Conoscere e Curare il Cuore 2019

VENERDI' 1 MARZO

LA MONOTERAPIA A LUNGO TERMINE CON TICAGRELOR DOPO LO STENT. LO STUDIO GLOBAL LEADERS

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ASPIRIN AFTER CORONARY STENTING

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Recommendation	COR	LOE
Life-long single antiplatelet therapy, usually aspirin, is recommended.[1,2]	I	A

[1] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.

[2] Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860.

Neumann FJ, et al. Eur Heart J. 2018 Aug 25. [Epub ahead of print]

ASPIRIN FOR SECONDARY PREVENTION

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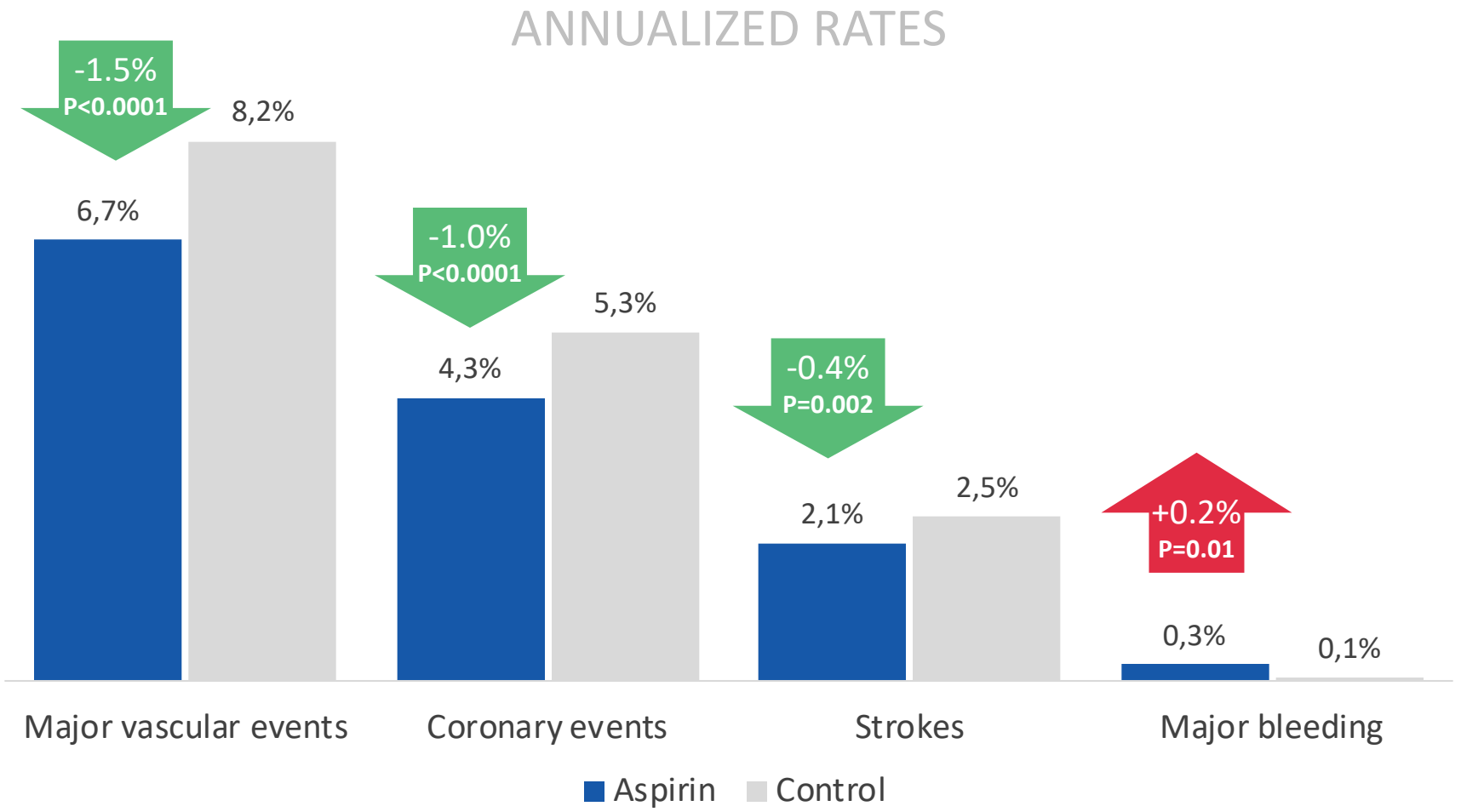

Treating 10,000 patients with aspirin for 1 year

Ischemic fatal and nonfatal events	-100-200
Major extracranial (e.g. GI) bleeding events	+10-20
Hemorrhagic stroke events	+1

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ATT Collaboration. Lancet. 2009;373:1849-60

DAPT DURATION AFTER DRUG-ELUTING STENTS

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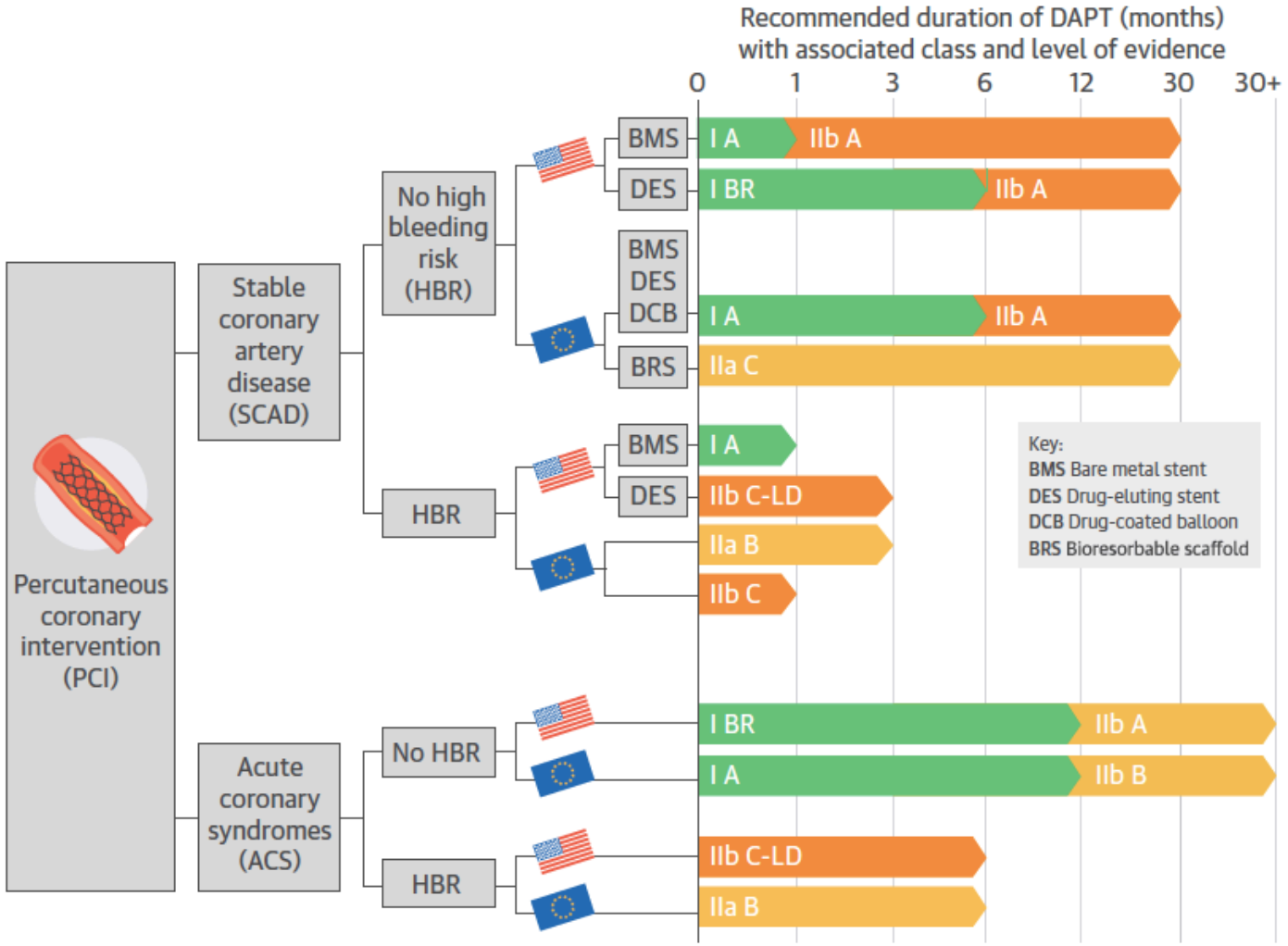
Stable CAD

No HBR	6 to 12 months
HBR	1 to 3 months

ACS

No HBR	12 to 12+ months
HBR	6 months



Capodanno D, et al. J Am Coll Cardiol. 2018;72:2915-2931

CLINICAL OUTCOMES OF DIFFERENT DAPT DURATIONS

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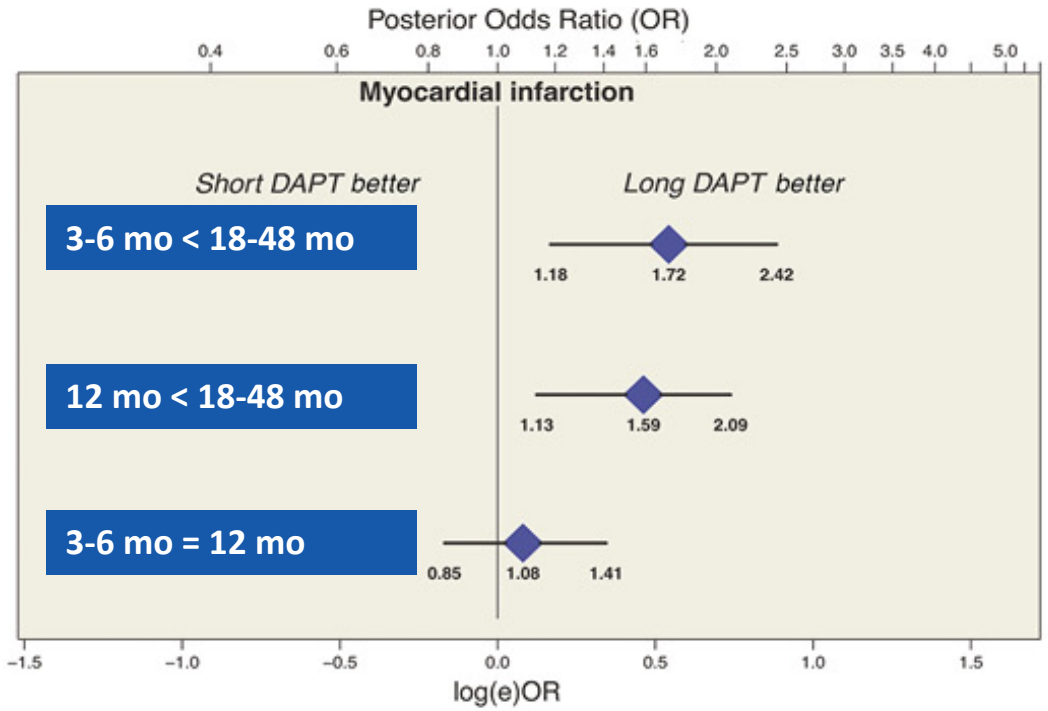
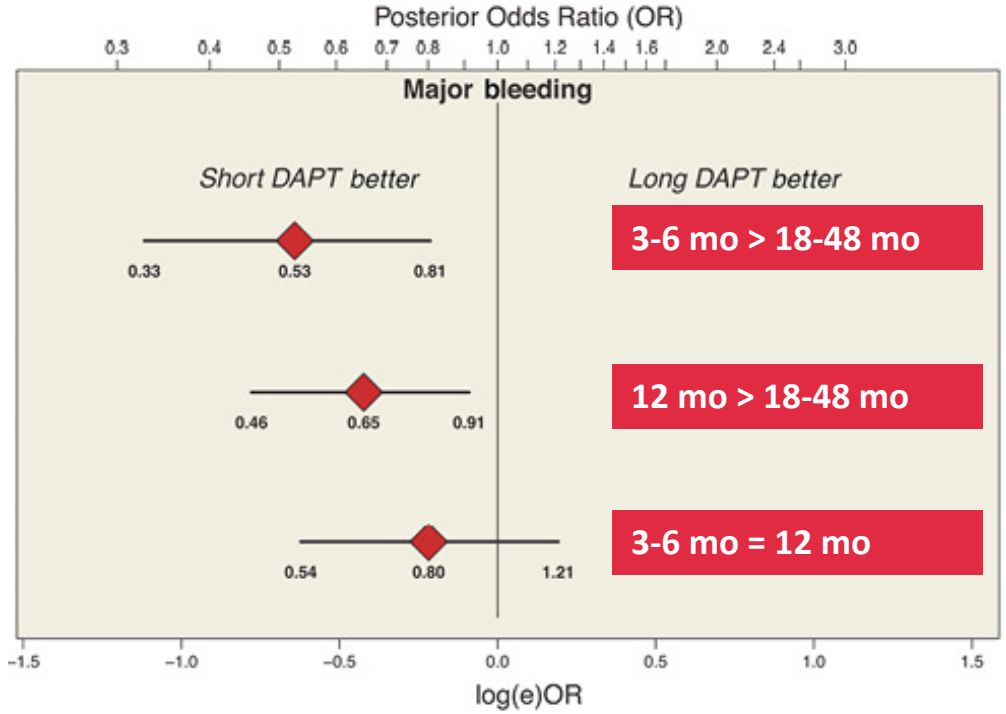
MYOCARDIAL INFARCTION



MAJOR BLEEDING



No credible reduction or increase in mortality for all comparisons

Gargiulo G, et al. EuroIntervention. 2017;13:717-733

STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI

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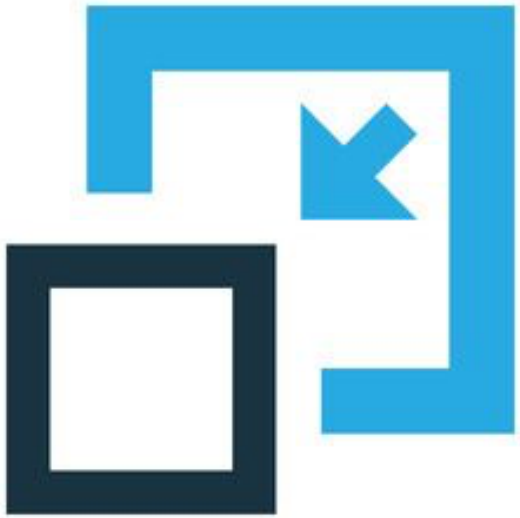
Shortening DAPT

11 TRIALS OF SHORT VS. STANDARD DAPT



De-escalation

TOPIC
TROPICAL ACS

Aspirin withdrawal

GLOBAL LEADERS
GLASSY ACC 2019
SMART-CHOICE ACC 2019
STOPDAPT-2 ACC 2019

STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI

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GLASSY ACC 2019

SMART-CHOICE ACC 2019

STOPDAPT-2 ACC 2019

RATIONALE FOR ASPIRIN-FREE STRATEGIES AFTER PCI

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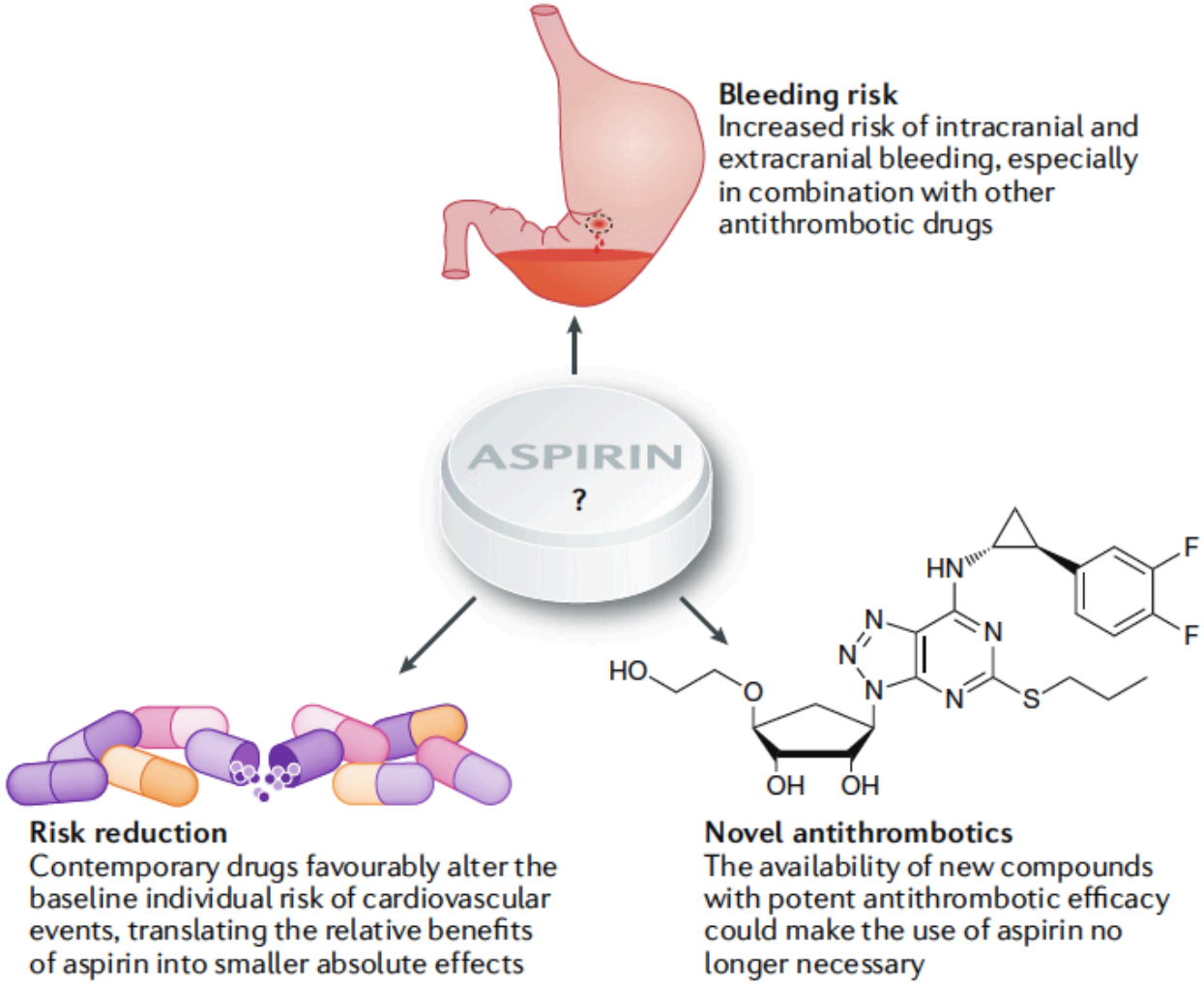

Three major uncertainties surround the use of aspirin for secondary prevention:

- Major bleeding (e.g. GI and intracranial)
- Actual risk reduction on top of – for example - statins
- Role of newer antiplatelet drugs (e.g. ticagrelor)

Capodanno D, Angiolillo DJ. Nat Rev Cardiol. 2018;15:480-496

PHARMACODYNAMICS OF ASPIRIN WITHDRAWAL

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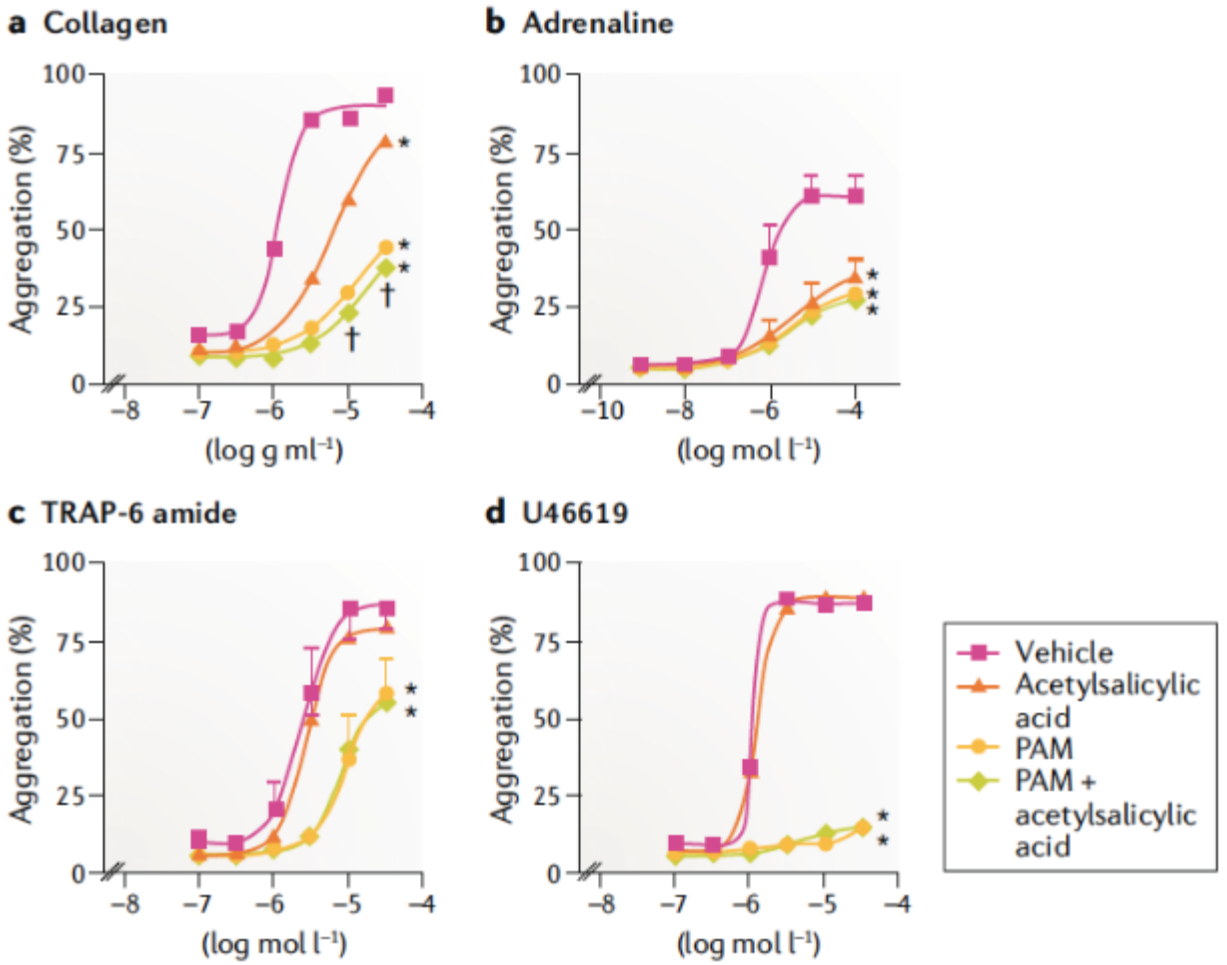
In vitro assessment of platelet aggregation with 4 agonists in presence of aspirin, prasugrel active metabolite (PAM) or aspirin+PAM

Little additional platelet inhibition following stimuli with several agonists in the presence of potent $P2Y_{12}$ receptor blockade



Armstrong PC, et al. J Thromb Haemost. 2011;9:552-61; Capodanno D, Angiolillo DJ. Nat Rev Cardiol. 2018;15:480-496

ASPIRIN IN TRIALS OF ANTITHROMBOTIC DRUGS

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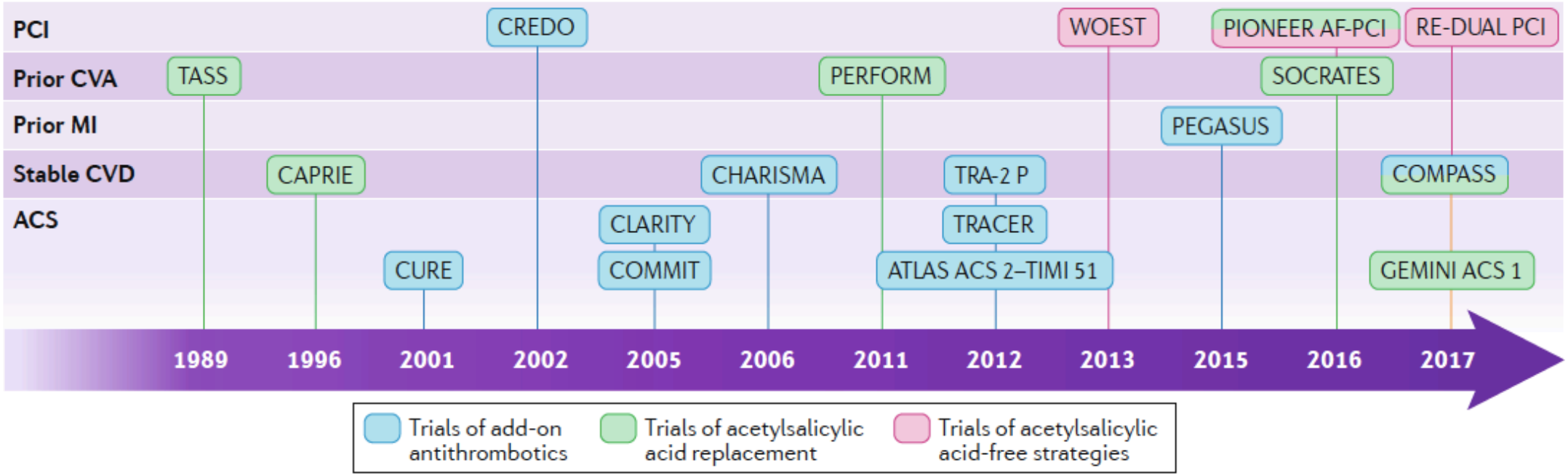
TIMELINE OF STUDIES INVESTIGATING ANTITHROMBOTIC THERAPIES ACROSS DIFFERENT PRESENTATIONS OF CARDIOVASCULAR DISEASE



Capodanno D, Angiolillo DJ. Nat Rev Cardiol. 2018;15:480-496

TRIALS OF ASPIRIN-FREE STRATEGIES IN OAC-PCI

Study	n	Intervention(s)	Control	Primary finding
WOEST COMPLETED!	573	DAT with clopidogrel for 1–12 months	DAPT for 1–12 months	Less bleeding episodes with DAT
PIONEER-AF PCI COMPLETED!	2,124	► DAT with rivaroxaban 10–15 mg OD for 12 months ► DAT with rivaroxaban 2.5 mg BID for 1, 6 or 12 months	VKA + DAPT for 1, 6 or 12 months followed by VKA + SAPT	Less bleeding episodes with rivaroxaban DAT and TAT regimens
RE-DUAL PCI COMPLETED!	2,725	► DAT with dabigatran 110 mg BID for 12 months ► DAT with dabigatran 150 mg BID for 12 months	VKA + DAPT for 1-3 months, followed by VKA + SAPT	Less bleeding episodes with both dabigatran DAT regimens

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Capodanno D, et al. Heart. 2018;104:1976-1983

RANDOMIZED TRIALS OF ASPIRIN-FREE STRATEGIES IN PCI

Study	n	Population	Treatment groups	Primary outcome
GLOBAL LEADERS COMPLETED!	16,000	PCI	DAPT for 1 month followed by ticagrelor for 23 months versus DAPT for 12 months followed by acetylsalicylic acid for 12 months	Death or nonfatal MI at 24 months
SMART-CHOICE ACC 2019	3,000	PCI	DAPT for 3 months followed by clopidogrel for 9 months versus DAPT for 12 months	Death, MI, or stroke at 12 months and major bleeding at 12 months
STOPDAPT-2 ACC 2019	3,045	PCI	DAPT for 1 month followed by clopidogrel for 59 months versus DAPT for 12 months followed by acetylsalicylic acid for 48 months	NACE at 12 months
TWILIGHT	9,000	High- risk PCI on ticagrelor, event-free at 3 months	Placebo for 12 months versus acetylsalicylic acid for 12 months	Bleeding at 12 months
TICO	3,056	ACS-PCI	DAPT for 3 months followed by ticagrelor for 9 months versus DAPT for 12 months	MACCE at 12 months and major bleeding at 12 months

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Capodanno D, Angiolillo DJ. Nat Rev Cardiol. 2018;15:480-496

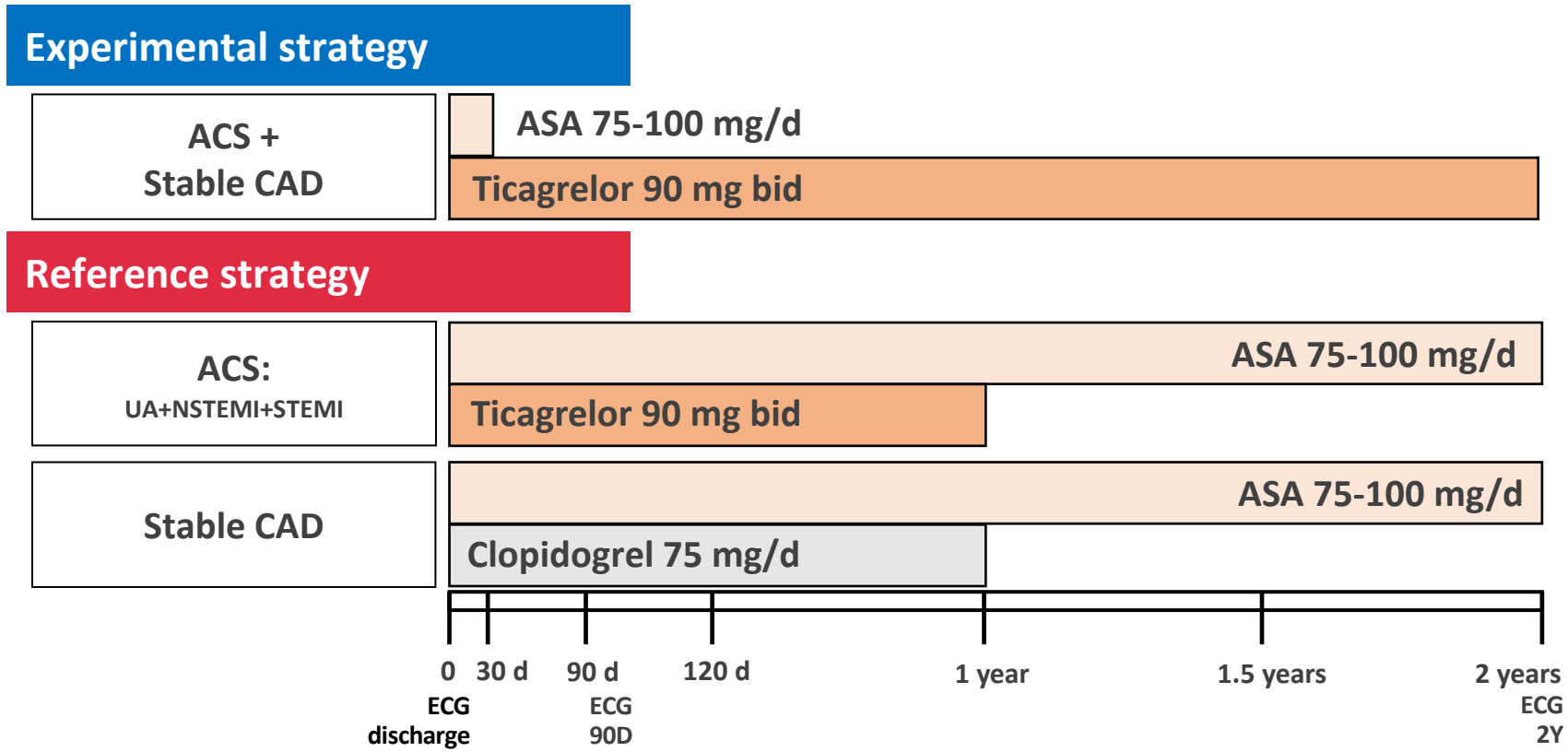
TICAGRELOR MONOTHERAPY AFTER PCI

"All-comers" PCI population
N = 15,991
1:1 Randomization,
open-label design,
130 centers worldwide

Any type of lesions:
Left main, SVG, CTO,
bifurcation, ISR, etc.

Unrestricted use of DES
(number, length)

Bivalirudin-supported
BioMatrix DES by default



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Vranckx P, et al. Lancet. 2018;392:940-949

TICAGRELOR MONOTHERAPY AFTER PCI | 12 MONTHS

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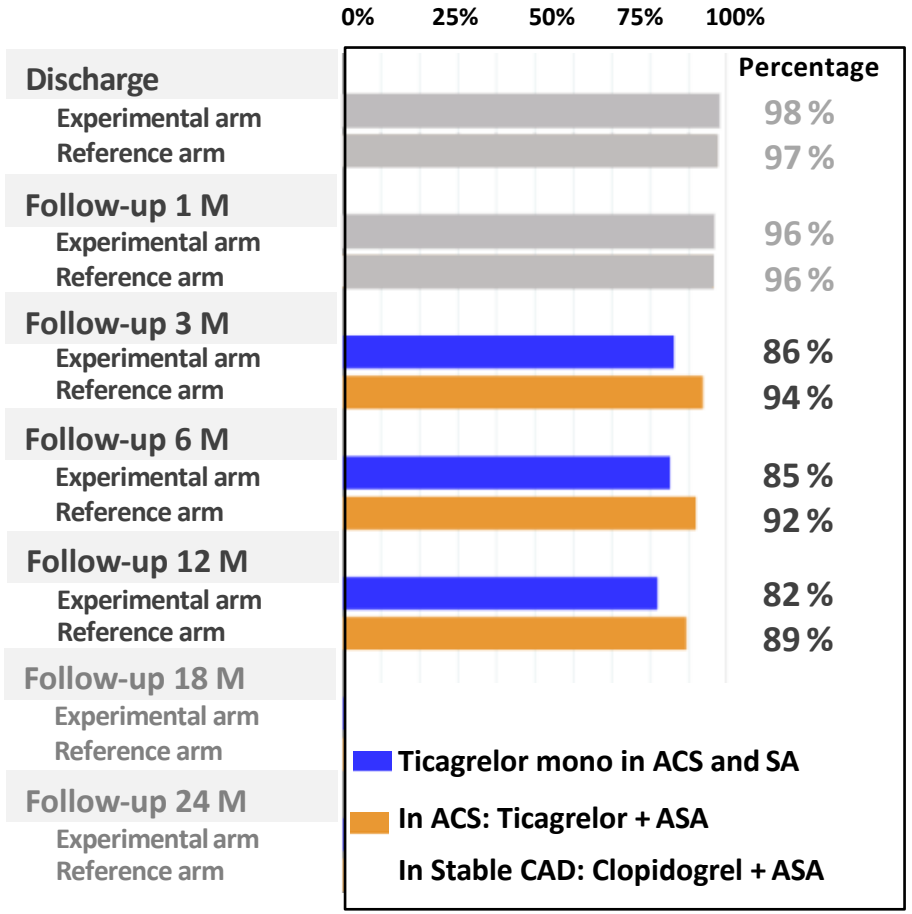
ADHERENCE TO TREATMENT STRATEGIES



PRIMARY AND SECONDARY OUTCOMES AT 12 MONTHS (ITT)

	Experimental group N=7,980	Reference group N=7,988	Risk ratio (95% CI)	P-value
Death or Q-wave MI	**1.95%**	**2.47%**	**0.79 (0.64-0.98)**	**0.028**
Death	1.35%	1.64%	0.82 (0.64-1.06)	0.14
Q-wave MI	0.60%	0.86%	0.70 (0.48-1.00)	0.052
BARC 3 or 5 bleeding	**1.47%**	**1.70%**	**0.86 (0.67-1.11)**	**0.24**
BARC 3 bleeding	0.18%	0.20%	0.88 (0.43-1.80)	0.72
BARC 5 bleeding	1.34%	1.60%	0.84 (0.65-1.08)	0.18

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Vranckx P, et al. Lancet. 2018;392:940-949

TICAGRELOR MONOTHERAPY AFTER PCI | 24 MONTHS

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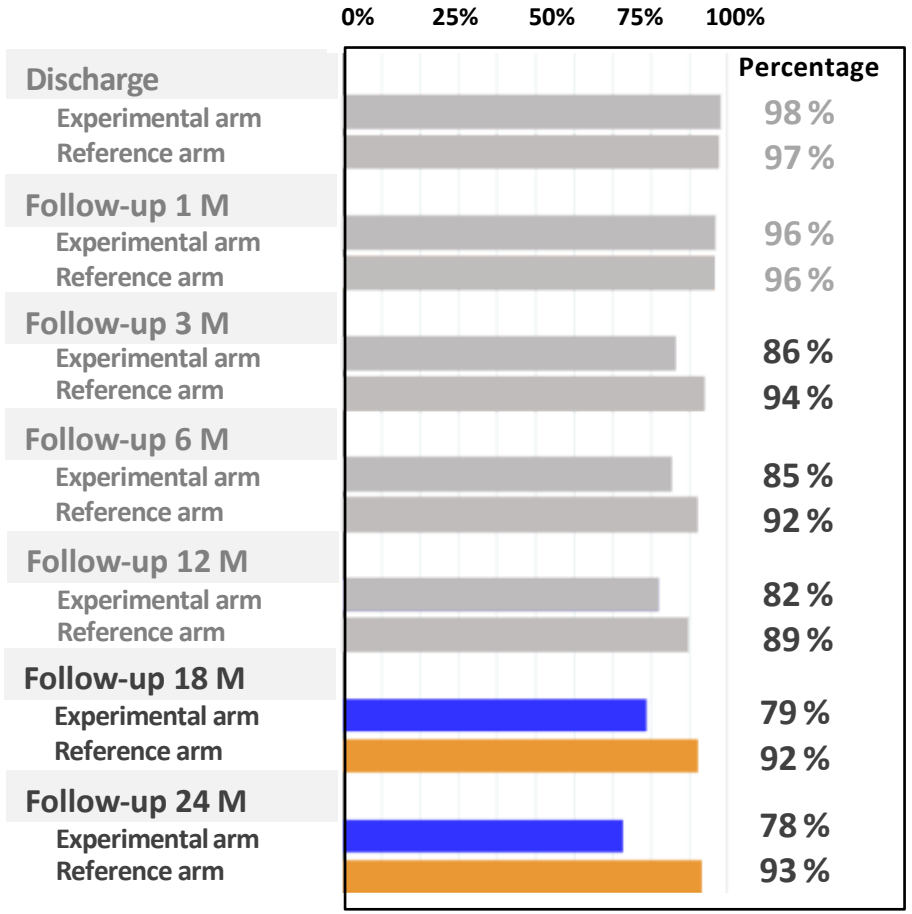
ADHERENCE TO TREATMENT STRATEGIES



PRIMARY AND SECONDARY OUTCOMES AT 24 MONTHS (ITT)

	Experimental group N=7,980	Reference group N=7,988	Risk ratio (95% CI)	P-value
Death or Q-wave MI *	**3.81%**	**4.37%**	**0.87 (0.75-1.01)**	**0.073**
Death	2.81%	3.17%	0.88 (0.74-1.06)	0.18
Q-wave MI	1.04 %	1.29%	0.80 (0.60-1.07)	0.14
BARC 3 or 5 bleeding	**2.04%**	**2.12%**	**0.97 (0.78-1.20)**	**0.77**
BARC 3 bleeding	0.28%	0.30%	0.92 (0.52-1.64)	0.78
BARC 5 bleeding	1.88%	1.99%	0.95 (0.76-1.18)	0.63

* Primary endpoint

Vranckx P, et al. Lancet. 2018;392:940-949

TICAGRELOR MONOTHERAPY AFTER PCI | 12-24 MONTHS

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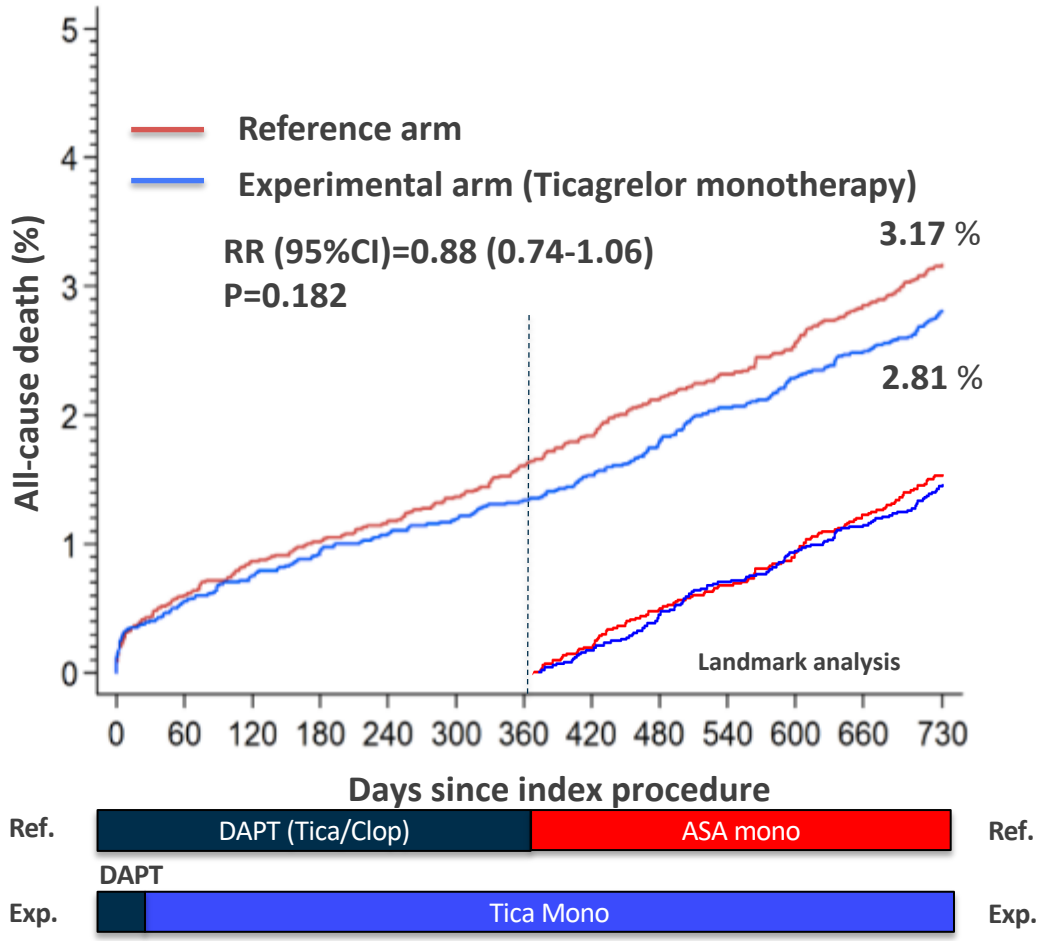
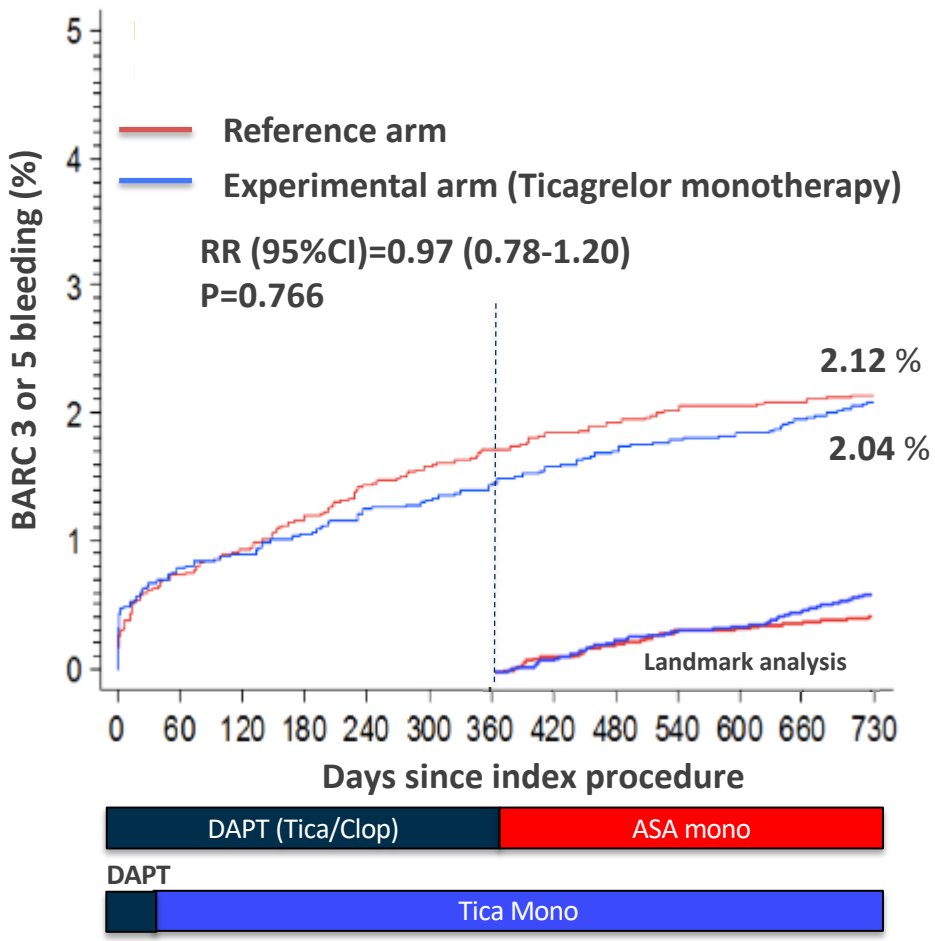
DEATH



BARC 3 OR 5 BLEEDING



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Vranckx P, et al. Lancet. 2018;392:940-949

NO WIN FOR TICAGRELOR VS. ASPIRIN HEAD-TO-HEAD!

VS.

Trial	n	Population	Primary outcome	Results
SOCRATES	13,199 (1:1)	Acute stroke/TIA	Death, stroke, MI at 3 months	Ticagrelor 6.7% vs. Aspirin 7.5%, p=0.07
DACAB	500 (1:1:1)	CABG	SVG patency at 12 months	Ticagrelor 82.8% vs. Aspirin 76.5%, p=0.10
TiCAB	1,893 (1:1)	CABG	CV death, MI, stroke, or revascularization at 12 months	Ticagrelor 9.7% vs. Aspirin 8.2%, p=0.27

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Johnston SC, et al. N Engl J Med. 2016;375:35-43; Zhao Q, et al. JAMA. 2018;319:1677-1686; Schunkert H, AHA 2018, Chicago

A SUBGROUP OF INTEREST

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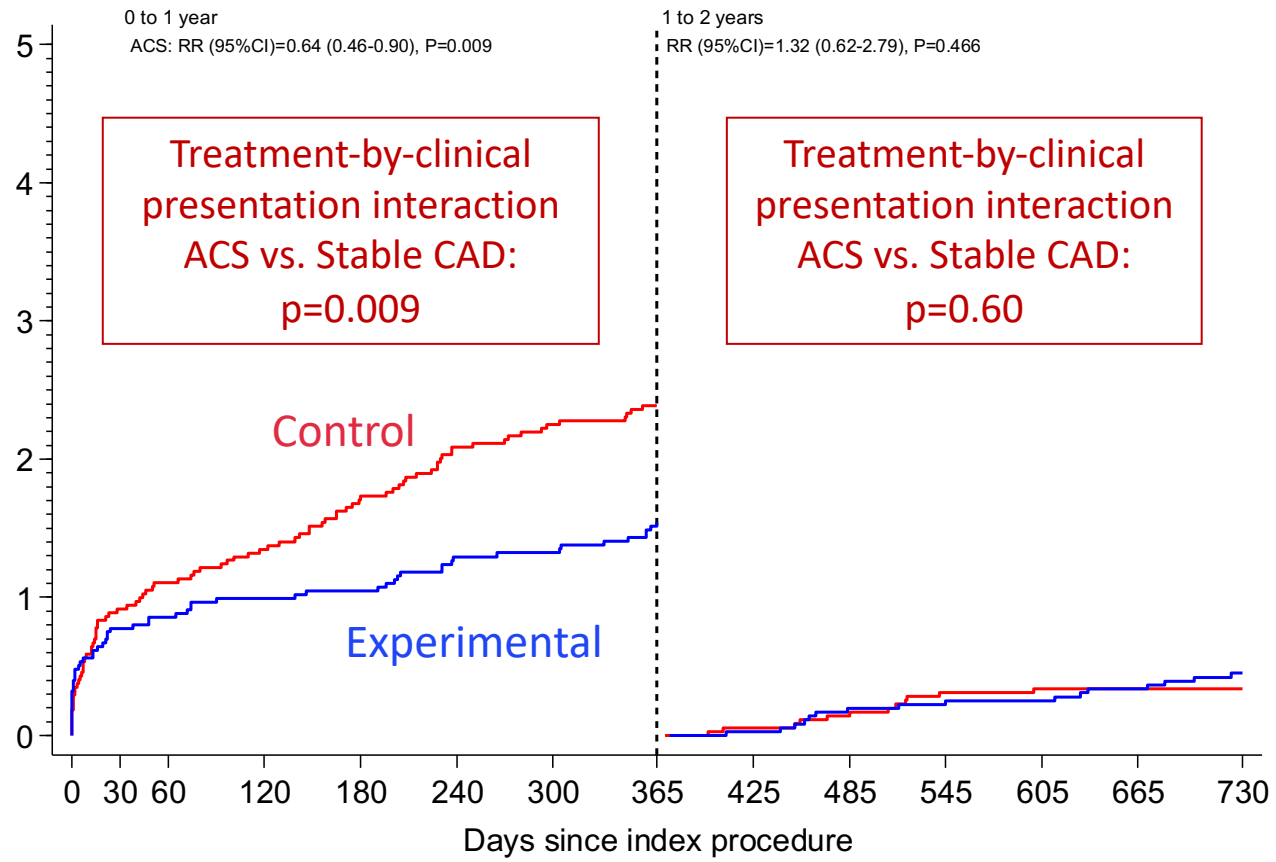
BARC 3 OR 5 BLEEDING | ACS SUBGROUP



Significant treatment-by-subgroup interaction for BARC 3 or 5 bleedings at 24 months by clinical presentation (ACS vs. SCAD)

Ticagrelor monotherapy might be safer than DAPT in ACS patients, but would it be equally protective in a randomized trial powered for ischemic endpoints?

Vranckx P, et al. TCT 2018, San Diego

STUDY LIMITATIONS

- **Complex design, hampering the formal assessment of non-inferiority**
  - > Different antiplatelet regimens and different durations of dual antiplatelet therapy were concomitantly assessed
- **Open label design**
  - > Potential for performance and detection bias
- **Short follow-up of 2 years**
  - > Would the numerical trends in the trial become significant?
- **Relatively small number of events**
  - > Limited power for subgroups of interest (e.g. ACS)
- **Lack of adjudication for nonfatal ischemic and major bleeding events**
  - > This will be the object of the GLASSY substudy (expected at ACC 2019)

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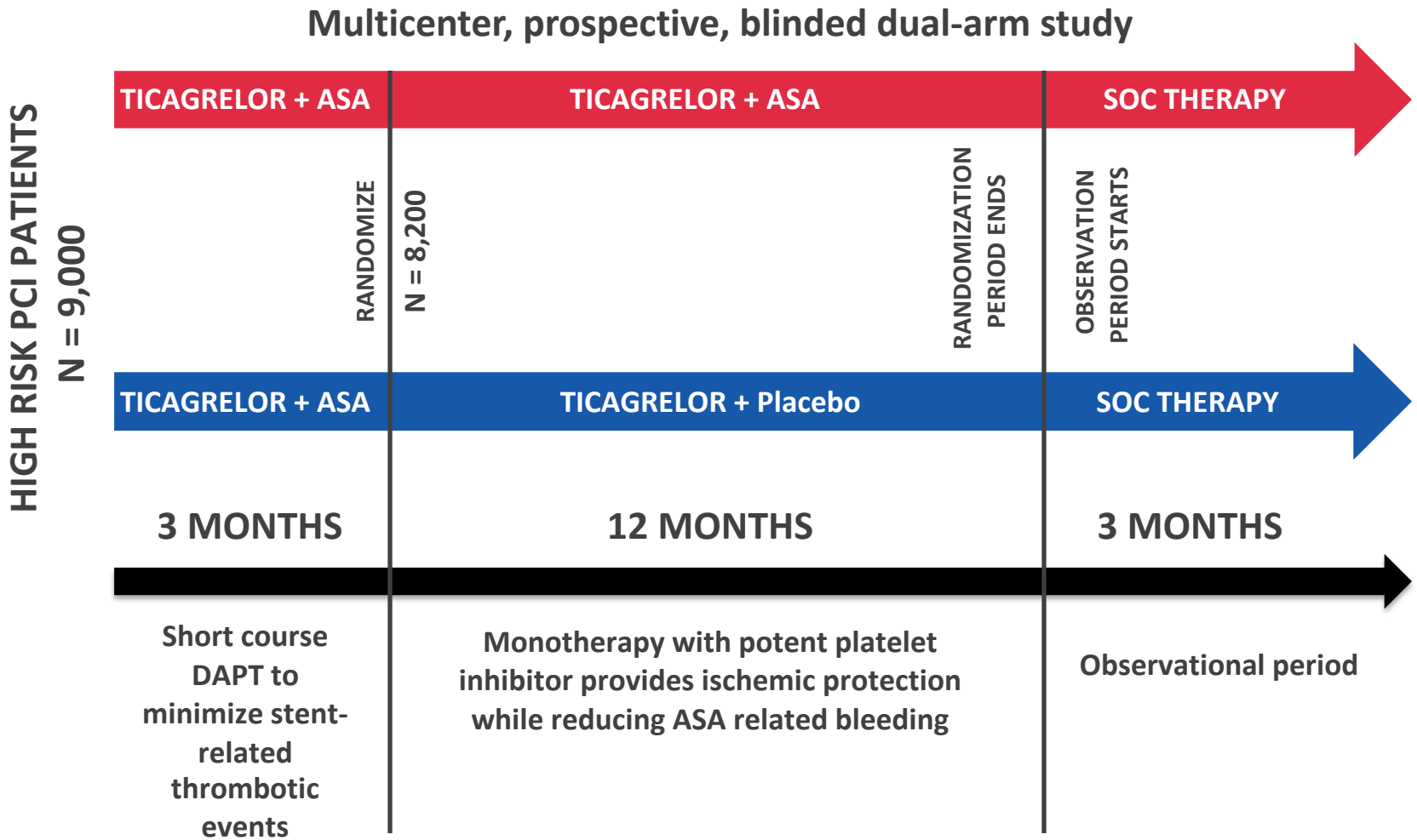
TWILIGHT



Primary Endpoint

BARC 2, 3, 5 bleeding between 3 and 15 months

Status

Enrollment completed

Expected at TCT 2019

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Baber U, et al. Am Heart J. 2016;182:125-134

LONG TERM MONOTHERAPY WITH TICAGRELOR?

- **In PLATO, ticagrelor has been typically tested on a background of aspirin.**
  - The balance of risk and benefit for its use as antiplatelet monotherapy after PCI is largely unknown.
- **An interesting array of studies are exploring the possibility of avoiding aspirin in favor of long-term $P2Y_{12}$ inhibition.**
- **In GLOBAL LEADERS, ticagrelor monotherapy after PCI had no clear benefits and no clear harm.**
  - However, in view of the higher rates of discontinuation, the increased frequency of dyspnea and the higher cost with the experimental strategy, as well as the as the necessity of twice daily dosing with ticagrelor, the current standards of care for antiplatelet therapy should continue for the time being.

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