NEJM Evidence

Published May 6, 2023

DOI: 10.1056/EVIDoa2300067

ORIGINAL ARTICLE

Apixaban or Warfarin in Patients with an On-X Mechanical Aortic Valve

Tracy Y. Wang, M.D., M.H.S.,[1] Lars G. Svensson, M.D., Ph.D.,[2] Jun Wen, M.S.,[1] Andrew Vekstein, M.D.,[1] Marc Gerdisch, M.D.,[3] Vijay U. Rao, M.D., Ph.D.,[3] Michael Moront, M.D.,[4] Doug Johnston, M.D.,[2] Renato D. Lopes, M.D., Ph.D.,[1] Alma Chavez,[1] Marc Ruel, M.D., M.P.H.,[5] Eugene H. Blackstone, M.D.,[2] Richard C. Becker, M.D., M.Ed.,[6] Vinod Thourani, M.D.,[7] John Puskas, M.D., M.Sc.,[8] Hussein R. Al-Khalidi, Ph.D.,[1] David G. Cable, M.D.,[9] John A. Elefteriades, M.D.,[10] Alberto Pochettino, M.D.,[11] J. Alan Wolfe, M.D.,[12] Allen Graeve, M.D.,[13] Ibrahim Sultan, M.D.,[14] Ashraf A. Sabe, M.D.,[15] Hector I. Michelena, M.D.,[11] and John H. Alexander, M.D., M.H.S.,[1] for the PROACT Xa Investigators*

Abstract

BACKGROUND Vitamin K antagonists are the only oral anticoagulants approved to prevent valve thrombosis and valve-related thromboembolism in patients with mechanical heart valves. Whether patients with an On-X mechanical aortic valve can be safely anticoagulated with apixaban is unknown.

METHODS Patients with an On-X aortic valve implanted at least 3 months before enrollment were randomly assigned to receive apixaban 5 mg twice daily or warfarin (target international normalized ratio 2.0 to 3.0). The primary efficacy end point was the composite of valve thrombosis or valve-related thromboembolism with coprimary analyses comparing apixaban with warfarin for noninferiority and comparing the apixaban event rate with an objective performance criterion (OPC).

RESULTS The trial was stopped after 863 participants were enrolled owing to an excess of thromboembolic events in the apixaban group. Most (94%) participants took aspirin. A total of 26 primary end-point events occurred, 20 (in 16 participants) in the apixaban group (4.2%/patient-year; 95% confidence interval [CI], 2.3 to 6.0) and 6 (in 6 participants) in the warfarin group (1.3%/patient-year; 95% CI, 0.3 to 2.3). The difference in primary end-point rates between the apixaban and warfarin groups was 2.9 (95% CI, 0.8 to 5.0); noninferiority and OPC success criteria were not met. Major bleeding rates were 3.6%/patient-year with apixaban and 4.5%/patient-year with warfarin.

CONCLUSIONS Apixaban did not demonstrate noninferiority to warfarin and is less effective than warfarin for the prevention of valve thrombosis or thromboembolism in patients with an On-X mechanical aortic valve. (Funded by Artivion; ClinicalTrials.gov number, NCT04142658.)

A complete list of investigators in the PROACT Xa trial is provided in the Supplementary Appendix, available at evidence.nejm.org.

The author affiliations are listed at the end of the article.

Dr. Alexander can be contacted at john.h.alexander@duke.edu or at Duke Clinical Research Institute, Duke University School of Medicine, 300 W. Morgan Street, Durham, NC 27701.

Introduction

Patients with mechanical heart valves require lifelong anticoagulation with vitamin K antagonists to prevent valve thrombosis and valve-related thromboembolism.[1,2] Warfarin has a narrow therapeutic window and numerous food and drug interactions, thus requiring frequent blood monitoring.[3] These limitations influence patients' preferences and physicians' decisions to use mechanical versus bioprosthetic valves, including those that can be implanted nonsurgically.[2,4,5] Direct oral anticoagulants are efficacious alternatives to warfarin to prevent thromboembolic events and may be safer than warfarin with lower rates of intracranial bleeding in patients with atrial fibrillation and venous thromboembolism.[6-10] However, the direct thrombin inhibitor dabigatran failed to prevent thromboembolic events in patients with mechanical valves and the use of direct oral anticoagulants in patients with mechanical valves is currently contraindicated.[2,11,12]

Material and design characteristics of the On-X mechanical valve may make it less susceptible to thrombosis than other mechanical heart valves.[13-15] On the basis of the results of PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial), the On-X aortic valve can be used with a lower intensity of anticoagulation with warfarin, as measured by the international normalized ratio (INR), than other mechanical heart valves.[16,17] Preclinical data suggest apixaban may be an effective alternative to warfarin for thromboembolism prophylaxis in patients with mechanical heart valves.[18] The objective of the PROACT Xa trial was to determine whether apixaban was noninferior to warfarin in preventing valve thrombosis or valve-related thromboembolism in patients with an On-X mechanical aortic valve and also whether apixaban provided acceptable anticoagulation on the basis of criteria established by the U.S. Food and Drug Administration (FDA) (see below).

Methods

STUDY DESIGN AND OVERSIGHT

PROACT Xa was a prospective, randomized, open-label trial with blinded end-point adjudication. The study was designed by the steering committee and the sponsor (Artivion, formerly CryoLife, Kennesaw, GA) with input from the FDA.[14] The trial protocol was approved by institutional review boards at participating sites and all participants provided written informed consent. Data were collected by sites and reported to the Duke Clinical Research Institute (Durham, NC) where the data were analyzed. The first and senior authors wrote the paper and vouch for the data and analysis; all authors decided to publish the paper. Duke University has a contract with the study sponsor that allows Duke University to use the trial data for academic purposes. An independent data safety monitoring board monitored unblinded data from the trial at least every 6 months and received monthly counts of the primary end point; additional unscheduled data reviews and ad hoc analyses were conducted at the discretion of the data safety monitoring board. There were no predefined stopping rules.

STUDY POPULATION

Participants were enrolled at 64 sites in the United States and were eligible for inclusion if they were at least 18 years of age, underwent implantation of an On-X mechanical aortic valve at least 3 months before they were randomly assigned, and were able to receive warfarin at a targeted INR range between 2.0 and 3.0. In addition, participants were required to take aspirin 81 mg daily or have a documented contraindication to aspirin use.[19] The complete eligibility criteria are available in the protocol provided with the full text of this article. Eligible patients were treated with warfarin from the time of surgery to randomization.

RANDOMIZATION AND STUDY INTERVENTIONS

Participants were randomly assigned in a 1:1 ratio to receive apixaban 5 mg twice daily or warfarin with a target INR of 2.0 to 3.0. Randomization was stratified on the basis of whether the On-X valve was implanted greater or less than 1 year before randomization. If a participant randomly assigned to receive apixaban met at least two of the three dose reduction criteria (age $\geq$80 years, weight $\leq$60 kg, creatinine $\geq$1.5 mg/dl) at any time during the trial, the apixaban dose was reduced to 2.5 mg twice daily. Participants randomly assigned to receive warfarin were required to undergo at least monthly INR monitoring with a target range of 2.0 to 3.0. Follow-up occurred monthly in both groups to assess adverse events and medication changes. At study termination, all participants were instructed to transition off the study drug and resume warfarin.

STUDY END POINTS

The primary efficacy end point was the composite of valve thrombosis or valve-related thromboembolism. Valve thrombosis was defined as any thrombus, not caused by infection,

attached to or near an implanted On-X valve that occluded part of the blood-flow path, interfered with valve function, or was sufficiently large to warrant treatment other than continued oral anticoagulation. Valve thrombus found at autopsy in a participant whose cause of death was not valve-related or found at operation for an unrelated indication was considered valve thrombosis.[20] Valve-related thromboembolism was defined as any thromboembolic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism to an organ or limb that was not associated with infection or an intracardiac tumor and was definitely or possibly related to the valve. All suspected valve thrombosis and thromboembolism events were adjudicated by the clinical events committee. Whether thromboembolism was related to the valve was adjudicated on the basis of review of clinical, surgical, and autopsy data blinded to treatment assignment. Thromboembolic events that were clearly unrelated to the valve were not included in the primary end point.

The primary safety end point was major bleeding defined as any episode of internal or external bleeding that caused death, hospitalization, or permanent injury or necessitated transfusion, pericardiocentesis, or reoperation. These events were also independently adjudicated by the clinical events committee. Prespecified secondary end points included components of the primary efficacy end point (valve thrombosis or valve-related thromboembolism) as well as bleeding assessed using the Bleeding Academic Research Consortium[21] and International Society on Thrombosis and Hemostasis[22] scales. Detailed end-point definitions are provided in the Supplementary Appendix.

SAMPLE SIZE

The event rate of the primary efficacy end point was projected to be 1.75%/patient-year with warfarin on the basis of available experience with the On-X aortic valve.[17,23-26] With an assumed similar event rate of 1.75%/patient-year in both warfarin and apixaban groups, an absolute noninferiority margin of 1.75%/patient-year (equivalent to a doubling of the event rate), a one-sided alpha of 2.5%, 90% power, and 5% possible lost to follow-up rate, the estimated sample size was 990.[14]

STATISTICAL ANALYSIS

PROACT Xa was designed with coprimary analyses: to determine whether apixaban is noninferior to warfarin for the primary end point of valve thrombosis or valve-related thromboembolism and to determine whether apixaban provides acceptable anticoagulation for the primary end point compared with an objective performance criterion (OPC).[23] Initially issued by the FDA in 1994 on the basis of extracted data using FDA-approved devices that were implanted in adherence to heart valve guidelines, OPC defined average expected complication rates that would be acceptable when new valve prostheses were considered for approval.[27] The updated OPC for mechanical valves in the aortic position described a linearized event rate of 1.6%/patient-year for thromboembolism and 0.1%/patient-year for valve thrombosis.[23]

All randomly assigned participants were included in both coprimary efficacy analyses. Linearized event rates for each group were calculated as the total number of adjudicated valve thrombosis or valve-related thromboembolic events divided by the total patient time and presented as percentage per patient-year with 95% confidence intervals (CI). The linearized event rate assumes that the occurrence of events follows a Poisson distribution and Wald's normal approximation was used to estimate the difference between the two rates and its associated 95% CI.[28] For the first coprimary analysis, noninferiority would be concluded if the upper bound of the 95% CI of the difference (apixaban minus warfarin event rates) was less than 1.75%/patient-year. For the second coprimary analysis, the comparison against the OPC would be passed if the apixaban group achieved at least 800 patient-years of follow-up and the event rate was less than 2 times the OPC (3.4%/patient-year because the OPC was 1.6%/patient-year for thromboembolism and 0.1%/patient-year for valve thrombosis). Cumulative incidence curves were used to describe rates of the primary end point in the apixaban and warfarin groups. A Cox proportional-hazards regression model described the risk of the primary end point for apixaban compared with warfarin.

The primary safety end point of major bleeding was evaluated as the total number of adjudicated major bleeding events divided by total patient-years and rates for both groups were compared with 2 times the major bleeding OPC for mechanical aortic valves (3.2%/patient-year because the OPC for major bleeding is 1.6%/patient-year). A Cox proportional-hazards regression model described the risk of the primary safety end point for apixaban compared with warfarin.

Sensitivity analyses included repeated testing of the primary composite efficacy end point among as-treated and on-treatment populations. In the as-treated analysis, all

events were compared between groups among participants who took at least one dose of the assigned study drug. In the on-treatment analysis, all events occurring while on study drug up to 7 days after its discontinuation were attributed to the randomized treatment group, and any event occurring more than 7 days after discontinuation of the study drug were censored.

Prespecified subgroups for the primary efficacy end point included age, race, sex, concomitant aortic root replacement, time from surgery, valve size, baseline apixaban dose, and high- versus low-risk patients. High-risk patients included those having atrial fibrillation, left ventricular ejection fraction less than 30%, left atrial dimension greater than 50 mm, significant vascular disease, or history of a neurological event within 1 year.[17]

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) at the Duke Clinical Research Institute (Durham, NC).

Results

STUDY POPULATION

Between May 2020 and September 2022, 863 participants were randomly assigned (Fig. 1). On September 21, 2022, the data safety monitoring board unanimously recommended stopping the trial on the basis of a higher rate of thromboembolic events in participants randomly assigned to apixaban than in those assigned to warfarin. Enrollment was stopped and all participants were transitioned back to standard-of-care warfarin and followed for 30 days after stopping the study drug.

Among enrolled participants, the median age was 56 years, 24.0% were female, 47.9% had aortic valve replacement within the year before randomization, and 17.3% had aortic valve replacement with concomitant aortic root replacement. One third of participants in both groups were previously anticoagulated with warfarin with a target INR range of 1.5 to 2.0. Baseline characteristics were balanced between treatment groups (Table 1 and Table S1 in the Supplementary Appendix).

STUDY DRUG AND ASPIRIN EXPOSURE

A total of 29 randomly assigned participants never started a study drug (13 apixaban and 16 warfarin). Among participants assigned to apixaban, 23 permanently discontinued the study drug and returned to the nonstudy drug warfarin before study completion. Apixaban interruptions greater than 3 days occurred in 70 (16.7%) participants; most interruptions (71.7%) were attributed to surgery or a procedure. Two participants met apixaban dose reduction criteria at randomization.

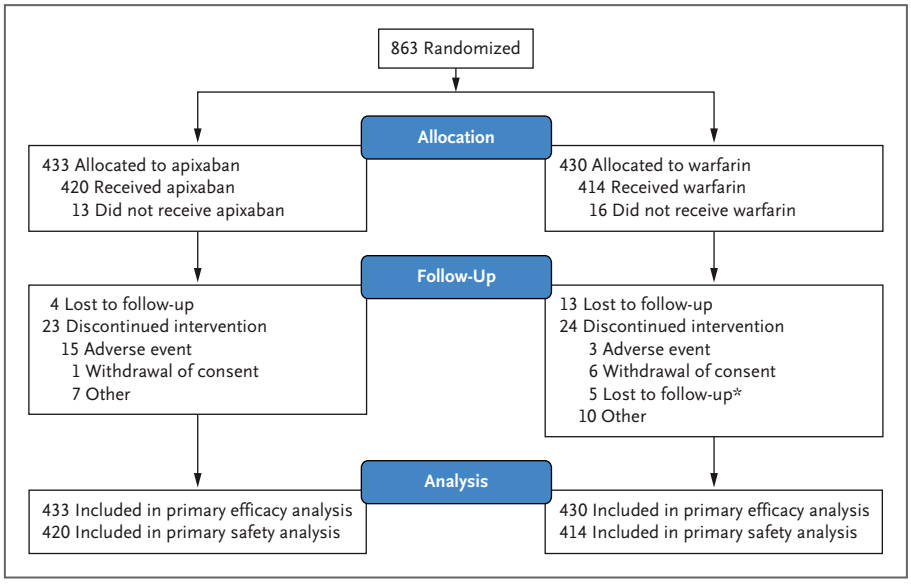

Figure 1. Study Flow Diagram.

*Patients with "lost to follow-up" as the reason they discontinued intervention (n=5) are included in the overall number lost to follow-up (n=13).

Table 1. Baseline Demographics and Characteristics.		
Demographics and Characteristics	**Apixaban (n=433)**	**Warfarin (n=430)**
Demographics		
Age, yr — median (25th, 75th)	56 (47, 63)	55 (47, 63)
Female sex — no. (%)	102 (23.6%)	105 (24.4%)
Race — no. (%)		
White	395 (91.2%)	390 (90.7%)
Black or African American	8 (1.8%)	14 (3.3%)
Asian	3 (0.7%)	5 (1.2%)
Other	10 (2.3%)	8 (1.9%)
Hispanic or Latinx ethnicity	29 (6.7%)	20 (4.7%)
Valve characteristics — no. (%)		
Valve implantation within 1 year of randomization	208 (48.0%)	205 (47.7%)
AVR with concomitant aortic root replacement	64 (14.8%)	85 (19.8%)
Valve size ≤21 mm	109 (25.2%)	103 (24.0%)
Reoperation of aortic valve	77 (17.8%)	59 (13.7%)
INR target range 1.5 to 2.0 prior randomization	145 (33.8%)	144 (33.5%)
Medical characteristics		
Body-mass index — median (25th, 75th)	29.9 (26.3, 34.3)	30.1 (26.3, 35.0)
Prior coronary artery disease — no. (%)	106 (24.5%)	96 (22.3%)
Prior stroke/TIA — no. (%)	43 (9.9%)	39 (9.1%)
Prior prosthetic valve thrombosis — no. (%)	3 (0.7%)	1 (0.2%)
Prior aortic valve infectious endocarditis — no. (%)	26 (6.0%)	21 (4.9%)
Heart failure — no. (%)	115 (26.6%)	102 (23.7%)
Left ventricular ejection fraction <40% — no. (%)	18 (4.3%)	13 (3.3%)
Atrial fibrillation — no. (%)	104 (24.0%)	101 (23.5%)
Diabetes mellitus — no. (%)	90 (20.8%)	74 (17.2%)
High risk* — no. (%)	208 (48.0%)	189 (44.0%)
INR level at randomization — median (25th, 75th)	2.1 (1.8, 2.5)	2.1 (1.8, 2.6)

* High risk was defined as having any of the following: atrial fibrillation, left ventricular ejection fraction less than 30%, left atrial dimension greater than 50 mm, significant vascular disease, and history of stroke/TIA within 1 year.[17] The body-mass index is the weight in kilograms divided by the square of the height in meters. AVR denotes aortic valve replacement; INR, international normalized ratio; and TIA, transient ischemic attack.

Among participants assigned to warfarin, 25 permanently discontinued the study drug and returned to the nonstudy drug warfarin before study completion. Study drug warfarin interruptions greater than 5 days occurred in 35 (8.5%) participants; most interruptions (68.0%) were attributed to surgery or a procedure. The median (25th, 75th) time in the therapeutic range on the basis of INR was 72.7% (55.9%, 83.4%).

At randomization, 408 (94.2%) participants assigned to apixaban and 404 (94.0%) assigned to warfarin were on concomitant aspirin, 99% taking less than 100 mg daily. Of those assigned to apixaban, 84.5% remained on aspirin throughout the study; similarly, of those assigned to warfarin 84.0% remained on aspirin.

The apixaban and warfarin groups had 479.9 and 467.0 patient-years of follow-up, respectively, with a median follow-up of 13.5 and 13.3 months, respectively. Withdrawal of consent occurred in 9 participants assigned to apixaban and 16 assigned to warfarin; 4 participants assigned to apixaban and 13 assigned to warfarin were lost to follow-up (Fig. 1).

EFFICACY

There were 20 primary composite end-point events occurring in 16 participants randomly assigned to apixaban (4.2%/patient-year; 95% CI, 2.3 to 6.0) and 6 events occurring in 6 participants randomly assigned to warfarin (1.3%/patient-year; 95% CI, 0.3 to 2.3). The difference between groups was 2.9 (95% CI, 0.8 to 5.0) percentage points per patient-year, so the margin for noninferiority was not met. Although there were less than 800 patient-years of follow-up in the apixaban group and thus wider CIs, the observed apixaban event rate of 4.2%/patient-year

was above 2 times the OPC for valve thrombosis or valve-related thromboembolism (3.4%/patient-year).

Cumulative incidence curves for the apixaban and warfarin groups are shown in Figure 2. Event rates for the primary end point and the individual components are shown in Table 2. The hazard ratio for the risk of valve thrombosis or valve-related thromboembolism for apixaban compared with warfarin was 2.6 (95% CI, 1.0 to 6.7). Three valve thromboses and 14 stroke events were observed, all occurring in the apixaban group. In the warfarin group, five thromboembolic transient ischemic attacks and one thromboembolic myocardial infarction were observed. Two participants assigned to apixaban and one assigned to warfarin died; the cause of death was adjudicated as valve-related thromboembolism for all three deaths.

Rates of valve thrombosis and valve-related thromboembolism in the as-treated and on-treatment populations were consistent with those in the intention-to-treat population (Table S2). Of the 26 primary outcome events, 22 (84.6%) occurred on-treatment (16/20 with apixaban and 6/6 with warfarin). Event rates for the primary composite end point in prespecified subgroups are shown in Figure 3.

SAFETY

Seventeen major bleeding events occurred in 11 participants in the apixaban group (3.6%/patient-year) and 21 events in 18 participants in the warfarin group (4.5%/patient-year). Major bleeding event rates in both groups exceeded twice the OPC for major bleeding (as noted above the OPC is 1.6%/patient-years and twice this value is 3.2%/patient-years). Cumulative incidence curves for apixaban compared with warfarin for major bleeding are shown in Figure S1. The hazard ratio for the risk of major bleeding for apixaban compared with warfarin was 0.6 (95% CI, 0.3 to 1.3). Intracranial hemorrhage occurred in one participant assigned to warfarin and three assigned to apixaban; all three in the apixaban group were in participants who also experienced a stroke. Bleeding severity classified according to several bleeding scales is shown in Table S3.

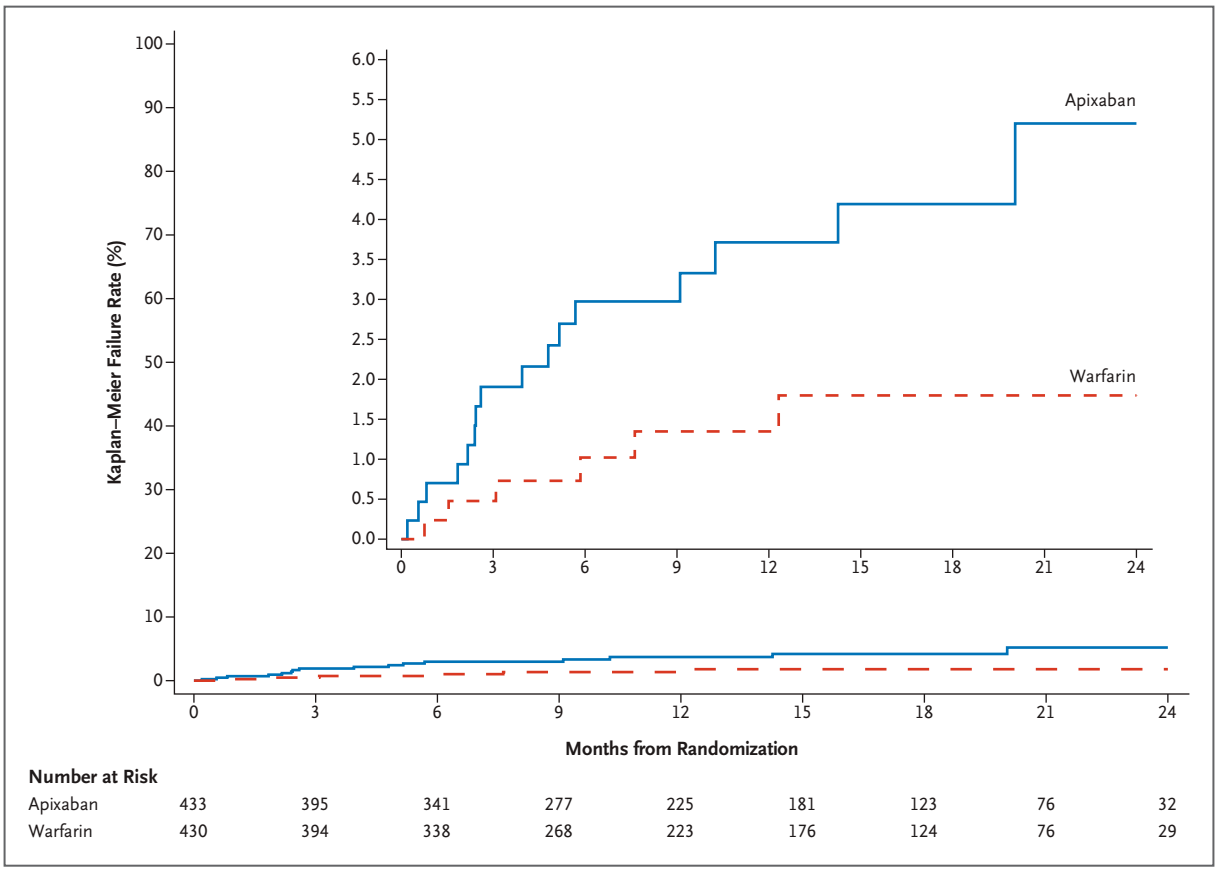

Figure 2. Cumulative Incidence of Valve Thrombosis or Valve-Related Thromboembolism.

Table 2. Event Rate of Primary Efficacy Outcome.					
	Apixaban (479.9 pt-yr) (n=433)		Warfarin (467.0 pt-yr) (n=430)		
Outcome	Event (n)	Rate (%/pt-yr) (95% CI)	Event (n)	Rate (%/pt-yr) (95% CI)	Rate Difference (95% CI) (Apixaban − Warfarin)
Primary efficacy outcome (valve thrombosis or valve-related thromboembolism)	20	4.2 (2.3–6.0)	6	1.3 (0.3–2.3)	2.9 (0.8–5.0)
Valve thrombosis	3	0.6 (0–1.3)	0	0.0	NA
Valve-related thromboembolism*	17	3.5 (1.9–5.2)	6	1.3 (0.3–2.3)	2.3 (0.3–4.2)
Thromboembolic stroke	14	2.9 (1.4–4.5)	0	0.0	NA
Thromboembolic TIA	0	0.0	5	1.1 (0.1–2.0)	NA
Thromboembolic myocardial infarction	0	0.0	1	0.2 (0–0.6)	NA
Thromboembolic arterial thromboembolism	3	0.6 (0–1.3)	0	0.0	NA

* Three additional thromboembolic events (one stroke, one TIA, and one arterial thromboembolism) were adjudicated as unrelated to the valve. All three were in the apixaban group. CI denotes confidence interval; n, number of outcome events; NA, not applicable; pt-yr, patient-years; and TIA, transient ischemic attack.

Discussion

In patients with an On-X mechanical aortic valve implanted more than 3 months earlier, apixaban at a dose of 5 mg twice daily did not demonstrate noninferiority to warfarin for the prevention of valve thrombosis or thromboembolism. Apixaban resulted in more valve thrombosis or valve-related thromboembolic events than warfarin, leading to the early termination of the PROACT Xa trial. Rates of major bleeding were not significantly different between apixaban- and warfarin-treated patients.

The requirement for lifelong anticoagulation with warfarin is a major limitation of mechanical prosthetic heart valves.[29] Warfarin is an effective anticoagulant but has well-described limitations that often lead patients to choose less-durable valve treatment options.[30] The availability of direct, selective thrombin and factor Xa inhibitors, initially developed for patients with atrial fibrillation and venous thromboembolism,[31] has raised the question of whether these agents might be treatment alternatives for patients with mechanical heart valves.[32] A previous study of dabigatran in patients with either aortic or mitral mechanical heart valves was stopped early because of higher rates of both thromboembolic and bleeding events in patients assigned to dabigatran compared with warfarin; many of the thromboembolic events and all of the excess significant bleeding occurred in the early postoperative period.[11] In PROACT Xa, we included patients with the On-X valve in the aortic position only, enrolled patients at least 3 months after valve surgery, and used a selective factor Xa inhibitor with better bioavailability and a more favorable bleeding profile than dabigatran.[14] Even with these design modifications, apixaban was not effective at preventing valve thrombosis or valve-related thromboembolism.

We specifically studied patients with an On-X mechanical valve in the aortic position. Mechanical aortic valves have higher velocity of flow and are thus less prone to thrombotic complications than mechanical mitral valves.[4,33] The On-X valve has a number of design features, including a flared inlet on the orifice inflow area that reduces turbulence and leaflet guards on the outflow rim that protect the leaflets in the closed position, which were thought to make it less prone to thrombosis than other mechanical heart valves.[15] A previous study in patients with On-X valves in the aortic position suggested that, compared with a target INR of 2.0 to 3.0, a lower target INR of 1.5 to 2.0 with warfarin results in similar rates of valve thrombosis or thromboembolism and lower rates of bleeding.[17] This lower target INR for the On-X valve has been incorporated into clinical practice guideline recommendations.[2,33] An INR target range of 2.0 to 3.0 was used in the PROACT Xa trial to ensure a control group with a well-accepted standard of care for the prevention of valve thrombosis and thromboembolism. Major bleeding rates were lower for apixaban than for warfarin, but a statistically significant difference was not demonstrated and both groups exceeded the 2-times OPC threshold we had set as our safety target. This may in part be attributed to the higher targeted INR range used in this trial. Although there was reason to believe that the On-X mechanical aortic valve would allow antithrombotic therapy other than warfarin, our trial did not provide evidence to support this hypothesis.

The PROACT Xa trial was successfully conducted during the Covid-19 pandemic owing to a number of pragmatic

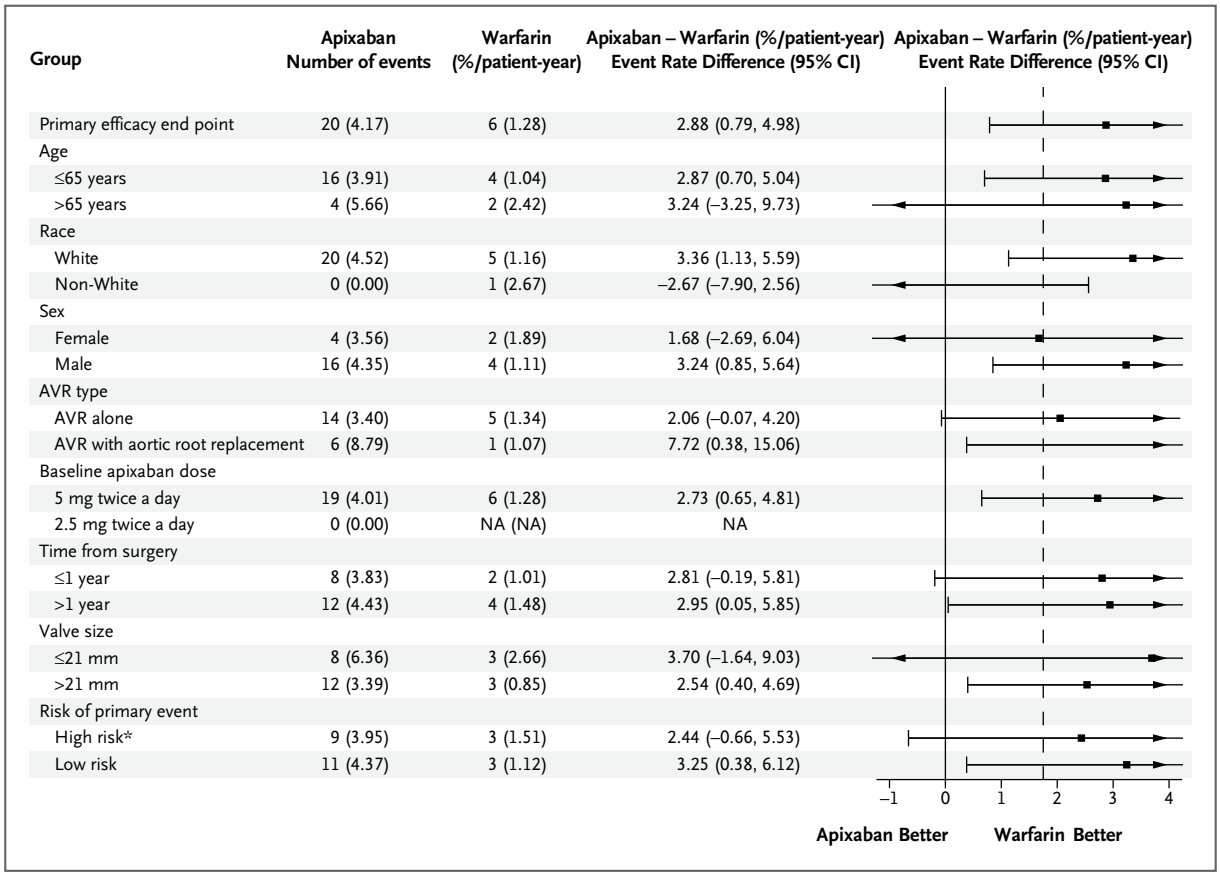

Figure 3. Event Rates and Event Rate Differences (Apixaban − Warfarin) for the Primary Efficacy End Point in Prespecified Subgroups.

The dashed line indicates noninferiority margin for the primary efficacy end point in the overall population (1.75%/patient-year). *High-risk patients defined as having any of the following: atrial fibrillation, left ventricular ejection fraction less than 30%, left atrial dimension greater than 50 mm, significant vascular disease, and history of stroke/transient ischemic attack within 1 year. AVR denotes aortic valve replacement; CI, confidence interval; and NA, not applicable.

design features. Because the valve manufacturer routinely collected implant data, clinical trial sites were selected on the basis of implant volumes and ability to quickly identify eligible patients with an On-X mechanical aortic valve. Intentionally simplified study eligibility criteria permitted, with local institutional review board oversight, remote trial recruitment, and informed consent. Both apixaban and warfarin study drugs were shipped directly to the participants' homes from a central pharmacy. Because both apixaban and warfarin were commercially available and had been extensively studied, following discussion with the FDA we limited serious and nonserious adverse event collection to the trial's thromboembolic and bleeding end points and cases of valve dysfunction. All follow-up visits were conducted remotely with collection of clinical documentation for patients with suspected potential end-point events to allow centralized blinded event adjudication. Many of these same design features may be applicable to future clinical trials.

PROACT Xa was designed with both a direct comparison between apixaban and warfarin with an absolute noninferiority margin of 1.75%/patient-year and a comparison between apixaban and the mechanical valve OPC for valve thrombosis or thromboembolism. The rate of valve thrombosis or thromboembolism we observed in the trial on warfarin was low and close to what was predicted on the basis of previous experience with the On-X valve in the aortic position.[17,34] On the basis of accumulating interim data, the rate of valve thrombosis or thromboembolism was

higher with apixaban than with warfarin and there was no plausible way that apixaban would have become statistically noninferior with the accumulation of more data on the basis of either comparative analysis. This excess in thromboembolic events with apixaban was not attributable to participants with a recent valve implant, inappropriate apixaban dosing, apixaban interruption, or any other factor we could identify. Almost all participants were taking concomitant aspirin. Hence, inhibition of factor Xa seems insufficient to prevent valve thrombosis or thromboembolism in patients with an On-X mechanical aortic valve. Additional studies are needed with new mechanical heart valves and new anticoagulants to potentially identify alternatives to warfarin for patients requiring mechanical heart valve replacement.

The study has some limitations. It was open-label, so patients and providers knew whether they were taking apixaban or warfarin. We addressed this by requiring identical follow-up in both groups, by using clinically overt end points (clinical valve thrombosis and valve-related thromboembolism) that would be unlikely to be subject to ascertainment bias, and by having all events centrally adjudicated and blinded to study drug assignment. We also mandated a target INR range of 2.0 to 3.0 for patients assigned to warfarin. This may have discouraged some patients from participating or from continuing in the study if they were assigned to warfarin because they were previously anticoagulated to a target INR of 1.5 to 2.0 in accordance with practice guidelines and the On-X valve's labeling. An on-treatment analysis, however, showed results similar to the primary intention-to-treat analysis. While the racial composition of On-X aortic valve recipients is unknown, 90% of participants in this study had self-declared "White" race despite concerted efforts to diversify enrollment.

In conclusion, in patients with an On-X mechanical aortic valve, apixaban was not noninferior to warfarin and failed to meet our safety threshold of twice the FDA-mandated OPC for the prevention of valve thrombosis or valve-related thromboembolism.

Disclosures

The PROACT Xa study was funded by Artivion (formerly CryoLife).

Author disclosures and other supplementary materials are available at evidence.nejm.org.

Elizabeth E. S. Cook of the Duke Clinical Research Institute provided editorial support.

The PROACT Xa trial data will be maintained at the Duke Clinical Research Institute for academic use by the PROACT Xa investigators and at Artivion; the data are not publicly available.

Author Affiliations

[1] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC
[2] Cleveland Clinic, Cleveland
[3] Franciscian Health, Indianapolis
[4] ProMedica Toledo Hospital, Toledo, OH
[5] University of Ottawa Heart Institute, Ottawa, ON
[6] University of Cincinnati College of Medicine, Cincinnati
[7] Piedmont Heart Institute, Atlanta
[8] Mount Sinai Morningside Hospital, New York
[9] OSF HealthCare Cardiovascular Institute, Rockford, IL
[10] Yale University School of Medicine, New Haven, CT
[11] Mayo Clinic, Rochester, MN
[12] Northeast Georgia Medical Center, Gainesville, GA
[13] MultiCare Institute for Research and Innovation, Tacoma, WA
[14] University of Pittsburgh Medical Center, Pittsburgh
[15] Brigham and Women's Hospital, Harvard Medical School, Boston

References

1. Ruel M, Masters RG, Rubens FD, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. Ann Thorac Surg 2004;78:77-84. DOI: 10.1016/j.athoracsur.2003.12.058.
2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227.
3. Rubboli A, Becattini C, Verheugt FWA. Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy. World J Cardiol 2011;3:351-358. DOI: 10.4330/wjc.v3.i11.351.
4. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. 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. DOI: 10.1016/S0735-1097(00)00834-2.
5. Guimarães HP, Lopes RD, de Barros e Silva PGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med 2020;383:2117-2126. DOI: 10.1056/NEJMoa2029603.
6. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708. DOI: 10.1056/NEJMoa1207541.
7. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992. DOI: 10.1056/NEJMoa1107039.
8. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509-1524. DOI: 10.1056/NEJMoa1817083.

9. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711-719. DOI: 10.1056/NEJMoa1814468.

10. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010;363:2487-2498. DOI: 10.1056/NEJMoa1006885.

11. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206-1214. DOI: 10.1056/NEJMoa1300615.

12. Kalra A, Raza S, Jafry BH, et al. Off-label use of direct oral anticoagulants in patients receiving surgical mechanical and bioprosthetic heart valves. JAMA Netw Open 2021;4:e211259. DOI: 10.1001/jamanetworkopen.2021.1259.

13. Chu MWA, Ruel M, Graeve A, et al. Low-dose versus standard warfarin after mechanical mitral valve replacement: a randomized trial. Ann Thorac Surg 2023;115:929-938. DOI: 10.1016/j.athoracsur.2022.12.031.

14. Jawitz OK, Wang TY, Lopes RD, 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 a mechanical On-X aortic heart valve. Am Heart J 2020;227:91-99. DOI: 10.1016/j.ahj.2020.06.014.

15. Chaudhary R, Garg J, Krishnamoorthy P, et al. On-X valve: the next generation aortic valve. Cardiol Rev 2017;25:77-83. DOI: 10.1097/CRD.0000000000000105.

16. Puskas J, Gerdisch M, Nichols D, 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;147:1202-1211. DOI: 10.1016/j.jtcvs.2014.01.004.

17. Puskas JD, Gerdisch M, Nichols D, et al. Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. J Am Coll Cardiol 2018;71:2717-2726. DOI: 10.1016/j.jacc.2018.03.535.

18. Lester PA, Coleman DM, Diaz JA, et al. Apixaban versus warfarin for mechanical heart valve thromboprophylaxis in a swine aortic heterotopic valve model. Arterioscler Thromb Vasc Biol 2017;37:942-948. DOI: 10.1161/ATVBAHA.116.308649.

19. Turpie A, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med 1993;329:524-529. DOI: 10.1056/NEJM199308193290802.

20. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008;85:1490-1495. DOI: 10.1016/j.athoracsur.2007.12.082.

21. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-2747. DOI: 10.1161/CIRCULATIONAHA.110.009449.

22. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-694. DOI: 10.1111/j.1538-7836.2005.01204.x.

23. Wu Y, Butchart EG, Borer JS, Yoganathan A, Grunkemeier GL. Clinical evaluation of new heart valve prostheses: update of objective performance criteria. Ann Thorac Surg 2014;98:1865-1874. DOI: 10.1016/j.athoracsur.2014.05.006.

24. 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.

25. McNicholas KW, Ivey TD, Metras J, et al. North American multicenter experience with the On-X prosthetic heart valve. J Heart Valve Dis 2006;15:73-79.

26. Chambers JB, Pomar 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;145:420-424. DOI: 10.1016/j.jtcvs.2011.12.059.

27. Division of Cardiovascular and Neurological Devices. Draft replacement heart valve guidance, version 4.1. Washington, DC: Center for Devices and Radiological Health, Food and Drug Administration, 1994.

28. Liu GF, Wang J, Liu K, Snavely DB. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. Stat Med 2006;25:1275-1286. DOI: 10.1002/sim.2335.

29. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995;333:11-17. DOI: 10.1056/NEJM199507063330103.

30. Iribarne A, Leavitt BJ, Robich MP, et al. Tissue versus mechanical aortic valve replacement in younger patients: a multicenter analysis. J Thorac Cardiovasc Surg 2019;158:1529-1538.e2. DOI: 10.1016/j.jtcvs.2019.02.076.

31. Carnicelli AP, Hong H, Giugliano RP, et al. Individual patient data from the pivotal randomized controlled trials of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (COMBINE AF): design and rationale: from the COMBINE AF (a Collaboration between Multiple institutions to Better Investigate Non-vitamin K antagonist oral anticoagulant use in Atrial Fibrillation) investigators. Am Heart J 2021;233:48-58. DOI: 10.1016/j.ahj.2020.12.002.

32. Kapadia SR, Svensson LG. Bioprosthetic valves and atrial fibrillation: Direct anticoagulants or warfarin. J Thorac Cardiovasc Surg 2023;165:71-75. DOI: 10.1016/j.jtcvs.2021.05.051

33. On-X Life Technologies Inc. On-X prosthetic heart valve: instructions for use. https://www.onxlti.com/wp-content/uploads/2019/05/010122103A-On-X-IFU-Booklet-English-Website-Version.pdf.

34. Kim JS, Kang Y, Sohn SH, Hwang HY, Choi JW, Kim KH. Long-term clinical outcomes of the On-X mechanical prosthetic valve in the aortic or mitral position — a single-center experience of up to 20 years' follow up. Circ J 2021;85:1042-1049. DOI: 10.1253/circj.CJ-20-1193.