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Recent Anticoagulation Trials for Mechanical Valves

RENOVATE Trial

Ho Jin Kim, MD; Joon Bum Kim, MD, PhD and Jung-Min Ahn, MD, PhD

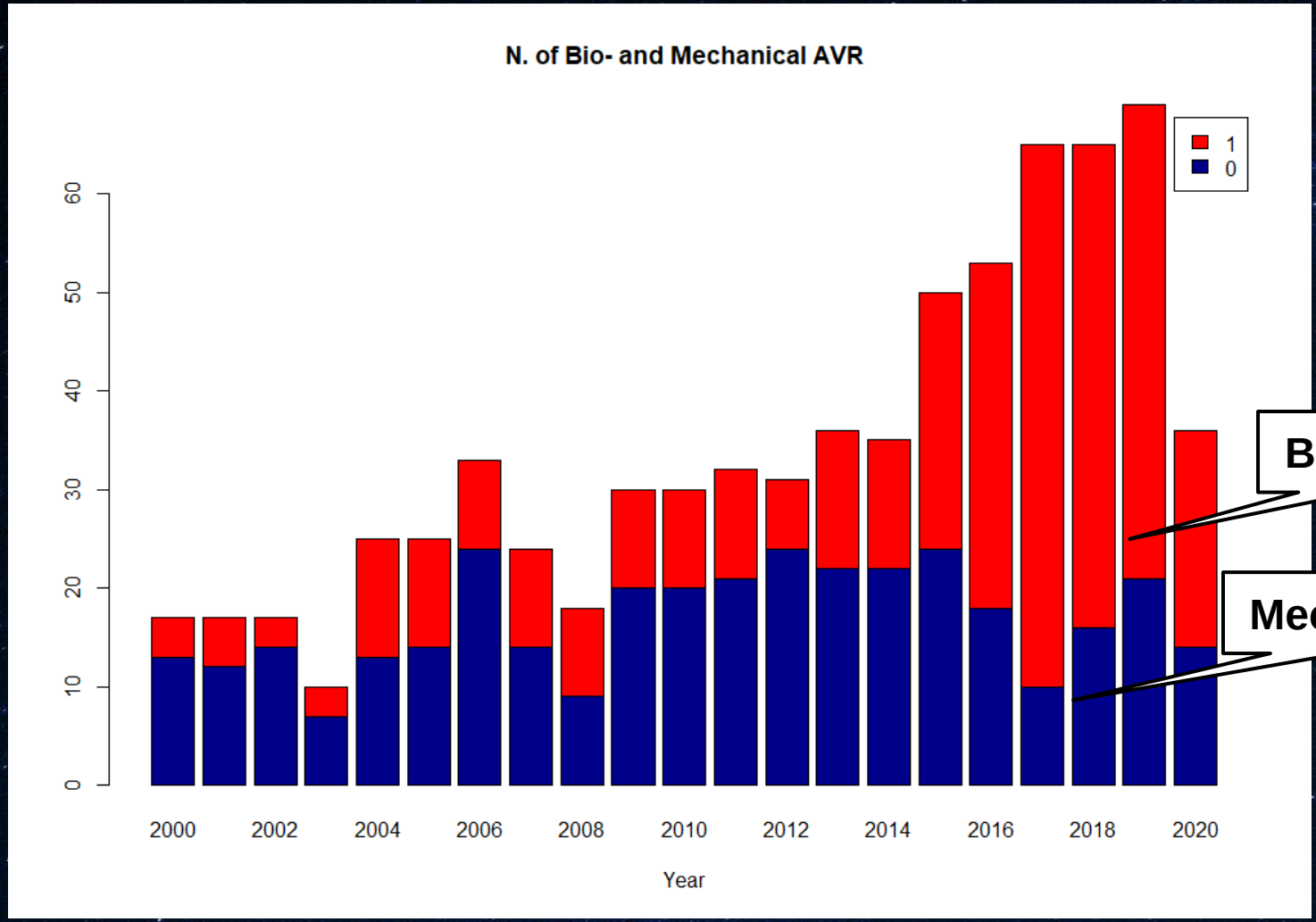
Dept. Thoracic and Cardiovascular Surgery
Asan Medical Center
University of Ulsan College of Medicine

Thrombo-embolism

Hemorrhage

Valve reoperation

Bio and Mechanical AVR: Age 60~70 yrs Asan Medical Center, 2000-2020



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National Data in Korea

JAMA Network Open

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

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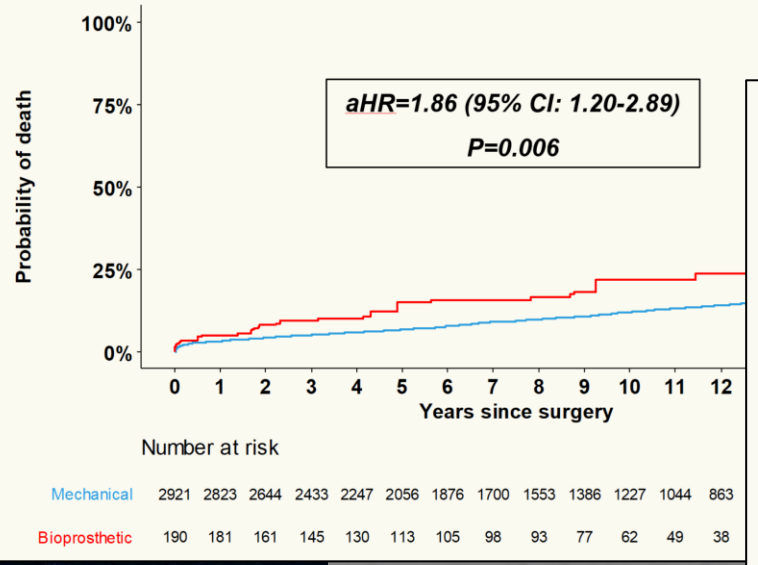
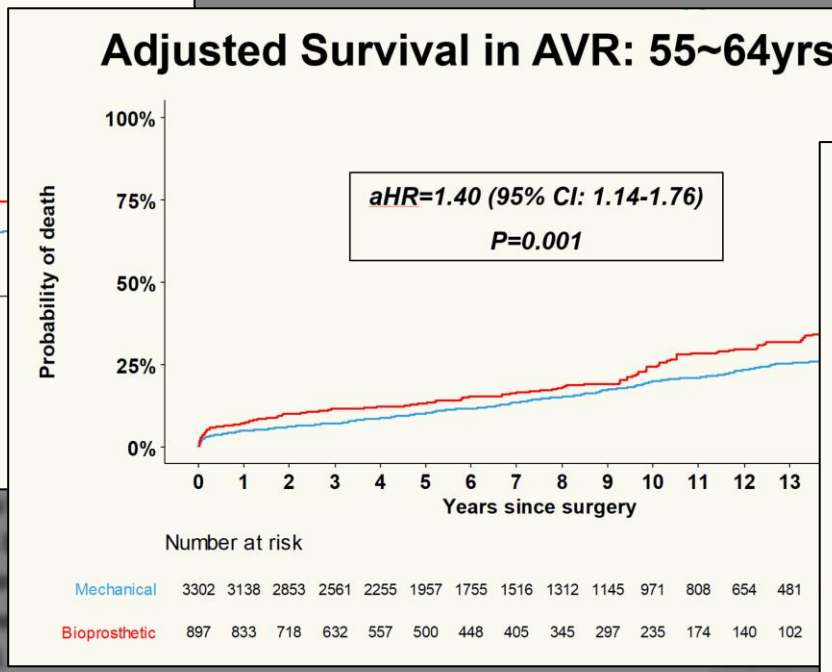
Evaluating Reference Ages for Selecting Prosthesis Types for Heart Valve

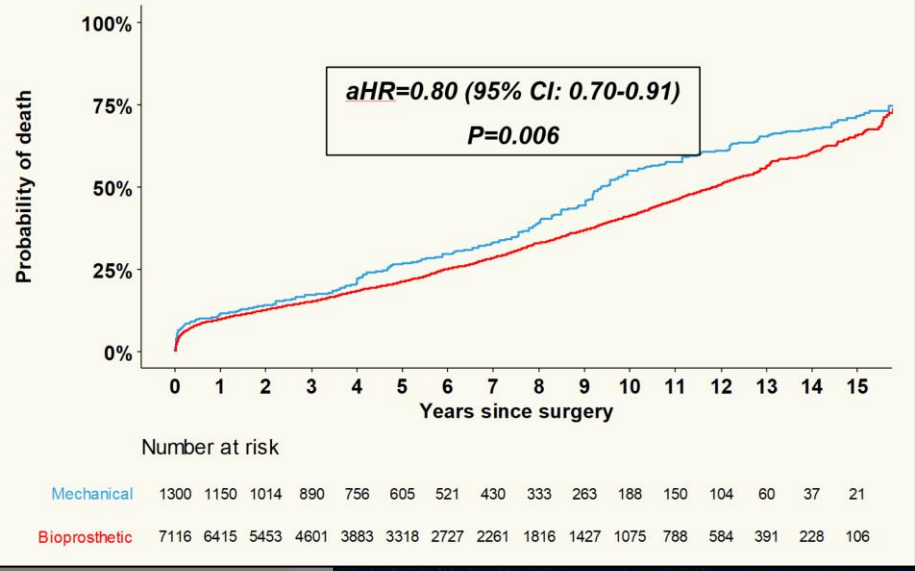
Adjusted Survival in AVR: <55yrs



Adjusted Survival in AVR: 55~64yrs



Adjusted Survival in AVR: ≥65yrs



JAMA Network | Open

Original Investigation | Cardiology

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

Sung Jun Park, MD; Joon Bum Kim, MD;

Abstract

IMPORTANCE

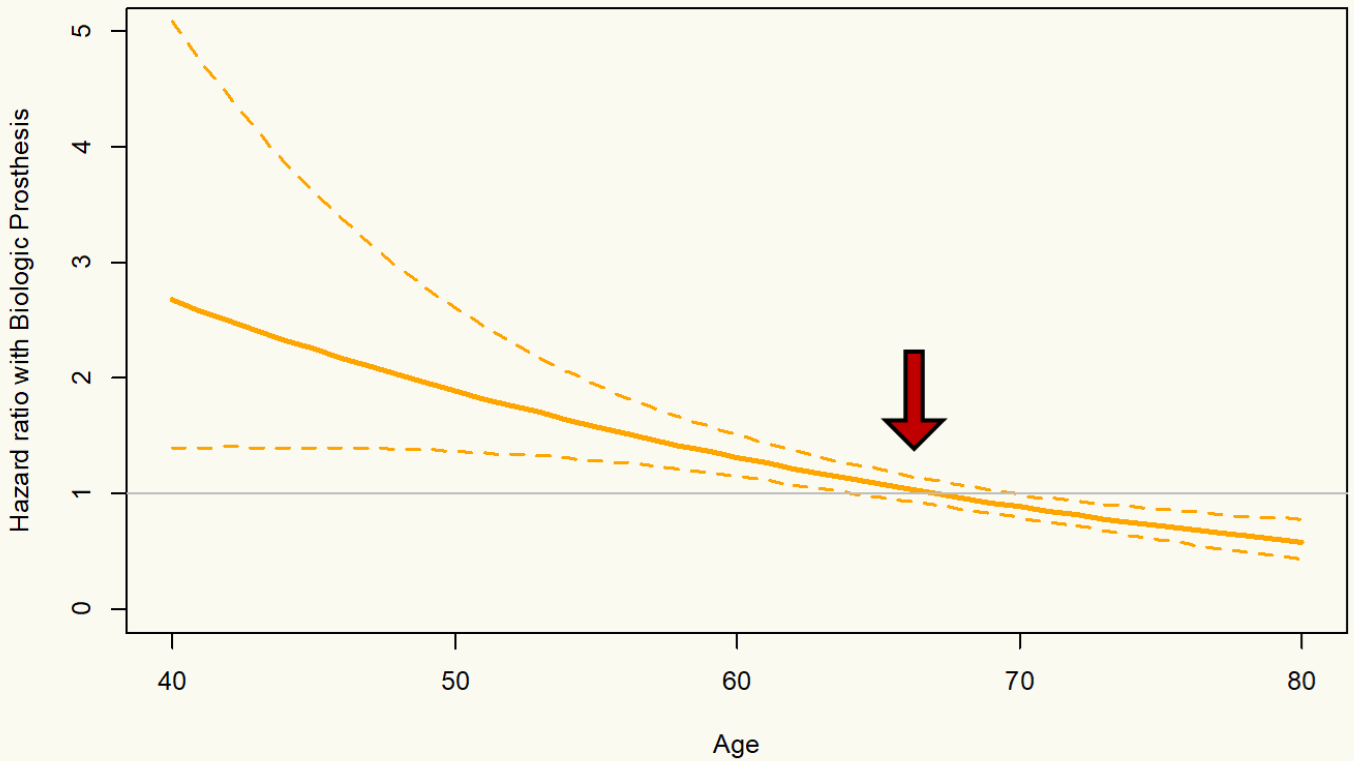
OBJECTIVE

DESIGN, SETTING

EXPOSURES

MAIN OUTCOMES

Age-Dependent Adjusted Survival in AVR



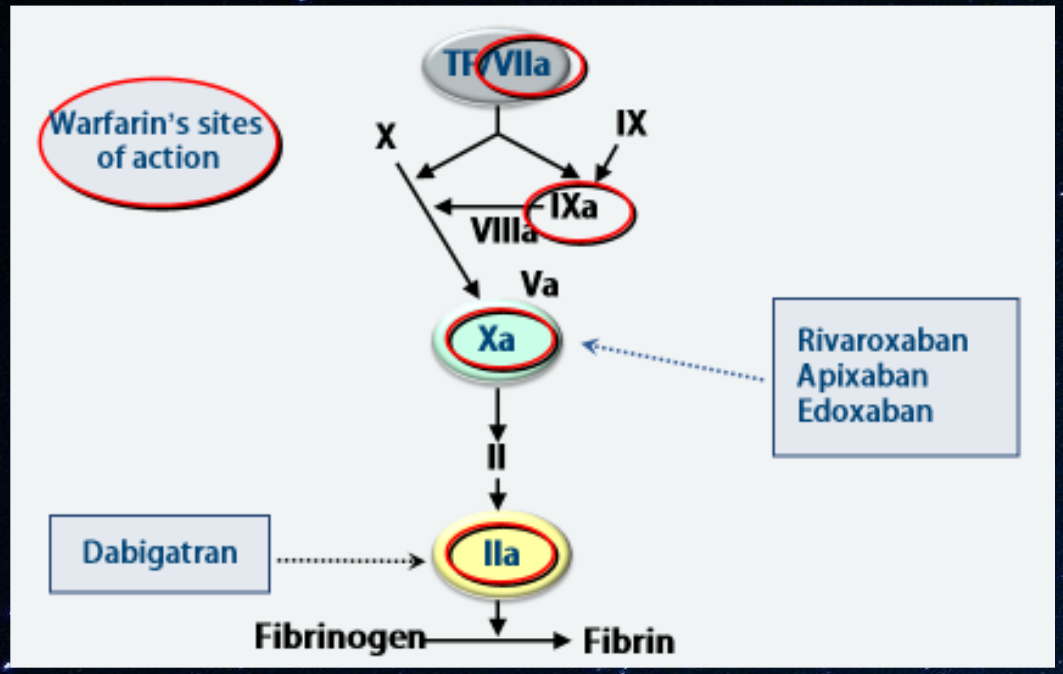
Living With Warfarin

"I feel my whole life is controlled by warfarin"
-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**

What if ……

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

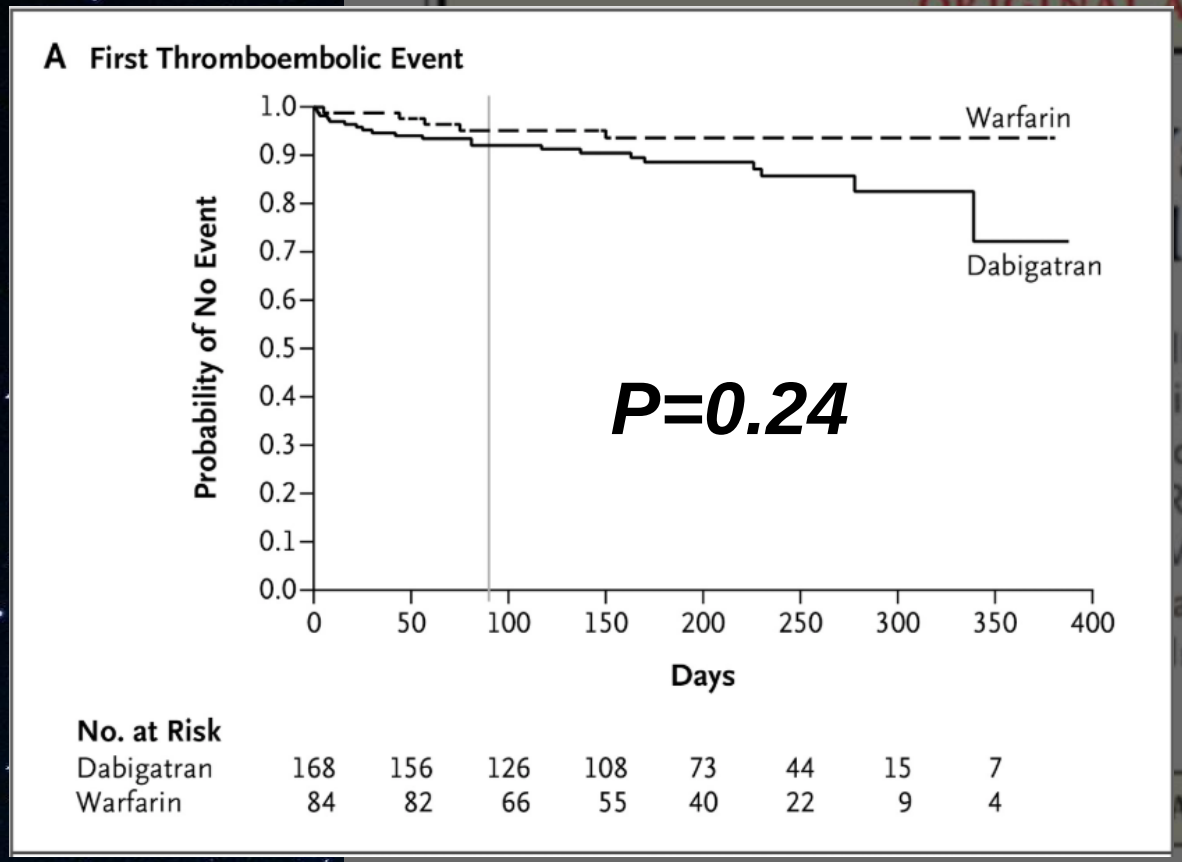
John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian 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*

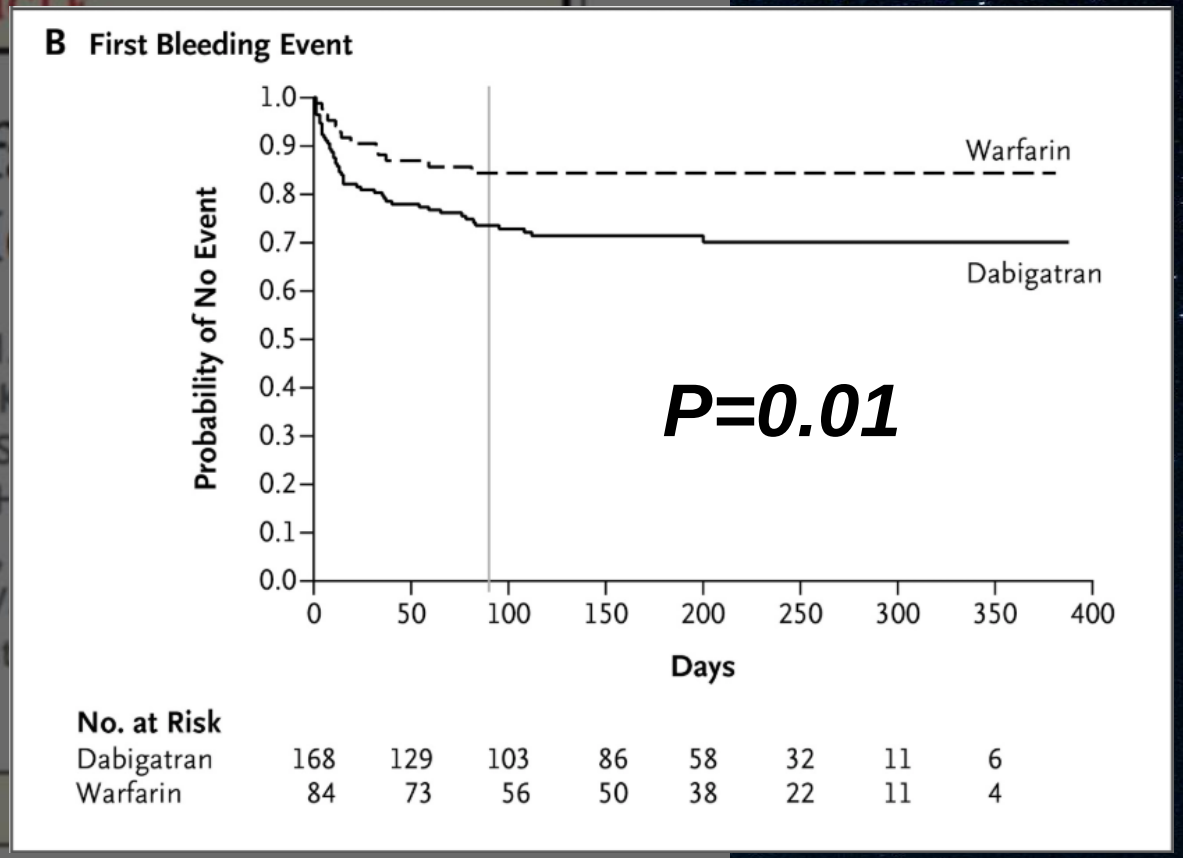
ABSTRACT

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE





BACKGROUND

NOAC for Mechanical Heart Valve

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

Circulation. 2018;138:1356–1365.

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RENOVATE Trial

Randomized **E**valuation of Lo**N**g-term Anticoagulation with **O**ral Factor Xa Inhibitor versus **V**itamin K Antagonist after Mechanical **A**or**T**ic Valve Replac**E**ment

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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 <15mL/min) or on hemodialysis
8. Left ventricular dysfunction: LVEF ≤40%
9. Hepatic impairment, or severe (Child-Pugh C) or with any hepatic disease associated with coagulopathy

Exclusion criteria

10. Clinically significant active bleeding
11. Bleeding or hemorrhagic disorder
12. The increased risk of bleeding
    a. History of gastrointestinal ulcers or active ulcerations within the last 6 months
    b. History of intracranial or intracerebral hemorrhage within the last 6 months
    c. Spinal cord vascular abnormalities or intracerebral vascular abnormalities
    d. History of the brain, spinal cord, or ophthalmic surgery within the last 6 months
    e. History of the brain or spinal cord injury within the last 6 months
    f. History of spinal tap, major regional anesthesia or, spinal anesthesia within the last 6 months
    g. Esophageal varices
    h. Arteriovenous malformation
    i. Vascular aneurysms
    j. Malignant tumor with a high risk of bleeding

Exclusion criteria

13. Bleeding tendencies associated with overt bleeding of
    a. gastrointestinal, genitourinary, respiratory tract or, colorectal cancer
    b. cerebrovascular hemorrhage
    c. aneurysms- cerebral, dissecting aorta
    d. pericarditis and pericardial effusions
    e. bacterial endocarditis
14. Hemodynamically unstable pulmonary embolism
15. Combination therapy with other anticoagulants
16. Uncontrolled moderate or severe hypertension
17. Hemoglobin level <10.0 g/dL or platelet count < 100 x 10x9/L
18. Infective endocarditis

Exclusion criteria

19. Hypersensitivity to Rivaroxaban or Vit K antagonist
20. Positive pregnancy test results, threatened abortion
21. Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption
22. Terminal illness with life expectancy <12 months
23. Vitamin K deficiency
24. Alcoholic or psychical disorder
25. Concomitant use with antiplatelet due to history stroke, TIA or ACS

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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 UniversitySeverance 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

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PROACT Xa Trial Issue

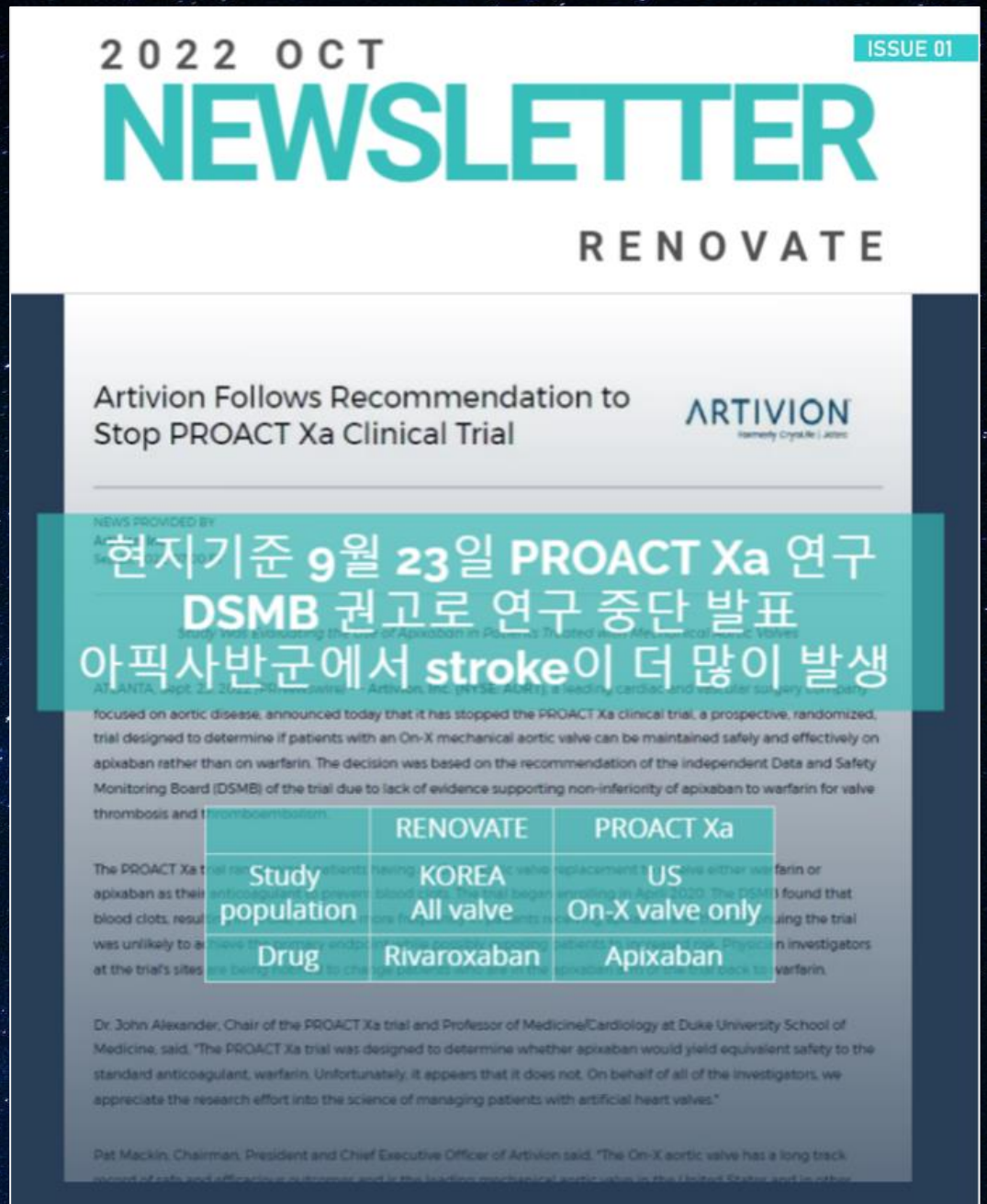
PROACT Xa 중지로 인하여 본 과제 DSMB 실시

PROACT Xa 연구와 RENOVATE 연구를 비교하여 보았을 때,
(1) 같은 계열이나 약이 다르고
(2) 대동맥 판막치환에 사용되는 인공밸브의 종류가 다르며
(3) 인구학적 특성이(ethnicity) 다른 점을 고려하여
본 연구는 일단 지속하되, 향후 Endpoint event, SAE 발생 시마다 DSMB에 관련 의무기록과 함께 제출하여(on a blined basis)
본 연구의 Risk & Benefit을 판단하여 균형이 깨지는 것으로 간주되면 연구 중단 예정임.

해당 DSMB 내용에 대해 식약처 안전성보고 진행

각 기관별 IRB에 따라 UP보고 진행

매년 12월 Safety report 전달 예정


2022 OCT

ISSUE 01

NEWSLETTER

RENOVATE

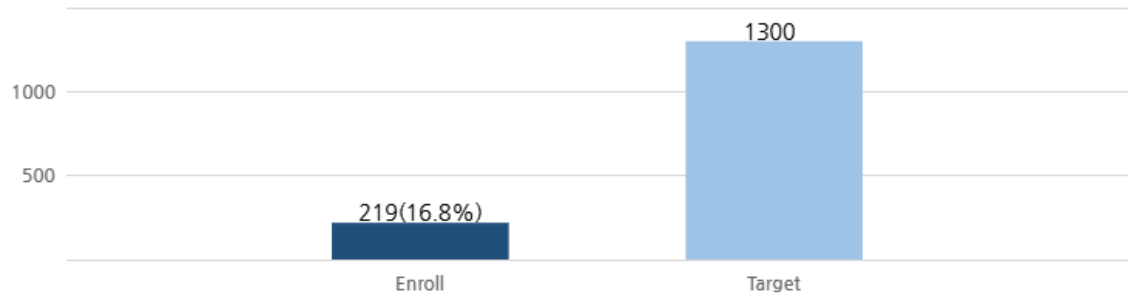
Artivion Follows Recommendation to Stop PROACT Xa Clinical Trial

ARTIVION

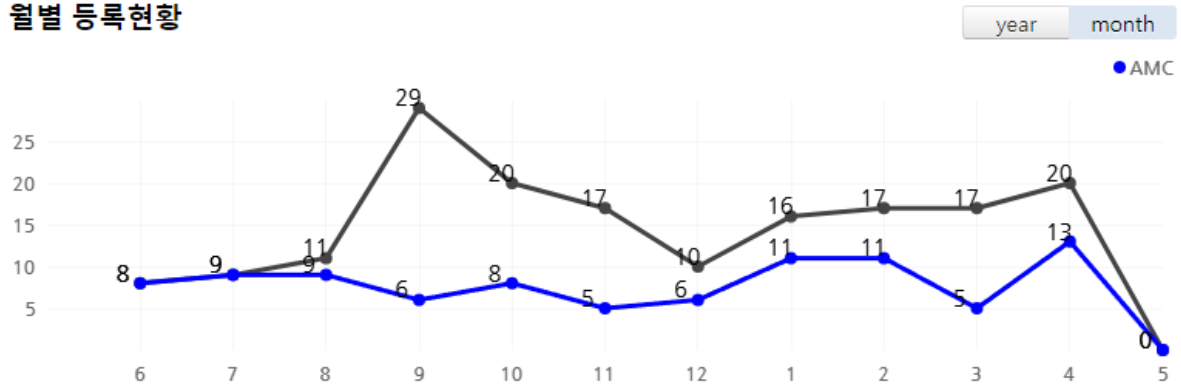
현지기준 9월 23일 PROACT Xa 연구 DSMB 권고로 연구 중단 발표
아픽사반군에서 stroke이 더 많이 발생

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

목표대비 등록현황

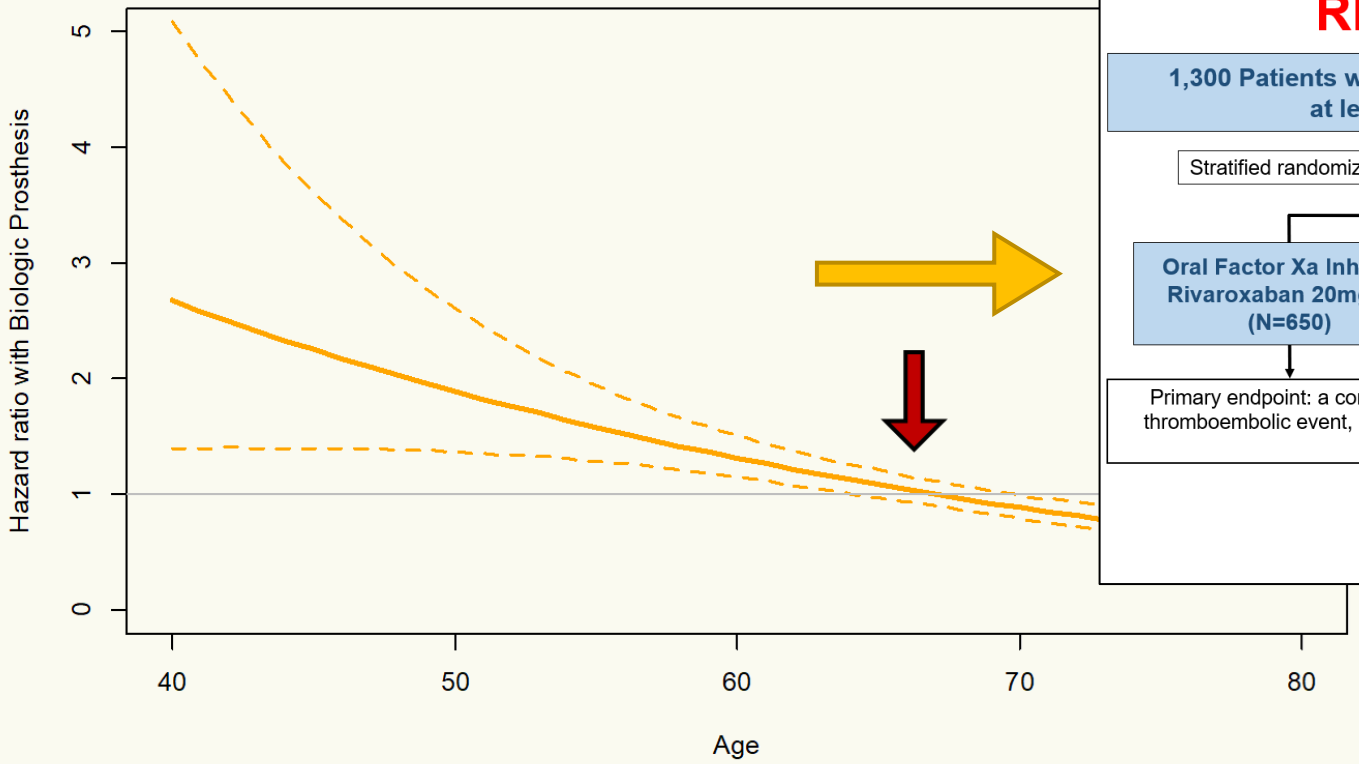


월별 등록현황



National Data in Korea

Age-Dependent Adjusted Survival in AVR



***R**andomized **E**valuation of Lo**N**g-term Anticoagulation with **O**ral Factor Xa Inhibitor versus **V**itamin K Antagonist after Mechanical **A**or**T**ic Valve R**E**placement*

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