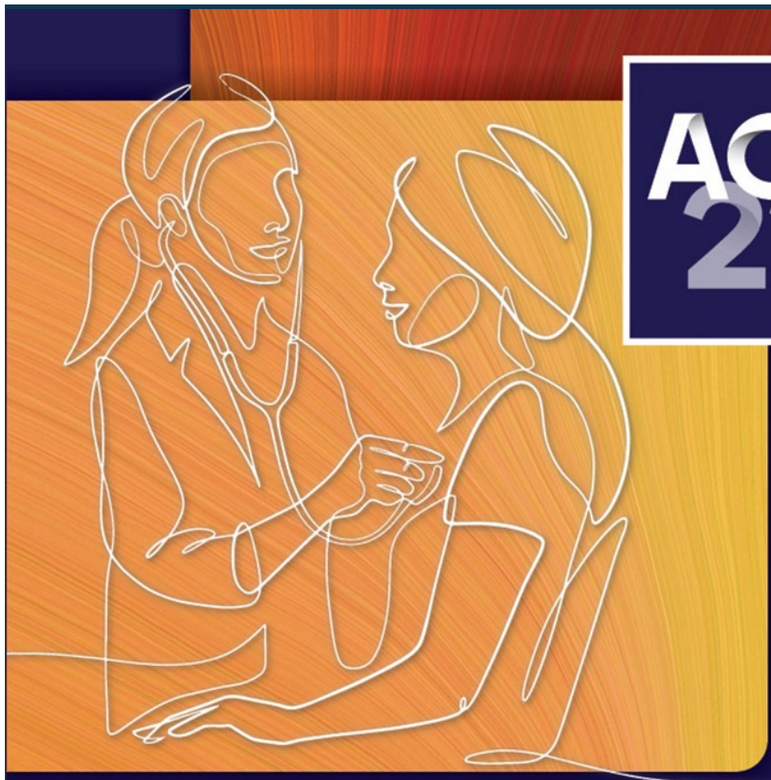

Multicenter, Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel Group, Dose-Finding Phase 2 Study Comparing the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation: PACIFIC-AF

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

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Disclosures

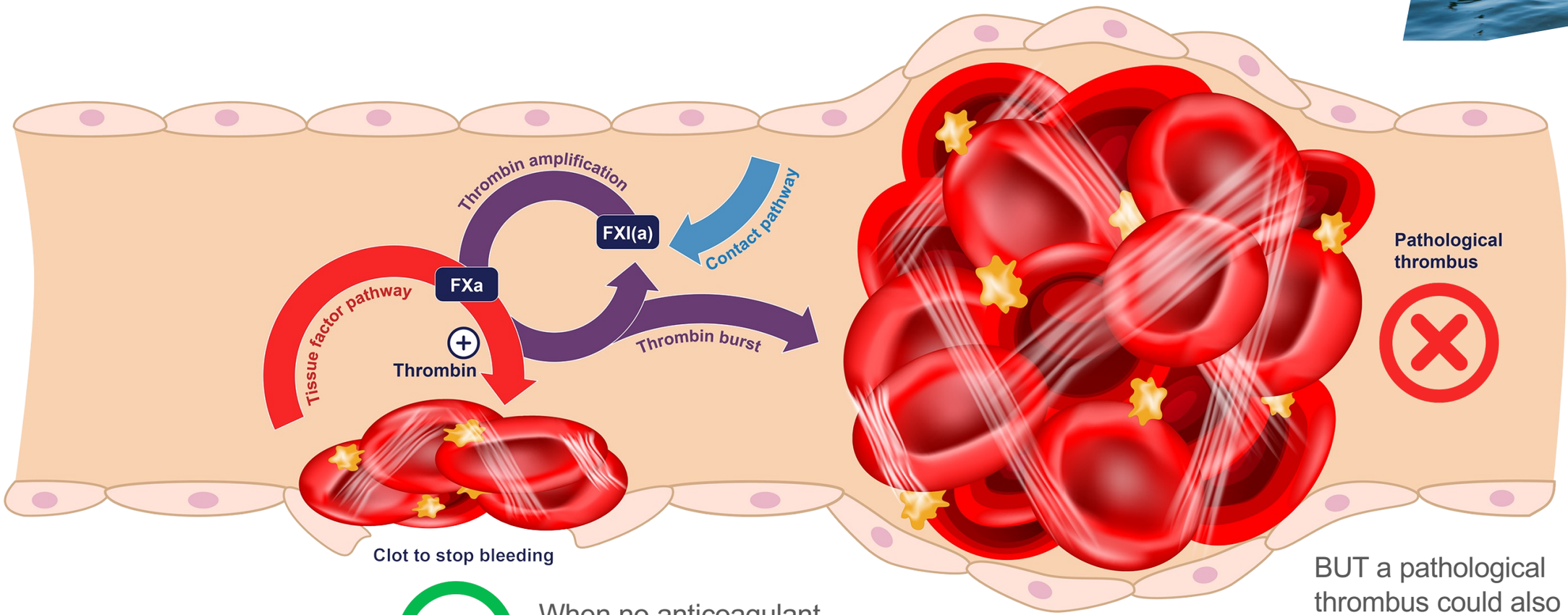
Research Grants:

PACIFIC-AF: Bayer

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

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

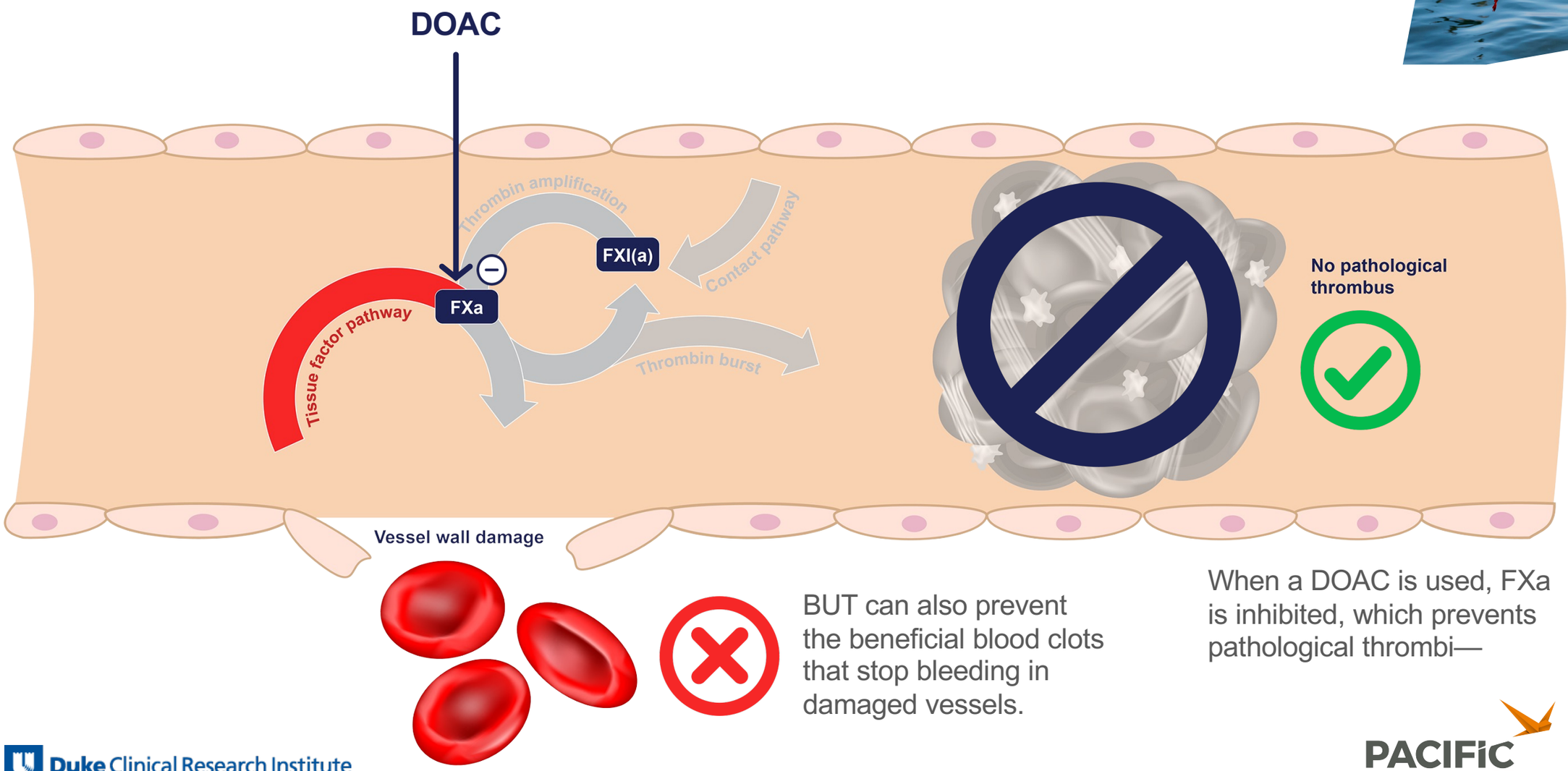
Normal Physiology: Without an Anticoagulant



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—

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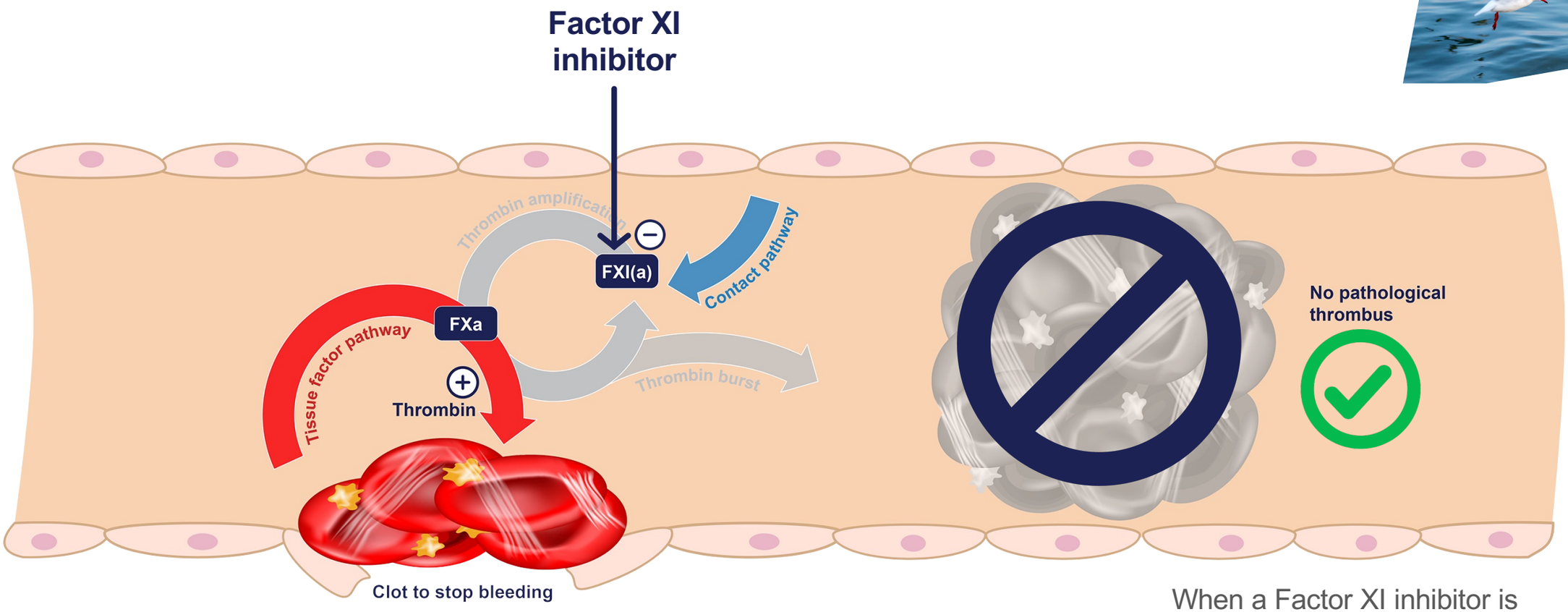
With a Factor XI Inhibitor (Hypothesis: Uncoupling Hemostasis from Thrombosis)



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—

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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

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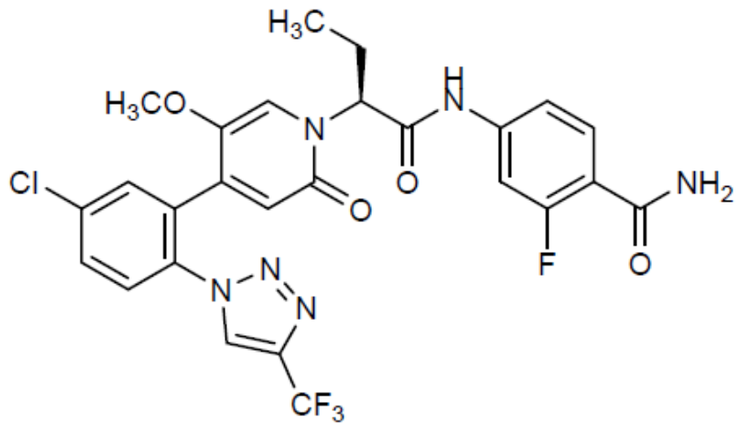
Asundexian: Oral Factor XI Inhibitor

$C_{26}H_{21}ClF_4N_6O_4$



- 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

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PACIFIC AMI

PACIFIC STROKE

PACIFIC Program

Concerted evaluation across large several Phase 2 programs

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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

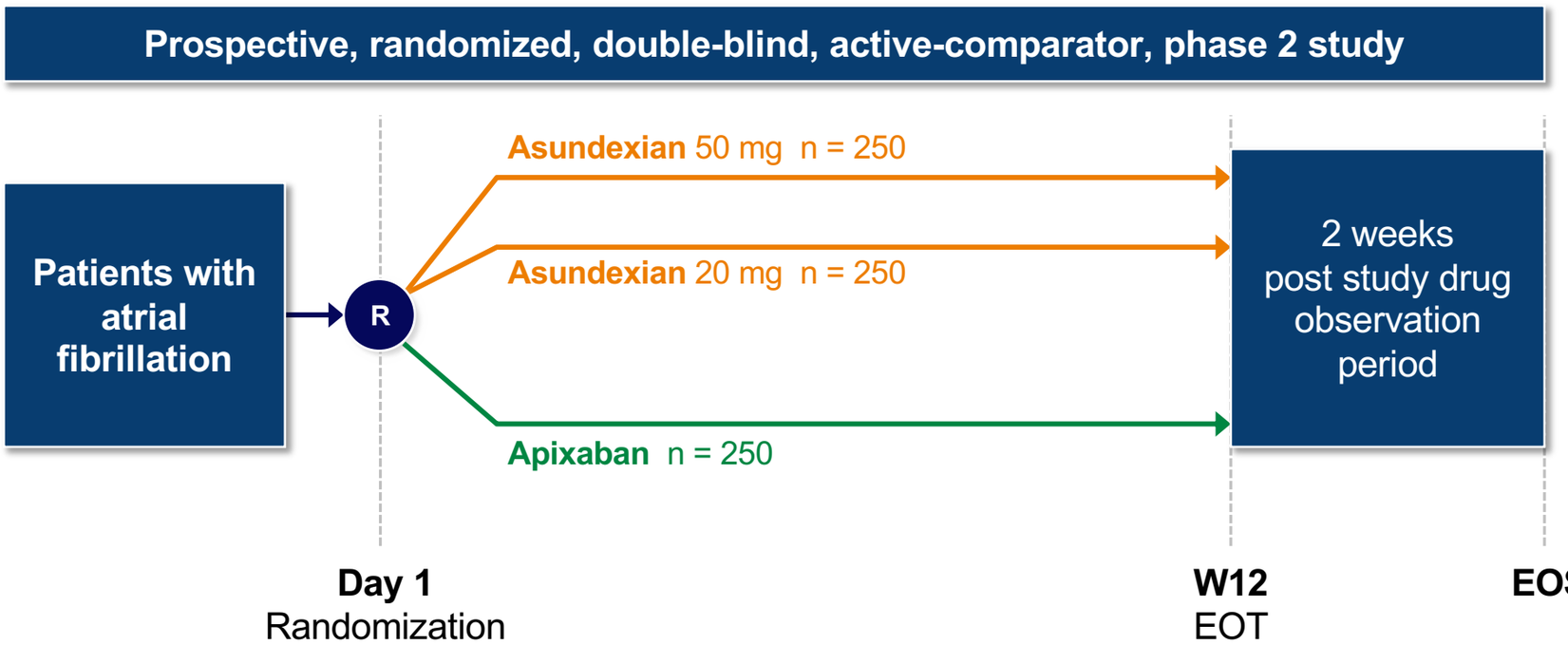
+ dual antiplatelet therapy

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

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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

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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

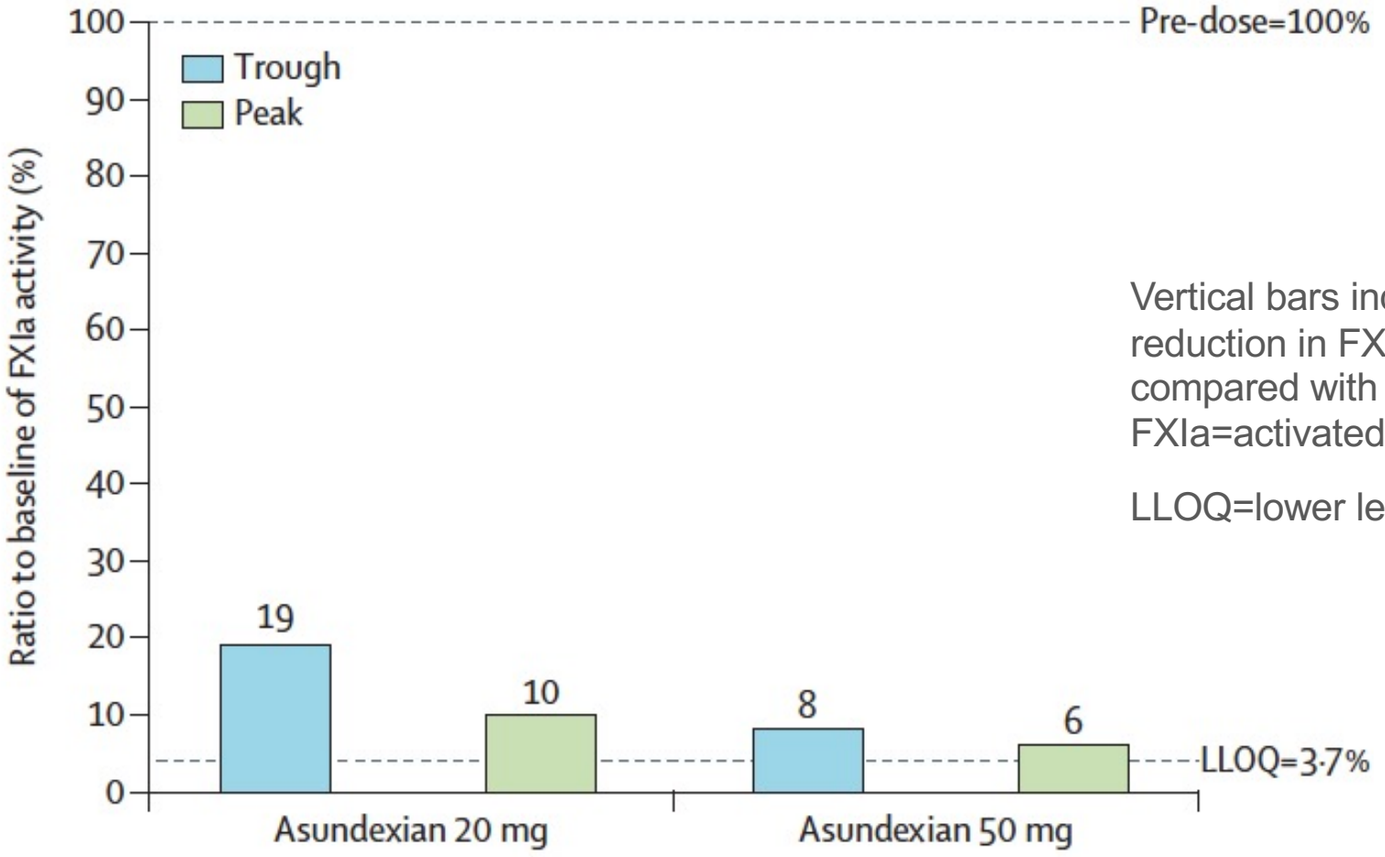
Demographics and Medical History — Well Balanced Across Treatment Arms

	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



	Asundexian 20 mg		Asundexian 50 mg	
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.

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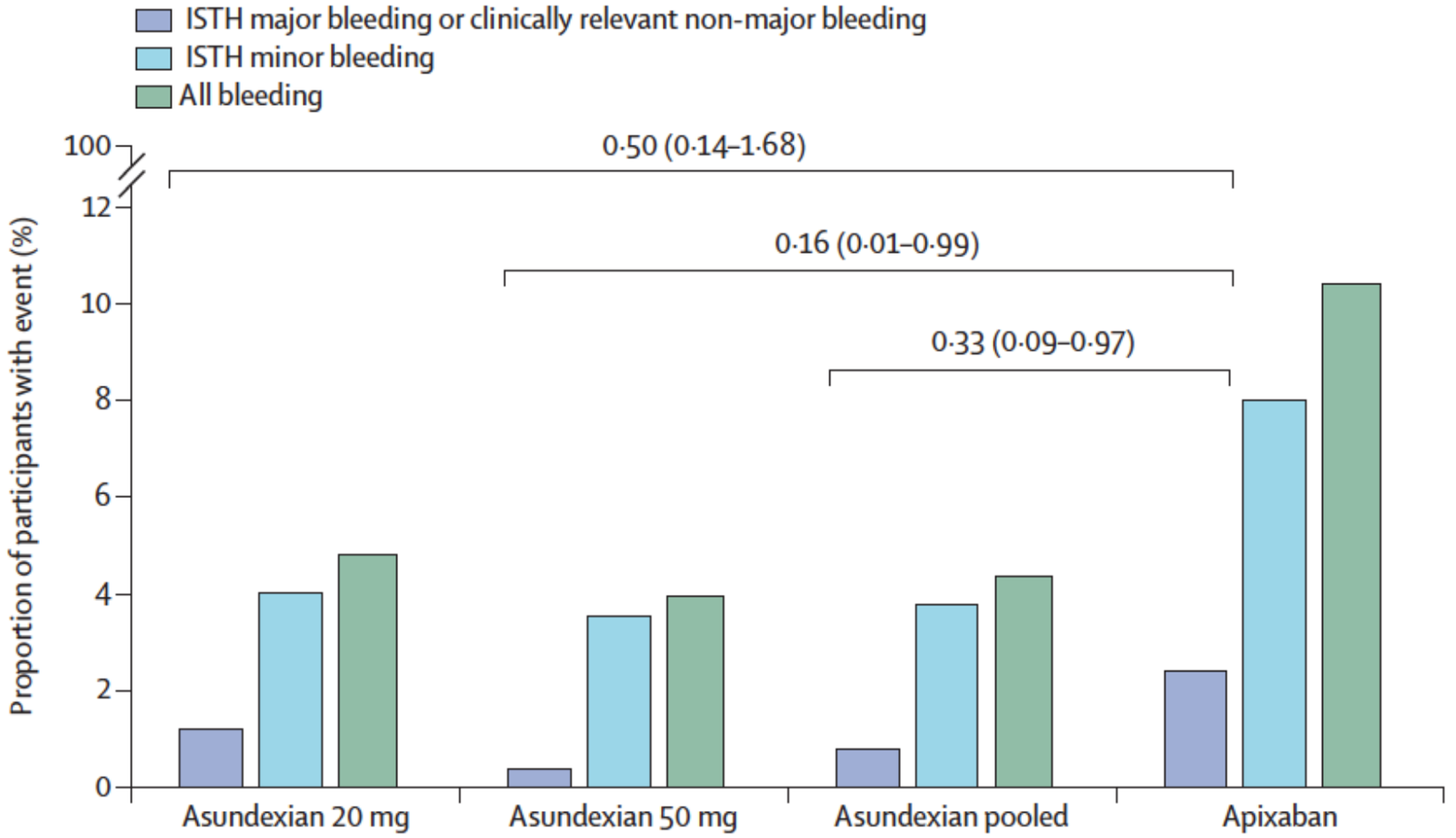
Primary Safety Outcome (ISTH bleeding classification)

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

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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

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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**

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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

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Christian Müller
Tobias Reichlin
Hans Rickli
Laurent M. Haegeli
Angelo Auricchio
François Mach
Joris de Groot
Dominik Linz
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Jeroen Stevenhagen
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Thank you!

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