On-X Valve: The Next Generation Aortic Valve.

Rahul Chaudhary MD

Jalaj Garg MD
Lehigh Valley Health Network, jalaj.garg@lvhn.org

Parasuram Krishnamoorthy MD

Neeraj Shah MD
Lehigh Valley Health Network, Neeraj_N.Shah@lvhn.org

Bruce Feldman DO
Lehigh Valley Health Network, bruce.feldman@lvhn.org

See next page for additional authors

Published In/Presented At

Chaudhary, R., Garg, J., Krishnamoorthy, P., Shah, N., Feldman, B. A., Martinez, M. W., & Freudenberger, R. (2017). On-X Valve: The Next Generation Aortic Valve. *Cardiology In Review*, *25*(2), 77-83. doi:10.1097/CRD.0000000000000105

Authors

Rahul Chaudhary MD, Jalaj Garg MD, Parasuram Krishnamoorthy MD, Neeraj Shah MD, Bruce Feldman DO, Matthew W. Martinez MD, and Ronald S. Freudenberger MD

On-X Valve

The Next Generation Aortic Valve

Rahul Chaudhary, MD, Jalaj Garg, MD,*† Parasuram Krishnamoorthy, MD,‡ Neeraj Shah, MD,† Bruce A. Feldman, DO,† Matthew W. Martinez, MD,† and Ronald Freudenberger, MD†*

Abstract: The On-X valve is a newer generation mechanical bileaflet valve. Its key features include the use of pure pyrolytic carbon (devoid of silicon), a length-to-diameter ratio similar to a native valve, an inlet flared orifice, a leaflet opening up to 90 degrees, a shorter leaflet closing angle, a 2-point leaflet contact, and an actuated pivot. These features have translated into increased strength, improved valve hemodynamics, reduced hemolysis, and thrombogenicity. The 2014 American Heart Association/American College of Cardiology guidelines for the management of patients with valvular heart disease recommend an international normalized ratio (INR) of 2.5 (range, 2–3) in patients with a mechanical valve at the aortic position. However, based on the results of the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT), the Food and Drug Administration approved this valve in April 2015 in the aortic position with a lower INR goal of 1.5–2.0. This reduction in INR goals led to a statistically significant reduction in the combined endpoint of clots, bleeding events, and stroke rates with 9/patient-years for the lower INR group compared with 12/patient-years in the standard INR group. This review compares the currently available literature on the On-X valve with that of other contemporary valves.

Key Words: On-X valve, thrombosis, warfarin, anticoagulation, PROACT

(*Cardiology in Review* 2017;25: 77–83)

The On-X valve is a new generation bileaflet valve first implanted in 1996 (approved in Europe and the United States in 1998 and 2001, respectively) with more than 200,000 implantations worldwide. Since then, there have been multiple studies and publications evaluating its safety and efficacy in the aortic and mitral positions. A study by Özyurda et al.[1] demonstrated a 30-day mortality rate up to 3.5% independent of valve-related complications. These complications were found to be comparable with other series of aortic and mitral valve prostheses in a similar population.[2–6] Prospective studies (with a 5-year follow-up duration) demonstrated promising short-term and mid-term performance of this valve.[7–11] Longer-term data of up to 12 years, as reported by Chambers et al.[12] in 691 patients with 761 valves (407 in mitral position, 214 in aortic position, and 70 in aortic + mitral positions) demonstrated low rate of adverse clinical events. A multicenter European study that evaluated the hemodynamics of the On-X valve demonstrated improved mean valve gradients and an effective orifice area with the On-X valve compared with earlier bileaflet models.[13,14] The improved hemodynamics were later reconfirmed in a study by Chambers et al.,[12] which the authors attributed to the valve's design as elucidated in a later section of this article. A particularly interesting finding that stood out in all the reported studies was the absence of thrombosis with the On-X valve in the aortic valve position. Williams and van Riet[15] demonstrated no thrombosis in the aortic valve position, with no or inadequate anticoagulation in up to 40% of the population. This formed the basis for the Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT trial) investigating the safety and efficacy of lower anticoagulation goals with the On-X valve, which will be discussed in this article.

FEATURES OF THE ON-X VALVE

The material used to construct the On-X valve is a newer generation pure pyrolytic carbon devoid of any silicon, which is 20% stronger and tough when compared with the material used to construct conventional mechanical valves.[16,17] The pyrolytic carbon used to manufacture conventional mechanical valves contains small amounts of silicon, which provides stiffness to the valve and also serves as a nidus for platelet aggregation and subsequent thrombus formation.

The On-X valve also has a length-to-diameter ratio similar to the native valve, an inlet flared orifice, an opening of leaflets up to 90 degrees, and a shorter leaflet closing angle, all of which reduces the turbulence and enhances increased blood flow across the valve.[17] The valve also has a 2-point leaflet contact and leaflet guards, features that prevent tissue ingrowth and pannus formation, and hence improved valve efficiency even in a low flow state (which was a major problem encountered with conventional mechanical valves in a low flow state). Also, the presence of an actuated pivot and greater pivot washing gives the On-X valve a better efficiency and lesser theoretical risk of clotting (Figs. 1 and 2).

ECHOCARDIOGRAPHIC APPEARANCE OF THE ON-X VALVE

The On-X valve has a unique echocardiographic appearance. In the midesophageal short-axis views of the aortic On-X valve, the ends of the leaflet guards are clearly visible during diastole (Fig. 3). During systole, 3 flow channels can be observed between each leaflet and its respective guard (Fig. 4). In the midesophageal long-axis view, the inlet flare gives the On-X valve a prominent profile (Fig. 4A). Washing or regurgitant jets flow through the hinge pivot sites cleansing the pivots of any debris, the mechanism that prevents thrombus formation and prevents leaflet malfunction. In the deep transgastric or midesophageal long-axis view, the washing jets are directed outward (away from the central axis of the On-X valve) toward the walls of the left ventricular outflow (LVO) tract, which contrasts with the St. Jude bileaflet valve, where the jets are directed inward (toward the central axis of the

From the *Department of Medicine, Sinai Hospital of Baltimore, Johns Hopkins University, Baltimore, MD; †Division of Cardiology, Lehigh Valley Health Network, Allentown, PA; and ‡Department of Medicine, Einstein Healthcare Network, Philadelphia, PA.

Disclosure: The authors have no conflicts of interest to report.

Drs Chaudhary and Garg have contributed equally for the article.

Correspondence: Jalaj Garg, MD, Division of Cardiology, Lehigh Valley Health Network, 1250 S Cedar Crest Blvd, Allentown, PA 18103. E-mail: garg.jalaj@yahoo.com.

ISSN: 1061-5377/17/2502-0077

DOI: 10.1097/CRD.0000000000000105

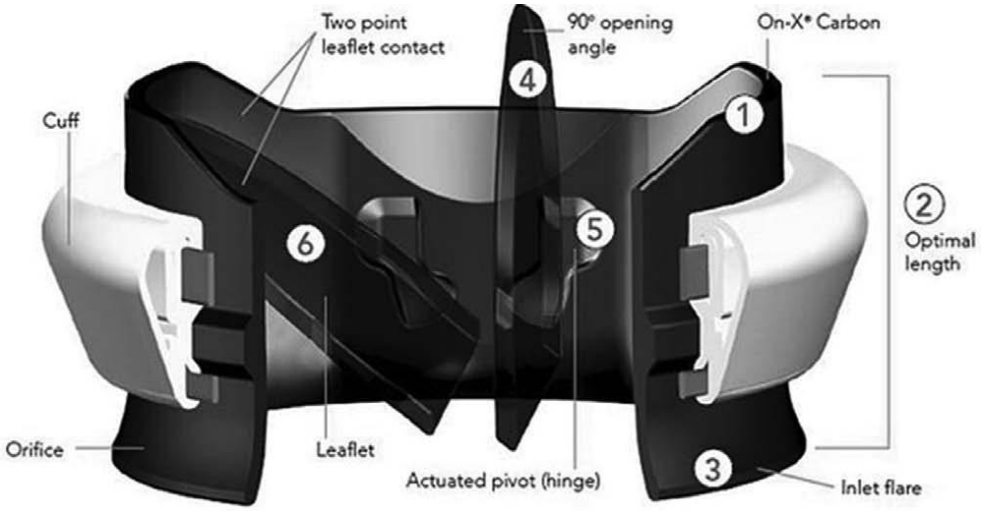

FIGURE 1. On-X Valve design features. Features of On-X valve: (1) pure carbon; (2) optimal longer length; (3) inlet flared orifice; (4) full 90 degree leaflet opening; (5) stasis-free pivots; and (6) 2-point closure. Reproduced with permission from On-X Life Technologies Inc.

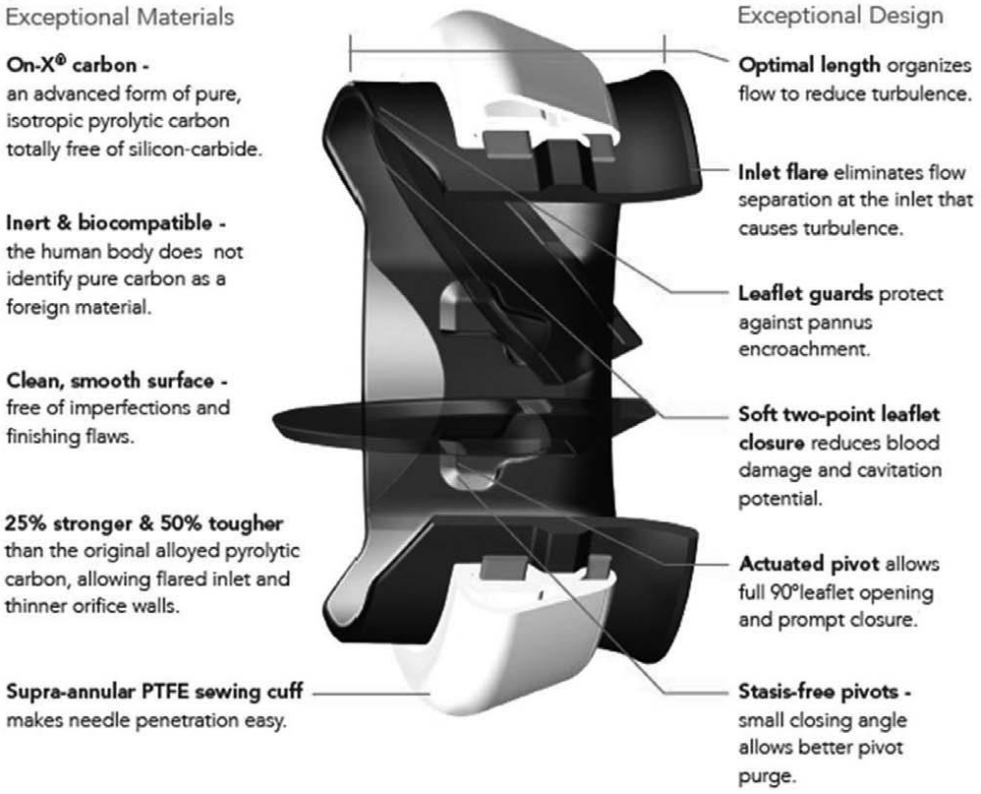

FIGURE 2. Features and advantages of the On-X valve. Reproduced with permission from On-X Life Technologies Inc.

valve).[18] Knowledge of these jets is important to avoid erroneous diagnosis of a valvular leak (assessed by measuring jet width, jet area, the ratio of jet diameter/LVO diameter, and jet area/LVO area). As reported by Chambers and Ely,[19] the effective orifice area (EOA) should be measured using the ratio of the LVO tract and transaortic velocity–time integrals in the continuity equations. Utilizing the peak LVO tract and transaortic valve velocities can lead to an inaccurate estimation of the EOA.

PROACT AND OTHER STUDIES EVALUATING LOWER INTERNATIONAL NORMALIZED RATIO GOALS

The interim results of the PROACT study [highlighting high-risk aortic valve replacement (AVR) patients] were published in April 2014.[20] In this trial, the "high-risk" AVR group was defined by the presence of any of the following: chronic atrial fibrillation, left ventricular ejection fraction <30%, enlarged left atrium >50 mm in diameter, spontaneous echocardiographic contrasts in the left atrium,

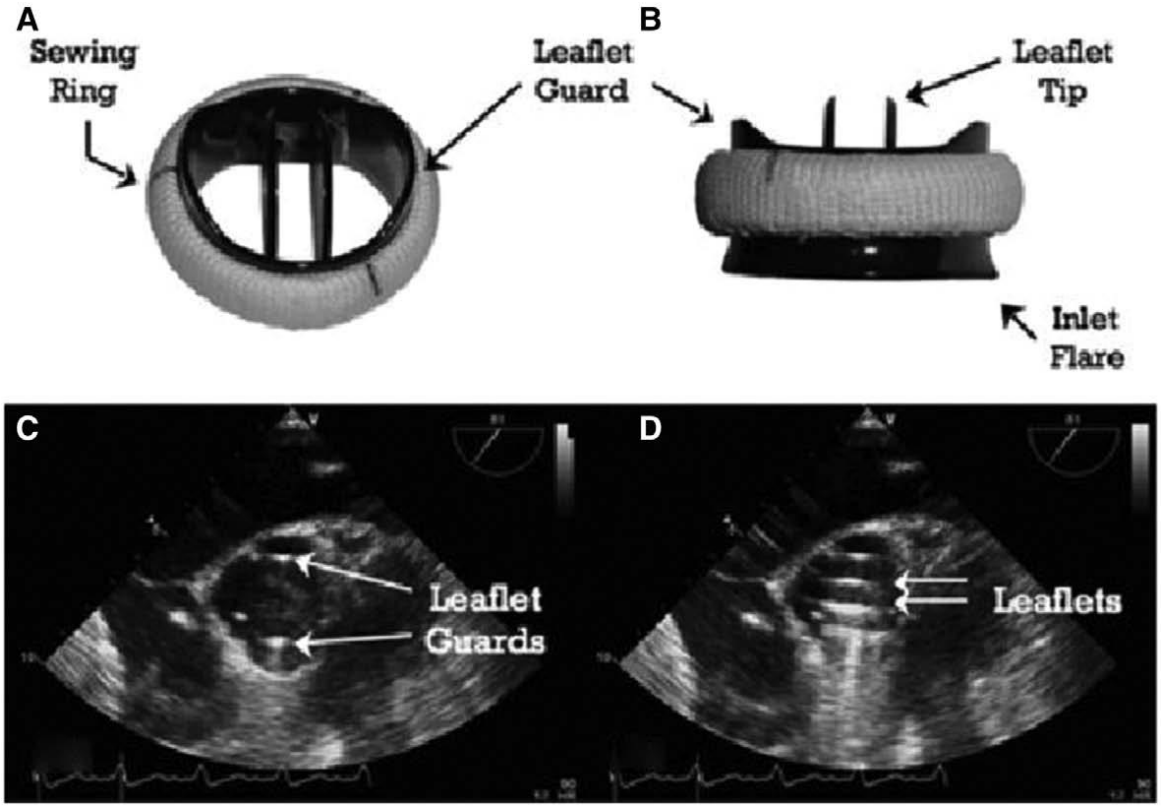

FIGURE 3. Echocardiographic features of the On-X valve. A, On-X valve short axis (SAX) in vitro; (B) On-X valve long axis (LAX) in vitro; (C) TEE image of the On-X valve closed in the midesophageal (ME) SAX view. D, TEE image of the On-X valve open in the ME SAX view. TEE indicates transesophageal echocardiogram.

vascular pathologic features, neurologic events, hypercoagulability, left or right ventricular aneurysm, lack of a platelet response to aspirin or clopidogrel, and women receiving estrogen replacement therapy. Three months after AV implantation, 375 patients were randomized into 2 groups: 190 patients received aspirin 81 mg/d with doses of warfarin titrated to maintain an international normalized ratio (INR) between 1.5 and 2.0 and 185 patients received aspirin 81 mg/d and warfarin titrated to an INR between 2.0 and 3.0. Warfarin dose adjustments were made using home INR monitoring. The mean study follow-up period was 3.82 years. The study demonstrated a higher safety and efficacy for low-dose aspirin and target INR of 1.5–2.0 in patients with high-risk AVR. There was a significant reduction in major and minor bleeding events in the lower INR group when compared with conventional INR goals (1.48% vs 3.31%/patient-years; $P = 0.032$ for major bleeding; and 1.18% vs 3.31%/patient-years; $P = 0.011$ for minor bleeding). The benefit was amplified when the INR was closer to 2.0 when compared with 1.5, with thromboembolic events being more common when the INR was <1.5. No statistical significance was found in transient ischemic attacks, stroke, or total neurologic events. The combined endpoint of clots, bleeding events, and stroke rates were 9/patient-years for the low INR group compared with 12/patient-years with the standard INR group ($P = 0.046$). No difference in all-cause mortality was seen between the 2 groups.[20]

LOWERING-IT (LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement) study was another trial that evaluated 396 "low-risk" patients undergoing single mechanical bileaflet valve implantation in the aortic position and compared INR goals of 1.5–2.5 (n = 197; low INR group) versus 2.0–3.0 (n = 199; conventional INR group).[21] The primary outcomes of the study were thromboembolic events including thrombosis and thromboembolism; the secondary outcomes included the occurrence of any bleeding events. Although the results were similar, there are some fundamental key differences from the PROACT trial (Table 1).[20–22]

The ESCAT II trial (INR Self-Management Permits Lower Anticoagulation Levels After Mechanical Heart Valve Replacement) evaluated patients with mechanical AVs (St. Jude Medical Standard and Medtronic Hall) for 2 years in 2 groups, with lower INR goals of 1.8–2.8 (n = 1327) and high INR goals of 2.5–4.5 (n = 1346).[22] This trial reported a thromboembolism rate of 0.24%/patient-years with a lower INR (versus 0.46% with high INR; $P > 0.05$) and bleeding complications were noted to be 1.42%/patient-years with lower INR goals (versus 1.78% with higher INR goals; $P > 0.05$) in the aortic position. An important similarity between this study and the PROACT study is that INR values were self-managed by patients, hence increasing compliance[23] (Table 1).

Caveats in the PROACT Trial

The PROACT study is not without its limitations. In the high-risk AV patient population, the prevalence of atrial fibrillation in the lower INR group was 2% (n = 3) versus 6% ($P = 0.06$) in the conventional INR group. This incidence was much lower than the national prevalence of 6.5% and from other studies evaluating mechanical valves like Medtronic ATS mechanical cardiac valve prosthesis, with a prevalence of 30%.[24,25] The thromboembolic risk imposed by atrial fibrillation is independent of the presence of an On-X valve in the aortic position, and an INR of 1.5 is considered subtherapeutic for

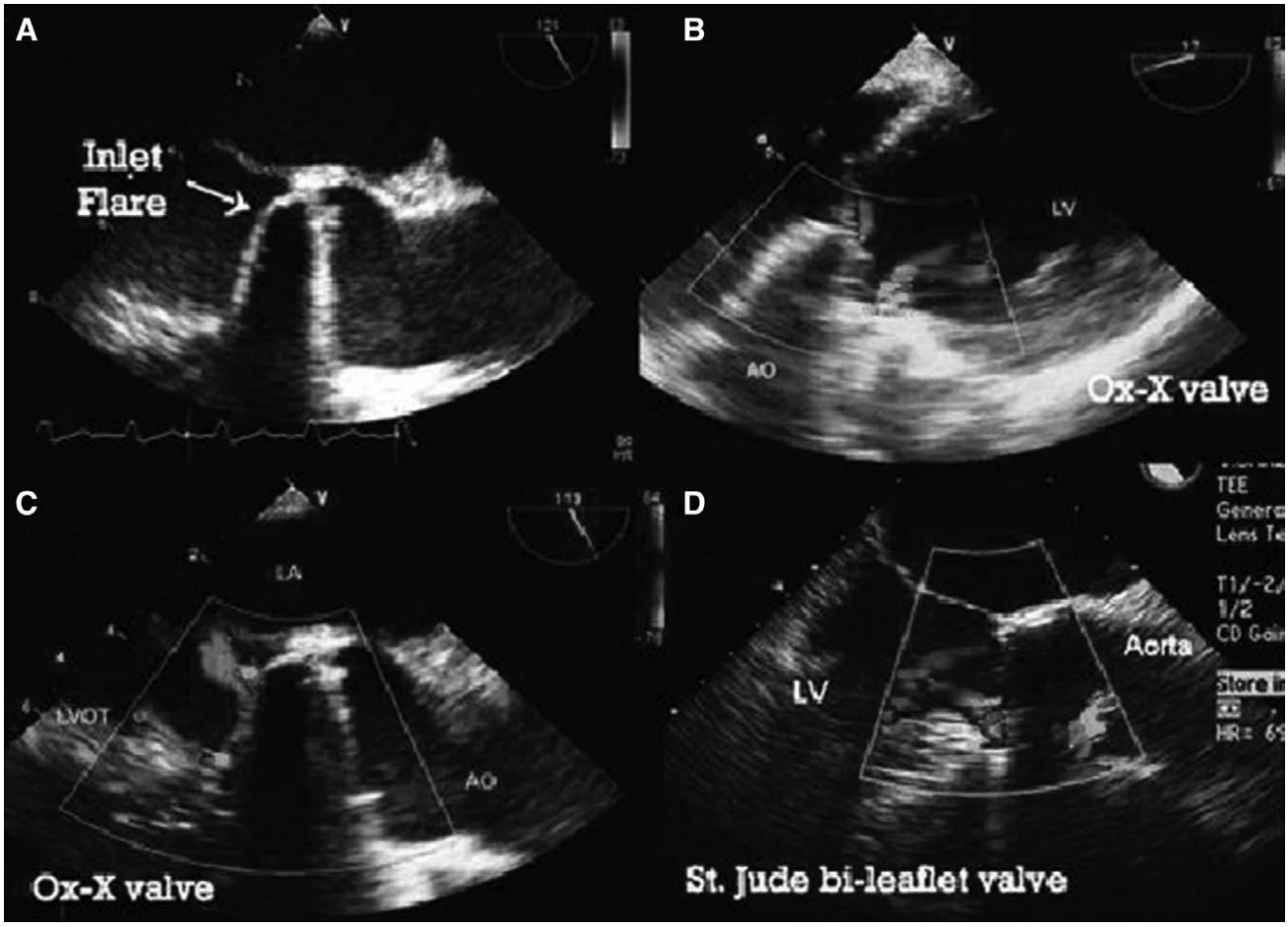

FIGURE 4. Echocardiographic features of the On-X valve (regurgitant jets positioning). A, TEE image of the On-X valve in the midesophageal long axis (ME LAX). B, Color flow Doppler image of On-X obtained in the deep transgastric view valve showing nonconverging washing jets. C, TEE image of On-X valve washing jets in ME LAX. D, TEE image of the St. Jude bileaflet valve in ME LAX showing typical converging washing jets. TEE indicates transesophageal echocardiogram.

thromboembolic prevention in atrial fibrillation patients. It has been demonstrated that the occurrence of stroke in patients with atrial fibrillation (especially with an INR <2.0) is associated with higher morbidity and mortality rates.[26] Also, according to the current anticoagulation guidelines in patients with nonvalvular atrial fibrillation, the assessment of CHA_2DS_2-VASc score and maintenance of INR ≥2 (target between 2.0 and 3.0) is a class I recommendation. However, in patients with atrial fibrillation mechanical heart valves, the target INR is aimed between 2.5 and 3.5 for both aortic and mitral positions.[27] Hence, this FDA approval for patients who received an On-X valve and chronic atrial fibrillation (as noted from the high-risk group of PROACT trial) at lower than guideline suggested INR levels (1.5–2.0 instead of 2.5–3.5) raise an important concern. Also, the differences in the 2 arms of the PROACT trial (low INR and conventional INR) for combined results of valve thrombosis and thromboembolic events were 2.96% per patient-years versus 1.85% per patient-years, respectively ($P = 0.18$), with a test to control ratio of 1.6. This could have shown statistical significance if the power of the study was greater.

Other factors leading to bias in interpretation of the study results include a relatively small number of patients in the lower INR goal group (1.5–2.0; n = 185) and exclusion of patients who are at highest thromboembolic risk (ie, within first 3 months postprocedure).[28–30] Also, the trial utilized self-monitored INR once a week that is not reflective of conventional outpatient anticoagulation management. Likewise, the patients in both groups had a high degree of compliance with home INR monitoring, as most INRs recorded in the test group were closer to 2.0, not reflective of an office-based community setting where the mean time in chosen therapeutic range was achieved in only 54% of the subjects.[31]

ADVANTAGES OF THE ON-X VALVE

In comparison with its other contemporary bileaflet valves, like the St. Jude valve, the On-X valve was associated with a reduced incidence of thrombosis, stenosis, and hemolysis in the aortic position. In a study comparing the St. Jude valve with the On-X valve in the aortic position, there was no significant difference between the 2 prostheses in hemodynamic parameters postoperatively and at 1 year of follow-up.[32] In 2013, Chambers et al.[12] reported on 12 years of prospective data (n = 214) demonstrating a zero valve thrombosis rate in patients with an On-X AVR. In contrast, other bileaflet valves have been reported to have valve thrombosis rates as follows: Medtronic open-pivot aortic valve (3.8%/patient-years), St. Jude valve (0–0.5%/patient-years), Carbomedics valve (0–0.07%/patient-years), Edwards-Tekna valve (0–0.21%/ patient-years), and Sorin Bicarbon valve (0%/patient-years).[33–35]

TABLE 1. Characteristics of Major Trials Evaluating the On-X Valve

Study Name	Inclusion Criteria	Exclusion Criteria	Groups (n)	Outcomes (*P* Value)
PROACT trial[20]	Adult patients (>18 years) Clinical indication for isolated AVR Concomitant cardiac surgery—CABG, mitral or tricuspid valve repair, ascending aortic replacement, Maze procedure were allowed High-risk group: Defined as follows: 1. Chronic afib 2. LVEF <30% 3. Enlarged LA >50 mm diameter 4. Spontaneous echocardiographic contrast in LA 5. Vascular pathologic features, neurologic events 6. Hypercoagulability 7. Left or right ventricular aneurysm 8. Lack of a platelet response to aspirin or clopidogrel 9. Women on estrogen replacement therapy	Right-sided valve replacement Double (aortic plus mitral) valve replacement Patients with active endocarditis at implantation	Low INR group 1.5–2.0 (n = 190) vs standard INR group 2.0–3.0 (n = 185)	(Results reported as rate %/patient-years) Major bleeding (1.48 vs 3.31, *P* = 0.032) Minor bleeding (1.18 vs 3.31, *P* = 0.011 Total bleeding events (2.67 vs 6.62, *P* < 0.001) TIA (1.33 vs 0.79, *P* = NS) Ischemic stroke (0.74 vs 0.66, *P* = NS) Hemorrhagic stroke (0.15 vs 0.26, *P* = NS) Neurologic event (2.07 vs 1.46, *P* = NS) All TE (2.67 vs 1.59, *P* = NS) Valve thrombosis (0.3 vs 0.26, *P* = NS) Major event (4.44 vs 5.16, *P* = NS) Death (1.48 vs 1.46, *P* = NS)
LOWERING-IT trial[21]	Patients with single AVR, valve prosthesis dimension ≥21 mm, normal LVEF and LA diameter <47 mm (defined preoperatively by echocardiogram), normal sinus rhythm, and warfarin-naive (ie, never been on warfarin before)	Contraindication to anticoagulant treatment (including pregnant women) Valvular prosthesis on another orifice Concomitant nonvalve procedures (including CABG) Dialyzed renal failure Hepatic insufficiency Patients with a high risk of TE events (ie, afib, history of cardiac TE, LA diameter >47 mm, thrombosis, or calcification of LA)	Low INR group 1.5–2.0 (n = 197) vs standard INR group 2.0–3.0 (n = 199)	(Results reported number of events) Valve thrombosis (0 events) Ischemic stroke/TIA (0 vs 2) Coronary and/or peripheral Embolism (0 events) Overall TE events (OR 0.33; 95% CI, 0.006–4.20; *P* = 0.62) Major bleeding (0 versus 3) Nonmajor bleeding (6 vs 13) Overall hemorrhagic events (OR 0.36; 95% CI, 0.11–0.99, *P* = 0.04)
ESCAT II trial[22]	Mechanical heart valve recipients	1. Contraindication to phenprocoumon (eg, allergy) 2. Known ulcerous disease with bleeding tendency 3. Hypo- or hypercoagulability 4. Age <18 years	Low INR of 1.8–2.8 (n = 1327) vs target INR of 2.5–4.5 (n = 1346)	(Results reported as rate %/patient-years) Thromboembolic complications in aortic position [0.24 vs 0.46 (*P* = NS)] Bleeding complications in aortic position [1.42 vs 1.78 (*P* = NS)]

Afib indicates atrial fibrillation; AVR, aortic valve replacement; CI, confidence interval; CABG, coronary artery bypass grafting; INR, international normalized ratio; LA, left atrium; LVEF, left ventricular ejection fraction; NS, not significant; OR, odds ratio; TE, thromboembolic; TIA, transient ischemic attack.

The study also reported that the rate of thromboembolism, including peripheral embolism, transient ischemic attack, and stroke, has a linearized rate of 0.6–0.88%/patient-years with the On-X aortic valves. This compares favorably with thromboembolic events with other mechanical valves in the aortic position: Medtronic open-pivot aortic valve (0.4–0.8%/patient years), St. Jude valve (0.62–4.48%/patient-years), Carbomedics valve (0.32–1.39%/patient-years), Edwards-Tekna valve (0.44–2.41%/patient-years), and Sorin Bicarbon valve (0.98%/patient-years).[12,13,33–42] Although the results demonstrated favorable valve thrombosis and thromboembolic outcomes, they need to be carefully interpreted, as the risk of thrombosis and related complications in patients with prosthetic heart valves also depend on the patients own risk factors along with the type of prosthesis. No structural failures have been reported with the On-X valve so far,[10–12,35,43] which contrasts with the St. Jude mechanical valve where incidents of leaflet escapes have been reported.[35–37] The rate of endocarditis was low (0.37%/patient-years) and of similar incidence when compared with other mechanical bileaflet valves: Medtronic open-pivot aortic valve 0.8%/patient-years, St. Jude valve 0.08–1.1%/patient-years, Carbomedics valve 0.16–0.48%/patient-years, Edwards-Tekna valve 0.29–0.41%/patient-years, and Sorin Bicarbon valve 0.49%/patient-years.[12,33–35] Mechanical valves have also been associated with chronic hemolysis, a reduction in levels of haptoglobin to below normal, and lactate dehydrogenase elevation to as much as 200% above upper normal. However, with the On-X valves, haptoglobin was reduced to 86% below normal in patients with AVR after 1 year of implantation and the lactate dehydrogenase value was seen to be at 98% of upper normal value, suggesting nonoccurrence of hemolytic anemia with this valve.[44] The bleeding rates observed were 0.40–0.77%/patient-years with standard INR goals, which is similar to the other mechanical bileaflet valves.[12,13]

Valve efficiency and hemodynamic performance are evaluated by EOA and gradient (pressure difference across the valve) as measured on echocardiography. Follow-up studies on the hemodynamics of older mechanical valves have demonstrated a poor efficiency in smaller sized valves.[45–47] However, the parameters of the On-X valve

TABLE 2. On-X Valve Comparison to Tissue Heart Valve Hemodynamics

	On-X Valve[48]		Medtronic ATS Valve[49]		St Jude Medical Standard Valve[49]		Sorin Bicarbon Bileaflet Valve[49]	
Valve Size	EOA (cm^2)	Gradient (mm Hg)	EOA (cm^2)	Gradient (mm Hg)	EOA (cm^2)	Gradient (mm Hg)	EOA (cm^2)	Gradient (mm Hg)
19	1.5	8.7	1.1	25.3	1.5	24.5	1.4	16.7
21	1.8	8.1	1.4	15.9	1.4	15.2	1.2	10.0
23	2.3	6.6	1.7	14.4	1.6	13.4	1.5	7.7
25	2.7	4.2	2.1	11.3	1.9	11.0	2.4	5.6

EOA indicates effective orifice area.

have demonstrated superior hemodynamics (larger EOA and smaller gradient) and thus increased efficiency. A comparison of the On-X valve hemodynamics with other tissue valves at varying sizes is presented in Table 2.[48,49]

ON-X VALVE DISADVANTAGES

Similar to other mechanical prostheses, the On-X valve is associated with an increased risk of bleeding, thromboembolism and stroke/transient ischemic attack, and endocarditis when compared with bioprosthetic valves.

ANTICOAGULATION WITH AN ON-X VALVE

Currently, the only oral anticoagulant indicated in patients receiving a mechanical prosthetic valve is warfarin (vitamin K antagonist). Multiple studies have been performed and are underway comparing the efficacy of newer oral anti-Xa inhibitors in patients with prosthetic mechanical valves. The RE-ALIGN study[50] was a randomized, prospective, phase II dose-validation study to evaluate dabigatran in comparison with warfarin for patients with mechanical prosthetic heart valves. The study was prematurely discontinued after recruitment of 252 patients because of unacceptable thromboembolic and bleeding event rates in the dabigatran group. The dabigatran group had a 5% stroke rate (versus 0% with warfarin), 3% of patients had valve thrombosis (versus 0% with warfarin), 4% of patients experienced major bleeding episodes (versus 2% with warfarin), and 27% of patients experienced any bleeding (versus 12% with warfarin). The composite of stroke, transient ischemic attack, systemic embolism, myocardial infarction, or death occurred in 9% of patients in the dabigatran group compared with 5% in the warfarin group.[48] However, studies have shown promising results with rivaroxaban in a porcine model with an implanted mechanical prosthetic heart valve, and one is currently under evaluation in the CATHAR trial (Comparison of Antithrombotic Treatments After Aortic Valve Replacement, NCT02128841) with mechanical prosthetic heart valves. To date, there have been no studies assessing the role of apixaban in patients with mechanical prosthetic heart valves.

Because of the increasing experience using novel oral anticoagulants and the trials evaluating the use of these agents in mechanical prosthetic heart valves, it is possible that anticoagulation in mechanical prosthetic valves might be managed with these agents in the near future. Whether these valves would require a reduced dosing regimen with the On-X valve compared with other mechanical prosthetic valves remains to be determined.

FUTURE DIRECTIONS FOR THE ON-X VALVE

The On-X valve has been implanted in both the mitral position and a dual valve replacement option (aortic and mitral valve). Data from clinical studies after the On-X valve implantation in the mitral position have demonstrated a valve thrombosis risk ranging from 0 to 0.1%/patient-years. These levels were found to be comparable with other valves in the mitral position, including the St Jude valve (0–0.45%/patient-years), Carbomedics valve (0.16–0.51%/patient-years), and Edwards-Tekna valve (0.49%/patient-years). Thromboembolic risk with the On-X valve was seen to be at a linearized rate of 1% in the mitral position and 1.8% for double valve replacement. This compares with the reported thromboembolic rate for other valves like the St Jude valve (0.21–7.15%/patient-years), Carbomedics valve (1.07–2.24%/patient-years), and Edwards-Tekna valve (0.49–1.20%/patient-years).[9,10,12,34]

Two arms of the PROACT study are still recruiting patients, and their results are anticipated to be available by March 2018. Their results may open new avenues for this valve with a potential use beyond the American Heart Association guidelines at positions other than the aortic valve with lower INR goals. The 2 arms are comparing (a) patients with low-risk AVR on aspirin/clopidogrel without anticoagulation compared with the addition of warfarin at an INR range of 2.0–3.0; (b) On-X valve implantation in the mitral position in patients on aspirin with the addition of warfarin at either an INR of 2.0–2.5 versus 2.5–3.5. The results of this study may usher in a new era of mechanical prosthetic valves, which are less thrombogenic and thus require lower levels of anticoagulation.

CONCLUSION

At present, with the limited data available only from one major trial (PROACT) evaluating lower INR goals in high-risk individuals, we recommend a cautious and patient-by-patient approach toward lowering INR goals in patients receiving an aortic On-X valve implantation.

REFERENCES

1. Ozyurda U, Akar AR, Uymaz O, et al. Early clinical experience with the On-X prosthetic heart valve. *Interact Cardiovasc Thorac Surg*. 2005;4:588–594.
2. Akalin H, Corapçioğlu ET, Ozyurda U, et al. Clinical evaluation of the Omniscience cardiac valve prosthesis. Follow-up of up to 6 years. *J Thorac Cardiovasc Surg*. 1992;103:259–266.
3. Akar AR, Szafranek A, Alexiou C, et al. Use of stentless xenografts in the aortic position: determinants of early and late outcome. *Ann Thorac Surg*. 2002;74:1450–1457; discussion 1457.
4. Christakis GT, Kormos RL, Weisel RD, et al. Morbidity and mortality in mitral valve surgery. *Circulation*. 1985;72(3 Pt 2):II120–II128.
5. Glower DD, Landolfo KP, Cheruvu S, et al. Determinants of 15-year outcome with 1,119 standard Carpentier-Edwards porcine valves. *Ann Thorac Surg*. 1998;66(6 suppl):S44–S48.
6. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152–1158.
7. Chambers J, Ely JL. Early postoperative echocardiographic hemodynamic performance of the On-X prosthetic heart valve: a multicenter study. *J Heart Valve Dis*. 1998;7:569–573.

8. Laczkovics A, Heidt M, Oelert H, et al. Early clinical experience with the On-X prosthetic heart valve. *J Heart Valve Dis*. 2001;10:94–99.
9. Moidl R, Simon P, Wolner E; On-X Prosthesis Heart Valve Trial. The On-X prosthetic heart valve at five years. *Ann Thorac Surg*. 2002;74:S1312–S1317.
10. McNicholas KW, Ivey TD, Metras J, et al. North American multicenter experience with the On-X prosthetic heart valve. *J Heart Valve Dis*. 2006;15:73–78; discussion 79.
11. Tossios P, Reber D, Oustria M, et al. Single-center experience with the On-X prosthetic heart valve between 1996 and 2005. *J Heart Valve Dis*. 2007;16:551–557.
12. Chambers JB, Pomar JL, Mestres CA, et al. 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;145:420–424.
13. Palatianos GM, Laczkovics AM, Simon P, et al. Multicentered European study on safety and effectiveness of the On-X prosthetic heart valve: intermediate follow-up. *Ann Thorac Surg*. 2007;83:40–46.
14. Wang Z, Grainger N, Chambers J. Doppler echocardiography in normally functioning replacement heart valves: a literature review. *J Heart Valve Dis*. 1995;4:591–614.
15. Williams MA, van Riet S. The On-X heart valve: mid-term results in a poorly anticoagulated population. *J Heart Valve Dis*. 2006;15:80–86.
16. Gilpin CB, Haubold AD, Ely JL. Finite element analysis of indentation tests on pyrolytic carbon. *J Heart Valve Dis*. 1996;5(suppl 1):S72–S78.
17. Ely JL, Emken MR, Accuntius JA, et al. Pure pyrolytic carbon: preparation and properties of a new material, On-X carbon for mechanical heart valve prostheses. *J Heart Valve Dis*. 1998;7:626–632.
18. Yezbick AB, Ho JK, Crowley R, et al. Echocardiographic signature of the On-X valve. *Echocardiography*. 2008;25:1016–1018.
19. Chambers J, Ely J. A comparison of the classical and modified forms of the continuity equation in the On-X prosthetic heart valve in the aortic position. *J Heart Valve Dis*. 2000;9:299–301; discussion 301.
20. Puskas J, Gerdisch M, Nichols D, et al.; PROACT Investigators. 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;147:1202–1210; discussion 1210.
21. Torella M, Torella D, Chiodini P, et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. *Am Heart J*. 2010;160:171–178.
22. Koertke H, Zittermann A, Tenderich G, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. *Eur Heart J*. 2007;28:2479–2484.
23. Koertke H, Minami K, Boethig D et al. INR self-management permits lower anticoagulation levels after mechanical heart valve replacement. *Circulation*. 2003;108(suppl):II-75–II-78.
24. Van Nooten GJ, Bové T, Van Belleghem Y, et al. Twenty-year single-center experience with the medtronic open pivot mechanical heart valve. *Ann Thorac Surg*. 2014;97:1306–1313.
25. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147.
26. Chan PS, Nallamothu BK, Krumholz HM, et al.; American Heart Association Get with the Guidelines–Resuscitation Investigators. Long-term outcomes in elderly survivors of in-hospital cardiac arrest. *N Engl J Med*. 2013;368:1019–1026.
27. January CT, Wann LS, Alpert JS, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–76.
28. Davis FB, Estruch MT, Samson-Corvera EB, et al. Management of anticoagulation in outpatients: experience with an anticoagulation service in a municipal hospital setting. *Arch Intern Med*. 1977;137:197–202.
29. Husted S, Andreasen F. Problems encountered in long-term treatment with anticoagulants. *Acta Med Scand*. 1976;200:379–384.
30. Second Report of the Sixty Plus Reinfarction Study Research Group. Risks of long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet*. 1982;1:64–68.
31. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. *Circulation*. 2014;129:1407–1414.
32. Walther T, Falk V, Tigges R, et al. Comparison of On-X and SJM HP bileaflet aortic valves. *J Heart Valve Dis*. 2000;9:403–407.
33. Emery RW, Petersen RJ, Kersten TE, et al. The initial United States experience with the ATS mechanical cardiac valve prosthesis. *Heart Surg Forum*. 2001;4:346–352; discussion 352.
34. Emery RW, Krogh CC, Jones DJ, et al. Five-year follow up of the ATS mechanical heart valve. *J Heart Valve Dis*. 2004;13:231–238.
35. Grunkemeier GL, Li HH, Naftel DC, et al. Long-term performance of heart valve prostheses. *Curr Probl Cardiol*. 2000;25:73–154.
36. Akin CW. Results with mechanical cardiac valvular prostheses. *Ann Thorac Surg* 1995;60:1836–1844
37. Emery RW, Krogh CC, Arom KV, et al. The St. Jude Medical cardiac valve prosthesis: a 25-year experience with single valve replacement. *Ann Thorac Surg*. 2005;79:776–782; discussion 782.
38. Emery RW, Emery AM, Krogh C, et al. The St. Jude Medical cardiac valve prosthesis: long-term follow up of patients having double valve replacement. *J Heart Valve Dis*. 2007;16:634–640.
39. Kang CH, Ahn H, Kim KH, et al. Long-term result of 1144 CarboMedics mechanical valve implantations. *Ann Thorac Surg*. 2005;79:1939–1944.
40. Tominaga R, Kurisu K, Ochiai Y, et al. A 10-year experience with the Carbomedics cardiac prosthesis. *Ann Thorac Surg*. 2005;79:784–789.
41. Toole JM, Stroud MR, Kratz JM, et al. Twenty-five year experience with the St. Jude medical mechanical valve prosthesis. *Ann Thorac Surg*. 2010;89:1402–1409.
42. Van Nooten GJ, Caes F, François K, et al. Fifteen years' single-center experience with the ATS bileaflet valve. *J Heart Valve Dis*. 2009;18:444–452.
43. Chan V, Jamieson WR, Lam BK, 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.e2.
44. Birnbaum D, Laczkovics A, Heidt M, et al. Examination of hemolytic potential with the On-X® prosthetic heart valve. *J Heart Valve Dis*. 2000;9:142–145.
45. Corbineau H, De La Tour B, Verhoye JP, et al. Carpentier-Edwards supraannular porcine bioprosthesis in aortic position: 16-year experience. *Ann Thorac Surg*. 2001;71(5 suppl):S228–S231.
46. Dellgren G, David TE, Raanani E, et al. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc Surg*. 2002;124:146–154.
47. Le Tourneau T, Vincentelli A, Fayad G, et al. Ten-year echocardiographic and clinical follow-up of aortic Carpentier-Edwards pericardial and supraannular prosthesis: a case-match study. *Ann Thorac Surg*. 2002;74:2010–2015.
48. Summary of Safety and Effectiveness, On-X Prosthetic Heart Valve, FDA PMA P000037 and P000037/S1, May 30, 2001 and March 6, 2002, European Primary Trial, updated May 31, 2003.
49. Zoghbi WA, Chambers JB, Dumesnil JG, et al.; American Society of Echocardiography's Guidelines and Standards Committee; Task Force on Prosthetic Valves; American College of Cardiology Cardiovascular Imaging Committee; Cardiac Imaging Committee of the American Heart Association; European Association of Echocardiography; European Society of Cardiology; Japanese Society of Echocardiography; Canadian Society of Echocardiography; American College of Cardiology Foundation; American Heart Association; European Association of Echocardiography; European Society of Cardiology; Japanese Society of Echocardiography; Canadian Society of Echocardiography. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2009;22:975–1014; quiz 1082.
50. Shazly A, Afifi A. RE-ALIGN: First trial of novel oral anticoagulant in patients with mechanical heart valves - The search continues. *Glob Cardiol Sci Pract*. 2014;2014:88–89.