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ORIGINAL INVESTIGATIONS

Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement

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ABSTRACT

BACKGROUND The burden oral anticoagulation is a limitation of mechanical valve prostheses.

OBJECTIVES The aim of this study was to test whether patients could be safely managed with dual-antiplatelet therapy (DAPT) (aspirin 325 mg and clopidogrel 75 mg) or lower warfarin after On-X mechanical aortic valve replacement (mAVR).

METHODS PROACT (Prospective Randomized On-X Anticoagulation Trial) (n = 576) is a multicenter (41 sites) noninferiority trial. From June 2006 through February 2014, 201 patients ≥18 years of age without thromboembolic risk factors undergoing mAVR were randomized to receive DAPT (n = 99) or standard warfarin plus aspirin (n = 102) 3 months after mAVR (low-risk arm). From June 2006 through October 2009, 375 patients with 1 or more thromboembolic risk factors were also randomized to lower intensity warfarin plus aspirin (international normalized ratio 1.5 to 2.0; n = 185) or standard warfarin plus aspirin (international normalized ratio 2.0 to 3.0; n = 190) 3 months after mAVR (high-risk arm).

RESULTS The low-risk arm was terminated for excess cerebral thromboembolic events (3.12% per patient-year vs. 0.29% per patient-year, p = 0.02) in the DAPT group at up to 8.8-year follow-up (631.6 patient-years), with no differences in bleeding or all-cause mortality. High-risk arm patients experienced significantly lower major (1.59% per patient-year vs. 3.94% per patient-year, p = 0.002) and minor (1.27% per patient-year vs. 3.49% per patient-year, p = 0.002) bleeding up to 8.7-year follow-up (2,035.2 patient-years), with no differences in thromboembolism (0.42% per patient-year vs. 0.09% per patient-year, p = 0.20) and all-cause mortality.

CONCLUSIONS DAPT was associated with higher rates of thromboembolism and valve thrombosis compared with control in the low-risk arm. International normalized ratios were safely maintained at 1.5 to 2.0 in high-risk patients, without differences in mortality or thromboembolic complications. (Randomized On-X Anticoagulation Trial [PROACT]; NCT00291525) (J Am Coll Cardiol 2018;71:2717–26) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

DAPT = dual-antiplatelet therapy

FDA = U.S. Food and Drug Administration

INR = international normalized ratio

Pt-yr = patient-year

PVL = paravalvular leak

TE = thromboembolic

VT = valve thrombosis

Surgical aortic valve replacement (AVR) remains the most common cardiac valvular procedure worldwide. Mechanical prostheses exhibit superior durability but require anticoagulation with vitamin K antagonists. There is a trend toward increasing use of bioprosthetic valves to avoid the inconvenience and risks associated with long-term anticoagulation (1–3). Investigational approaches to reduce the burden of anticoagulation for patients with mechanical heart valves have included targeting a lower international normalized ratio (INR), use of nonwarfarin oral anticoagulants, and dual-antiplatelet therapy (DAPT) for thromboembolic (TE) prophylaxis (4–8).

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The On-X valve (On-X Life Technologies, Austin, Texas) is a U.S. Food and Drug Administration (FDA)-approved, bileaflet mechanical heart valve designed to function with less anticoagulation than previously recommended (9,10). Observational studies have reported thromboembolism and bleeding rates that compare favorably with those of other mechanical prostheses (11–15). The PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial) tested the safety of DAPT or reduced anticoagulation therapy in patients undergoing mechanical AVR with the On-X valve. Here, we report outcomes comparing DAPT with aspirin and clopidogrel versus standard warfarin-plus-aspirin anticoagulation in patients without specified TE risk factors undergoing mechanical AVR. Interim results from patients with TE risk factors on low-dose warfarin plus aspirin were previously reported in 2014 (16,17); we now report end-of-study results comparing lower intensity versus standard warfarin therapy in patients with 1 or more TE risk factors after mechanical AVR.

METHODS

TRIAL DESIGN. PROACT (NCT00291525) was a prospective, randomized, unblinded, controlled trial of the On-X valve conducted under an investigational device exemption from the FDA (G050208) at 41 centers in the United States and Canada (Online Table 1).

PATIENTS. Patients who were scheduled to undergo mechanical AVR were eligible to participate. Those without 1 of the following conditions were considered in the low-risk group: chronic atrial fibrillation, left ventricular ejection fraction <30%, left atrial dimension >50 mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, history of neurological events within 1 year, hypercoagulability, left or right ventricular aneurysm, and women receiving estrogen replacement therapy (Online Tables 2 and 3). All enrolled patients underwent testing of platelet responsiveness to aspirin (urine thromboxane assay or Accriva, San Diego, California) and clopidogrel (Accriva $P2Y_{12}$). Inadequate responsiveness was considered a TE risk factor. Patients with 1 or more TE risk factors were enrolled in the high-risk group. All patients provided written informed consent.

RANDOMIZATION AND MASKING. Patients were randomly assigned (1:1) to intervention or a standard therapy control group via a secure Web-based central randomization system. The Clinical Events Committee was masked to group assignment while adjudicating events.

PROCEDURE. All patients received warfarin (target INR 2.0 to 3.0) and 81 mg aspirin daily for the first 3 post-operative months. The trial design intentionally

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*Additional investigators in the PROACT are listed in the Online Appendix.

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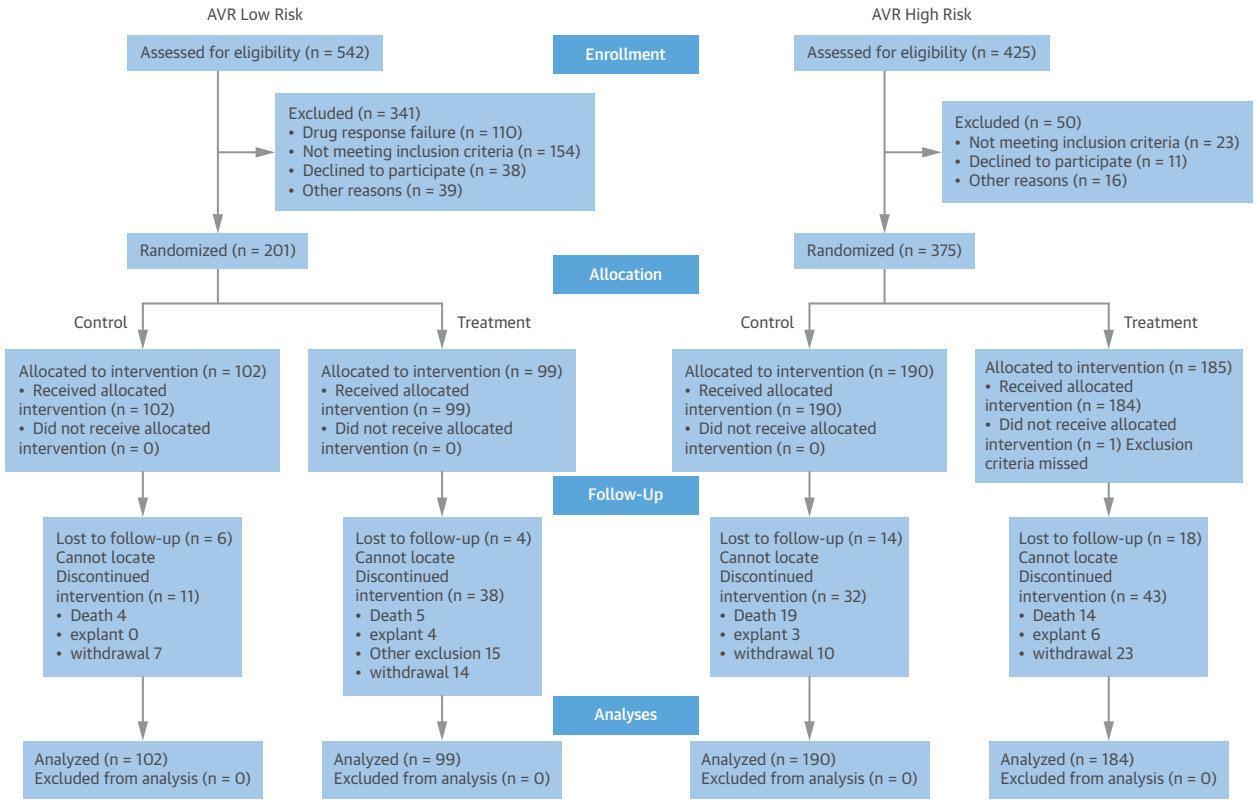
FIGURE 1 Trial Flow Diagram



PROACT (Prospective Randomized On-X Anticoagulation Trial) flow is depicted, from enrollment through allocation and follow-up to analysis of clinical outcomes. AVR = aortic valve replacement.

delayed randomization to allow an initial period of conventional anticoagulation, during which the sewing cuff of the prosthesis could become endothelialized. In the low-risk arm, at 90 post-operative days, 201 patients were randomized 1:1 to receive either DAPT (n = 99) with clopidogrel using a loading dose of 300 mg followed by 75 mg/day plus aspirin (325 mg/day) versus warfarin (n = 102) (target INR 2.0 to 3.0) plus aspirin (81 mg/day) (**Figure 1**). Higher dose aspirin (325 rather than 81 mg) was believed to be appropriate for the purpose of thromboprophylaxis in the setting of a mechanical aortic valve prosthesis. In the high-risk arm, at 90 post-operative days, 375 patients were randomized 1:1 to receive either warfarin (target INR 1.5 to 2.0; n = 185) plus aspirin (81 mg/day) or warfarin (target INR 2.0 to 3.0; n = 190) plus aspirin (81 mg/day) (**Figure 1**). Any patient in either investigational treatment group who experienced a TE event was crossed over to standard warfarin therapy, although such patients remained in the assigned treatment group for intention-to-treat analysis.

The trial was designed by the authors, refined and approved through discussions with FDA personnel, and finally approved by the Ethics Committee and Institutional Review Board at each participating center. The data were gathered online and analyzed by Clinipace Worldwide (Research Triangle Park, North Carolina).

OUTCOMES. The primary endpoint was the composite of major and minor bleeding, TE events, and valve thrombosis. Pre-specified secondary endpoints included all-cause mortality, prosthetic endocarditis, paravalvular leak (PVL), valve reoperation, and hemolysis or hemolytic anemia (Online Table 2). All adverse events were reviewed by the Clinical Events Committee.

INR MANAGEMENT. All patients who received warfarin were provided a home INR monitor at the time of randomization. INR control used weekly home testing; warfarin dose adjustments were made by clinical sites. Two or more INR measurements

TABLE 1 Baseline Characteristics in the Aortic Valve Replacement Arms

	Low-Risk Arm			High-Risk Arm		
	Standard Warfarin	DAPT	p Value	Standard Warfarin	Low-Dose Warfarin	p Value
Male	76 (75)	76 (77)	0.7	154 (81)	148 (80)	0.90
Age, yrs	52.5 ± 11.6	53.5 ± 10.9	0.6	55.8 ± 12.0	54.1 ± 13.0	0.20
Etiology						
Rheumatic	1 (1)	3 (3)	0.3	3 (2)	3 (2)	0.70
Calcific	62 (61)	63 (64)	0.7	130 (68)	121 (65)	0.60
Prosthetic dysfunction	3 (3)	3 (3)	1.0	9 (5)	8 (4)	0.80
Congenital	53 (52)	57 (58)	0.4	72 (38)	69 (37)	0.90
Endocarditis	6 (6)	1 (1)	0.06	5 (3)	8 (4)	0.80
Degenerative/ myxomatous	10 (10)	11 (11)	0.8	32 (17)	31 (17)	0.90
Other	4 (4)	9 (9)	0.2	8 (4)	11 (6)	0.50
Lesion						
Stenosis	55 (55)	55 (56)	0.8	97 (51)	95 (52)	0.20
Regurgitation	23 (23)	20 (20)		34 (18)	46 (25)	
Mixed	23 (23)	23 (23)		54 (28)	39 (21)	
Other	1 (1)	1 (1)		5 (3)	4 (2)	
NYHA functional class						
I	21 (21)	21 (21)	0.8	36 (19)	39 (21)	0.40
II	54 (53)	55 (56)		73 (38)	73 (39)	
III	19 (19)	19 (19)		51 (27)	50 (27)	
IV	1 (1)	1 (1)		16 (8)	7 (4)	
Unknown	7 (7)	3 (3)		14 (7)	16 (9)	

Values are n (%) or mean ± SD.
DAPT = dual-antiplatelet therapy; NYHA = New York Heart Association.

were required per month to consider a patient compliant with home monitoring.

NONINFERIORITY DESIGN AND STATISTICAL ANALYSIS. The noninferiority margin for this trial was selected on the basis of: 1) guidance from the FDA; 2) objective performance criteria for new valves with a margin equal to the expected rate; and 3) clinical judgment. The noninferiority design of the trial assumed an event rate for the composite primary endpoint in the control group of 7.3% per patient-year, on the basis of a composite of the objective performance criteria of the FDA. Sample-size calculations were based on a 1-sided proportion test. A total of 1,000 patient-years per group provided 80% power to demonstrate noninferiority of the investigational treatment regimen in the low-risk and high-risk groups compared with the control regimen of standard warfarin plus aspirin, assuming an expected event rate in the investigational treatment groups of 6% per patient-year, a noninferiority margin of 1.0%, and a type I error rate of 5%.

All analyses were conducted according to the intention-to-treat principle. Numeric measures are reported as mean ± SD and were compared using 2-sample z test. The chi-square (or Fisher exact) test was used for proportions. Early adverse events were those occurring before randomization and were calculated as percentages. Late (post-randomization) linearized adverse event rates, measured as percentage per patient-year, were compared using relative risk ratios in a 2-sided test. Kaplan-Meier survival curves and the associated comparisons between study groups were performed with the log-rank test.

ROLE OF THE FUNDING SOURCE. Other than providing the corresponding author access to all data and responding to author questions, On-X Life Technologies had no role in data collection, data analysis, or data interpretation for this report.

RESULTS

STUDY POPULATIONS. In the low-risk arm, from June 2006 through February 2014, 542 patients were enrolled and 201 randomized (**Figure 1**). The most common reason patients were withdrawn from the low-risk arm prior to randomization and moved to the high-risk arm of the PROACT trial was inadequate responsiveness to aspirin (urine thromboxane assay <298 pg/mg creatinine or Accriva aspirin <550 response units) and/or clopidogrel (Accriva $P2Y_{12}$ >35% inhibition). Other reasons are listed in Online Tables 3 and 4. Online Table 5 shows reasons for withdrawal after randomization. Baseline clinical characteristics, functional class, valve lesion, and etiology were well balanced between groups (**Table 1**). The median follow-up time was 2.9 years (interquartile range: 1.5 to 4.0 years) in the DAPT group and 3.4 years (interquartile range: 2.1 to 4.9 years) in the standard warfarin group (Online Table 6). Enrollment was closed in January 2014 when the Data and Safety Monitoring Board recommended to the Steering Committee and to the study sponsor that enrollment in the low-risk arm of the PROACT trial be terminated because of increased cerebral TE events in the treatment group. All available patients in the low-risk arm were contacted and were asked to retest for platelet responsiveness to clopidogrel and aspirin prior to returning to standard warfarin therapy plus aspirin (81 mg/day).

In the high-risk arm, from June 2006 through October 2009, a total of 425 patients were enrolled and 375 randomized. The baseline clinical characteristics were well balanced in the 2 randomized study groups (**Table 1**). The median follow-up time was 5.1 years (interquartile range: 4.0 to 6.6 years) in the low-dose warfarin group and 5.7 years (interquartile range: 5.3 to 6.9 years) in the standard warfarin group (Online Table 6). Nineteen patients had atrial

TABLE 2 Outcomes in the Low-Risk Arm

	Standard Warfarin (INR 2.0–3.0) (343.5 pt-yrs)		DAPT (288.1 pt-yrs)		Rate Ratio (DAPT/ Standard-Dose Warfarin)	95% CI	p Value
	n	Rate (%/pt-yr)	n	Rate (%/pt-yr)			
Primary endpoint	13	3.78	29	10.07	2.66	1.38–5.12	0.003
Components of co-primary endpoint							
Major bleeding	9	2.62	6	2.08	0.79	0.28–2.23	0.70
Cerebral bleeding	0	0.00	0	0.00	–	–	–
Minor bleeding	3	0.87	5	1.74	1.99	0.47–8.32	0.30
Total bleeding	12	3.49	11	3.82	1.09	0.48–2.48	0.80
Stroke	0	0.00	7	2.43	–	–	–
TIA	1	0.29	2	0.69	2.38	0.22–26.3	0.50
Any neurological event	1	0.29	9	3.12	10.73	1.36–84.7	0.02
Peripheral TE event	0	0.00	5	1.74	–	–	–
All TE events	1	0.29	14	4.86	16.69	2.20–127	0.007
Thrombosis	0	0.00	4	1.39	–	–	–
Major bleed, TE event, thrombosis	10	2.91	24	8.33	2.86	1.37–5.98	0.005
Sudden death	1	0.29	1	0.35	1.19	0.07–19.06	0.90
Valve-related mortality	3	0.87	2	0.69	0.79	0.13–4.76	0.80
Total mortality	4	1.16	5	1.74	1.49	0.40–5.55	0.60

The primary composite endpoint includes death, any bleeding (major or minor), and any TE and valve thrombosis event.
CI = confidence interval; DAPT = dual-antiplatelet therapy; INR = international normalized ratio; pt-yr(s) = patient-year(s); TE = thromboembolic; TIA = transient ischemic attack.

fibrillation at baseline and were enrolled in the high-risk arm of PROACT. None had a CHA_2DS_2-VASc score in excess of 1.

OPERATIVE DATA. There were no significant differences in operative variables between groups in the low- and high-risk arms. Concomitant procedures are listed in Online Table 7, and the distribution of valve sizes is given in Online Table 8.

LOW-RISK ARM: OUTCOMES WITH DAPT. In the low-risk arm, the composite primary endpoint of bleeding (major or minor), TE event, and valve thrombosis event occurred 29 times (10.07% per patient-year) in the DAPT group and 13 times in the standard warfarin group (3.78% per patient-year; rate ratio: 2.66; 95% confidence interval: 1.38 to 5.12; p = 0.003) (**Table 2**). Of the primary endpoint events in the DAPT group, there were 11 bleeding events, 14 TE events, of which 9 were neurological (7 strokes and 2 transient ischemic attacks), and 4 valve thrombosis events (a given patient may have more than 1 event). The linearized event rates of all TE events (4.86% per patient-year vs. 0.29% per patient-year; p = 0.007) and cerebral TE events (3.12% per patient-year vs. 0.29% per patient-year; p = 0.02) were increased in the DAPT group (**Table 2**). This arm of the trial was terminated prematurely by the Data and Safety Monitoring Board and Steering Committee, and the FDA was informed in January 2014. There was no difference in mortality between groups, with 1 death in each.

Among pre-specified secondary endpoints, prosthetic valvular endocarditis occurred once in the DAPT group and did not occur in the standard warfarin group (0.35% per patient-year vs. 0% per patient-year); PVL occurred once in the DAPT group and did not occur in the standard warfarin group (0.35% per patient-year vs. 0% per patient-year). Valve reoperation occurred 6 times in the DAPT group and did not occur in the standard warfarin group (2.08% per patient-year vs. 0% per patient-year); and there were no hemolytic events in either group. Valve-related reoperations were for prosthetic endocarditis (n = 1), PVL (n = 1), and valve thrombosis (n = 4).

The 5-year event-free rates for bleeding events and TE events in the low-risk arm are shown in **Table 3**. Freedom from bleeding was not different between groups (81.3 ± 6.8% per patient-year vs. 85.4 ± 4.6% per patient-year; p = 0.90), but freedom from TE events was statistically lower in the DAPT group than in the standard warfarin group (80.5 ± 5.5% per patient-year vs. 99.0 ± 1.0% per patient-year; p < 0.001) (**Central Illustration**). Among the 9 patients in the DAPT group who experienced neurological events, 2 were nonresponsive to clopidogrel when serum testing was repeated; 7 patients were converted to warfarin without clopidogrel retesting.

Clopidogrel retesting was attempted in all DAPT patients (n = 99). Of the 99 patients, 18 had crossed over to warfarin because of thrombotic events, as required by protocol, 15 withdrew from the trial, 3

TABLE 3 Kaplan-Meier Freedom From Bleeding and Thromboembolic Events at 5 Years

	Low-Risk Arm				
	Standard Warfarin (INR 2.0-3.0) (343.5 pt-yrs)		DAPT (288.1 pt-yrs)		
	Freedom Rate (%)	SE	Freedom Rate (%)	SE	p Value
Primary endpoint	84.4	4.6	63.5	7.2	0.02
Major bleeding	85.5	5.1	92.2	3.7	0.40
Total bleeding	85.4	4.6	81.3	6.8	0.90
Neurological TE events	99.0	1.0	86.2	5.3	0.01
Total TE events	99.0	1.0	80.5	5.5	<0.001
	High-Risk Arm				
	Standard Warfarin (INR 2.0-3.0) (1,090.0 pt-yrs)		Low-Dose Warfarin (INR 1.5-2.0) (945.2 pt-yrs)		
	Freedom Rate (%)	SE	Freedom Rate (%)	SE	p Value
Primary endpoint	72.8	3.4	79.5	3.2	0.20
Major bleeding	89.2	2.4	94.9	1.7	0.05
Total bleeding	77.9	3.1	90.8	2.3	0.002
Neurological TE events	93.6	1.9	91.1	2.3	0.40
Total TE events	93.1	1.9	89.3	2.5	0.20

Abbreviations as in Table 2.

were lost to follow-up, 4 underwent valve explantation, and 4 died before end of trial. Of the 55 patients who remained on DAPT, 46 were retested for clopidogrel responsiveness (84%). Twenty-four percent of retested patients (11 of 46) were nonresponsive to clopidogrel at the time of retesting. Forty-four percent of patients (24 of 55) on DAPT declined conversion to warfarin. Thus, 31 patients were converted to warfarin at the end of the study, and 2 of these (6%) had TE events within the FDA-mandated 3 months of continued follow-up.

HIGH-RISK ARM: OUTCOMES WITH LOWER INTENSITY WARFARIN. At 5 years in the high-risk arm, the composite primary endpoint of major or minor bleeding, TE event, and valve thrombosis event occurred 5.50% per patient-year in the low-dose warfarin group versus 9.35% per patient-year in the standard warfarin group (rate ratio: 0.59; 95% confidence interval: 0.42 to 0.82; $p = 0.002$) (Table 4). The linearized event rates of both major (1.59% per patient-year vs. 3.94% per patient-year, $p = 0.002$) and minor bleeding (1.27% per patient-year vs. 3.49% per patient-year, $p = 0.002$) were reduced in the low-dose warfarin group, with an overall reduction in bleeding events (Table 4). There were no statistically significant differences in the rates of valve thrombosis, stroke, transient ischemic attack, or TE events (0.42% per patient-year vs. 0.09% per patient-year, $p = 0.20$). There was no significant difference in mortality between groups.

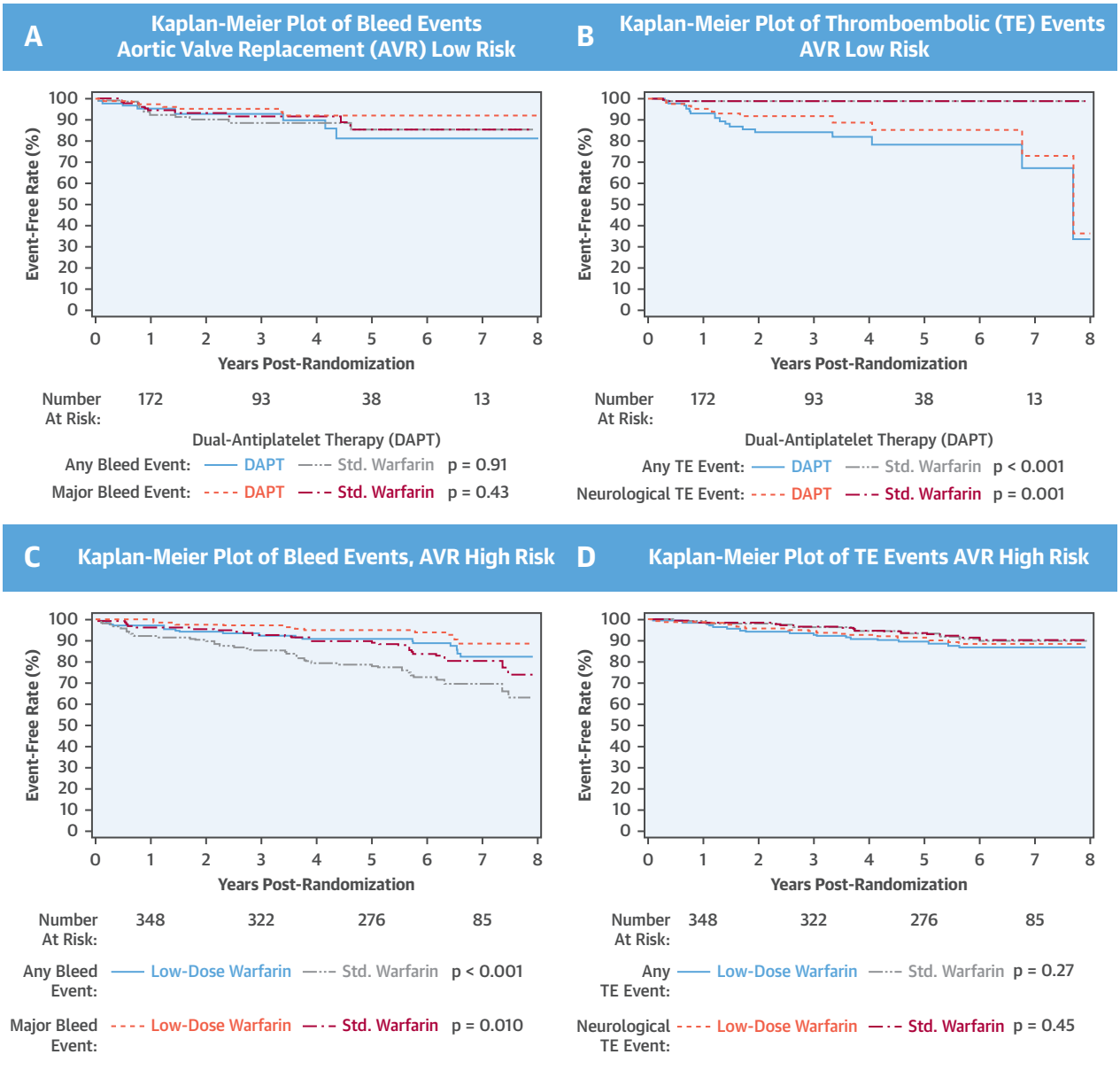
Secondary endpoint events, including prosthetic endocarditis (0.63% per patient-year vs. 0.37% per patient-year, $p = 0.40$), PVL (0.11% per patient-year vs. 0.28% per patient-year, $p = 0.41$), and valve reoperation (0.74% per patient-year vs. 0.37% per patient-year, $p = 0.26$), were not statistically different between low-dose and standard warfarin groups. There were no hemolytic events in either group. Valve reoperations were for prosthetic endocarditis ($n = 5$), PVL ($n = 2$), valve thrombosis ($n = 3$), and heart transplantation ($n = 1$). Twenty-two patients (11.9%) crossed over from low- to standard-dose warfarin because of TE or valve thrombosis events. No patients crossed from standard-dose to low-dose warfarin. The 5-year event-free rates for bleeding events and TE events in the high-risk arm are given in Table 3. At 5 years, total bleeding events favored low-dose warfarin over standard warfarin; TE rates were not different between groups (Central Illustration).

HIGH-RISK ARM: HOME INR MONITORING. In the high-risk arm, the mean INR was 1.90 ± 0.49 for the low-dose warfarin group (target INR 1.5 to 2.0) and 2.50 ± 0.63 for the standard warfarin group (target INR 2.0 to 3.0; $p < 0.001$) (Online Table 9). The inverse relationship between bleeding and TE events at various INR levels is shown in Figure 2. Percentage of time in therapeutic range was 66.4% in the AVR high-risk control group and 55.3% in the high-risk treatment group. All patients were given home monitoring, and 96% patients in the high-risk control group reported results at regular intervals, while 97% of patients in the high-risk treatment group reported results. Strict compliance was defined as an average of at least 2 reports per month during follow-up; with that definition, 75% of control patients were in compliance, and 76% of treatment patients were in compliance.

DISCUSSION

In this FDA investigational device exemption trial, 2 antiplatelet and anticoagulation strategies were tested in select patient populations with the On-X mechanical prosthesis to reduce the burden of anticoagulation. In patients without risk factors for TE events, DAPT with 325 mg aspirin was associated with no difference in bleeding events but statistically higher cerebral TE event rates compared with standard warfarin therapy. In patients with 1 or more risk factors for TE events, lower intensity warfarin was associated with a reduction in bleeding events compared with standard warfarin, without an increase in TE event rates.

CENTRAL ILLUSTRATION **Kaplan-Meier Curves for Bleeding and Thromboembolic Events at 5 Years**



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(A) Major and total bleeding in the low-risk arm. **(B)** Cerebral and total thromboembolic (TE) events in the low-risk arm. **(C)** Major and total bleeding in the high-risk arm. **(D)** Cerebral TE and total TE events in the high-risk arm. The figure presents Kaplan-Meier plots of bleeding and TE events in the aortic valve replacement (AVR) low-risk and AVR high-risk groups. In the AVR low-risk arm of the PROACT (Prospective Randomized On-X Anticoagulation Trial) trial, patients randomized to dual-antiplatelet therapy (DAPT) (clopidogrel 75 mg plus aspiring 325 mg) experienced significantly more TE events and a statistically similar rate of bleeding events compared with patients maintained on standard warfarin plus aspirin 81 mg. In the AVR high-risk arm of the PROACT trial, patients randomized to lower intensity warfarin therapy (target international normalized ratio [INR] 1.5 to 2.0) plus aspirin 81 mg/day experienced fewer bleeding events and a statistically similar rate of TE events compared with patients maintained on standard intensity warfarin (target INR 2.0 to 3.0) plus aspirin 81 mg/day.

TABLE 4 Outcomes in the High-Risk Arm

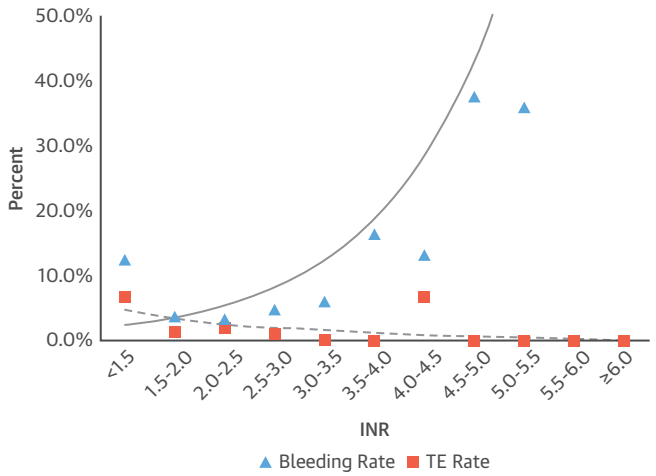
	Standard Warfarin (INR 2.0-3.0) (1,090.0 pt-yrs)		Low-Dose Warfarin (INR 1.5-2.0) (945.2 pt-yrs)		Rate Ratio (Standard/Low-Dose Warfarin)	95% CI	p Value
	n	Rate (%/pt-yr)	n	Rate (%/pt-yr)			
Primary endpoint	102	9.35	52	5.50	0.59	0.42-0.82	0.002
Components of co-primary endpoint							
Major bleeding	43	3.94	15	1.59	0.40	0.22-0.72	0.002
Minor bleeding	38	3.49	12	1.27	0.36	0.19-0.70	0.002
Cerebral bleeding	4	0.37	1	0.11	0.29	0.03-2.58	0.30
Total bleeding	81	7.43	27	2.86	0.38	0.25-0.59	<0.001
Stroke	7	0.64	7	0.74	1.15	0.40-3.29	0.80
TIA	11	1.01	12	1.27	1.26	0.56-2.85	0.60
Any neurological event	18	1.65	19	2.01	1.22	0.64-2.32	0.50
Peripheral TE event	1	0.09	4	0.42	4.61	0.52-41.28	0.20
Valve thrombosis	2	0.18	2	0.21	1.15	0.16-8.19	0.90
Major bleed, TE event or thrombosis	64	5.87	40	4.23	0.72	0.49-1.07	0.10
Sudden death	3	0.28	3	0.32	1.15	0.23-5.72	0.90
Valve-related mortality	4	0.37	2	0.21	0.58	0.11-3.15	0.50
Total mortality	17	1.56	13	1.38	0.88	0.43-1.82	0.70

The primary composite endpoint includes death, any bleeding (major or minor), and any TE and valve thrombosis.
Abbreviations as in Table 2.

This is the first report of results from the PROACT low-risk AVR arm and the final end-of-study report of results from the high-risk AVR arm of the PROACT trial. The On-X valve uses a novel design and manufacture to create laminar flow, low gradients, limited turbulence, and reduced thrombogenicity. Small observational studies have reported low incidence of bleeding, stroke, and valve thrombosis with DAPT for mechanical prostheses (18,19). In a single-center report of 438 patients in whom On-X mechanical valves were implanted, 40% of patients received insufficient or no anticoagulation therapy because of social conditions, yet no short-term valve thrombosis events were reported (14). DAPT is the current guideline-directed TE prophylaxis for transcatheter biological AVR (20-22). However, we showed that treatment with DAPT alone resulted in an excess risk for cerebral TE events with the On-X mechanical prosthesis. The absolute incidence of TE in the DAPT group was low enough to meet current FDA objective performance criteria. Nonetheless, the decision to terminate this arm of the trial was based in part on recent literature indicating that long-term responsiveness to clopidogrel may be variable and the observation that 24% of patients retested at the end of the PROACT trial were no longer adequately responsive to clopidogrel per protocol requirements (23,24).

In the high-risk arm end-of-trial results, we report a reduction in bleeding events without an increase in TE event rates in patients at high TE risk with the On-X mechanical aortic prosthesis. The optimal anticoagulation for any prosthesis exists near the intersection of the curves for thromboembolism and bleeding events across a range of INR values. Whereas

FIGURE 2 Relationship of International Normalized Ratio to Bleeding and Thromboembolic Rates in the High-Risk Arm



Shows the relationship between international normalized ratio (INR) and both bleeding and thromboembolic (TE) events in all patients in the aortic valve replacement high-risk arm of the PROACT (Prospective Randomized On-X Anticoagulation Trial). As expected, higher INRs are associated with higher rates of bleeding, while lower INRs are associated with higher rates of TE. These 2 curves intersect at INR 1.5 to 2.0 for the On-X mechanical valve in the aortic position, defining an optimal range of oral anticoagulation for this prosthesis.

the rate of bleeding events is primarily dependent on patient-related factors and the level of anticoagulation, the thrombotic event curve is also influenced by prosthesis-related factors (25,26). The guideline recommendation for anticoagulation of bileaflet mechanical valves in the aortic position is an INR of 2.0 to 3.0 (21). On the basis of the interim results of this study, the FDA approved a labeling recommendation for the On-X valve with an INR of 1.5 to 2.0 plus aspirin 81 mg/day starting 3 months after AVR. The 2017 updated American Heart Association/American College of Cardiology guideline also supports a lower target INR of 1.5 to 2.0 in patients without TE risk factors with mechanical On-X AVR despite this study of patients with TE risk factors (27).

STUDY LIMITATIONS. Importantly, the low rates of adverse hemorrhagic and TE events observed in the lower INR cohort of the high-risk AVR arm might have been due in part to the use of home INR monitoring and the high degree of compliance among enrolled patients (28,29). All patients in the present study underwent AVR with a single, approved, bileaflet mechanical valve prosthesis. The results of the present trial should not be extrapolated to other aortic valve prostheses or to mechanical mitral valve replacements with any prosthesis. Warfarin remains the only approved oral anticoagulant agent for patients with mechanical prosthetic heart valves. The use of blinding was not possible because of the need for home INR monitoring, which reported results directly to the patient. The use of a nonwarfarin oral anticoagulant agent for prosthetic valve anticoagulation is currently a Class III recommendation (will cause harm; Level of Evidence: B) (21). Notably, all patients on warfarin were also placed on aspirin, and thus we cannot comment on the clinical outcomes of the use of warfarin alone.

CONCLUSIONS

The use of DAPT after On-X mechanical AVR in patients without risk factors for TE was associated with increased rates of TE complications compared with standard warfarin anticoagulation, with no difference in bleeding events. Patients with 1 or more risk factors for TE randomized to low-dose warfarin plus aspirin experienced significantly fewer major and minor bleeding events than those treated with standard warfarin plus aspirin, while the incidence rates of stroke, transient ischemic attack, all thromboembolism, and all-cause mortality were not different. These findings led the FDA to support an indication for use for the On-X valve in the aortic position with an INR of 1.5 to 2.0 plus 81 mg of aspirin after 3 post-operative months of standard warfarin therapy and aspirin 81 mg/day.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Conventional antithrombotic therapy for patients with mechanical prosthetic valves consists of warfarin or another oral vitamin K antagonist anticoagulant agent plus low-dose aspirin, but sustaining this over time is a challenge that increases as patients age. In low-risk patients with bileaflet mechanical aortic valves, a dual-antiplatelet regimen of aspirin plus clopidogrel was associated with higher rates of thromboembolism compared with conventional therapy, while in higher risk patients, lower intensity anticoagulation (INR 1.5 to 2.0) reduced bleeding without increasing thromboembolism or mortality compared with a goal INR of 2.0 to 3.0.

TRANSLATIONAL OUTLOOK: Future research should explore ways to improve the time in narrow target ranges and develop safer, more effective alternatives to long-term anticoagulation using combinations of target-specific agents or novel compounds for patients with mechanical heart valves.

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KEY WORDS anticoagulation, dual-antiplatelet therapy, mechanical aortic valve replacement, thromboembolism

APPENDIX For supplemental tables, please see the online version of this paper.