PROACT Xa

PROACT Xa and the Wizard of Oz

Behind the Curtain of a Pragmatic Decentralized Clinical Trial

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Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

ARTIVION™
Formerly CryoLife | Jotec

Disclosures

PROACT Xa

- **PROACT Xa was sponsored by Artivion (formerly CryoLife)**
- **Research Grants:** Artivion/CryoLife, Bayer, Bristol-Myers Squibb, CSL Behring, Ferring, U.S. FDA, U.S. NIH
- **Advisory Board/Consulting:** AbbVie, Akros, Artivion/CryoLife, AtriCure, Bayer, Bristol-Myers Squibb, Ferring, GlaxoSmithKline, Humacyte, Janssen, Novostia, Pfizer, Portola, Veralox

In 2017 two men walked into my office at DCRI

PROACT Xa

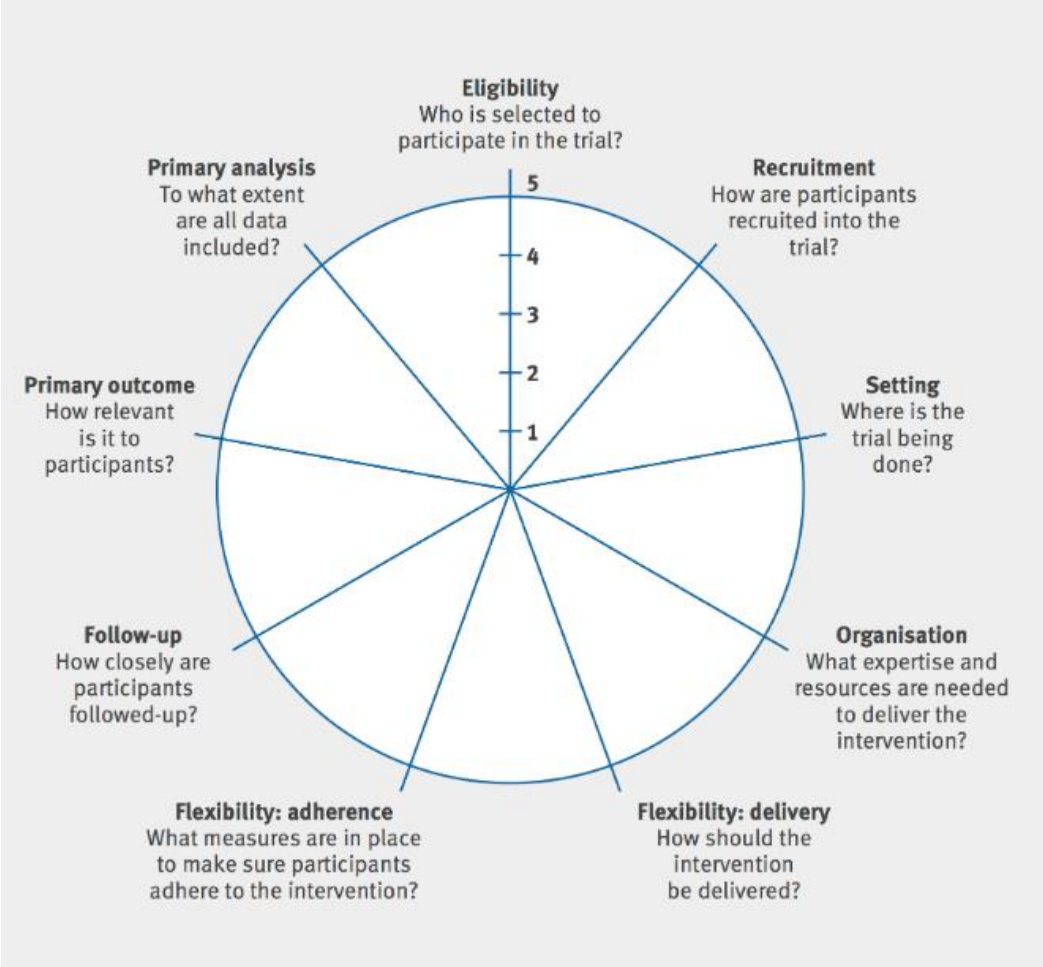
- Pat Mackin and Scott Capps – CryoLife
- The On-X mechanical heart valve might need less intense oral anticoagulation than other mechanical heart valves
- Wanted to study the FXa inhibitor apixaban vs warfarin (SOC) to prevent valve related thromboembolic events in patients with an On-X aortic valve replacement
- And as a device manufacturer, they have a registry of all the patients with On-X aortic valve replacement in the US including…..
  - When the valve was implanted
  - Where (hospital) the valve was implanted
  - Who (surgeon) implanted the valve
  - The patient's name and address

Novel approaches to clinical trials

- Pragmatic
- Embedded
- Decentralized

- Quality by Design (Martin Landry)
  - "Just think"
  - Quality = the absence of errors that matter

PRECIS 2 – Pragmatism



https://www.precis-2.org/
PRECIS 2 BMJ 2015;350:h2147

Novel approaches to clinical trials

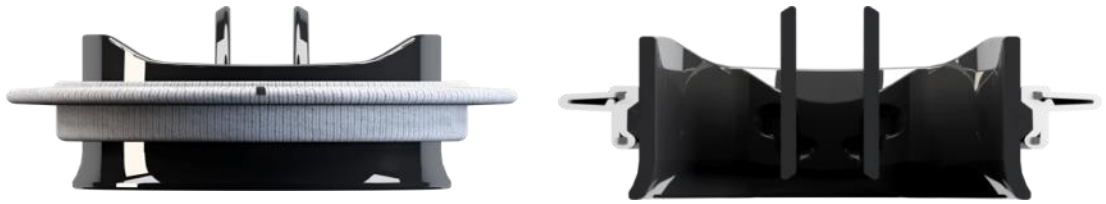
prag·mat·ic

adjective

dealing with things sensibly and realistically in a way that is based on practical rather than theoretical considerations

Hypothesis

Patients with an On-X mechanical valve implanted in the aortic position can be maintained on a factor Xa inhibitor (apixaban) with a safe level of thromboembolic events compared to standard warfarin



Design

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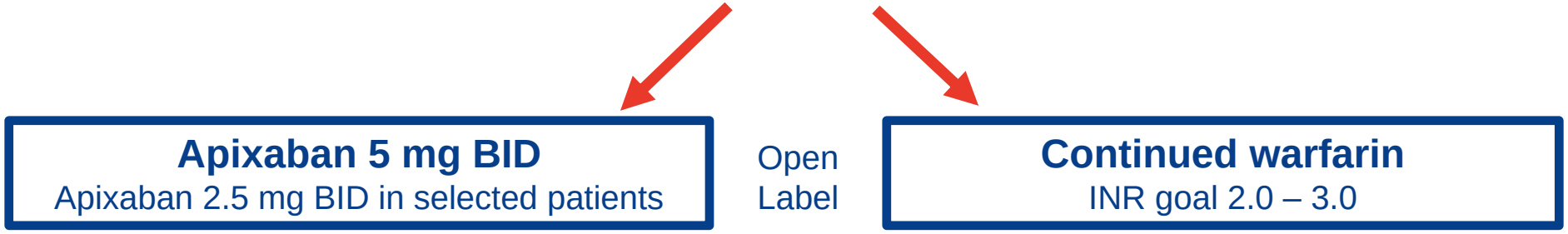
*Stratified by whether the On-X valve was implanted ≥ or < 1 year before randomization

Patients with On-X aortic valve replacement >3 months prior (n=1000)

Randomize*



Concomitant Low-Dose Aspirin
Follow-up for ≥800 pt-yrs in each group

Primary efficacy endpoint: composite of valve thrombosis or valve-related thromboembolism

Primary Safety endpoint: major bleeding

Study Organization

PROACT Xa

STEERING COMMITTEE

John H. Alexander, MD, MHS (Co-Chair)
Lars Svensson, MD (Co-Chair)
Tracy Y. Wang, MD, MHS (PI)
Richard C. Becker, MD
Eugene Blackstone, MD
Marc Gerdisch, MD
Douglas Johnston, MD
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John D. Puskas, MD
Marc Ruel, MD
Marshall Stanton, MD
Vinod Thourani, MD

COORDINATING CENTER

Duke Clinical Research Institute

INVESTIGATORS & COORDINATORS FROM 64 US SITES

PARTICIPANTS

863 patients with an On-X mechanical aortic heart valve

SPONSOR

Artivion (formerly CryoLife)

DATA SAFETY MONITORING BOARD

Robert P. Giugliano, MD (Chair)
Elaine M. Hylek, MD, MPH
Sidney Levitsky, MD
Richard Whitlock, MD
Karen S. Pieper, MS

Eligibility Criteria

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Inclusion Criteria

- On-X aortic valve placed ≥3 months ago
- Age ≥18 years
- Able to receive warfarin with target INR 2-3
- Able to take aspirin 75-100 mg daily or have a documented contraindication

Exclusion Criteria

- Mechanical valve in any other position
- Any cardiac surgery in 3 months
- Ischemic stroke or ICH within 3 months
- Creatinine clearance <25 ml/min
- Concomitant combined P-gp and strong CYP3A4 inducers

Endpoints and Analyses

Primary Efficacy Endpoint: Composite of valve thrombosis or valve-related thromboembolism (myocardial infarction, stroke, TIA, arterial thromboembolism)

Primary Safety Endpoint: Major bleeding that caused death, hospitalization, transfusion, pericardiocentesis, or reoperation

Co-Primary Analyses:

1. Noninferiority: upper bound of the 95% confidence interval of the apixaban minus warfarin event rate less than the noninferiority margin of 1.75%/pt-yr
2. Comparison with objective performance criteria (OPC): apixaban event rate less than 2 times the OPC for VT/TE of 1.70%/pt-yr (3.40%/pt-yr)

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ORIGINAL ARTICLE

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

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Operational Design Elements

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- Potential patients from Artivion valve implant data (site selection and patient lists)
- Centralized outreach to all potential patients (On-X AVR) with site matching
- Potential for remote informed consent & enrollment
- Local labs (hemoglobin, platelets, creatinine) for eligibility and during trial from any local lab
- Study drug (apixaban or warfarin) distributed from central pharmacy directly to participants
- Remote telephone follow-up with standardized script for event ascertainment
- Potential transfer of patients from one site to another
- Medical records collected for suspected event adjudication
- No adverse event collection (including serious AEs) other than thromboembolic events, bleeding, and On-X valve dysfunction, all of which were collected on the eCRF

Conclusions

- The “right” trial design/operational plan depends on the specifics of the trial
- There are lots of innovative approaches that are feasible
- It is really important that we share experience with these approaches within the research community
- It is better to ask for forgiveness than permission

Artivion On-X AVR implant data

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In the last 3 years

- 10,099 On-X implants (aortic position) in the US and Canada
  - 9,076 in US
  - 1,023 in Canada
- 4,489 On-X implants (aortic position) in top 50 hospitals/sites

	2016	2017	2018	Average
Total (all hospitals)	2,212	3,211	3,575	2,999
• US	1,983	2,922	3,196	2,700
• Canada	229	289	379	322

Potential patients from Artivion valve implant data

Site selection and patient lists

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- Potential for single center decentralized clinical trial
  - Elected to engage sites to leverage surgeon/patient relationships
- Sites selected based on On-X AVR volume
- Provided lists of potential participants to sites

Centralized outreach to all patient w/ On-X AVR

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- Artivion central outreach by mail to all US patients w/ On-X AVR
- Directed to clinical trials.gov
  - Listed all recruiting sites
- Several sites could enroll participants from outside of their system
  - Regional or state based requirement from local IRBs
- Central recruiting options for “unaffiliated” patients
  - Duke/DCRI (discussed)
  - Yale and Multicare/Tacoma

Potential for remote informed consent & enrollment

- Decision regarding remote enrollment left to local IRBs
- Central IRB (WCG) covered roughly 50% of centers
  - Allowed remote informed consent & enrollment
  - >50% of remaining sites also allowed remote informed consent & enrollment
- Emphasized potential for remote consent and enrollment in site training
- COVID helped a great deal
- People travel for AoV surgery. Established relationship with surgeon
- State licensure rarely came up regarding remote enrollment discussions

Local labs for eligibility and during trial

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- Limited labs to hemoglobin, creatinine, platelet count
  - Baseline and annually
- Could be provided from any local laboratory
  - Reported by patient or lab report
- Per protocol described as routine labs & standard of care
  - Protocol required within 30 days
  - Challenges with site / patient reimbursement for non-SOC labs
- Tried to set up central lab but not worth it by the time we got to it

Study drug distributed directly to participants
apixaban or warfarin

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- Fisher BioServices (Thermofisher)
  - US based commercial centralized pharmacy
  - CN going to ship to sites, cannot ship direct to participant
- Investigational drug labels for apixaban and warfarin
  - Participant specific labels with just-in-time labeling
- Used normal clinical prescription process
  - Warfarin 1 & 5 mg tablets (QD), added 2 mg at site request
  - Apixaban 5 & 2.5 mg tablets (BID)
- Prescribed via the EMR (90%)
  - Back up FAX prescription template provided

Study drug distributed directly to participants
apixaban or warfarin

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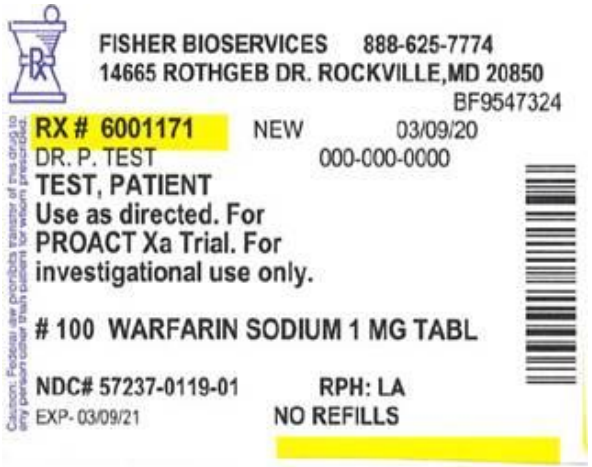
- Study drug mailed directly to participants
  - Took 2-3 days, shipping/FedEx challenges
    - During trial, extended (>30 days) participant drug supply
  - No problem if participants changed address
    - One patient on a 6 month camper road trip across the US
    - One patient incarcerated – shipped drug to sister who brought it to patient w/ approval of IRB and Dept of Corrections
- At end of trial, participants instructed to destroy drug
  - Discard, return to pharmacy, etc.
- Apixaban ($600 per bottle/$6M) & Warfarin ($50K)
  - Donated residual apixaban to Sirum (>$100K) https://sirum.org/



Remote follow-up with standardized script

- Monthly follow-up in both apixaban and warfarin groups
  - Protocol agnostic re: follow-up method (phone, video, in-person)
- Standardized scripts to ascertain events
  - Valve thrombosis or thromboembolism and bleeding
  - Death, hospitalized, AoV procedure, new HF symptoms
- Discussed routine imaging (echo or CT)
  - Clinical outcomes
  - Routine imaging not practical or cost effective
- COVID helped a great deal

Transfer of patients from one site to another

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- Facilitated by potential for remote enrollment and follow-up
- 2 sites closed during the trial
  - Florida site to Yale
  - Washington site to Multicare/Tacoma
- Patient awareness and IRB approval
  - Site payments

Medical records collected for event adjudication

- Limited monitoring
  - Remote monitoring
  - Patient existence, eligibility, consent, follow-up
- For suspected events medical records uploaded into the eCRF
  - CEC request source from the sites
  - CRA would help track down medical records.
- Bleeding & valve thrombosis/thromboembolism
  - Related, unknown, unrelated

Event Type	Suspected Events
Bleed	1062
Death	3
Hospitalization	437
Thrombembolism	133
Valve Dysfunction/Thrombosis	32
Total	1667

No adverse event collection

- Conducted under IND (investigational new drug application)
  - Move from CDRH (devices) to CDER (drugs)
  - Different evidence criteria, safety reporting requirements
- Apixaban/warfarin extensively studied with well known safety profiles
  - No safety issues other than thrombosis and bleeding
  - In similar or higher risk populations
- VT/TE events and bleeding collected as endpoints on eCRF
  - Also deaths, hospitalizations
  - No other AE or serious AE reporting required
- Discussed and agreed upon w/ FDA
  - Approach was not acceptable to Health Canada

No adverse event collection

- CDRH (devices) also wanted cases of serious On-X valve dysfunction to be collected
  - OK to not report individually but in aggregate at end of study
  - Artivion had existing mechanism for management of cases
    - Site were asked if valve dysfunction was “directly related to the valve”
    - If yes, Artivion’s Field Assurance office investigated (n=5)

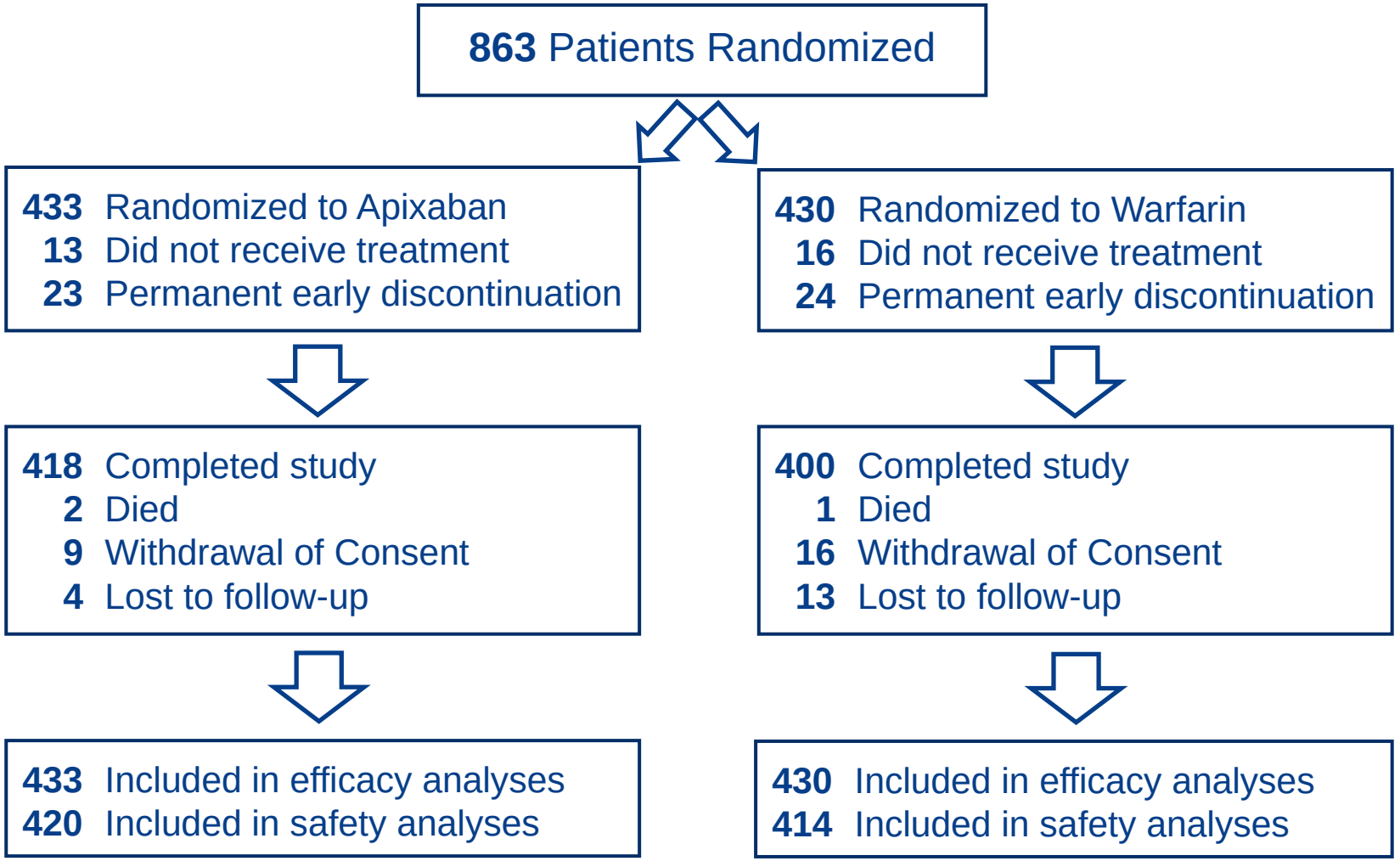
Investigators Meetings

- All virtual / remote due to COVID
- Adequate for education
- Not adequate for engagement

Trial Termination

- On September 21st, 2022, the PROACT Xa DSMB recommended stopping enrollment and transitioning patients off of study drug due to an observed excess in thromboembolic events in the apixaban arm compared to the warfarin arm
- Enrollment was stopped and all enrolled patients were contacted to transition off of study drug (apixaban or warfarin) and back onto standard of care warfarin

Participant Flow



Baseline Characteristics

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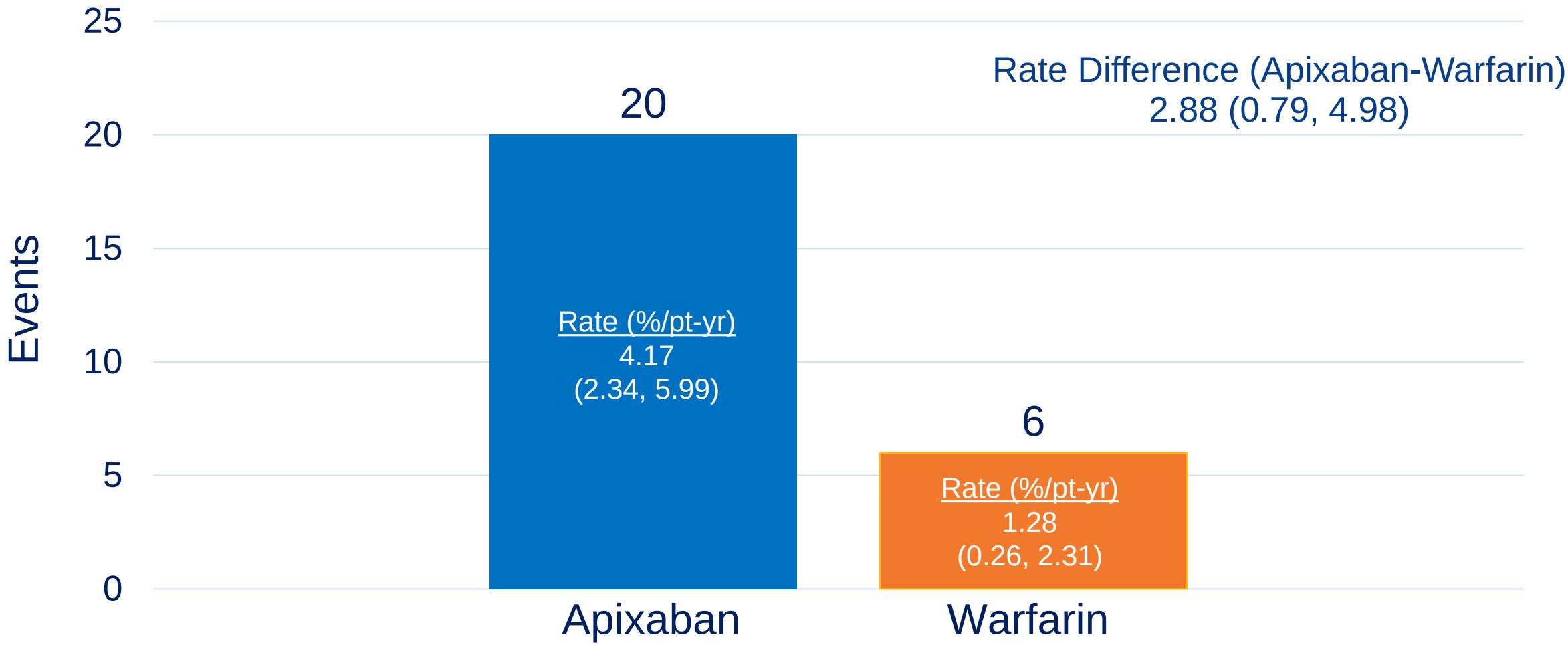
	Apixaban (n=433)	Warfarin (n=430)
Age (years)	56	55
Female sex (%)	23.6	24.4
White race (%)	91.2	90.7
Valve implantation within 1 year of randomization (%)	48.0	47.7
AVR with concomitant aortic root replacement (%)	14.8	19.8
Valve size ≤ 21 mm (%)	25.2	24.0
Re-operation of aortic valve (%)	17.8	13.7
INR target range 1.5 to 2.0 prior randomization (%)	33.8	33.5
Prior coronary artery disease (%)	24.5	22.3
Prior stroke/TIA (%)	9.9	9.1
Heart failure (%)	26.6	23.7
High risk* (%)	48.0	44.0
Concomitant aspirin (%)	94.2	94.0

*High risk includes atrial fibrillation, left ventricular ejection fraction <30%, left atrial dimension >50mm, vascular disease, or history of stroke/TIA within 1 year

Valve Thrombosis or Valve-Related* Thromboembolism



*Three additional non-valve related thromboembolic events, all in the apixaban group

Valve Thrombosis or Valve-Related* Thromboembolism

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	Apixaban N=433, 480 pt-yrs	Warfarin N=430, 467 pt-yrs
Primary efficacy endpoint	20	6
Valve thrombosis	3	0
Thromboembolism*	17	6
Stroke	14	0
TIA	0	5
Myocardial infarction	0	1
Arterial thromboembolism	3	0
Death	2	1

*Three additional non-valve related thromboembolic events, all in the apixaban group

Valve Thrombosis or Valve-Related Thromboembolism

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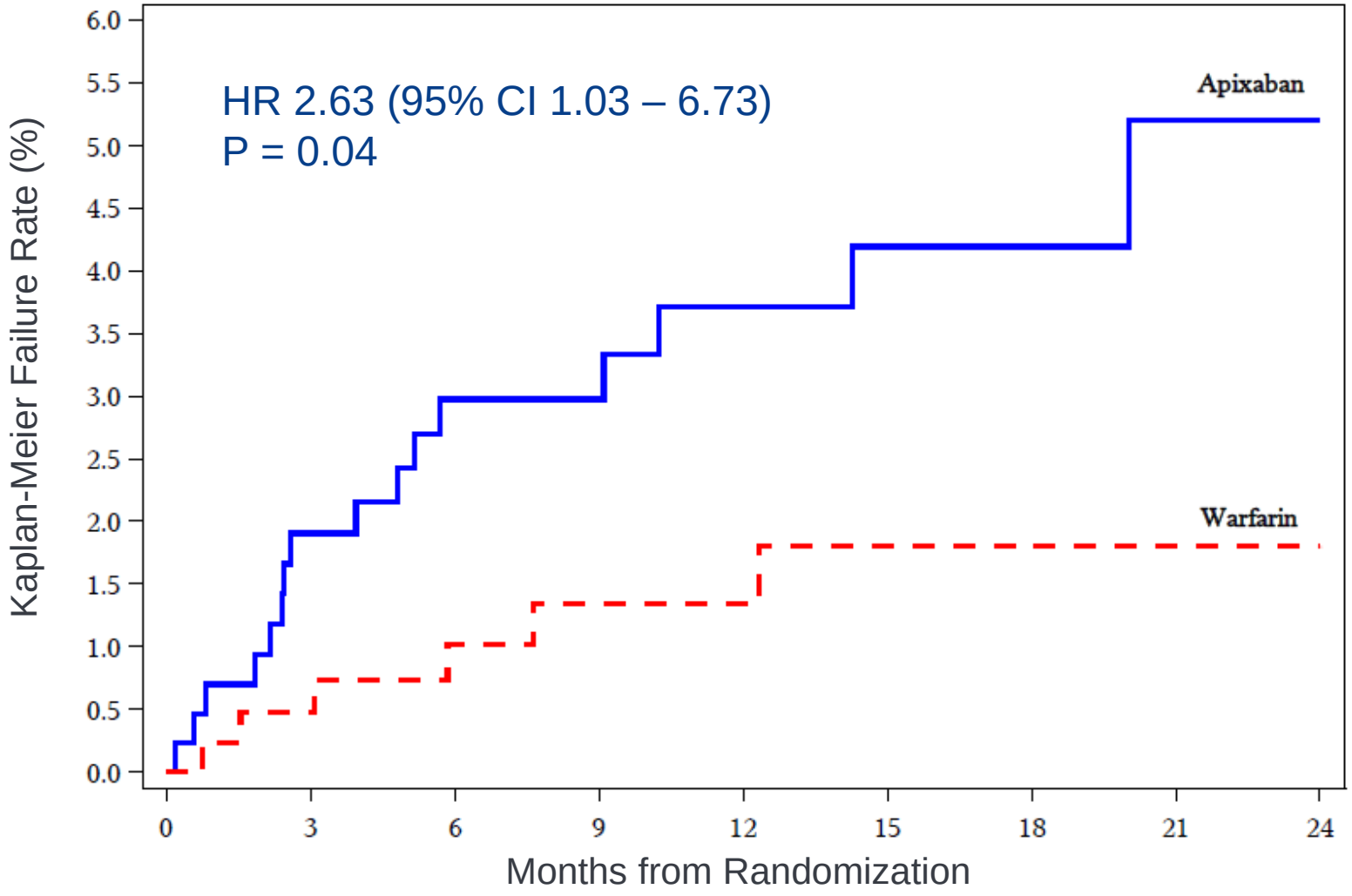
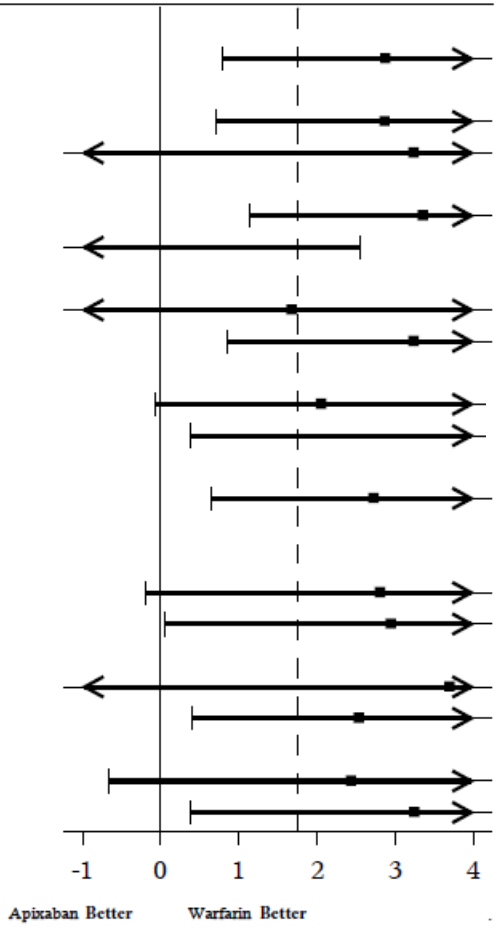


Subgroups

Group	Apixaban Number of events	Warfarin (%/patient-year)	Apixaban-Warfarin (%/patient-year) Event Rate Difference (95% CI)
Primary efficacy endpoint	20 (4.17)	6 (1.28)	2.88 (0.79, 4.98)
Age			
≤65 years	16 (3.91)	4 (1.04)	2.87 (0.70, 5.04)
>65 years	4 (5.66)	2 (2.42)	3.24 (-3.25, 9.73)
Race			
White	20 (4.52)	5 (1.16)	3.36 (1.13, 5.59)
Non-white	0 (0.00)	1 (2.67)	-2.67 (-7.90, 2.56)
Sex			
Female	4 (3.56)	2 (1.89)	1.68 (-2.69, 6.04)
Male	16 (4.35)	4 (1.11)	3.24 (0.85, 5.64)
AVR type			
AVR alone	14 (3.40)	5 (1.34)	2.06 (-0.07, 4.20)
AVR with aortic root replacement	6 (8.79)	1 (1.07)	7.72 (0.38, 15.06)
Baseline apixaban dose			
5 mg BID	19 (4.01)	6 (1.28)	2.73 (0.65, 4.81)
2.5 mg BID	0 (0.00)	NA (NA)	NA
Time from surgery			
≤1 year	8 (3.83)	2 (1.01)	2.81 (-0.19, 5.81)
>1 year	12 (4.43)	4 (1.48)	2.95 (0.05, 5.85)
Valve size			
≤21 mm	8 (6.36)	3 (2.66)	3.70 (-1.64, 9.03)
>21 mm	12 (3.39)	3 (0.85)	2.54 (0.40, 4.69)
Risk of primary event			
High risk*	9 (3.95)	3 (1.51)	2.44 (-0.66, 5.53)
Low risk	11 (4.37)	3 (1.12)	3.25 (0.38, 6.12)



Major Bleeding

Death, Hospitalization, Transfusion, Pericardiocentesis, Reoperation

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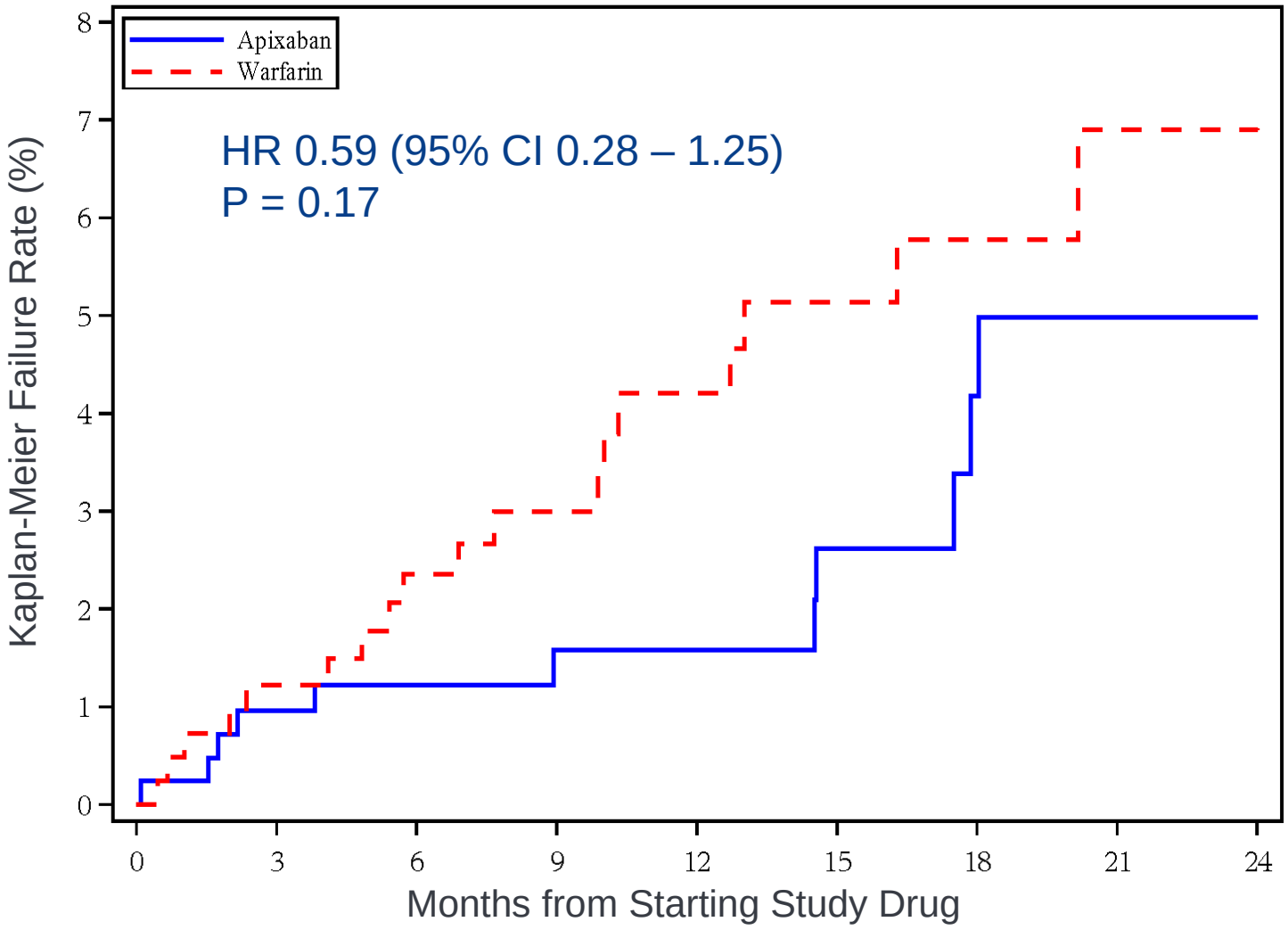

Summary

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- Apixaban was not non-inferior to warfarin for the prevention of valve thrombosis or valve-related thromboembolism and resulted in more thromboembolic events than warfarin in patients with an On-X mechanical aortic valve.
- Thromboembolic events rates with warfarin (INR 2-3) were low 1.28%/pt-yr in patients with an On-X mechanical aortic valve.
- Rates of major bleeding were similar with apixaban and warfarin.

Clinical Implications

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- Apixaban is not an effective alternative to warfarin for thromboembolism prophylaxis in patients with an On-X mechanical valve in the aortic position.
- In the absence of other compelling evidence of effectiveness, these results can probably be extrapolated to other factor Xa inhibitors and other mechanical heart valves.

Conclusions

- The “right” trial design/operational plan depends on the specifics of the trial
- There are lots of innovative approaches that are feasible
- It is important that we share experience with these approaches within the research community
- It is better to ask for forgiveness than permission

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Thank you!

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