



# RENOVATE:

## Can NOAC Replace VKA after Mechanical AVR?

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Asan Medical Center

University of Ulsan College of Medicine





**Thrombo-embolism**  
**Hemorrhage**

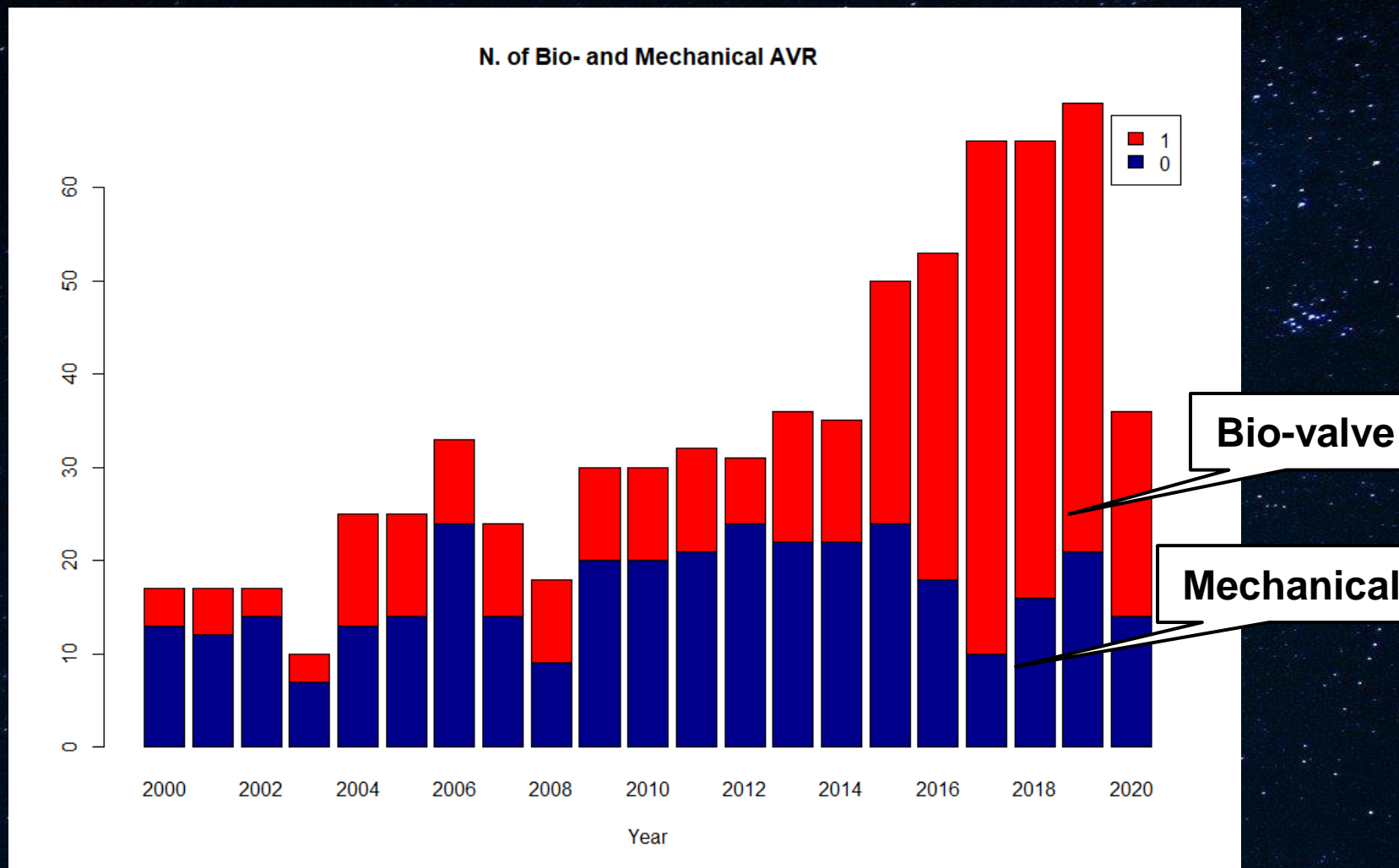


**Valve reoperation**



# Bio and Mechanical AVR: Age 60~70 yrs

## Asan Medical Center, 2000-2020





# National Data in Korea

JAMA  
Network | **Open**<sup>™</sup>



Original Investigation | Cardiology

## Evaluating Reference Ages for Selecting Prosthesis Types for Heart Valve Replacement in Korea

Sung Jun Park, MD; You Jung Ok, MD; Ho Jin Kim, MD; Ye-Jee Kim; Seonok Kim; Jung-Min Ahn, MD, PhD; Dae-Hee Kim, MD, PhD; Jae-Sung Choi, MD, PhD; Joon Bum Kim, MD, PhD

### Abstract

**IMPORTANCE** Although a patient's age may be the only objective figure that can be used as a reference indicator in selecting the type of prosthesis in heart valve surgery, different clinical guidelines use different age criteria.

**OBJECTIVE** To explore the age-associated survival-hazard functions associated with prosthesis type in aortic valve replacement (AVR) and mitral valve replacement (MVR).

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study compared the long-term outcomes associated with mechanical and biologic prostheses in AVR and MVR according to recipient's age using a nationwide administrative data from the Korean National Health Insurance Service. To reduce the potential treatment-selection bias between mechanical and biologic prostheses, the inverse-probability-of-treatment-weighting method was used. Participants included patients who underwent AVR or MVR in Korea between 2003 and 2018. Statistical analysis was performed between March 2022 and March 2023.

**EXPOSURES** AVR, MVR, or both AVR and MVR with mechanical or biologic prosthesis.

**MAIN OUTCOMES AND MEASURES** The primary end point was all-cause mortality after receiving prosthetic valves. The secondary end points were the valve-related events, including the incidence of reoperation, systemic thromboembolism, and major bleeding.

### Key Points

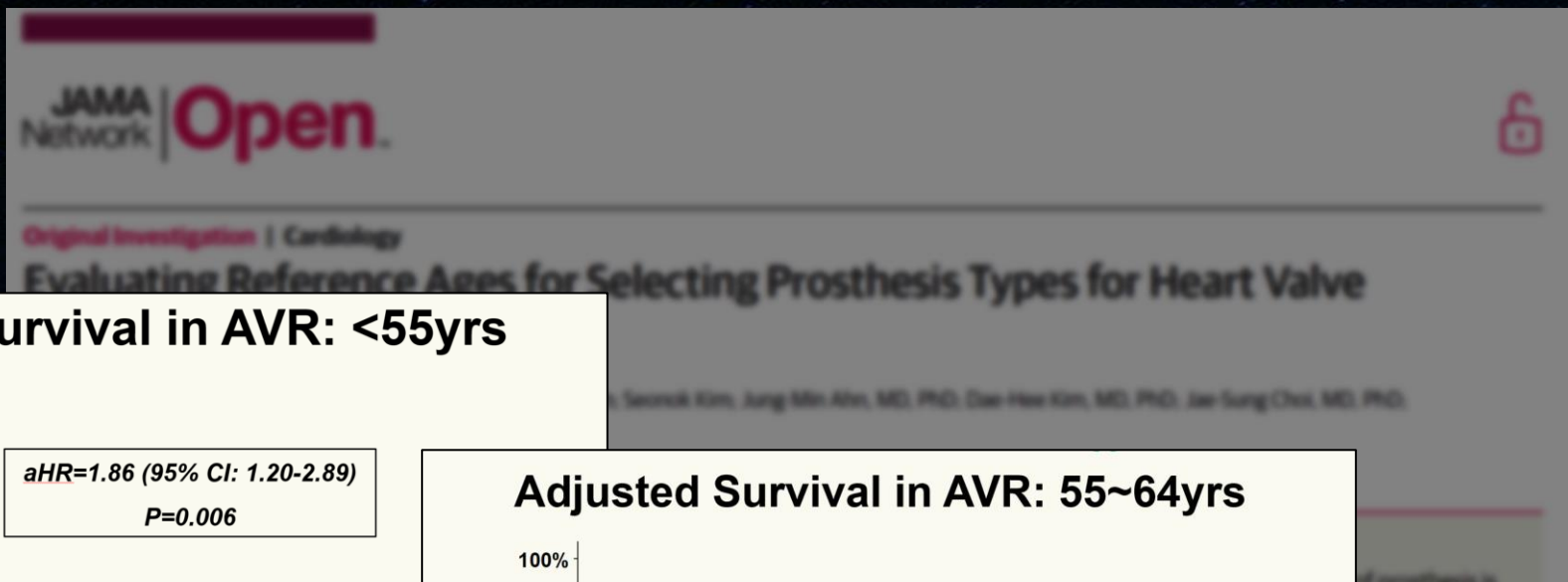
**Question** Which type of prosthesis is associated with the best outcomes by age of the recipient undergoing aortic or mitral valve replacement?

**Findings** This cohort study of 24 347 patients who underwent aortic or mitral valve replacement compared the long-term outcomes associated with mechanical and bioprostheses according to the recipient's age found that the mechanical prosthesis was associated with a survival benefit over bioprosthesis, and the benefit was maintained in patients up to age 65 years for replacements in the aortic position and age 70 years for replacements in the mitral position.

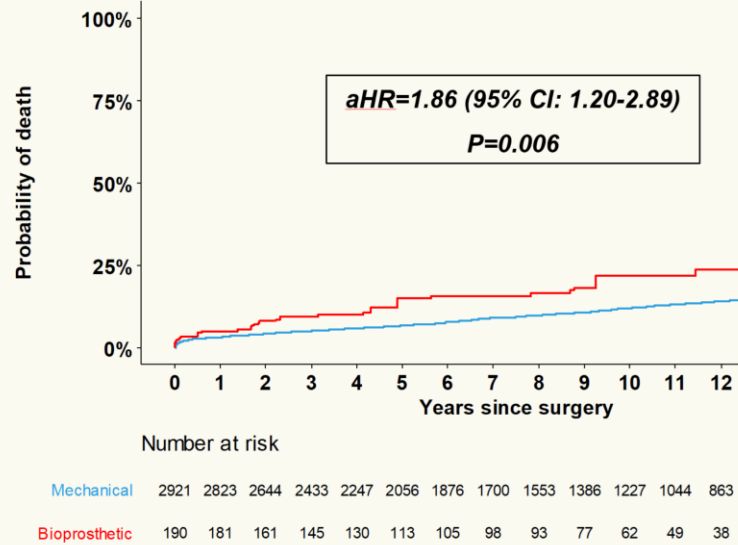
**Meaning** The findings of this study may encourage health care practitioners to adopt a more conservative approach in

**NHIS Database, AVR  
Between 2003 and 2018  
Age: 40-80yrs  
N = 15,726**

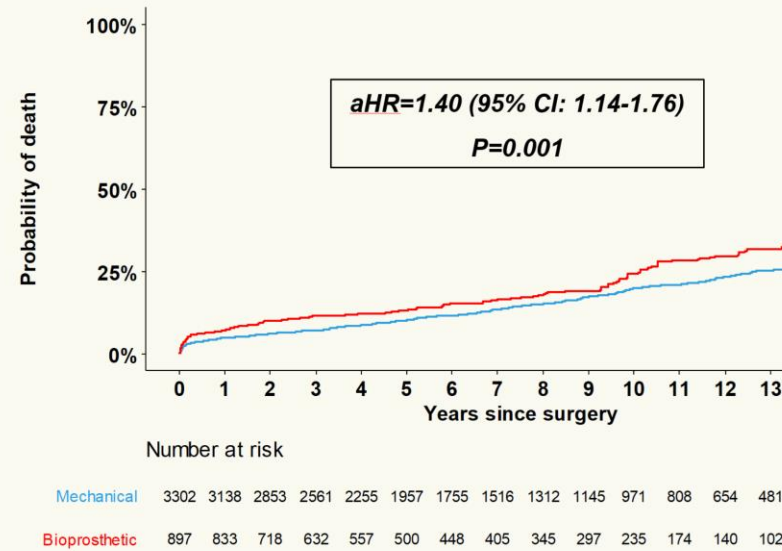




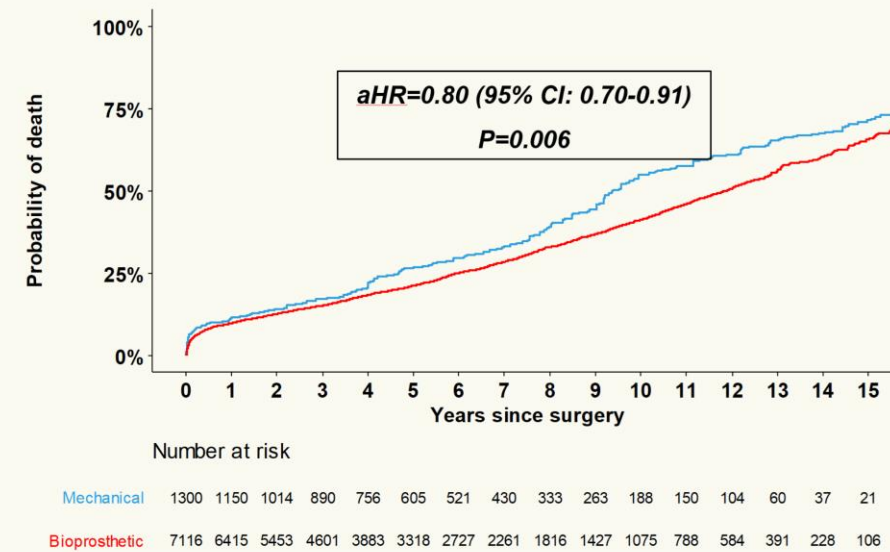
### Adjusted Survival in AVR: <55yrs



### Adjusted Survival in AVR: 55~64yrs



### Adjusted Survival in AVR: ≥65yrs



using a nationwide administrative data...  
the potential treatment selection bias...  
probability of treatment weighting...  
underwent AVR or MVR in Korea between...  
between March 2022 and March 2023

**EXPOSURES** AVR, MVR, or both AVR and MVR with mechanical or biologic prosthesis.

**MAIN OUTCOMES AND MEASURES** The primary end point was all-cause mortality after receiving...  
prosthetic valves. The secondary end points were the valve-related events, including the incidence of...  
reoperation, systemic thromboembolism, and major bleeding.

years for...  
proton...  
replacem...

**Meaning** The findings of this study may...  
encourage health care practitioners to...  
adopt a more conservative approach in...

# Living With Warfarin

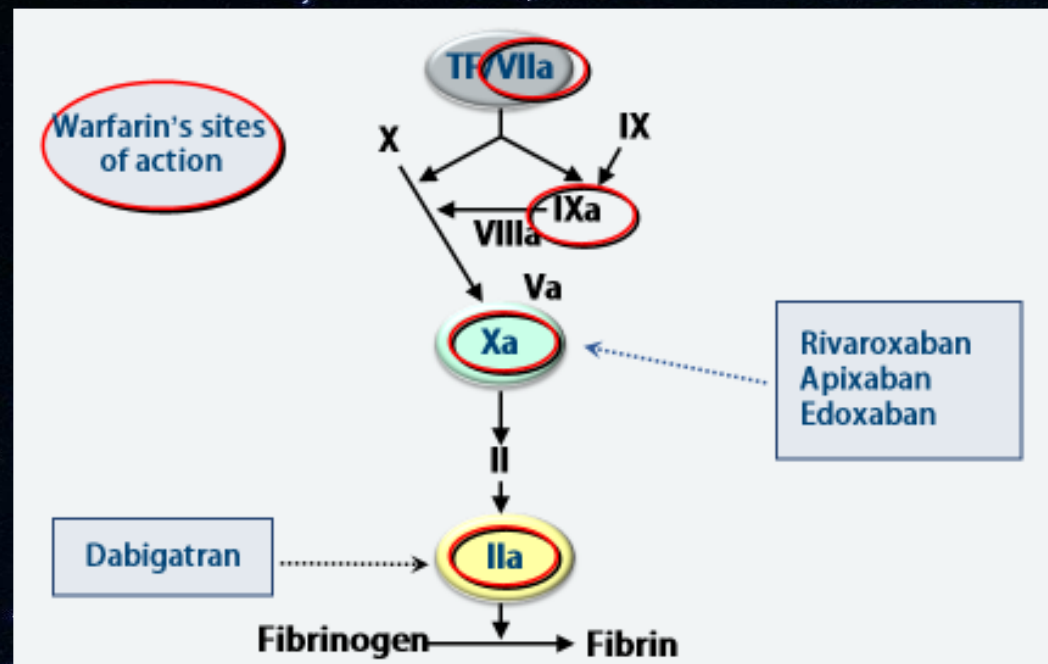
“I feel my whole life is controlled by warfarin”

-[www.afa.org.uk](http://www.afa.org.uk)-

- Regular **blood test** at least once a 12 weeks: even shorter in fluctuating INR
- Don't make changes to your **diet or alcohol intake** – consistency is the key
  - Green leafy vegetables
  - Eat same amount of these foods each week to help keep your INR stable
- Check before starting a **new medicine**
- Take precautions to **prevent injuries**



# Non-Vit K Oral Anticoagulant



- Fixed doses qd or bid
- No food/ alcohol restriction
- No blood testing
- Fast onset / clearance
- Lower bleeding risks proven in AF
- Comparable efficacy proven in AF

Reproducible in  
mechanical heart valves?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D.,  
Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D.,  
Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc.,  
Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D.,  
Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D.,  
Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D.,  
for the RE-ALIGN Investigators\*

ABSTRACT

N Engl J Med 2013;369:1206-14.

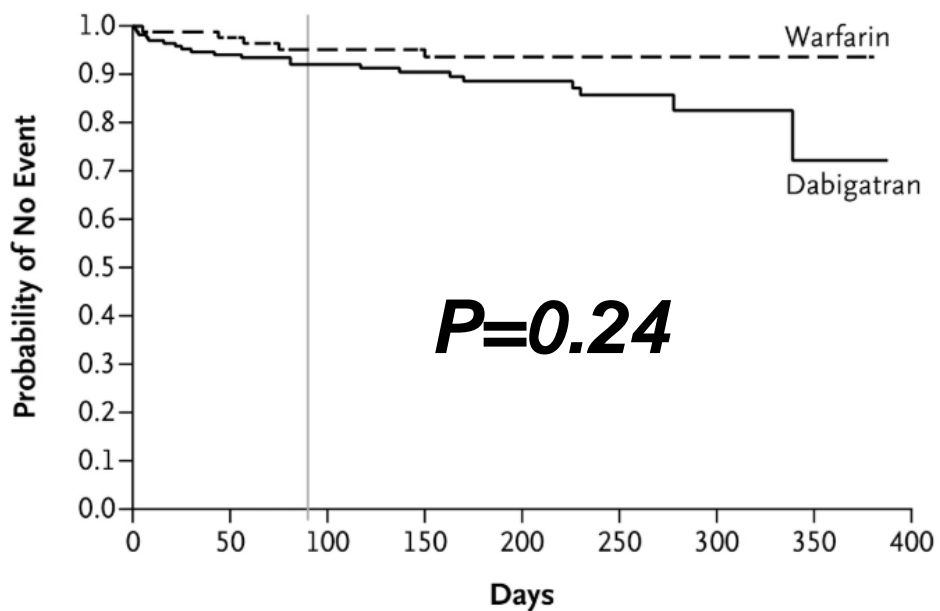
BACKGROUND



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

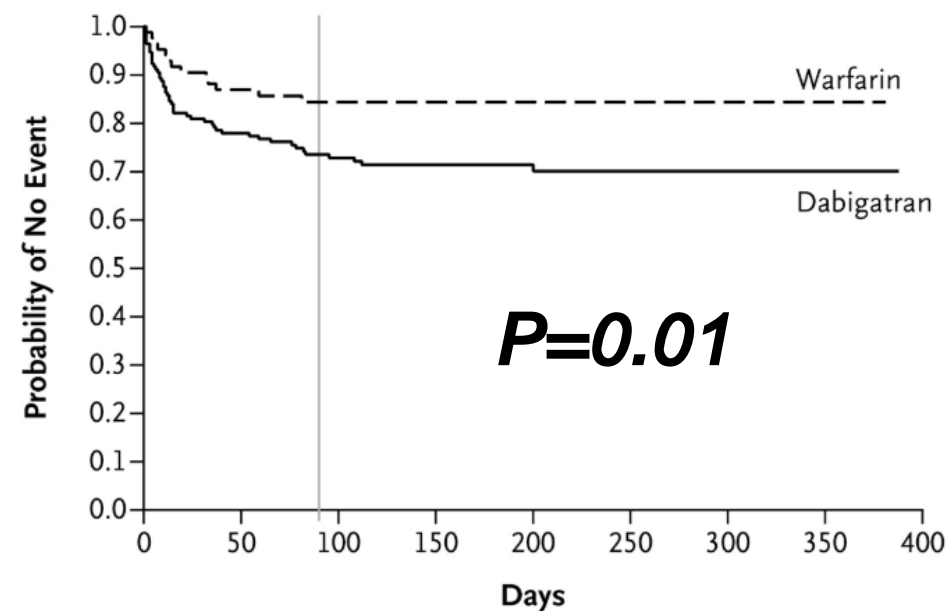
**A First Thromboembolic Event**



**No. at Risk**

Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

**B First Bleeding Event**



**No. at Risk**

Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4



# NOAC for Mechanical Heart Valve

	More likely to be effective	Less likely to be effective
<b>Time from surgery</b>	>3 months	<3 months
<b>Position</b>	Aortic	Mitral/right heart valve
<b>Systolic function</b>	Preserved	Reduced
<b>Bleeding risk</b>	Low	Intermediate-high
<b>Hypercoagulability</b>	No	Yes
<b>Compliance to therapy</b>	Good	Poor





# RENOVATE Trial

**R**andomized **E**valuation of Lo**N**g-term Anticoagulation with  
**O**ral Factor Xa Inhibitor versus **V**itamin K Antagonist after  
Mechanical **AorTic** Valve Replac**E**ment



Randomized Evaluation of LoNg-term Anticoagulation with Oral Factor Xa Inhibitor versus Vitamin K Antagonist after Mechanical AorTic Valve REplacement

# RENOVATE Trial

1,300 Patients with Mechanical Aortic Valve Replacement  
at least 3 months after Operation

Stratified randomization by (1) atrial fibrillation and (2) participating site

Oral Factor Xa Inhibitor  
Rivaroxaban 20mg QD  
(N=650)

Vitamin K Antagonist  
INR 2.0 ~ 3.0  
(N=650)

**Primary endpoint:** a composite of cardiac death, valve thrombosis, valve-related thromboembolic event, major bleeding, and clinically-relevant non-major bleeding (BARC 2,3, or 5) at 12 months



# Sample Size

- Non-inferiority trial design
- % of primary endpoint: 15.0% in the WARF group based on results from ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF trials
  - *Death: 1.76%; Thromboembolism: 1.75%; Major bleeding: 3.63%; Non-major bleeding: 8%*
- Non-inferiority margin: 5.0% (1/3 of 15.0%)
- Dropout rate: 3%
- Power=80%; Alpha-level=0.05
- Final N=1300 (650 vs. 650)



# Study Design

- Multi-center, randomized, open-label trial
- Randomization: stratified by the presence of AF and participating sites
- Interventions:
- **Rivaroxaban Group:**
  - Rivaroxaban oral tablet 20mg once daily
  - Creatinine clearance 15-49 mL/min, 15mg once daily
- **Warfarin Group:**
  - Target INR of 2.0-3.0



# Secondary Endpoint

- All-cause death
- Individual components of primary endpoint
- Valve thrombosis confirmed by echocardiography, cine fluoroscopy, CT or autopsy
- Transient ischemic attack
- Myocardial infarction
- Echocardiographic parameters (max/mean PG, EOA) at 1 year



# Inclusion criteria

1. Age 19 years and more
2. At least 3 months after mechanical SAVR
3. NYHA Fc I or II
4. Mean AV gradient  $<20$  mm Hg or peak velocity  $<3$  m/s,  
AND no moderate or severe prosthetic valve regurgitation
5. Voluntarily participated in the written agreement



# Exclusion criteria

1. Old generation mechanical valve
2. History of mechanical valve implantation in the MV, PV or TV
3. Valvular atrial fibrillation (moderate or severe MS)
4. Moderate to severe mitral stenosis
5. History of hemorrhagic stroke
6. Clinically overt stroke within the last 3 months
7. Renal failure(creatinine clearance  $<15\text{mL}/\text{min}$ ) or on hemodialysis
8. Left ventricular dysfunction:  $\text{LVEF} \leq 40\%$
9. Hepatic impairment, or severe (Child-Pugh C) or with any hepatic disease associated with coagulopathy



*Randomized Evaluation of Long-term Anticoagulation with Oral Factor Xa Inhibitor versus Vitamin K Antagonist after Mechanical Aortic Valve Replacement*

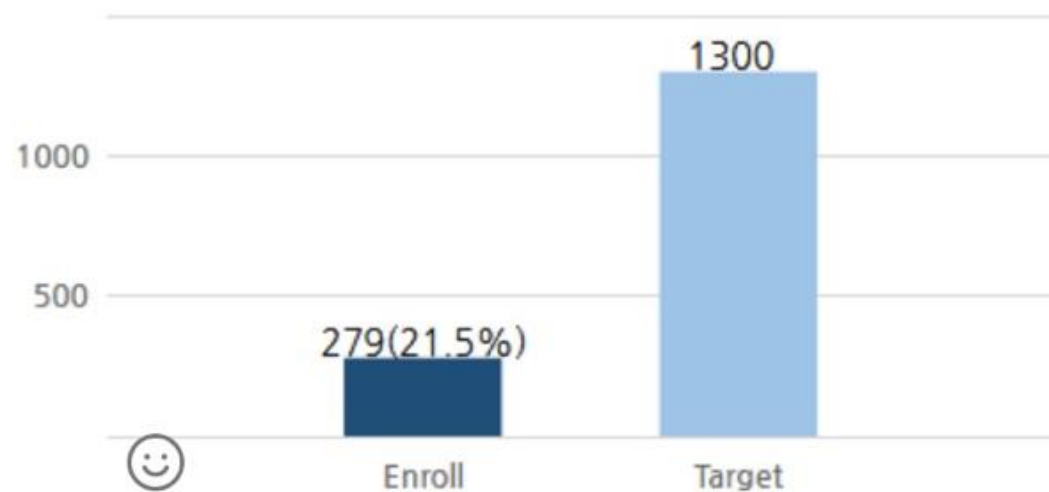
## RENOVATE Trial

### Participating Centers

1. Asan Medical Center
2. Bucheon Sejong Hospital
3. Pusan National University Yangsan Hospital
4. Yonsei University Severance Hospital
5. Seoul National University Hospital
6. Samsung Medical Center
7. Gangneung Asan Medical Center
8. Korea University Anam Hospital
9. Chonnam National University Hospital
10. Chungnam National University Hospital
11. Keimyong University Dong San Hospital
12. Ulsan University Hospital



### 목표대비 등록현황



### 연월별 등록현황







2022 OCT

ISSUE 01

# NEWSLETTER

## RENOVATE

### Artivion Follows Recommendation to Stop PROACT Xa Clinical Trial



NEWS PROVIDED BY

Artivion, Inc.

# 현저기준 9월 23일 PROACT Xa 연구 DSMB 권고로 연구 중단 발표 아픽사반군에서 stroke이 더 많이 발생

ATLANTA, Sept. 23, 2022 — Artivion, Inc. (NYSE:ARTV), leading cardiac and vascular technology company

focused on aortic disease, announced today that it has stopped the PROACT Xa clinical trial, a prospective, randomized, trial designed to determine if patients with an On-X mechanical aortic valve can be maintained safely and effectively on apixaban rather than on warfarin. The decision was based on the recommendation of the independent Data and Safety Monitoring Board (DSMB) of the trial due to lack of evidence supporting non-inferiority of apixaban to warfarin for valve thrombosis and thromboembolism.

The PROACT Xa trial compared apixaban as their anticoagulant to warfarin as their anticoagulant. The trial began enrolling in April 2020. The DSMB found that blood clots, resulting in stroke, were more likely to occur in patients receiving the trial drug than in patients receiving warfarin. The trial was unlikely to achieve its primary endpoint of non-inferiority of apixaban to warfarin for valve thrombosis and thromboembolism. The trial is being discontinued and patients are being returned to warfarin.

	RENOVATE	PROACT Xa
Study population	KOREA All valve	US On-X valve only
Drug	Rivaroxaban	Apixaban

Dr. John Alexander, Chair of the PROACT Xa trial and Professor of Medicine/Cardiology at Duke University School of Medicine, said, "The PROACT Xa trial was designed to determine whether apixaban would yield equivalent safety to the standard anticoagulant, warfarin. Unfortunately, it appears that it does not. On behalf of all of the investigators, we appreciate the research effort into the science of managing patients with artificial heart valves."

Pat Mackin, Chairman, President and Chief Executive Officer of Artivion said, "The On-X aortic valve has a long track record of safe and effective outcomes and is the leading mechanical aortic valve in the United States and in other



# PROACT Xa Trial Terminated

RESOURCE TYPE: PRESENTATION



## 71. PROACT XA: A MULTICENTER, RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF APIXABAN VS. WARFARIN IN PATIENTS WITH A MECHANICAL BILEAFLET AORTIC HEART VALVE

May 6, 2023

**Presented by:**

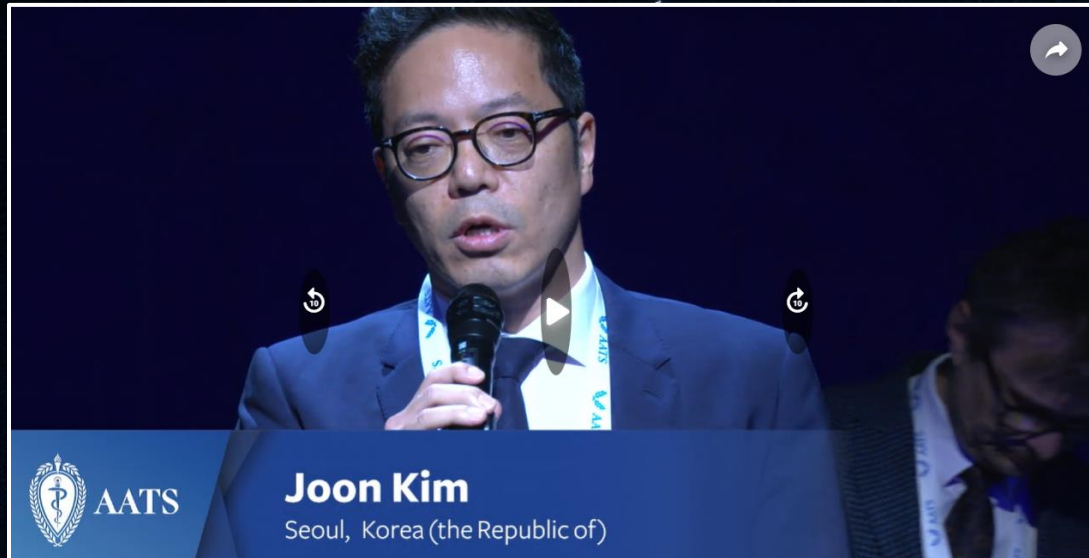
[Leonard Girardi](#), [Invited Discussant](#), [Weill Cornell Medicine](#)  
[Lars Svensson](#), [Abstract Presenter](#), [Cleveland Clinic](#)

**Source:**

103rd Annual Meeting, the Los Angeles Convention Center,  
Los Angeles, CA, USA  
*Los Angeles Convention Center, West Hall B*



# PROACT Xa Trial Terminated



## RENOVATE

- Rivaroxaban once daily
- High compliance to medication



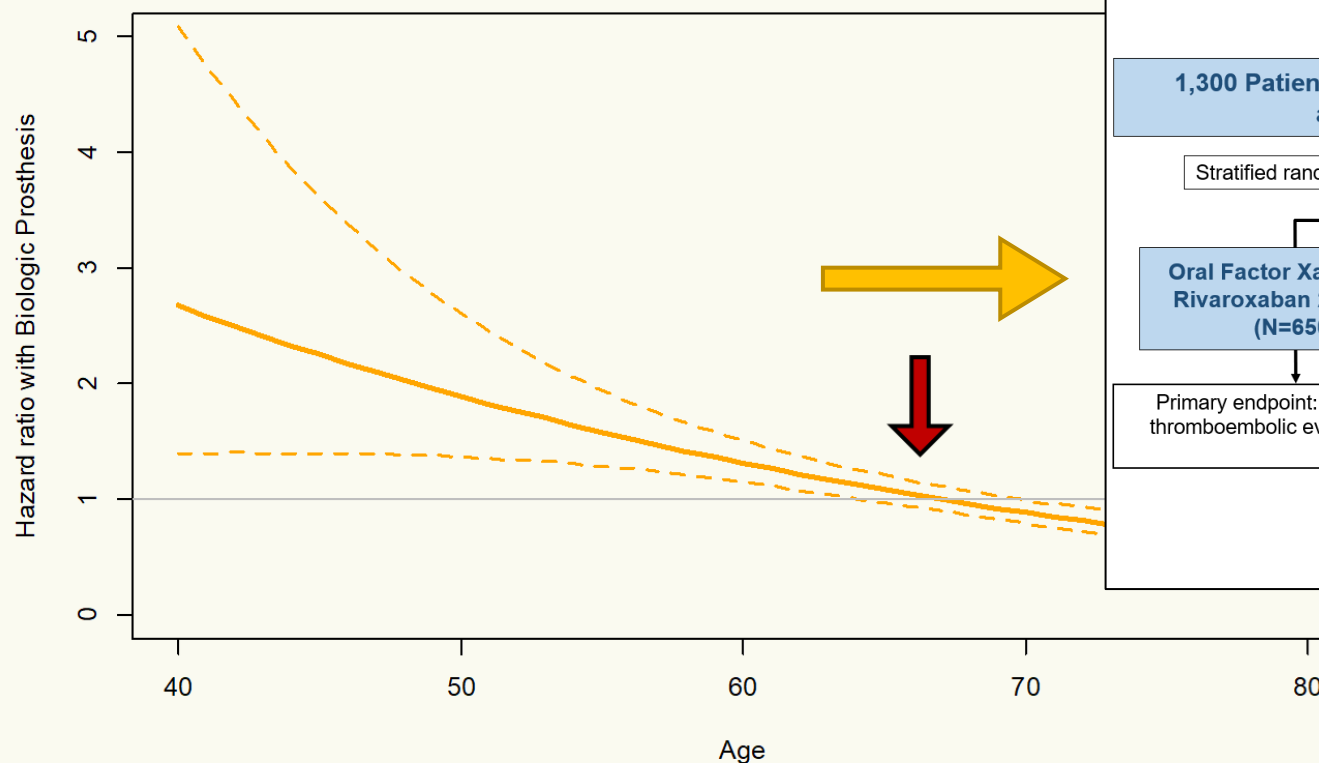
## PROACT Xa

- Apixaban twice daily
- Lack of compliance monitoring



# National Data in Korea

## Age-Dependent Adjusted Survival in AVR



*Randomized Evaluation of Long-term Anticoagulation with Oral Factor Xa Inhibitor versus Vitamin K Antagonist after Mechanical Aortic Valve Replacement*

### RENOVATE Trial

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Primary endpoint: a composite of cardiac death, valve thrombosis, valve-related thromboembolic event, major bleeding, and clinically-relevant nonmajor bleeding at 12 months





Looking forward seeing exciting future





ASAN  
Medical C

ITY OF ULSAN  
E OF MEDICINE

*Thank you*