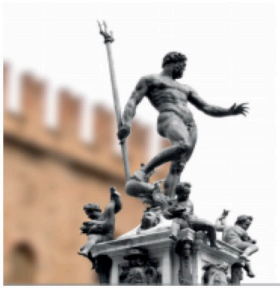


fondazione arianna ANTICOAGULAZIONE PROMUOVE IL

2° CONVEGNO DI ANTICOAGULAZIONE.it

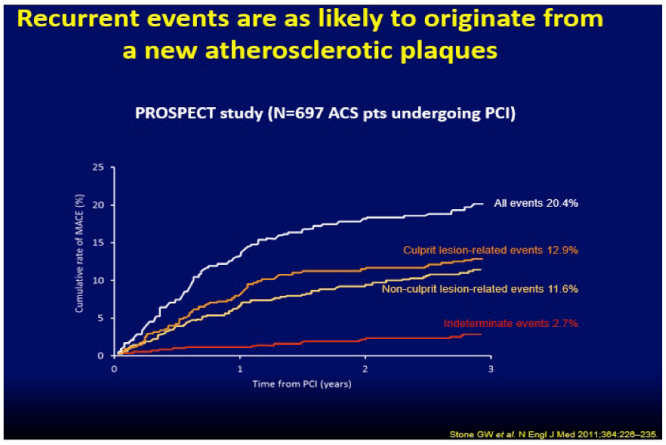
scienza e pratica clinica per il management dei pazienti anticoagulati

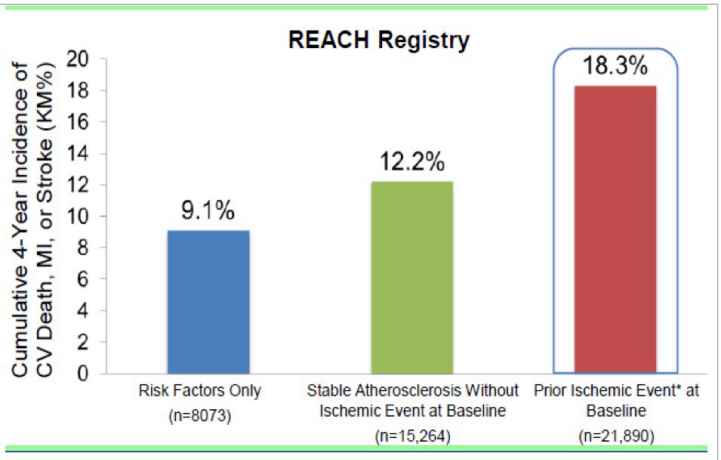
AGGIORNAMENTI 2017

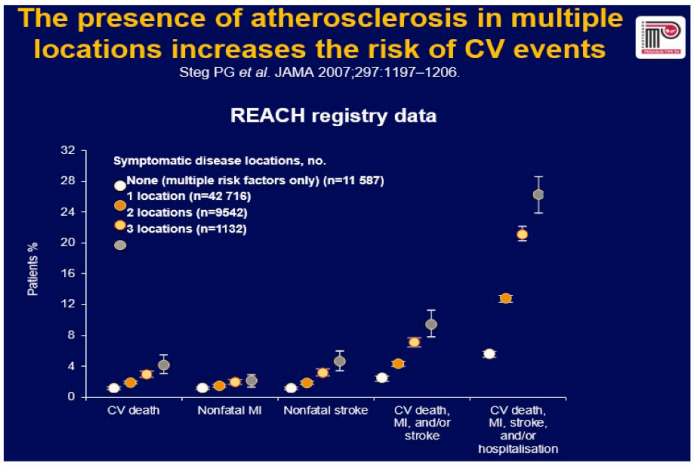
Anticoagulazione quando i nuovi anticoagulanti orali diretti (NAO) non sono indicati

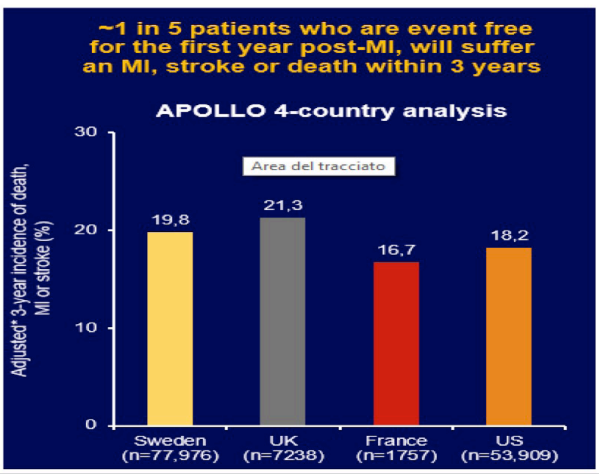
Giuseppe Patti

Università Campus Bio-Medico di Roma







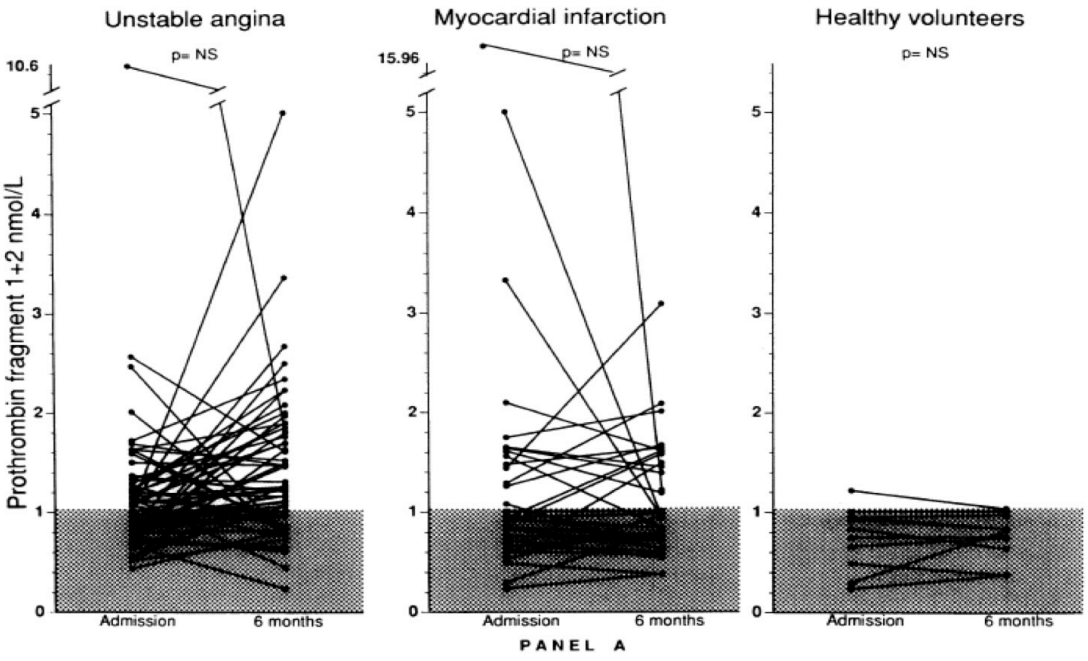


Causes of recurrent events in high-risk pts with ACS:

- Persistent platelet activation (Thrombin-rich milieu)
- High inflammatory status
- Stent thrombosis/TVR
- Multifocal plaque instability
- CAD progression

… Beyond Cox-1 and P2Y12 inhibition

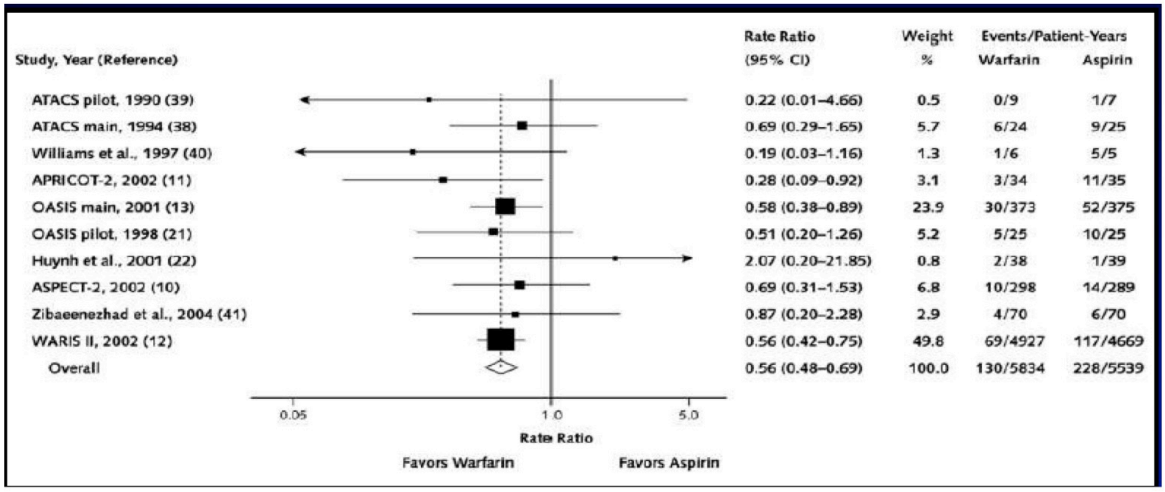
Persistent thrombin generation after an ACS



Merlini PA, Circulation 1994

Efficacy of anticoagulation with warfarin

RECURRENT MI

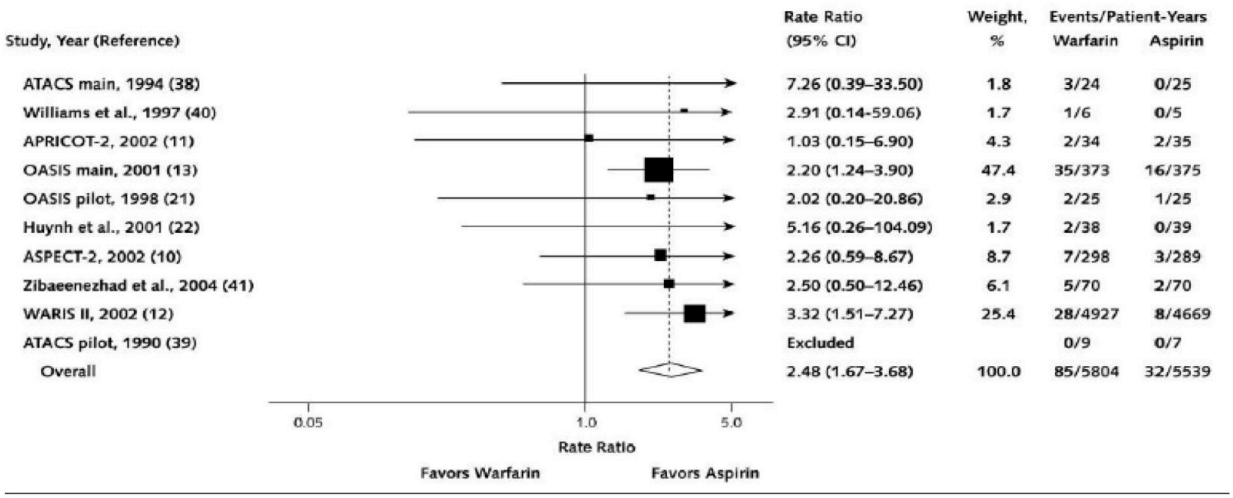


Prevent 19 MI per 1000 pts/year

Rothberg et al., Ann Inter Med 2005

Safety of anticoagulation with warfarin

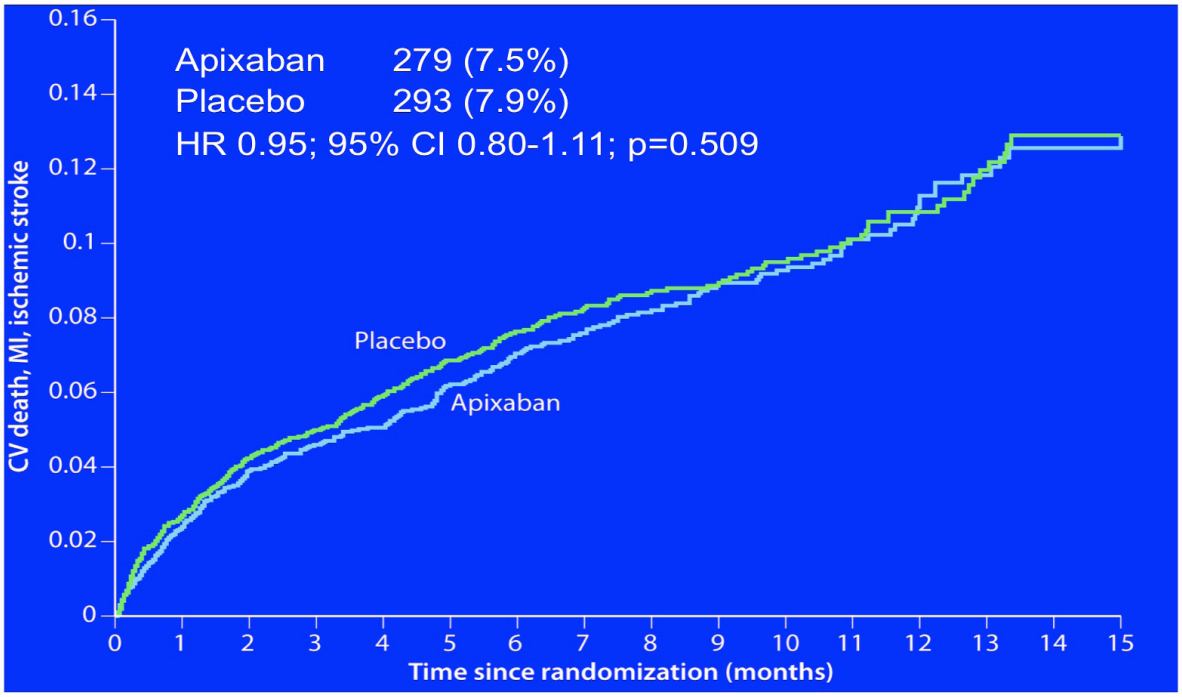
Major Bleeding



Increase 9 bleeds per 1000 pts/year

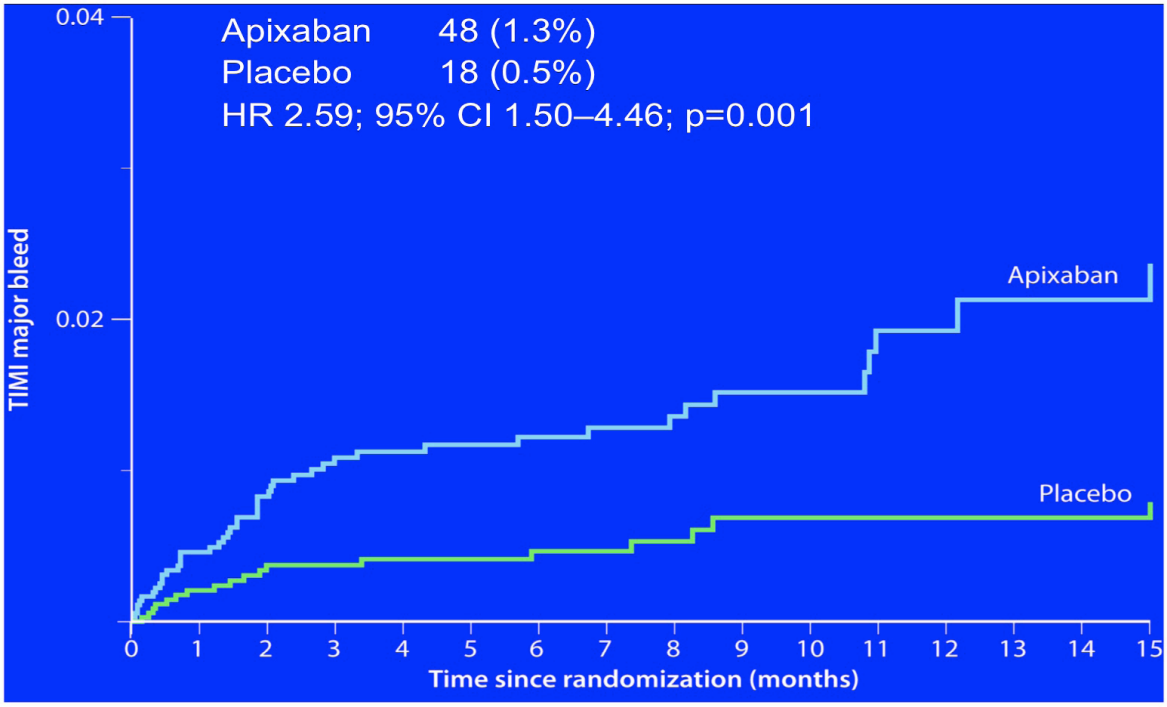
Rothberg et al., Ann Inter Med 2005

APPRAISE 2 - Primary End-point: CV Death, MI, Ischemic Stroke



Alexander JH et al. N Engl J Med 2011

APPRAISE 2 - TIMI Major Bleeding



Alexander JH et al. N Engl J Med 2011

ATLAS ACS 2

Rivaroxaban in recent ACS

Recent ACS: STEMI, NSTEMI, UA
No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine
Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

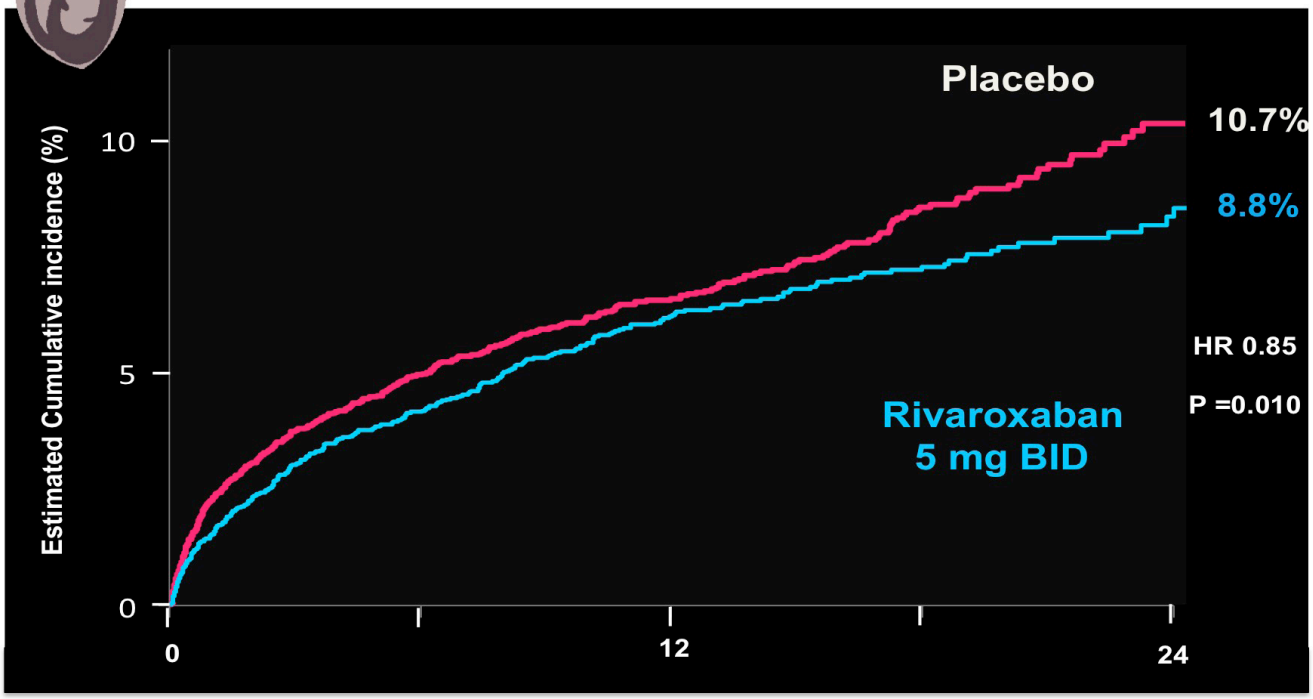
+ ASA 75 to 100 mg/day

Placebo	RIVAROXABAN 2.5 mg BID	RIVAROXABAN 5.0 mg BID
N=5,176	n=5,174	N=5,176
ASA + Thieno, n=4,821	ASA + Thieno, n=4,825	ASA + Thieno, n=4,827
ASA, n=355	ASA, n=349	ASA, n=349

PRIMARY END-POINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG

ATLAS ACS 2

Primary Efficacy End-point: 5.0 mg BID
CV Death / MI / Stroke (Ischemic + Hemorr.)

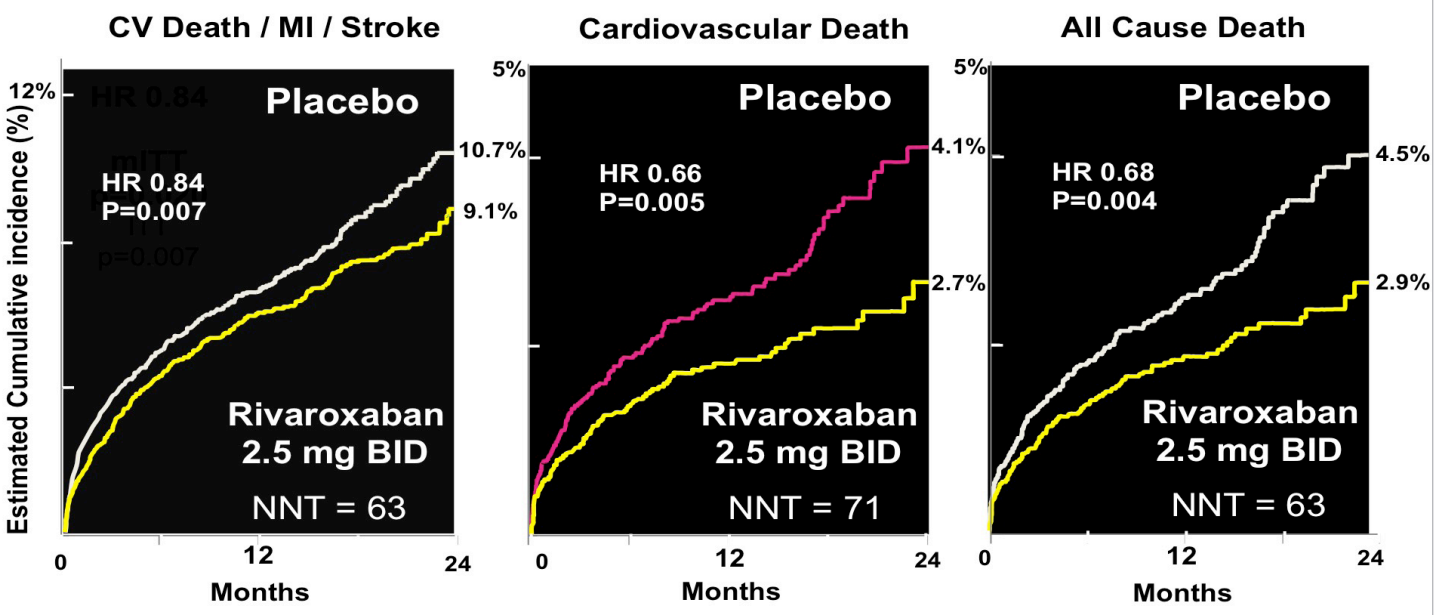


Rivaroxaban at 5 mg PO BID primarily reduced MI (4.9% vs 6.6%, OR 0.79, P=0.008)

Mega JL et al. N Engl J Med 2012

ATLAS ACS 2

Efficacy End-points: 2.5 mg BID



MI: 6.1% 2.5 mg vs 6.6% placebo, P=0.09

Mega JL et al. N Engl J Med 2012

ATLAS ACS 2

Safety End-points

Non CABG TIMI Major Bleeding

Analysis	Placebo	2.5 mg Rivaroxaban	5.0 mg Rivaroxaban
2 Yr KM Estimate	0.6%	1.8% HR 3.46	2.4% HR 4.47

p<0.001

p<0.001

Post-Treatment Ischemic Events

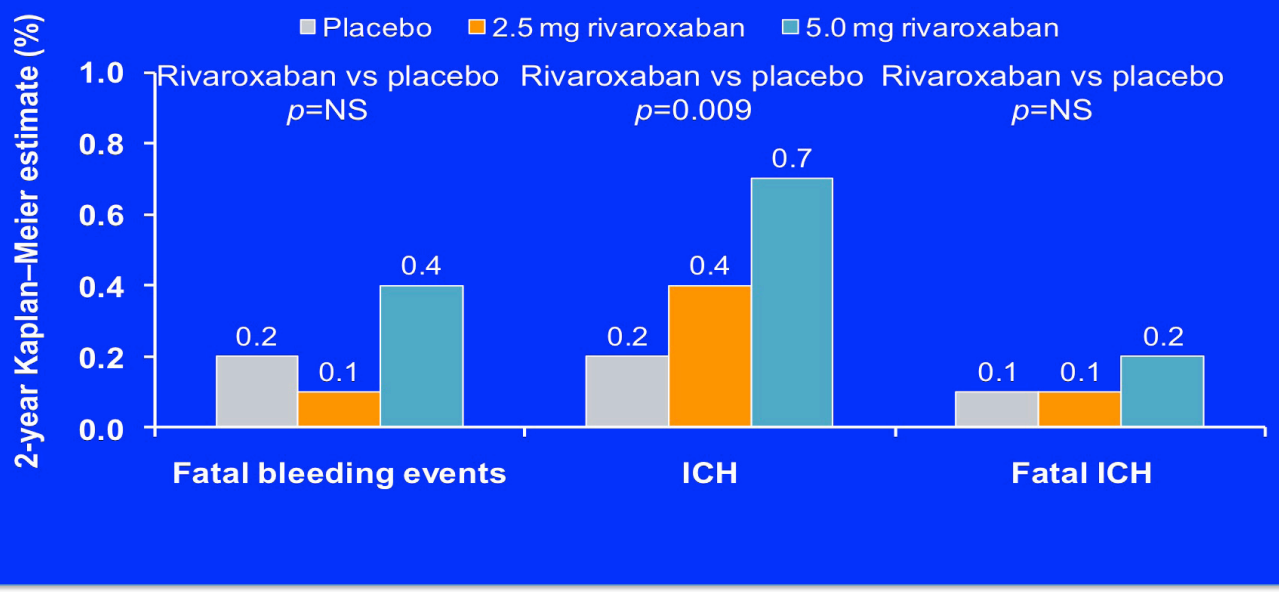
1-10 Days After Last Dose	1.8%	1.4% p=NS	2.2% p=NS

Liver Function Test (ALT > 3xULN)

Treatment-Emergent	1.6%	1.3% p=NS	1.4% p=NS

Mega JL et al. N Engl J Med 2012

ATLAS ACS 2 TIMI 51: Treatment-emergent fatal bleeding events and ICH
Separate rivaroxaban doses, both strata



Mega JL et al. N Engl J Med 2012

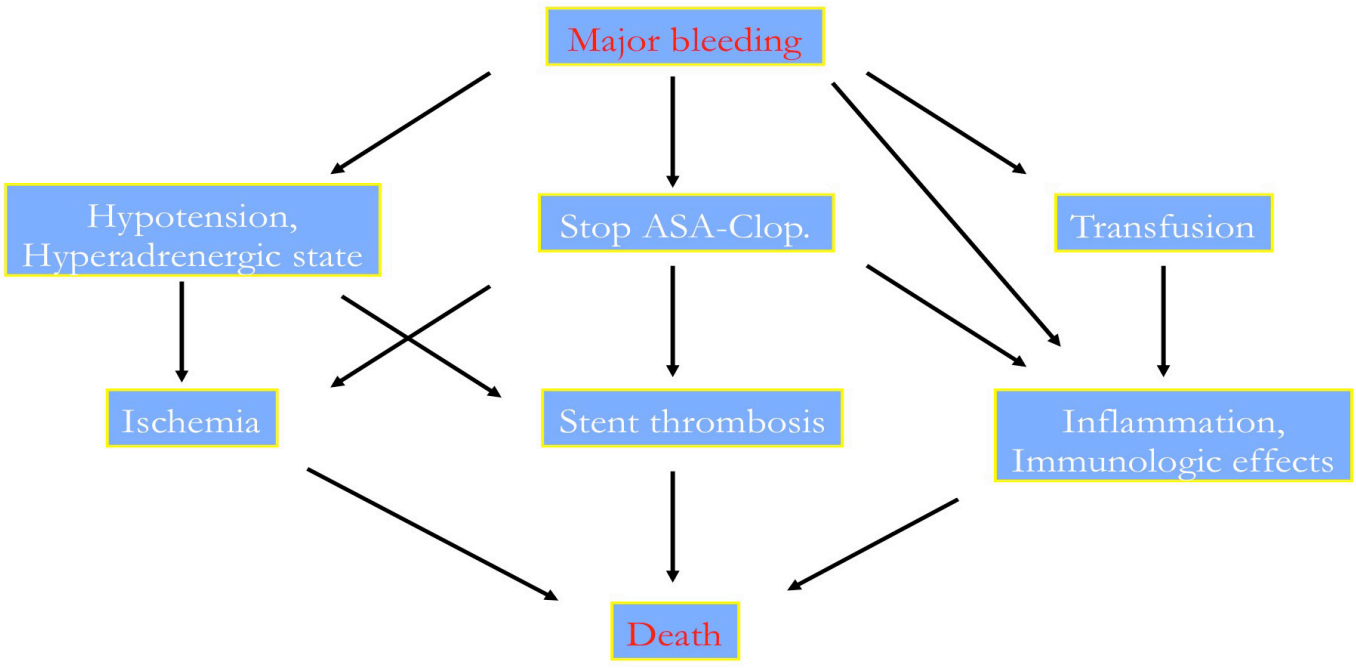
	APPRAISE 2 - 5 mg BID (N=7,048)	ATLAS 2 - 2.5/5 mg BID (N=15,526)
Male gender	**68%**	75%
Diabetes mellitus	**48%**	32%
Prior MI	**38%**	27%
Heart failure or LVEF<40%	**40.2%**	-
Prior cerebrovascular disease	**10%**	excluded
Renal function	**28.9% with CKD**	Median CrCl 85 ml/min
Index ACS event type		
STEMI	39.6%	50.3%
NSTEMI/UA	60.4%	49.7%
PCI	44%	60%
ASA	97%	99%
Thienopyridine	81% (dual)	93%
Follow up	8.0 months (median)	13.1 months (mean duration of treatment with study drug)
Primary end-point	7.5% vs 7.9%	8.9% vs 10.7%
Safety end-point (TIMI major)	1.3% vs 0.5% (HR 2.6)	2.1% vs 0.6% (HR 3.5)
ICH	0.3% vs 0.1%	0.7% vs 0.4% vs 0.2%

2014 ESC Guidelines on Myocardial revascularization

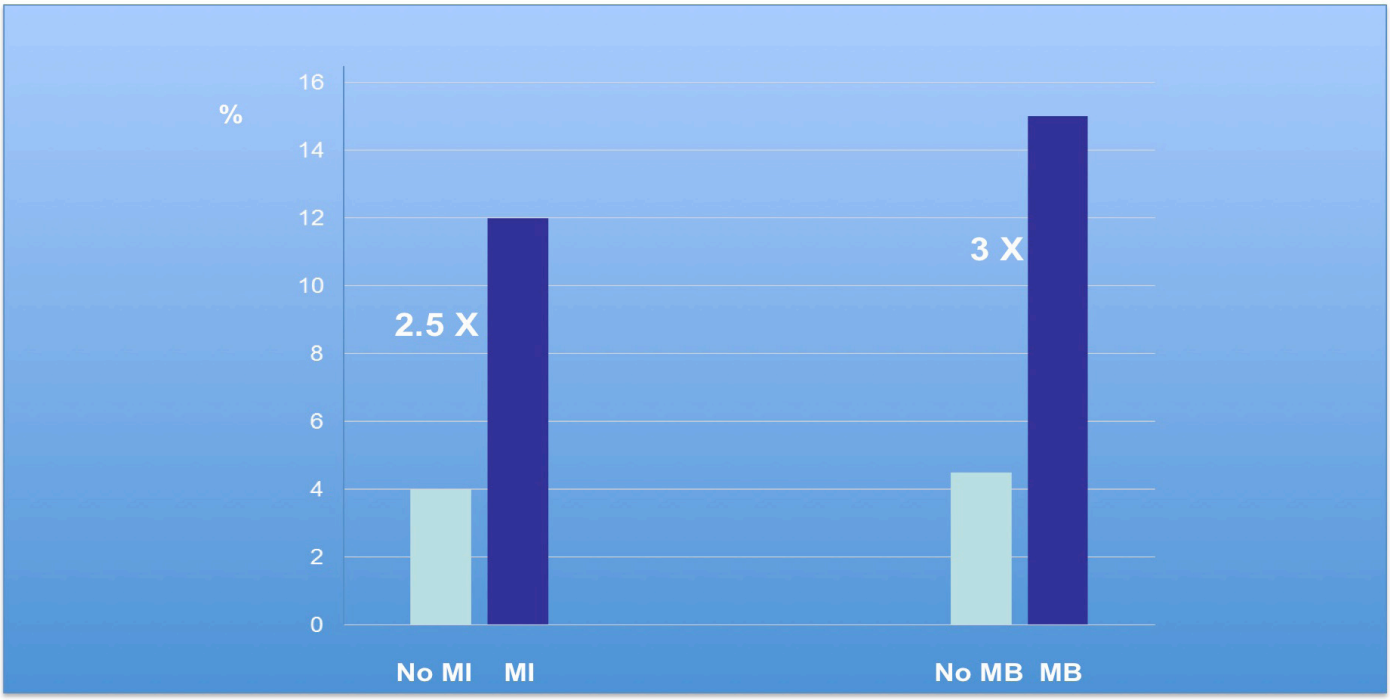
Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C	
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended	III	C	
Anticoagulation therapy after PCI in ACS patient			
In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk.	IIb	B	855
Anticoagulation during PCI in patients on oral anticoagulation			
It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC.	I	C	
Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI.	IIa	C	

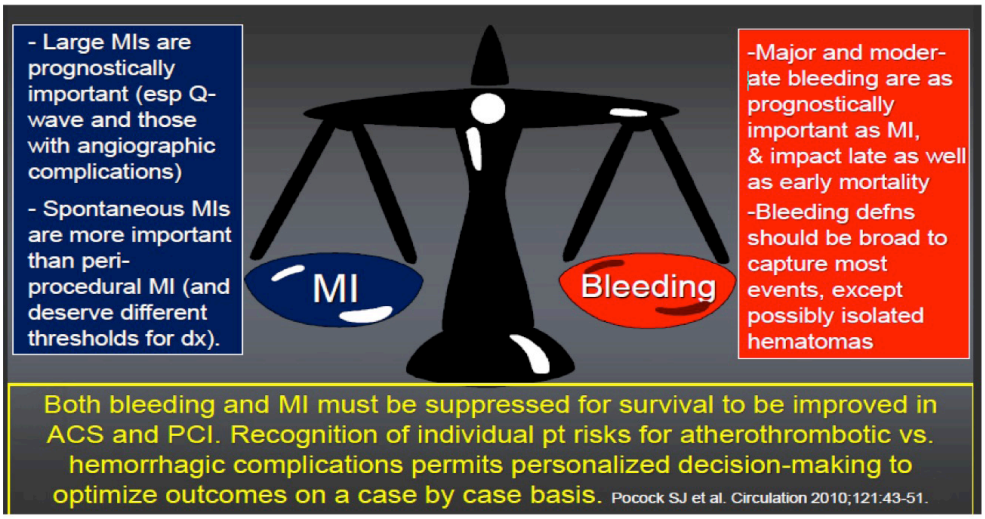
Relationship between major bleeding and mortality in CAD patients (especially in ACS)



Impact of MI and major bleeding (MB) on 1-yr mortality in ACS pts undergoing PCI

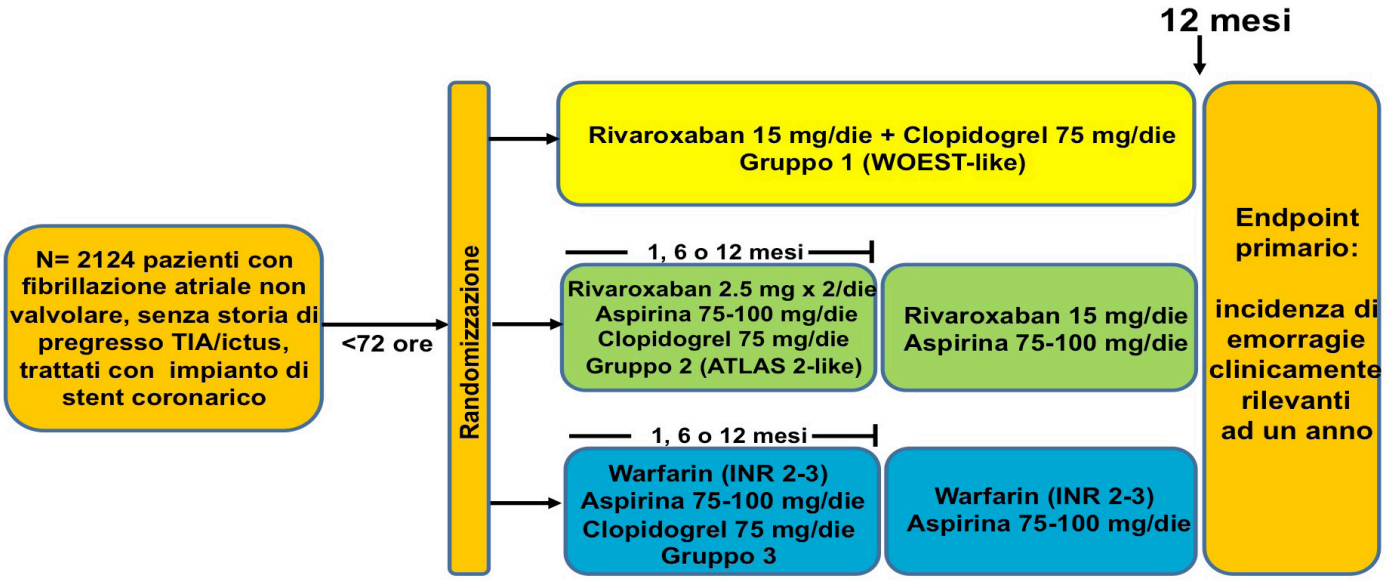


Impact of MI and Bleeding on Subsequent Mortality in ACS and PCI



- Doses issues
- Increase of bleeding in APPRAISE 2 and ATLAS 2
- No data on safety for association of new anticoagulants with prasugrel/ticagrelor
- Identify pts achieving the greatest benefit, without safety concerns

Disegno dello studio PIONEER AF-PCI (N Engl J Med 2016)



Incidenza cumulativa di eventi cardiovascolari (infarto miocardico, ictus) e di complicanze emorragiche nei vari bracci di trattamento e per diverse durate della triplice terapia