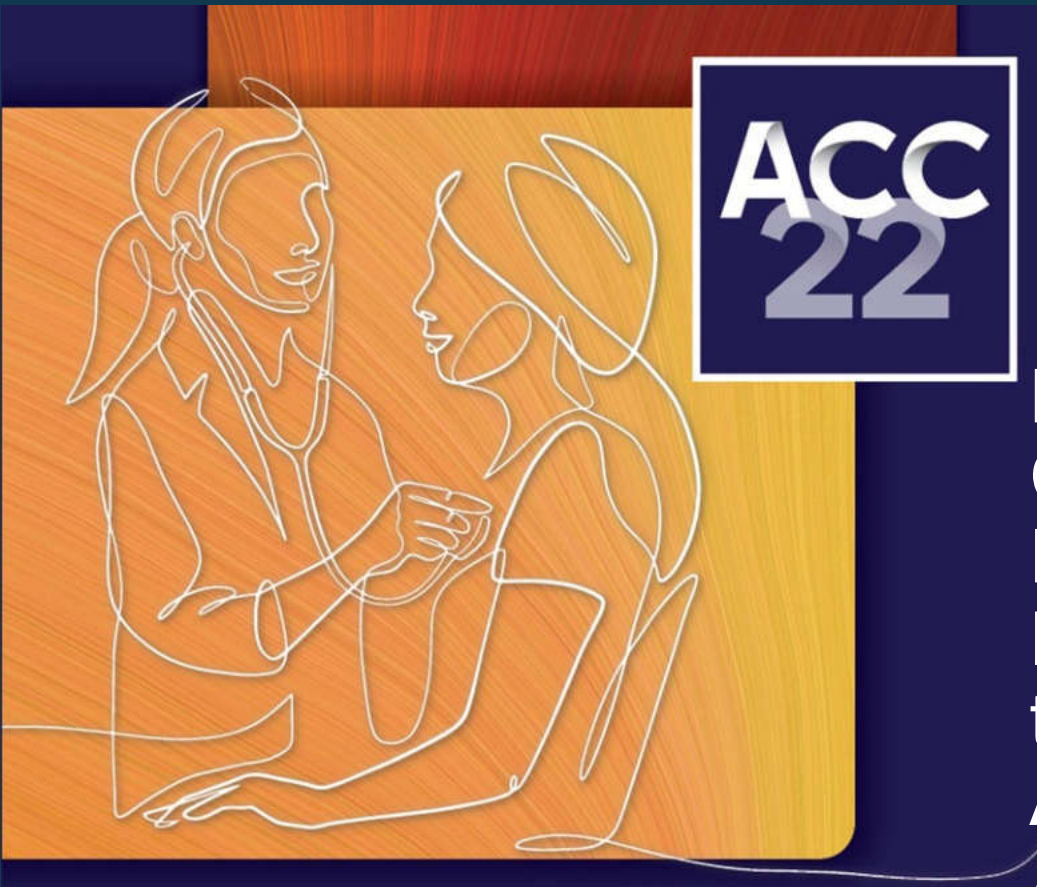


Multicenter, Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation: PACIFIC-AF

Manesh R. Patel, MD on behalf of the PACIFIC-AF Investigators

@manesh_patelMD

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

Duke Clinical Research Institute

PACIFIC AF

Disclosures

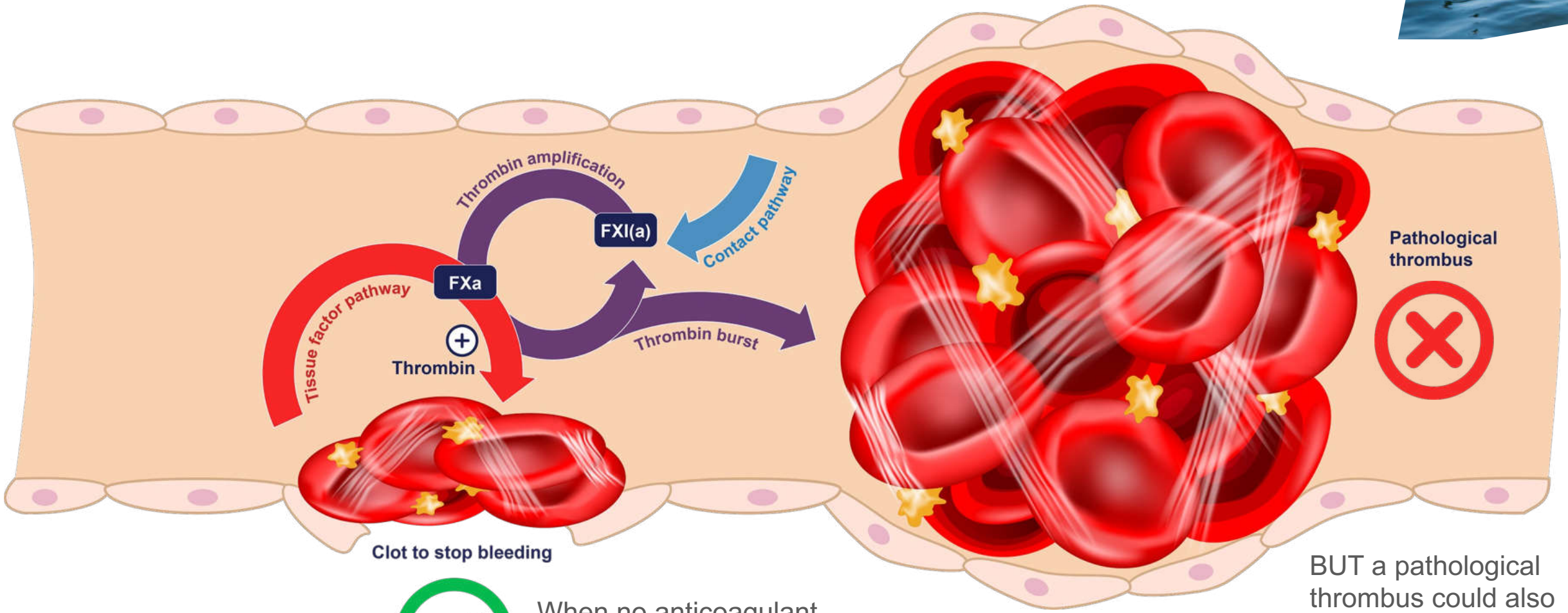
Research Grants:

PACIFIC-AF: Bayer

Other Research Support: Janssen, Heartflow, Idorsia, NHLBI, Novartis

Advisory Board/Consulting: Bayer, Janssen, Heartflow, Medscape

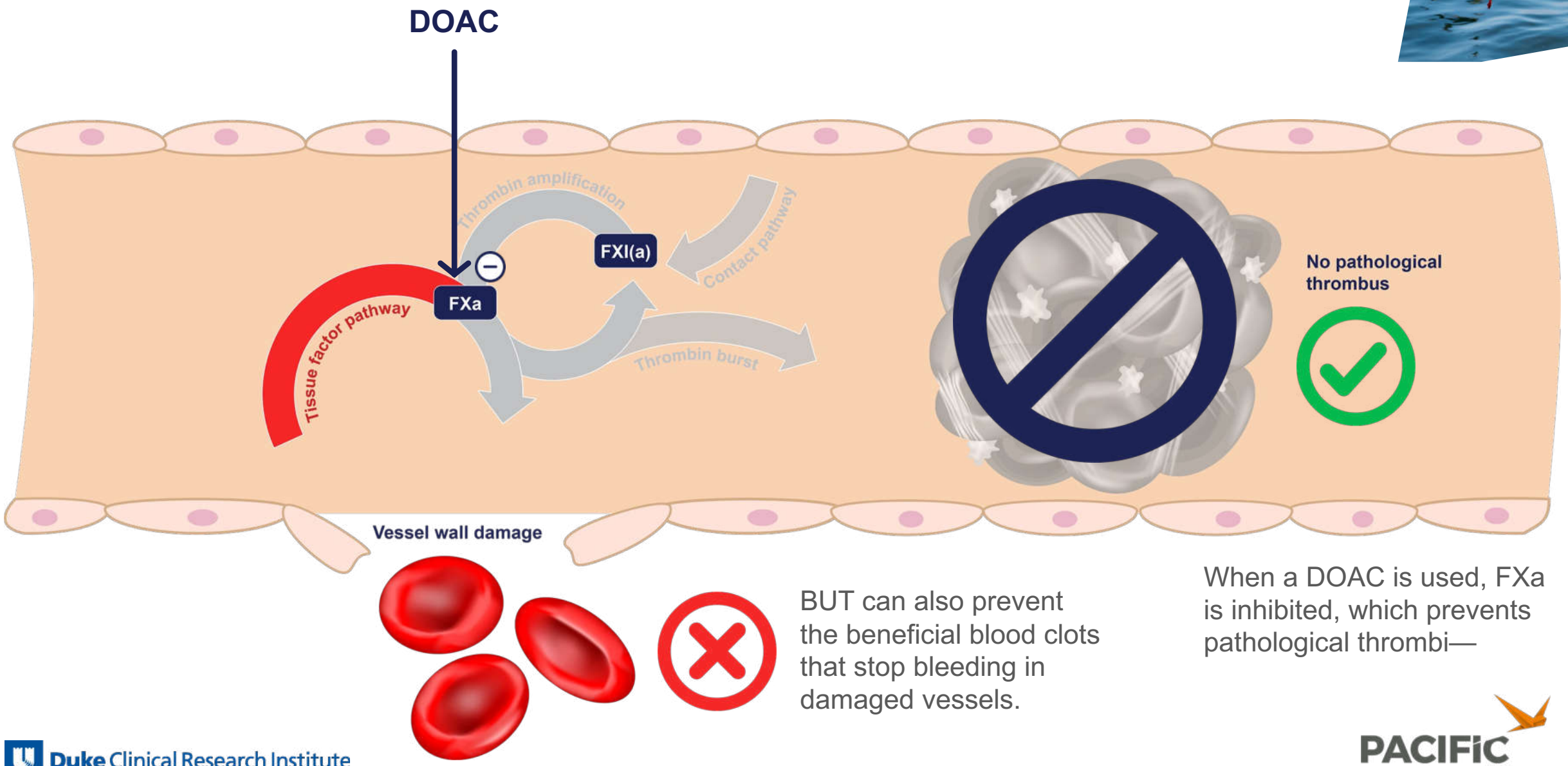
Normal Physiology: Without an Anticoagulant



When no anticoagulant is used, a clot is formed to stop the bleeding—

BUT a pathological thrombus could also be created.

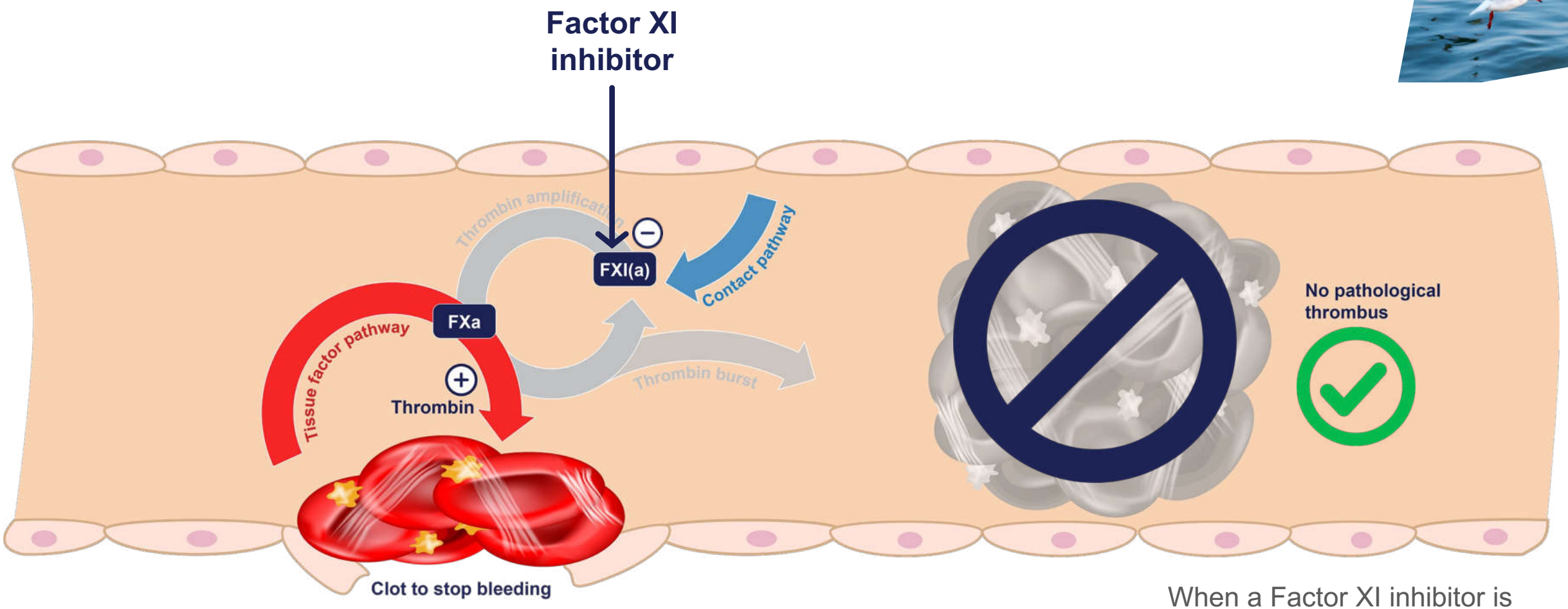
With a DOAC (e.g., apixaban or rivaroxaban)



BUT can also prevent the beneficial blood clots that stop bleeding in damaged vessels.

When a DOAC is used, FXa is inhibited, which prevents pathological thrombi—

With a Factor XI Inhibitor (Hypothesis: Uncoupling Hemostasis from Thrombosis)



AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—

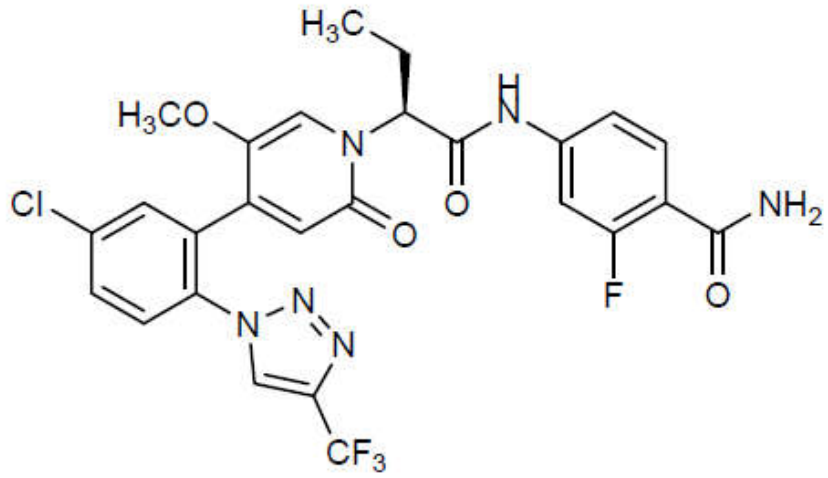
Current Evidence Supporting FXI(a) Inhibition as a Target

CONDITION	OBSERVATION
FXI-knockout mice[1]	• Homozygous FXI-knockout mice **are protected from thrombosis** • At the same time, they **do not show a bleeding phenotype** differing from wild-type mice
***In vivo* animal models**[2]	• Reducing/inhibiting FXI showed **strong antithrombotic** effects *in vivo* • **No increase in bleeding time** even at very high doses or on top of dual antiplatelet therapy
Inherited FXI deficiency[3]	• Individuals with FXI deficiency are reported to have a **reduced incidence of VTE and stroke** • **Hemorrhage occasionally** reported after trauma or surgery (dental extractions, tonsillectomies, surgery in the urinary and genital tracts, and nasal surgery)
FXI clinical experience	• **Antisense technology of IONIS**[4]**: Phase 2 study in TKA**: Improved VTE risk reduction together with numerically less bleeding vs enoxaparin (**of note, surgery was performed at suppressed FXI levels**) • **Anti-FXI-AB** (MAA868[5] and xisomab); **Anti-FXIa-AB** (osocimab[2]): Published data from Phase 1 studies confirmed **good safety and tolerability** even when high levels of **FXI or FXIa inhibition** were maintained for more than **1 month**. TKA study for osocimab completed confirming FXIa-inhibition being efficacious and well tolerated. **Oral selective FXIa inhibitor** (milvexian): Phase 2 work showing FXIa inhibition efficacious in **prevention of VTE** and associated with **low risk of bleeding**.[6]

[1] Schumacher WA et al. Arterioscler Thromb Vasc Biol. 2010;30(3):388-92.
[2] Data on file
[3] Puy C et al. Thromb Res. 2016;141(Suppl 2):S8–S11
[4] Büller HR et al. N Engl J Med. 2015;372(3):232-40
[5] Koch AW et al. Blood. 2019;133(13):1507-1516
[6] Weitz et al. N Engl J Med. 2021;385(23):2161-2172

Asundexian: Oral Factor XI Inhibitor

$C_{26}H_{21}ClF_4N_6O_4$



- Small molecule FXIa inhibitor
  - $t_{1/2}$ 14.2-17.4 hours
  - 15% Renal Elimination
- Well-tolerated in Phase 1 trials
- Dose-dependent FXIa inhibition
- Does not interact with clopidogrel to affect bleeding time
- No difference across age or sex
- Does not inhibit or induce CYP3A4
- Not impacted by food or pH modulating drugs

The PACIFIC Trials: Coordinated Phase 2 Programs

- Together, will allow to assess the bleeding and efficacy profile of asundexian
- **Primary objective of PACIFIC-AF: evaluate comparative bleeding rate of asundexian vs apixaban in patients with AF**
- No assessment of efficacy possible given low event #
- PACIFIC-AMI and PACIFIC-STROKE as placebo-controlled studies on top of antiplatelet therapy
- PACIFIC-AF is the first Phase 2 study that will read out

PACIFIC AF

PACIFIC AMI

PACIFIC STROKE

PACIFIC Program

Concerted evaluation across large several Phase 2 programs

PACIFIC AF

Atrial fibrillation

20mg asundexian
50mg asundexian
apixaban

750 patients randomized
Results at ACC 2022

PACIFIC STROKE

Non-cardioembolic ischemic stroke

10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ single or dual antiplatelet therapy

1800 patients randomized
Results later this year

PACIFIC AMI

Acute myocardial infarction

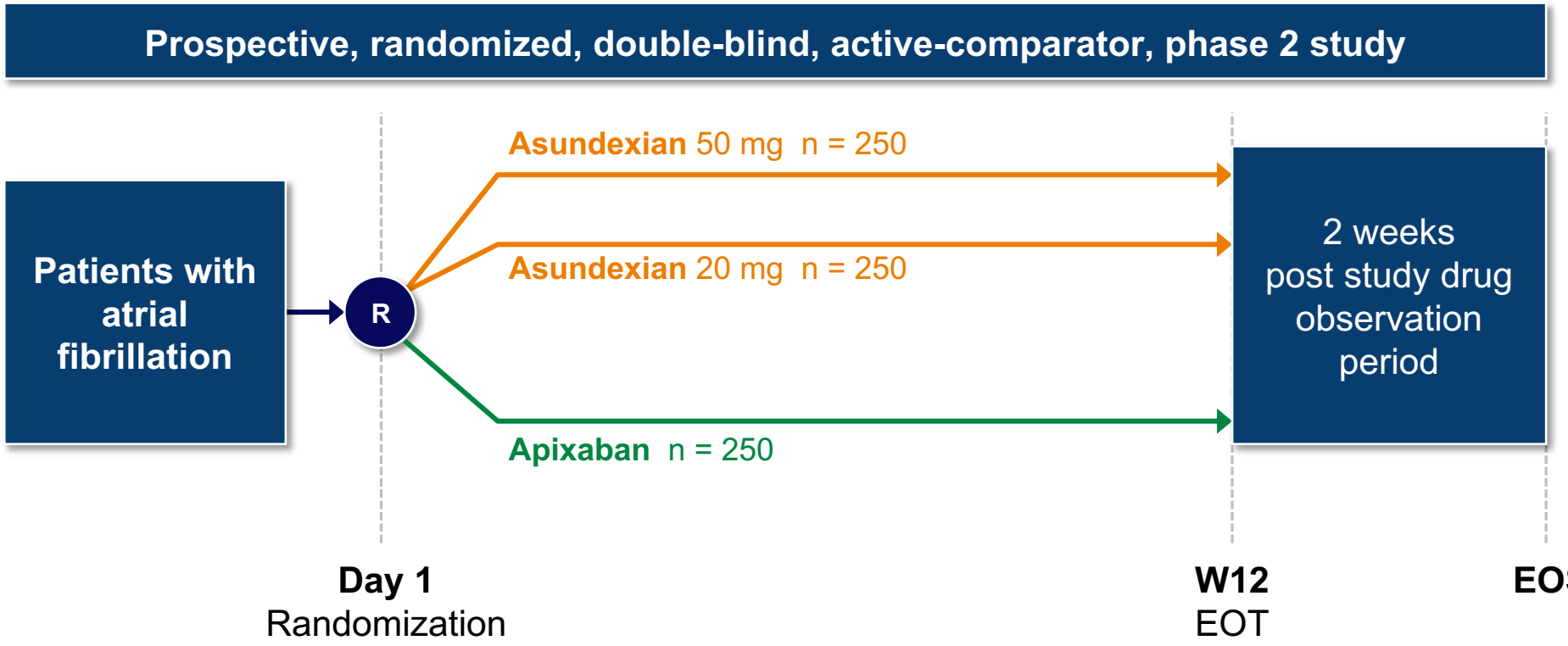
10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ dual antiplatelet therapy

1600 patients randomized
Results later this year

// One coordinated IDMC
// One blinded CEC with uniform process

Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study to Compare the Safety of the Oral FXIa Inhibitor Asundexian to Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF)



Primary safety endpoint: bleeding (ISTH major and non-major clinically relevant bleeding)

Quantification of Factor XI inhibition

Exploratory efficacy endpoint: stroke, systemic embolism, CV death, MI

Primary Objective:
to evaluate that the oral FXIa inhibitor asundexian when compared to apixaban leads to a **lower incidence of bleeding** in participants with AF

PACIFIC AF

AXIA: Factor XIa Inhibition Assay

- Proprietary assay
- ~220 patients/ arm
- 4 weeks on once daily drug
- ~ trough (24-28 hours from last dose) and then again 2-4 hours afterwards
- Quantify degree of Factor XIa inhibition

Results of PACFIC-AF

Duke Clinical Research Institute

PACIFIC AF

Disposition / Study Flow

Enrolled
862

Randomized (FAS)
755

Treatment Phase started (SAF)
753

Treatment Phase completed
671

Screening failures 107

Inclusion/exclusion criteria 69
Withdrawal by subject 28
Other reasons 10

Never took any study drug 2

Did not complete treatment phase 82

Adverse event 38
Other reasons 25
Death 6
Physician decision 6
Withdrawal by subject 6
Non-compliance with study drug 1

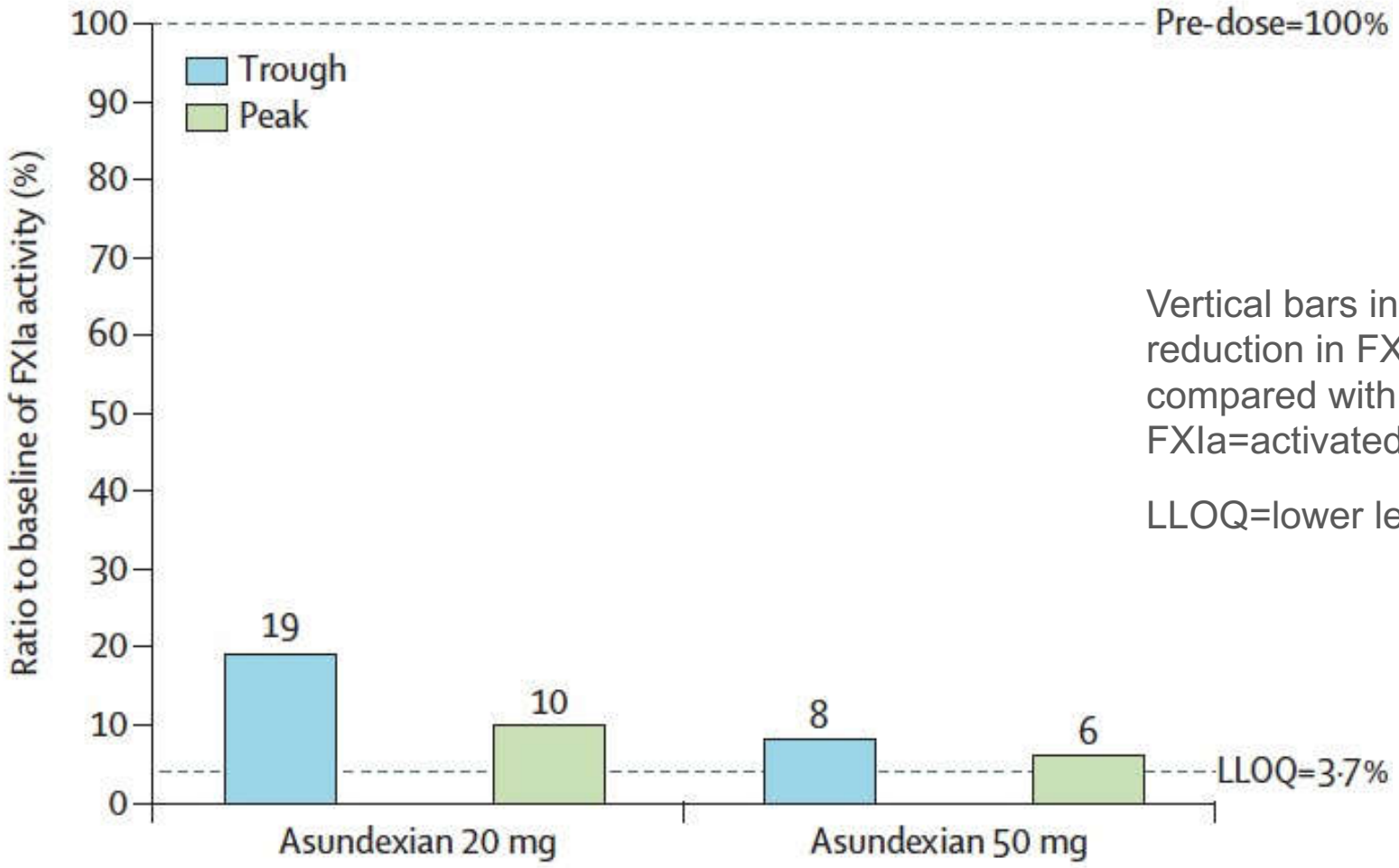
Demographics and Medical History — Well Balanced Across Treatment Arms

	Asundexian 20 mg N = 251	Asundexian 50 mg N = 254	Apixaban N = 250	Total N = 755
Age (years) (SD)	73.6 (8.0)	73.1 (8.5)	74.3 (8.3)	**73.7 (8.3)**
Female	103 (41.0%)	97 (38.2%)	109 (43.6%)	**309 (40.9%)**
Race				
White	211 (84.1%)	212 (83.5%)	209 (83.6%)	**632 (83.7%)**
Asian	39 (15.5%)	40 (15.7%)	40 (16.0%)	**119 (15.8%)**
Hypertension	226 (90.0%)	227 (89.4%)	220 (88.0%)	**673 (89.1%)**
Hyperlipidaemia	142 (56.6%)	153 (60.2%)	152 (60.8%)	**447 (59.2%)**
Cardiac failure chronic	108 (43.0%)	107 (42.1%)	117 (46.8%)	**332 (44.0%)**
Coronary artery disease	76 (30.3%)	71 (28.0%)	85 (34.0%)	**232 (30.7%)**
Diabetes mellitus	83 (33.1%)	74 (29.1%)	87 (34.8%)	**244 (32.3%)**
Chronic kidney disease	55 (21.9%)	84 (33.1%)	77 (30.8%)	**216 (28.6%)**
CHA_2DS_2-VASc score (SD)	3.99 (1.39)	3.83 (1.29)	4.10 (1.46)	**3.97 (1.38)**

Medical History of Special Interest

	Asundexian 20 mg N = 251	Asundexian 50 mg N = 254	Apixaban N = 250	Total N = 755
Cerebrovascular accident	22 (8.8%)	18 (7.1%)	25 (10.0%)	**65 (8.6%)**
Coronary artery bypass	22 (8.8%)	16 (6.3%)	17 (6.8%)	**55 (7.3%)**
Peripheral arterial occlusive disease	16 (6.4%)	10 (3.9%)	20 (8.0%)	**46 (6.1%)**
Transient ischemic attack	13 (5.2%)	10 (3.9%)	13 (5.2%)	**36 (4.8%)**
Major bleed	7 (2.8%)	14 (5.5%)	3 (1.2%)	**24 (3.2%)**
Carotid revascularization	3 (1.2%)	2 (0.8%)	4 (1.6%)	**9 (1.2%)**
Embolism arterial	3 (1.2%)	2 (0.8%)	2 (0.8%)	**7 (0.9%)**

FXIa Activity - Inhibition Data



n	224	222	228	228
Analysis value (95% CI)	14·82 (12·65–16·99)	7·42 (6·33–8·51)	6·59 (5·15–8·02)	4·32 (3·60–5·05)
Mean ratio to baseline (95% CI)	0·19 (0·16–0·22)	0·10 (0·08–0·12)	0·08 (0·07–0·10)	0·06 (0·05–0·07)

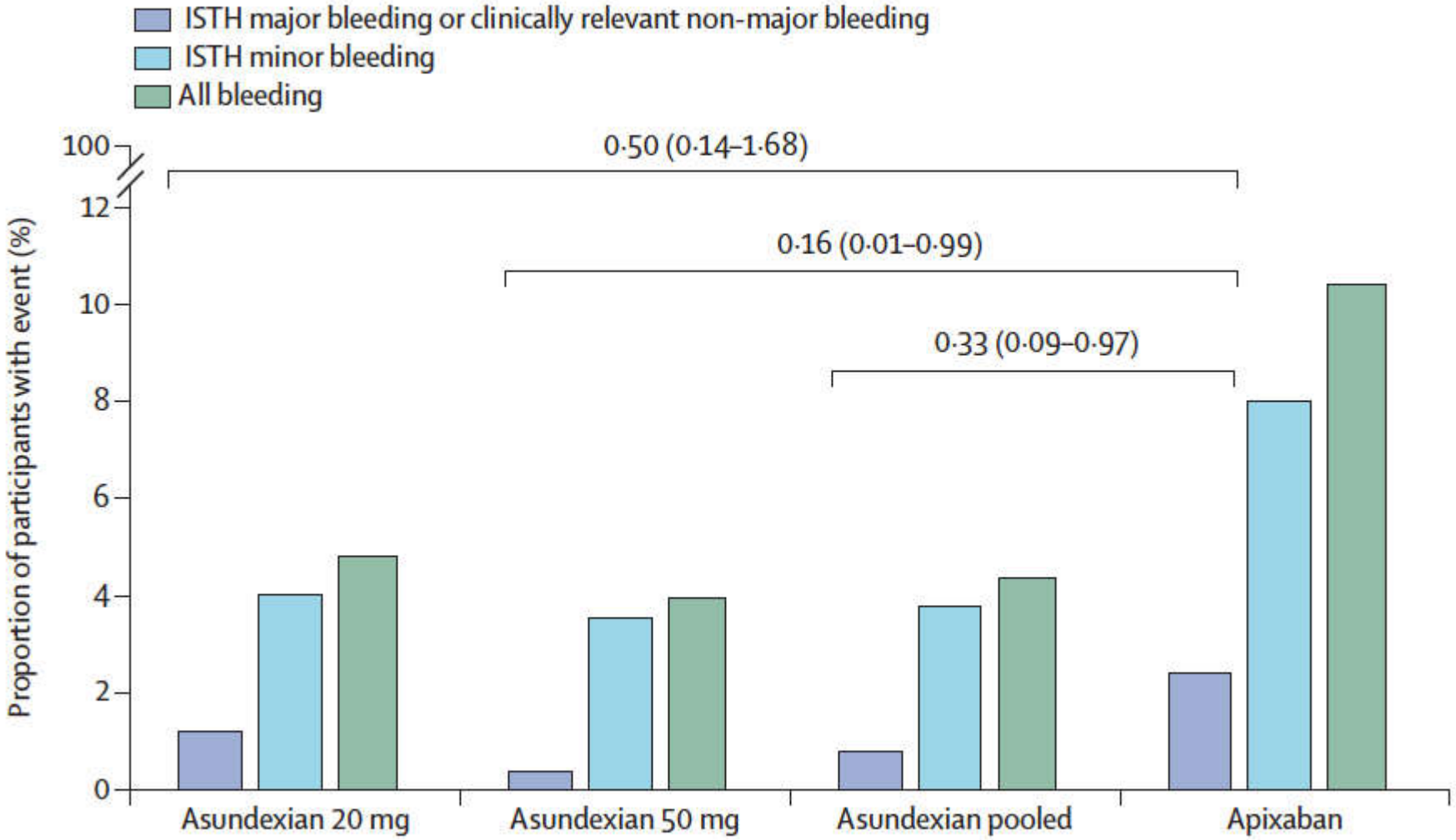
Vertical bars indicate the percent reduction in FXIa activity when compared with baseline.
FXIa=activated coagulation factor XI.

LLOQ=lower level of quantification.

PACIFIC AF

Primary Safety Outcome (ISTH bleeding classification)

On-treatment analysis, % of patients



- No ISTH **major** bleeding in any treatment arm
- Less bleeding in the 2 asundexian arms reported, when compared to apixaban for different severities of bleeding
- Consistent also for BARC and TIMI bleeding definitions

Primary Safety

(Pooled) ratio of the incidence proportions for the safety outcome in the treatment emergent data scope

	Asundexian 20 mg vs. Apixaban CIR (90% CI)	**Asundexian 50 mg vs. Apixaban** CIR (90% CI)	**Asundexian (pooled) vs. Apixaban** CIR (90% CI)
ISTH major bleeding or CRNM bleeding	0.50 (0.14 - 1.68)	0.16 (0.01 - 0.99)	0.33 (0.09 - **0.97**)
ISTH major bleeding	n.c.	n.c.	n.c.
CRNM bleeding	0.50 (0.14 - 1.68)	0.16 (0.01 - 0.99)	0.33 (0.09 - **0.97)**
ISTH minor bleeding	0.50 (0.23 - 0.99)	0.44 (0.18 - 0.86)	0.47 (0.28 - **0.83)**
All bleeding	0.46 (0.23 - 0.83)	0.38 (0.16 - 0.68)	0.42 (0.26 - **0.67)**

Adverse Events

	Asundexian 20 mg N = 249 (100%)	Asundexian 50 mg N = 254 (100%)	Apixaban N = 250 (100%)	Asundexian Total N = 503 (100%)	Total N = 753 (100%)
Any AE	118 (47.4%)	120 (47.2%)	122 (48.8%)	238 (47.3%)	360 (47.8%)
Any study drug-related AE	29 (11.6%)	26 (10.2%)	37 (14.8%)	55 (10.9%)	92 (12.2%)
Any AE leading to discontinuation of study drug	15 (6.0%)	16 (6.3%)	13 (5.2%)	31 (6.2%)	44 (5.8%)
Any study drug-related SAE	4 (1.6%)	0	0	4 (0.8%)	4 (0.5%)
AE with outcome death	1 (0.4%)	3 (1.2%)	2 (0.8%)	4 (0.8%)	6 (0.8%)

Asundexian was well tolerated in patients with AF.

Exploratory Efficacy Analysis

	Asundexian 20 mg N = 251 IR (90% CI)	Asundexian 50 mg N = 254 IR (90% CI)	Apixaban N = 250 IR (90% CI)	Total N = 755 IR (90% CI)
CV death, MI, ischemic stroke, or systemic embolism	2 (0.80 %)	4 (1.57 %)	3 (1.20 %)	9 (1.19 %)
CV death	1 (0.40 %)	3 (1.18 %)	3 (1.20 %)	7 (0.93 %)
MI	0	1 (0.39 %)	0	1 (0.13 %)
Ischemic stroke	2 (0.80 %)	1 (0.39 %)	0	3 (0.40 %)
Systemic embolism	0	0	0	0
All cause mortality (ITT)	2 (0.80 %)	4 (1.57 %)	4 (1.60 %)	10 (1.32 %)

As expected only single efficacy endpoints were reported in the study.

→ No conclusion on efficacy can be drawn

Summary

Duke Clinical Research Institute

PACIFIC AF

Summary of Findings

- First randomized active comparator (apixaban) data with small molecule Factor XIa inhibitor (asundexian)
- Near complete inhibition of Factor XI activity with 20 and 50 mg dose asundexian
- Only few bleeding outcome events were observed
  - 48 participants with a bleeding event in total
- Point estimators of risk ratios in favor of asundexian
  - For the pooled 20 and 50 mg doses as well as for 50 mg alone the confidence intervals could exclude 1 for CRNM bleeding as well as for minor bleeding and all bleeding
  - Overall bleeding rates lower than expected (for Apixaban: 4% assumed vs. 2.4% observed)
- As expected — no information on efficacy events: limited events with fewer than 10 events total

Conclusions

- Asundexian, a small oral FXIa inhibitor was well tolerated in a Phase 2 trial of 750 patients with atrial fibrillation
- Significantly lower bleeding rates were seen for patients randomized to either dose asundexian compared to apixaban
- Factor XI inhibition is a promising strategy to prevent pathologic thrombi while minimizing bleeding risk in AF patients — Phase 3 trial required

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

*Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators**

Next Steps:
Engaging Patients and International Communities to Perform Clinical CV Outcomes Trial

- Net clinical benefit endpoints in upcoming OCEANIC AF trial will be informed by patient preference survey
- AFIBOPPORTUNITIES.COM
- Live Spring, 2022
- Engaging investigators who want to be part of innovative patient-centered trials (manesh.patel@duke.edu)

PEARL AF

SC Members

Manesh Patel
Valeria Caso
Stuart Connolly
Keith Fox
Jonas Oldgren
Jonathan Piccini

IDMC Members

Jonathan Halperin
Steven Greenberg
Thomas Cook
Saskia Middeldorp
Christoph Bode

Investigators & Teams

Johann Auer
Andreas Schober
Christopher Adlbrecht
Matthias Frick
Michael Lichtenauer
Robert Schönbauer
Daniel Scherr
Markus Stühlinger
Helmut Pürerfellner
Johan Vijgen
Karl Dujardin
Rene Tavernier
Tom Rossenbacker
Hein Heidbuchel
Gert Vervoort
Thomas Vanassche
Christian Constance
Jafna Cox
Laurent Macle
Isabelle Nault
Zdenek Coufal
Ondrej Cermak
Hana Linkova
Jiri Kettner
Ivo Podpera
Vlastimil Vancura
Vratislav Dedek
Vaclav Durdil
Nicolas Lellouche
GuillaumeTaldir
Emmanuel Boiffard
Hervé Gorka
Fabrice Extramiana
Haten Boughanmi
Meyer Elbaz
Robert Kiss
Bela Benczur
Laszlo Nagy
Andras Matoltsy
Bela Merkely
Kalman Toth
Zsolt Zilahi
Daniel Aradi
Leonardo Bolognese
Simona D'Orazio
Cecilia Becattini
Vito Maurizio Parato
Pietro Ameri
Maria Lorenza Muiesan
Pasquale Pignatelli
Eiji Tamiya
Shinichi Higashiue
Katusmi Saito
Yuichiro Nakamura
Akira Shimane
Tetsuo Betsuyaku
Hideki Ueno
Koshi Matsuo
Yoshiki Hata
Iveta Sime
Ilze Reinholde
Janina Romanova
Natalja Pontaga
Artis Kalnins
Arcils Gersamija
Nadezda Rozkova
Ignasi Anguera Camós
Rafael Salguero Bodes
Juan José Gómez-Doblas
Ignacio Ferreira González
Xavier Viñolas Prat
Carl-Johan Lindholm
Håkan Wallén
Ken Eliasson
Jens Olsson
Markus Lind
Niclas Svedberg
Thomas Mooe
Christian Müller
Tobias Reichlin
Hans Rickli
Laurent M. Haegeli
Angelo Auricchio
François Mach
Joris de Groot
Dominik Linz
Marco Alings
Louis Bartels
Ron Pisters
Aaf Kuijper
Ewout van den Bos
Jeroen Stevenhagen
Gregory Lip
Anthony Gunstone
Diana Gorog
Roxy Senior
Yuk-Ki Wong

Duke Clinical Research Institute

PACIFIC AF

Thank you!

Duke Clinical Research Institute

PACIFIC AF