victoria, British Columbia, Canada	August 1, 2018	C2018-036

TABLE E2. On-X Valve models and sizes in clinical registry study

Device trade name	Model designator	
	With standard holder	With extended holder
On-X Prosthetic Heart Valve (Aortic)	ONXA-19	ONXAE-19
	ONXA-21	ONXAE-21
	ONXA-23	ONXAE-23
	ONXA-25	ONXAE-25
	ONXA-27/29	ONXAE-27/29
On-X Conform-X Aortic Prosthetic Heart Valve	ONXAC-19	ONXACE-19
	ONXAC-21	ONXACE-21
	ONXAC-23	ONXACE-23
	ONXAC-25	ONXACE-25
	ONXAC-27/29	ONXACE-27/29
On-X Aortic Prosthetic Heart Valve with Anatomic Sewing Ring	ONXAN-19	ONXANE-19
	ONXAN-21	ONXANE-21
	ONXAN-23	ONXANE-23
	ONXAN-25	ONXANE-25
	ONXAN-27/29	ONXANE-27/29

TABLE E3. Historical control rates from PROACT trial

Adverse event	High-risk control*		Low-risk control†		Composite control‡	
	LOR (%/pt-yr)	95% CI	LOR (%/pt-yr)	95% CI	LOR (%/pt-yr)	95% CI
Composite§	5.80	4.32-7.63	3.96	1.90-7.28	5.39	4.12-6.93
Major bleeding	3.87	2.68-5.41	3.56	1.63-6.76	3.80	2.75-5.12
Thromboembolism	1.70	0.96-2.82	0.40	0.01-2.21	1.41	0.81-2.30
Valve thrombosis	0.23	0.03-0.82	0.00	0.0-1.46	0.18	0.02-0.64
Total bleeding	7.85	6.11-9.94	4.53	2.17-7.79	7.07	5.61-8.80

pt-yr(s), Patient-year(s); PROACT, Prospective Randomized On-X Valve Anticoagulation Clinical Trial; LOR, linearized occurrence rate; CI, confidence interval from the Poisson distribution; TIA, transient ischemic attack. *From P000037/S030. †From G050208 2014 Annual Report. ‡Weighted average of control groups. §Major bleeding, total TE, valve thrombosis. ||Ischemic stroke, TIA, and peripheral TE.

TABLE E4. Adverse event definitions

The Clinical Registry study uses adverse event definitions that were established in guidelines issued in 2008 by the American Association for Thoracic Surgery, The Society of Thoracic Surgeons, and the European Association for Cardio-Thoracic Surgery. These definitions are stated to follow. (Reference: Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions; *J Thorac Cardiovasc Surg.* 2008;135:732-738.)

Bleeding Event

A *bleeding event* is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (eg, vision loss) or necessitates transfusion. Major bleeding unexpectedly associated with minor trauma should be reported as a *bleeding event*, but bleeding associated with major trauma or a major operation should not. *Bleeding events* are reported for all patients regardless of whether they are taking anticoagulants or antiplatelet drugs. Although total *bleeding events* must be reported, *bleeding events* can also be reported separately for those who are taking anticoagulants or antiplatelet agents and those who are not.

Embolism

Embolism is any embolic event that occurs in the absence of infection after the immediate perioperative period. *Embolism* may be manifested by a *neurologic event* or a *noncerebral embolic event*.

A *neurologic event* includes any central, new neurologic deficit, whether temporary or permanent and whether focal or global, that occurs after the patient emerges from anesthesia.

Stroke is a prolonged (>72 hours) or permanent neurologic deficit that is usually associated with abnormal results of magnetic resonance imaging or computed tomographic scans. Patients with minimal, atypical, or protean symptoms that lead to radiographic imaging demonstrating an acute ischemic event are considered to have sustained a *stroke*.

Transient ischemic attack is characterized by fully reversible symptoms of short duration. If radiographic imaging demonstrates an acute central neurologic lesion (“cerebral infarction with transient symptoms”); however, such patients are reclassified as having sustained a *stroke*.

Multiple or repeated transient events occurring during a short period (a burst or *cluster*) should be recorded as one event for calculation of event rates, but documented as a *cluster*. Rate calculations should be provided not only for all embolic events but also separately for *strokes*, *transient ischemic attacks*, and *clusters*.

Postoperative neurologic symptoms that mimic those of a preoperatively documented neurologic event and that are confirmed radiographically to be consistent with the former event are not counted as a new neurologic event. Central neurologic events that are clearly related to aortic, internal carotid artery, or vertebral artery disease, such as acute thrombotic occlusion, atheroembolism, or spontaneous arterial dissection, are also not counted.

Psychomotor deficits found by specialized testing are not considered neurologic events related to operated valves. Patients who do not awaken or who awaken after operation with a new stroke are not considered to have sustained valve-related neurologic events.

A *noncerebral embolic event* is an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. Intraoperative myocardial infarctions are not counted. Postoperative myocardial infarction is also not counted unless the infarction is caused by a coronary embolus (as detected by operation, autopsy, or clinical imaging). Emboli consisting of non-thrombotic material (eg, atherosclerosis, myxoma) are not counted.

Valve Thrombosis

Valve thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve-related or found at operation for an unrelated indication should also be counted as *valve thrombosis*.

Reintervention

Reintervention is any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis or repaired valve. In addition to surgical reoperations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered *reinterventions*. Indications for *reintervention* must be reported. Open surgical and percutaneous catheter *reinterventions* should be listed separately.

Valve-Related Mortality

Valve-related mortality is any death caused by *structural valve deterioration*, *nonstructural dysfunction*, *valve thrombosis*, *embolism*, *bleeding event*, or *operated valve endocarditis*; death related to *reintervention* on the operated valve; or *sudden, unexplained death*. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not counted. Specific causes of valve-related deaths should be reported.

Sudden, Unexplained Death

A *sudden, unexplained death* is one in which the cause of death has not been determined by clinical investigation or autopsy findings and the relationship to the operated valve is undefined. These deaths should be reported as a separate category, but also included in *valve-related mortality*.

TABLE E5. Key clinical registry event rates versus historical control, linearized occurrence rate

Event	Control (2.0-3.0 INR)			Registry (1.5-2.0 INR)				
	All patients	High risk	Low risk	All patients	INR clinic monitored	INR home monitored	High risk	Low risk
	LOR, %/pt-yr (n)				LOR, %/pt-yr (n)			
Composite primary end point*	5.39% (61)	5.80% (51)	3.96% (10)	1.83% (18)	1.81% (15)	1.98% (3)	1.62% (4)	1.91% (14)
TE†	1.41% (18)	1.71% (15)	0.40% (3)	1.32% (13)	1.21% (10)	1.98% (3)	1.62% (4)	1.23% (9)
VT	0.18% (2)	0.23% (2)	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)	0.00% (0)
MB	3.80% (43)	3.87% (34)	3.56% (9)	0.51% (5)	0.60% (5)	0.00% (0)	0.00% (0)	0.68% (5)
All bleeding	7.07% (80)	7.85% (69)	4.53% (11)	2.04% (20)	1.93% (16)	2.63% (4)	1.21% (3)	2.32% (17)
All-cause mortality	1.63% (20)	1.82% (16)	1.16% (4)‡	0.92% (9)	0.96% (8)	0.66% (1)	0.40% (1)	1.09% (8)
Patients	292	190	102	229	192	37	59	170
pt-yrs	1131.2	878.6	252.6	981.3	829.5	151.8	247.1	734.3

INR, International normalized ratio; LOR, linearized occurrence rate; pt-yrs, patient-years; TE, thromboembolism; VT, valvular thrombosis; MB, major bleeding; TIA, transient ischemic attack. *All TE, VT, and major bleeding. †Ischemic stroke/cerebral vascular accident, TIA, and peripheral TE. ‡Puskas and colleagues.⁴

ADULT

TABLE E6. Primary and secondary end point complications after initiation of low INR therapy with INR near time of complication

Patient ID	Risk	INR method	Days after implant	Event description (adjudicated)	INR near event
10	Low	Clinic	1498	Major bleed (uterine bleeding)	1.6
10	Low	Clinic	1656	Major bleed (excess bleeding in premenopausal period/elective hospitalization for laparoscopic total hysterectomy/bilateral salpingo-oophorectomy)	1.1
11	High	Clinic	812	Explant, prosthetic endocarditis, explant	4.93
28	Low	Home	1254	Minor bleed (major trauma)	2.6
29	Low	Clinic	177	Minor bleed (major trauma)	2.4
29	Low	Clinic	1460	Minor bleed	1.66
29	Low	Clinic	1461	Major bleed, hemorrhagic stroke	1.58
31	Low	Clinic	1149	Minor bleed	2.9
40	Low	Clinic	951	Minor bleed	2.1
40	Low	Clinic	1487	Minor bleed	1.81
41	Low	Clinic	1672	TE, CVA	1.54
46	Low	Clinic	384	Prosthetic valve dysfunction/PVL, major	1.2
49	Low	Home	958	Minor bleed	1.3
50	Low	Home	124	TE, CVA	1.4
88	Low	Clinic	845	Minor bleed	3.2
106	High	Clinic	944	TE, CVA	1.3
112	Low	Clinic	291	Major bleed (vaginal bleeding/heavy period)	.
114	High	Clinic	112	TE, CVA	2.4
116	Low	Home	1228	TE, CVA	1.4
118	High	Clinic	306	Minor bleed	1.8
126	Low	Clinic	92	Explant, prosthetic valve dysfunction/PVL, major, explant	2
134	Low	Clinic	474	TE, TIA	1.6
135	Low	Clinic	1443	TE, CVA	1.6
135	Low	Clinic	1502	Minor bleed	3.8
138	High	Clinic	1309	Minor bleed	2
140	Low	Clinic	1339	Nonthrombotic ischemic stroke	2.4
142	High	Clinic	1119	TE, TIA	4.8
165	Low	Clinic	1744	TE, TIA	1.4
169	Low	Clinic	1702	Minor bleed	2.6
177	Low	Clinic	137	Major bleed (mesenteric bleed)	5.5
193	High	Home	1036	Minor bleed	1.6
197	Low	Clinic	1460	TE, CVA	1.2
207	High	Clinic	217	TE, TIA	1.6
224	Low	Clinic	1191	Explant, prosthetic endocarditis, explant	2.5
234	Low	Clinic	619	Minor bleed	1.9
235	Low	Home	751	Minor bleed	2
243	Low	Clinic	1484	TE, TIA	2.7
252	Low	Clinic	1631	Major bleed (admitted with CHF and severe epistaxis secondary to an INR of 5.2).	5.2
279	Low	Home	855	TE, CVA	1.32

INR, International normalized ratio; TE, thromboembolism; CVA, cerebral vascular accident; TIA, transient ischemic attack; PVL, paravalvular leak; CHF, congestive heart failure.