04/12/17

Beyond NV AF: a different indication to oral anticoagulation

Secondary prevention in cardiovascular disease

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Disclosure

Speaker fee: Aspen, Astra Zeneca, BMS, Boehringer, Daichii Sankio, Bayer, Pfizer

Advisory board member: Astra Zeneca, Bayer, Boeheringer, Daiichi Sankyo, BMS, Pfizer, Sanofi

Overview

CAD and long-term outcome

Anticoagulants on top of antiplatelet therapy

Rivaroxaban and the ATLAS ACS studies

Rivaroxaban in secondary prevention: the COMPASS trial

Efficacy and safety: a difficult balance

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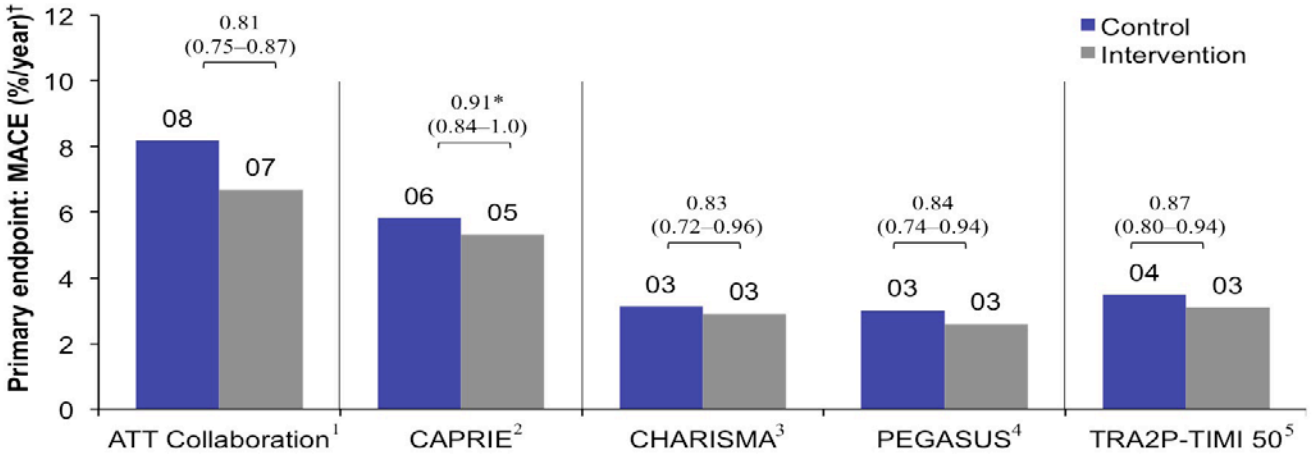
- ✓ *The management of acute coronary syndromes has improved significantly in recent years with the introduction of interventional treatment strategies, potent antiplatelet inhibitory drugs, and secondary risk-modifying drug treatment regimens*
- ✓ *Incorporation of these therapies has resulted in reduced mortality and morbidity*
- ✓ *However the risk of recurrent ischemic events is still high at 30 days and long term*
- ✓ *Moreover, in the secondary prevention setting, despite the use of effective secondary prevention strategies, 5 to 10% of pts have recurrent events*

Patients with Chronic CAD or PAD Remain At Risk of Vascular Events Despite Current Optimal Medical Therapy



% Use of key therapies in intervention arm	Control ‖ Aspirin	Aspirin ‖ Clopidogrel	Placebo + Aspirin ‖ Clopidogrel + Aspirin	Placebo + Aspirin ‖ Ticagrelor + Aspirin	Vorapaxar ‖ Placebo + Aspirin ± Thienopyridine
ACEI/ARB	*Meta-analysis of 16 trials*	*NR*	*up to 85.3*	*80.4*	*73.5*
Statin/ lipid-lowering		*NR*	*77.1–89.3*	*92.4*	*91.0*

*Estimate calculated from reported relative risk reductions; †Estimate calculated from reported overall % across 28 months of median follow up for CHARISMA; and from reported 3-year Kaplan-Meier event rates for PEGASUS & TRA2P-TIMI50

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413

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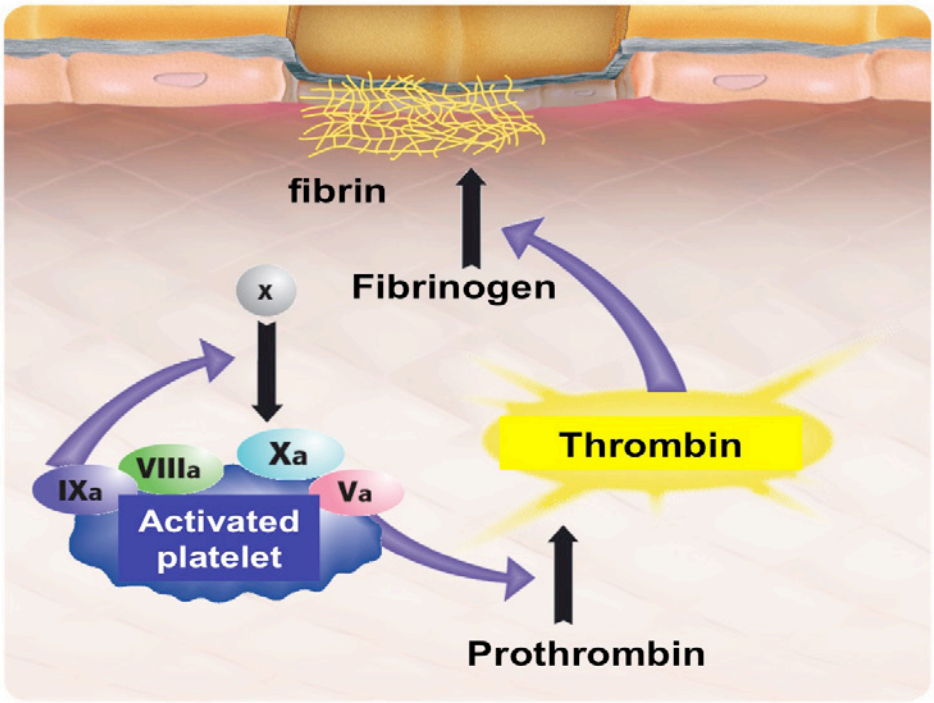
ACS and thrombosis process



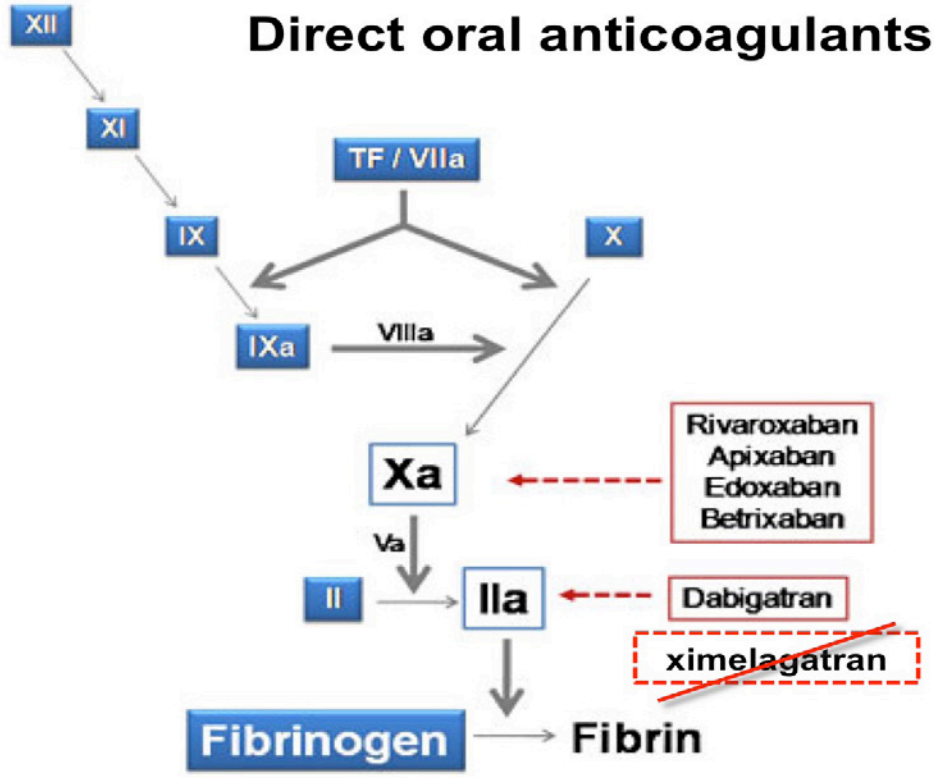
Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: a meta-analysis of 25307 pts

MAE	Absolute incidence (%)		Summary odds ratio (95% CI)	P
	A+W	ASA alone		
Non-fatal thrombo-embolic stroke				
Studies with INR 2–3	0.6	1.48	0.43 (0.27–0.70)	0.0007
All studies	1.6	2.1	0.81 (0.67–0.97)	0.02
Non-fatal myocardial infarction				
Studies with INR 2–3	4.7	5.6	0.70 (0.52–0.95)	0.0003
All studies	7.4	9	0.96 (0.88–1.05)	0.37
All cause death				
Studies with INR of 2–3	2.8	2.9	0.99 (0.81–1.22)	0.95
All studies	7.2	8.5	1.00 (0.91–1.10)	0.96

All bleeds OR 2.32 (1.63-3.29)

Andreotti F et al Eur Heart J 2006; 27: 519

Direct oral anticoagulants



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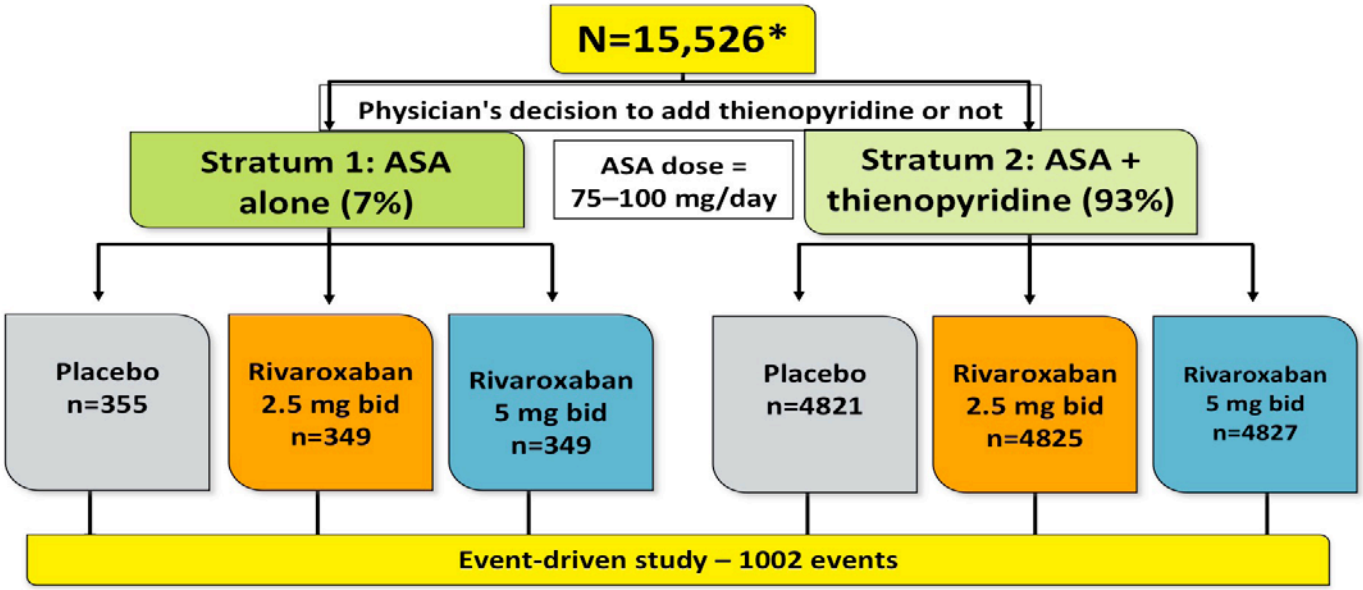
ATLAS ACS 2 TIMI 51 – Study design



*184 patients were excluded from the efficacy analyses prior to unblinding because of trial misconduct at three sites

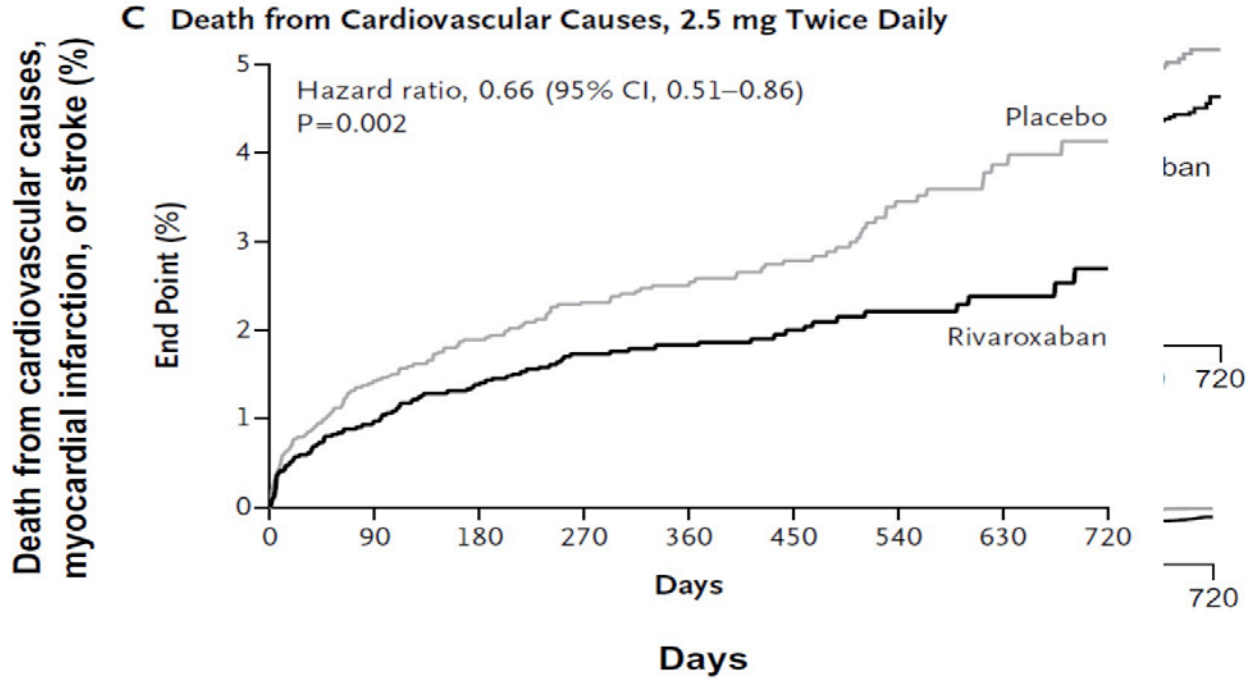
Mega JL et al. *N Engl J Med. 2012;366(1):9–19*

ATLAS ACS 2 TIMI 51: Patient characteristics

	Rivaroxaban 2.5 mg bid (n=5174)	Rivaroxaban 5 mg bid (n=5176)	Placebo (n=5176)
Mean age, years (SD)	62 (9)	62 (9)	62 (9)
Male sex, %	75	74	75
Median weight, kg	78	78	78
Median CrCl, ml/min	85	85	86
Medical history, %			
Prior MI	26	27	27
Hypertension	67	68	68
Diabetes mellitus	32	32	32
Index diagnosis, %			
STEMI	50	50	51
NSTEMI	26	26	26
UA	24	24	24
PCI or CABG for index	61	60	60

Mega JL et al. *N Engl J Med. 2012;366(1):9–19*

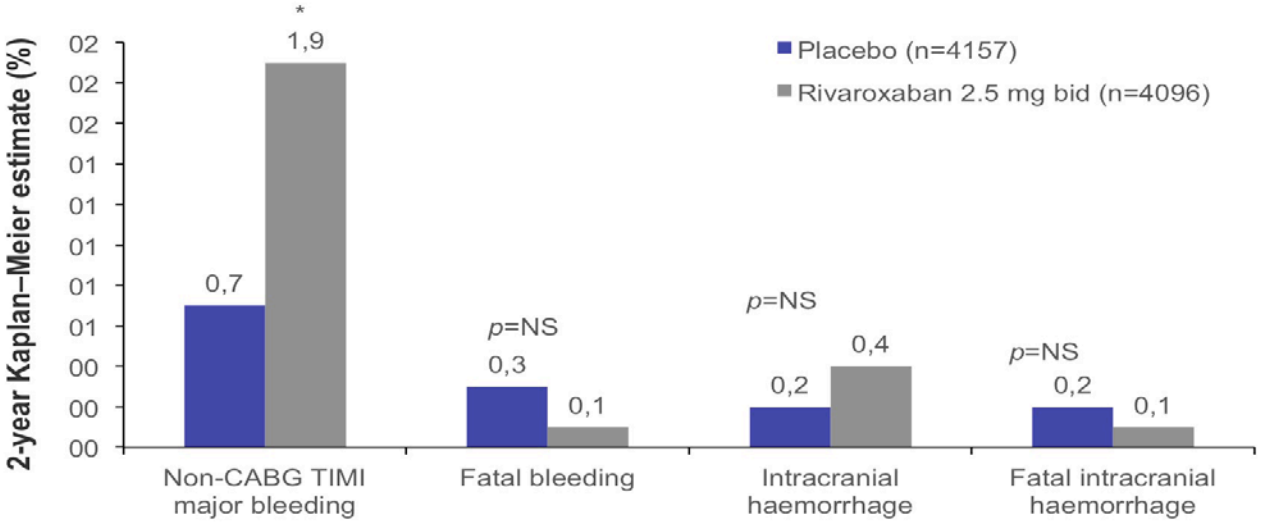
ATLAS ACS 2- TIMI 51: primary endpoint



Mega JL et al. *N Engl J Med. 2012;366(1):9–19*

ATLAS ACS 2 TIMI 51: Rivaroxaban Vascular Dose Increased Major Bleeding but Not Fatal Bleeding

Patients with elevated cardiac biomarkers and no prior stroke/transient ischaemic attack



CABG, coronary artery bypass grafting; NS, not significant; TIMI, Thrombolysis In Myocardial Infarction
*p<0.001 vs placebo

Mega JL *et al*, *Eur Heart J* 2014;35(Suppl.):992. Abstract P5518 (poster presentation)

ATLAS ACS TIMI 51

ATLAS ACS 2- TIMI 51: editorial comments

We believe that the results of this study are an important development for relatively young and healthy patients with an ACS

Many of the major bleeding events occurred after 180 days, with no plateau effect observed, and the risk of bleeding was consistent among all major subgroups.

Better predictors of intracranial hemorrhage are needed….this finding may be concentrated in patients with a history of cerebrovascular disease

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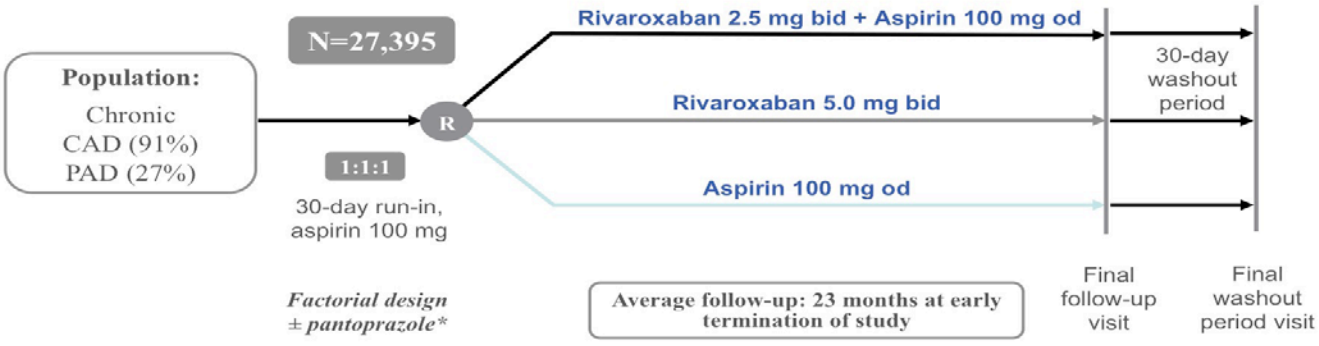
A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

COMPASS

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI

daily or 5 mg twice daily resulted in a lower rate of major adverse cardiovascular events than placebo, and the dose of 2.5 mg twice daily resulted in lower mortality,[8] findings consistent with the COMPASS results. The mean duration of rivaroxaban treatment in the ATLAS ACS 2–TIMI 51 trial was 13.3 months, whereas persons enrolled in the COMPASS trial who had a history of myocardial infarction were enrolled a mean of 7.1 years after the acute event and continued to receive treatment for a mean of 23 months.

The definition of major bleeding in the COMPASS trial was based on the ISTH definition, which includes fatal bleeding, symptomatic bleeding into a critical area or organ, bleeding causing a decrease in the hemoglobin level of 2 g or more per deciliter, or bleeding that led to transfusion of 2 or more units of whole blood or

sponse to a request from r
the ISTH definition in tl
account whether bleeding
decrease in the hemoglol
transfusion, and it inclu
led to hospitalization wi
night stay, thus including
be considered major ble
Although there was also a
the rate of major bleeding
the use of the ISTH sca
mately one third fewer ma
this definition than with
ISTH definition. Our de
benefit balanced the lowe
death, stroke, or myocar
the most serious bleedin
significant benefit of con

Eikelboom JW *et al. N Engl J Med* 2017 COMPASS

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Rivaroxaban 5 mg bid N=9117	Aspirin 100 mg N=9126
Modified major ISTH bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)
Non-fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg		Rivaroxaban 5 mg bid vs aspirin 100 mg	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Modified ISTH major bleeding	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Non-fatal ICH*	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Non-fatal other critical organ*	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06

The use of the standard ISTH major bleeding definition would have led to approximately one third fewer major bleeding events than with the use of the modified ISTH definition

Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. For each outcome, the first event experienced per patient is considered. Subsequent events of the same type are not shown. Therefore subcategories do not necessarily sum up to overall category. *Symptomatic

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118 COMPASS

Rivaroxaban Has Shown Improved Outcomes for Patients with High Need for Increased Vascular Protection

In patients with chronic CAD or PAD, dual pathway inhibition with rivaroxaban vascular dose 2.5 mg bid plus aspirin, versus aspirin alone:

- Significantly reduced the combined risk of stroke, CV death and MI by 24%
- Demonstrated 42% reduction in stroke, 22% reduction in CV death, and 18% reduction in all-cause mortality
- Significantly reduced major amputation by 70% versus aspirin in patients with PAD
- As expected, resulted in increased major bleeding, however bleeding rates were low and notably, there was no significant increase in intracranial, critical organ or fatal bleeding
- Showed a substantial improvement in net clinical benefit of 20%

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

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European Heart Journal (2013) **34**, 1670–1680
doi:10.1093/eurheartj/eht049

New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis

Jonas Oldgren[1,2]*, Lars Wallentin[1,2], John H. Alexander[3], Stefan James[1,2], Birgitta Jönelid[1], Gabriel Steg[4,5,6], and Johan Sundström[1,2]

30866 patients, 7 trials

Eur Heart J 2013; 34: 1670 - 1680

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CLINICAL RESEARCH
Acute coronary syndromes

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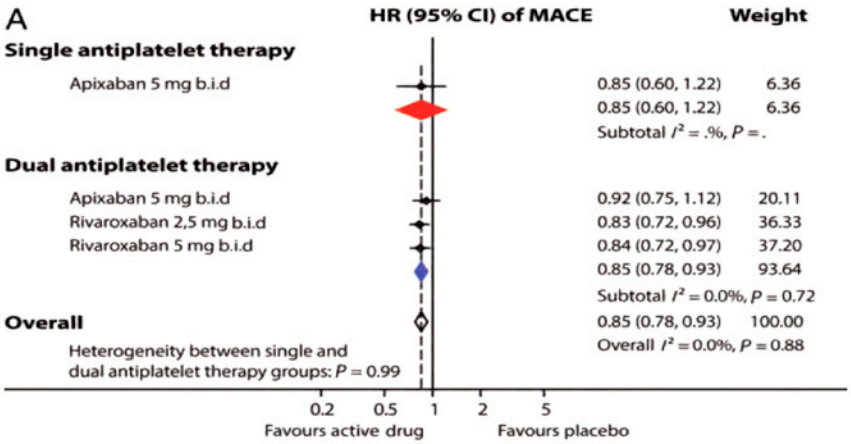

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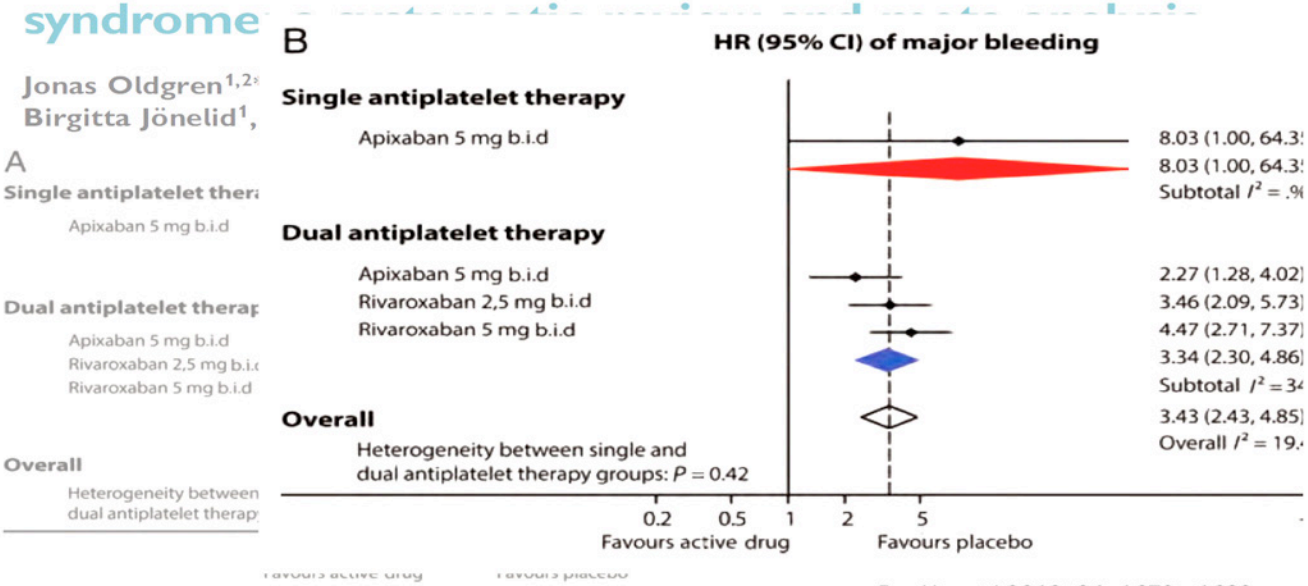

Eur Heart J 2013; 34: 1670 - 1680

New antiplatelet agents vs NOACs in ACS

Table 1. Rates of Ischemic and Bleeding Events in Drug Trials for Acute Coronary Syndrome.*

Event	TRITON–TIMI 38		PLATO		APPRAISE-2†		ATLAS ACS 2–TIMI 51‡	
	Prasugrel	Clopidogrel	Ticagrelor	Clopidogrel	Apixaban	Placebo	Rivaroxaban (2.5 mg)	Placebo
	percent							
Death, myocardial infarction, or stroke	10.7	12.7	10.2	12.3	8.8	8.9	9.1	10.7
Death from cardiovascular causes	2.1	2.4	4.0	5.1	2.8	3.0	2.7	4.1
Bleeding								
Major TIMI (non-CABG)	2.4	1.8	2.8	2.2	1.3	0.5	1.8	0.6
Fatal	0.4	0.1	0.3	0.3	0.1	0	0.1	0.2
Intracranial	0.3	0.3	0.3	0.2	0.3	0.1	0.4	0.2

N Engl J Med. 2012;366(1):85

STEMI: ESC guidelines 2017

AMI = acute myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LV = left
percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]History of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid user, and ≥2 or more of the follow
dyspepsia, gastro-oesophageal reflux disease, *H. pylori* infection, and chronic alcohol use.
[d]Oral anticoagulant, aspirin, and clopidogrel.
[e]Defined as age ≥50 years, and at least one of the following additional high-risk features: age ≥65 years, diabetes mellitus on medication, a prior spontaneou
CAD, or chronic renal dysfunction (eGFR <60 ml/min/1.73 m^2).

7.3 Beta-blockers

7.3.1 Early intravenous beta-blocker administration

In patients undergoing fibrinolysis, early i.v. beta-blocker treatment reduces the incidence of acute malignant ventricular arrhythmias, although there is no clear evidence of long-term clinical benefit.[344–346]

In patients undergoing primary PCI, the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction arms ($P = 0.065$).[348] Metoprolol treatment was a
significant reduction in the incidence and extent
Early Intravenous Beta-Blockers in Patients W
Elevation Myocardial Infarction Before Primary
Coronary Intervention (EARLY-BAMI) tria
683 patients with STEMI within 12 h of onset to
(5 mg at recruitment and an additional 5 mg imm
PCI) or placebo.[350] All patients without c

In conclusion

There is no place for routine use of NOACs in CAD or ACS

Long term benefit are significantly affected by the excess of bleeding complications

It is difficult to identify the subset of patients potentially candidate to this type of treatment and we are still missing elements to better stratify patients at risk of severe hemorrhages

Ideally low dose rivaroxaban might be administered to high risk patients with CAD, PAD or ACS, provided that the risk of bleeding complications is very low