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. Valve thrombosis occurred more often in mitral valves, Developing populations, and younger patients.
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/Artivia 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, 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. 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 cities 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.

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 2020 (Microsoft) calculated rates, whereas all other statistics, including all P values, were calculated by investigators. The 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. Confirmation of randomness creating no clinically important bias was published in the prior paper.

JTCVS Open • December 2022

Copyright © 2022 The Author(s). Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jtcvs.2022.07.011

Abbreviations and Acronyms

| Acronym   | Description                                                                 |
|-----------|-----------------------------------------------------------------------------|
| 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                                                            |

To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

vania, Philadelphia, Pa; 6Division of Cardiac Surgery, Victoria Heart Institute, Victoria, British Columbia, Canada; 7Department of Cardiothoracic and Vascular Surgery, Apollo Multispecialty Hospital, Madurai, India; 8Department of Surgery, Robert Wood Johnson Medical School, New Brunswick, NJ; 9Department of Thoracic Surgery, Kaiser-Permanente Hospital, Los Angeles, Calif; and 10Division of Cardiovascular Surgery, St Paul’s Hospital, Vancouver, British Columbia, Canada.

Read at the 102nd Annual Meeting of The American Association for Thoracic Surgery, Boston, Massachusetts, May 14-17, 2022.

Received for publication March 19, 2022; revisions received June 4, 2022; accepted for publication June 23, 2022; available ahead of print Sept 21, 2022.

Address for reprints: W. R. Eric Jamieson, MD, Vancouver Coastal Health Research Institute, University of British Columbia, 272 Waterleigh Dr, Vancouver, British Columbia V5Y 4T2, Canada (E-mail: wreric.jamieson@gmail.com).

2666-2736

Copyright © 2022 The Author(s). Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jtcvs.2022.07.011
FIGURE 1. On-X Prosthetic Heart Valve (On-X Life Technologies/Arti-vion Inc).

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

The current documented thromboembolic rates with the On-X prosth-
thesis 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% reduc-
tion 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
percent power to detect the difference between a rate of 0.0100 for the On-X pro-
thesis 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 adjudica-
tion 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 collec-
tion 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.7 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 distrib-
uted 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 prosthe-
ses are those associated with all prosthetic replacement surgery, including
TE, which was the focus of this study. The risks versus benefits of partici-
pating 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 pro-
theses 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 pa-
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 require-
ments was 91.4% (4224 out of 4620). A consolidated stan-
dards of reporting trials flow diagram is provided in
Figure E1.

The preoperative demographic characteristics and risk
factors for the total population and the preoperative demo-
graphic 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 pa-
tients, 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 Devel-
oping country populations provided the most significant dif-
fences for both preoperative and operative demographic
characteristics and for preoperative and operative risk factors.
All statistically significant (P < .01), preoperative demo-
graphic characteristics revealed the patients in the Devel-
oping 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
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 ($98.1 \pm 91.0$ µmol/L vs $82.9 \pm 28.5$ 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 ($P = .601$) (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
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 \((P < .005\),
95% CI 0.05-0.009). VT was predicted by younger age in the whole population (P <0.0001, 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
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.

| 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.
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 valves7,13-17 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.

The authors thank Alanna Dyck, research coordinator, Division of Cardiovascular Surgery, Department of Surgery, University of British Columbia, British Columbia, Canada, who had responsibility throughout essentially the total length of the Prospective Randomized Trial of the On-X Mechanical Prosthesis and the St Jude Medical Mechanical Prosthesis Evaluation study for the complete study.

The authors thank all research coordinators at all the study centers who provided extensive support throughout the extended length of the study. ClinicalTrials.gov registration No. NCT000639782.

References

1. Jamieson WRE, Ely JL, Brink J, Pennel T, Bannon P, Patel J, et al. PROSE: Prospective Randomized Trial of the On-X Mechanical Prosthesis and the St Jude Medical Mechanical Prosthesis Evaluation: part I: patient dynamics; preoperative demographics and preoperative and operative risk factors. J Cardiothorac Surg. 2021;16:323-34.
2. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg. 2008;135:732-8.
3. US Food and Drug Administration. On-X valve summary of safety and effectiveness. PMA P000037, May 30, 2001, and PMA P000037 S002. March 6, 2002. Accessed August 15, 2022. https://www.accessdata.fda.gov/cdrh_docs/pdf/P000037S001b.pdf
4. Palatianos GM, Laczkovics AM, Simon P, Pomer JL, Birbaum DE, Greve HH, et al. Multicentered European study on safety and effectiveness on the On-X prosthetic heart valve: intermediate follow-up. Ann Thorac Surg. 2007;83:40-6.
5. McNicholas KW, Ivie TD, Metras J, Szentpetery S, Marra SW, Masters RG, et al. North American multicenter experience with the On-X prosthetic heart valve. J Heart Valve Dis. 2006;15:73-9.
6. Laczkovics A, Heidt M, Oelert H, Laufer G, Greve H, Pomer JL, et al. Early clinical experience with the On-X prosthetic heart valve. J Heart Valve Dis. 2001;10:94-9.
7. Chan V, Jamieson WRE, Lam B-K, Ruel M, Ling H, Fradet G, et al. Influence of the On-X mechanical prosthesis on intermediate-term major thromboembolism and hemorrhage: a prospective multicenter study. J Thorac Cardiovasc Surg. 2010;140:1053-8.
8. Emery RW, Krogh C, Arom KV, Emery AM, Benyo-Albrecht K, Joyce LD, et al. The St Jude Medical Cardiac Valve Prostheses: a 25-year experience with single valve replacement. Ann Thorac Surg. 2005;79:776-82.
9. Ekonomidou JS, Krantz JM, Crambley AJ, Strand MR, Bradley SM, Sade RM, et al. Twenty-year experience with the St Jude Medical valve prosthesis. J Thorac Cardiovasc Surg. 2003;126:2022-31.
10. Arom KV, Emery RW, Petersen B, Radosovich DM. St Jude Medical valve prosthesis: health status of the patient after 15 years. Ann Thorac Cardiovasc Surg. 1996;2:45-9.
11. Emery RW, Arom KV, Kshettry VR, Kroshus TJ, Von R, Kersten TE, et al. Decision-making in the choice of heart valve for replacement in patients aged 60-70 years: twenty-year follow-up of the St Jude Medical aortic valve prosthesis. J Heart Valve Dis. 2001;11(Suppl 1):S37-44.
12. Land O, Nielsen SL, Arildsen H, Ilijker LB, Pilegaard HK. Standard aortic St Jude valve at 18 years: performance profile and determinants of outcome. Ann Thorac Surg. 2000;69:1459-65.
13. Chambers JB, Pomer JL, Mestres CA, Palatianos GM. Clinical event rates with the On-X bileaflet mechanical heart valve: a multicenter experience with follow-up to 12 years. J Thorac Cardiovasc Surg. 2013;145:420-4.
14. Baudet EM, Puel V, McBride JT, Grimaud JP, Roques F, Clerc F, et al. Surgery for acquired heart disease, long-term results of valve replacement with the St Jude Medical Prosthesis. J Thorac Cardiovasc Surg. 1995;109:858-70.
15. Isomura T, Hisatomi K, Hirano A, Kosuga K, Ohishi K. The St. Jude Medical Cardiac Valve Prosthesis: a 25-year experience with single valve replacement. Ann Thorac Cardiovasc Surg. 2001;79:776-82.
16. Remadi JP, Bizouarn P, Baron O, Habashi OA, Despins P, Michaal JL, et al. Mitral valve replacement with the St. Jude Medical Prosthesis: a 15-year follow-up. Ann Thorac Surg. 1998;66:762-7.
17. Smith JA, Westlake GW, Mullerworth MH, Skillington PD, Tatoulis J. Excellent long-term results of cardiac valve replacement with the St Jude Medical Prosthesis. J Cardiothorac Surg. 1995;109:858-70.
18. Puskas J, Gerdtsch M, Nichols D, Quinn R, Anderson C, Rhemman B, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the Prospective Randomized On-X Valve Anticoagulation Clinical Trial Randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147:1202-11.
19. Jawitz OK, Wang TY, Lopes RD, Chavez A, Boyer B, Kim H, et al. Rationale and design of PROACT Xa: a randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with an On-X mechanical aortic valve. Am Heart J. 2020;227:91-9.

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.
Assessed for eligibility (n = 939)

Excluded (n = 84)
• Not meeting inclusion criteria (n = )
• Declined to participate (n = )
• Other reasons (n = )

Randomized (n = 855)

Allocated to intervention (n = 462)
• Received allocated intervention (n = 462)
• Did not receive allocated intervention (give reasons) (n = 0)

Lost to follow-up (give reasons) (n = 48)
Discontinued intervention (give reasons) (n = 7)
Explants

Allocated to intervention (n = 393)
• Received allocated intervention (n = 393)
• Did not receive allocated intervention (give reasons) (n = 0)

Lost to follow-up (give reasons) (n = 36)
Discontinued intervention (give reasons) (n = 4)
Explants

Analysed (n = 407)
• Excluded from analysis (give reasons) (n = 0)

Analysed (n = 353)
• Excluded from analysis (give reasons) (n = 0)

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.
Linearized TE and VT Rates Within Mitral Valve Cohorts

| Cohort       | TE  | VT  |
|--------------|-----|-----|
| On-X         | 5 (0.6) | 3 (0.4) |
| Western      | 3 (1.2) | 0 (0.0) |
| Mitral       | 8 (0.5) | 8 (0.5) |
| SJM          | 3 (0.4) | 5 (0.7) |
| Developing   | 5 (0.4) | 8 (0.6) |

No statistically significant differences. Small western mitral sample made achieving significance difficult.

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.

Linearized TE and VT Rates Within Aortic Valve Cohorts

| Cohort       | TE  | VT  |
|--------------|-----|-----|
| On-X         | 7 (0.5) | 2 (0.1) |
| Western      | 15 (0.7) | 1 (0.05) |
| Aortic       | 14 (0.6) | 2 (0.1) |
| SJM          | 7 (0.6) | 0 (0.0) |
| Developing   | 1 (0.2) | 1 (0.2) |

No statistically significant differences. Small developing aortic sample made achieving significance difficult.

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.

62 JTCVS Open • December 2022
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‡          | Late‡         |              |
|                              | N = 462     | N = 393 | ptyr = 2219.8   | ptyr = 1858.3 |
| Major bleed                  | 28 (3.3)    | 46 (1.1) | 17 (3.7)        | 23 (1.0)      | .462         |
| Cerebrovascular accident     | 5 (0.6)     | 22 (0.5) | 2 (0.4)         | 12 (0.5)      | .444         |
| Peripheral thromboembolism   | 2 (0.05)    | 1 (0.05) | 1 (0.05)        | 1 (0.05)      | .900         |
| Valve thrombosis             | 10 (0.2)    | 5 (0.2)  | 5 (0.2)         | 5 (0.3)       | .778         |
| Prosthetic endocarditis      | 1 (0.1)     | 7 (0.2)  | 1 (0.2)         | 4 (0.2)       | .375         |
| Major paravalvular leak      | 1 (0.1)     | 7 (0.2)  | 1 (0.2)         | 6 (0.3)       | .375         |
| Oversized valve              | 1 (0.1)     | 1 (0.2)  | 1 (0.2)         |               | .375         |
| Broken leaflet               | 1 (0.1)     | 1 (0.3)  | 1 (0.3)         |               | .239         |
| Explants                     | 4 (0.5)     | 11 (0.3) | 3 (0.6)         | 7 (0.3)       | .519         |
| All mortality                | 22 (2.6)    | 58 (1.4) | 14 (3.0)        | 31 (1.4)      | .355         |
| 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         |

Values are presented as n (%). *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‡            | Late‡         |              |
|                              | N = 502     | N = 353 | ptyr = 2519.4    | ptyr = 1558.7 |
| Major bleed                  | 28 (3.3)    | 46 (1.1) | 18 (3.6)        | 30 (1.2)      | .517         |
| Cerebrovascular accident     | 5 (0.6)     | 22 (0.5) | 2 (0.4)         | 14 (0.6)      | .584         |
| Peripheral thromboembolism   | 2 (0.05)    | 1 (0.2)  | 2 (0.1)         |               | .266         |
| Valve thrombosis             | 10 (0.2)    | 2 (0.1)  | 2 (0.1)         |               | .007         |
| Prosthetic endocarditis      | 1 (0.1)     | 7 (0.2)  | 6 (0.2)         | 1 (0.3)       | .220         |
| Major paravalvular leak      | 1 (0.1)     | 7 (0.2)  | 1 (0.2)         | 4 (0.2)       | .401         |
| Oversized valve              | 1 (0.1)     | 1 (0.2)  | 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)       | .531         |
| All mortality                | 22 (2.6)    | 58 (1.4) | 8 (1.6)         | 35 (1.4)      | .030         |
| Valve-related mortality      | 17 (0.4)    | 7 (0.3)  | 10 (0.6)        |               | .080         |
| Cardiac mortality            | 8 (0.2)     | 7 (0.3)  | 10 (0.6)        |               | .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).

JTCVS Open • Volume 12, Number C 63
### 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†        | N = 418      | ptyr = 2213.3 | 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)| 10 (0.2)   | 1 (0.04)      | 9 (0.5)      | .005        |              |               |
| Valve thrombosis             | 10 (0.2)    | 7 (0.2) | 1 (0.2)    | 7 (0.3)       | .361         | .015        |              |               |
| 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         | .361        |              |               |
| Broken leaflet               | 1 (0.1)     | 1 (0.2) |           |               | .361         | .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         | .278        |              |               |
| Cardiac mortality            | 8 (0.2)     | 5 (0.2) | 3 (0.2)    |               | .640         | .640        |              |               |
| Noncardiac mortality         | 15 (0.4)    | 10 (0.5)| 5 (0.3)    |               | .335         | .335        |              |               |
| Sudden or unknown mortality  | 18 (0.4)    | 6 (0.3) | 12 (0.6)   |               | .074         | .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‡            | ptyr = 1379.4 | 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)          |               | 1 (0.1)     |               | .893          |               |
| Valve thrombosis             | 2 (0.1)      | 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         | .338         |               |               |
| Broken leaflet               | 1 (0.2)      | 1 (0.4) |               |               | .296         | .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         |               |               |               |

*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<sup>a</sup> | St Jude Medical<sup>b</sup> | P value early | P value late |
|------------------------------|--------------|-------------------|----------------------------|---------------|--------------|
|                              | Early<sup>c</sup> | Late<sup>c</sup> | Early<sup>c</sup> | Late<sup>c</sup> |               |               |
|                              | N = 189      | ptyr = 625.9      | N = 164                   | ptyr = 540.7  |               |               |
| Major bleed                  | 10 (2.8)     | 16 (1.0)          | 6 (3.2)                   | 6 (0.7)       | .652         | .195         |
| Cerebrovascular accident     | 3 (0.8)      | 8 (0.5)           | 5 (0.6)                   | 3 (1.8)       | .064         | .616         |
| Peripheval thromboembolism   |              |                   |                           |               |              |              |
| Valve thrombosis             | 8 (0.5)      | 3 (0.4)           | 5 (0.7)                   |               | .360         |              |
| Prosthetic endocarditis      | 1 (0.3)      | 1 (0.06)          | 1 (0.5)                   |               | .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)       | .365         | .651         |
| All mortality                | 14 (4.0)     | 23 (1.5)          | 8 (4.2)                   | 12 (1.4)      | .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         |              |

<sup>a</sup> On-X Life Technologies (On-X)/Artivion Inc.  
<sup>b</sup> St Jude Medical.  
<sup>c</sup> 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<sup>a</sup> | Early<sup>a</sup> N = 381 | Late<sup>a</sup> | ptyr = 1963.7 | Late<sup>a</sup> | ptyr = 555.7 |
|                              | Late<sup>a</sup> | ptyr = 1963.7 | Late<sup>a</sup> | ptyr = 555.7 |               |               |
| Major bleed                  | 18 (3.6)     | 17 (4.5) | 24 (1.2)   | 1 (0.8)       | 6 (1.1)       | .058         | .786         |
| Cerebrovascular accident     | 2 (0.4)      | 2 (0.5)  | 13 (0.7)   | 1 (0.2)       |               | .660         | .178         |
| Peripheval 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)      | 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)      | 3 (0.8)  | 7 (0.4)    | 1 (0.2)       | .324         | .514         |
| All mortality                | 8 (1.6)      | 35 (1.4) | 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         |              |              |

<sup>a</sup> Values are presented as n (%).  

**Bold P values indicate statistical significance.** 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 E7. Adverse event rates for mitral valves by economic development

| Event                        | Mitral total | Western Early* | Western Late* | Developing Early* | Developing Late* | P value early | P value late |
|------------------------------|--------------|----------------|---------------|-------------------|------------------|--------------|--------------|
|                              | Early*      | Late*          | Early*        | Late*             |                  |              |              |
|                              | N = 56      | N = 297        | N = 56       | N = 297           |                  |              |              |
| 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 I/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 I/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| I   | II  | III | IV  | Total |
|-------|-----|-----|-----|-----|-------|
| I     |     | 53  | 5   | 0   | 58    |
| II    |     | 131 | 10  | 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| 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) | <.0001 |
| Postop | 578 (87.4) | 63 (9.5) | 19 (2.9) | 1 (0.2) | |
| **On-X** | | | | | |
| Preop | 338 (75.1) | 105 (23.3) | 1 (0.2) | 6 (1.3) | <.0001 |
| Postop | 327 (88.9) | 30 (8.2) | 11 (3.0) | 0 (0.0) | |
| **St Jude Medical** | | | | | |
| Preop | 289 (75.3) | 88 (22.9) | 2 (0.5) | 5 (1.3) | .0001 |
| Postop | 251 (85.7) | 33 (11.3) | 8 (2.7) | 1 (0.3) | |
| **Aortic** | | | | | |
| Preop | 448 (92.4) | 27 (5.6) | 3 (0.6) | 7 (1.4) | .0002 |
| Postop | 360 (94.2) | 9 (2.4) | 13 (3.4) | 0 (0.0) | |
| **Mitral** | | | | | |
| Preop | 179 (51.3) | 166 (47.6) | 0 (0.0) | 4 (1.1) | <.0001 |
| Postop | 218 (78.1) | 54 (19.4) | 6 (2.2) | 1 (0.4) | |
| **Western** | | | | | |
| Preop | 364 (87.5) | 44 (10.6) | 1 (0.2) | 7 (1.7) | <.0001 |
| Postop | 303 (89.9) | 19 (5.6) | 15 (4.5) | 0 (0.0) | |
| **Developing** | | | | | |
| Preop | 263 (62.9) | 149 (35.6) | 2 (0.5) | 4 (1.0) | <.0001 |
| Postop | 275 (84.9) | 44 (13.6) | 4 (1.2) | 1 (0.3) | |

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**

| Group | Event* | All-cause mortality | Valve-related plus sudden death | TE | VT | Thrombotic events |
|-------|--------|---------------------|---------------------------------|----|----|-------------------|
| Whole | <.0001, congestive HF, .97 to .001, NYHA, .64 to .016 | .005, congestive HF, 1.01 to .03, NYHA, .84 to .027 | .005, age, .05 to .009 | <.0001, age, -.15 to .001 inverse to age | No relationships |
| Developing | <.0001, age, .03 to .029, congestive HF 1.25 to .001 | .01, congestive HF 1.06 to .01 | No relationships | .0001, age, -.13, -.002 inverse to age | No relationships |
| Western | .0001, BMI, .08 to .008, CVA, 1.43 to .044, NYHA, .95 to .33 | .001, BMI, .11 to .006 | No relationships | No relationships (only 1 event) | No relationships |
| On-X | .007, BMI, .03 to .048, NYHA, .87 to .018 | .009, congestive HF, 1.17 to .008 | No relationships | .0001, age, -.15 to .002 inverse to age | No relationships |
| St Jude Medical | .006, congestive HF, 1.28 to .005 | 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, -.012 to .003 inverse to age | No relationships |

*Values are presented as model P value, factor(s) coefficient P value. †On-X Life Technologies/Artivion Inc. ‡Abbott/St Jude Medical.

TE: Thromboembolism. VT: valve thrombosis; HF: heart failure; NYHA, New York Heart Association functional class; BMI, body mass index; CVA, cardiovascular accident.