ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

Next Target for Valve Pharmacology:

Mechanical Valve Revisited with NOAC

RENOVATE Trial

Joon Bum Kim, MD, PhD

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

Thrombo-embolism

Hemorrhage

Valve reoperation

National Data in Korea

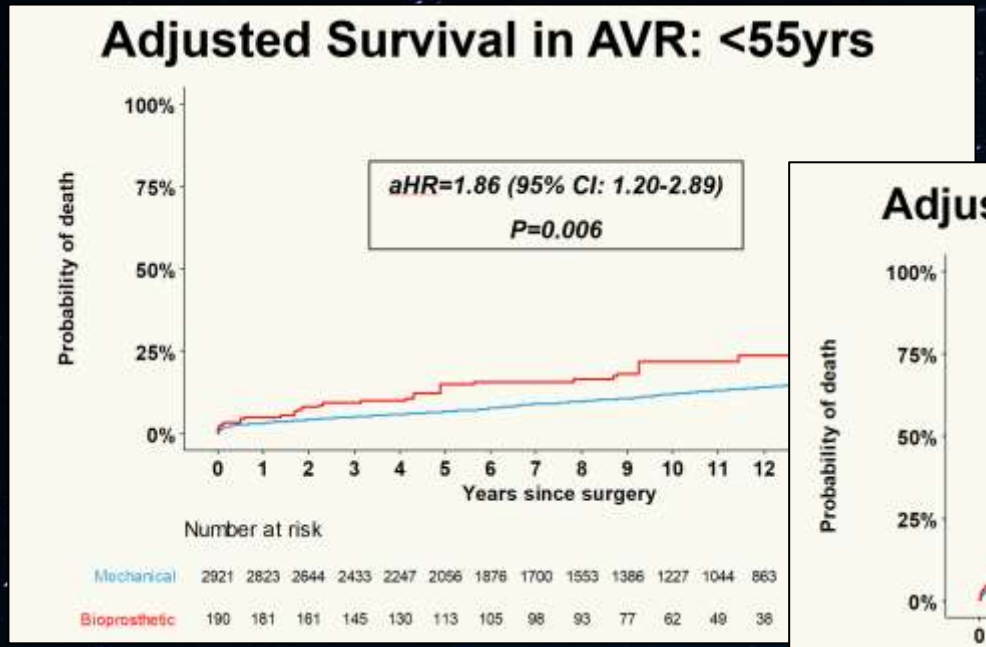
NHIS Database, AVR

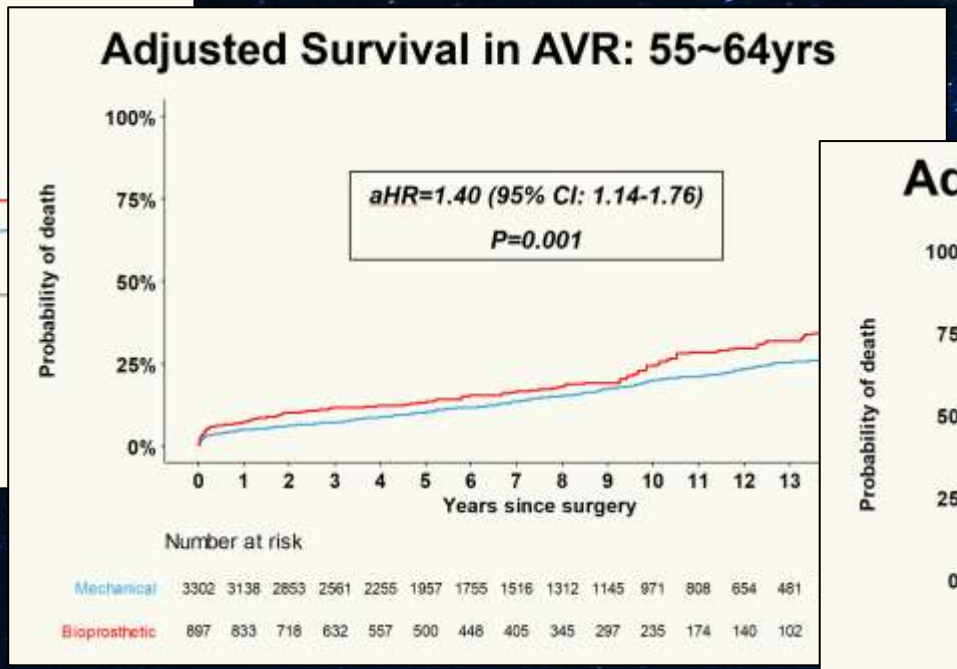
Between 2003 and 2018

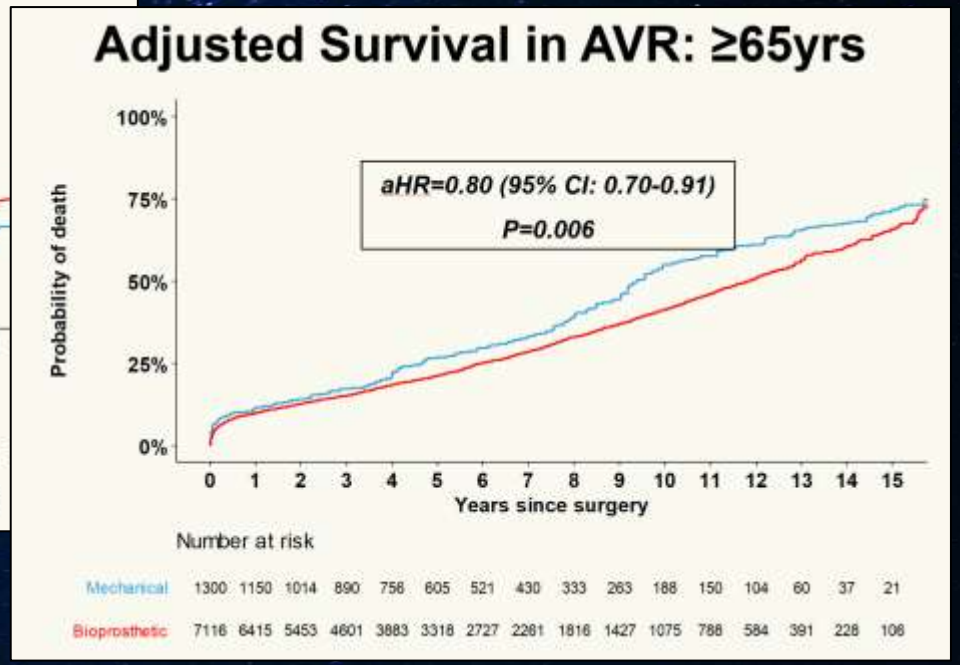
Age: 40-80yrs

N = 15,726

National Data in Korea

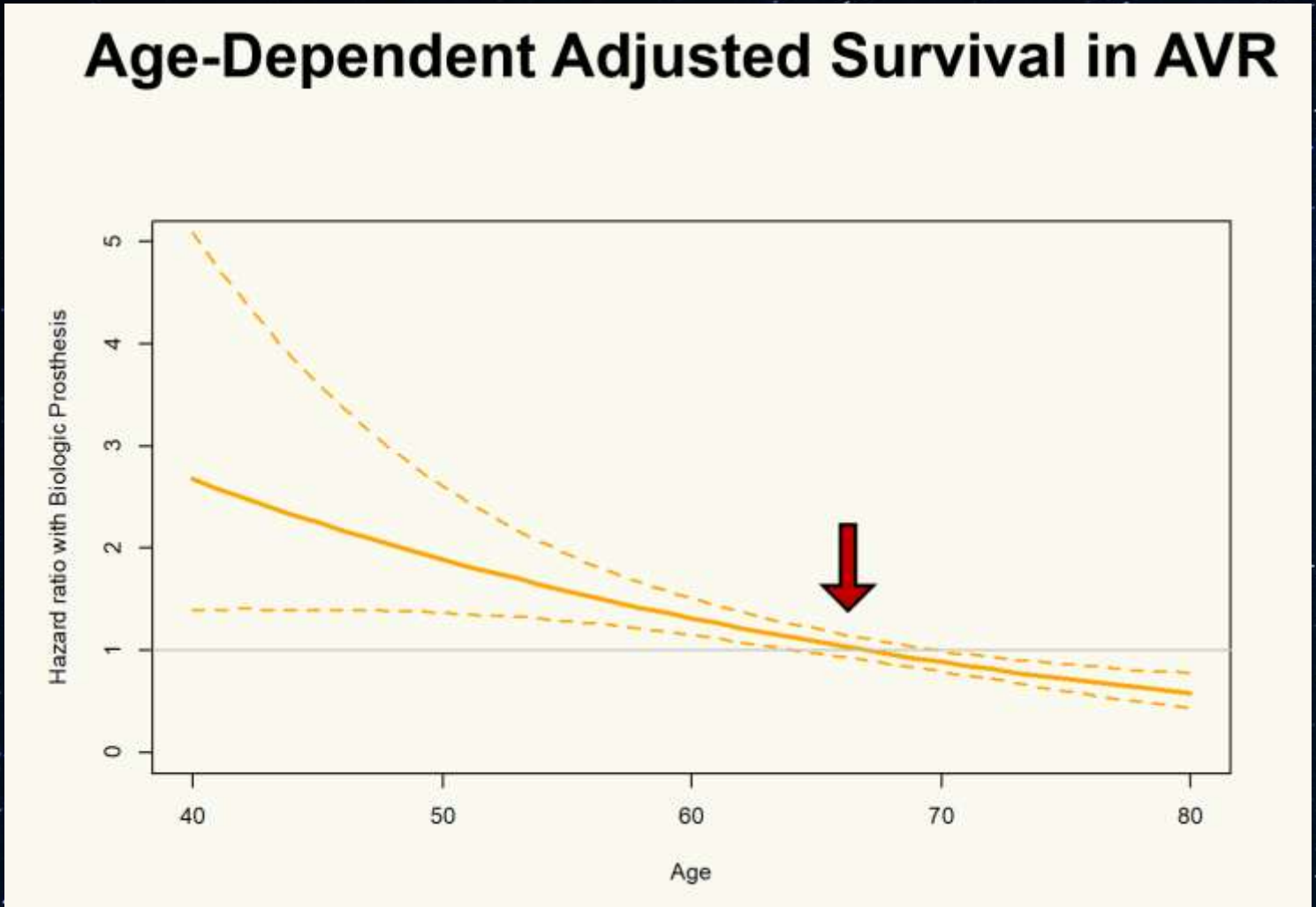






Presented in 2022 AATS, under peer review

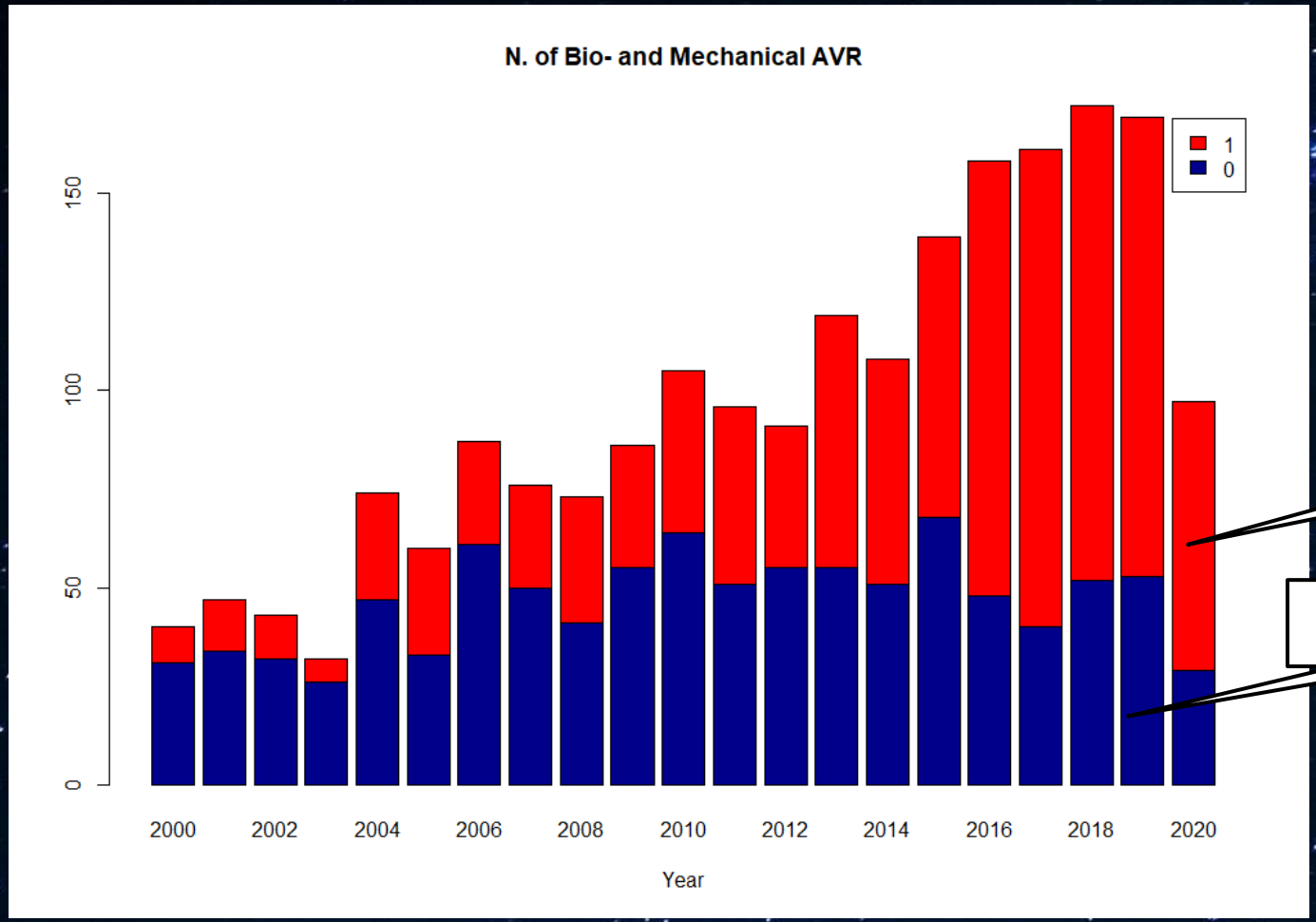
National Data in Korea



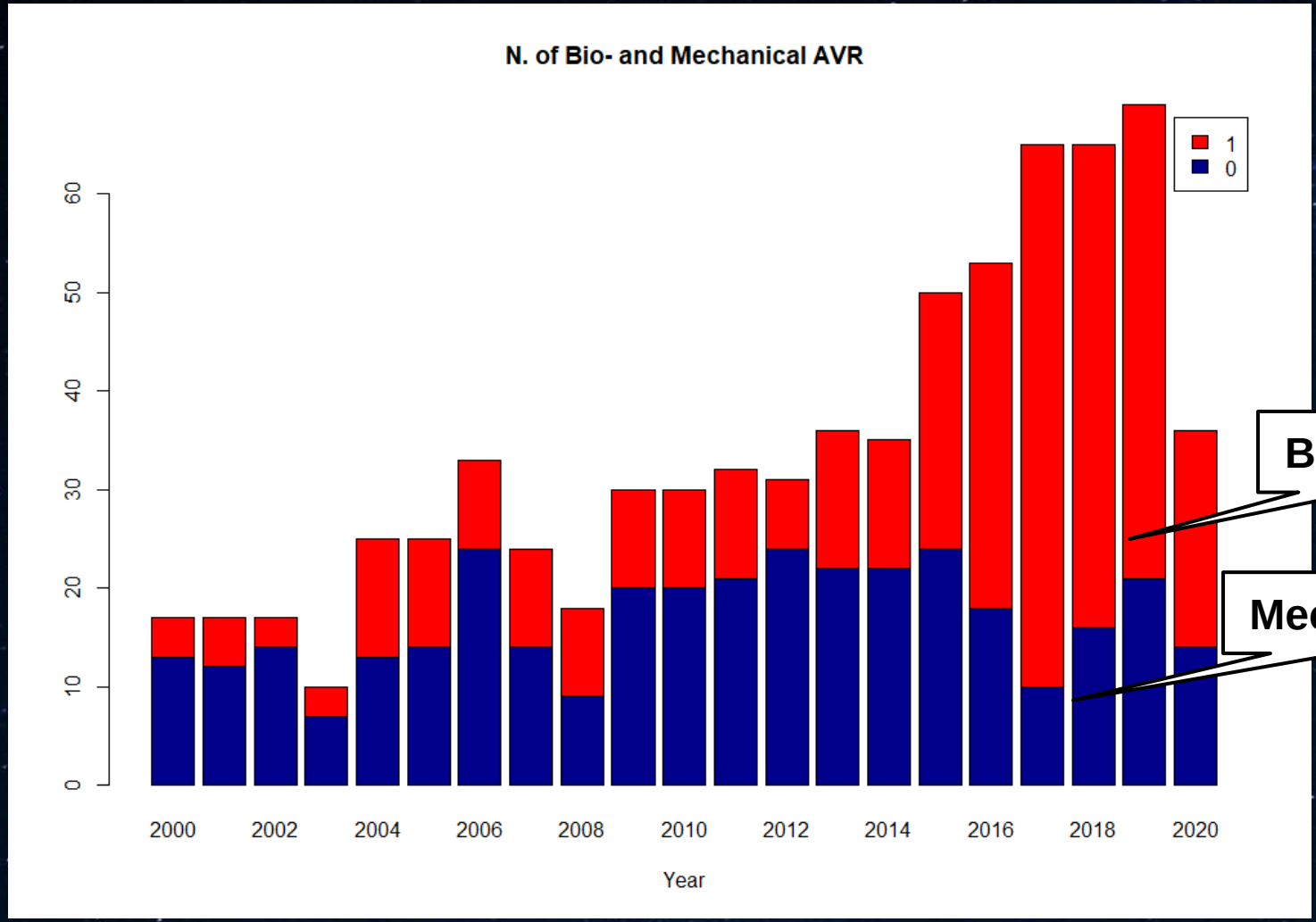
Presented in 2022 AATS, under peer review

Bio and Mechanical AVR: All age

2000-2020 AMC



Bio and Mechanical AVR: Age >=60, <70 yrs

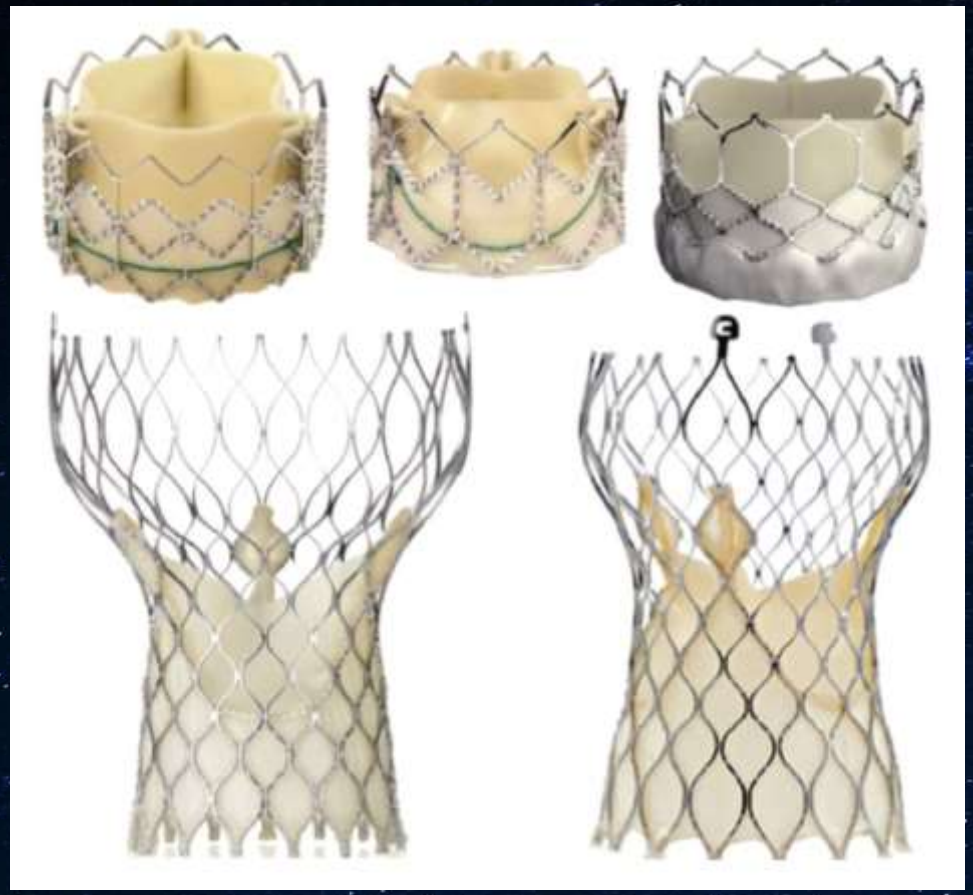


Living With Warfarin

"I feel my whole life is controlled by warfarin"

-www.afa.org.uk-

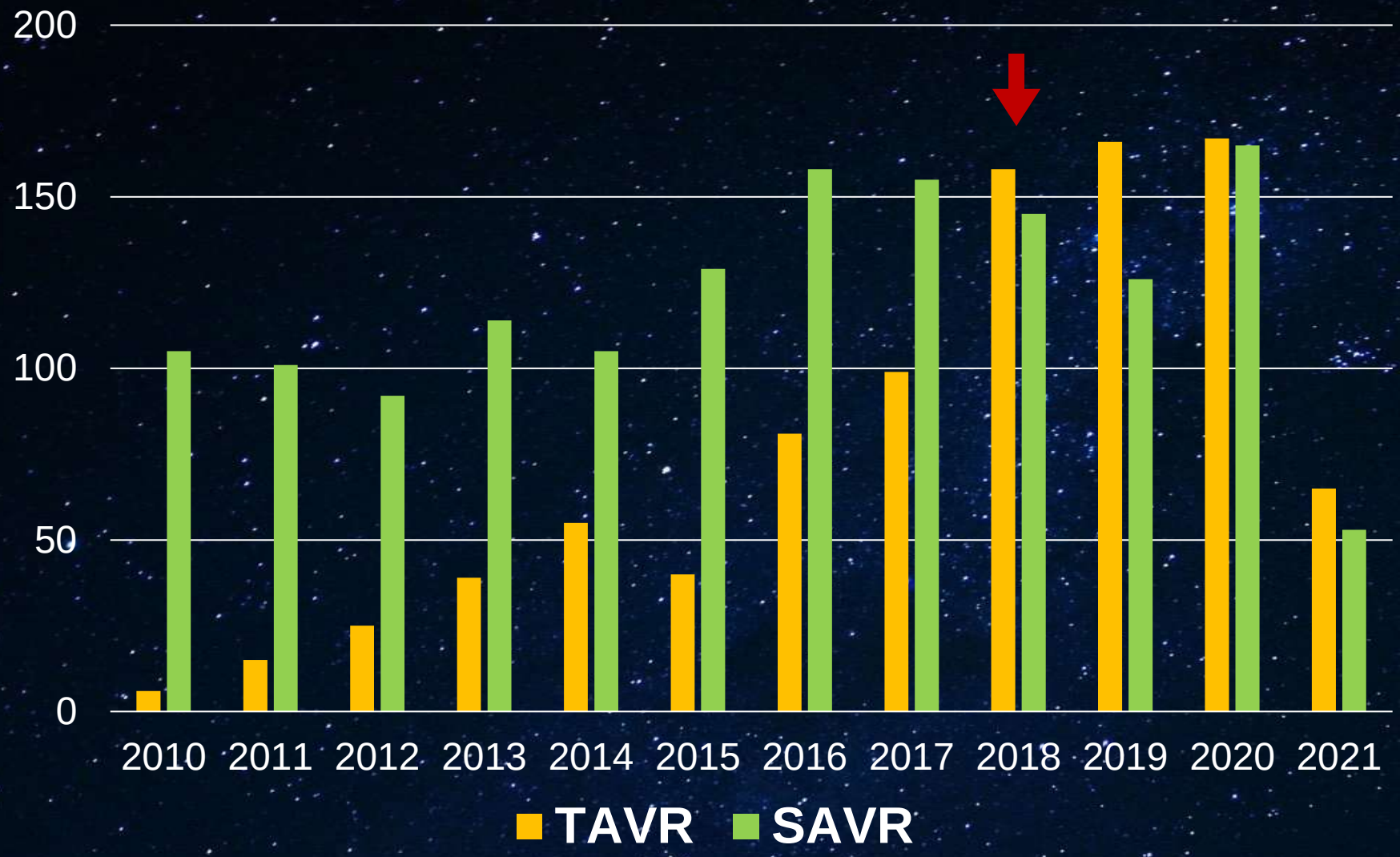
- Regular **blood test** at least once a 12 weeks: even shorter in fluctuating INR
- Don't make changes to your **diet or alcohol intake** – consistency is the key
  - Green leafy vegetables
  - Eat same amount of these foods each week to help keep your INR stable
- Check before starting a **new medicine**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



ASAN Medical Center

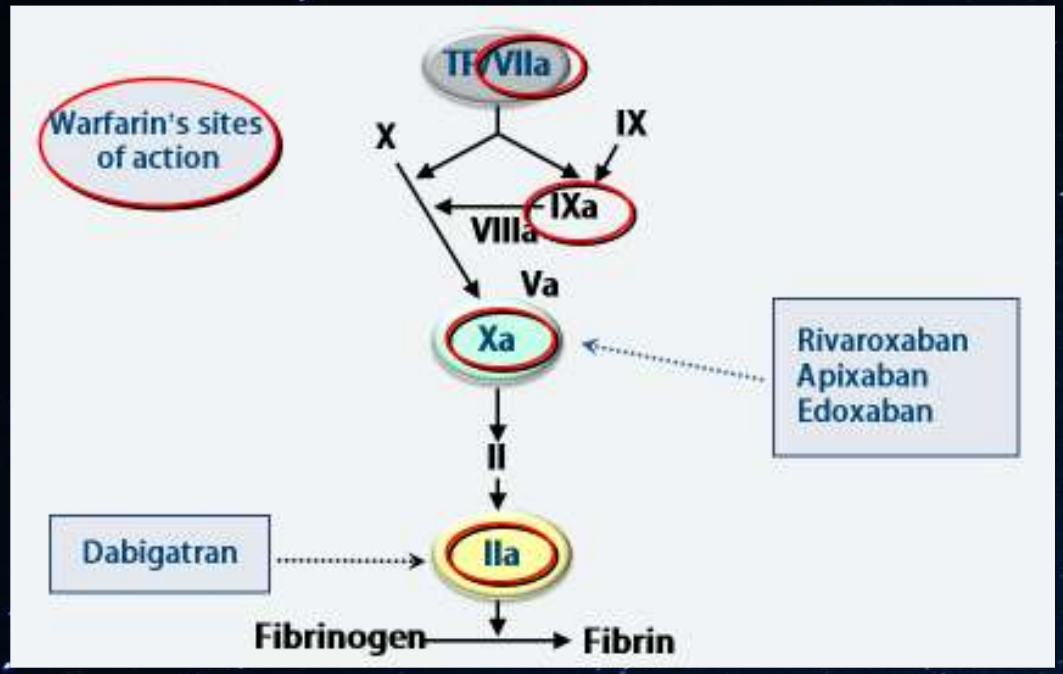
UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

Trends in AMC



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

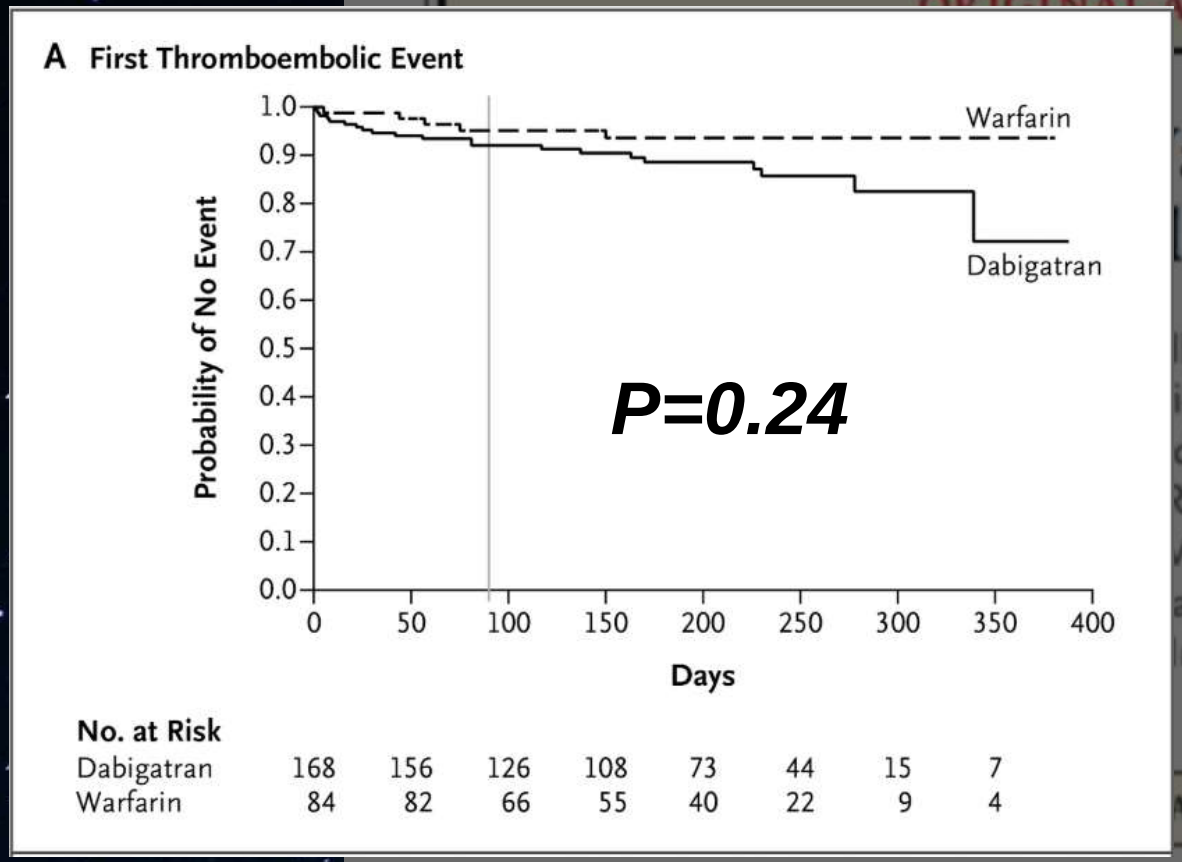
John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian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

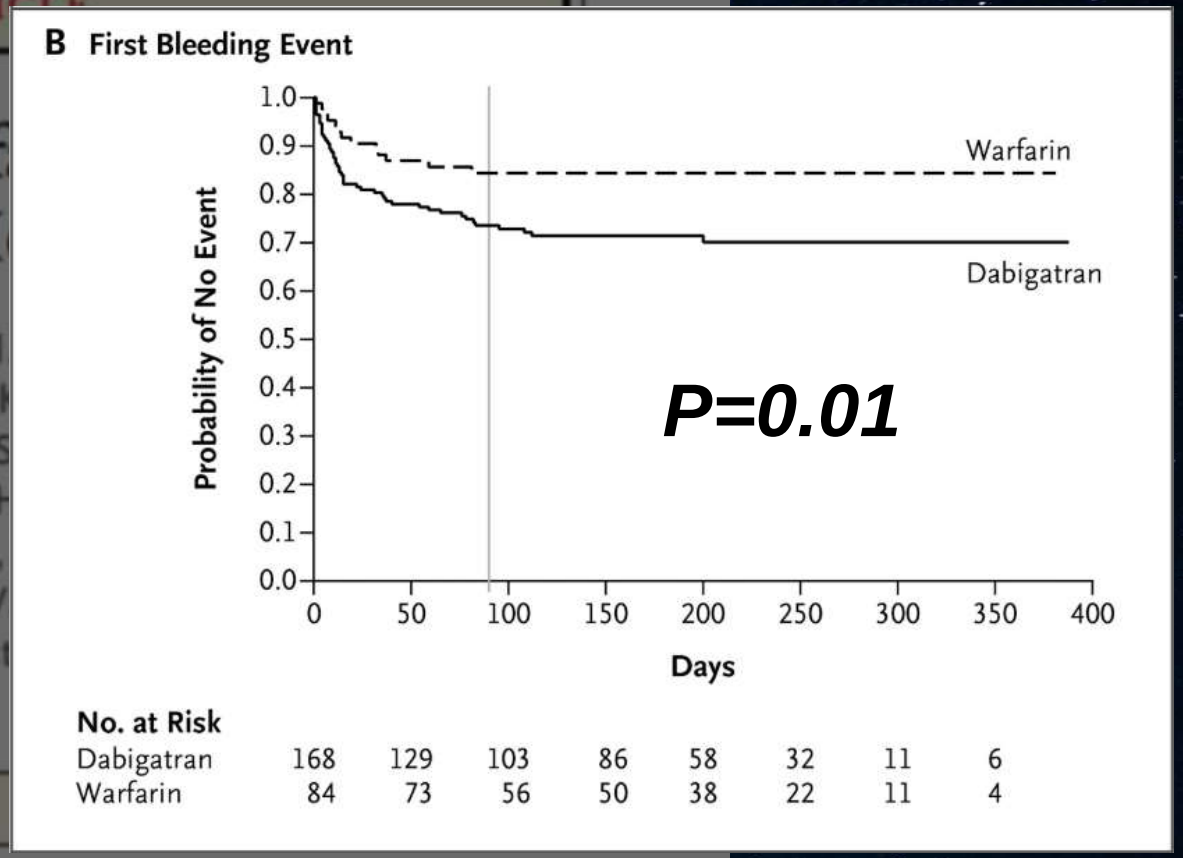
ABSTRACT

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

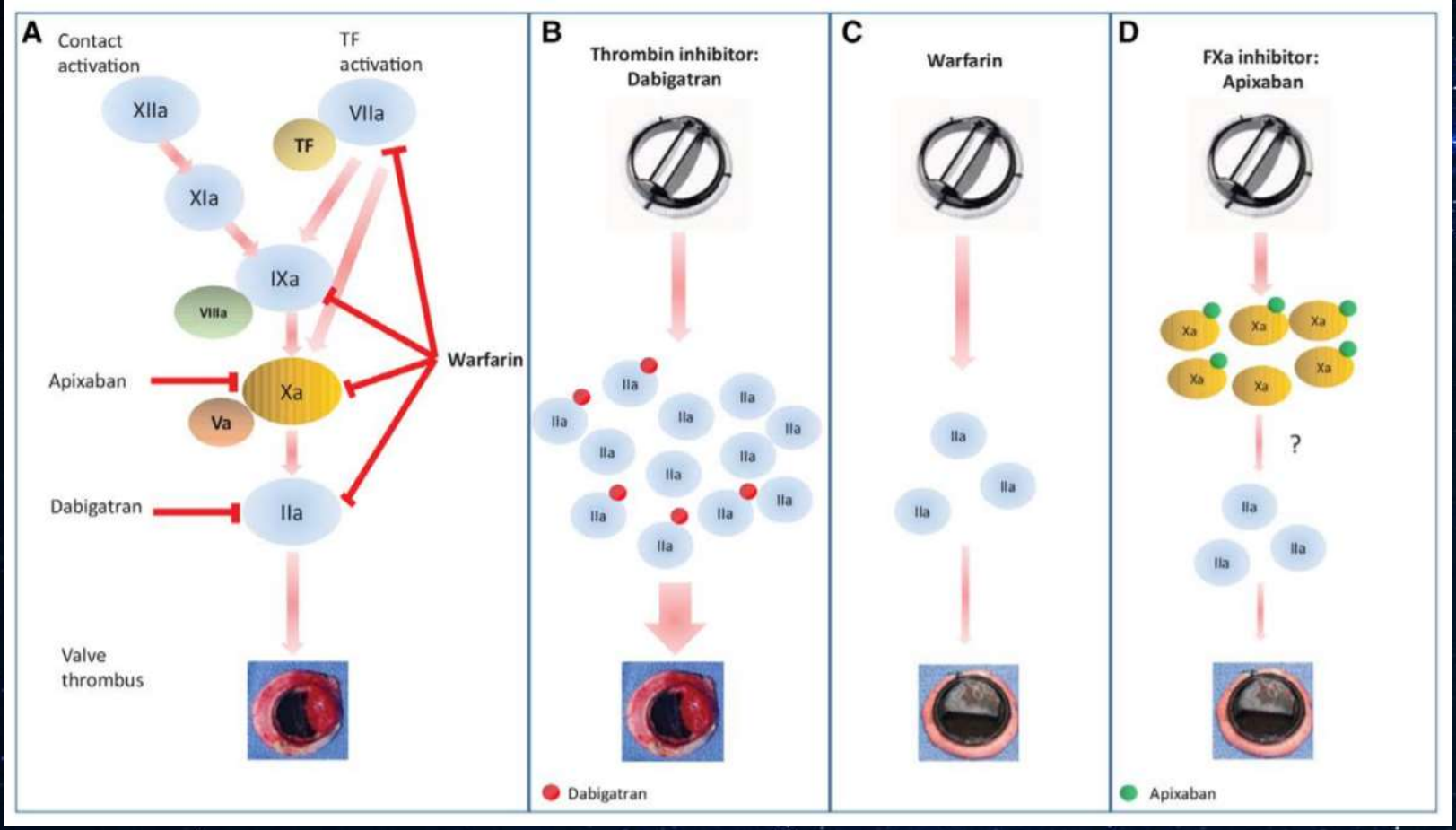




BACKGROUND

Lesson from the Re-Align Trial:

1. Drug Choice: Dabigatran



Factor X :
x1000 of Factor II

Noel C. Chan et al. Arterioscler Thromb Vasc Biol. 2017;37:743-745.

Lesson from the Re-Align Trial:

2. Dose Escalation

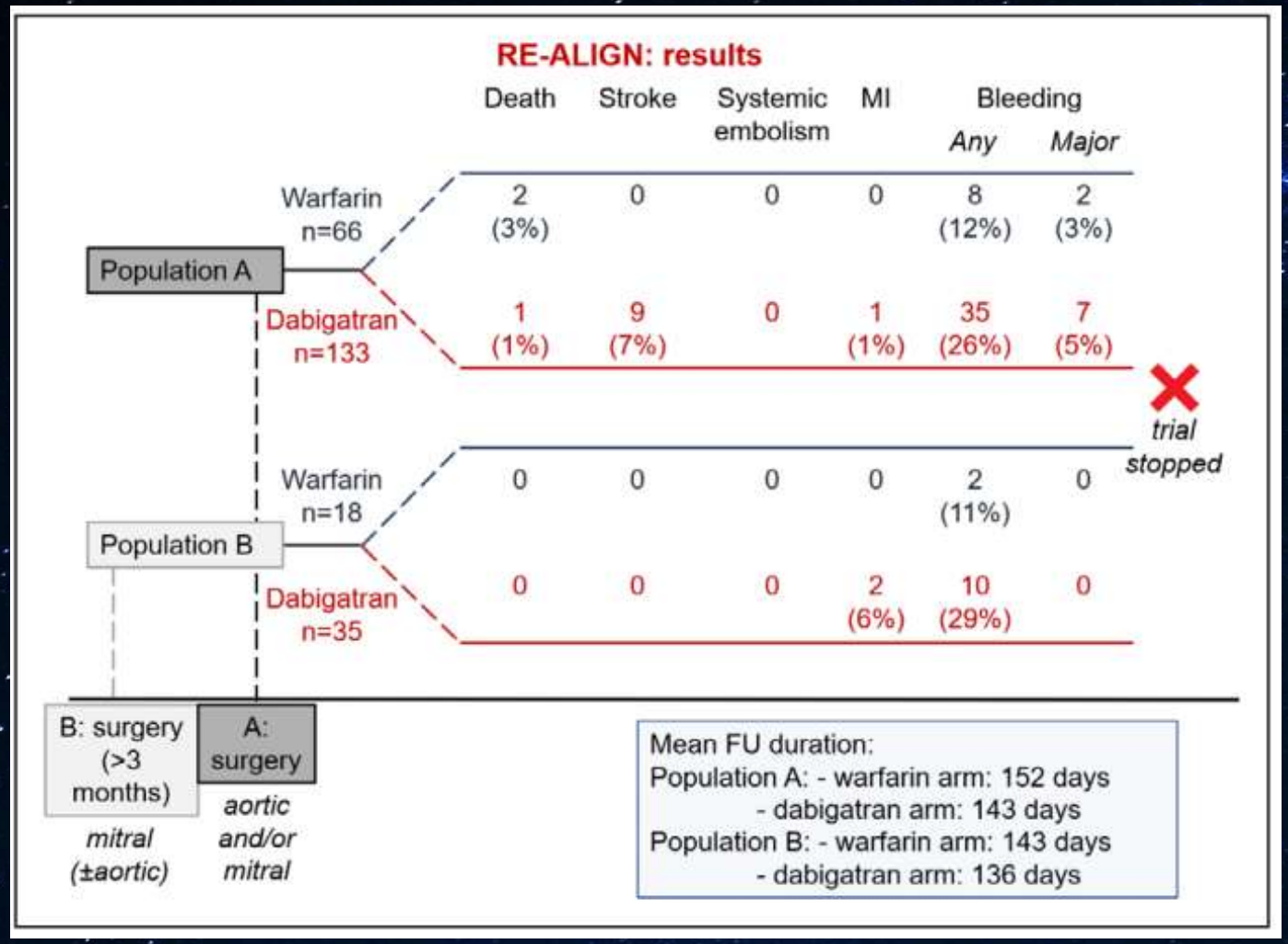
Table 2. Patients Requiring Dose Escalation or Discontinuation of Dabigatran and Mean Percentage of Time above the Target Trough Plasma Level of Dabigatran.*

Dabigatran Dose	Population A (N=127)		Population B (N=35)		All Patients (N=162)	
	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡
All doses	47/127 (37)	84	5/35 (14)	96	52/162 (32)	86
150 mg twice daily	4 /11 (36)	99	2/13 (15)	98	6/24 (25)	98
220 mg twice daily	32/71 (45)	84	1/16 (6)	100	33 /87 (38)	87
300 mg twice daily	11/45 (24)	79	2/6 (33)	83	13/51 (25)	79

Target blood concentration: >50ng/mL

Lesson from the Re-Align Trial:

3. Timing of Medication

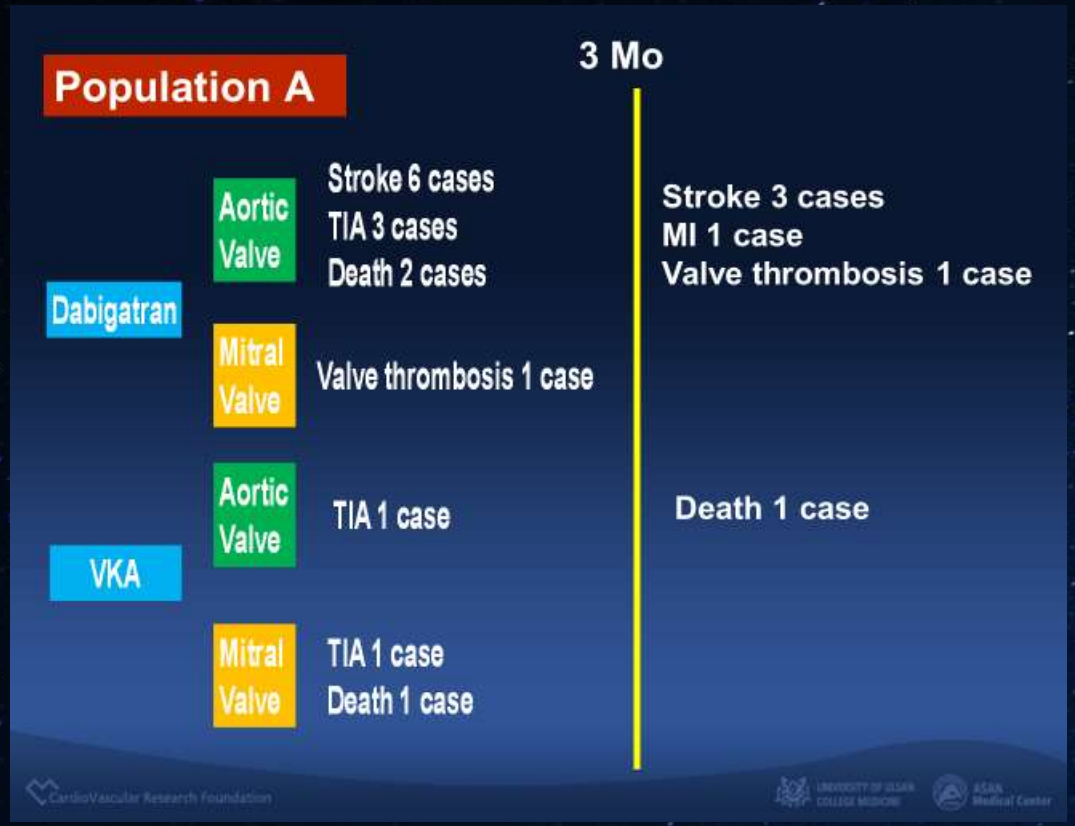


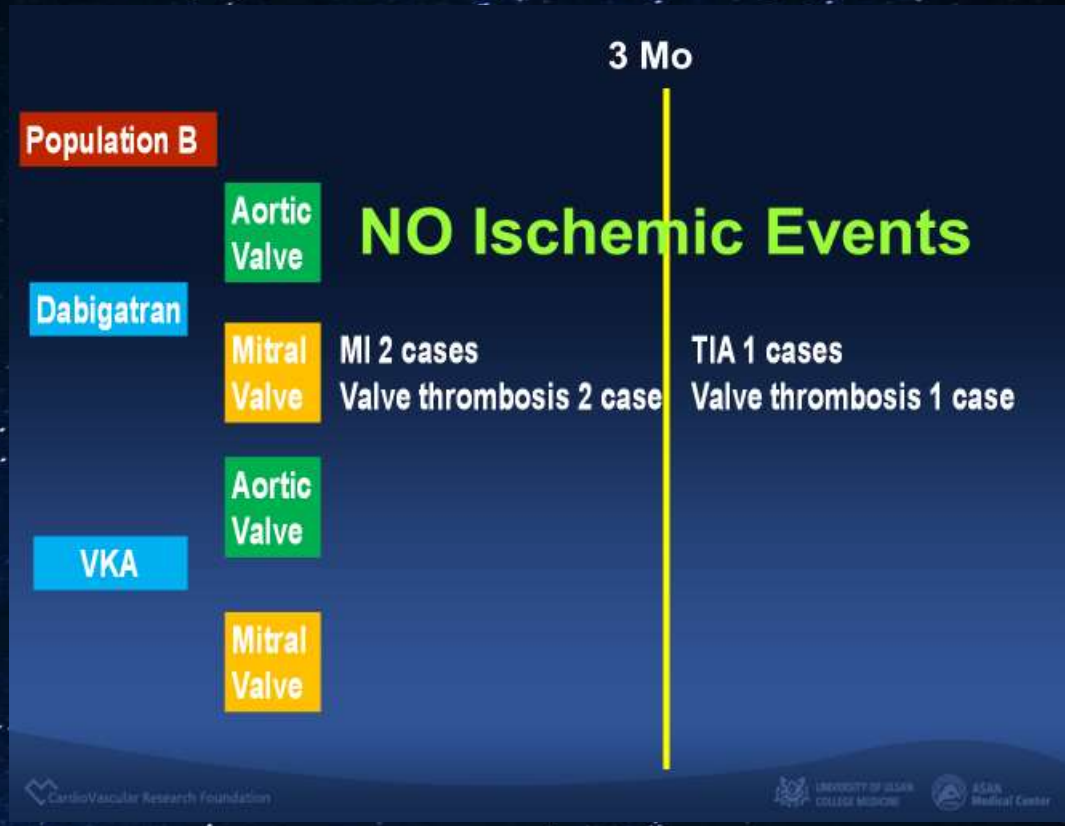
ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

Lesson from the Re-Align Trial:

3. Timing of Medication





Lesson from the Re-Align Trial:

4. Valve Position

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dabigatran (N=168)	Warfarin (N=84)
Type of valve-replacement surgery — no. (%)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)

MVR > 30%

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.

PROACT Xa Trial

INCLUSION
- On-X aortic valve replacement > 3 months prior
- Able to receive warfarin with target INR 2-3
- At least 18 years of age

Randomize
n~1100 patients
On-X aortic valve replacement > 3 months prior

EXCLUSION
- Non-aortic mechanical valve
- Requiring ASA > 100 mg daily or P2Y12 inhibitor
- Apixaban hypersensitivity
- Creatinine clearance < 25 ml/min
- Ischemic or hemorrhagic stroke in prior 3 months
- Active bleeding, pregnancy, or unable to consent
- On concomitant combined P-gp and strong CYP3A4 inducers

Apixaban 5 mg BID Apixaban 2.5 mg BID in selected patients	Open Label	**Continued warfarin** INR goal 2.0 – 3.0

2 year follow-up

Primary endpoint: composite of valve thrombosis, valve-related thromboembolism, valve thrombosis related mortality

Secondary endpoints: components of primary composite endpoint, major bleeding

Study Chair: Lars Svensson, MD, PhD and John Alexander, MD

ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

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

ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

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 yrs and more
2. At least 3months 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

ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

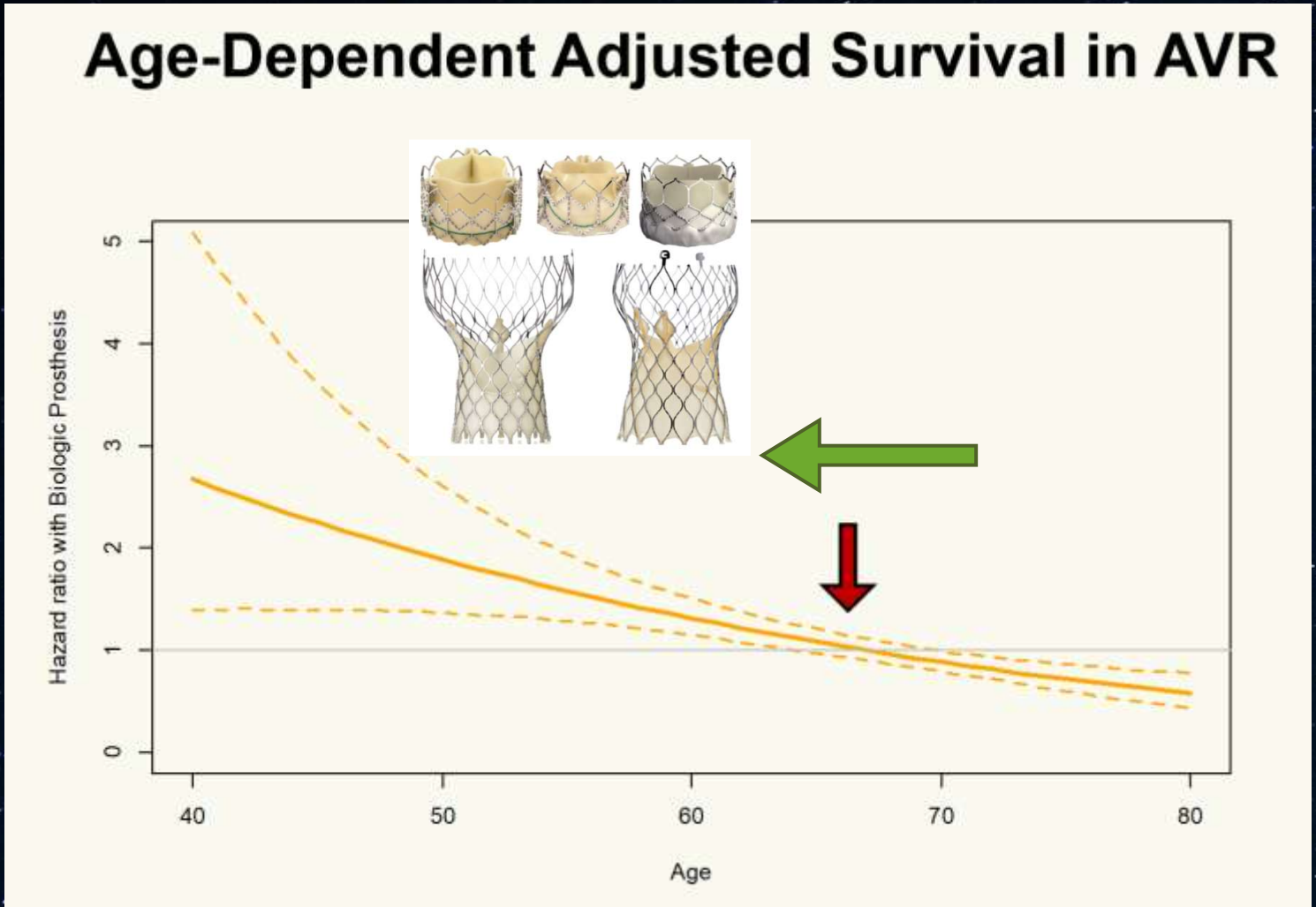
Randomized Evaluation of LoNg-term Anticoagulation with Oral Factor Xa Inhibitor versus Vitamin K Antagonist after Mechanical AorTic Valve REplacement

RENOVATE Trial

Participating Centers

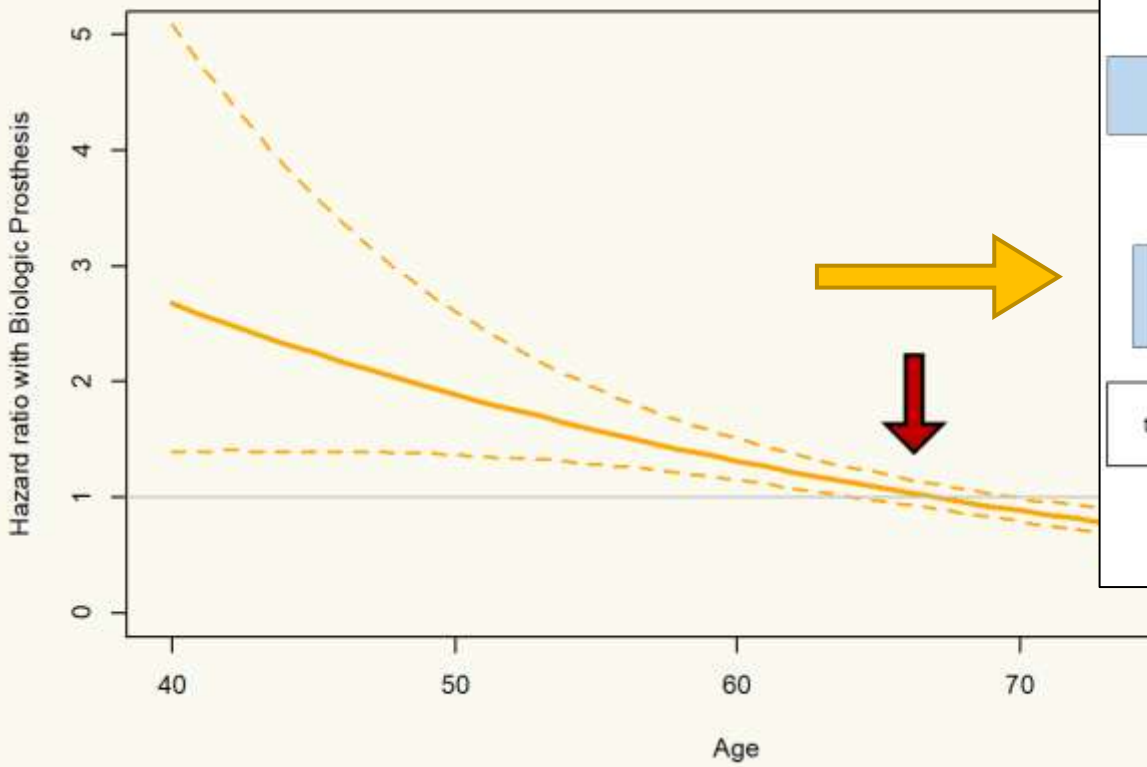
1. Asan Medical Center
2. Bucheon Sejong Hospital
3. Pusan National University Yangsan Hospital
4. Yonsei UniversitySeverance Hospital
5. Seoul National University Hospital
6. Samsung Medical Center
7. Gangneung Asan Medical Center
8. Korea University Anam Hospital
9. Chonnam National University Hospital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

National Data in Korea



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

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	Vitamin K Antagonist
Rivaroxaban 20mg QD	INR 2.0 ~ 3.0
(N=650)	(N=650)

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

ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

Looking forward seeing exciting future