The Approach to the High Bleeding Risk Patient

Tailoring Antithrombotic Therapy in HBR Patient

Dominick J. Angiolillo, MD, PhD
Professor of Medicine
Director - Cardiovascular Research
Program Director – Interventional Cardiology Fellowship
University of Florida College of Medicine - Jacksonville

Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:
a) Consulting fee or honorarium from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company;
b) Honorarium for participation in review activities (DSMB member) from CeloNova.
c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member) and American College of Cardiology (Associate Editor JACC Cardiovasc Interventions)

Institutional payments for:
a) Grant support industry: from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions.
b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
c) Federal agency: NIH

Facts about antithrombotic therapy & bleeding

1. All antithrombotic agents are associated with bleeding risk.

2. More potent antithrombotic therapies are associated with increased bleeding risk.

3. Prolonging the duration of more potent antithrombotic regimens is associated with increased bleeding risk.

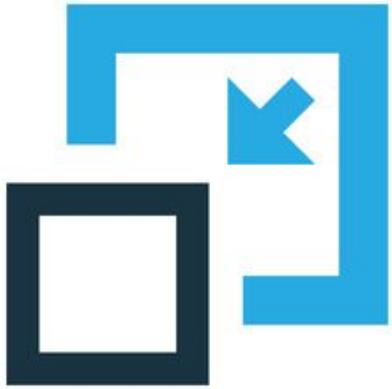
4. Stacking on antithrombotic therapies (triple>dual>single) is associated with increased bleeding risk.

ONGOING DIRECTIONS IN TAILORING ANTITHROMBOTIC PHARMACOTHERAPY FOR HBR PATIENTS

STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI

Shortening DAPT

11 TRIALS OF SHORT
VS. STANDARD DAPT



De-escalation

TOPIC
TROPICAL ACS

AF + PCI

WOEST
PIONEER- AF-PCI
RE-DUAL PCI
AUGUSTUS ACC 2019
ENTRUST ESC 2019

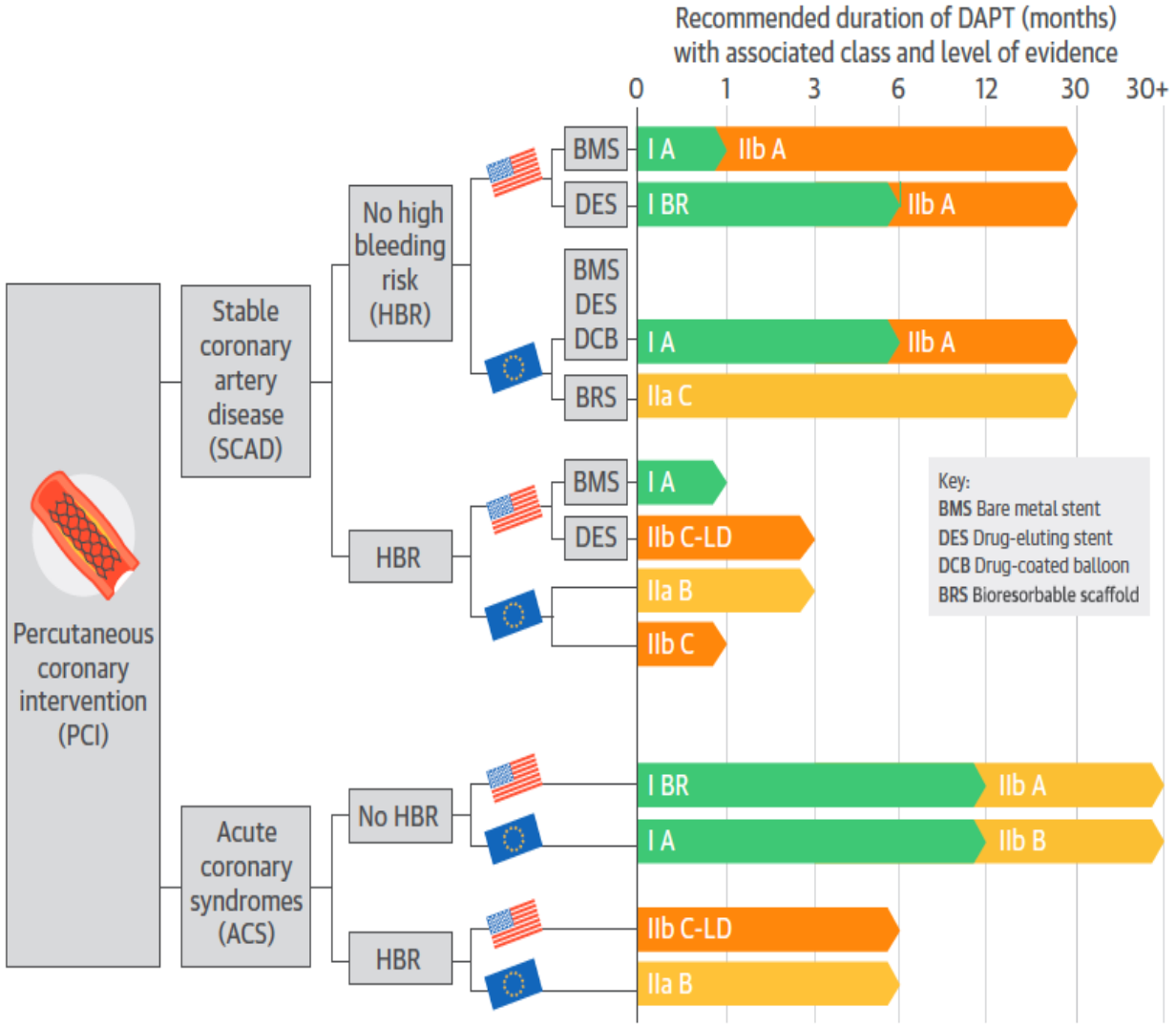
Aspirin withdrawal

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

Bleeding Reduction Strategies Post-PCI: Definitions

- **Short DAPT duration**
  - Discontinuation of P2Y12 inhibitor sooner than guideline recommended minimum duration
  - Stable CAD: <6 months (eg, 3 months)
  - ACS: <12 months (eg, 6 months)
  - Opportunity to further classify in “very” short (eg, 1 month for stable CAD and 3 months for ACS)

DAPT DURATION AFTER PCI: ACC/AHA vs ESC GUIDELINES



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 & Angiolillo DJ. J Am Coll Cardiol. 2018;72:2915-2931

Studies of DAPT duration

ACC/AHA*	ESC*	Trial	Comparison (Months)	Design
PCI				
Yes	Yes	RESET (N = 2,217)	3 vs. 12	Noninferiority
Yes	Yes	OPTIMIZE (N = 2,199)	3 vs. 12	Noninferiority
Yes	Yes	EXCELLENT (N = 1,443)	6 vs. 12	Noninferiority
Yes	Yes	SECURITY (N = 1,399)	6 vs. 12	Noninferiority (halted)
Yes	Yes	ISAR-SAFE (N = 4,000)	6 vs. 12	Noninferiority (halted)
No	No	I-LOVE-IT-2 (N = 1,829)	6 vs. 12	Noninferiority
No	No	IVUS-XPL (N = 1,400)	6 vs. 12	Noninferiority
No	No	OPTIMA-C (N = 1,368)	6 vs. 12	Noninferiority
No	No	NIPPON (N = 2,772)	6 vs. 24	Noninferiority (halted)
Yes	Yes	PRODIGY (N = 1,970)	6 vs. 24	Superiority
Yes	Yes	ITALIC (N = 1,822)	6 vs. 24	Noninferiority (halted)
Yes	Yes	ARCTIC (N = 1,259)	12 vs. 18	Superiority
Yes	Yes	DAPT (N = 9,961)	12 vs. 30	Superiority
Yes	Yes	DES-LATE (N = 5,045)	12 vs. 36	Superiority
Yes	No	OPTIDUAL (N = 1,385)	12 vs. 48	Superiority (halted)
ACS-PCI				
No	No	DAPT-STEMI (N = 870)	6 vs. 12	Noninferiority
No	No	REDUCE (N = 1,496)	3 vs. 12	Noninferiority
No	No	SMART-DATE (N = 2,172)	6 vs. 12	Noninferiority

***The availability status at the time of the ACC/AHA and ESC guidelines publication is indicated.**

Capodanno D & Angiolillo DJ. J Am Coll Cardiol. 2018;72:2915-2931

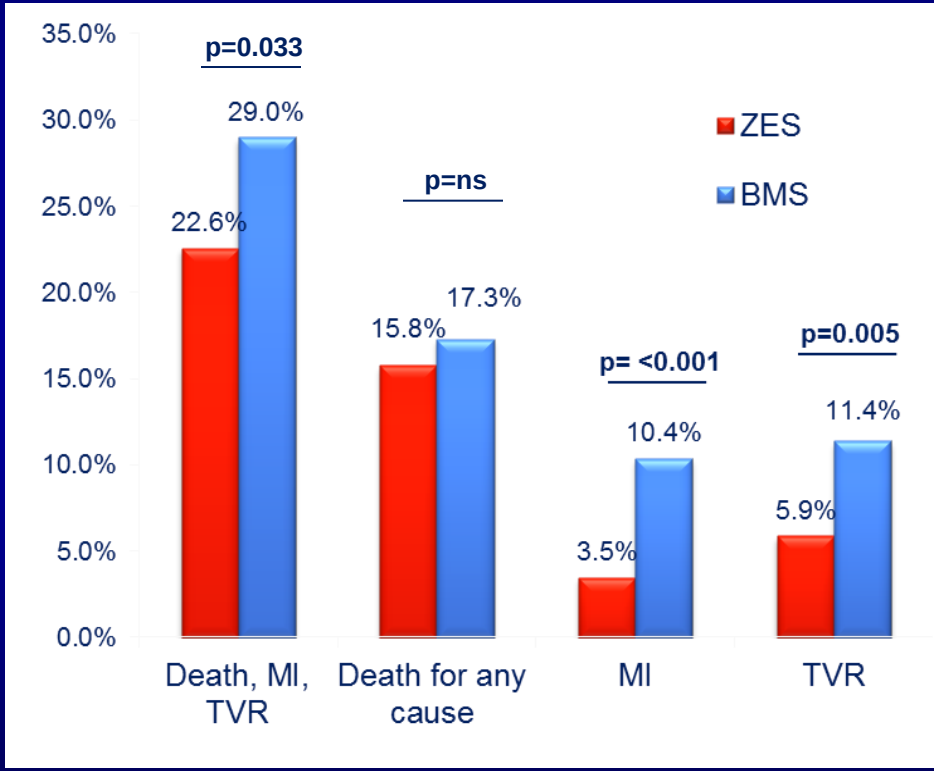
Risk Scores for DAPT Duration

Score	Number of variables	Development cohort (patients, design)	Setting	Predicted outcome(s)	Validation cohort(s) (patients, c-index)
DAPT	5 clinical, 3 procedural	N=11,648, multicentre randomized clinical trial	PCI patients on DAPT who were event-free for 12 months	Ischemia and bleeding between 12 and 30 months after PCI	N=8,136, 0.64 for both ischemia and bleeding
PARIS	Coronary thrombosis risk score: 6 clinical Major bleeding risk score: 6 clinical	N=4,190 patients, multicentre registry	PCI patients on DAPT	Ischemia and bleeding at 24 months after PCI	N=8,665, 0.65 for ischemia and 0.64 for bleeding
PRECISE-DAPT	5 clinical	N=14,963, pooled analysis of randomized clinical trials	PCI patients on DAPT	Bleeding at 12 months after PCI	N=8,595, 0.70 N=6,172, 0.66

Capodanno D, Angiolillo DJ. Lancet 2017; 389:987-989

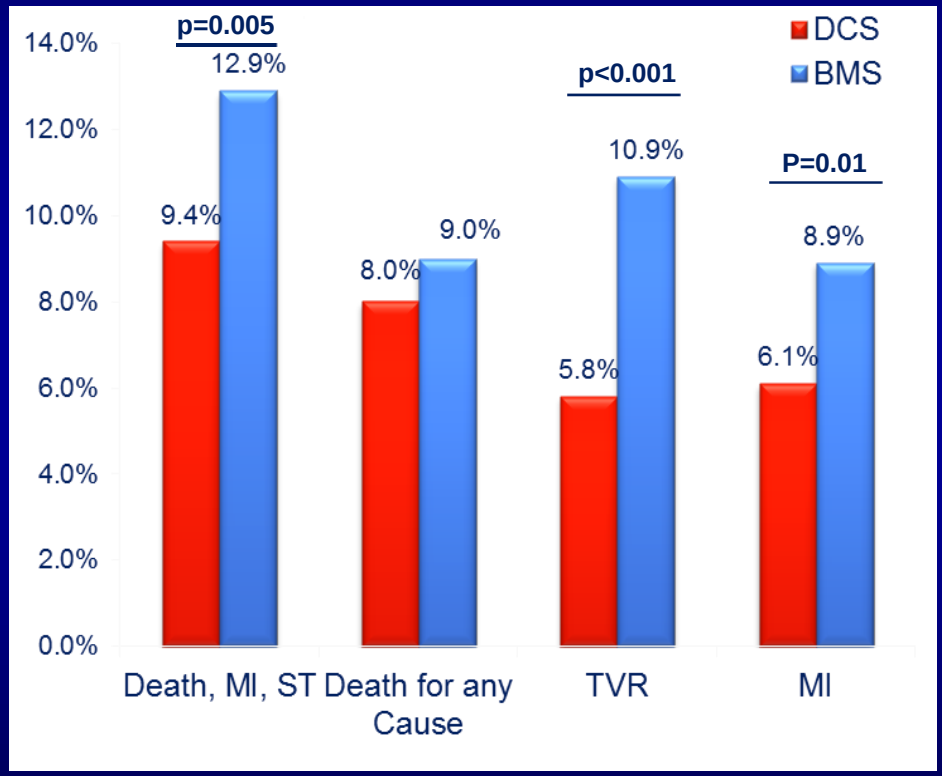
Outcomes in HBR patients: 1-year follow-up

ZEUS Trial



Ariotti S, et al. JACC Cardiovasc Interv. 2016 Mar 14;9(5):426-36

LEADERS Free Trial

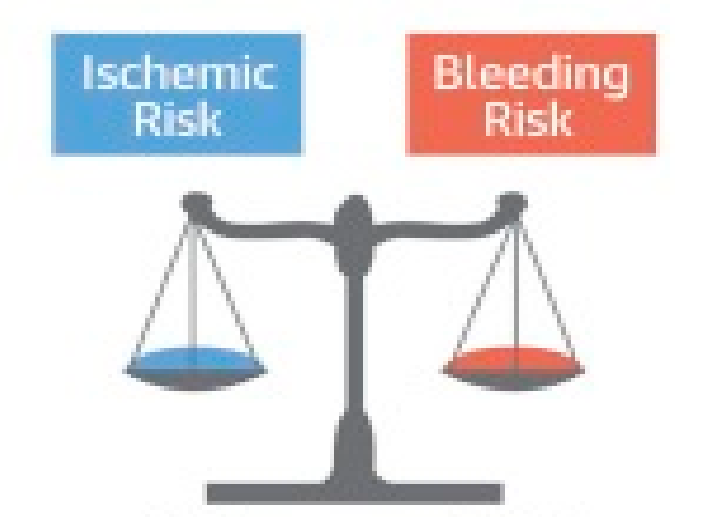


Urban P. Et al. N Engl J Med. 2015 Nov 19;373(21):2038-47

Ongoing trials in HBR patients with new generation DES

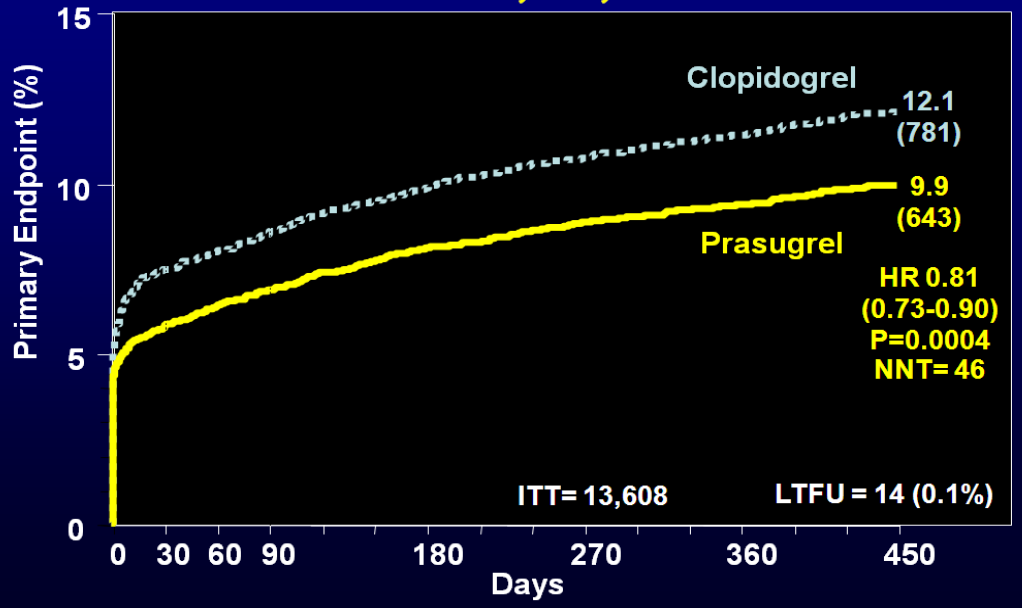
Bleeding reduction strategies: De-escalation

De-escalation (switching from prasugrel or ticagrelor to clopidogrel) as a strategy to reduce long-term bleeding events without a trade-off in ischemic protection

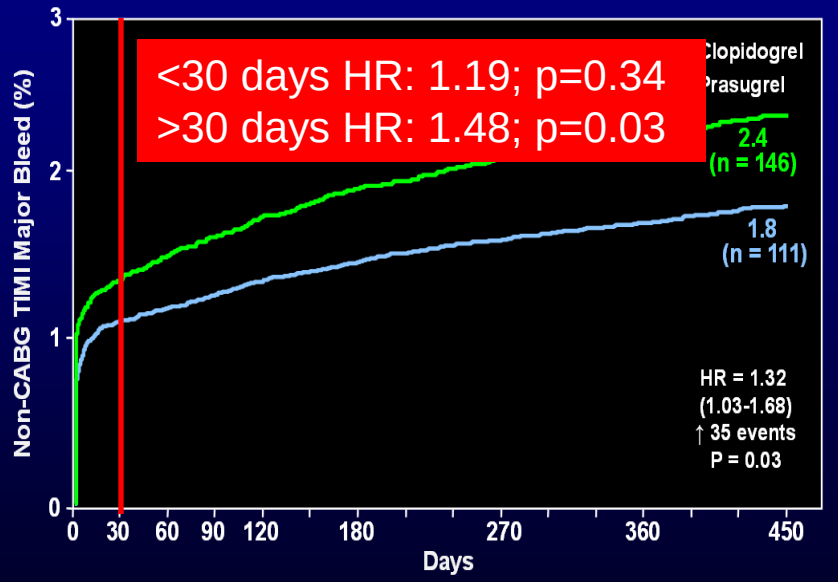


Angiolillo DJ, Rollini F, et al. Circulation. 2017

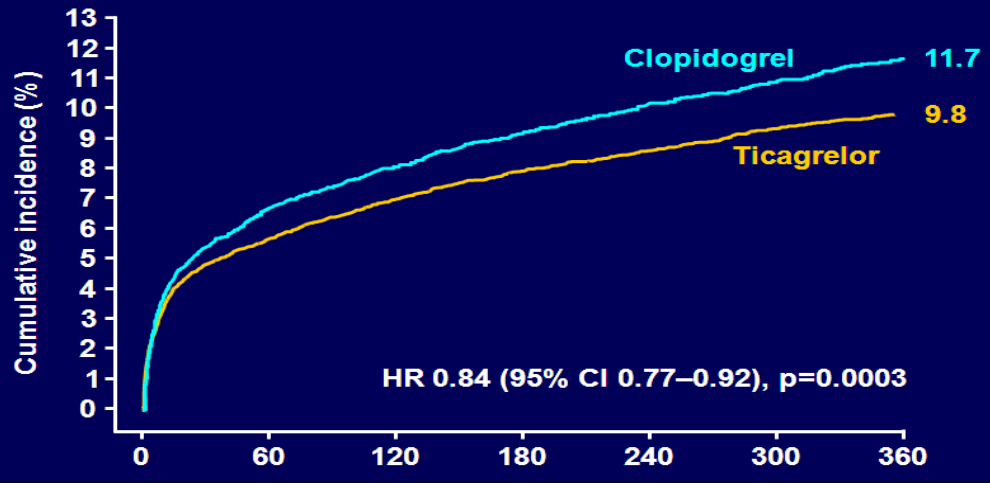
Primary Endpoint
CV Death, MI, Stroke



Non-CABG TIMI Major Bleed
All ACS Population

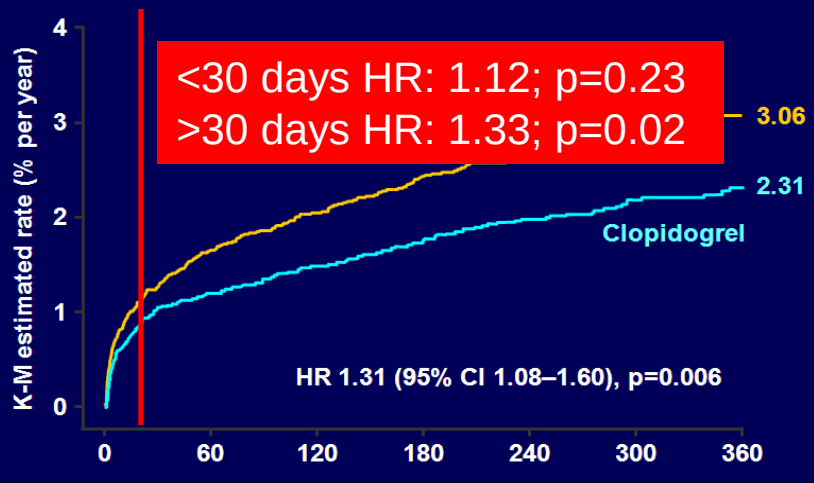


K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



Time to non-procedure-related PLATO major bleeding

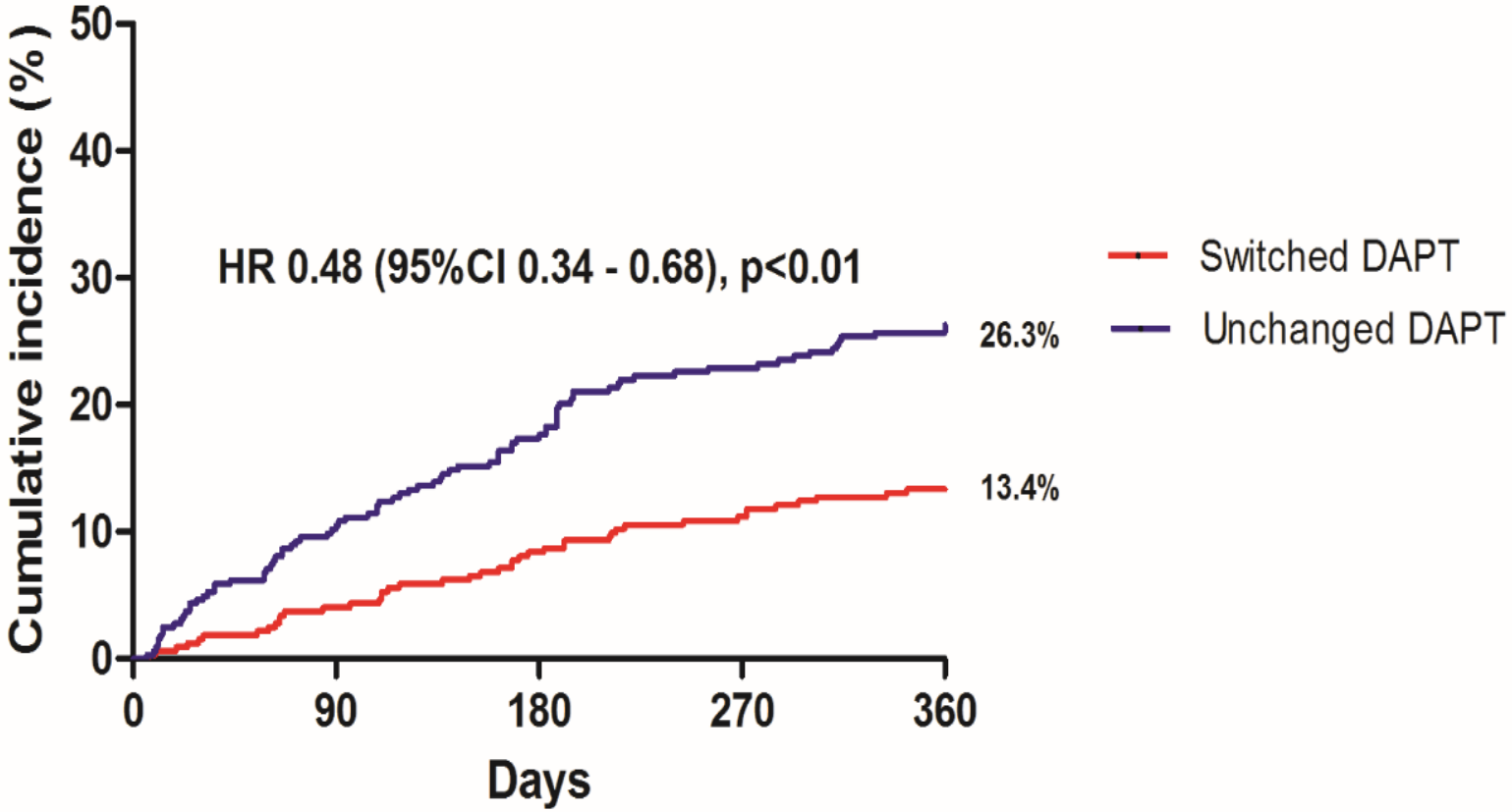
Completeness of follow-up 99.97% = five patients lost to follow-up



TOPIC Study

Primary Endpoint

Death, Urgent revasc., Stroke, BARC ≥ 2

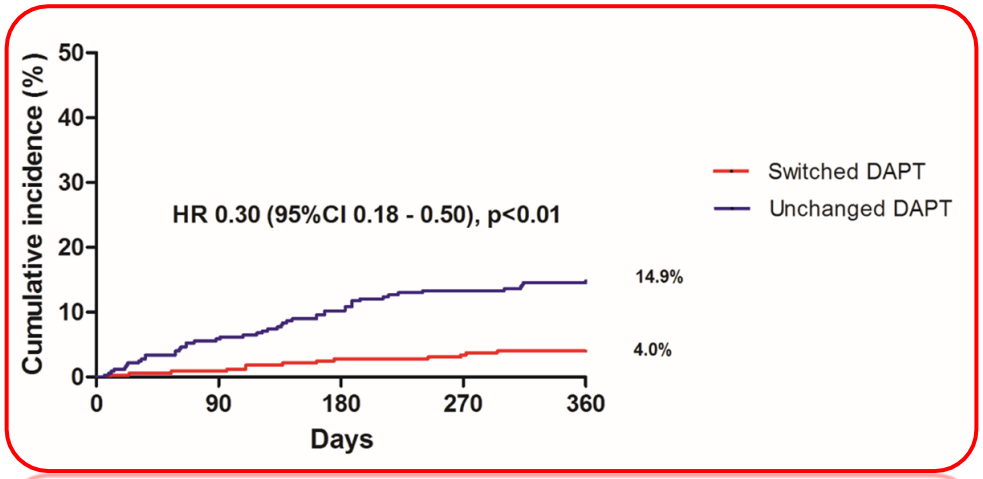


Better Prognosis with switched DAPT

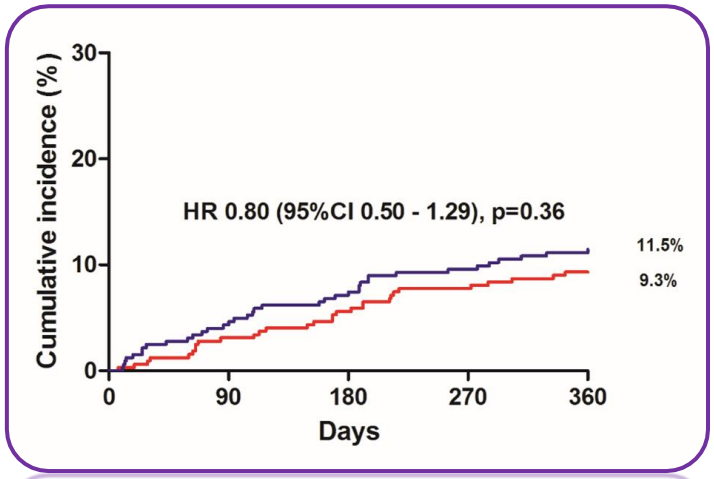
Cuisset T et al. Eur Heart J. 2017

TOPIC Study

BARC bleeding ≥ 2



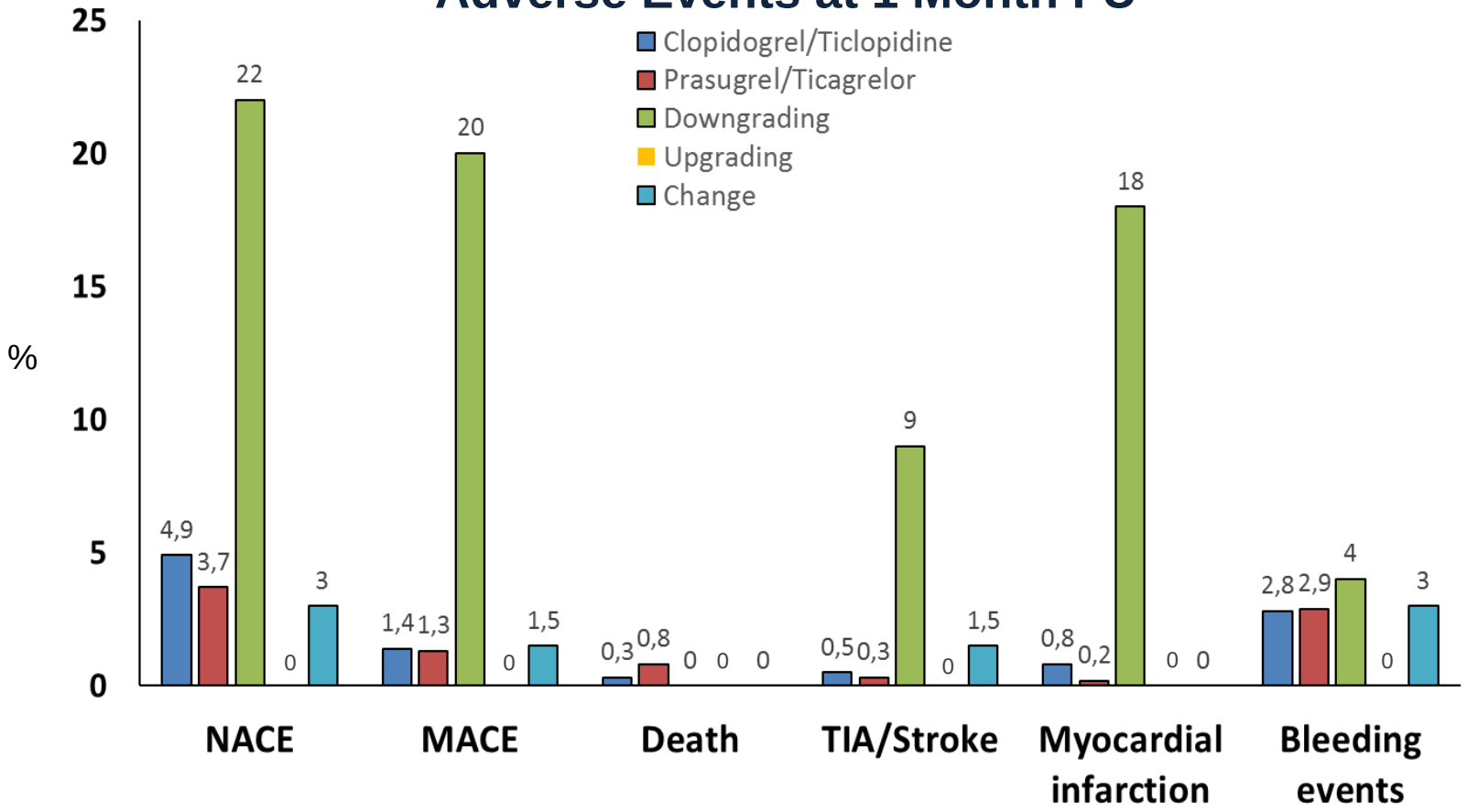
Any ischemic endpoint



Cuisset T et al. Eur Heart J. 2017

SCOPE (Switching from Clopidogrel to New Oral Antiplatelet Agents during PErcutaneous Coronary Intervention)

Adverse Events at 1 Month FU



1363 ACS patients undergoing PCI enrolled during a 3-month period at 40 Italian medium-to-high volume centers

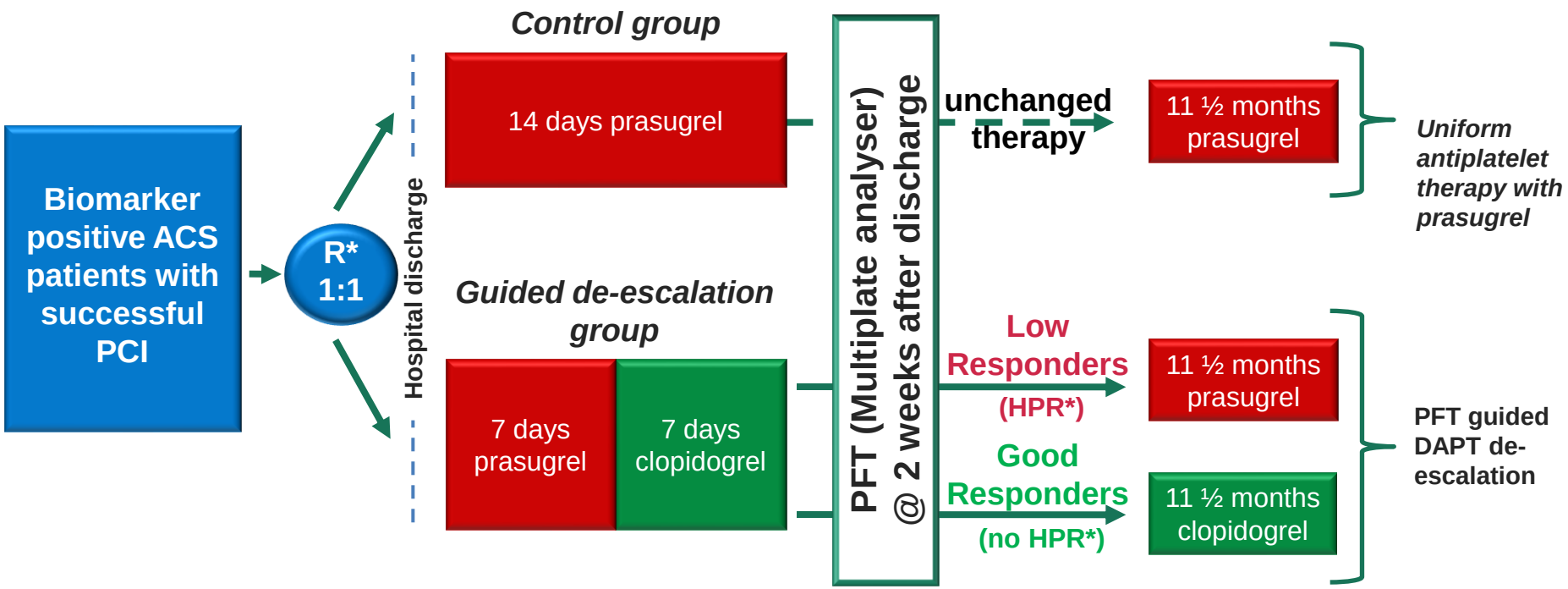
De Luca L et al. EuroIntervention. 2017

Should we routinely de-escalate P2Y12 Receptor Inhibitors?

Probably not

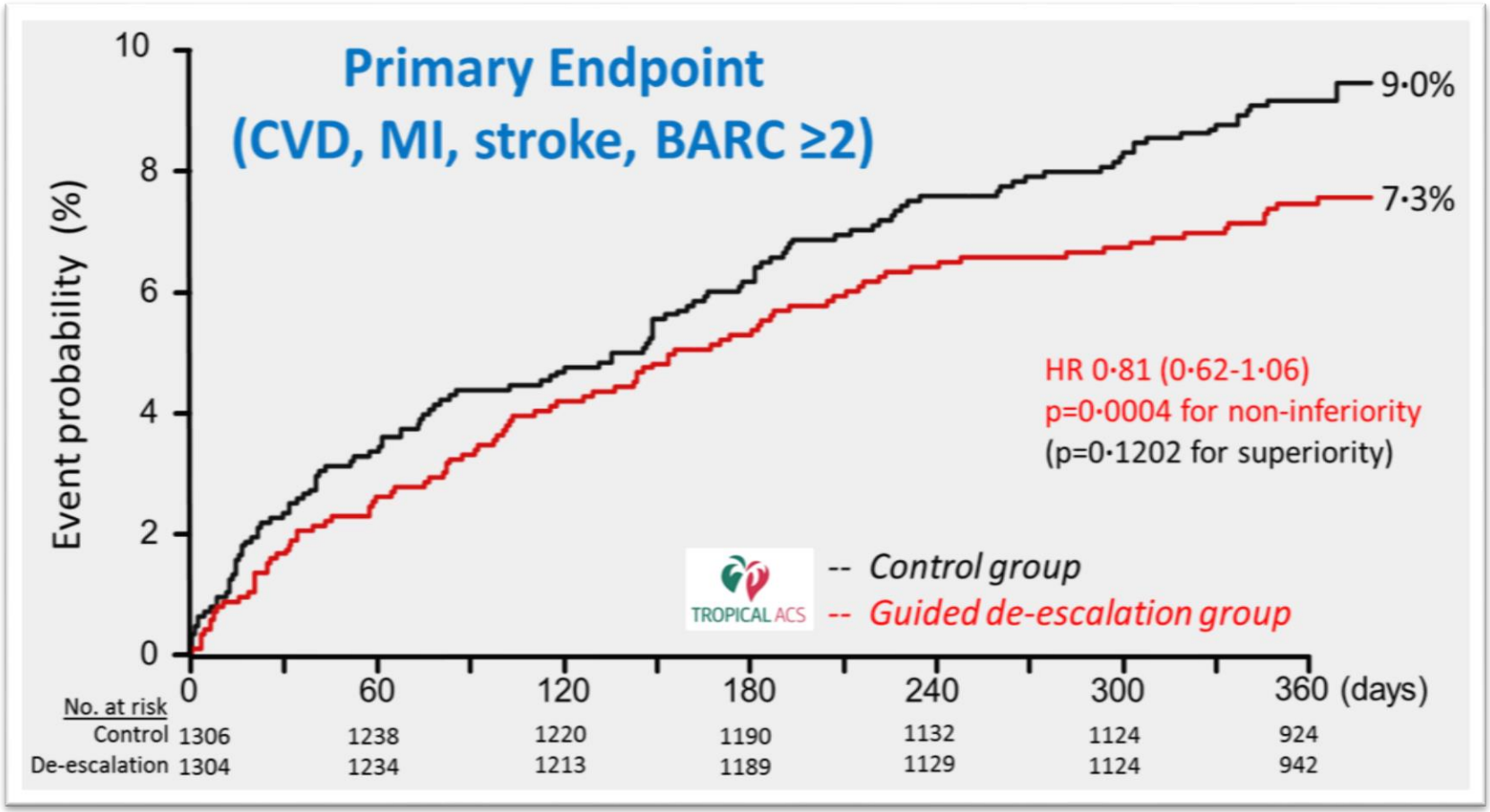
- **Identify patients who can benefit from de-escalation**
  - History of major bleeding
  - Patients with high bleeding risk (need for OAC, prior stroke, elderly)
  - Patients with low ischemic risk
  - Platelet function/genetic testing?
  - Need more investigations (currently ongoing)

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS)



Sibbing D, et al. Lancet. 2017

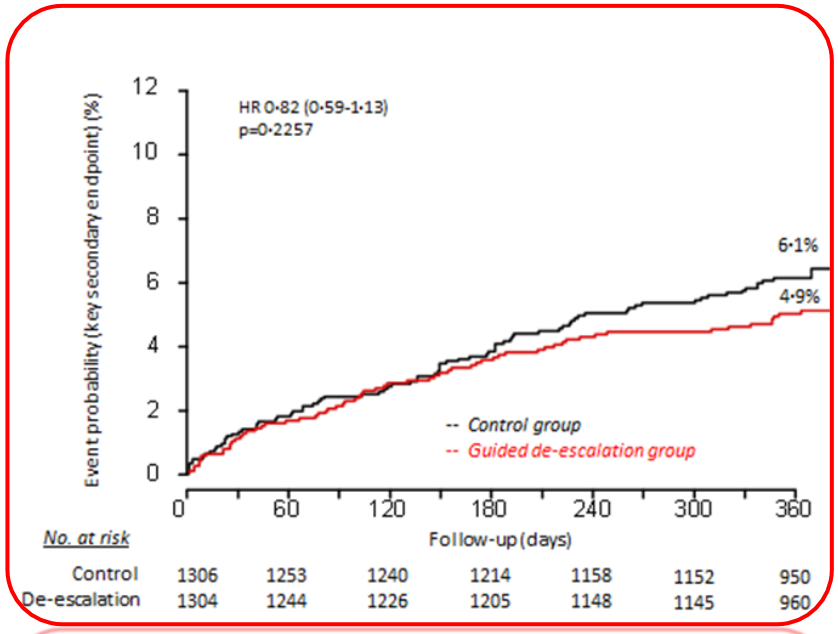
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS)



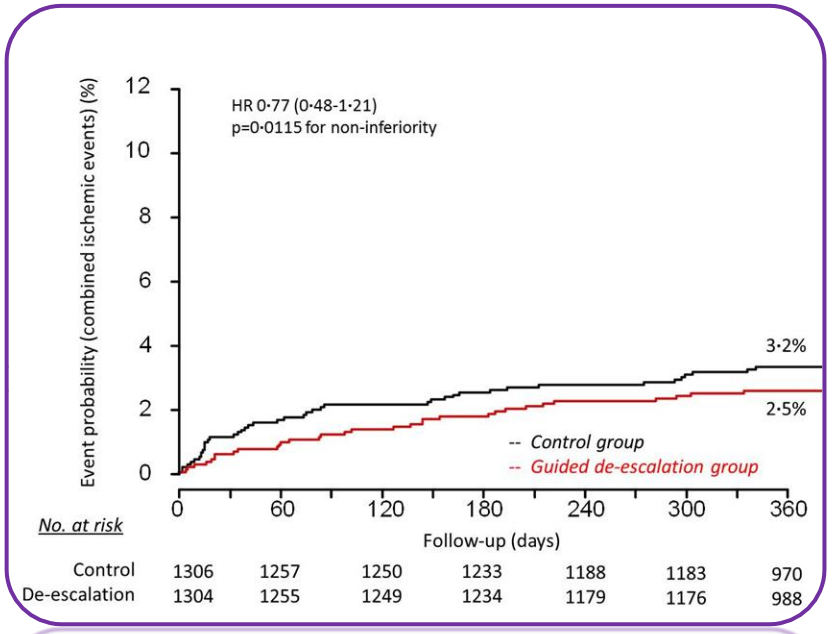
Sibbing D, et al. Lancet. 2017

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS)

BARC bleeding ≥ 2



Any ischemic endpoint



Sibbing D, et al. Lancet. 2017

What is new in the 2018 Guidelines?

New recommendations

Class IIb	Class III
Double-kissing crush technique preferred over provisional T-stenting in true left main bifurcations	Routine revascularization of non-IRA lesions in myocardial infarction with cardiogenic shock
Cangrelor in PY_{12}-inhibitor naïve patients undergoing PCI	Current generation BRS for clinical use outside clinical studies
GP IIb/II Ia inhibitors for PCI in $P2Y_{12}$-inhibitor naïve patients with ACS undergoing PCI	
Dabigatran 150-mg dose preferred over 110-mg dose when combined with single antiplatelet therapy after PCI	
De-escalation of $P2Y_{12}$-inhibitor guided by platelet functon testing in ACS patients	
Routine non-invasive imaging surveillance in high-risk patients 6 months after revascularization	

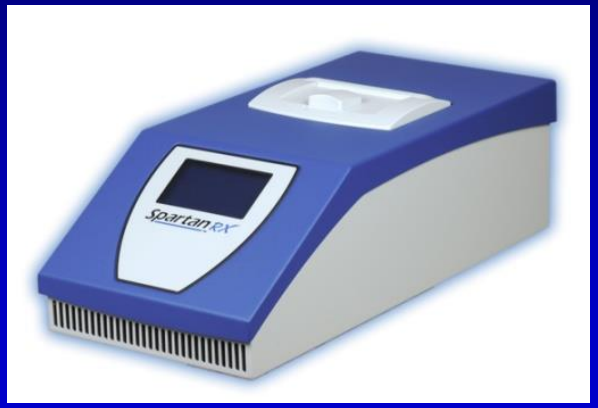
Changes compared with the 2014 version of the Myocardial Revascularization Guidelines that were due to updates for consistency with other ESC Guidelines published since 2014 are not shown.

Limitations of PFT-guided de-escalation

- **Availability of PFT**
- **Back and forth management of antiplatelet therapy**
- **Variability in PFT results**

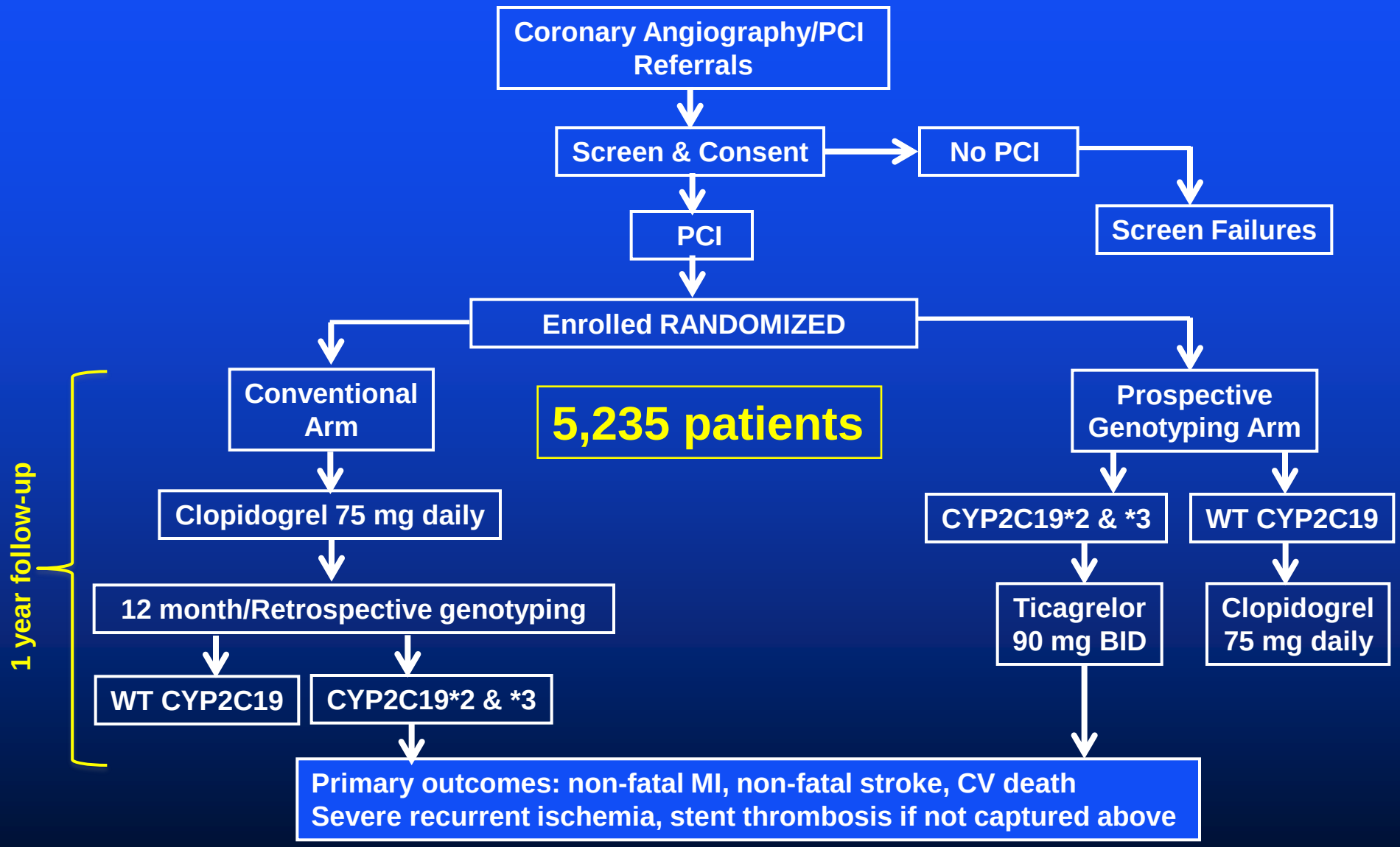
Angiolillo DJ. Lancet.2017

The RAPID Program: Spartan RX CYP2C19



- Buccal Swab performed by nurses (no prior training in genetics) – ½ hour course on machine
- 1 step insertion into machine
- 60 minutes to identify:
  - CYP2C19*2 carrier status
  - Heterozygous vs. Homozygous

TAILOR-PCI Study Design



ONGOING DIRECTIONS IN TAILORING ANTITHROMBOTIC PHARMACOTHERAPY FOR HBR PATIENTS

STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI

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
TWILIGHT

AF + PCI

WOEST
PIONEER- AF-PCI
RE-DUAL PCI
AUGUSTUS ACC 2019
ENTRUST ESC 2019

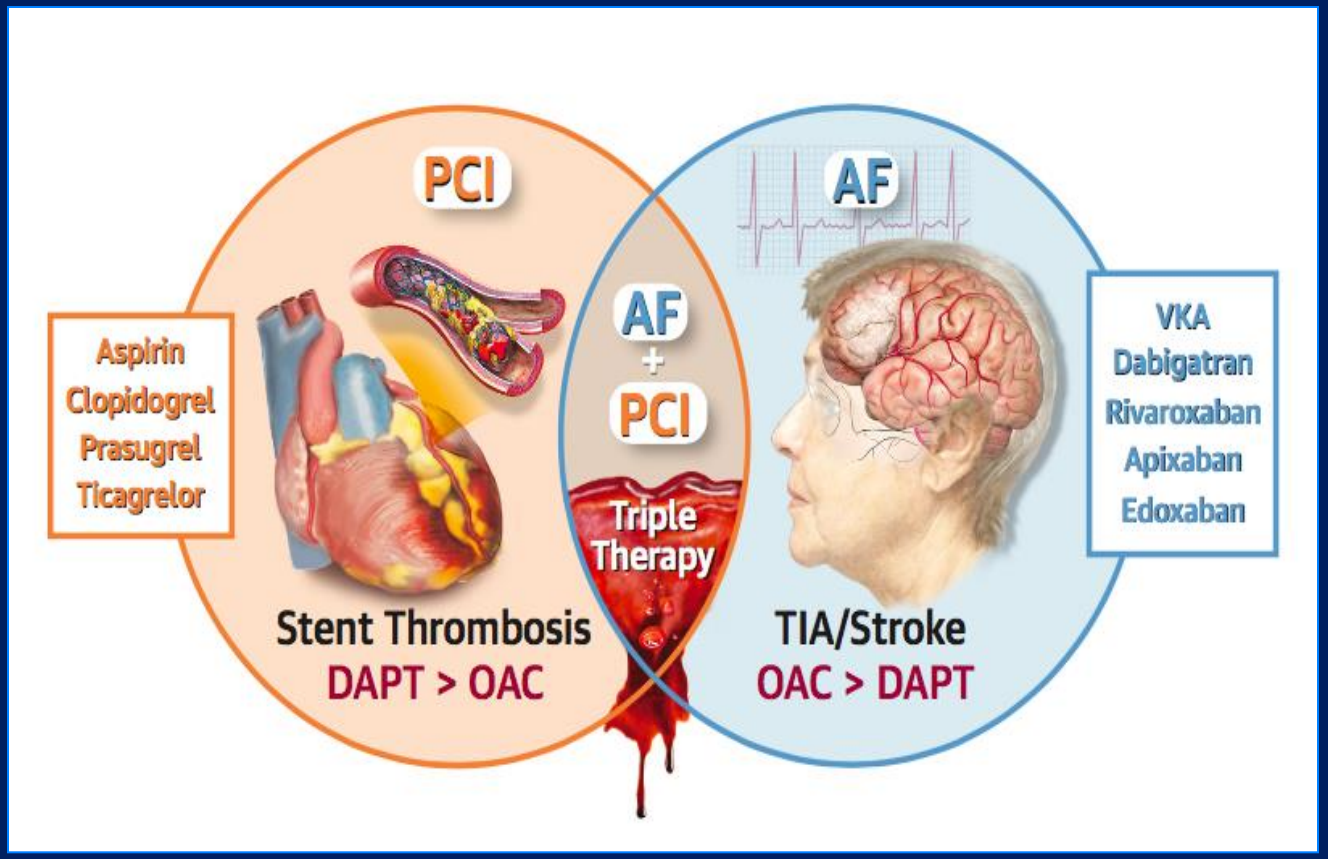
TWILIGHT Study Design

Multicenter, prospective, blinded dual-arm study

twilight

Mount Sinai Heart

Atrial Fibrillation and PCI: Key Concepts



Stent thrombosis and coronary events

↓

High shear stress platelet-rich thrombi

↓

Antiplatelet therapy

Stroke, TIA and systemic embolism

↓

Low shear stress, less platelet-dependent thrombi

↓

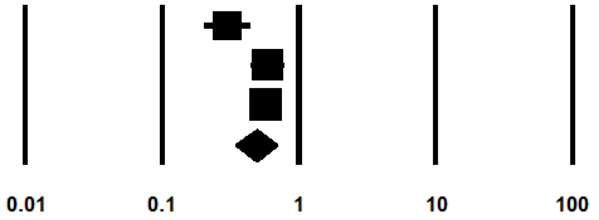
Anticoagulation therapy

Capodanno D, Angiolillo DJ. JACC Cardiovasc Interv. 2017;10:1086-1088

Meta-analysis of RCT of aspirin withdrawal in AF+PCI

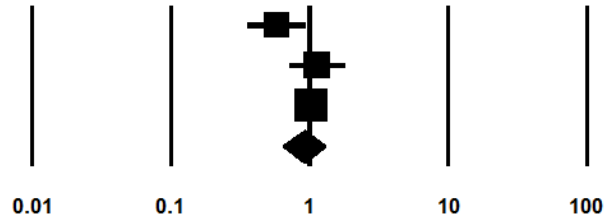
Safety: Major & Minor Bleeding

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Bleeding / Total Dual	Bleeding / Total Triple	Relative weight
WOEST	0.301	0.206	0.439	-6.223	0.000	54 / 279	126 / 284	28.27
PIONEER AF	0.589	0.451	0.771	-3.861	0.000	109 / 696	167 / 697	33.91
REDUAL PCI	0.576	0.477	0.694	-5.772	0.000	305 / 1744	264 / 981	37.83
	0.483	0.341	0.684	-4.106	0.000			

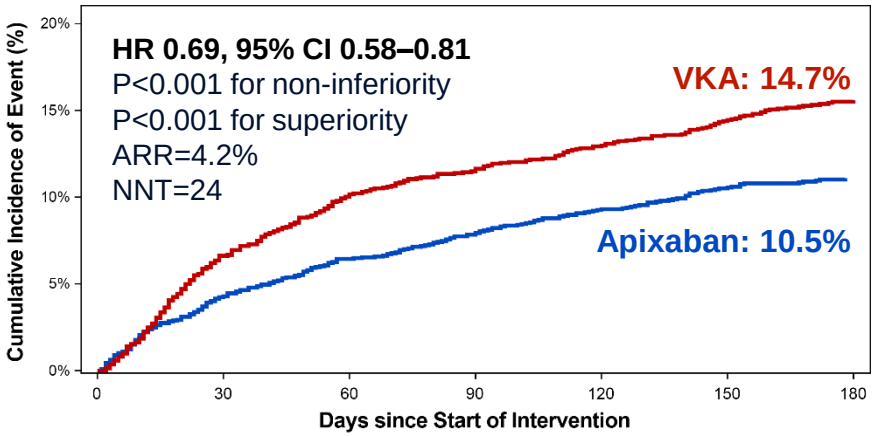


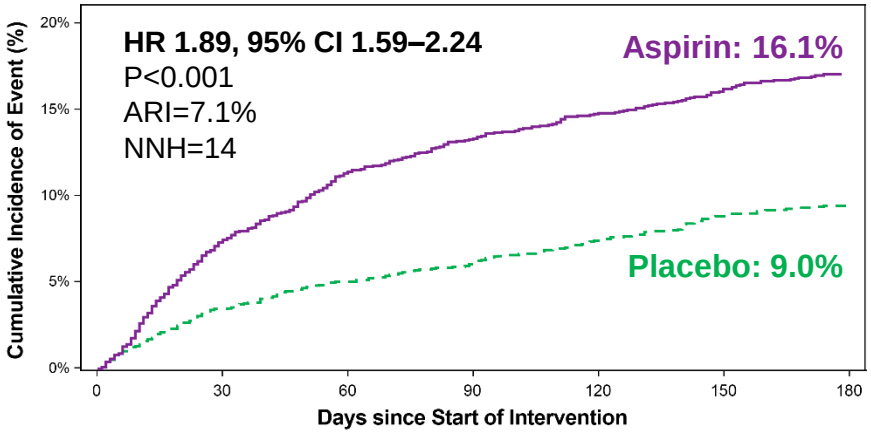
Efficacy: Major Adverse Cardiovascular Events

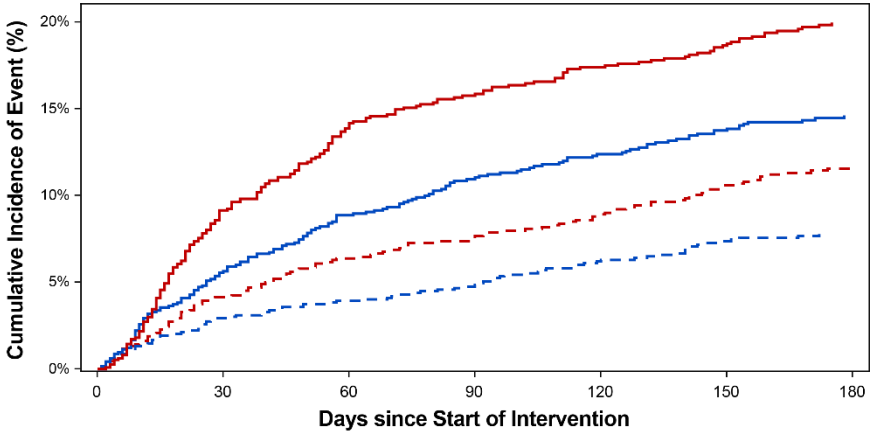
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	MACE / Total Dual	MACE / Total Triple	Relative weight
WOEST	0.585	0.361	0.948	-2.179	0.029	31 / 279	50 / 284	26.95
PIONEER AF	1.149	0.725	1.822	0.592	0.554	41 / 694	36 / 695	28.24
REDUAL PCI	1.030	0.819	1.296	0.256	0.798	239 / 1744	131 / 981	44.81
	0.912	0.643	1.293	-0.515	0.606			



Piccini JP, Jones WS. N Engl J Med. 2017;377:1580-158







VKA + Aspirin: 18.7%

Apixaban + Aspirin: 13.8%

VKA + Placebo: 10.9%

Apixaban + Placebo: 7.3%

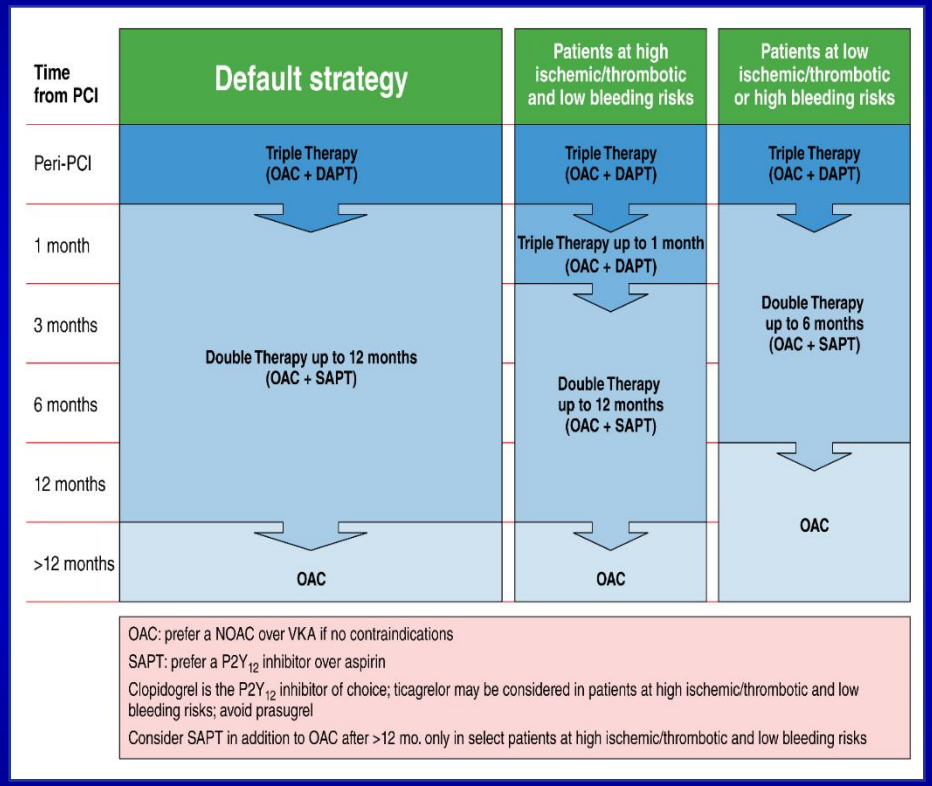
Apixaban + Placebo vs. VKA + Aspirin:
ARR=11.4% (NNT=9)

Major / CRNM Bleeding

ARR: absolute risk reduction
NNT: number needed to treat
ARI: absolute risk increase
NNH: number needed to harm

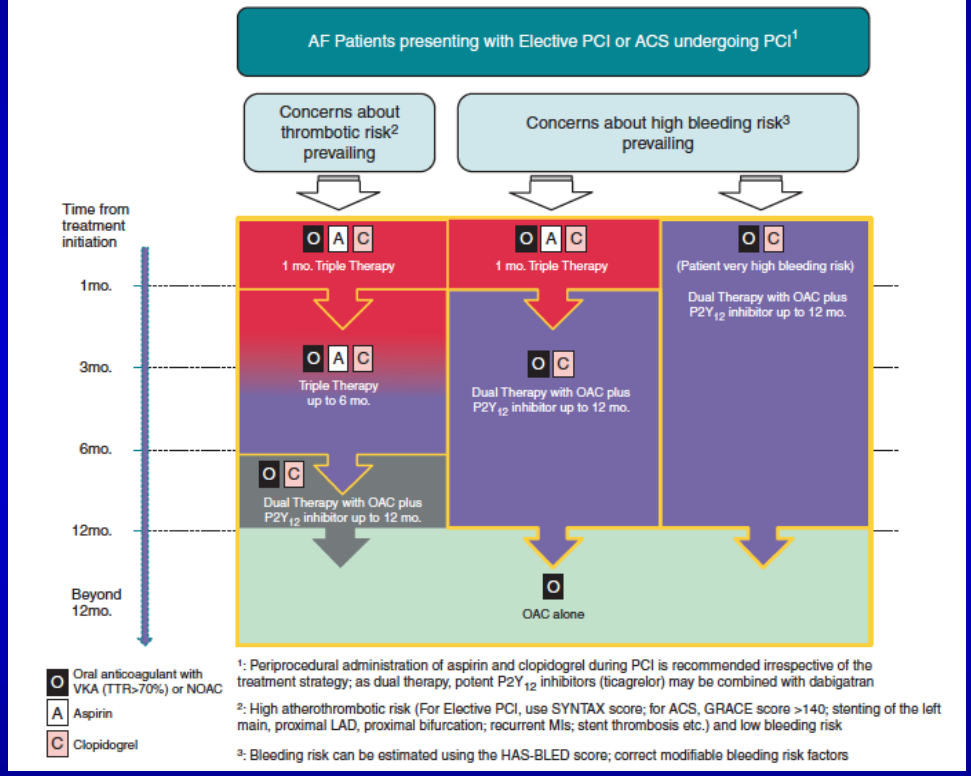
Management of antithrombotic therapy in AF patients with ACS and/or undergoing PCI

North American Expert Consensus



Angiolillo DJ et al. Circulation 2018; 138:527–536.

EHRA/ESC Expert Consensus



Lip GYH et al. Europace. 2019;21:192-193.

Post PCI Optimal DAPT in HBR Patients

- No single DAPT recommendation applies to every patient.
- Short DAPT duration should be considered in HBR patients
  - Stable CAD: <6 months (eg, 3 months)
  - ACS: <12 months (eg, 6 months)
  - Opportunity to further classify in “very” short (eg, 1 month for stable CAD and 3 months for ACS).
- Although risk scores may help guide decision making, the fine details of DAPT duration must be defined by clinicians for each patient on an individual basis taking into consideration patient preference.
- In patients requiring OAC, current data suggesting dropping aspirin by time of hospital discharge. In these patients a NOAC should be preferred over VKA and clopidogrel should be the P2Y12 inhibitor of choice.
- De-escalation can be considered after early acute phase (>30 days) if patients also deemed to be at low ischemic risk and/or patients known to have good response to clopidogrel.