

Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare
Direttore Prof. Massimo Volpe
Facoltà di Medicina e Psicologia, Università di Roma Sapienza
Anno Accademico 2013-2014

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Progetto Formazione Avanzata in Cardiologia nel Web 2014
Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare

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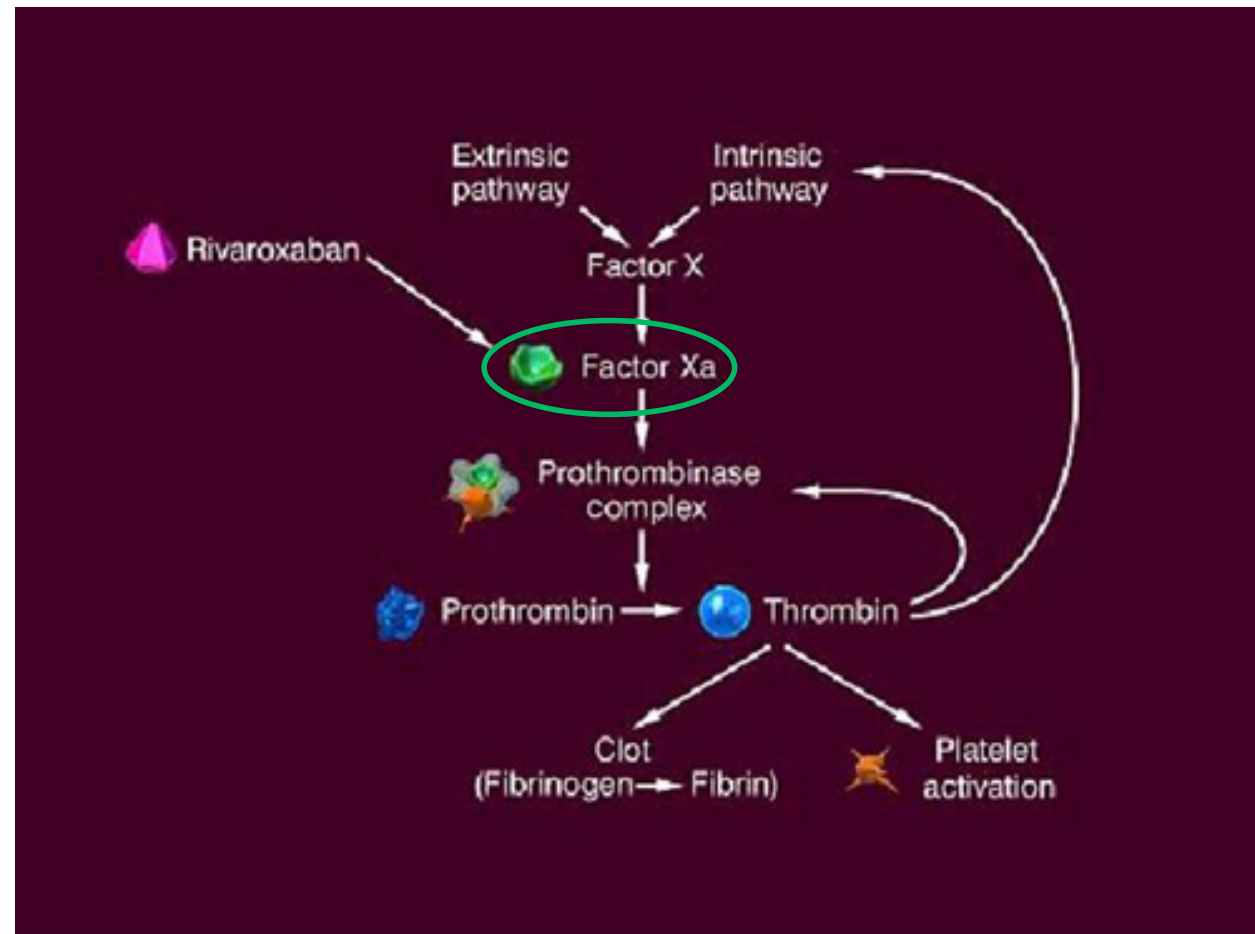
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Rivaroxaban
in patients with a recent acute coronary syndrome

ATLAS ACS 2- TIMI 51





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AIM

- To evaluate how the inhibition of factor Xa with low-dose Rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.



METHODS

- Enrollment:
 - November 2008 - September 2011
 - 15526 patients in 44 Countries
- Randomization:
 - Rivaroxaban 2,5 mg bid
 - Rivaroxaban 5 mg bid
 - Placebo



INCLUSION CRITERIA

- Patients >18 years of age in whom an STEMI, NSTEMI, or unstable angina had been diagnosed.
- Patients <55 years with diabetes mellitus or previous myocardial infarction in addition to the index event.



EXCLUSION CRITERIA

- Platelet count < 90000 per mm^3
- Hemoglobin level < 10 g/dl
- Renal Disease (Clcr < 30 ml/min)
- Gastrointestinal bleeding within 12 months before randomization
- Previous intracranial hemorrhage, ischemic stroke or TIA



STUDY ENDPOINTS

- The primary efficacy endpoint was composite of death from cardiovascular causes, myocardial infarction or stroke.
- The secondary efficacy endpoint was death from any causes, myocardial infarction or stroke.
- The primary safety endpoint was TIMI major bleeding not related to CABG.

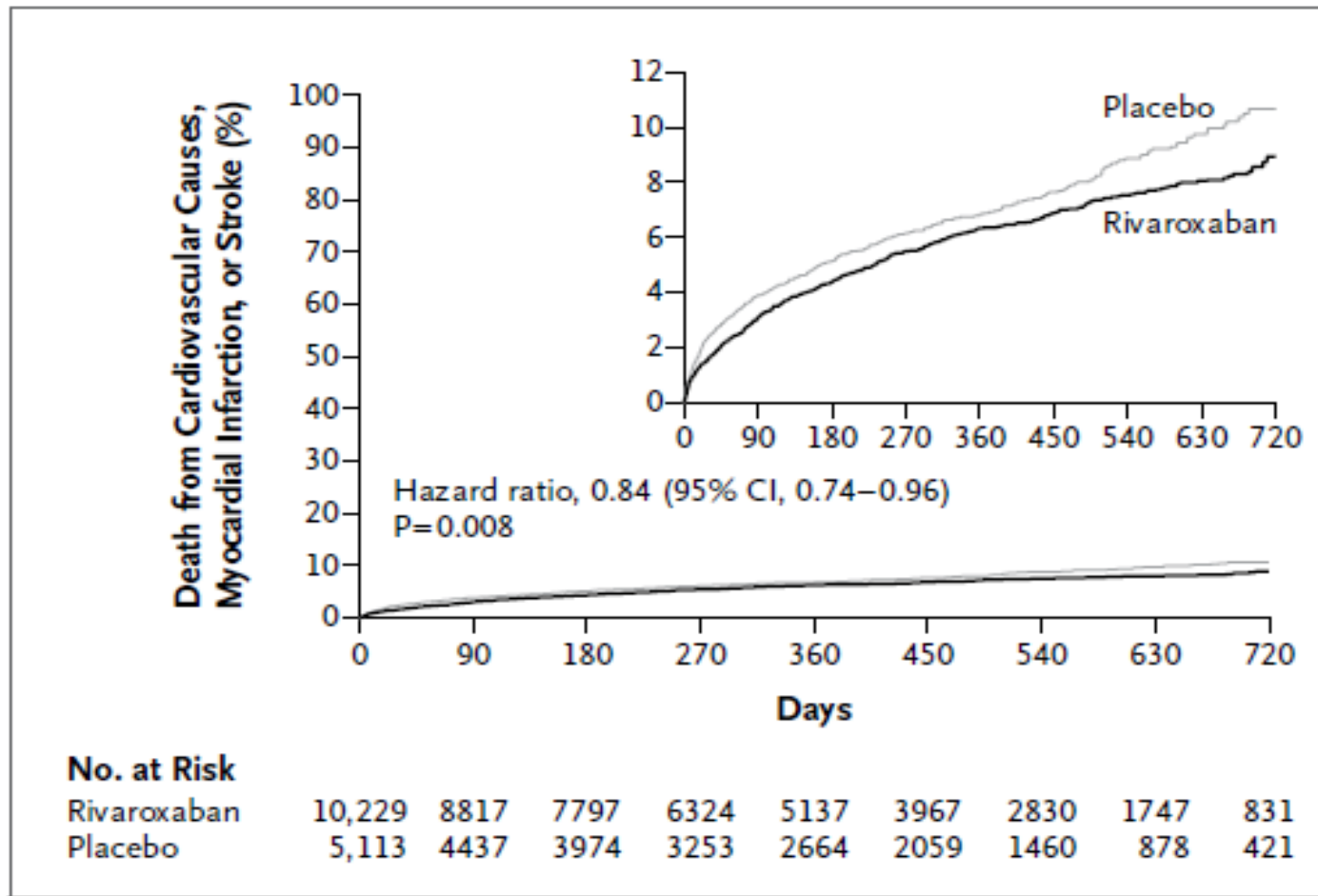


GENERAL CHARACTERISTICS

Characteristic	Rivaroxaban		Placebo (N= 5176)
	2.5 mg Twice Daily (N=5174)	5 mg Twice Daily (N=5176)	
Age			
Mean — yr	61.8±9.2	61.9±9.0	61.5±9.4
≥65 yr — no. (%)	1905 (36.8)	1921 (37.1)	1835 (35.5)
≥75 yr — no. (%)	466 (9.0)	441 (8.5)	498 (9.6)
Male sex — no. (%)			
	3875 (74.9)	3843 (74.2)	3882 (75.0)
Race — no. (%)†			
White	3798 (73.4)	3815 (73.7)	3796 (73.3)
Black	34 (0.7)	34 (0.7)	39 (0.8)
Asian	1099 (21.2)	1055 (20.4)	1075 (20.8)
Other	243 (4.7)	272 (5.3)	266 (5.1)
Weight — kg			
Median	78.0	78.0	78.0
Interquartile range	68.0–90.0	68.0–88.0	68.0–88.5
Creatinine clearance — ml/min‡			
Median	85.1	84.8	85.6
Interquartile range	68.3–105.0	68.5–104.7	68.1–105.1
Medical history — no. (%)			
Previous myocardial infarction	1363 (26.3)	1403 (27.1)	1415 (27.3)
Hypertension	3470 (67.1)	3499 (67.6)	3494 (67.5)
Diabetes	1669 (32.3)	1648 (31.8)	1647 (31.8)
Hypercholesterolemia	2498 (48.3)	2544 (49.1)	2496 (48.2)
Index diagnosis — no. (%)			
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)
Unstable angina	1252 (24.2)	1257 (24.3)	1221 (23.6)
PCI or CABG for index event — no. (%)			
	3138 (60.6)	3123 (60.3)	3126 (60.4)
Region — no. (%)			
North America	269 (5.2)	293 (5.7)	312 (6.0)
South America	546 (10.6)	583 (11.3)	540 (10.4)
Western Europe	707 (13.7)	775 (15.0)	759 (14.7)
Eastern Europe	2042 (39.5)	2025 (39.1)	2007 (38.8)
Asia	1088 (21.0)	1044 (20.2)	1063 (20.5)
Other	522 (10.1)	456 (8.8)	495 (9.6)
Medications — no. (%)			
Aspirin	5105 (98.7)	5099 (98.5)	5108 (98.7)
Thienopyridine	4790 (92.6)	4812 (93.0)	4811 (92.9)
Beta-blocker	3426 (66.2)	3394 (65.6)	3444 (66.5)
ACE inhibitor or ARB	2022 (39.1)	1977 (38.2)	2050 (39.6)
Statin	4304 (83.2)	4342 (83.9)	4321 (83.5)
Calcium-channel blocker	820 (15.8)	742 (14.3)	764 (14.8)



Kaplan-Meier Curves for the Incidence of the Primary Endpoint





RESULTS

- Rivaroxaban significantly reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates of 8.9% and 10.7%, respectively.



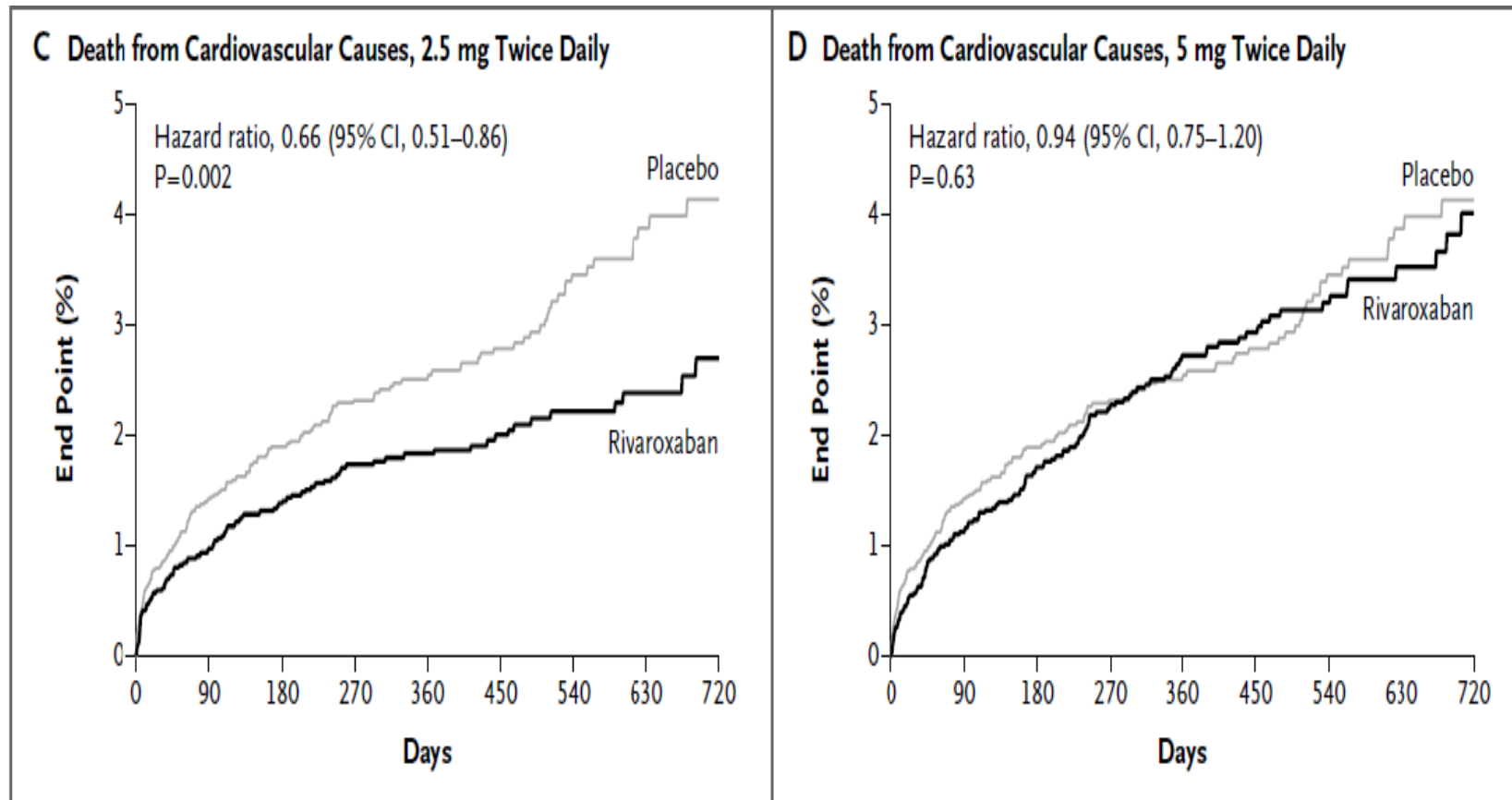
Kaplan-Meier Estimates and Hazard Ratios for Efficacy / Safety Endpoints

End Point	Rivaroxaban			Placebo (N=5113)
	2.5 mg Twice Daily (N=5114)	5 mg Twice Daily (N=5115)	Combined (N=10,229)	
Efficacy				
	<i>number (percent)</i>			
Death from cardiovascular causes, myocardial infarction, or stroke — primary end point	313 (9.1)	313 (8.8)	626 (8.9)	376 (10.7)
Death from cardiovascular causes	94 (2.7)	132 (4.0)	226 (3.3)	143 (4.1)
Myocardial infarction	205 (6.1)	179 (4.9)	384 (5.5)	229 (6.6)
Stroke				
Any	46 (1.4)	54 (1.7)	100 (1.6)	41 (1.2)
Ischemic	30 (1.0)	35 (0.9)	65 (0.9)	34 (1.0)
Death from any cause, myocardial infarction, or stroke — secondary end point	320 (9.3)	321 (9.1)	641 (9.2)	386 (11.0)
Death from any cause	103 (2.9)	142 (4.4)	245 (3.7)	153 (4.5)
Stent thrombosis	47 (2.2)	51 (2.3)	98 (2.3)	72 (2.9)
	(N=5115)	(N=5110)	(N=10,225)	(N=5125)
Safety				
TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (14.5)	282 (7.5)
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)

P: 0.006



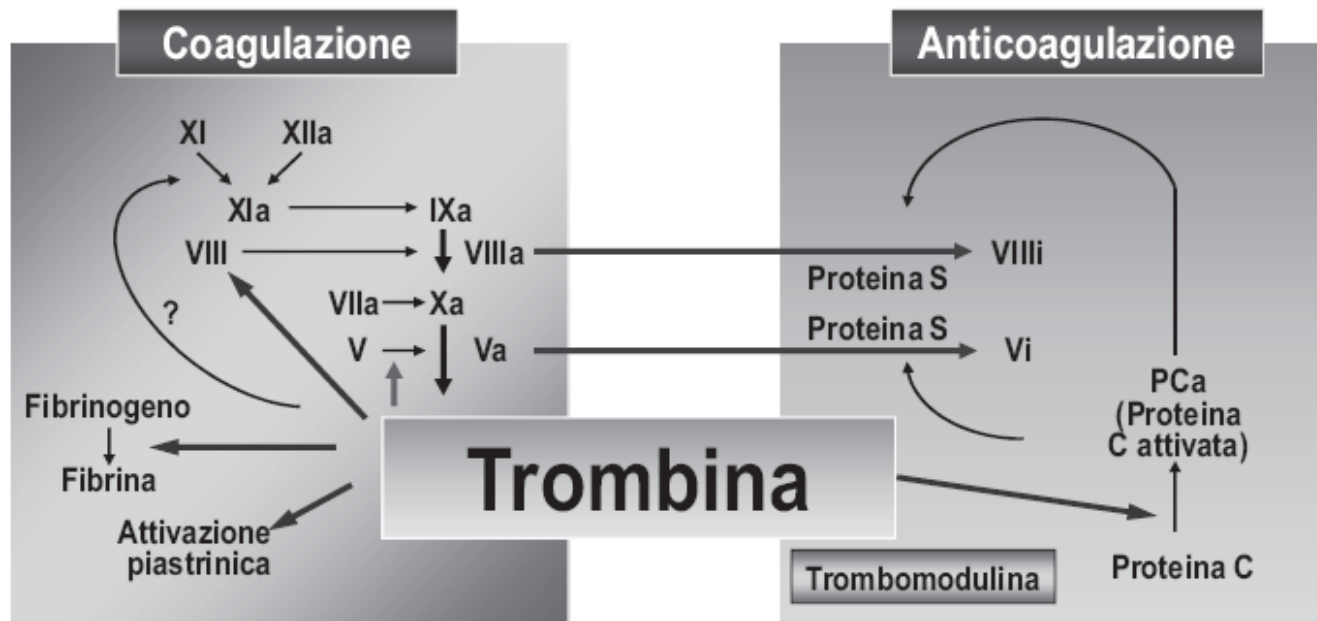
Kaplan-Meier for the Incidence of Cardiovascular Deaths





Via della Coagulazione e dell'Anticoagulazione (proteina C)

“PARADOSSO DELLA TROMBINA”

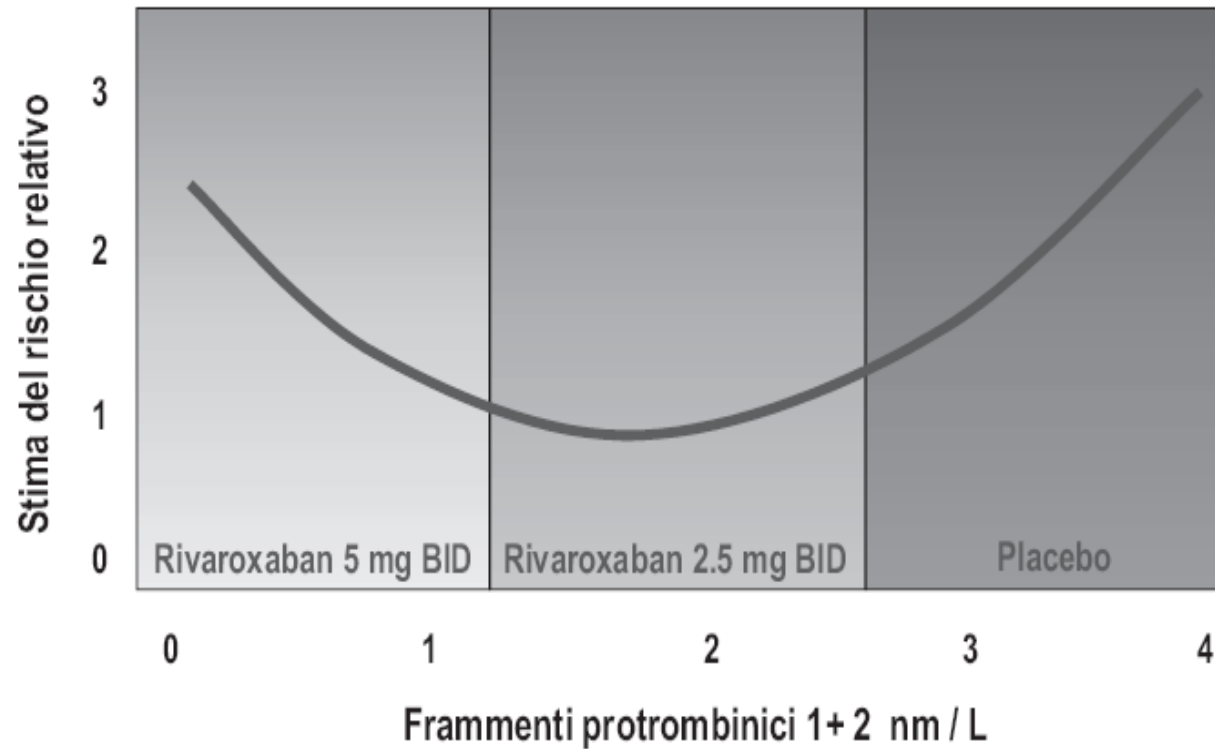


La trombina può essere procoagulante o anticoagulante a seconda della concentrazione.



Rapporto tra livelli plasmatici di fibrinopeptide 1+2 e rischio di reinfarto

“PARADOSSO DELLA TROMBINA”





CONCLUSIONS

Rivaroxaban:

- Reduced the risk of death from cardiovascular causes, myocardial infarction or stroke.
- Did not increase significantly the rate of fatal bleeding.
- At the twice-daily 2.5-mg dose reduced cardiovascular mortality.
- The addition of very-low-dose anticoagulation with rivaroxaban may represent a new treatment strategy in patients with a recent acute coronary syndrome.

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Grazie per la Vostra Attenzione!



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