

PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

9^a Edizione

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30 Settembre
1 Ottobre
2022

Centro Congressi di Confindustria
Auditorium della Tecnica



Il futuro della terapia antitrombotica: **Anticoagulanti e cardiopatia ischemica**

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Roma

30 Settembre 2022



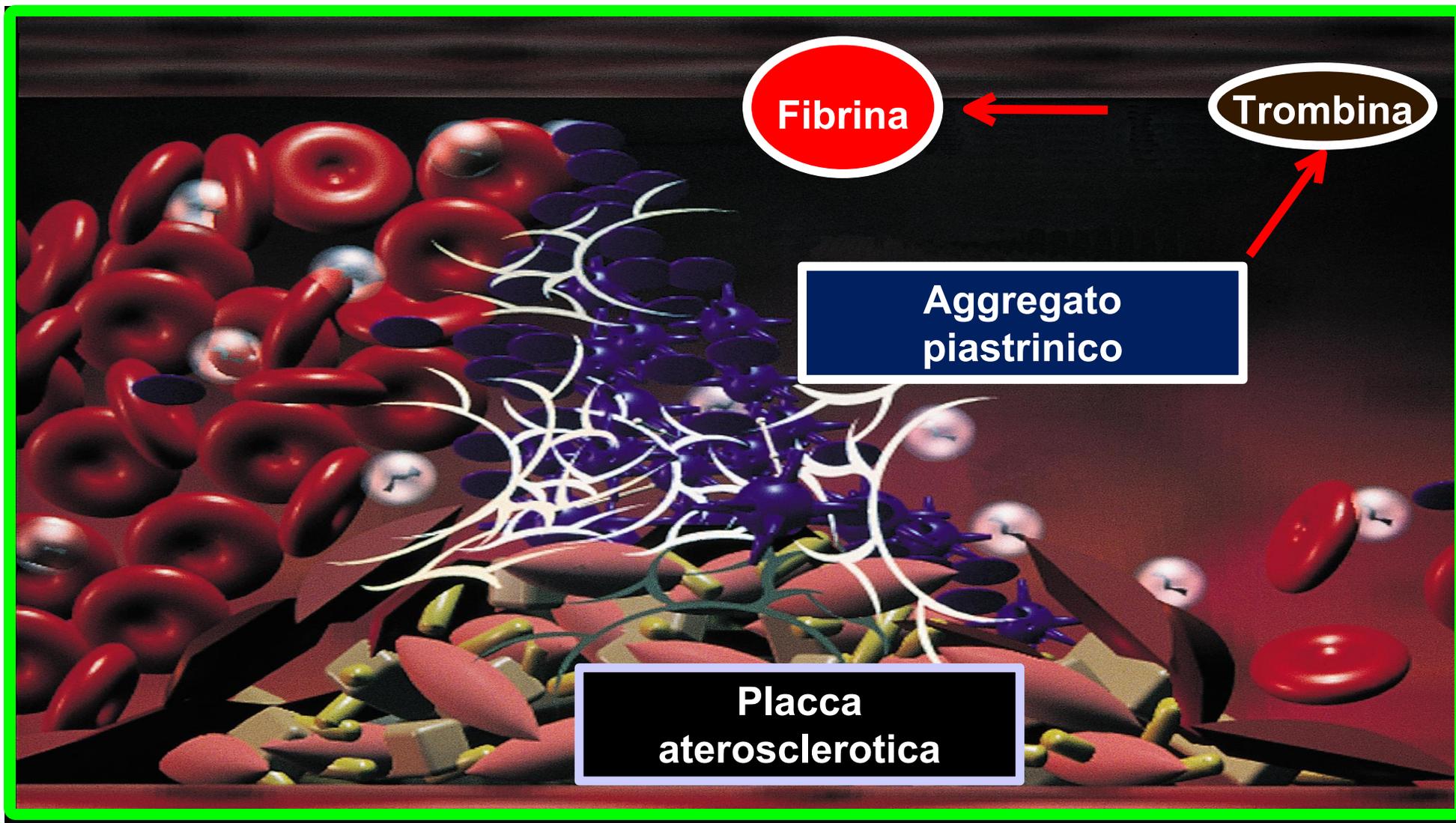
Conflitto di interessi



Nessuno

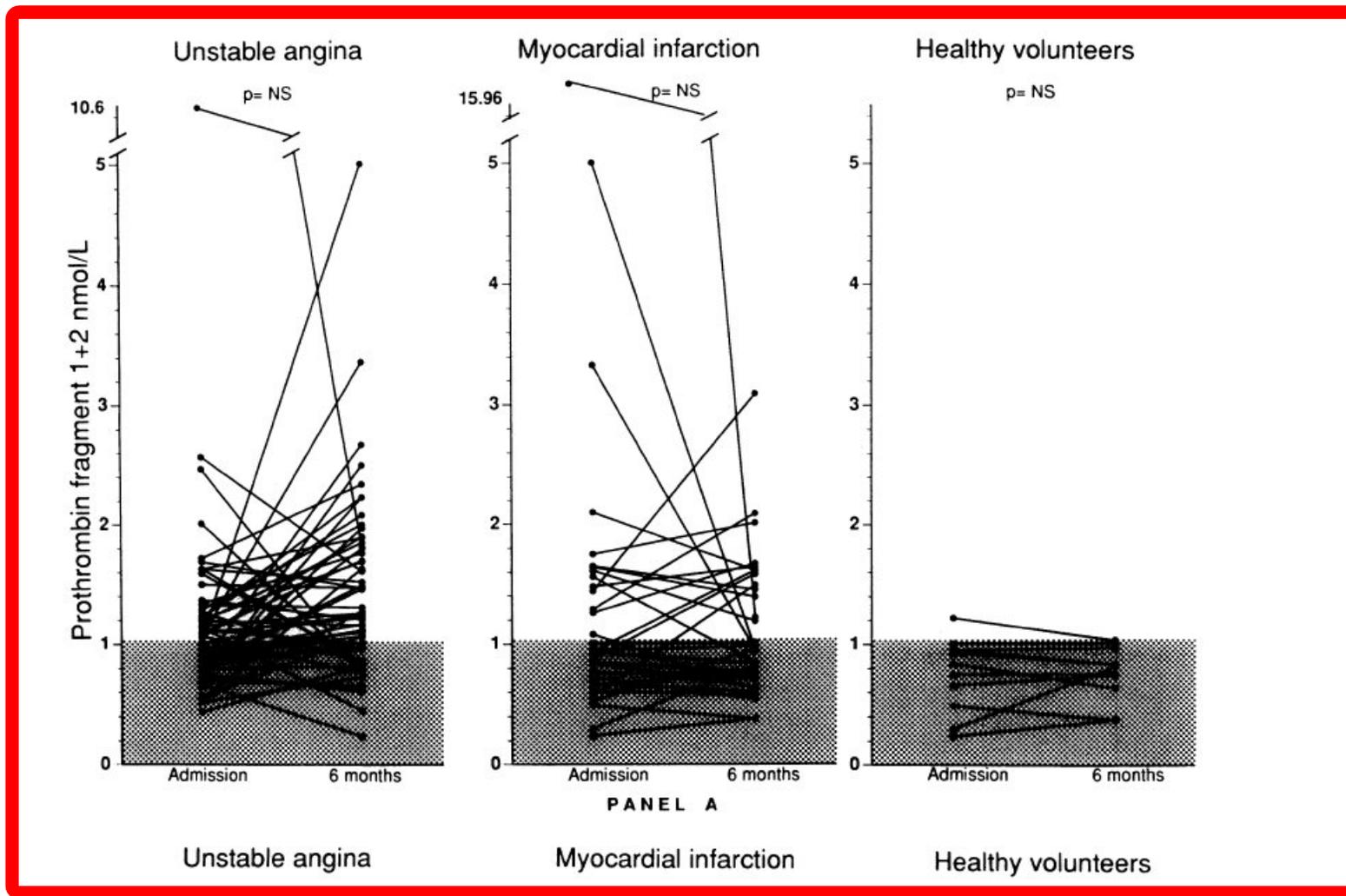


Anticoagulanti orali nella cardiopatia ischemica?





Persistente produzione di trombina nel tempo



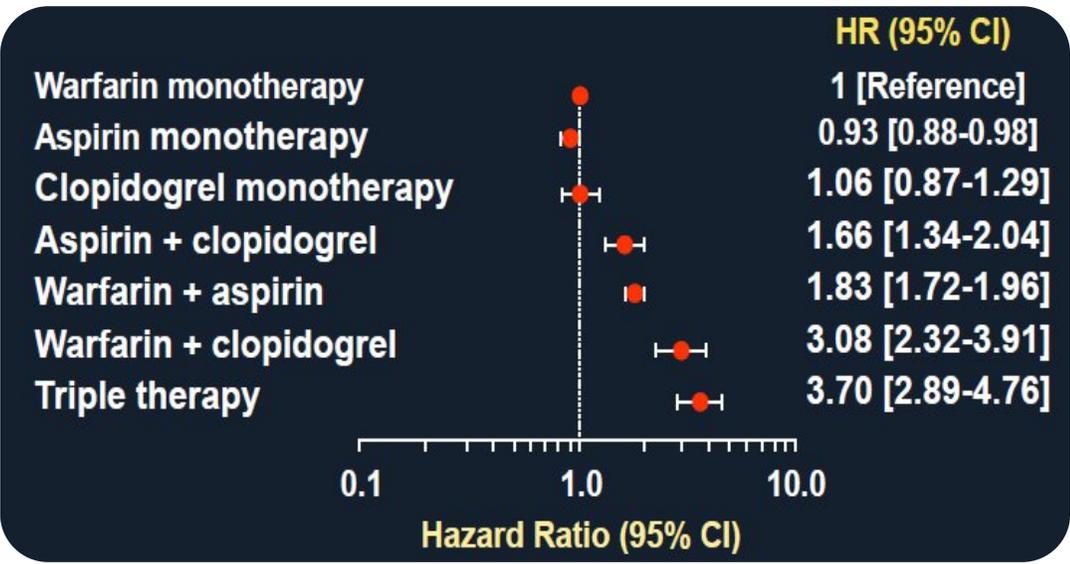
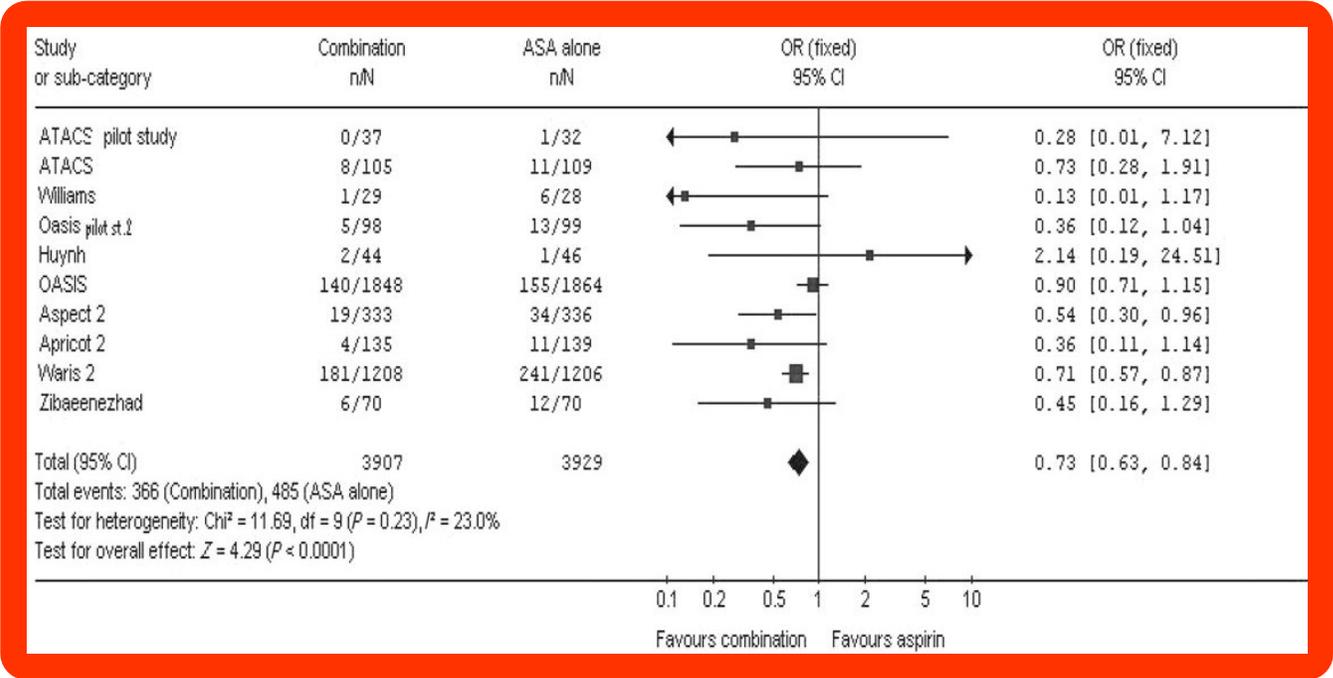


Studi con il Warfarin



BUT...

Morte, infarto non fatale ed ictus



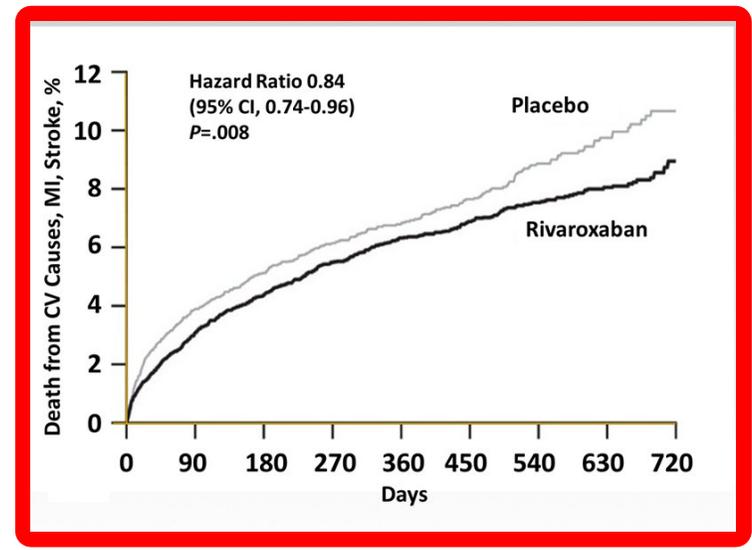
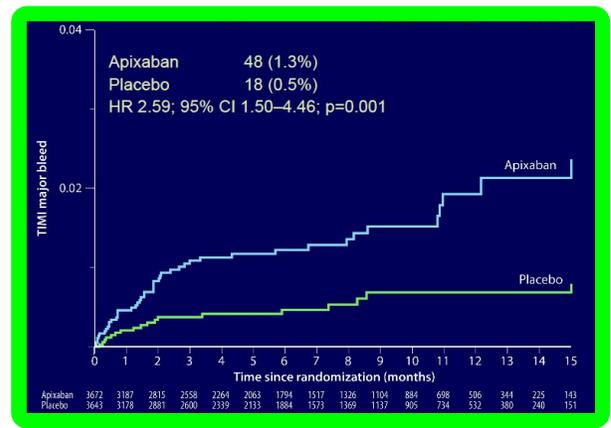
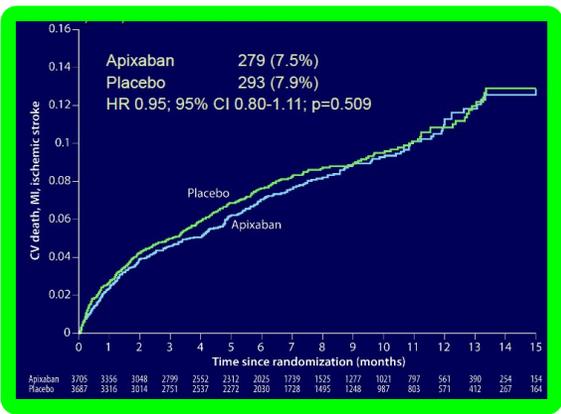


DOAC nella cardiopatia ischemica



APPRAISE-2: Apixaban

ATLAS TIMI 51: Rivaroxaban

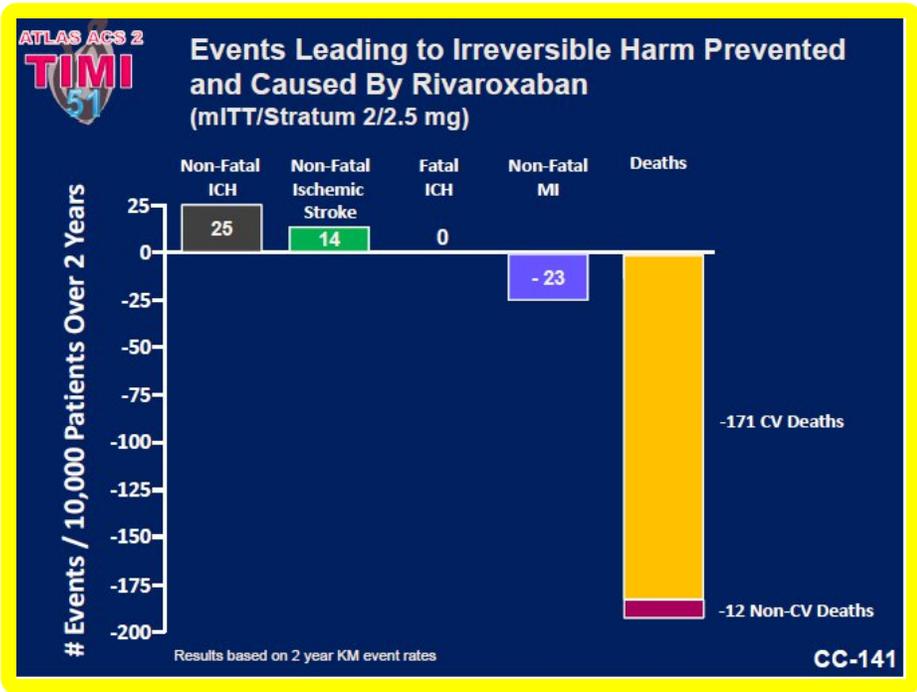


Studio interrotto precocemente per sanguinamenti in assenza di efficacia





Scarsa possibilità di impiego



ESC
European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575

ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

• Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.^{182,183}

I	C
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Vantaggio significativo



Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001



Net clinical benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005





Confronto con altre terapie



	Rivaroxaban + aspirin ^[a]	Lipid-lowering (1 mmol/L) ^[b]	BP-lowering (10 mm Hg) ^[c]	ACE Inhibitor ^[d]	SGLT2 inhibitor (Empagliflozin) ^[e]	PCSK9 inhibitor (Alirocumab) ^[f]
Triple outcome	-24%	-21%	-20%	-18%	-14%	-14%
Death	-18%	-9%	-13%	-14%	-32%	-15%
Stroke	-42%	-15%	-27%	-23%	+18%	-27%
MI	-14%*	-24%	-17%	-18%	-13%	-14%

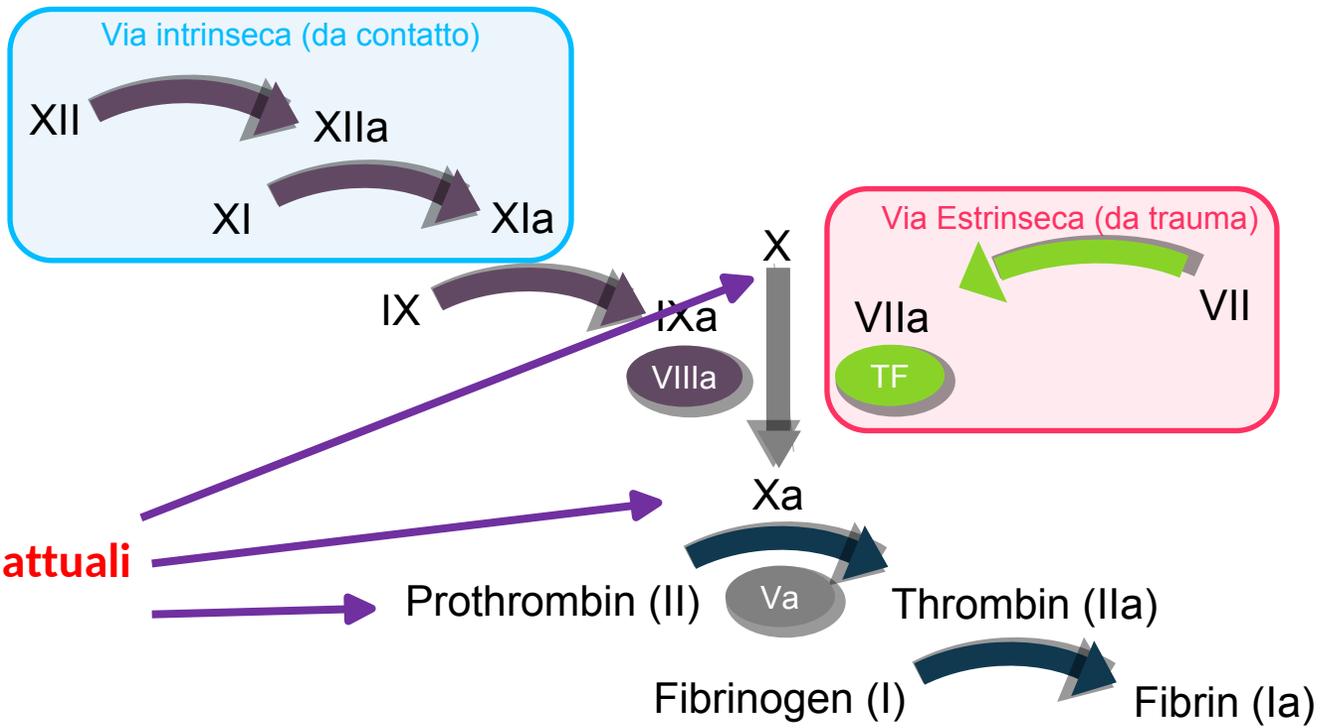
*Not significant,

a. Eikelboom JW, et al. *N Engl J Med.* 2017;377:1319-1330; b. CTT Collaboration. *Lancet.* 2015;385:1397-1405; c. Ettehad D, et al. *Lancet.* 2016;387:957-967; d. Dagenais GR, et al. *Lancet.* 2006; 368:581-588; e. Zinman B, et al. *N Engl J Med.* 2015; 373: 2117-2128; f. Schwartz GG, et al. *N Engl J Med.* 2018;379:2097-2107.



E il domani?

L'emostasi è prevalentemente mediata dalla via estrinseca della coagulazione



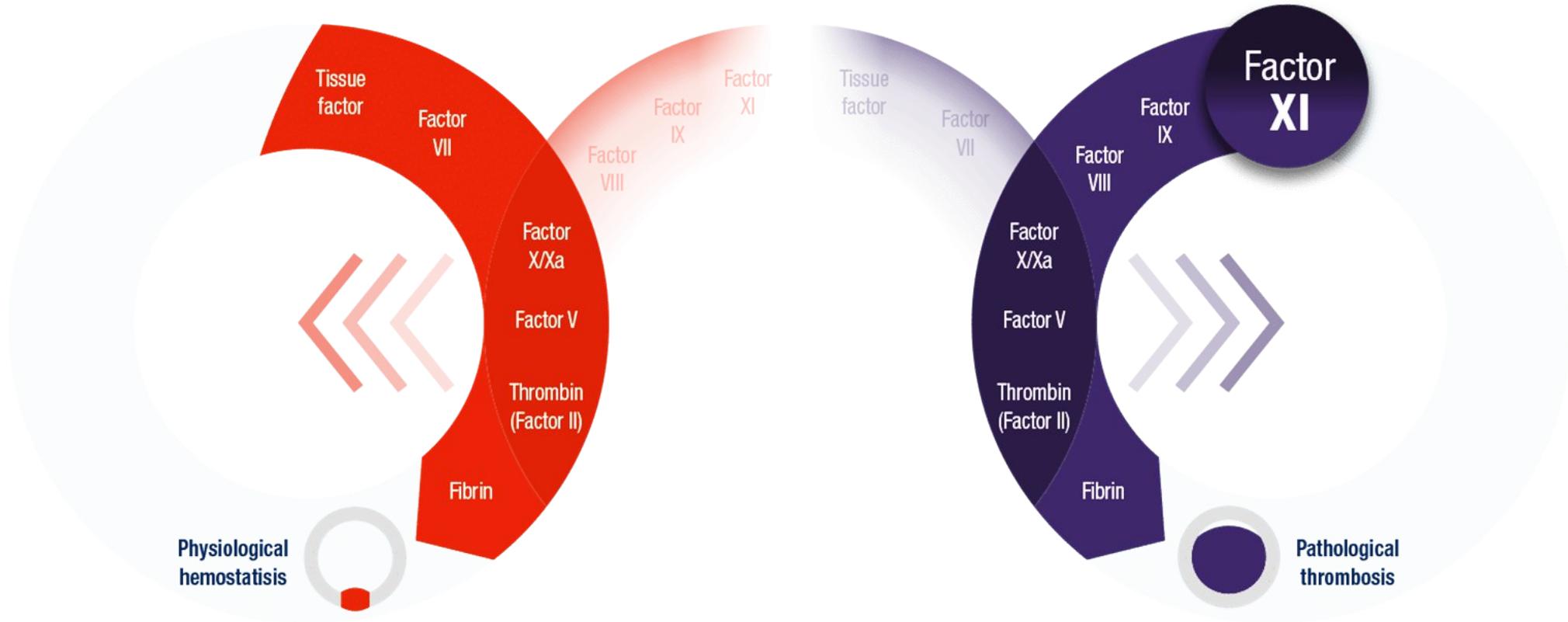
Target dei farmaci attuali

L'attivazione del fattore XI è essenziale per la crescita e stabilizzazione del trombo



Lo scenario ideale

Pharmacologically **uncouple** the pathways

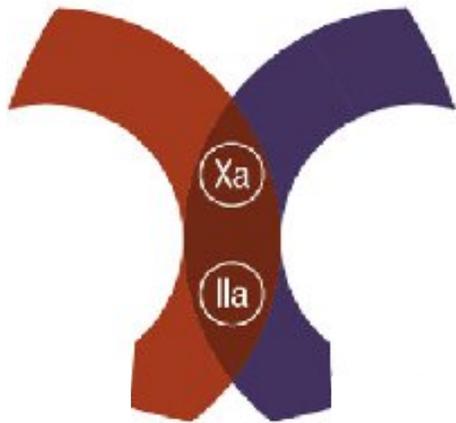


Hsu C et al. JACC 2021;78:625-631



Gli attuali farmaci

Heparins





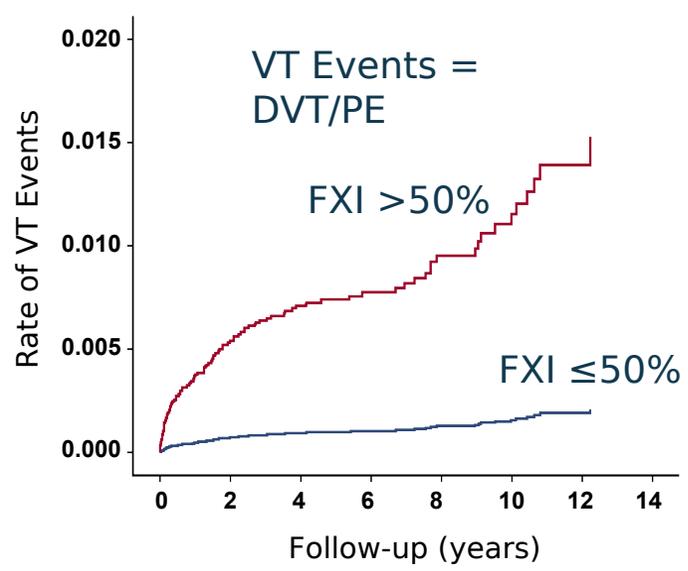
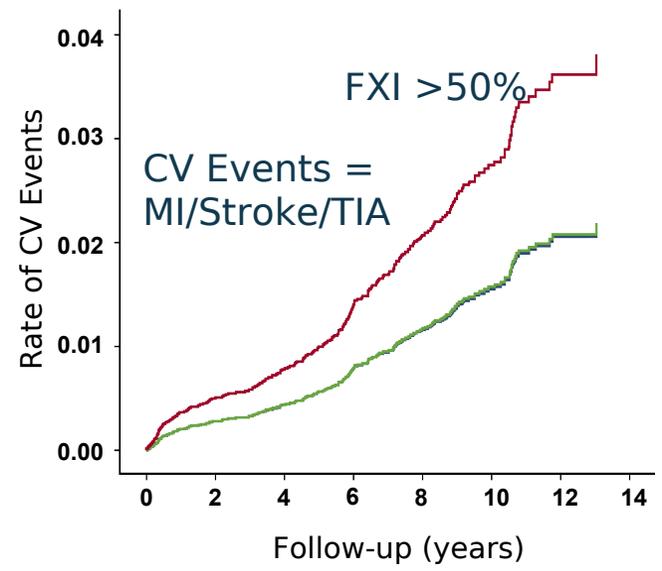
Perchè inibire il fattore XI?



FXI deficiency and CV- as well as VT-events

Razionale

FXIa inhibition may decouple hemostasis from thrombosis, preventing pathologic clots and strokes while preserving clotting after injury



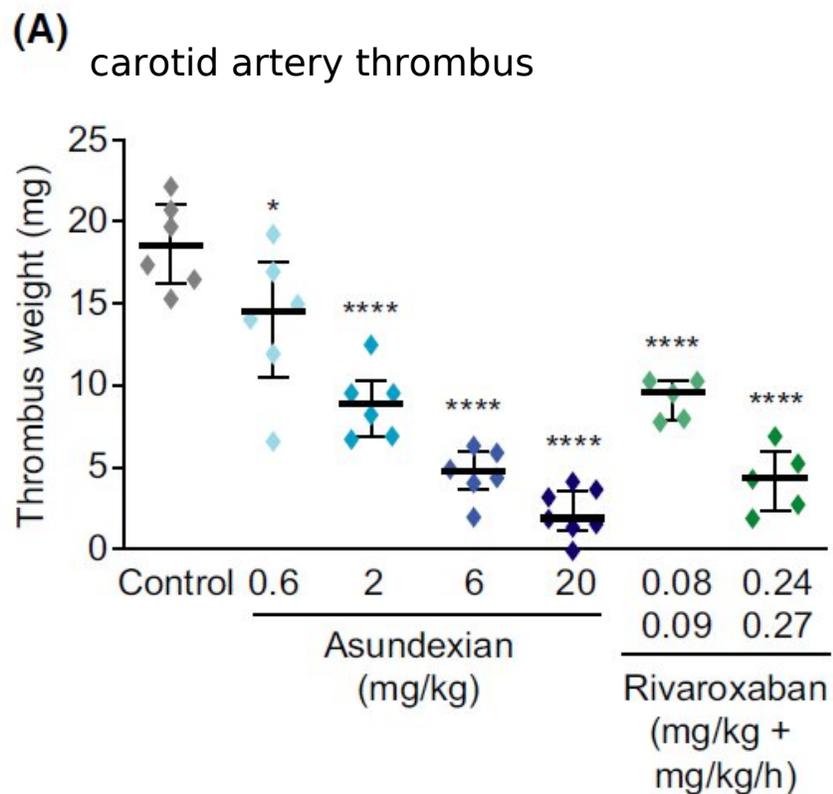
Studi di genetica

Preis M, Blood 2017



Risultati sull'animale

FeCl2-induced damage to carotid artery model in rabbits



FXIa inhibitor vs FXa inhibitor:
similar anticoagulant effects results, different bleeding effects

Heitmeier S et al. *J Thromb Haemost* 2022;20(6):1400-1411



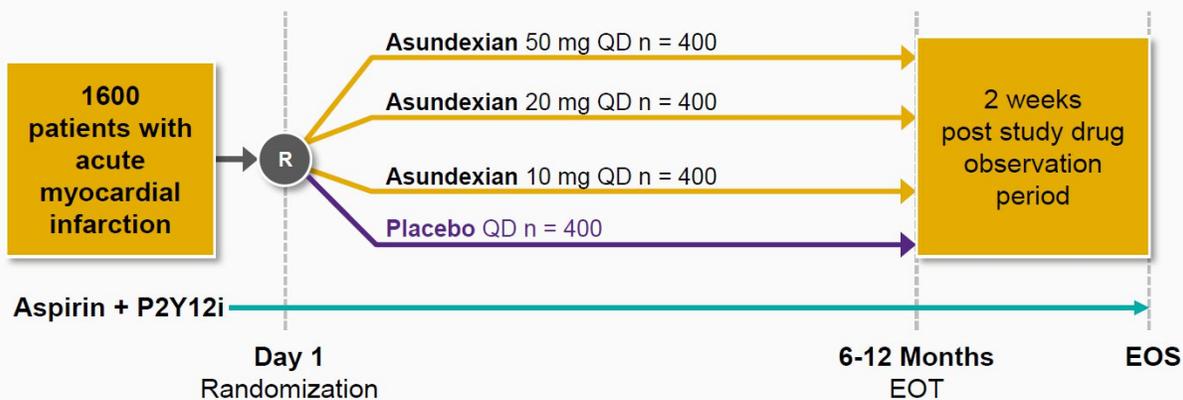
Primi studi nella cardiopatia ischemica



Prospective, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study

Objective:

To evaluate safety and explore the efficacy of 3 doses of asundexian vs placebo in with acute MI treated with dual antiplatelet therapy



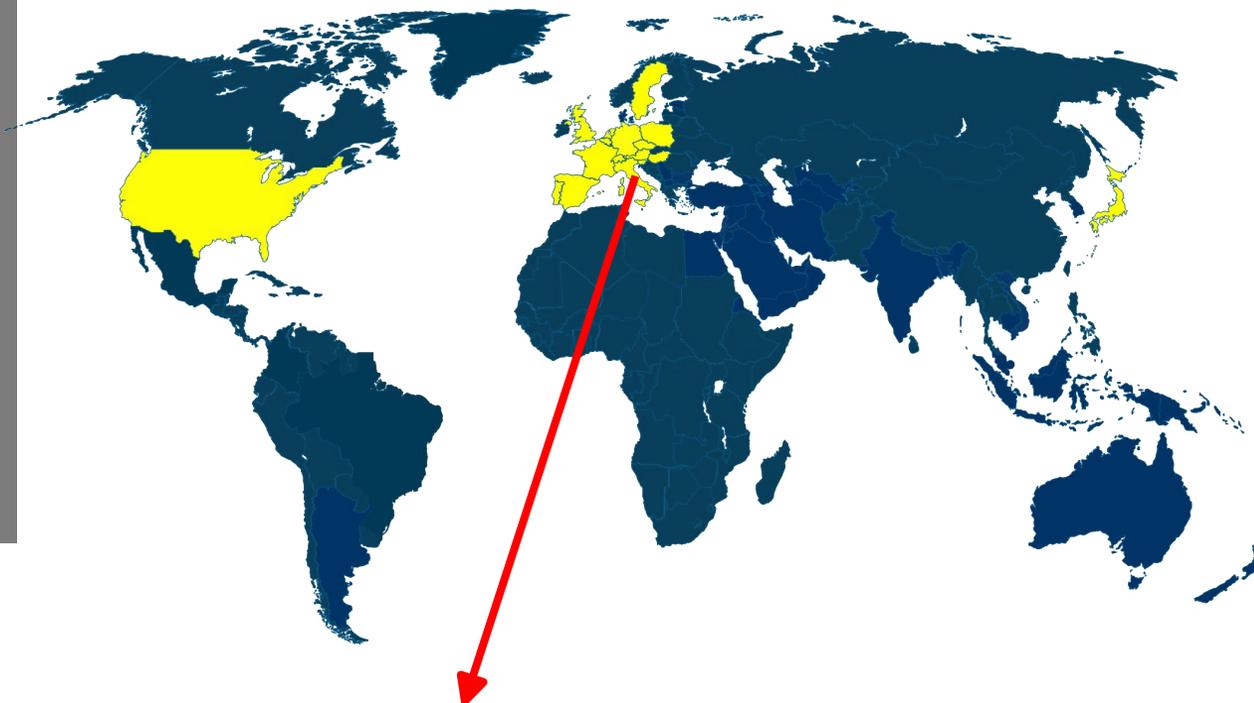
Quantification of Factor XIa inhibition

Safety outcomes:

Significant (BARC type 2, 3, or 5) bleeding and any bleeding

Efficacy outcome: CV-death, MI, stroke, or stent thrombosis

157 sites, 14 countries
 June 2020 to July 2021



Ospedale Sandro Pertini – 
 Dott. Alessandro Sciahbasi



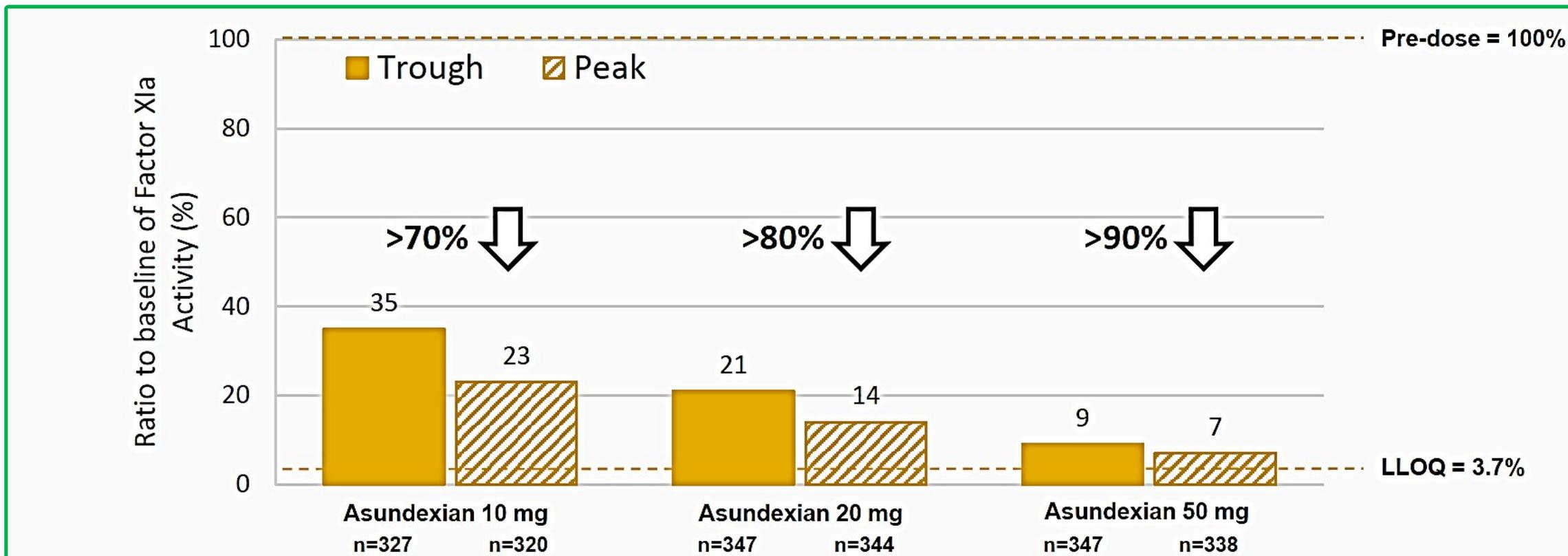
PACIFIC-AMI- Caratteristiche di base



	Asundexian 10 mg N = 397	Asundexian 20 mg N = 401	Asundexian 50 mg N = 402	Placebo N = 401
Age (yrs), median (25 th , 75 th)	67 (62, 73)	68 (61, 73)	68 (63, 73)	68 (60, 73)
Female, %	23	22	25	22
Race, % White	84	86	86	85
Asian	13	13	12	13
Weight (kg), median (25 th , 75 th)	80 (70, 91)	80 (70, 92)	80 (72, 94)	81 (70, 92)
Diabetes mellitus, %	42	38	39	42
Prior MI, %	27	33	25	27
Prior stroke, %	5.8	4.5	6.5	5.0
Days from MI, median (25 th , 75 th)	4 (3, 5)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Type of MI, % STEMI	54	54	50	46
NSTEMI	46	46	50	54
PCI for Index MI, %	100	99	100	99
P2Y12i, % Ticagrelor/Prasugrel	80	80	80	80
Clopidogrel	20	20	20	20

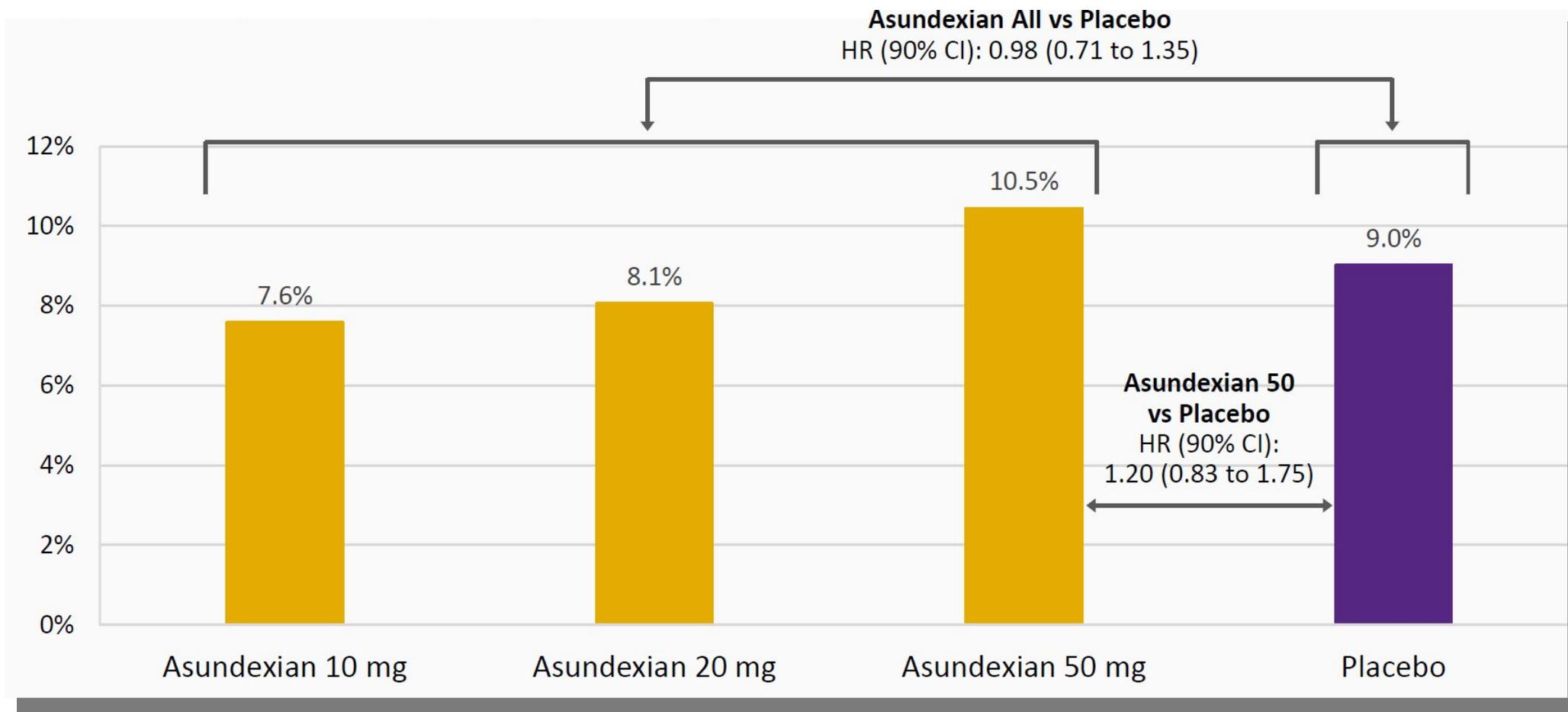


Inibizione Xla





Sanguinamenti (BARC 2, 3 e 5)

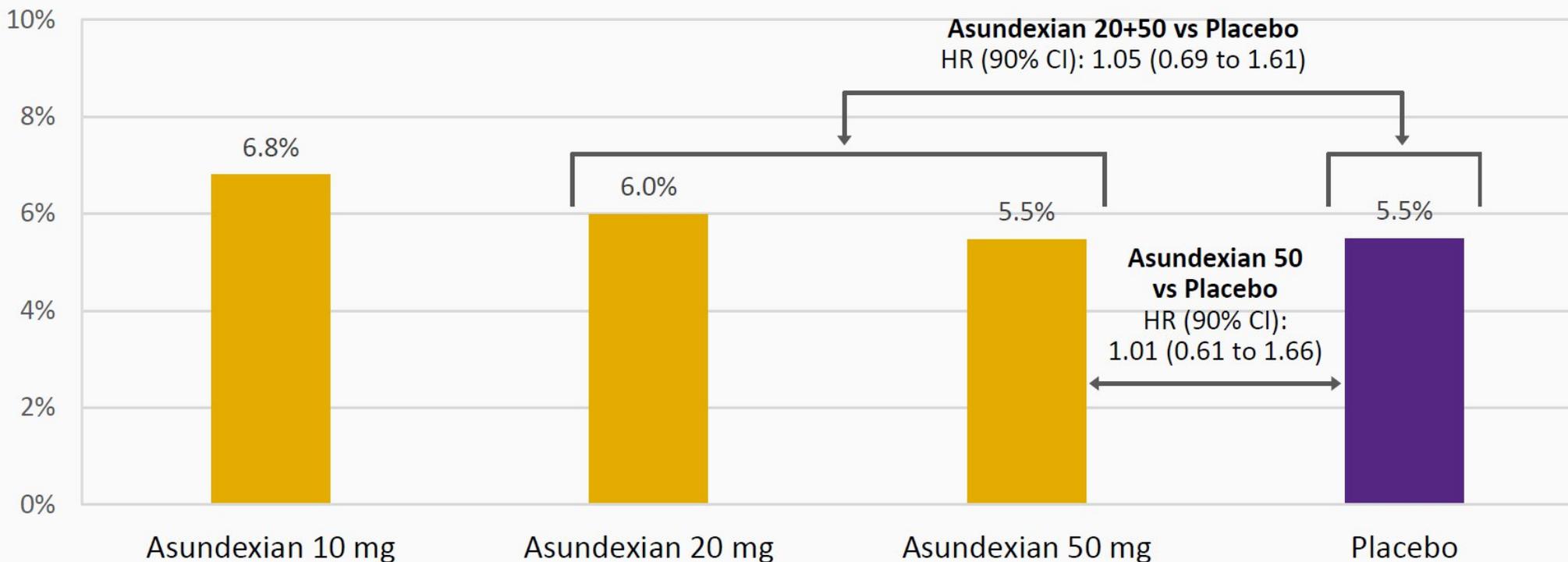




End-point di efficacia



CV Death, MI, Stroke or Stent Thrombosis



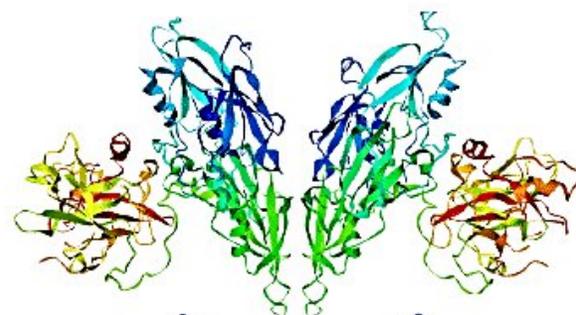
- No reduction in ischemic events with any dose of asundexian compared with placebo, however only 95 events across 4 arms and thus wide confidence intervals.

These data, together with existing genetic and preclinical evidence, support the further investigation of asundexian, as a potentially safer anticoagulant, in an adequately powered phase 3 clinical trial of patients following an acute myocardial infarction.



E dopo-domani?

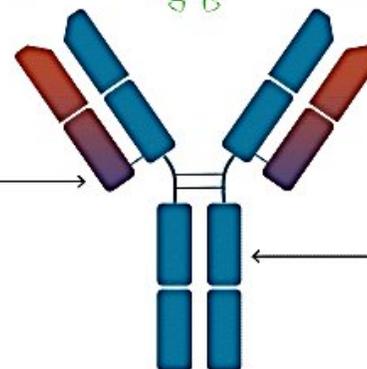
Abelacimab is a highly selective, fully human monoclonal antibody



Factor XI
Homodimeric structure¹
(two identical subunits)



Binds to both Factor XI and Factor XIa with very high affinity and selectivity



Modified to minimize the chances of off target effects

Abelacimab

Phase I and 2 clinical studies confirmed that a single 150mg dose of abelacimab (intravenous or subcutaneous) effectively suppresses Factor XI for at least 30 days.



Il nostro piccolo contributo

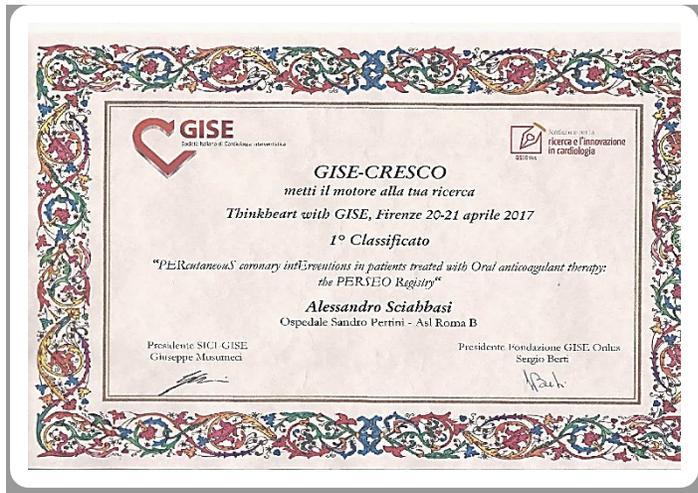


**PERcutaneous coronary
intErventions in patients treated
with Oral anticoagulant therapy:
the PERSEO Registry**



Reclutati oltre 1200 pazienti

**Follow up ad 1 anno atteso a
Febbraio 2023**



Grazie per l'attenzione...