The Great debate: thrombocardiology post-COMPASS

Anticoagulation should replace antiplatelets in CAD prevention - CON

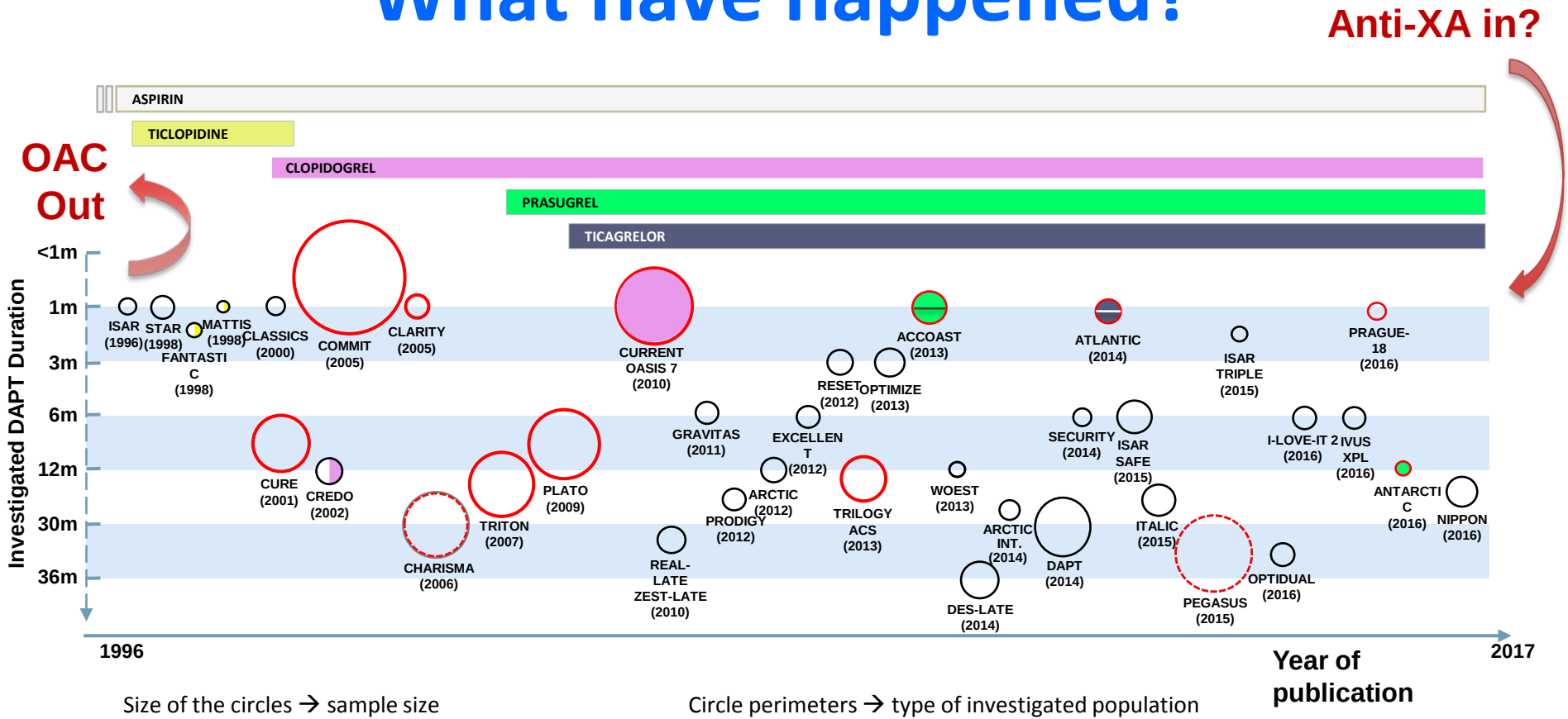
Jean-Philippe COLLET Jean-philippe.collet@psl.aphp.fr

Sorbonne Université_Action Study Group (action-cœur.org)_Head of the INSERM UMRS 1166 on thrombosis and of the Cathleterization Laboratory_Institut de Cardiologie (APHP)_Pitié-Salpêtrière_Paris, France

ESC Congress
Munich 2018

COI: Dr Collet has received research grants from Bristol-Myers Squibb; consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis (action-coeur.org).

What have happened?



ASA in SCAD

ESC and AHA/ACC Guidelines

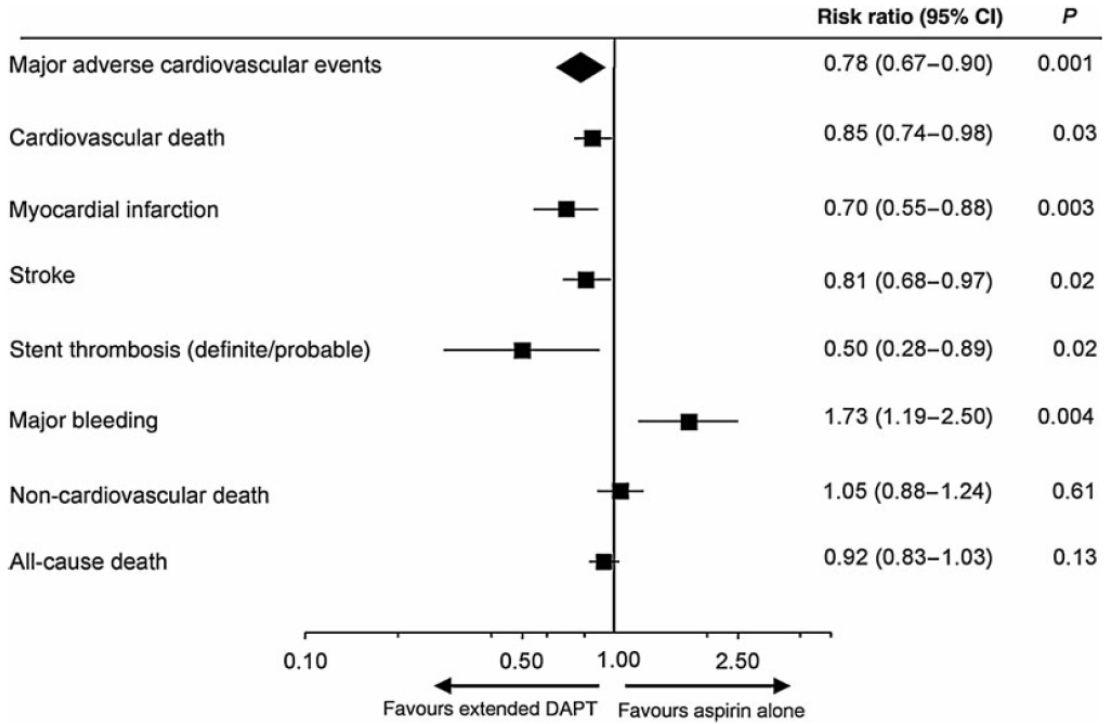
Clinical setting	European Society of Cardiology	ACC/AHA
SCAD	Low-dose **aspirin daily is recommended** in all SCAD patients **(class I LOE A)**	**Treatment with aspirin** 75 to 162 mg daily should be continued indefinitely in the absence of CI in patients with SIHD (**class I LOE A**) **Treatment with aspirin** 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD (class IIb LOE B)
PCI	**ASA is indicated before elective stenting (class I LOE B)** **Life-long single antiplatelet therapy, usually ASA**, is recommended (**class I LOE A**)	Patients already on daily aspirin therapy should take 81 mg to 325 mg before PCI (**class I LOE B)** Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI (**class I LOE B**)
Secondary prevention	In the chronic phase (>12 months) after MI, **aspirin is recommended (class I LOE A)**	**Aspirin 75–162 mg daily** is recommended in all patients with coronary artery disease unless contraindicated **(class I LOE A)**

Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LOE, level of evidence; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCAD, stable coronary artery disease; SIHD, stable ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

DAPT in SCAD

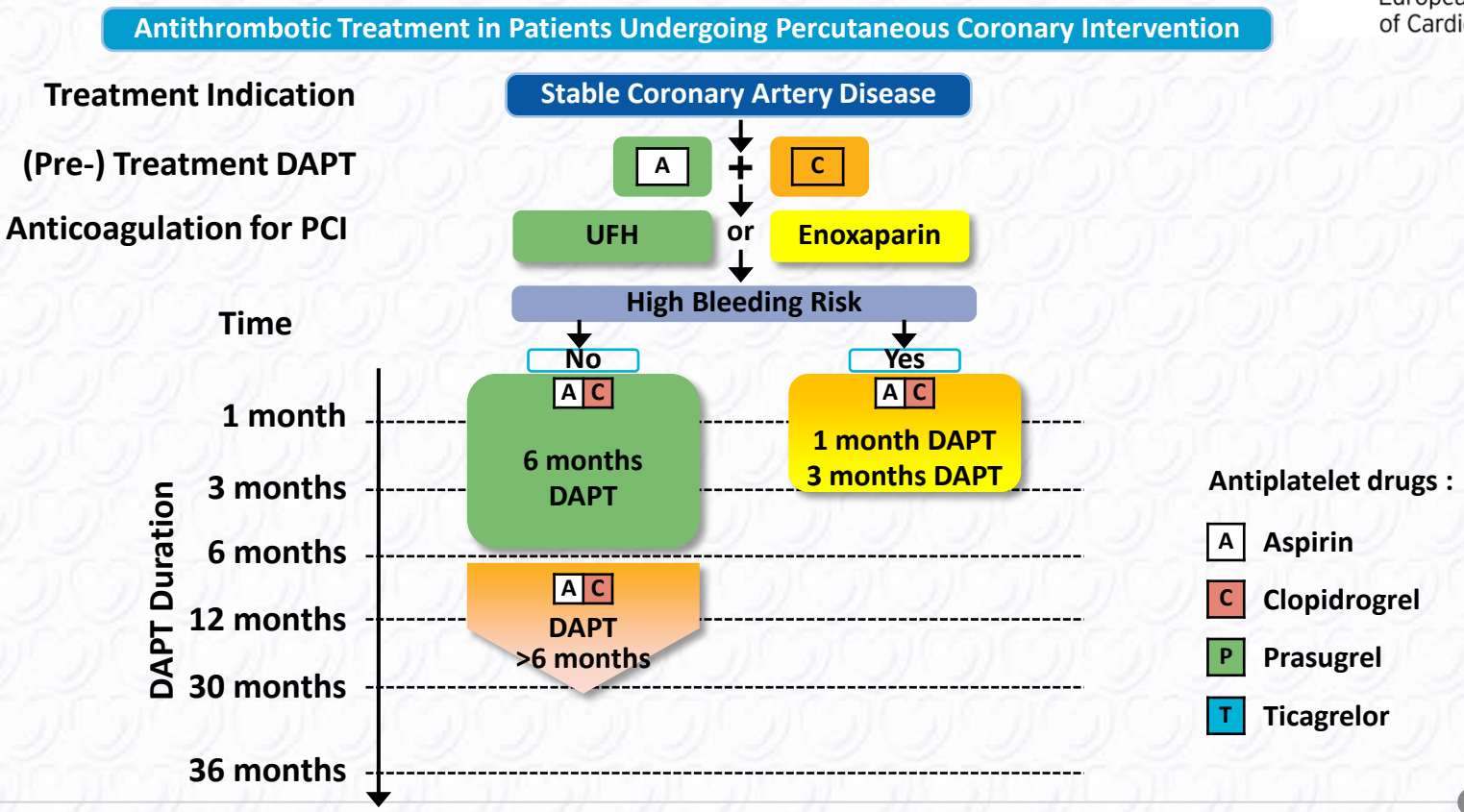
DAPT beyond one year after ACS

N=33 435 patients from 6 RCT followed over a mean 31months



1. Udell J, Bonaca M, Collet JP et al. **Eur Heart J. 2015 Aug 31. pii: ehv443. [Epub ahead of print]**

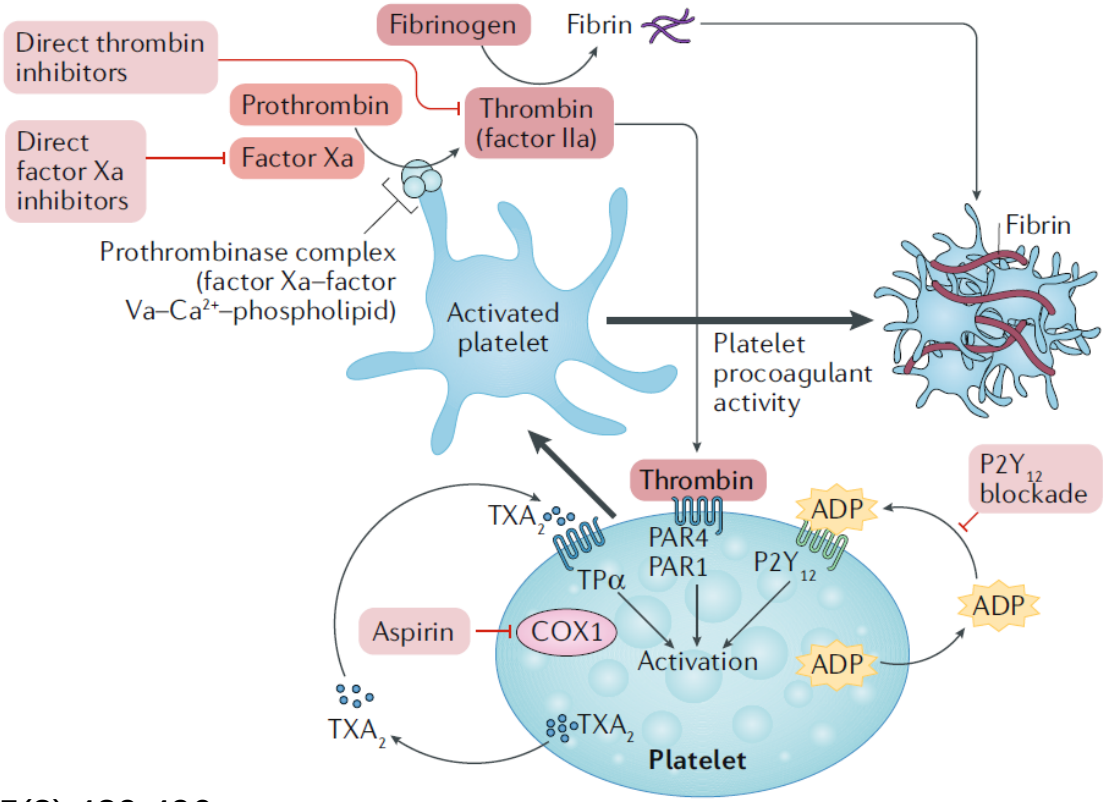
Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention (2)



2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

Adding anti-Xa blockade to DAPT

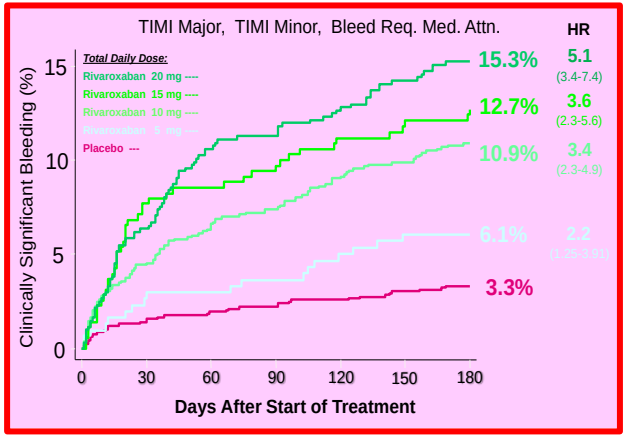
Synergy between anti-Xa and APT

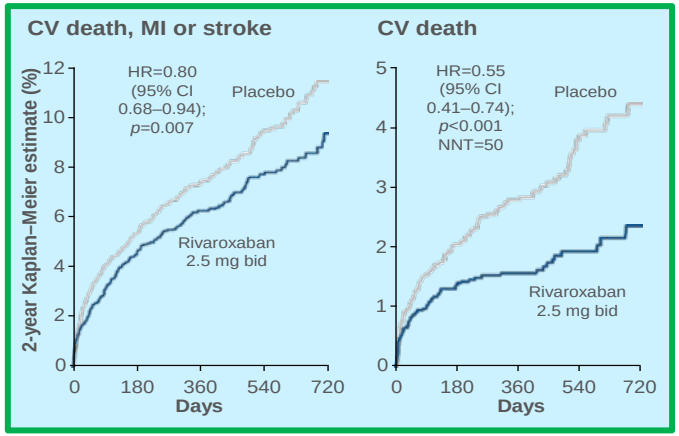


Nat Rev Cardiol. 2018 Aug;15(8):480-496.

Phase-2 strategy trials

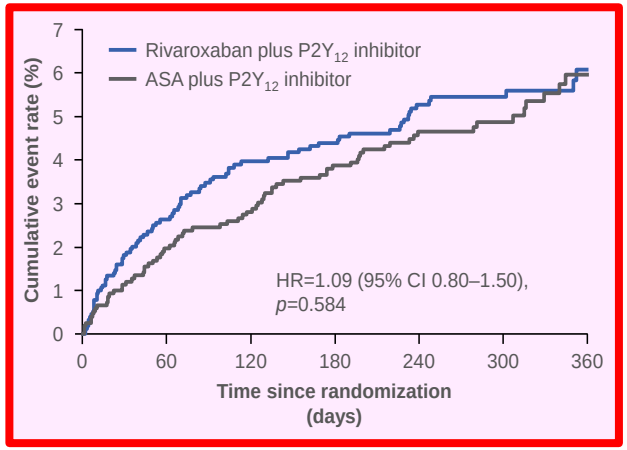
TIMI-46

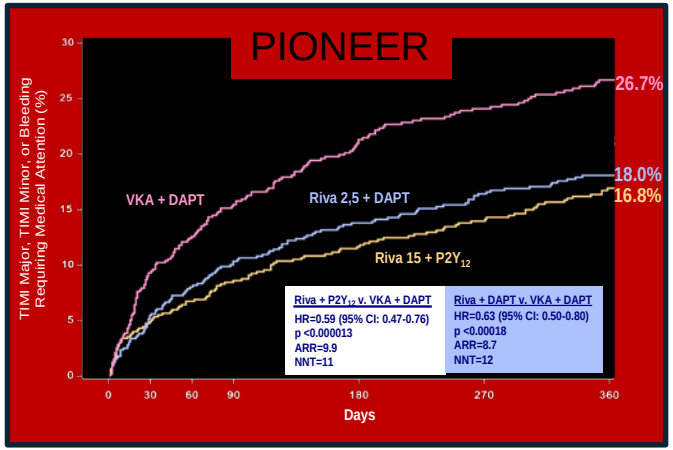




ATLAS-TIMI 51

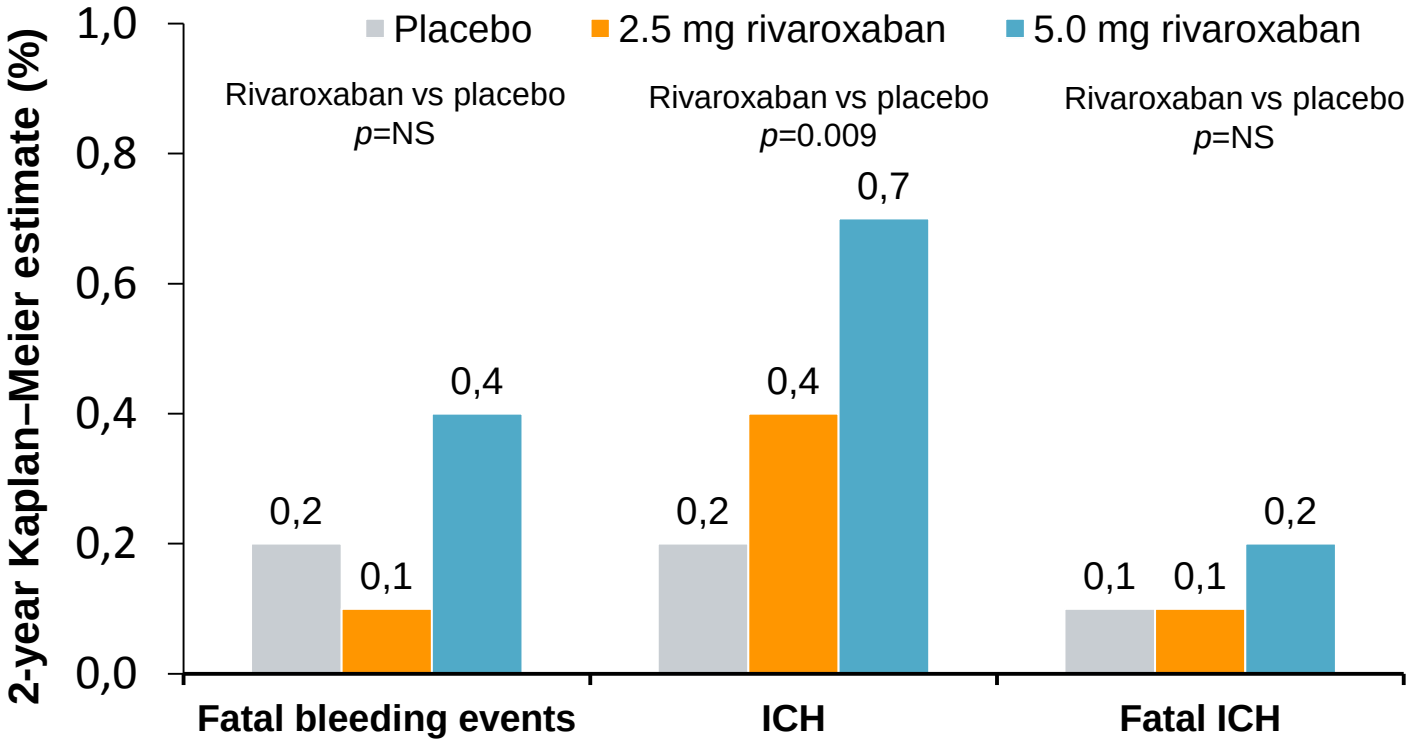
GEMINI





MÉDECINE SORBONNE UNIVERSITÉ

Safety issues



ATLAS ACS 2–TIMI 51 Investigators; NEJM 2012;366:9–19.

MÉDECINE SORBONNE UNIVERSITÉ

2018 Myocardial Revascularization

Recommendations for post-interventional and maintenance treatment in patients with MI undergoing percutaneous coronary intervention

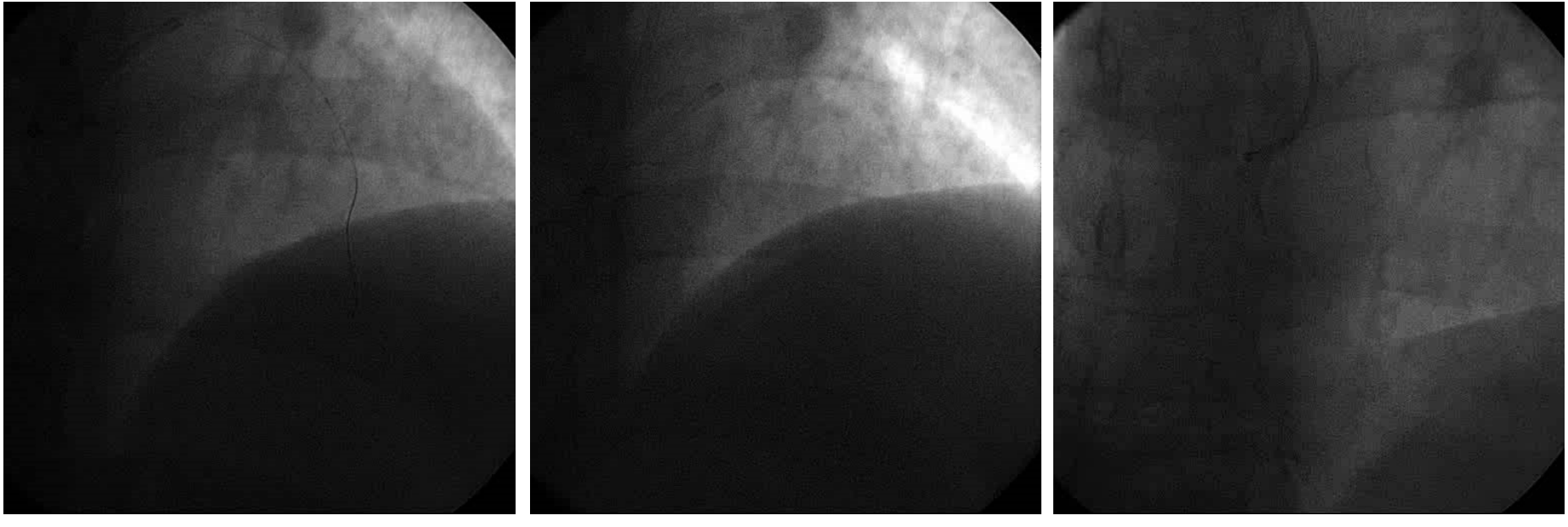
Recommendations	Class[a]	Level[b]
In ACS patients with no prior stroke/TIA, and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.[720]	IIb	B

ATLAS ACS 2–TIMI 51 Investigators; NEJM 2012;366:9–19.

Transition into practice

An ideal case?

- 38 year-old male with anterior NSTEMI (06/2012)
- Discharge on aspirin and prasugrel after LAD stenting (Double Vessel Disease)
- Active smoker/heredity/no comorbidities & Physical activity 6 hrs/week



Question #1

Would you add anti-Xa before discharge?

1. YES
2. NO

Question #1→Probably Not

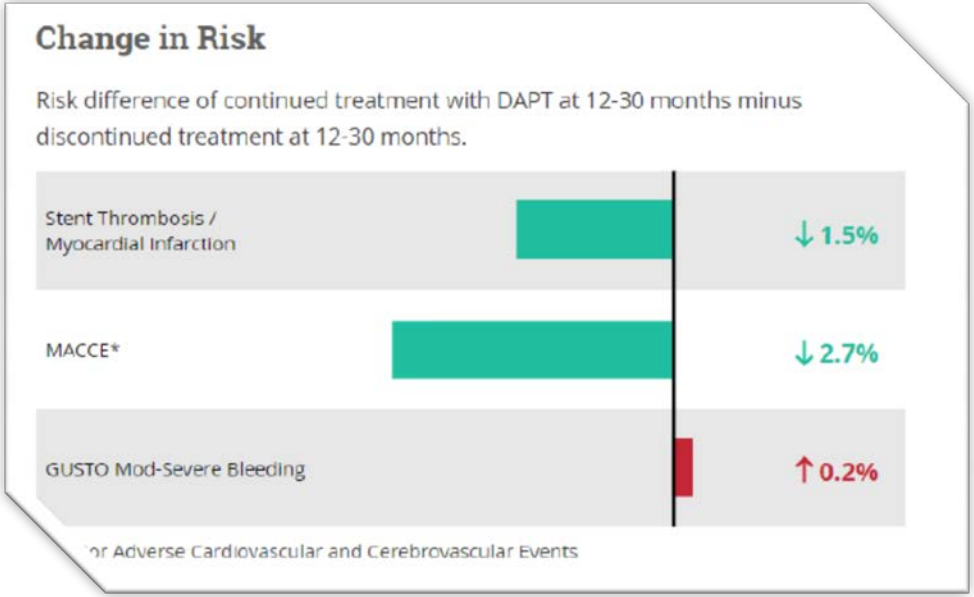
- No labelling
- No reimbursement
- Unpredictable risk of Intra-cranial Hemorrhage
- Established alternatives with less safety hazards

After one year?

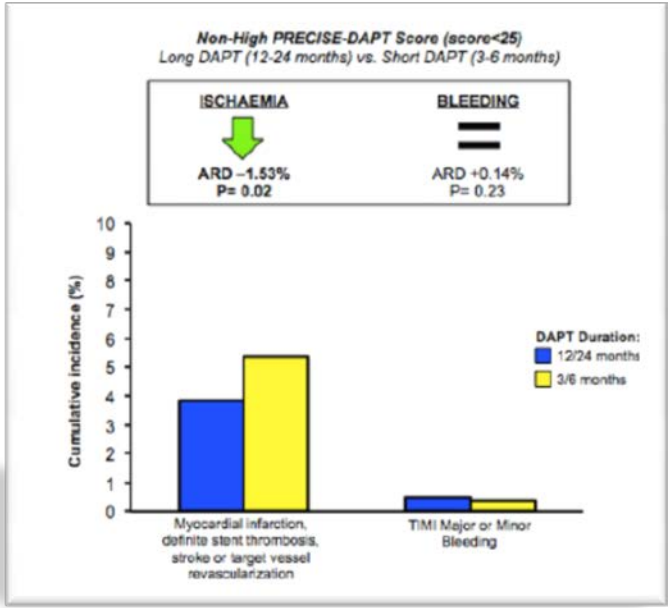
Risk stratification

- **Asymptomatic and no ischemia/MI scare (stress MRI)**
- **Occasional smoker/LDL at 1.2g/L**

DAPT Score = 2



PRECISE-DAPT = 6

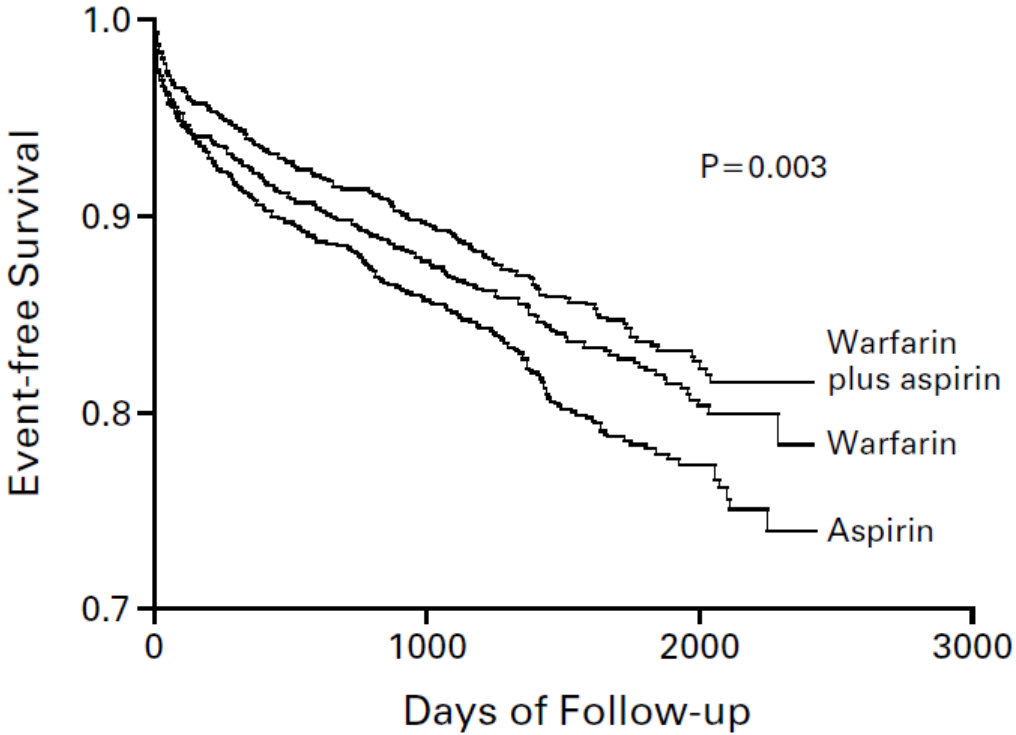


Question #2

1. Stop the $P2Y_{12}$ inhibitor
2. Maintain the same DAPT regimen
3. De-escalation from prasugrel to clopidogrel
4. Switch from $P2Y_{12}$ inh to low dose Anti-Xa

Safety/Efficacy issues with dual therapy

The WARIS-2 Study (n=3630)



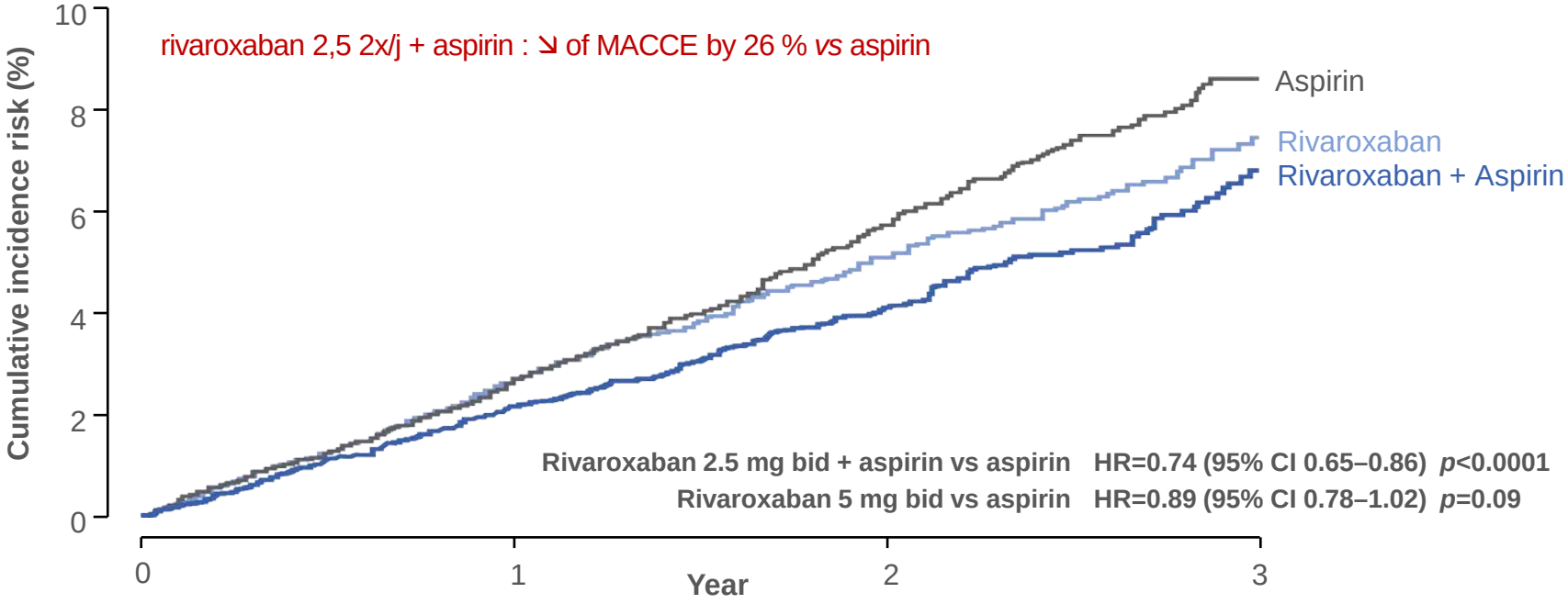
Episodes of major, nonfatal bleeding 0.62% vs 0.17% year (P<0.001).

Drug adherence Issues

N Engl J Med 2002;347:969-74

COMPASS

Stroke/MI/Cardiovascular death



Connolly SJ et al. *Lancet* 2017; doi:10.1016/S0140-6736(17)32458-3.

Lack of efficacy of anti-Xa alone

Crude incidence over mean follow-up of 23 months	Rivaroxaban 5 mg bid n (%) N=8250	Aspirin n (%) N=8261	HR (95% CI)	p-value
MI, Stroke or CV death*	411 (5)	460 (6)	0.89 (0.78–1.02)	0.094
CV death	175 (2)	184 (2)	0.95 (0.77–1.17)	0.63
Non CV death	141 (2)	155 (2)	0.91 (0.73–1.15)	0.43
Myocardial Infarction	176 (2)	195 (2)	0.90 (0.74–1.11)	0.18
Ischemic Stroke	79 (1)	120 (2)	0.66 (0.50–0.87)	0.0037
Haemorragic Stroke	27 (<1)	10 (<1)	2.70 (1.31–5.59)	<0·0051
Stent thrombosis	50 (1)	46 (1)	1.09 (0.73–1.62)	0.68

Lack of efficacy on ischemic endpoint

Significant increase in intracranial bleeding

Connolly SJ et al. *Lancet* 2017; doi:10.1016/S0140-6736(17)32458-3.

SAFETY ISSUE WITH THE LOW DOSE+ASA

Crude incidence over mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin n (%)	Aspirin n (%)	HR (95% CI)	p-value
Major bleeding (modified ISTH)	263 (3)	158 (2)	1.66 (1.37–2.03)	<0.0001
Fatal	14 (0.2)	9 (0.1)	1.55 (0.67–3.58)	0.30
ICH	19 (0.2)	19 (0.2)	0.99 (0.52–1.87)	0.98
Critical organ	36 (0.4)	25 (1)	1.42 (0.85–2.36)	0.18
Other	194 (2)	105 (1)	1.85 (1.46–2.34)	<0.0001
ISTH major bleeding	186 (2)	105 (1)	1.77 (1.39–2.24)	<0·0001
Pre-specified net clinical benefit (CV death, stroke, MI, fatal bleeding, or critical organ bleeding)	392 (5)	494 (6)	0.78 (0.69–0.90)	0.0003

Significant increase major bleeding → Almost doulbed+++
Plus a trend towards more fatal bleeds

Connolly SJ et al. *Lancet* 2017; doi:10.1016/S0140-6736(17)32458-3.

PENDING ISSUES

- Early termination → overstimation of the Tx effect?
- Bleedings requiring blood transfusion/hospitalisation → NCB?
- Add-on therapy → Treatment adherence and cost-issues?

What should I tell my patient?

Question #2 → DAPT

1. Strong evidence for maintaining DAPT in his situation
2. De-escalation of $P2Y_{12}$ inhibition → not an option → LOW SCORES
3. Dual therapy with Anti-Xa → Higher risk of bleed than with DAPT

NNT and NNH in SCAD trials

	DAPT[1]	PEGASUS[2,*]	COMPASS[3**]	COMPASS[3***]
NNT (death/MI/Stroke)	64	79	72	72
NNH (TIMI/ISTH major)	111	114	80	59

**Cohorte ticagrélor 60 mg*

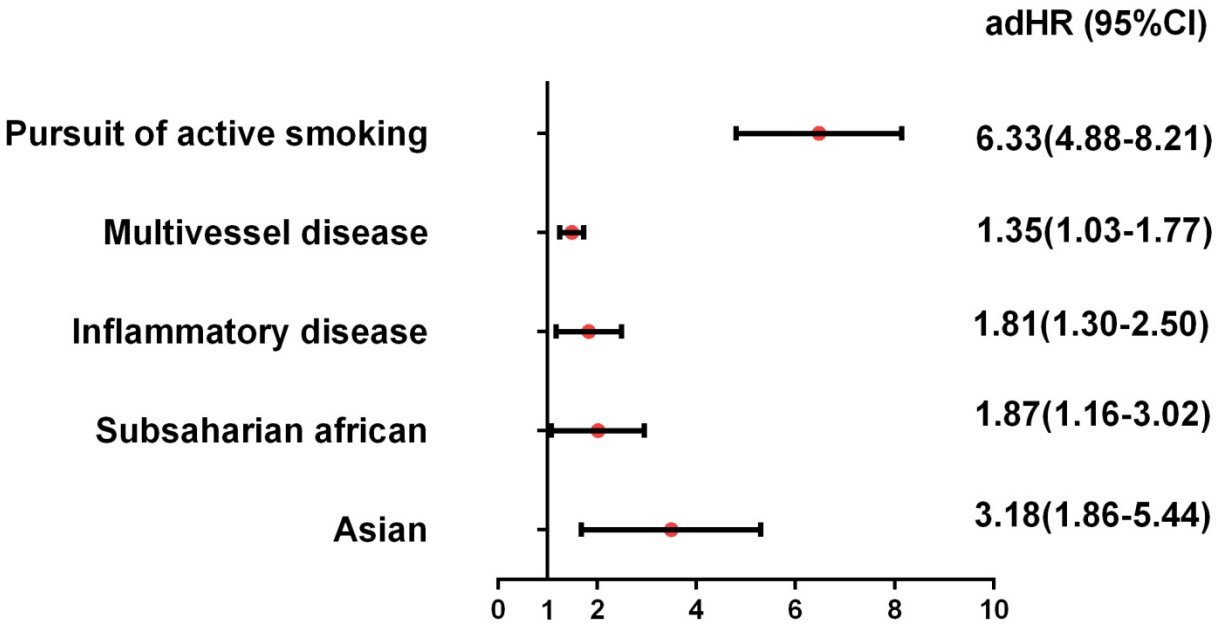
***Cohort rivaroxaban 2.5mg bid plus aspirin*

****Considering blood transfusion*

1. *N Engl J Med. 2014 Dec 4;371(23):2155-66*
2. *N Engl J Med. 2015 May 7;372(19):1791-800*
3. *Lancet 2017; doi:10.1016/S0140-6736(17)32458-3*

Independent correlates of MACE

OR plot for multivariate Cox Model using repeated measurements for multiple recurrences



The natural history of premature coronary artery disease over 20 years : the AFIJI registry (ESC 2018 POSTER XX)

Epilogue

How did I treat my patient?

- Prasugrel was switched to clopidogrel in 02/2013
- Clopidogrel was stopped in 02/2014 (on PCP request)
- March 2018 → Acute occlusion of the PL from RCA

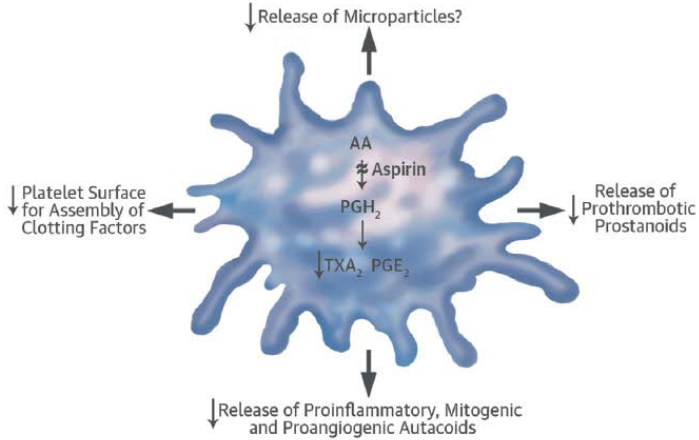
Conclusions

- **Aspirin → The SOC for SCAD**
- **DAPT → May be used when the bleeding risk is low**
- **Dual Therapy with anti-Xa may be an OPTION but:**
  - ***Only in addition to Aspirin***
  - ***Without possible titration of the treatment intensity***
  - ***Without possible early initiation after PCI***
  - ***With a lower net clinical benefit than DAPT***
- **Higher risk patient would not have change my decision**

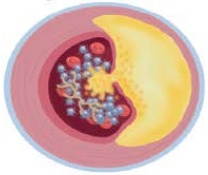
Rebuttal

- **Failure of aspirin+rivaroxaban 2.5mg bid versus APT?**
- **Non-inferiority of ticagrelor versus ticagrelor plus aspirin?**

The multiple facette of aspirin

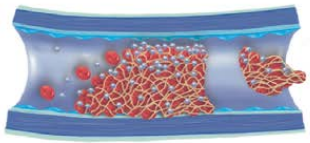


Coronary Atherothrombosis



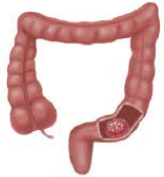
Evidence from >50 RCTs and meta-analyses

Venous Thromboembolism



Evidence from several RCTs and meta-analyses

Colorectal Cancer

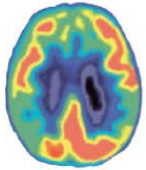


Evidence from observational studies and meta-analyses

Evidence from post-hoc long-term follow-up of RCTs and meta-analyses

Currently being tested prospectively in primary prevention and adjuvant RCTs

Cognitive Impairment

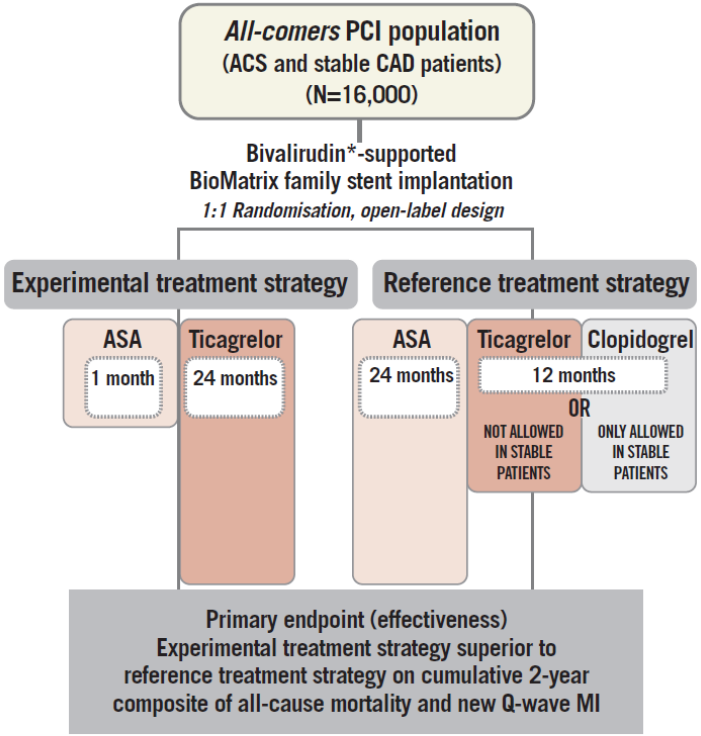


Limited evidence from observational studies

Currently being tested in the ASPREE primary prevention trial

J Am Coll Cardiol 2015;66:74–85

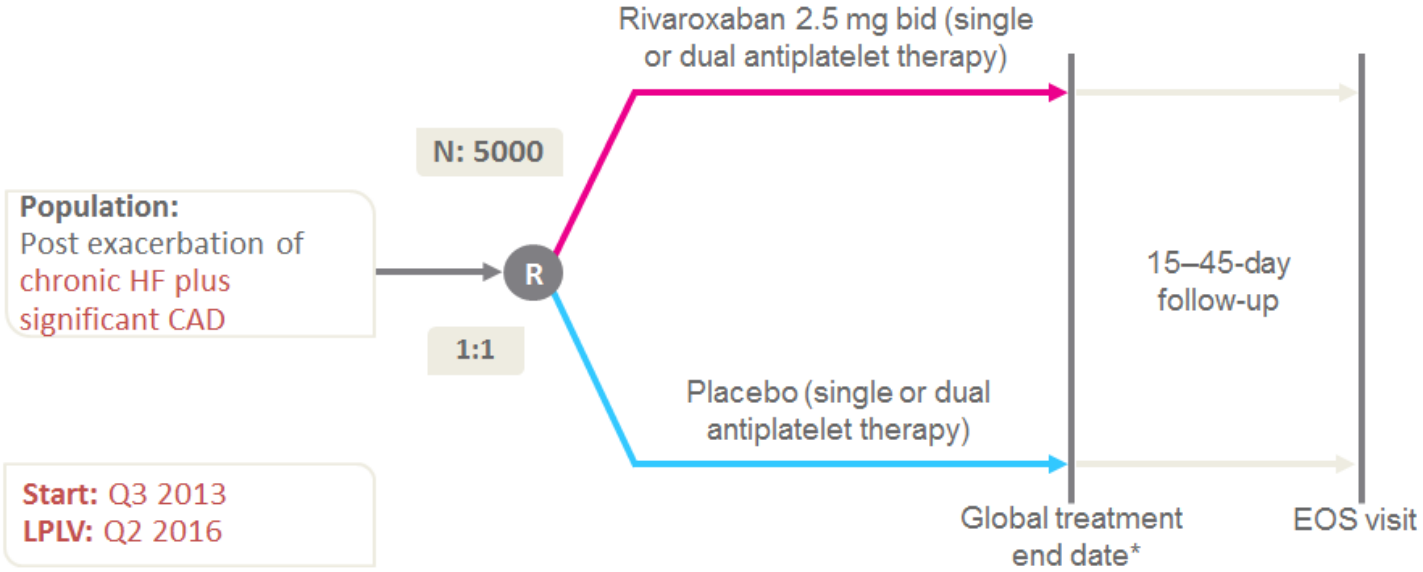
GLOBAL LEADERS



IMPORTANT: In the Reference treatment strategy arm, ticagrelor is not allowed in stable patients, and clopidogrel must be given in combination with ASA. However, patients already on stable maintenance treatment with ticagrelor (or prasugrel) can continue with ticagrelor treatment (for 12 months post index PCI).

COMMANDER: Overview Chronic HF/CAD study

Objective: Efficacy and safety of rivaroxaban for reducing the risk of MI, stroke or death in HF with CAD



www.clinicaltrials.gov/ct2/show/NCT01877915

Conclusions

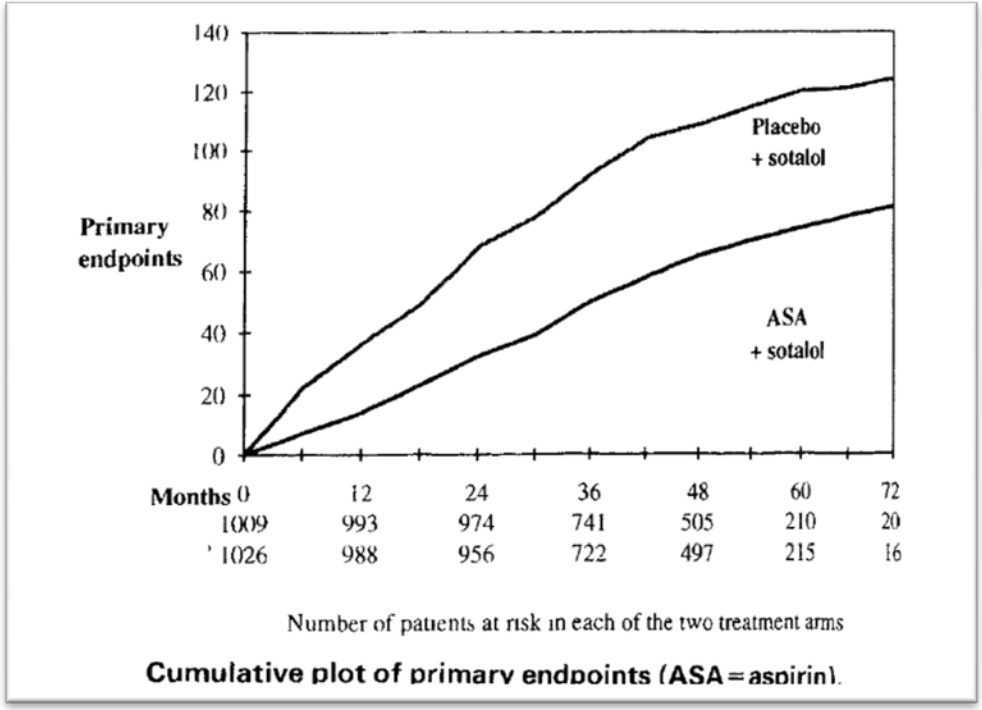
- Aspirin → The standard of care for SCAD
- DAPT → When the bleeding risk is low
- Ticagrelor alone may be an alternative to DAPT?
- Dual Therapy is NOT needed as an alternative to APT

The presentation can be downloaded at action-cœur.org

SAPAT (stable angina)

—	All (n = 2035)	Aspirin + sotalol (n = 1009)	Placebo + sotalol (n = 1026)
Male (%)	52	51	53
Age (yr)	67	67 (8)	67 (8)
Heart rate (min)	65	65 (14)	64 (9)
Blood pressure (mm Hg)	152/86	152 (19)/85 (9)	153 (19)/86 (9)
Serum potassium (mmol/l)	4·3	4·3 (0·3)	4·3 (0 3)
Serum cholesterol (mmol/l)	6·8	6·7 (1·3)	6·8 (1·5)
Serum triglycerides (mmol/l)	1·9	1·9 (1·2)	1·9 (1·2)
Duration of angina (yr)	4·7	4·6 (5·0)	4·7 (5·0)
Smoking (%)	16	17	16
Heredity for cardiovascular disease (%)	34	34	33
Treated:			
for hypertension (%)	41	43	40
with calcium channel blockers (%)	9	9	9
with diuretics (%)	26	27	25
for type II diabetes (%)	7	6	7
Sotalol, median dose (mg)	160	160 (80–160)	160 (80–160)

Mean (SD) unless otherwise indicated: for sotalol dose interquartile range is given



Cumulative plot of primary endpoints (ASA = aspirin).

34% (81 vs 124 patients) reduction in MI & sudden death; 95% CI 24-49%; p=0·003)

Lancet. 1992 Dec 12;340 (8833):1421-25