PROSE: Prospective Randomized Trial of the On-X Mechanical Prosthesis and the St Jude Medical Mechanical Prosthesis Evaluation

Part 2: Study results—prostheses, positions, and economic development

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ABSTRACT

Objectives: The Prospective Randomized On-X Mechanical Prosthesis Versus St Jude Medical Mechanical Prosthesis Evaluation (PROSE) trial purpose was to investigate whether a current-generation mechanical prosthesis (On-X; On-X Life Technologies/Artivion Inc) reduced the incidence of thromboembolic-related complications compared with a previous-generation mechanical prosthesis (St Jude Medical Mechanical Prosthesis; Abbott/St Jude Medical). This second report documents the valve-related complications by individual prostheses and by Western and Developing populations.

Methods: The PROSE trial study was conducted in 28 worldwide centers and incorporated 855 subjects randomized between 2003 and 2016. The study enrollment was discontinued on August 31, 2016. The study protocol, and analyses of 10 demographic variables and 24 risk factors were published in detail in 2021.

Results: The total patient population (N = 855) included patients receiving an On-X valve (n = 462) and a St Jude Medical valve (n = 393). The overall freedom evaluation showed no differences at 5 years between the prostheses for thromboembolism or for valve thrombosis. There were also no differences in mortality. There were several differences between Developing and Western populations. The freedom relations at 5 years for mortality favored Western over Developing populations. Valve thrombosis was differentiated by position and site: aortic < mitral ($P = .007$) and Western < Developing ($P = .005$). In the mitral position there were no cases in Western populations, whereas there were 8 in Developing populations ($P = .217$).

Conclusions: The On-X valve and St Jude Medical valve performed equally well in the study with no differences found. The only differentiation occurred with valve thrombosis in the mitral position more than the aortic position and occurring in Developing more than Western populations. The occurrence of valve thrombosis was also related to a younger population possibly due to anticoagulation compliance based on record review. (JTCVS Open 2022;12:51-70)

On-X Prosthetic Heart Valve (On-X Life Technologies/Artivion Inc).

CENTRAL MESSAGE

The study valves performed equally well in the study with no differences found. Valve thrombosis occurred more often in mitral valves, Developing populations, and younger patients.

PERSPECTIVE

This work documents the potential differences in thromboembolic event rates between 2 mechanical prostheses: an earlier-generation St Jude Medical valve and a more recent-generation On-X valve. The study assesses prostheses types and positions, as well as Western versus Developing countries based on the United Nations Human Development Index.

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Abbreviations and Acronyms

BMI = body mass index
CHF = congestive heart failure
INR = international normalized ratio
NYHA = New York Heart Association
PROSE = Prospective Randomized On-X Mechanical Prosthesis Versus St Jude Medical Mechanical Prosthesis Evaluation
TE = thromboembolism
VT = valve thrombosis

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The purpose of the Prospective Randomized On-X Prosthesis Versus St Jude Medical Prosthesis Evaluation (PROSE) study was to investigate whether a current-generation mechanical prosthesis (On-X Life Technologies/Artivion Inc) (Figure 1) reduced the incidence of thromboembolism (TE)-related complications compared with a previous-generation mechanical prosthesis (St Jude Medical Mechanical Prosthesis; Abbott/St Jude Medical Inc). The study hypothesis assessed the null and alternative hypotheses for a reduction in rate from 2% to 1%.

METHODS

The study design of the PROSE trial was a multicenter, randomized trial with enrollment in 28 worldwide centers incorporating Western and Developing countries. The study used the United Nations Development Programme value for the Human Development Index arbitrarily as 0.9 and above for Western (ie, developed) countries and 0.75 and below for Developing countries. This categorization resulted in essentially a 50–50 split in the total study population.

The study methods were published in detail in the *Journal of Cardiothoracic Surgery* in 2021,[1] including inclusion/exclusion criteria, sample size calculations, and all study procedures. This resulted in a randomized total patient population of 855 with an On-X population of 462 (54%) and a St Jude Medical population of 393 (46%). As previously described, this apparent difference resulted from a 2:1 randomization in the Australian center shifting the expected On-X percentage to 52% and the difference is not statistically significant.[1] Confirmation of randomness creating no clinically important bias was published in the prior paper. The study was registered with ClinicalTrials.gov as NCT000639782. The institutional review board or equivalent ethics committee of the University of British Columbia approved the study protocol and publication of data. The patient(s) provided informed written consent for the publication of the study data. All other sites were required to receive local ethics review before commencing enrollment. Renewals of ethics approvals were maintained throughout each center's participation.

Study enrollment began in the Western cites during March 2003 and was slowed by a general reluctance from physicians and patients to randomization. Additionally, the Western populations were contributing too few mitral position patients to allow for valid analyses, so Developing country populations were added during March 2012. Enrollment ended in November 2015 in the Western sites and in August 2016 at all sites.

The follow-up of patients occurred at discharge, 3 months, 6 months, at 1 year, and annually thereafter during the conduct of the study and the longitudinal evaluation to approximately 5 years, resulted in a total of 4078.1 patient-years of follow-up. Follow-up of patients was limited to 5 years for most patients, although data beyond 5 years was included when made available by an investigator. Data collected included information regarding adverse events as defined as the "Guidelines for reporting morbidity and mortality after cardiac valvular operations" of the Society of Thoracic Surgeons and the American Association for Thoracic Surgery.[2]

The target anticoagulation level for both prostheses was: for aortic position prostheses international normalized ratio (INR) between 2.2 and 2.8, and for mitral position prostheses INR between 2.5 and 3.5. No special effort was made to track INR values for each patient and control was left to standard of care at each site as a means of testing real-world results. The data analysis was performed using intent to treat, with no crossovers allowed in the trial. For the data analysis, the patients were included in the treatment group in which they were assigned.

Primary end points were rate of major TE and valve thrombosis (VT), and secondary end points were rate of major hemorrhage and all-cause and valve-related mortality. Linearized occurrence rates were used to determine the performance of the prostheses regarding major TE events and major hemorrhage events. Kaplan-Meier analysis was used to evaluate the performance of the 2 prostheses regarding freedom from TE events at 5 years. A log-rank test was used to validate the significance of the Kaplan-Meier analysis. Multiple logistic regression analysis examined the relationship between important demographic variables and adverse event rates. The statistics features of Excel version 2202 (Microsoft) calculated rates, whereas all other statistics, including all *P* values,

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FIGURE 1. On-X Prosthetic Heart Valve (On-X Life Technologies/Artivion Inc).

were performed by the authors using MedCalc Software Ltd version 20.023.

The current documented thromboembolic rates with the On-X prosthesis came from the regulatory trials conducted for the Food and Drug Administration of the United States, and clinical studies.[3-7] The TE rates for the St Jude Medical prosthesis are documented in the literature from publications over the past 20 years.[8-12] From the literature cited above, the weighted average of TE for all valve positions was 1.09% per patient-year On-X and 2.03% per patient-year for the St Jude Medical prosthesis. Thus, for the purpose of sample size calculations, the TE rate for the On-X prosthesis used was 1.0% per patient-year and that of the St Jude Medical prosthesis was 2.0% per patient-year. It was assumed that the treatment group (On-X prosthesis) would experience a 50% reduction in the incidence of major TE events relative to the St Jude Medical prosthesis group. An exponential maximum likelihood test of equality of survival curves with a 0.050 1-sided significance level would have 80% power to detect the difference between a rate of 0.0100 for the On-X prosthesis and a rate of 0.0200 for the St Jude Medical prosthesis, given a sample size of at least 250 patients in each group and follow-up of 5 years.

The Adjudication Committee of the PROSE study consisted of the Data Safety Monitoring Board and the coordinating center principal investigator for the PROSE study at the Vancouver site. The primary end point adjudication was conducted blinded to the committee. This method of adjudication blinding of end point events is the only achievable method in a heart valve prosthesis study. The PROSE study utilized Case Report Forms for collection of the data. Each principal investigator monitored his or her center for severe adverse events as defined by the Society of Thoracic Surgeons and the American Association for Thoracic Surgery guidelines.[2] The sponsor and each of the centers reported the serious adverse events to the appropriate governments, as required by each country's law for commercially distributed products. The PROSE study was performed according to the principals of the Helsinki Declaration and all patients received informed consent to those rules or more stringent rules as locally appropriate.

The risks of valve replacement with either of these mechanical prostheses are those associated with all prosthetic replacement surgery, including TE, which was the focus of this study. The risks versus benefits of participating in the study was that patients (50% of patients) could turn out to receive a prosthesis type that was associated with fewer TE events than the other prosthesis type they could have received. The study was designed to determine which prosthesis was safer in terms of TE. The relative safety of the 2 prosthesis types was unknown before the trial, although both prostheses are approved for commercial use by Canadian and United States governments, and all major worldwide governments. The determination of the relative safety was the reason for the study.

RESULTS

The total population for analysis in the PROSE trial was 855 patients implanted between 2003 and 2016. There were 939 patients screened for the trial. Of the trial patients, 16 discontinued/withdrew and 84 were lost to follow-up. The total population of On-X prosthesis recipients was 462 patients and the St Jude Medical recipient population was 393 patients. Patient follow-up in the trial was 4078.1 patient-years total: On-X n = 2219.8 and St Jude Medical n = 1858.3; Western population n = 2213.3 and Developing country population n = 1864.8; and aortic valve position population n = 2519.4 and mitral valve position population n = 1558.7. On schedule, follow-up to protocol requirements was 91.4% (4224 out of 4620). A consolidated standards of reporting trials flow diagram is provided in Figure E1.

The preoperative demographic characteristics and risk factors for the total population and the preoperative demographic characteristics and risk factors by aortic and mitral valve positions are detailed elsewhere and are summarized here for convenience.[1] The detailed results are provided in Tables E1 through E16 and Figures E1 through E3.

The mean age of the total population was 49.0 ± 12.6 years. The gender distribution was 58.8% men. Rheumatic valve etiology was 41.6%, whereas calcific valvular disease was 29.8%. Sinus rhythm was present in 75.2% of patients and atrial fibrillation was present in 23.1% of patients. The mean age for aortic prostheses patients was 52.3 ± 11.4 years. Aortic position patients were 13.7% rheumatic and 46.9% were calcific valve disease. Of the aortic position patients, 92.4% were in sinus rhythm and only 5.6% were in atrial fibrillation. The mean age for mitral position prostheses patients was 44.4 ± 12.8 years. Mitral position patients had 81.7% rheumatic and 5.0% had calcific valve disease. Of the mitral position patients 51.3% were in sinus rhythm and 47.6% were in atrial fibrillation.

There were no significant differences between On-X and St Jude Medical prosthesis patients for all preoperative and operative risk factors. As expected, the Western and Developing country populations provided the most significant differences for both preoperative and operative demographic characteristics and for preoperative and operative risk factors. All statistically significant ($P < .01$), preoperative demographic characteristics revealed the patients in the Developing country populations were younger (43.3 ± 12.6 years vs 54.5 ± 9.8 years), predominantly female (54.0% vs 29.0%), predominantly presenting with rheumatic disease (70.1% vs 7.9%), and more frequently in atrial fibrillation (35.6% vs 10.1%). Aortic stenosis was more common in the Western populations (66.5% vs 26.1%), whereas aortic regurgitation was more common in the Developing country populations (27.7% vs 13.0%). Mixed mitral disease was more common in the Developing populations (60.7% vs

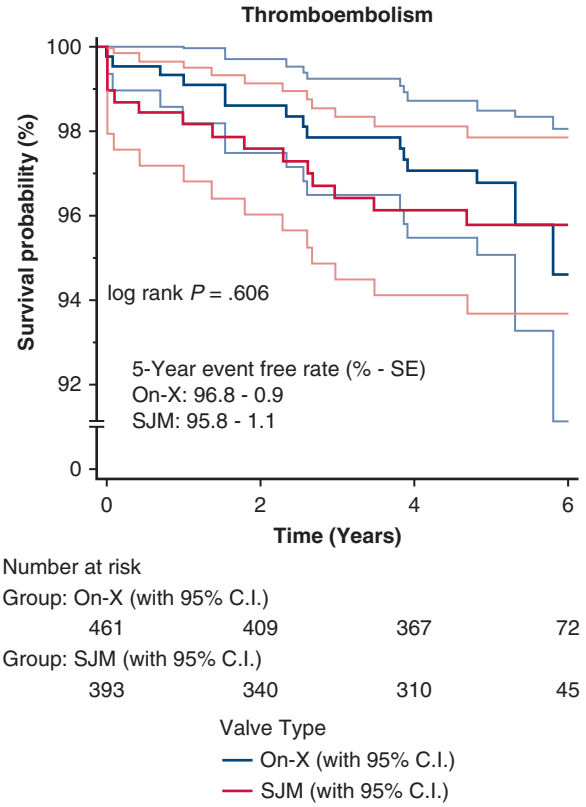

FIGURE 2. Freedom from thromboembolism by valve type with 95% CIs. Five-year event-free rate in percent ± SE and log rank *P* value. On-X Prosthetic Heart Valve (On-X Life Technologies [*On-X*]/Artivion Inc); St Jude Medical Mechanical Prosthesis (Abbott/St Jude Medical [*SJM*]). *CI*, Confidence Interval; *SE*, standard error.

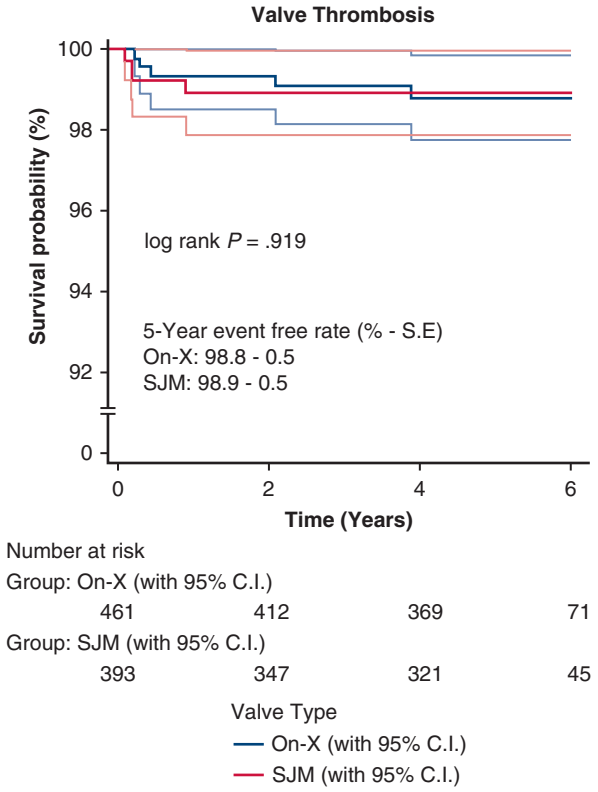

FIGURE 3. Freedom from Valve Thrombosis by Valve Type with 95% CIs. Five-year event-free rate in percent ± SE, and log rank *P* value. On-X Prosthetic Heart Valve (On-X Life Technologies [*On-X*]/Artivion Inc); St Jude Medical Mechanical Prosthesis (Abbott/St Jude Medical [*SJM*]). *CI*, Confidence interval; *SE*, standard error.

32.0%), whereas mitral regurgitation was more common in the Western populations (42.0% vs 15.9%).

The preoperative and operative risk factors for Western and Developing populations revealed a complete contrast for almost all risk factors with the significant factors predominantly in the Western populations. The comparative risk factors that had statistically significant ($P < .01$) higher occurrence rates or measured values in the Western world population were coronary artery disease (29.1% vs 4.3%), diabetes mellitus (15.1% vs 7.7%), hypercholesterolemia (44.2% vs 6.7%), preoperative creatinine (98.1 ± 91.0 μmol/L vs 82.9 ± 28.5 μmol/L), hypertension (55.6% vs 20.6%), chronic obstructive pulmonary disease (14.0% vs 4.8%), previous myocardial infarction (8.2% vs 1.2%), and angina pectoris (20.6% vs 6.2%). The aortic valve percentage was more common in the Western population (87.2% vs 29.0%). Intraoperative adverse events were more common in the Western world (12.8% vs 4.8%). Congestive heart failure, on the other hand, was more common in the Developing populations (29.3% vs 21.7%).

Study Comparison by Prosthesis Type (5-Year Event Rate [% ± SE])

Kaplan-Meier analysis showed freedom from all-cause mortality was 89.0% to 1.9% for the On-X prosthesis and 90.7% to 1.5% for the St Jude Medical prosthesis ($P = .746$); valve-related mortality and sudden death was 94.7% to 1.1% for the On-X prosthesis and 95.6% to 1.1% for the St Jude Medical prosthesis ($P = .601$); TE was 96.8% to 0.9% for the On-X prosthesis and 95.8% to 1.1% for the St Jude Medical prosthesis ($P = .606$) (Figure 2); and VT was 98.8% to 0.5% for the On-X prosthesis and 98.9% to 0.5% for the St Jude Medical prosthesis (Figure 3). The prosthesis type for aortic and mitral positions was nonsignificant for both life tables and linearized rates for all-cause mortality, valve-related mortality plus sudden death, TE, and VT.

Study Comparison by Prosthesis Position (5-Year Event Rate [% ± SE])

Kaplan-Meier analysis showed freedom from all-cause mortality for the aortic position was 91.2% to 1.3% and

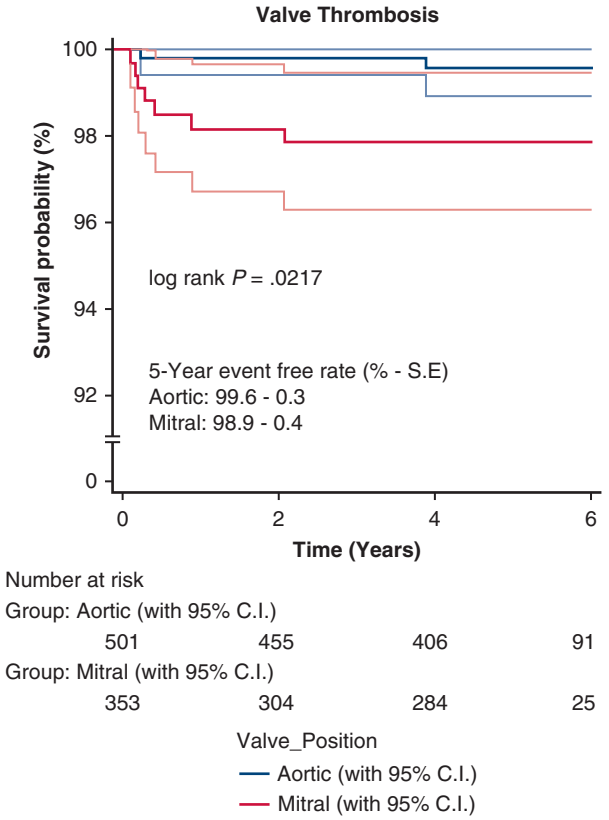

FIGURE 4. Freedom from valve thrombosis by valve position with 95% CIs. Five-year event-free rate in percent ± SE, and log rank *P* value. *CI*, Confidence interval; *SE*, standard error.

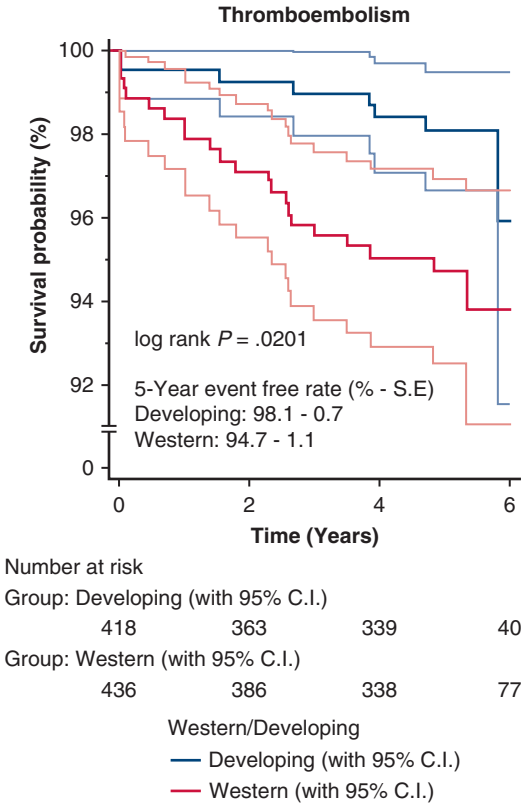

FIGURE 5. Freedom from thromboembolism by site with 95% CIs. Five-year event-free rate in percent ± SE, and log rank *P*-value. *CI*, Confidence interval; *SE*, standard error.

for the mitral position was 90.1% to 1.6% ($P = .153$); valve-related mortality plus sudden death for aortic was 95.4% to 1.0% and for the mitral position was 94.6% to 1.3% ($P = .174$); TE for aortic was 96.0% to 0.9% and for the mitral position was 96.9% to 1.0% ($P = .944$); and VT for the aortic position was 96.6% to 0.3% and for the mitral position was 97.8% to 0.8% ($P = .0217$) (Figure 4).

Study Comparison by Economic Development (5-Year Event Rate [% ± SE])

Kaplan-Meier analysis showed freedom from all-cause mortality for the Developing country population was 88.4% to 1.6% and for the Western population was 92.9% to 1.3% ($P = .0055$); valve-related mortality and sudden death for the Developing population was 93.3% to 1.3% and for the Western population was 96.8% to 0.9% ($P = .0106$); TE for the Developing population was 96.1% to 0.7% and for the Western population was 94.7% to 1.1% ($P = .0201$) (Figure 5); and VT for Developing countries was 97.9% to 0.7% and for the Western population was 99.8% to 0.2% ($P = .0137$) (Figure 6). The 5-year event rate for Developing and Western populations was nonsignificant for the aortic valve position patients for freedom from all-cause mortality, valve-related mortality and sudden death, TE, and VT.

The 5-year event rate for Developing and Western populations for mitral valve position patients showed freedom from all-cause mortality for Developing populations was 88.4% to 1.9% and for Western populations was 100.0% to 0.0% ($P = .0306$); valve-related mortality and sudden death for Developing populations was 93.6% to 1.5% and for Western populations was 100.0% to 0.0% ($P = .208$); TE for Developing populations was 97.7% to 0.9% and for Western populations was 92.4% to 3.6% ($P = .0072$): and VT for Developing populations was 97.4% to 1.0% and for Western populations was 100.0% to 0.0% ($P = .244$).

The overall risk assessment was conducted for 7 parameters: age, body mass index (BMI), congestive heart failure (CHF), chronic obstructive pulmonary disease, cerebrovascular accident, New York Heart Association (NYHA) functional class, and cardiac rhythm. The significant predictors of all-cause mortality were increases in age, CHF, BMI, NYHA functional class, and CVAs, whereas for valve-related mortality and sudden death there were increases in CHF, BMI, and NYHA functional class. The only predictor of TE in the whole population was increasing age ($P < .005$,

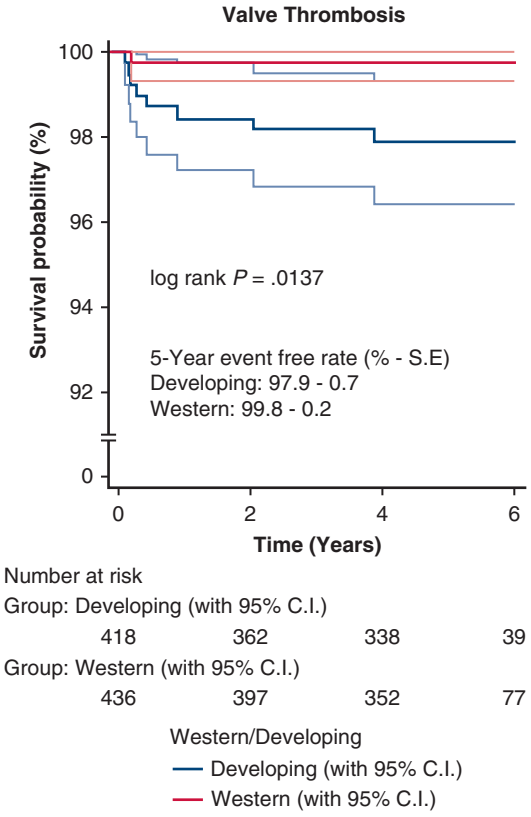

FIGURE 6. Freedom from valve thrombosis by site with 95% CI. Five-year event-free rate in percent ± SE, and log rank *P* value. *CI*, Confidence interval; *SE*, standard error.

95% CI 0.05-0.009). VT was predicted by younger age in the whole population ($P < .0001$, 95% CI 0.15-0.0001), as well as in the Developing country population, both valve prostheses, and both aortic and mitral valve positions. There was no predictor of VT in the Western population due to lack of events.

The major late hemorrhagic rate for the On-X prosthesis was 1.0% per patient-year (n = 23) and for the St Jude Medical prosthesis was 1.2% per patient-year (n = 23). The major hemorrhagic rates were not differentiated by prostheses overall, by aortic and mitral valve positions, or by economic development. The TE event rates were undifferentiated for the On-X prosthesis at 0.5% per patient-year (n = 12) and for the St Jude Medical prosthesis at 0.5% per patient-year (n = 10). There were TE events in the aortic valve (n = 14) and mitral valve (n = 8) position populations, and in patients in Western (n = 16) and Developing (n = 6) positions. The TE events were more prevalent with aortic versus mitral valve position prostheses, and with aortic valve position in Western versus Developing populations but not the mitral valve position by economic development. Figure 7 shows a breakout of the TE and VT event rates across the various study cohorts. Tables E1 through E16 show the TE and VT event rates across the various study cohorts for aortic and mitral valve position patients separately.

The most prominent major complication was VT (10 events in 9 patients). Within the total population, the On-X prosthesis major complication rate was 0.2% per patient-year (n = 5) and St Jude Medical prosthesis major complication rate was 0.3% per patient-year (n = 5). The aortic valve position major complication rate was 0.1% per patient-year (n = 2) and the mitral valve position major complication rate was 0.5% per patient-year (n = 8) ($P = .007$). The thrombosis rate was differentiated by economic development: 0.04% per patient-year (n = 1) for the Western population versus 0.5% per patient-year (n = 9) in the Developing country population ($P = .005$). There were 2 aortic valve positions for the On-X prosthesis (0.1% per patient-year) and 0 in the aortic valve position for the St Jude Medical prosthesis ($P = .199$). There were 3 mitral valve position prostheses for the On-X (0.4% per patient-year) and 5 mitral valve position St Jude Medical prostheses (0.7% per patient-year) ($P = .360$). The rate of aortic VT by economic development was 0.05% per patient-year for the Western population (n = 1) and 0.2% per patient-year for the Developing country population (n = 1) ($P = .340$). Mitral valve thrombosis by economic development was 0 in the Western population, whereas it was 8 in the Developing country population (0.6% per patient-year) ($P = .217$). One might expect that the occurrence of 0 versus 8 events would be statistically significant, but the lack of mitral patients in the Western population prevents achieving significance here.

The mean age for prosthesis thrombosis was 28.8 ± 16.0 years, whereas the total population mean age was 45.0 ± 11.5 years. There were a total of 4 St Jude Medical prosthesis cases and 5 On-X prosthesis cases among the initial cases. There were 5 cases treated with thrombolysis, 2 experienced explant surgery, and 1 experienced explant surgery after thrombolysis. There were 2 primary deaths and 1 additional late sudden death. The 2 deaths were due to multisystem failure with shock syndromes. Review of anticoagulant therapy records in all VT patients showed that the INR status varied extensively or was not followed. The time postoperation from the original surgery was mostly relatively early (<1 year) but varied up to 4 years. One of the On-X prosthesis aortic position cases was not receiving anticoagulation therapy at all.

The postoperative patient status was very satisfactory in the total population, with 77.6% experiencing NYHA functional class improvement and 20.8% experiencing NYHA functional class stability. There was no significant differentiation in postoperative status by prosthesis type, prosthesis position, or economic development status. The cardiac rhythm status in the whole population was atrial fibrillation

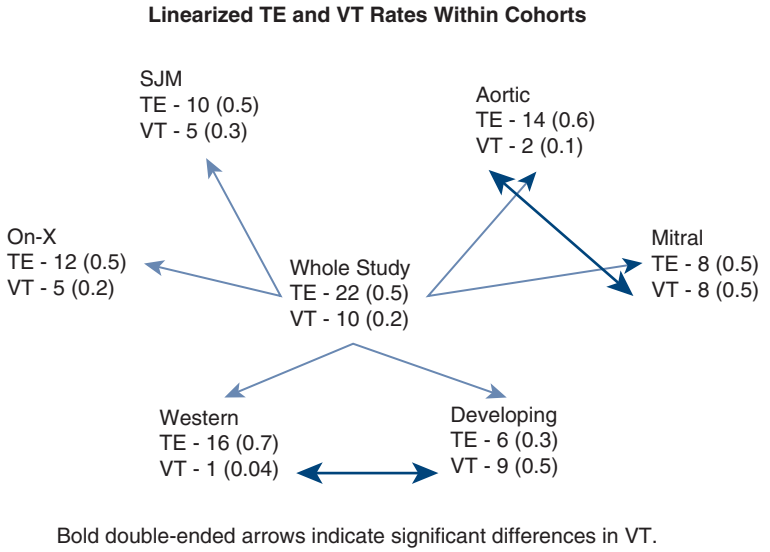

FIGURE 7. Thromboembolism (*TE*) and valve thrombosis (*VT*) event rates by study cohort: Summary figure for TE and VT linearized rates in percent per patient-year for all cohorts analyzed with indicators for statistically significant differences at $P < .05$. *Bold double-ended arrows* indicate significant differences in VT. *SJM*, St Jude Medical; *On-X*, On-X Life Technologies.

in 23.1% of patients preoperation and in 9.5% postoperation at 1 year ($P < .0001$). Similarly, the aortic position population was 5.6% and 2.4% ($P = .0002$), whereas the mitral valve population was 47.6% and 19.4% ($P < .0001$). The Western population rates were 10.6% and 5.6% ($P < .0001$) and in the Developing population 35.5% and 13.6% ($P < .0001$). In general, improvement in both NYHA functional class and sinus rhythm occurred across the entire trial.

DISCUSSION

On-X Prosthesis-Specific Design Features

As shown in Table 1 and Figure 8, *A* and *C*, the On-X prosthesis is a pure pyrolytic carbon prosthesis with a supra-annular sewing ring. The prosthesis design facilitates pannus protection (pannus protection was not a comparative feature of the PROSE trial). The long, flared orifice of the On-X prosthesis facilitates organized flow through the prosthesis (height-to-diameter ratio of about 0.6). The actuated pivots of the On-X prosthesis allow the leaflets to follow the blood flow through the prosthesis. The pivot purge of the On-X prosthesis facilitates the elimination of blood stasis in the prosthesis. The leaflet swing angle through closure is 50°, reducing closing volume and allowing for more pivot purge. The 2-point closure of the On-X prosthesis reduces the impact of leaflet closure.

St Jude Medical Prosthesis-Specific Design Features

As shown in Table 1 and Figure 8, *B* and *D*, the St Jude Medical prosthesis is made from a silicon-alloyed pyrolytic carbon that is less strong and more brittle than pure pyrolytic carbon. It also features a supra-annular sewing ring, but its orifice does not extend above and below the ring except at the pivot ears providing little barrier to pannus overgrowth.

TABLE 1. On-X valve (On-X Life Technologies [On-X]/Artivion Inc) versus St Jude Medical valve (St Jude Medical [SJM]) design comparison

Feature	On-X valve*	SJM valve†
Material	Pure pyrolytic carbon	Silicon-alloyed pyrolytic carbon
Sewing ring position	Supra-annular	Supra-annular
Valve position	Intra–supra-annular	Supra-annular
Pannus overgrowth protection	Yes	No
Orifice length	Longer natural length-to-diameter ratio	Shorter less than natural length-to-diameter ratio
Pivot design	Actuated by remote center of rotation	Fixed rotation point
Leaflet angles	Open 90°, closed 40°, swing 50°	Open 85°, closed 30°, swing 55°
Leakage path	Smooth through contoured pivot with set gap tolerances	Jet through angular pivot
Closing geometry	Two points at 45° from leaflet tip reducing closing velocity	Single point at tip of leaflet

*See Figure 8, *A* and *C*. †See Figure 8, *B* and *D*.

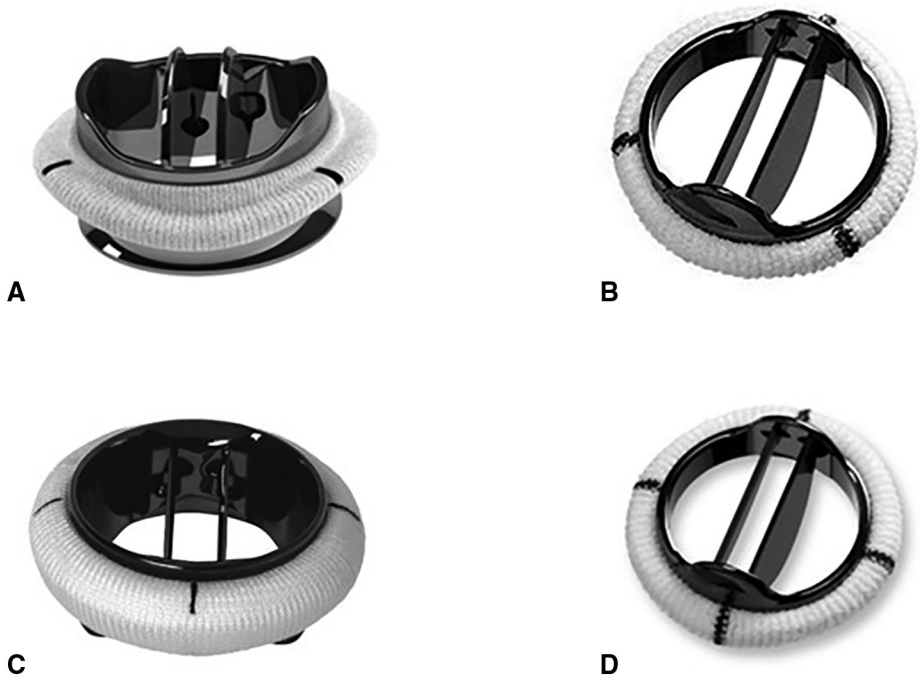

FIGURE 8. Prostheses used: A, On-X aortic valve (On-X Life Technologies/Artivion Inc). B, St Jude Medical aortic valve (Abbott/St Jude Medical). C, On-X mitral valve. D, St Jude Medical mitral valve.

The height-to-diameter ratio of the housing is approximately 0.3. Its leaflets rotate on a fixed pivot with a leaflet swing of 55° increasing closing volume, thus limiting pivot purge. Its closing contact points are at the tips of the leaflets resulting in a higher likelihood of cavitation.

Although the results did not bear out the original hypothesis that TE event rates would be significantly lower for the On-X prosthetic valve than for the St Jude Medical prosthetic valve, they do establish that these valves both perform well across the many cohorts in the trial when managed on target anticoagulation levels for both prostheses (aortic prostheses INR, 2.2-2.8 and for mitral prostheses INR, 2.5-3.5). There are many limiting reasons for finding that the historic literature observations are not discovered to hold under a randomized trial, including but not limited to references not being contemporary such that practice can change to improve results, methods of follow-up can be slightly different even using the same event definitions, observer differences are likely, and the variability of results within studies and valves is large enough to mask the small difference being sought. This study attempted to look at these valves under as close to real-world conditions. A brief survey of the literature finds studies for both valves[7,13-17] with rates of TE <1% per patient-year, also conducted under real-world conditions, illustrating the difficulty of establishing small adverse event rate differences, which is a limitation of the study.

The lack of detailed INR follow-up limits the ability to discern potential effects of varying anticoagulation protocols. However, since this study was completed, a more recent study, Prospective Randomized On-X Anticoagulation Trial (PROACT), has found that for the On-X valve, warfarin anticoagulant therapy can be reduced to create a reduction in bleeding events without increase in thromboembolism for the aortic valve.[18] The currently underway PROACT Xa study (NCT04142658) should also determine whether patients with an On-X mechanical aortic valve can be effectively anticoagulated with apixaban as an alternative to warfarin.[19]

This study allowed a direct comparison of Western and Developing populations but is also limited in comparative power for subset analyses by these same differences. Many of the differences between these 2 populations were assumed to exist based on literature reports, but this trial confirms these assumed differences, such as younger age, rheumatic etiology, mitral versus aortic positions and rates of atrial fibrillation. Unexpectedly, the study also showed that, although TE events increase with age as expected, VT events were associated with younger age. VT events also occurred in patients who had erratic INR results or were simply noncompliant to their therapy.

CONCLUSIONS

The PROSE trial revealed essentially equal performance for the On-X and St Jude Medical prostheses regarding influence of prosthesis type on major TE, VT, and major hemorrhage, as well as all-cause, valve-related, or unexpected mortality, when managed at target INR levels in the protocol representing standard of care. The only important differentiation occurred with VT occurring in the Developing country populations more than in the Western populations. The mitral thrombosis in the Developing populations occurred in a younger population, identified on multiple logistic regression, possibly due to anticoagulation compliance status because widely variable anticoagulation therapy was consistent in VT patients. The future evaluation of mechanical valve prostheses needs to include extensive randomized evaluation of anticoagulation protocols.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/1318.

Conflict of Interest Statement

On-X Life Technologies (2003-2016)/Artivion Inc (2016 to present) provided reimbursement payments to each center's research department. All other authors 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: prosthesis, position, economic development

Discussion

Presenter: W. R. Eric Jamieson

Unidentified Speaker 1. The invited discussant is Dr Grubb from Emory.

Dr Kendra Grubb *(Atlanta, Ga)*. Hi. Good afternoon. Thank you to the Association for the opportunity to discuss this paper. I appreciated the opportunity to read your manuscript. I was impressed with the results that you found, such low instance of valve thrombosis or valve embolism in either valve I wasn't surprised about, but the excellent results coming out of the developed world. Your last comments about anticoagulation, can you explain to us how the patients were followed so we get a better understanding of the rigorous nature of their follow-up?

Dr W. R. Eric Jamieson *(Vancouver, British Columbia, Canada)*. Thank you, Dr Grubb. The study was conducted as a standard care evaluation. Each center managed its own patients, in accordance with the international normalized ratio (INR) protocol. There was no central monitor attending the facilities. The central coordinator in Vancouver was able to maintain 92% of patients to meet the criteria of timelines of follow-up. The study did not monitor anticoagulation control.

Dr Grubb. And in your population, help us understand a little bit the implication of the difference with the mitrals. From the manuscript, the majority of the patients in the mitral arm came from within the Developing world. Do you think that the data is rigorous enough that we can apply the same information to a Western population? And are the data that you derived applicable to the Western population in a situation where the INRs weren't being monitored?

Dr Jamieson. As you state, Dr Grubb, the majority of the mitral patients came from the developing world, not from the Western world where mitral valve repair is predominant. We are confident that the mitral patients' performance in the developing world populations can be considered appropriate for the Western world with the same INR protocol management. We decided in 2014 to add South Africa and India into the study to achieve an adequate number of mitral patients.

Dr Grubb. And then my final question, as we look to the guidelines now with the reduced INR for the On-X valve (On-X Life Technologies/Artivion Inc), what do you predict if we were to repeat this with a lower INR for the same groups of patients in the aortic position?

Dr Jamieson. There are several reasons that the St Jude Medical prosthesis (Abbott/St Jude Medical) patients should not be managed in the aortic position with the lower INR levels (ie, 1.5-2.0) identified in the Prospective Randomized On-X Anticoagulation Trial (PROACT) study. First, the mechanical function of the 2 prosthetic valves is different. Second, an earlier presentation from the University of Ottawa showed that enzymatic performance of the On-X valve is similar to other bioprostheses and superior to all mechanical prostheses. Because of subtle differences in performance, our opinion at this time is that low-level anticoagulation should not be utilized with the St Jude Medical prosthesis without a proper randomized trial. There is currently an additional study of the On-X aortic prosthesis being evaluated in a randomized trial, PROACT Factor Xa using Eliquis (Bristol-Myers Squibb). This study is progressing with the approval of the Data Safety Monitoring Board and the Food and Drug Administration.

Dr Grubb. Well, thank you very much. I'm sure our patients are looking forward to that time. Thank you.

Unidentified Speaker 2. Sorry. Eric, can I ask the 1 last question that was from the iPad, if PROACT Xa does show equivalent results with the dual anticoagulation therapy, do you think that these mechanical valves will be implanted more in developing countries? Will that have effect in developing countries? Will the patients take Eliquis there more frequently than they would take warfarin? It's just a speculative question.

Dr Jamieson. In response to your enquiry, the On-X prosthesis in the aortic position with Xa inhibitor instead of warfarin could become a reality not just in the developing world but worldwide. At the present time a repeat transcatheter aortic valve implantation procedure needs to have, at least, an initial size 23 bioprosthesis to avoid subsequent problems. A previous study from Erasmus-Vancouver identified a population group beyond bioprostheses and mechanical prostheses for which there is no known cause of mortality. These studies reveal that further research is a necessity with regard to prosthesis type selection.

Unidentified Speaker 2. Thanks. Thanks very much, Eric.

Unidentified Speaker 1. I guess the question will be whether or not they're willing to take the Eliquis versus warfarin, or is it because of the monitoring?

Unidentified Speaker 2. Yeah. That's the question, but maybe we'll get into that in the panel.

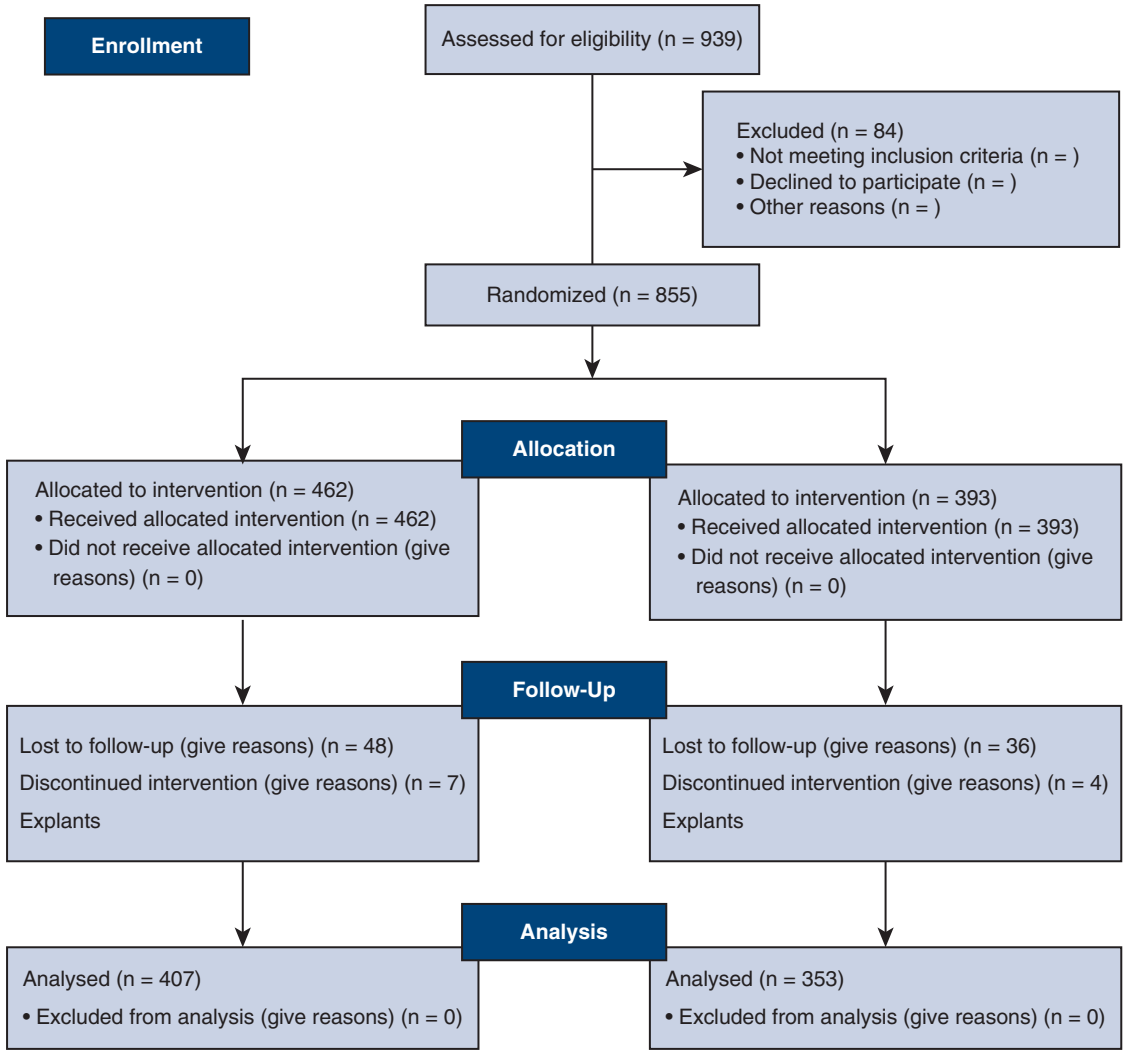

FIGURE E1. Consolidated standards of reporting trials flow diagram for randomized groups in the Prospective Randomized On-X Prosthesis Versus St Jude Medical Mechanical Prosthesis Evaluation trial.

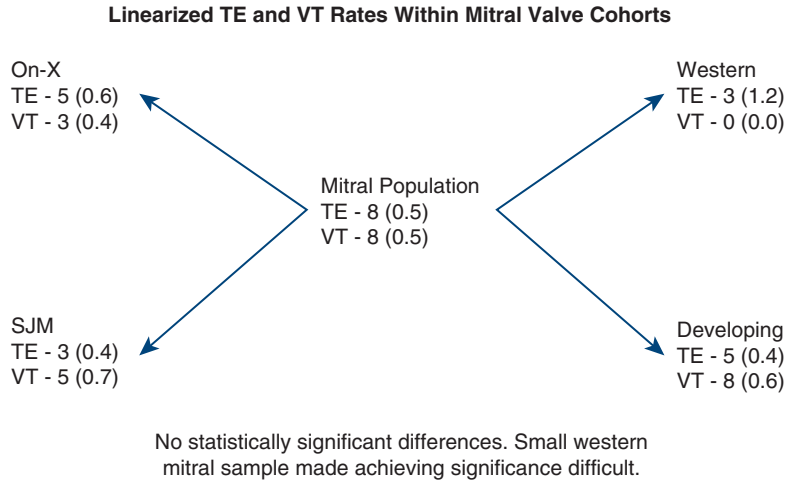

FIGURE E2. Thromboembolism (*TE*) and valve thrombosis (*VT*) rates for mitral patients by cohort. Summary figure for TE and VT linearized rates among mitral valve patients in percent per patient-year for all cohorts analyzed with indicators for statistically significant differences at $P < .05$. *On-X*, On-X Life Technologies; *SJM*, St Jude Medical.

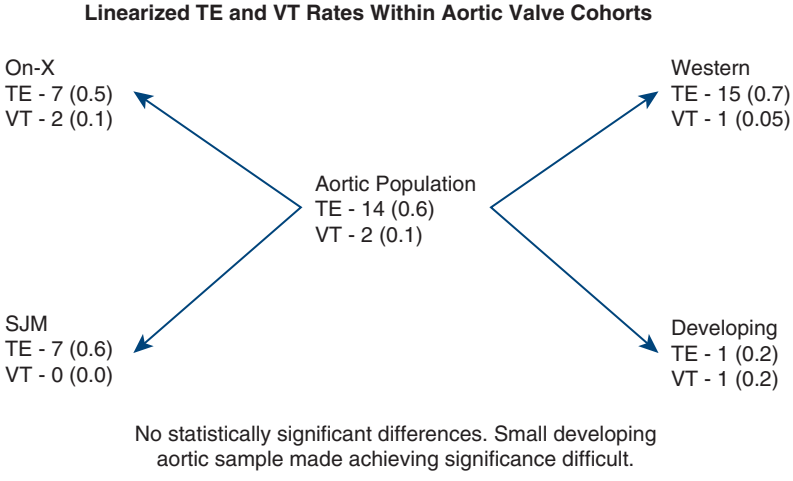

FIGURE E3. Thromboembolism (*TE*) and valve thrombosis (*VT*) rates for aortic patients by cohort. Summary figure for TE and VT linearized rates among aortic valve patients in percent per patient-year for all cohorts analyzed with indicators for statistically significant differences at $P < .05$. *On-X*, On-X Life Technologies; *SJM*, St Jude Medical.

TABLE E1. Adverse event rates for the whole population

Event	Whole study		On-X*		St Jude Medical†		*P* value early	*P* value late
	Early‡	Late§	Early‡ N = 462	Late§ ptyr = 2219.8	Early‡ N = 393	Late§ ptyr = 1858.3		
Major bleed	28 (3.3)	46 (1.1)	17 (3.7)	23 (1.0)	11 (2.8)	23 (1.2)	.462	.546
Cerebrovascular accident	5 (0.6)	22 (0.5)	2 (0.4)	12 (0.5)	3 (0.8)	10 (0.5)	.444	.992
Peripheral thromboembolism		2 (0.05)		1 (0.05)		1 (0.05)		.900
Valve thrombosis		10 (0.2)		5 (0.2)		5 (0.3)		.778
Prosthetic endocarditis	1 (0.1)	7 (0.2)	1 (0.2)	4 (0.2)		2 (0.1)	.375	.547
Major paravalvular leak	1 (0.1)	7 (0.2)	1 (0.2)	6 (0.3)		1 (0.05)	.375	.096
Oversized valve	1 (0.1)		1 (0.2)				.375	
Broken leaflet	1 (0.1)				1 (0.3)		.239	
Explants	4 (0.5)	11 (0.3)	3 (0.6)	7 (0.3)	1 (0.3)	4 (0.2)	.519	.540
All mortality	22 (2.6)	58 (1.4)	14 (3.0)	31 (1.4)	8 (2.0)	27 (1.5)	.355	.880
Valve-related mortality		17 (0.4)		12 (0.5)		5 (0.3)		.181
Cardiac mortality		8 (0.2)		4 (0.2)		4 (0.2)		.801
Noncardiac mortality		15 (0.4)		7 (0.3)		8 (0.4)		.546
Sudden or unknown mortality		18 (0.4)		8 (0.4)		10 (0.5)		.395

ptyr, Patient-year. *On-X Life Technologies/Artivion Inc. †St Jude Medical. ‡Values are presented as n (%). §Values are presented as n (%/patient-year).

TABLE E2. Adverse event rates whole population by position

Event	Whole study		Aortic		Mitral		*P* value early	*P* value late
	Early*	Late†	Early* N = 502	Late† ptyr = 2519.4	Early* N = 353	Late† ptyr = 1558.7		
Major bleed	28 (3.3)	46 (1.1)	18 (3.6)	30 (1.2)	10 (2.8)	16 (1.0)	.517	.631
Cerebrovascular accident	5 (0.6)	22 (0.5)	2 (0.4)	14 (0.6)	3 (0.8)	8 (0.5)	.584	.858
Peripheral thromboembolism		2 (0.05)		2 (0.1)				.266
Valve thrombosis		10 (0.2)		2 (0.1)		8 (0.5)		**.007**
Prosthetic endocarditis	1 (0.1)	7 (0.2)		6 (0.2)	1 (0.3)	1 (0.06)	.220	.192
Major paravalvular leak	1 (0.1)	7 (0.2)	1 (0.2)	4 (0.2)		3 (0.2)	.401	.801
Oversized valve	1 (0.1)		1 (0.2)				.401	
Broken leaflet	1 (0.1)		1 (0.2)				.401	
Explants	4 (0.5)	11 (0.3)	3 (0.6)	8 (0.3)	1 (0.3)	3 (0.2)	.531	.455
All mortality	22 (2.6)	58 (1.4)	8 (1.6)	35 (1.4)	14 (4.0)	23 (1.5)	**.030**	.822
Valve-related mortality		17 (0.4)		7 (0.3)		10 (0.6)		.080
Cardiac mortality		8 (0.2)		7 (0.3)		1 (0.06)		.134
Noncardiac mortality		15 (0.4)		10 (0.4)		5 (0.3)		.697
Sudden or unknown mortality		18 (0.4)		11 (0.4)		7 (0.5)		.954

Bold *P* values indicate statistical significance. *ptyr*, Patient-year. *Values are presented as n (%). †Values are presented as n (%/patient-year).

TABLE E3. Adverse event rates for Western versus Developing worlds

Event	Whole study		Western		Developing		*P* value early	*P* value late
	Early*	Late†	Early* N = 437	Late† ptyr = 2213.3	Early* N = 418	Late† ptyr = 1864.8		
Major bleed	28 (3.3)	46 (1.1)	18 (4.1)	29 (1.3)	10 (2.4)	17 (0.9)	.162	.232
Cerebrovascular accident	5 (0.6)	22 (0.5)	4 (0.9)	16 (0.7)	1 (0.2)	6 (0.3)	.170	.082
Peripheral TE		2 (0.05)		2 (0.09)				.194
Valve thrombosis		10 (0.2)		1 (0.04)		9 (0.5)		**.005**
Prosthetic endocarditis	1 (0.1)	7 (0.2)	1 (0.2)	7 (0.3)			.361	**.015**
Major paravalvular leak	1 (0.1)	7 (0.2)		4 (0.2)	1 (0.2)	3 (0.2)		.879
Oversized valve	1 (0.1)		1 (0.2)				.361	
Broken leaflet	1 (0.1)		1 (0.2)				.361	
Explants	4 (0.5)	11 (0.3)	3 (0.7)	7 (0.3)	1 (0.2)	4 (0.2)	.278	.533
All mortality	22 (2.6)	58 (1.4)	3 (0.7)	28 (1.3)	19 (4.5)	30 (1.6)	**.0004**	.359
Valve-related mortality		17 (0.4)		7 (0.3)		10 (0.5)		.278
Cardiac mortality		8 (0.2)		5 (0.2)		3 (0.2)		.640
Noncardiac mortality		15 (0.4)		10 (0.5)		5 (0.3)		.335
Sudden or unknown mortality		18 (0.4)		6 (0.3)		12 (0.6)		.074

Bold *P* values indicate statistical significance. *ptyr*, Patient-year. *Values are presented as n (%). †Values are presented as n (%/patient-year).

TABLE E4. Adverse event rates for aortic valves by valve type

Event	Aortic total		On-X*		St Jude Medical†		*P* value early	*P* value late
	Early‡	Late§	Early† N = 273	Late § ptyr = 1379.4	Early† N = 229	Late§ ptyr = 1140.0		
Major bleed	18 (3.6)	30 (1.2)	12 (4.4)	17 (1.2)	6 (2.6)	13 (1.1)	.280	.833
Cerebrovascular accident	2 (0.4)	14 (0.6)	1 (0.4)	7 (0.5)	1 (0.4)	7 (0.6)	1.000	.721
Peripheral thromboembolism		2 (0.1)		1 (0.07)		1 (0.1)		.893
Valve thrombosis		2 (0.1)		2 (0.1)				.199
Prosthetic endocarditis		6 (0.2)		4 (0.3)		2 (0.2)		.558
Major paravalvular leak	1 (0.2)	4 (0.2)	1 (0.4)	4 (0.3)			.338	.069
Oversized valve	1 (0.2)		1 (0.4)				.338	
Broken leaflet	1 (0.2)				1 (0.4)		.296	
Explants	3 (0.6)	8 (0.3)	2 (0.7)	6 (0.4)	1 (0.4)	2 (0.2)	.655	.250
All mortality	8 (1.6)	35 (1.4)	6 (2.2)	19 (1.4)	2 (0.9)	16 (1.4)	.249	.956
Valve-related mortality		7 (0.3)		6 (0.4)		1 (0.1)		.100
Cardiac mortality		7 (0.3)		3 (0.2)		4 (0.4)		.527
Noncardiac mortality		10 (0.4)		5 (0.4)		5 (0.4)		.763
Sudden or unknown mortality		11 (0.4)		5 (0.4)		6 (0.5)		.536

ptyr, Patient-year. *On-X Life Technologies (*On-X*)/Artivion Inc. †St Jude Medical. ‡Values are presented as n (%). §Values are presented as n (%/patient-year).

TABLE E5. Adverse event rates for mitral valves by valve type

Event	Mitral total		On-X*		St Jude Medical†		*P* value early	*P* value late
	Early‡	Late§	Early‡ N = 189	Late§ ptyr = 625.9	Early‡ N = 164	Late§ ptyr = 540.7		
Major bleed	10 (2.8)	16 (1.0)	6 (3.2)	6 (0.7)	4 (2.4)	10 (1.4)	.652	.195
Cerebrovascular accident	3 (0.8)	8 (0.5)		5 (0.6)	3 (1.8)	3 (0.4)	.064	.616
Peripheral thromboembolism								
Valve thrombosis		8 (0.5)		3 (0.4)		5 (0.7)		.360
Prosthetic endocarditis	1 (0.3)	1 (0.06)	1 (0.5)			1 (0.1)	.365	.282
Major paravalvular leak		3 (0.2)		2 (0.2)		1 (0.1)		.651
Oversized valve								
Broken leaflet								
Explants	1 (0.3)	3 (0.2)	1 (0.5)	2 (0.2)		1 (0.1)	.365	.651
All mortality	14 (4.0)	23 (1.5)	8 (4.2)	12 (1.4)	6 (3.7)	11 (1.5)	.811	.887
Valve-related mortality		10 (0.6)		6 (0.7)		4 (0.6)		
Cardiac mortality		1 (0.06)				1 (0.1)		.282
Noncardiac mortality		5 (0.3)		3 (0.4)		2 (0.3)		.776
Sudden or unknown mortality		7 (0.5)		3 (0.4)		4 (0.6)		.567

ptyr, Patient-year. *On-X Life Technologies (*On-X*)/Artivion Inc. †St Jude Medical. ‡Values are presented as n (%). §Values are presented as n (%/patient-year).

TABLE E6. Adverse event rates for aortic valves by economic development

Event	Aortic total		Western		Developing		*P* value early	*P* value late
	Early*	Late†	Early* N = 381	Late† ptyr = 1963.7	Early* N = 121	Late† ptyr = 555.7		
Major bleed	18 (3.6)	30 (1.2)	17 (4.5)	24 (1.2)	1 (0.8)	6 (1.1)	.058	.786
Cerebrovascular accident	2 (0.4)	14 (0.6)	2 (0.5)	13 (0.7)		1 (0.2)	.660	.178
Peripheral thromboembolism		2 (0.1)		2 (0.1)				.452
Valve thrombosis		2 (0.1)		1 (0.05)		1 (0.2)		.340
Prosthetic endocarditis		6 (0.2)		6 (0.3)				.193
Major paravalvular leak	1 (0.2)	4 (0.2)	1 (0.3)	3 (0.2)		1 (0.2)	.547	.887
Oversized valve	1 (0.2)		1 (0.3)				.547	
Broken leaflet	1 (0.2)		1 (0.3)				.547	
Explants	3 (0.6)	8 (0.3)	3 (0.8)	7 (0.4)		1 (0.2)	.324	.514
All mortality	8 (1.6)	35 (1.4)	3 (0.8)	27 (1.4)	5 (4.1)	8 (1.4)	**.012**	.909
Valve-related mortality		7 (0.3)		6 (0.3)		1 (0.2)		.620
Cardiac mortality		7 (0.3)		6 (0.3)		1 (0.2)		.620
Noncardiac mortality		10 (0.4)		8 (0.4)		2 (0.4)		.875
Sudden or unknown mortality		11 (0.4)		7 (0.4)		4 (0.7)		.252

Bold *P* values indicate statistical significance. *ptyr*, Patient-year. *Values are presented as n (%). †Values are presented as n (%/patient-year).

TABLE E7. Adverse event rates for mitral valves by economic development

Event	Mitral total		Western		Developing		*P* value early	*P* value late
	Early*	Late†	Early* N = 56	Late† ptyr = 249.6	Early* N = 297	Late† ptyr = 1309.1		
Major bleed	10 (2.8)	16 (1.0)	1 (1.8)	6 (2.4)	9 (3.0)	11 (0.8)	.619	.030
Cerebrovascular accident	3 (0.8)	8 (0.5)	1 (1.8)	3 (1.2)	1 (0.3)	5 (0.4)	.160	.098
Peripheral thromboembolism								
Valve thrombosis		8 (0.5)		0		8 (0.6)		.217
Prosthetic endocarditis	1 (0.3)	1 (0.06)	1 (1.8)	1 (0.4)	0	0	**.021**	**.022**
Major paravalvular leak		3 (0.2)		1 (0.4)		2 (0.2)		.413
Oversized valve								
Broken leaflet								
Explants	1 (0.3)	3 (0.2)	1 (1.8)	0	0	3 (0.2)	**.021**	.450
All mortality	14 (4.0)	23 (1.5)	0	1 (0.4)	14 (4.7)	22 (1.7)	**.003**	.127
Valve-related mortality		10 (0.6)		1 (0.4)		9 (0.7)		.604
Cardiac mortality		1 (0.06)		0		1 (0.08)		.662
Noncardiac mortality		5 (0.3)		0		5 (0.4)		.329
Sudden or unknown mortality		7 (0.5)		0		7 (0.5)		.248

Bold *P* values indicate statistical significance. *ptyr*, Patient-year. *Values are presented as n (%). †Values are presented as n (%/patient-year).

TABLE E8. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for the whole cohort

Postop\Preop	I	II	III	IV	Total
I	56	6	0	0	62
II	212	40	4	1	257
III	192	76	43	0	311
IV	19	15	4	0	38
Total	479	137	51	1	668
Percent improved					77.6
Percent stable					20.8
Percent worsened					1.6

TABLE E9. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for On-X (On-X Life Technologies/Artivion Inc) patients

Postop\Preop	I	II	III	IV	Total
I	33	3	0	0	36
II	112	18	2	1	133
III	105	42	19	0	166
IV	22	10	2	0	34
Total	272	73	23	1	369
Percent improved					79.4
Percent stable					19.0
Percent worsened					1.6

TABLE E10. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for St Jude Medical patients

Postop\Preop	I	II	III	IV	Total
I	23	3	0	0	26
II	100	22	2	0	124
III	87	34	24	0	145
IV	19	5	2	0	26
Total	229	64	28	0	321
Percent improved					76.9
Percent stable					21.5
Percent worsened					1.6

TABLE E11. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for aortic patients

Postop\Preop	I	II	III	IV	Total
I	52	5	0	0	57
II	141	21	1	1	164
III	110	32	20	0	162
IV	22	9	3	0	34
Total	325	67	24	1	417
Percent improved					77.9
Percent stable					22.3
Percent worsened					1.7

TABLE E12. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for mitral patients

Postop\Preop	I	II	III	IV	Total
I	4	1	0	0	5
II	71	19	3	0	93
III	82	44	23	0	149
IV	19	6	1	0	26
Total	176	70	27	0	273
Percent improved					81.7
Percent stable					16.8
Percent worsened					1.5

TABLE E13. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for the Western population

Postop\Preop	I	II	III	IV	Total
I	53	5	0	0	58
II	131	10	1	1	143
III	105	21	13	0	139
IV	24	11	4	0	39
Total	313	47	18	1	379
Percent improved					78.1
Percent stable					20.1
Percent worsened					1.8

TABLE E14. New York Heart Association functional class cross-tabulation: Preoperation (Preop) to 1-year postoperation (Postop) for the developing population

Postop\Preop	I	II	III	IV	Total
I	3	1	0	0	4
II	81	30	3	0	114
III	87	55	30	0	172
IV	17	4	0	0	21
Total	188	90	33	0	311
Percent improved					78.5
Percent stable					20.3
Percent worsened					1.3

TABLE E15. Preoperative (Preop) and 1-year postoperative (Postop) cardiac rhythm

Patient group	Sinus	Atrial fibrillation	Paced	Other	*P* value for postop improvement
Whole cohort					
Preop	627 (75.2)	193 (23.1)	3 (0.4)	11 (1.3)	
Postop	578 (87.4)	63 (9.5)	19 (2.9)	1 (0.2)	**<.0001**
On-X*					
Preop	338 (75.1)	105 (23.3)	1 (0.2)	6 (1.3)	
Postop	327 (88.9)	30 (8.2)	11 (3.0)	0 (0.0)	**<.0001**
St Jude Medical†					
Preop	289 (75.3)	88 (22.9)	2 (0.5)	5 (1.3)	
Postop	251 (85.7)	33 (11.3)	8 (2.7)	1 (0.3)	**.0001**
Aortic					
Preop	448 (92.4)	27 (5.6)	3 (0.6)	7 (1.4)	
Postop	360 (94.2)	9 (2.4)	13 (3.4)	0 (0.0)	**.0002**
Mitral					
Preop	179 (51.3)	166 (47.6)	0 (0.0)	4 (1.1)	
Postop	218 (78.1)	54 (19.4)	6 (2.2)	1 (0.4)	**<.0001**
Western					
Preop	364 (87.5)	44 (10.6)	1 (0.2)	7 (1.7)	
Postop	303 (89.9)	19 (5.6)	15 (4.5)	0 (0.0)	**<.0001**
Developing					
Preop	263 (62.9)	149 (35.6)	2 (0.5)	4 (1.0)	
Postop	275 (84.9)	44 (13.6)	4 (1.2)	1 (0.3)	**<.0001**

Values are presented as n (%). Bold *P* values indicate statistical significance. *On-X Life Technologies (*On-X*)/Artivion Inc. †Abbott/St Jude Medical.

TABLE E16. Multiple logistic regression modeling results

	Event*				
Group	All-cause mortality	Valve-related plus sudden death	TE	VT	Thrombotic events
Whole	<.0001, congestive HF, .97 to .0001, NYHA, .64 to .016	.0005, congestive HF, 1.01 to .003, NYHA, .84 to .027	.005, age, .05 to .009	<.0001, age, –.15 to .0001 inverse to age	No relationships
Developing	<.0001, age .03 - .029, congestive HF 1.25 – .0001	.01, congestive HF 1.06 – 0.01	No relationships	.0001, age -0.13, .002 inverse to age	No relationships
Western	.0001, BMI, .08 to .0008, CVA, 1.43 to .044, NYHA, .95 to .33	.001, BMI, .11 to .0006	No relationships	No relationships (only 1 event)	No relationships
On-X†	.007, BMI, .038 to .048, NYHA, .87 –.018	.009, congestive HF, 1.17 to .008	No relationships	.0001, age, –.15 to .002 inverse to age	No relationships
St Jude Medical‡	.0006, congestive HF, 1.28 to .0005	No relationships	.005, age, .08 to .013	.017, age, –.10 to .03 inverse to age	.03, NYHA, 1.15 to .046
Aortic	<.0001, BMI, .07 to .0005, CVA, 1.38 to .017, congestive HF, .93 to .010	.0004, BMI, .08 to .004, congestive HF, 1.29 to .008	No relationships	.027, age, –.12 to .043 inverse to age	No relationships
Mitral	.010, congestive HF, 0.93 to .010	No relationships	.01, age .06 to .016	.0004, age –0.12 to .003 inverse to age	No relationships

TE, Thromboembolism. *VT*, valve thrombosis; *HF*, heart failure; *NYHA*, New York Heart Association functional class; *BMI*, body mass index; *CVA*, cardiovascular accident. *Values are presented as model *P* value, factor(s) coefficient *P* value. †On-X Life Technologies/Artivion Inc. ‡Abbott/St Jude Medical.