AZALEA-TIMI 71

A Multicenter, RandomiZed, Active-ControLled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared with Open-Label Rivaroxaban in Patients with Atrial Fibrillation

Christian T. Ruff, MD, MPH

on behalf of the AZALEA-TIMI 71 Steering Committee & Investigators

American Heart Association Scientific Session

Late-Breaking Clinical Trial

November 12, 2023

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Disclosures

Research grants through institution:
Anthos, AstraZeneca, Daiichi Sankyo, Janssen and Novartis

Honoraria for scientific advisory boards and consulting:
Altimmune, Anthos, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Merck and Pfizer.

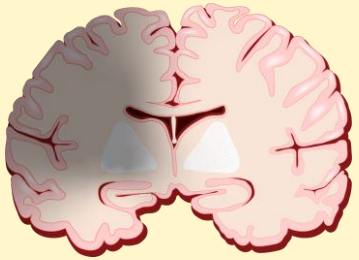
Member of TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from:
Abbott, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, The Medicines Company, Zora Biosciences

Stroke Prevention in AF
DOACs vs. Warfarin

Meta-Analysis: ARISTOTLE, ENGAGE AF-TIMI 48, ROCKET-AF & RE-LY Trials

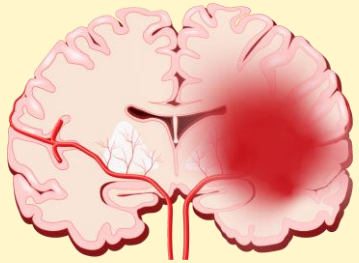
Stroke

Ischemic



Similar

Hemorrhagic

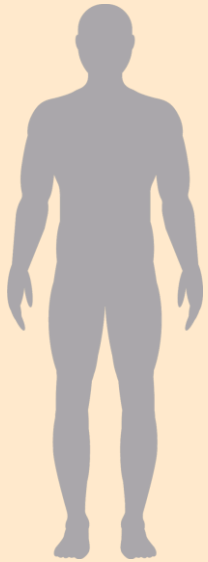


↓50%

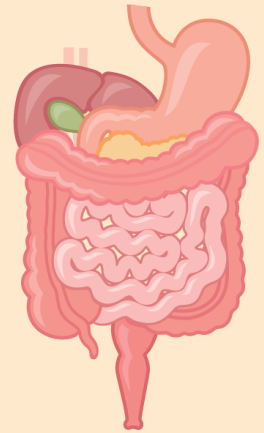
Death

↓10%

Major Bleeding



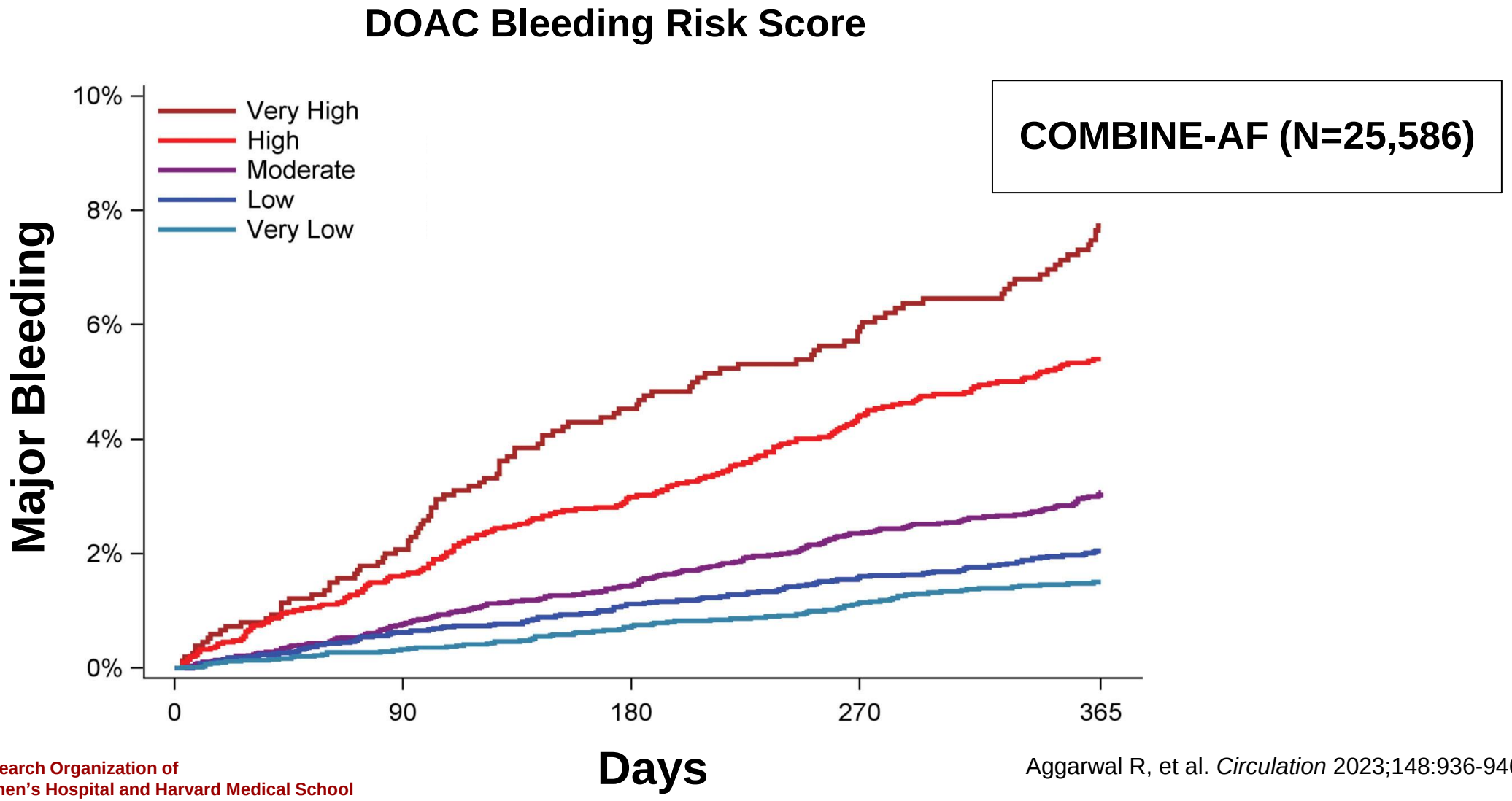
↓14%



↑25%

Ruff CT, et al. *Lancet* 2014;383:955-962
Carnicelli AP, et al. *Circulation* 2022;145:242-255

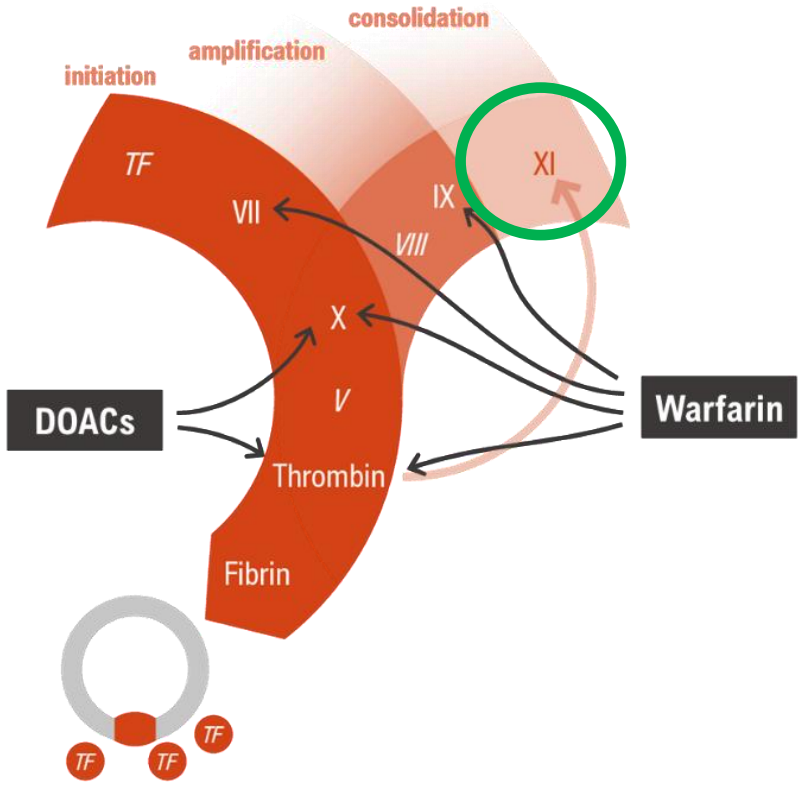
DOACs Safer than VKAs but Bleeding Still a Problem



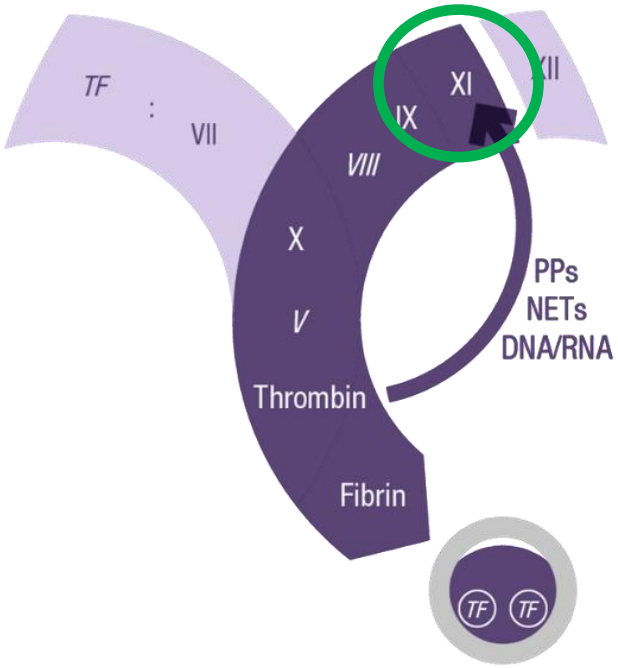
Aggarwal R, et al. *Circulation* 2023;148:936-946

Factor XI Inhibition

Potential to Uncouple Hemostasis from Thrombosis



Consolidated clot

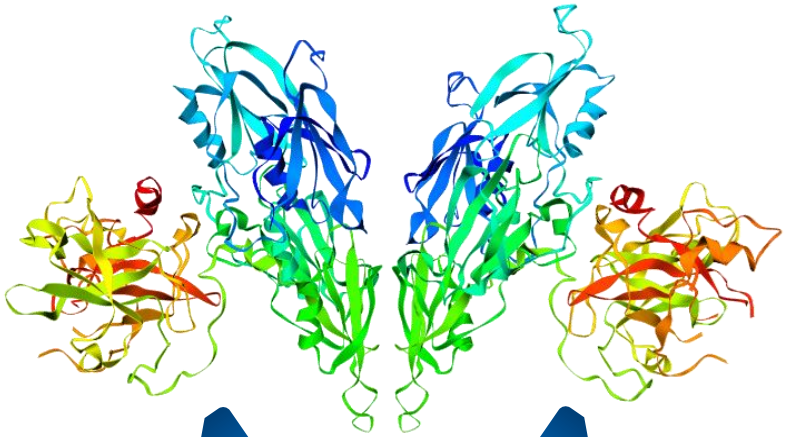


Stable thrombus

Hsu C, et al. *J Am Coll Cardiol* 2021;78:625-631

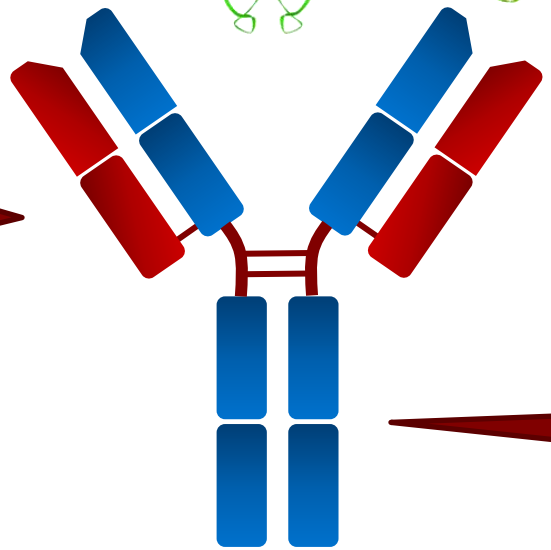
Abelacimab

Highly selective, fully human monoclonal antibody



Factor XI

Homodimeric structure (two identical subunits)



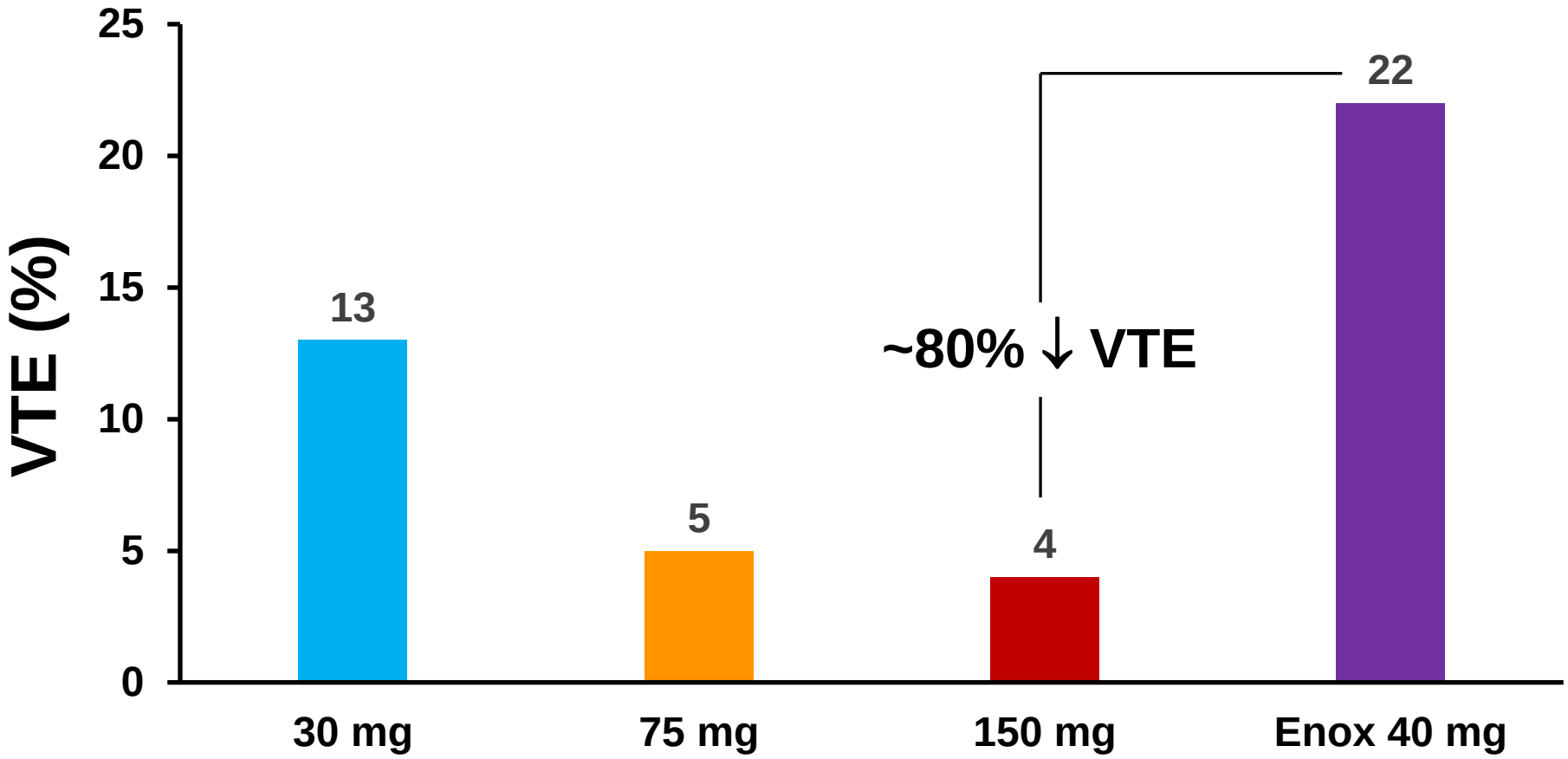
Binds to Factor XI and locks it in the inactive state preventing the formation of activated factor XI (FXIa).

Modifications to minimize the chances of off-target effects

Papagrigoriou E, et al. *Nat Struct Mol Biol* 2006;13:557-558

Abelacimab for Prevention of Venous Thromboembolism

Phase 2, Open-Label, RCT in 400 Patients After Total Knee Placement

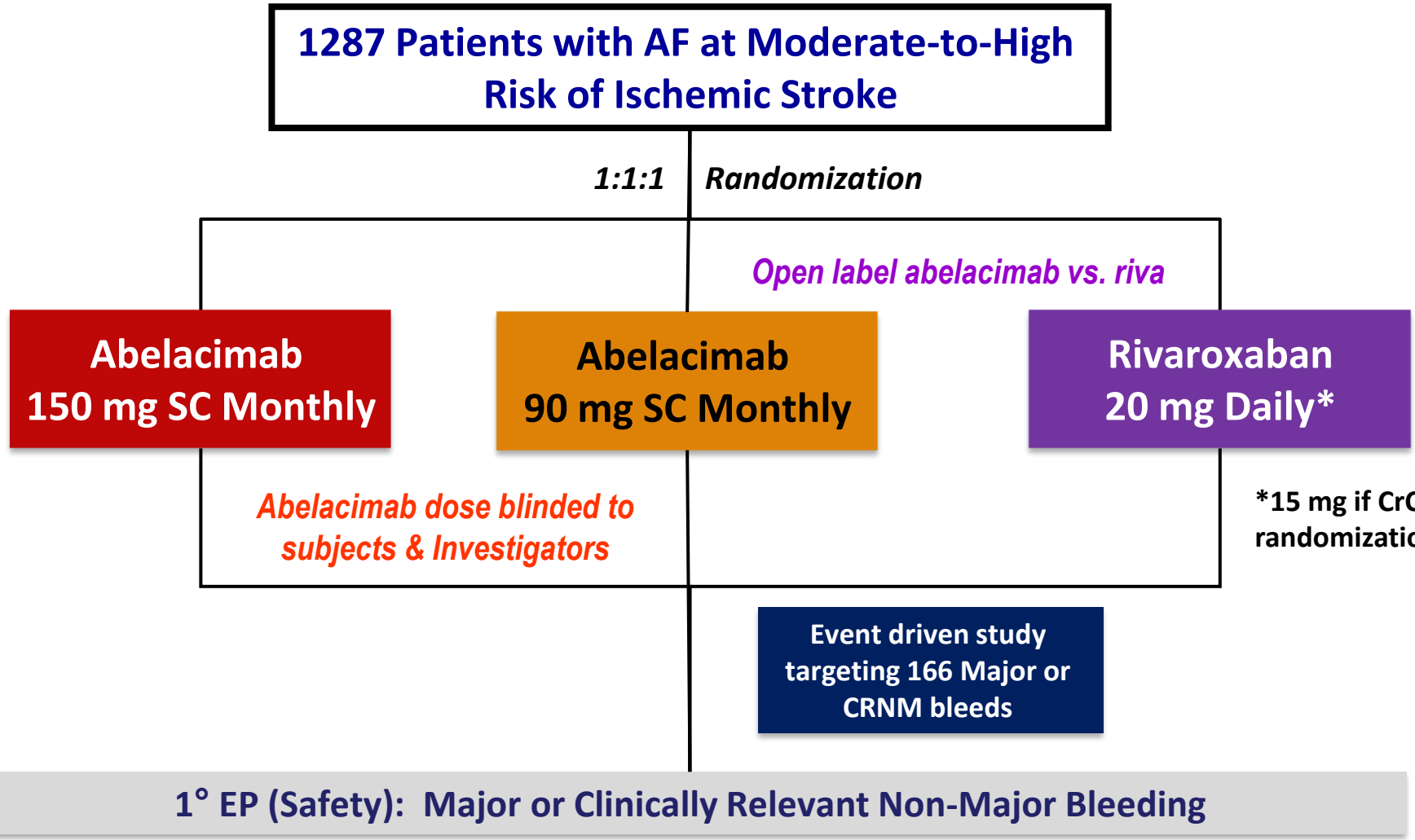


Verhamme P, et al. *N Eng J Med* 2021;385:609-617

Objective

To evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with AF at moderate-to-high risk of stroke

Trial Design



Trial Organization

TIMI Study Group

Marc S Sabatine (Chair)
Robert P Giugliano (Sr Investigator)
Polly Fish (Director of Operations)
Stephen D. Wiviott (CEC Chair)
Christian T Ruff (Global PI)
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S. MacDonnell & M. Lee (Operations)
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Erica Goodrich (Statistics)

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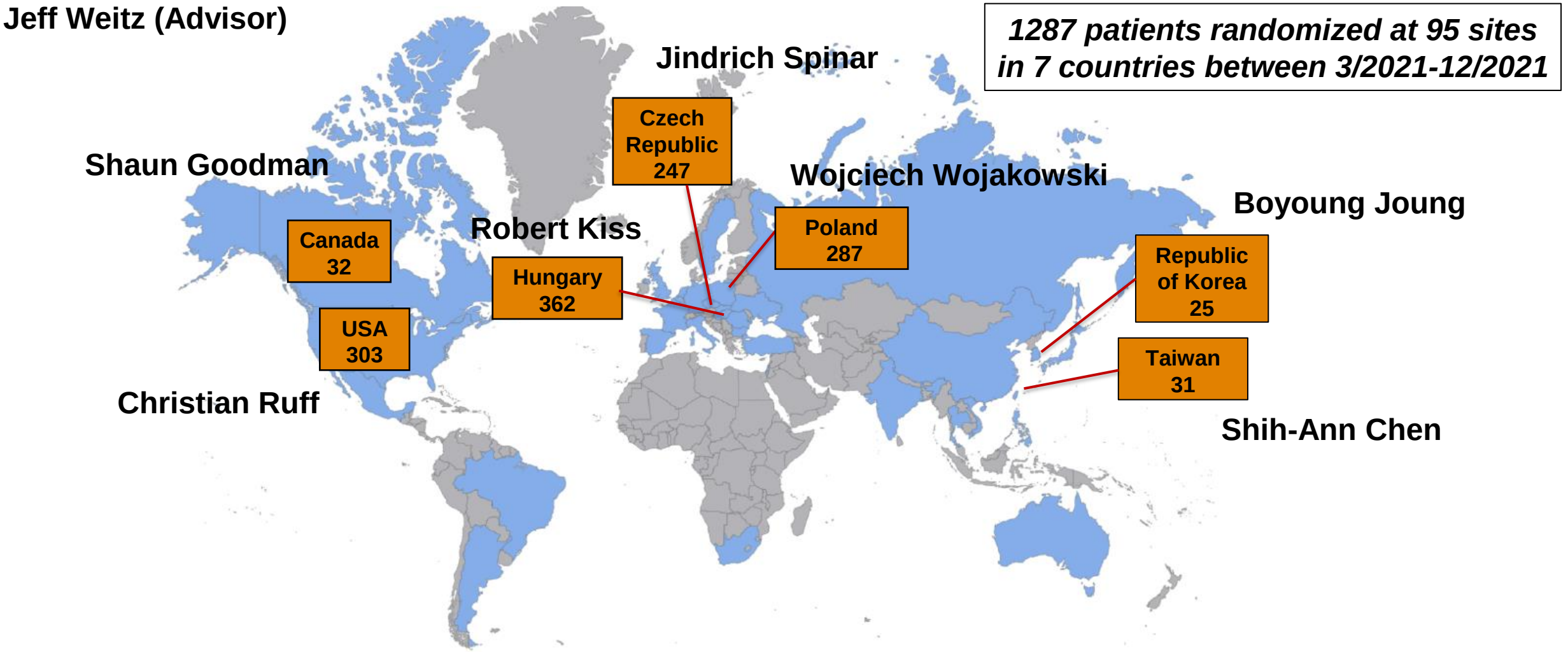
Jonathan Halperin
Phil Wells
John Eikelboom
Sheryl Kelsey
Anthony Maraveyas

Global Enrollment & National Lead Investigators



1287 patients randomized at 95 sites in 7 countries between 3/2021-12/2021

Key Inclusion Criteria

- **Age ≥55 years**
- **Any history of AF or atrial flutter with planned anticoagulation**
- **CHA_2DS_2-VASc ≥4** ***or***

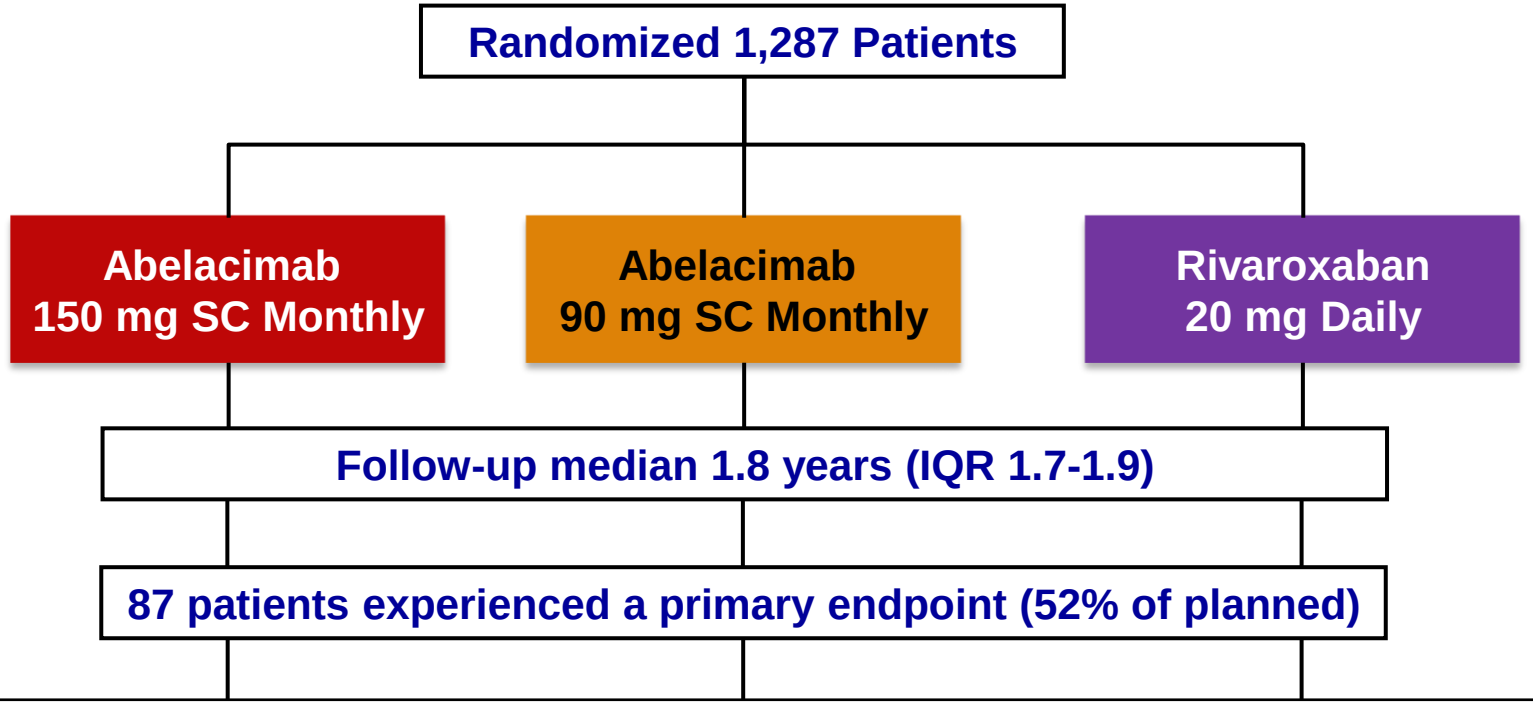
  CHA_2DS_2-VASc = 3 with at least one of the following factors:
  - **Planned concomitant use of antiplatelet medications**
  - **CrCl ≤50 ml/min**

DMC Recommendation

September 14, 2023

"The IDMC members unanimously agreed to recommend termination of the AZALEA trial because of the substantially greater than anticipated reduction in major and clinically relevant non-major bleeds in the abelacimab arms compared to rivaroxaban and a benefit:risk favoring abelacimab."

Follow-up



Premature prem. drug discontinuation	4.7%/yr	4.5%/yr	4.1%/yr
Withdrew consent	0.4%/yr	1.3%/yr	0.5%/yr
Lost to follow-up	0	0	2

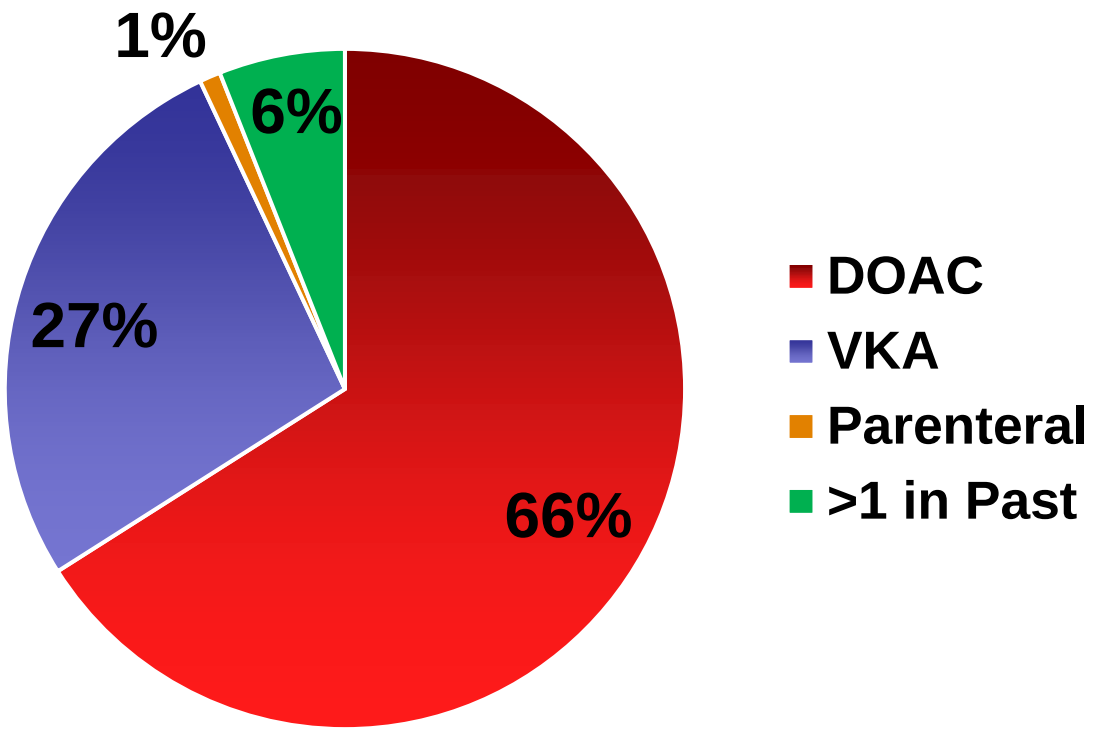
Baseline Characteristics

Characteristic	Value
Age, years, median (IQR)	74 (69-78)
Female Sex (%)	44
CHA_2DS_2-VASc Score, median (IQR)	5 (4-5)
3-4 (%)	46
5 (%)	31
≥6 (%)	22
Prior Ischemic Stroke (%)	15
Prior Bleed (%)	7
Creatinine Clearance ≤ 50 mL/min (%)	21

Pooled data; no differences between treatment arms

Baseline Antithrombotic Use

Anticoagulation Experienced (≥ 60 Days): 92%

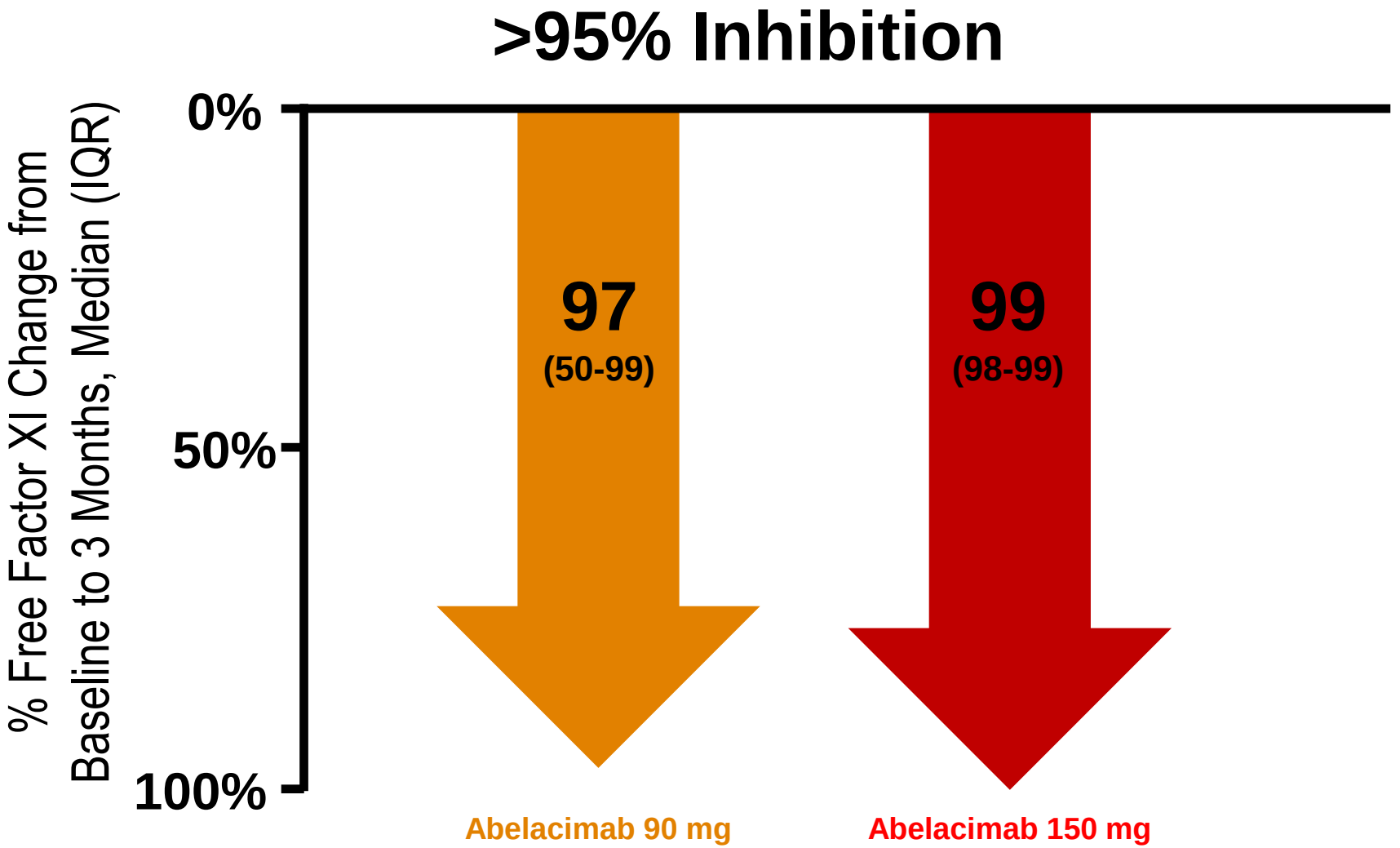


Planned Antiplatelet Use: 24%

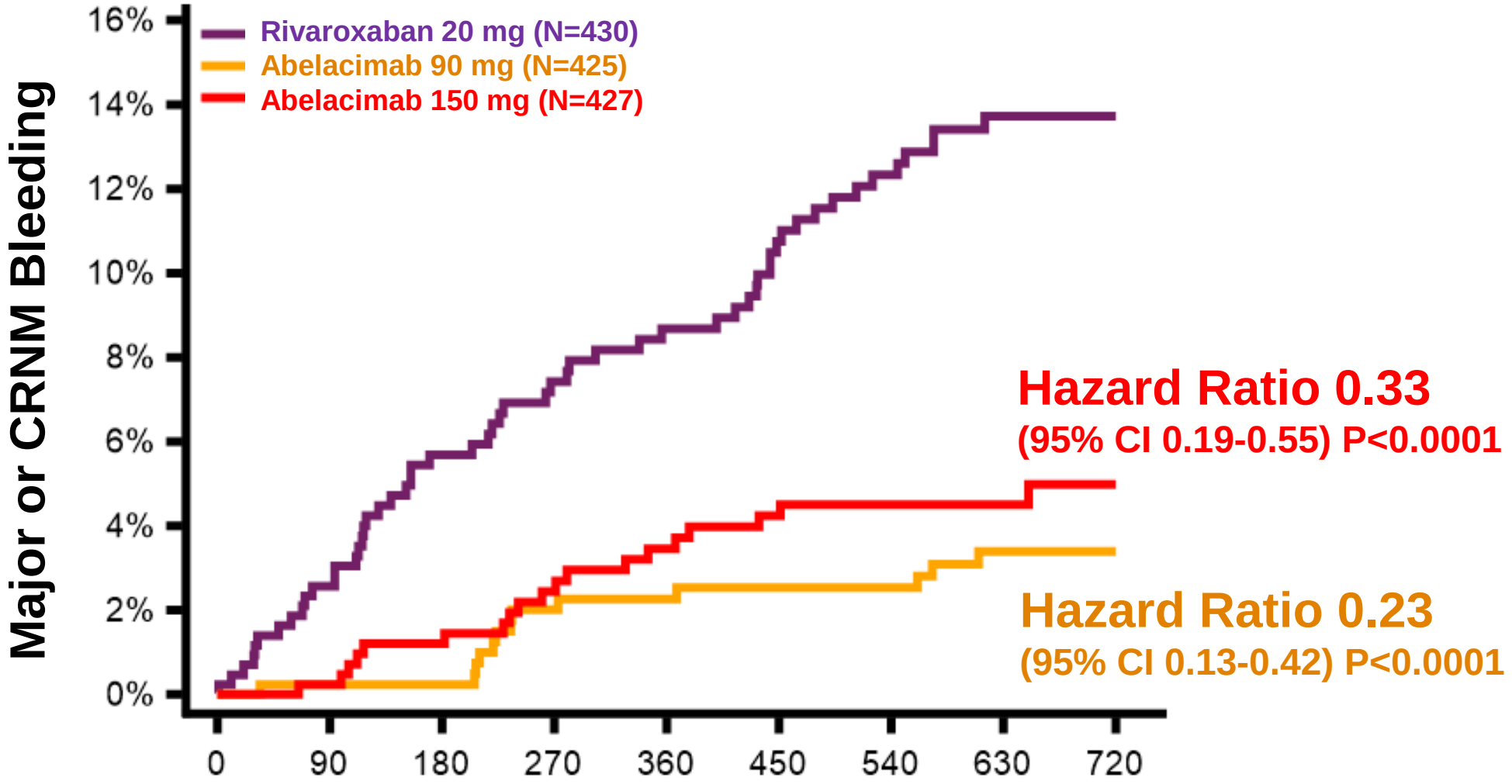
Antiplatelet Regimen	%
Aspirin	16
$P2Y_{12}$ Inhibitor	8
DAPT	2

Pooled data; no differences between treatment arms

Factor XI Inhibition (%)



Primary Endpoint



On-Treatment Population
Based on final DMC Datacut

Bleeding Endpoints

Endpoint (ISTH Definition)	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Major + CRNM Bleeding	8.1	2.7	0.33 (0.19-0.55)	<0.001	1.9	0.23 (0.13-0.42)	<0.001
Major Bleeding	3.7	1.0	0.26 (0.11-0.61)	0.002	0.7	0.19 (0.07-0.50)	<0.001
GI Bleeding	2.1	0.1	0.07 (0.01-0.50)	0.008	0.1	0.07 (0.01-0.51)	0.009
ICH	0.6	0.3	0.50 (0.09-2.72)	0.42	0.6	1.03 (0.26-4.10)	0.97
CRNM Bleeding	4.6	1.8	0.39 (0.21-0.75)	0.004	1.1	0.25 (0.11-0.54)	<0.001

Incidence rates per 100 Pt-years

On-Treatment Population
Based on final DMC Datacut

Exploratory Endpoints

Endpoint	Riva 20 mg (N=430) Incidence Rate	Abelacimab 150 mg (N=427) Incidence Rate	HR (95% CI)	P Value	Abelacimab 90 mg (N=425) Incidence Rate	HR (95% CI)	P-Value
Stroke or SEE	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Stroke	1.0	1.1	1.13 (0.41-3.12)	0.81	1.4	1.45 (0.55-3.80)	0.45
Ischemic	0.7	1.1	1.59 (0.52-4.85)	0.42	1.3	1.82 (0.61-5.45)	0.28
Hemorrhagic	0.3	0	N/A	N/A	0.1	0.51 (0.05-5.62)	0.58
All-Cause Death	3.1	2.4	0.77 (0.41-1.46)	0.43	2.8	0.93 (0.51-1.71)	0.83
Net Clinical Outcome	11.3	5.5	0.49 (0.33-0.71)	<0.001	5.6	0.49 (0.34-0.73)	<0.001

Net Clinical Outcome: Ischemic Stroke, Systemic Embolism, Major or CRNM Bleed, All-Cause Death
Incidence rates per 100 Pt-years

On-Treatment Population
Based on final DMC Datacut

Safety

	Rivaroxaban 20 mg (N=430)	Abelacimab 150 mg (N=427)	P Value	Abelacimab 90 mg (N=425)	P-Value
Adverse Event (%)					
Any	79	82	0.29	81	0.50
Serious	35	31	0.22	33	0.60
Led to D/C of Study Drug	6	6	0.65	6	0.85
Injection Site Reaction	N/A	3	N/A	2	NA

On-Treatment Population
Based on final DMC Datacut

Summary for Abelacimab

Potent inhibition of FXI:

- >95% inhibition over the dosing interval

Substantial reduction in bleeding with the 150 mg dose compared with rivaroxaban:

- 67% ↓ major or clinically relevant non-major bleeding
- 74% ↓ major bleeding
- 93% ↓ major GI bleeding

Ongoing Phase 3 Trial of Abelacimab in AF