Antiplatelets In ACS Review

Brandon Martinez, PharmD

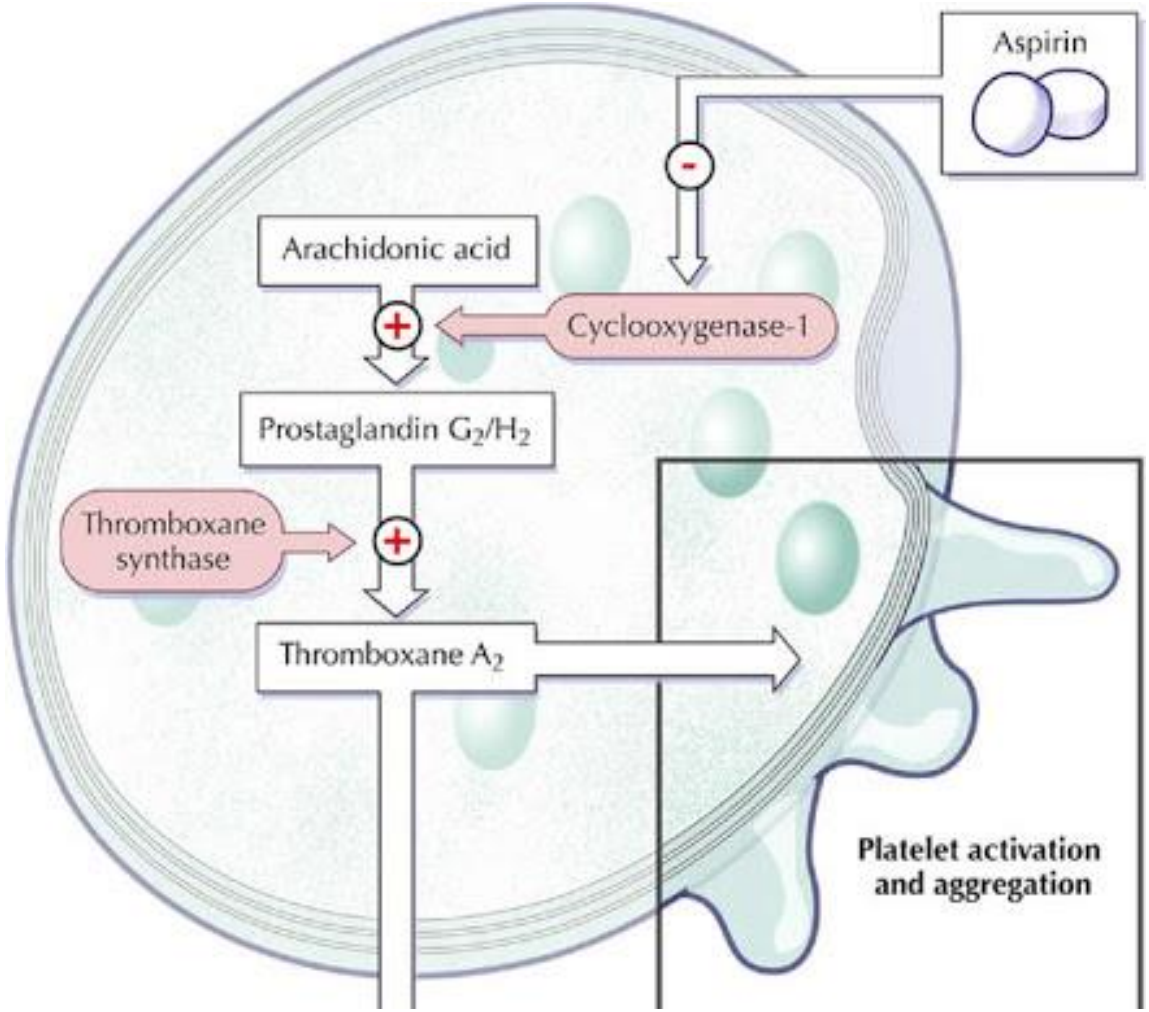
Objectives

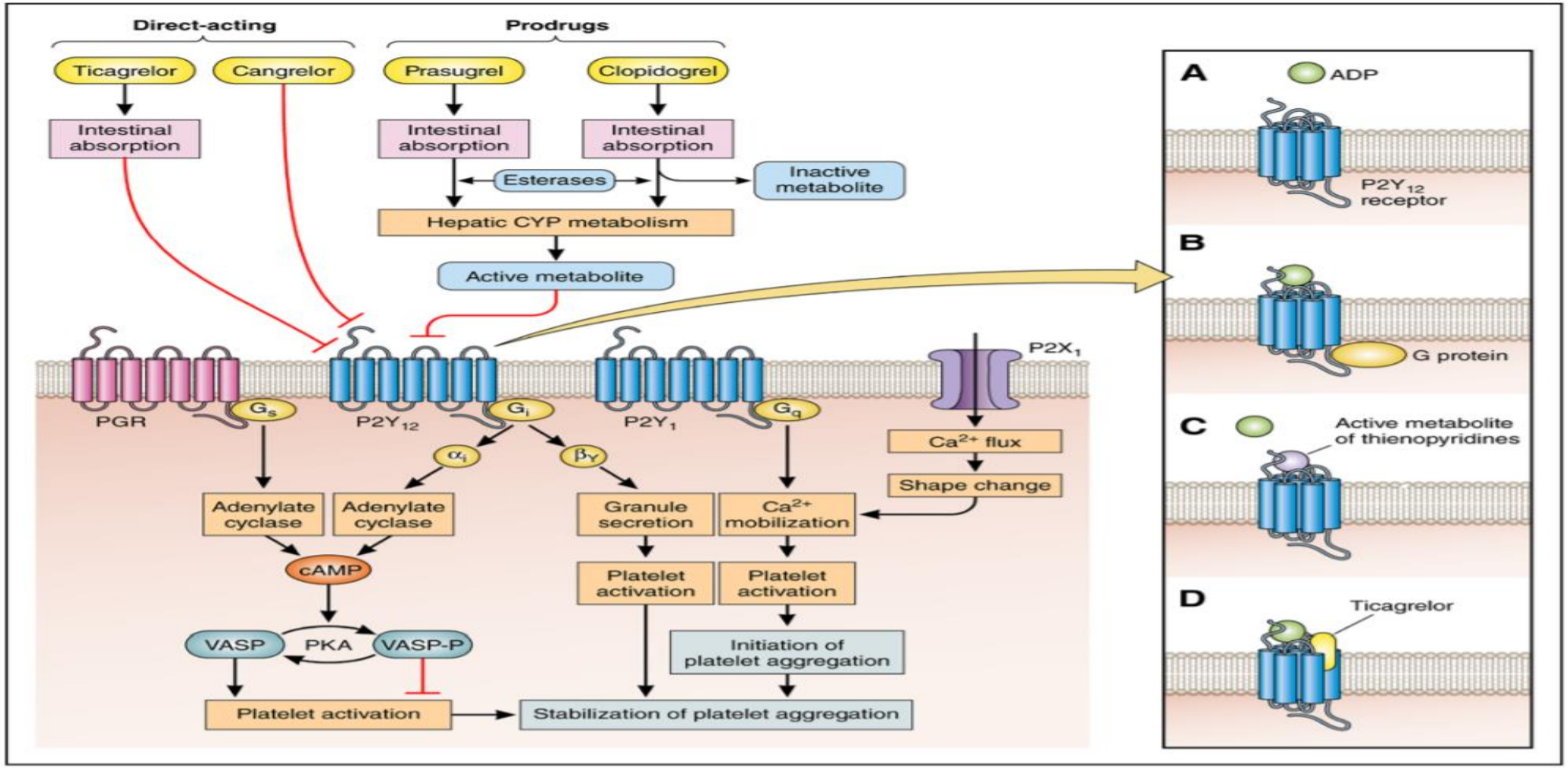
- Recognize pharmacologic differences in antiplatelet agents
- Identify optimal duration of dual antiplatelet therapy (DAPT)
- Understand tools for assessing thrombotic and bleeding risk
- Determine the appropriate antiplatelet strategy for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI)

Differences in Antiplatelets

Aspirin

- Irreversibly inhibits formation of thromboxane A_2 via acetylation of platelet cyclooxygenase-1 (COX-1), inhibiting platelet aggregation
- Irreversible effect lasts for duration of platelet lifespan (7-10 days)
- Typical dosing:
  - **LD:** 325mg
  - **MD:** 81mg – 325mg daily




Direct-acting
Prodrugs
Ticagrelor
Cangrelor
Prasugrel
Clopidogrel
Intestinal absorption
Intestinal absorption
Intestinal absorption
Esterases
Inactive metabolite
Hepatic CYP metabolism
Active metabolite
PGR
G_s
$P2Y_{12}$
G_i
$P2Y_1$
G_q
$P2X_1$
α_i
β_γ
Ca^{2+} flux
Shape change
Adenylate cyclase
Adenylate cyclase
Granule secretion
Ca^{2+} mobilization
cAMP
Platelet activation
Platelet activation
VASP
PKA
VASP-P
Initiation of platelet aggregation
Platelet activation
Stabilization of platelet aggregation
A
ADP
$P2Y_{12}$ receptor
B
G protein
C
Active metabolite of thienopyridines
D
Ticagrelor

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Prodrug	Yes	Yes	No	No
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Binding Site	ADP-binding site	ADP-binding site	Allosteric binding site	Undefined
Onset of action	2 - 8 h	30 min - 4 h	30 min - 4 h	2 min
Duration of effect	5 – 10 days	7 – 10 days	3 – 5 days	1 -2 h
Administration route	Oral	Oral	Oral	IV
Frequency	Once daily	Once Daily	Twice Daily	Continuous Infusion
Dosing	**LD:** 300-600mg **MD:** 75mg	**LD:** 60mg **MD:** 5-10mg*	**LD:** 180mg **MD:** 60-90mg BID*	**LD:** 30mcg/kg bolus **MD:** 4mcg/kg/min
Approved indications	ACS (invasive and noninvasive), Stable CAD, PCI, PAD, Ischemic stroke	ACS undergoing PCI (known coronary anatomy prior to initiation)	ACS (invasive or noninvasive) or history of MI	PCI in patients with or without ACS
Notes	• Can be used after thrombolytic therapy	• **BBW: Do not use in history of TIA or stroke; Not indicated in patients ≥75yo** • Dose adjust for patients <60kg*	• Do not use with Aspirin >100mg • Dyspnea side effect • Use 60mg BID if continued after 1 year*	• Bridging is off-label use currently

Patient with a history of STEMI s/p PCI x3 currently on DAPT is complaining of shortness of breath. CXR shows no signs of edema or infiltrates and patient is otherwise healthy

Which of the following medications is a potential cause for this patient's dyspnea?

a. Aspirin
b. Effient
c. Brilinta
d. Plavix

The NEW ENGLAND JOURNAL of MEDICINE

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Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

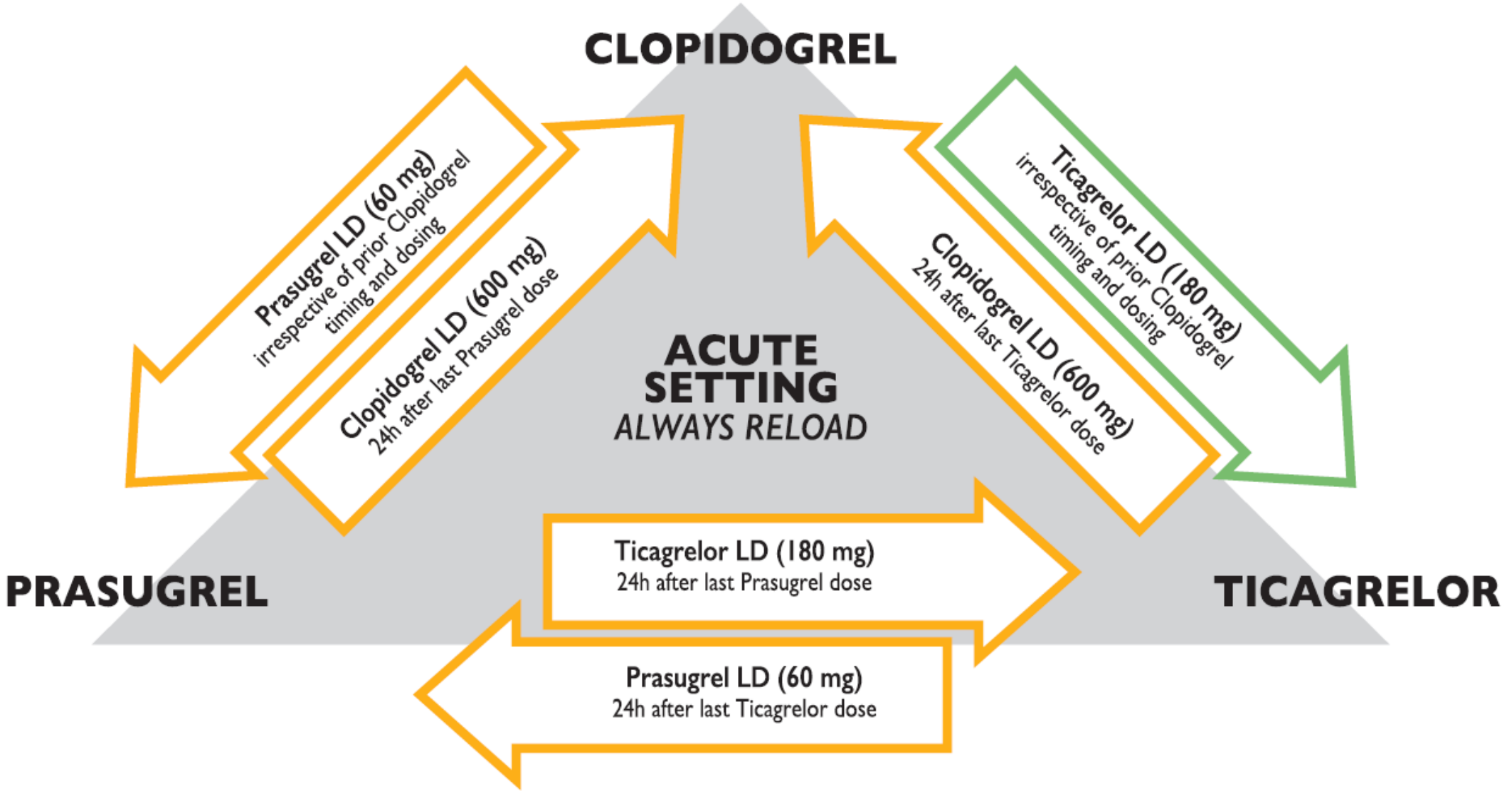
Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001

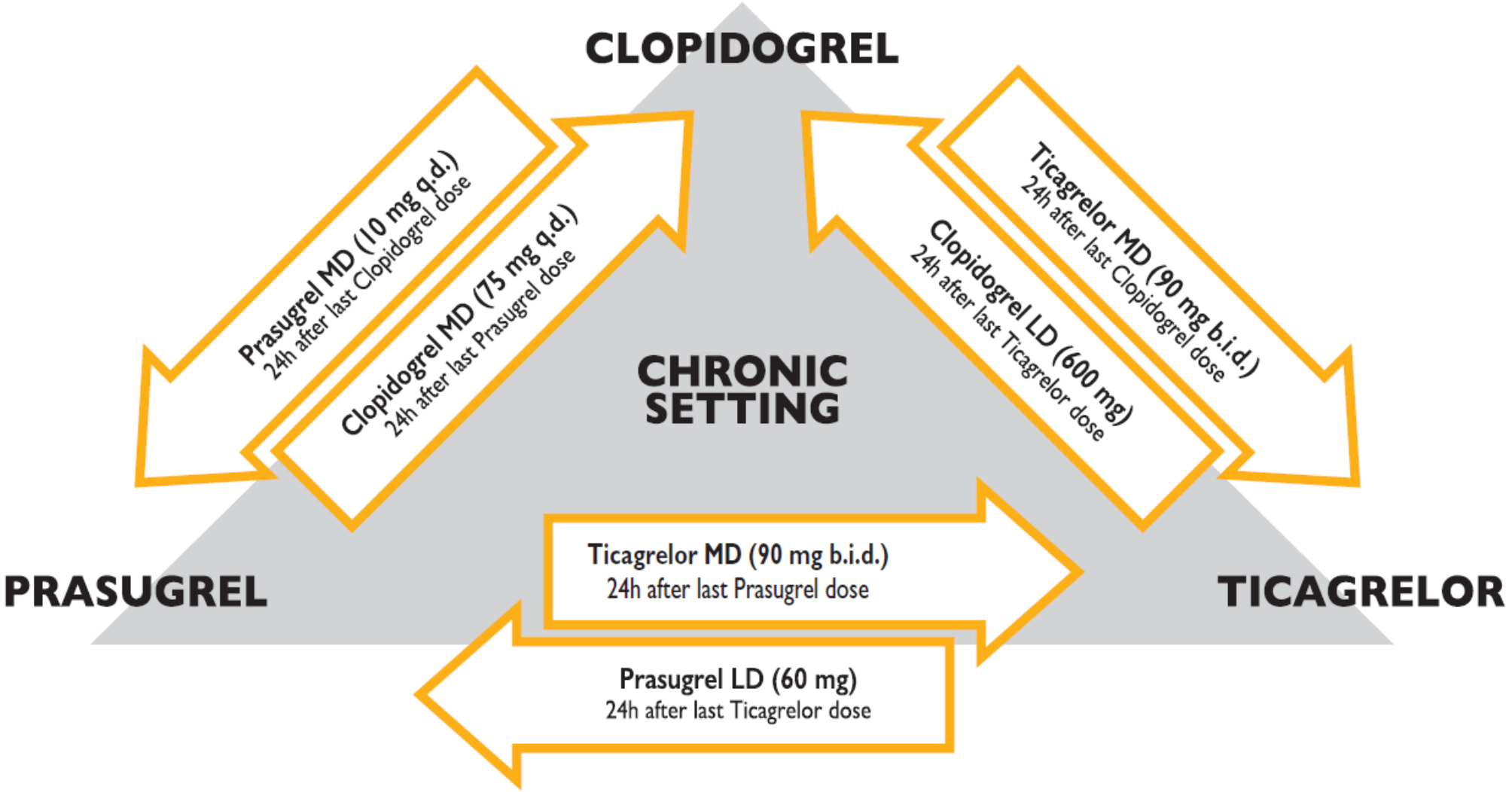
Patient is 78 years old 3 months s/p PCI x3 with a PMHx significant for TIA

How would you manage this patients antiplatelet therapy moving forward

a. Discontinue $P2Y_{12}$
b. Switch to Prasugrel
c. Switch to Clopidogrel
d. Continue Ticagrelor



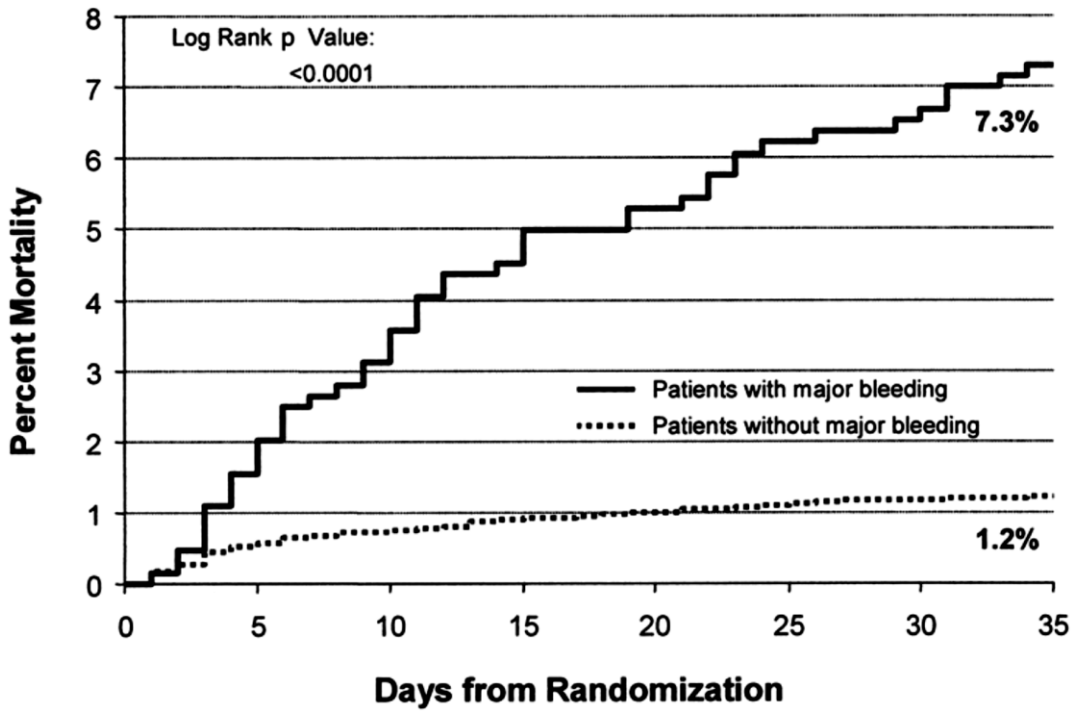
European Heart Journal 2018; 39:213-254

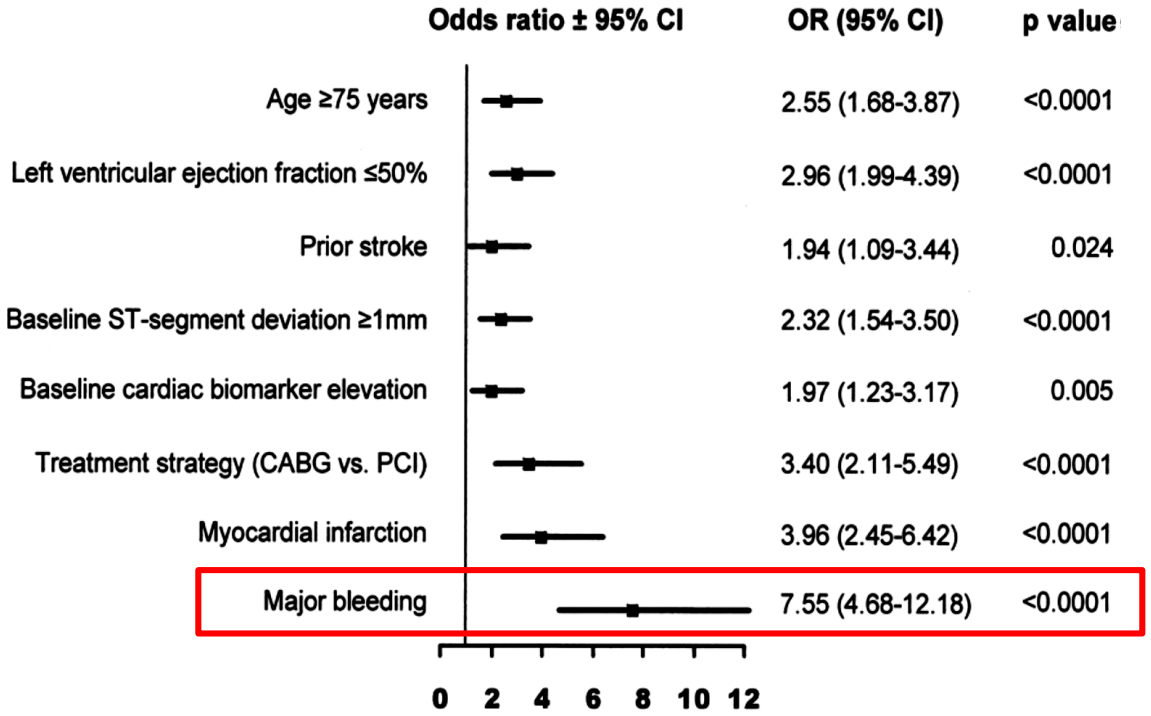


European Heart Journal 2018; 39:213-254

Intro to DAPT

Impact of Major Bleeding in ACS

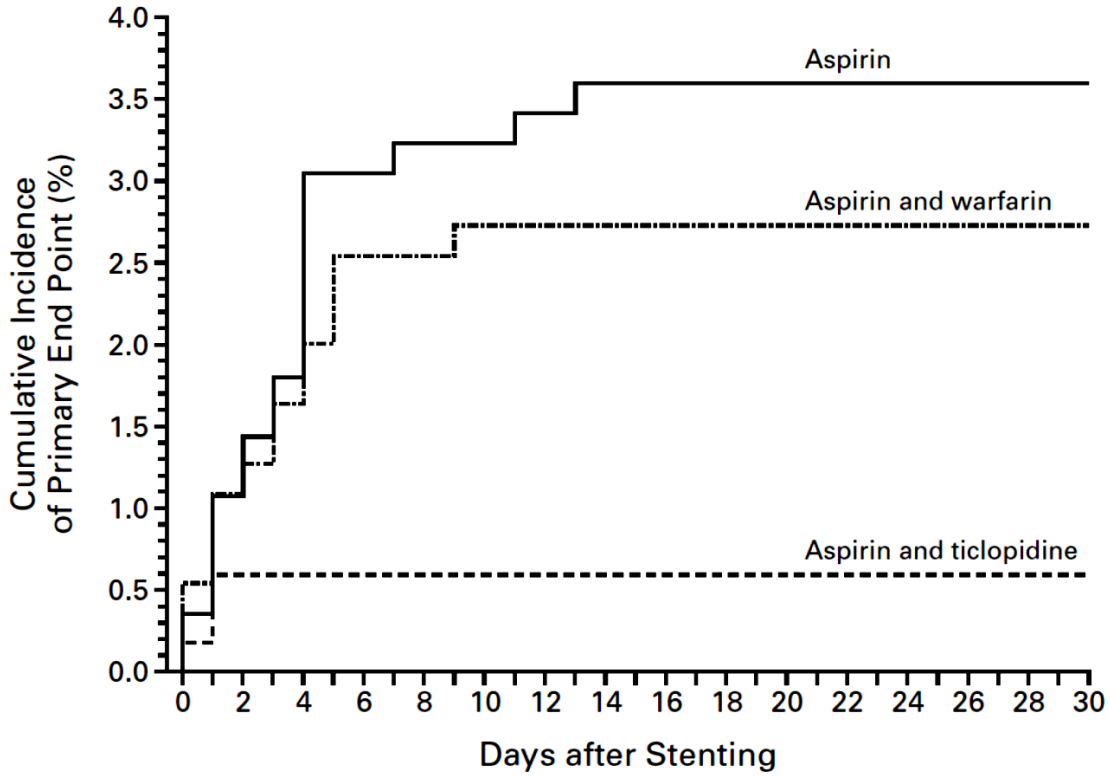




JACC 2007; 49:1362-8

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

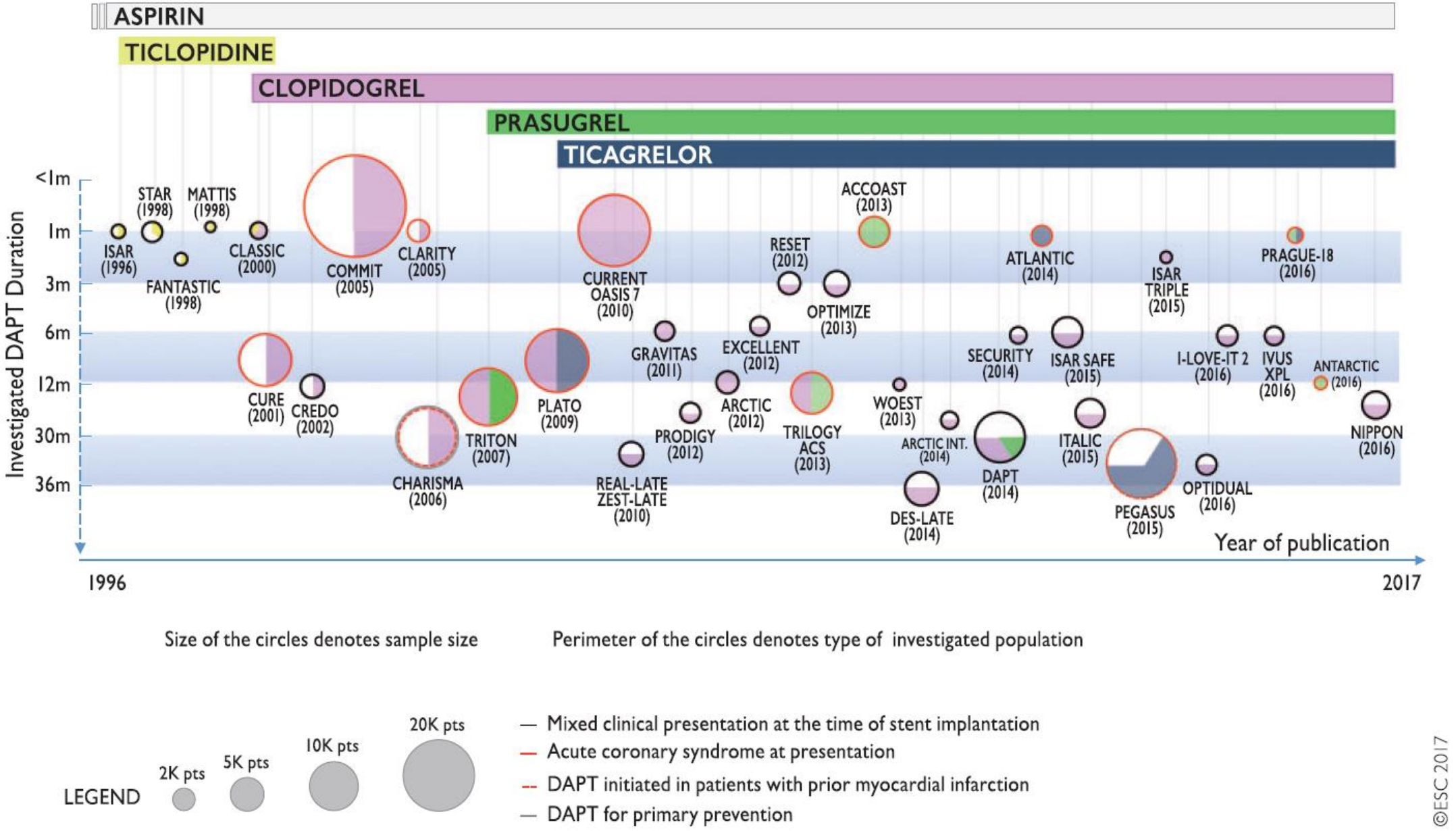
MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*



Primary Outcome

Death, Revascularization of Target Lesion, Angiographically Evident Thrombosis, MI within 30 days

N Engl J Med 1998;339:1665-71



Size of the circles denotes sample size

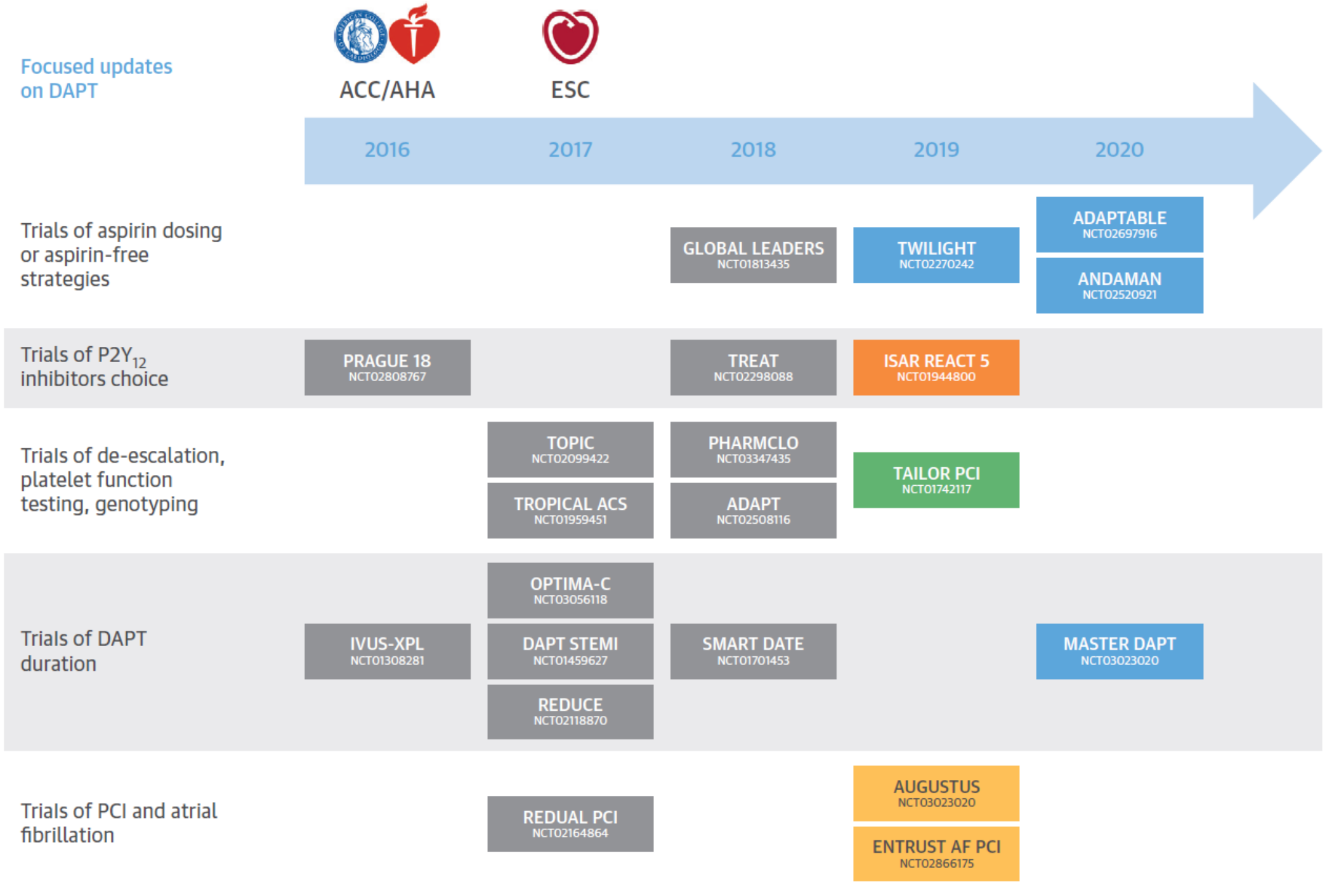
Perimeter of the circles denotes type of investigated population

LEGEND

2K pts 5K pts 10K pts 20K pts

— Mixed clinical presentation at the time of stent implantation
— Acute coronary syndrome at presentation
-- DAPT initiated in patients with prior myocardial infarction
— DAPT for primary prevention

European Heart Journal 2018; 39:213-254


Focused updates on DAPT
ACC/AHA
ESC
2016
2017
2018
2019
2020
Trials of aspirin dosing or aspirin-free strategies
GLOBAL LEADERS NCT01813435
TWILIGHT NCT02270242
ADAPTABLE NCT02697916
ANDAMAN NCT02520921
Trials of P2Y12 inhibitors choice
PRAGUE 18 NCT02808767
TREAT NCT02298088
ISAR REACT 5 NCT01944800
Trials of de-escalation, platelet function testing, genotyping
TOPIC NCT02099422
TROPICAL ACS NCT01959451
PHARMCLO NCT03347435
ADAPT NCT02508116
TAILOR PCI NCT01742117
Trials of DAPT duration
OPTIMA-C NCT03056118
IVUS-XPL NCT01308281
DAPT STEMI NCT01459627
REDUCE NCT02118870
SMART DATE NCT01701453
MASTER DAPT NCT03023020
Trials of PCI and atrial fibrillation
REDUAL PCI NCT02164864
AUGUSTUS NCT03023020
ENTRUST AF PCI NCT02866175

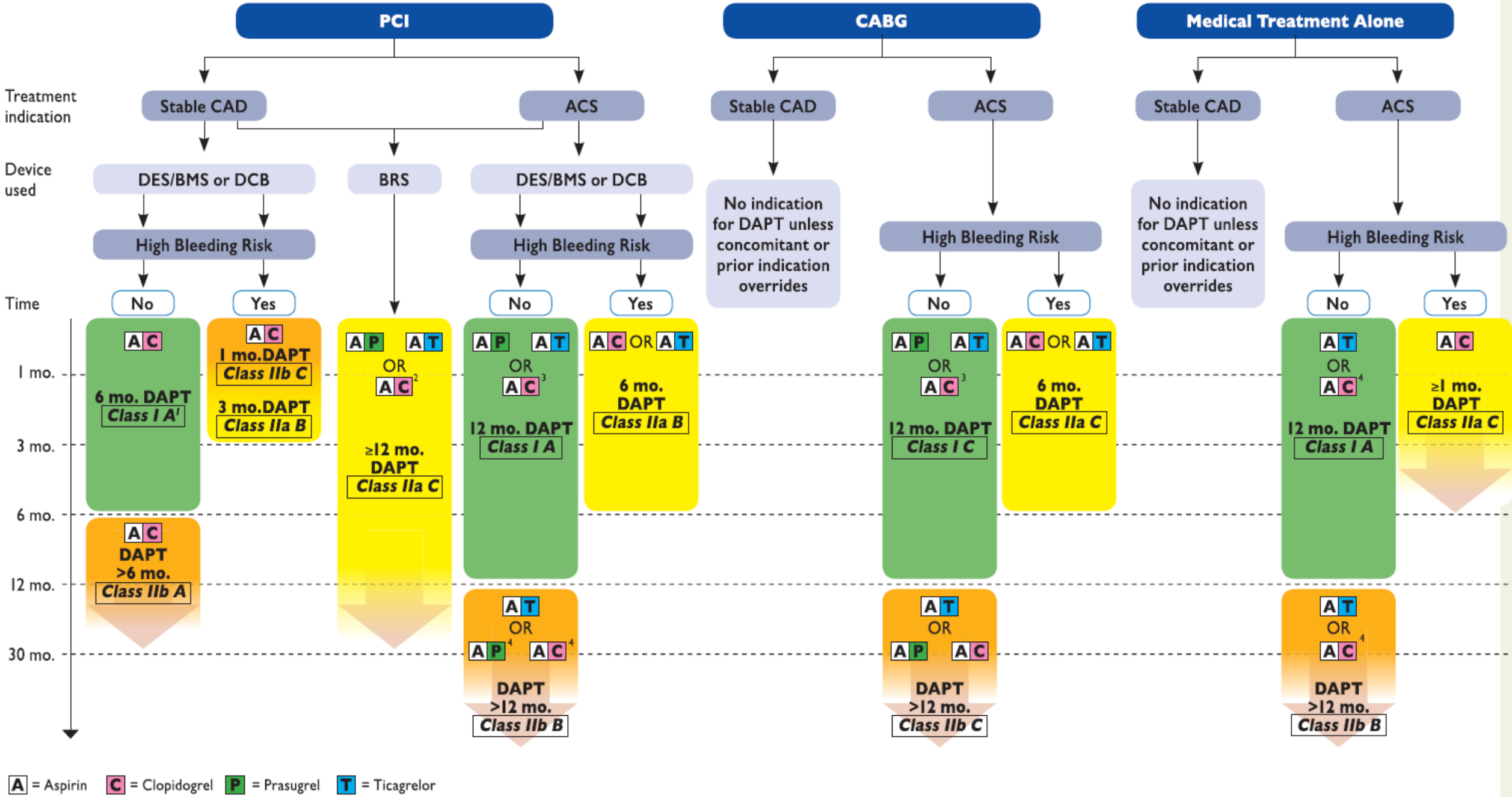
	TRITON-TIMI 38	PLATO	ISAR-REACT 5
Comparison	Clopidogrel vs Prasugrel	Clopidogrel vs Ticagrelor	Prasugrel vs Ticagrelor
Study Population	Patients with ACS with scheduled PCI; Moderate-to-high-risk unstable angina or NSTEMI and STEMI	Patients hospitalized for ACS with or without ST-segment elevation	Patients hospitalized for ACS (UA, NSTEMI, STEMI) for which invasive evaluation was planned
Primary Endpoint	Composite rate of death from CV causes, nonfatal MI, or non fatal stroke at 6 and 15 months	Composite death from vascular causes, MI, or stroke	Composite of death, MI, or stroke at 1 year
Primary Safety	TIMI major bleeding not related to CABG, non-CABG-related life-threatening bleeding, TIMI major or minor bleeding	Major bleeding; bleeding that led to clinically significant disability or bleeding associated with Hbg drop at least 3 g/dL or requiring 2-3 units RBC	Incidence of bleeding at 1 year (type 3, 4, or 5 on the Bleeding Academic Research Consortium [BARC] scale)
Results	Primary endpoint: HR 0.81 95% CI: (0.73-0.90) **in favor of Prasugrel** Non-CABG-related major bleeding significantly higher with prasugrel	Primary endpoint: HR 0.84 95% CI (0.77-0.92) **in favor of Ticagrelor** No difference in major bleeding but more non-procedure-related bleeding in Ticagrelor	Primary endpoint: HR 1.36 95% CI (1.09-1.70) **in favor of Prasugrel** No difference seen in BARC bleeding

55yo 58kg patient admitted to the hospital for STEMI; PMHx includes DMII, HTN, and prior TIA

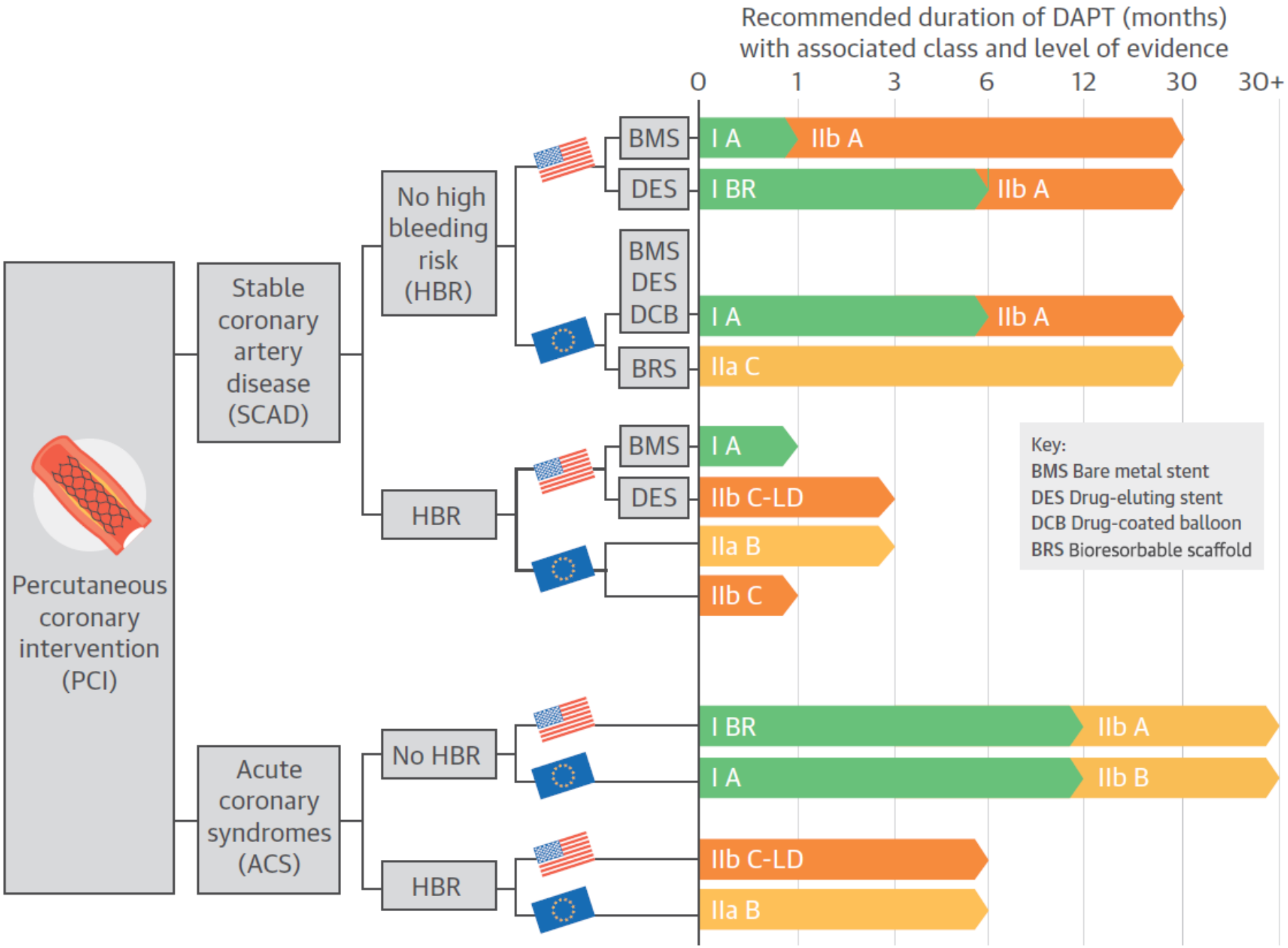
Which $P2Y_{12}$ Inhibitor would you start and why?

a. Clopidogrel 600mg x1 then 75mg daily
b. Prasugrel 60mg x1 then 10mg daily
c. Ticagrelor 180mg x1 then 90mg BID

Duration of DAPT

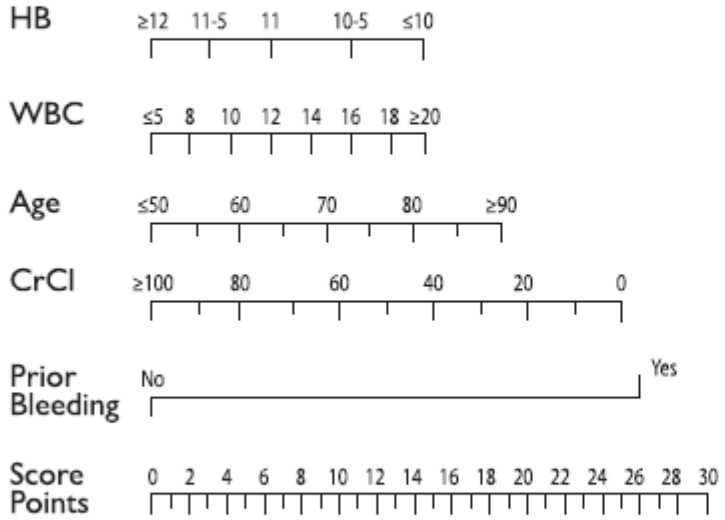


European Heart Journal 2018; 39:213-254



Capodanno, D. et al. J Am Coll Cardiol. 2018;72(23):2915-31.

Determining Bleeding Risk

	PRECISE-DAPT score[18]	DAPT score[15]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

European Heart Journal 2018; 39:213-254

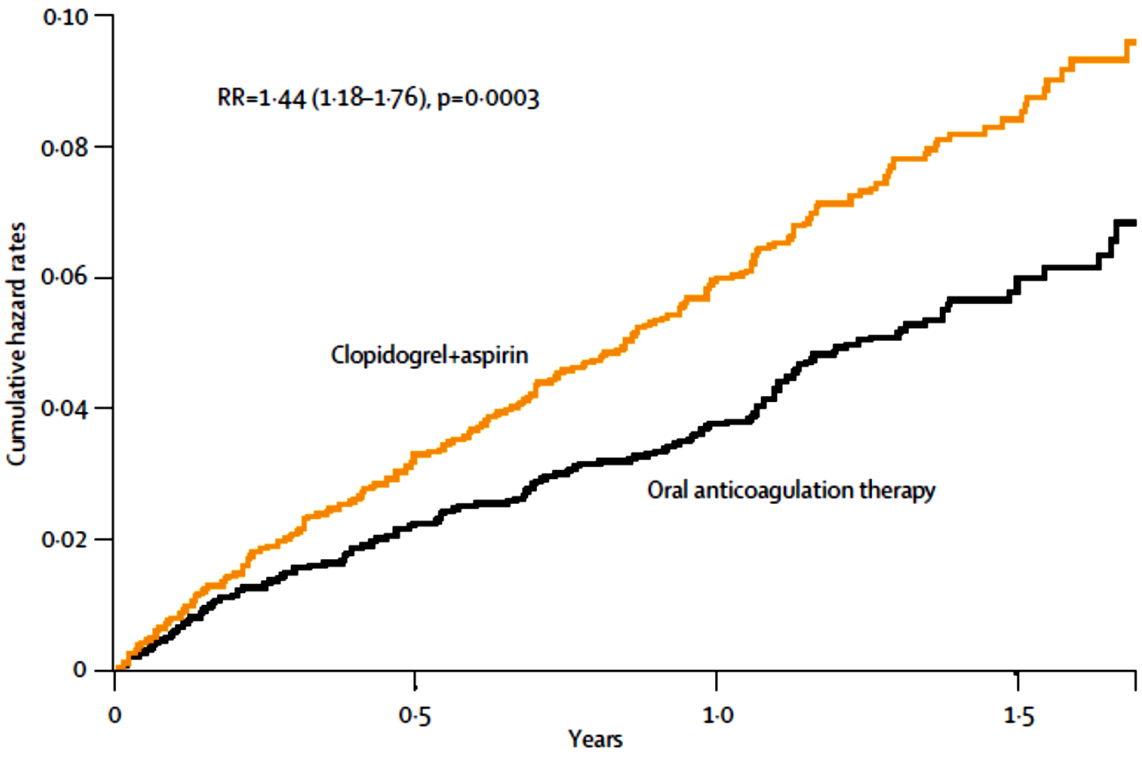
67yo patient is s/p STEMI PCI x2 12months ago. PMHx includes DMII and HF (LVEF 25%). Current labs include Hbg 11.2 g/dL, WBC 8.2 k, and estimated CrCl 65mL/min

Which of the following scenarios is correct?

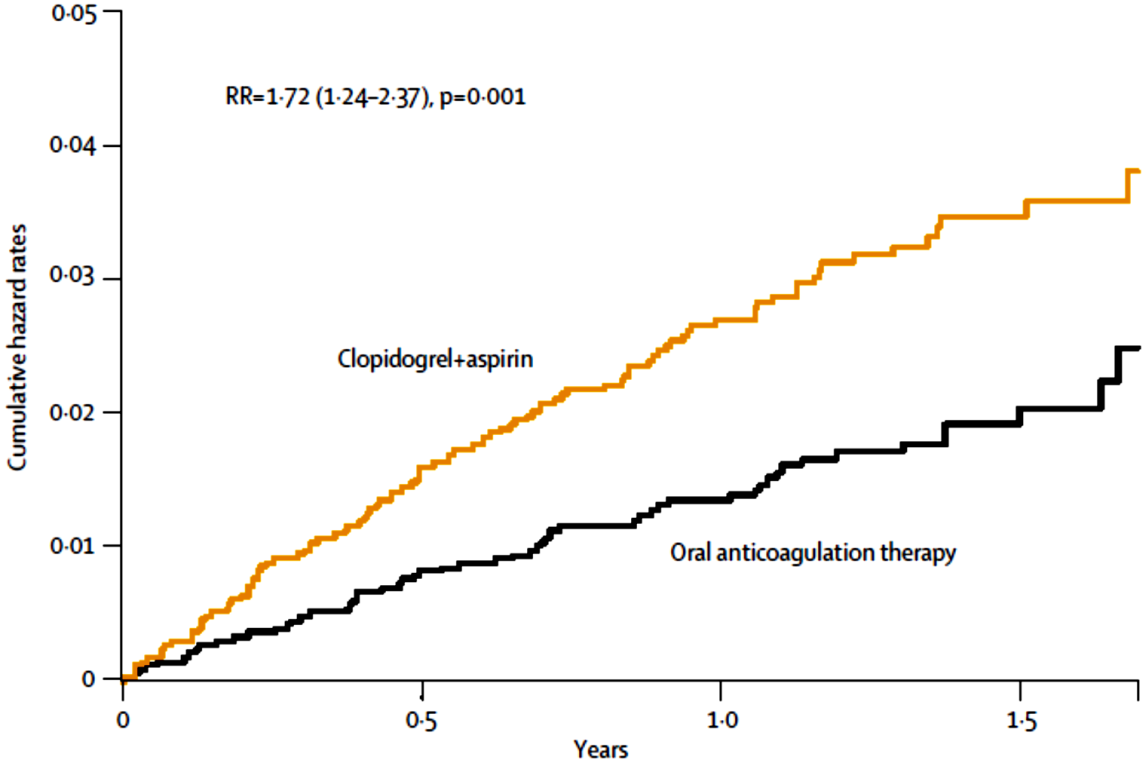
a. PRECISE-DAPT Score: 21 → Continue extended DAPT
b. PRECISE-DAPT Score: 21 → Discontinue DAPT
c. DAPT Score: 3 → Continue Extended DAPT
d. DAPT Score: 3 → Discontinue DAPT

AF + PCI

Stroke Reduction in Atrial Fibrillation



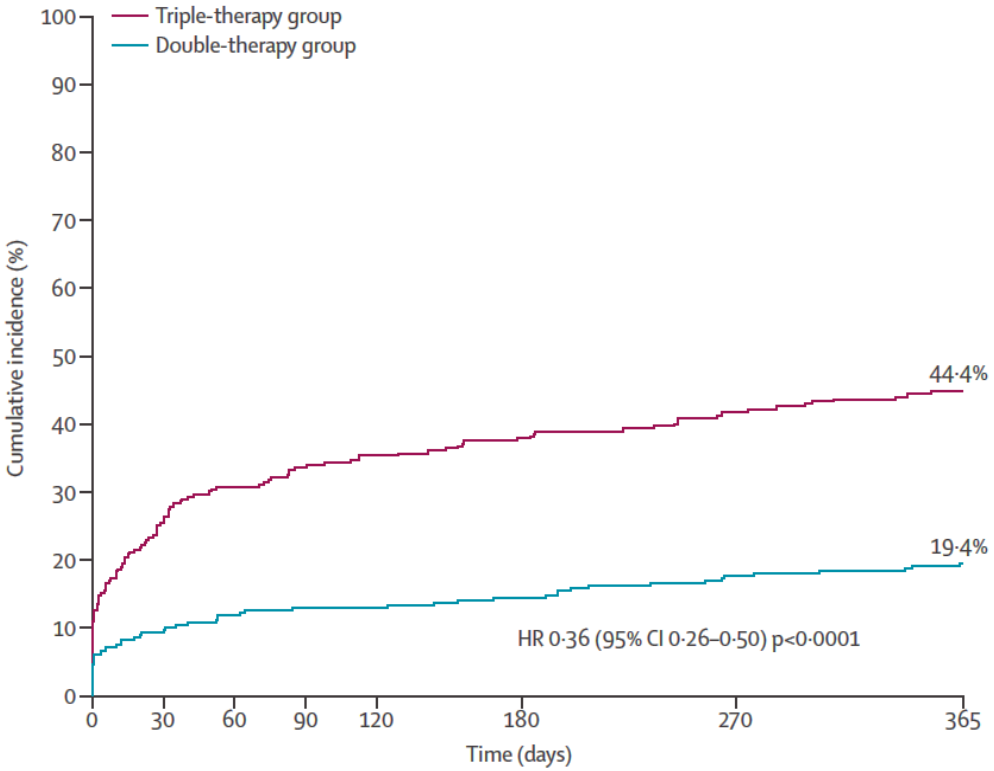
Primary Outcome
First occurrence of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death



Cumulative Risk of Stroke

Lancet 2006;367:1903-12

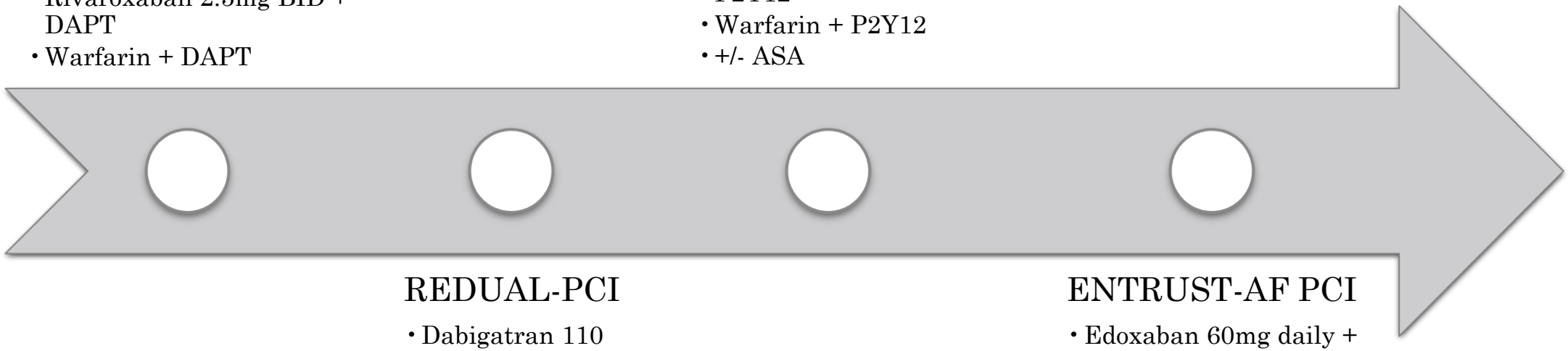
WOEST Trial



- Clopidgrel + ASA vs Warfarin + DAPT
- Bleeding episodes were seen in 54 (19 ·4%) patients receiving double therapy and in 126 (44 ·4%) receiving triple therapy (hazard ratio [HR] 0 ·36, 95% CI 0 ·26–0 ·50, p<0 ·0001)
- In the double-therapy group, six (2 ·2%) patients had multiple bleeding events, compared with 34 (12 ·0%) in the triple-therapy group
- 11 (3 ·9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9 ·5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0 ·39, 95% CI 0 ·17–0 ·84, p=0 ·011).

Lancet 2013;381:1107-15

DOAC Trials in AF + PCI



PIONEER AF-PCI

- Rivaroxaban 15mg Daily + P2Y12
- Rivaroxaban 2.5mg BID + DAPT
- Warfarin + DAPT

REDUAL-PCI

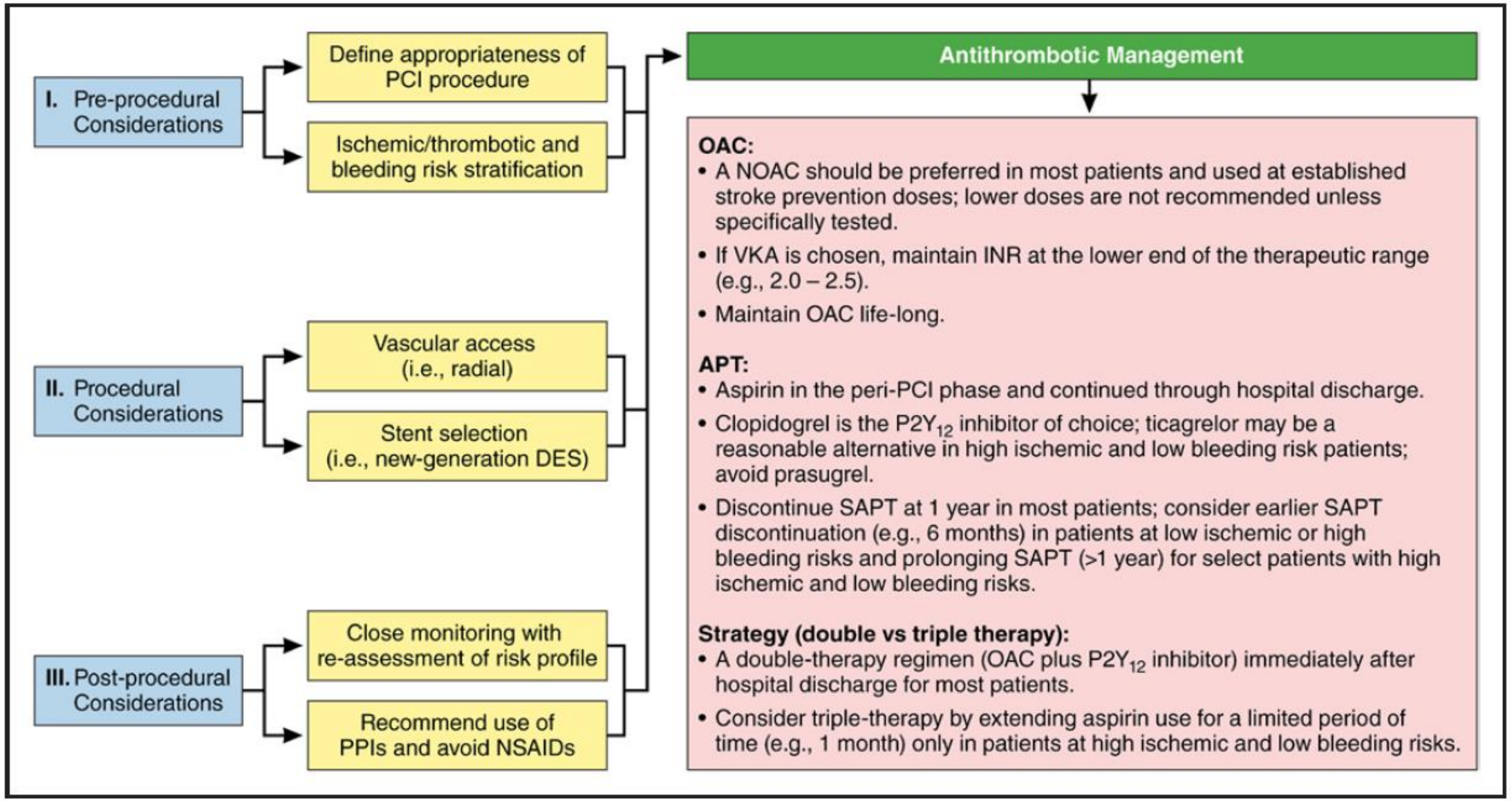
- Dabigatran 110 mg BID + P2Y12
- Dabigatran 150 mg BID + P2Y12
- Warfarin + DAPT

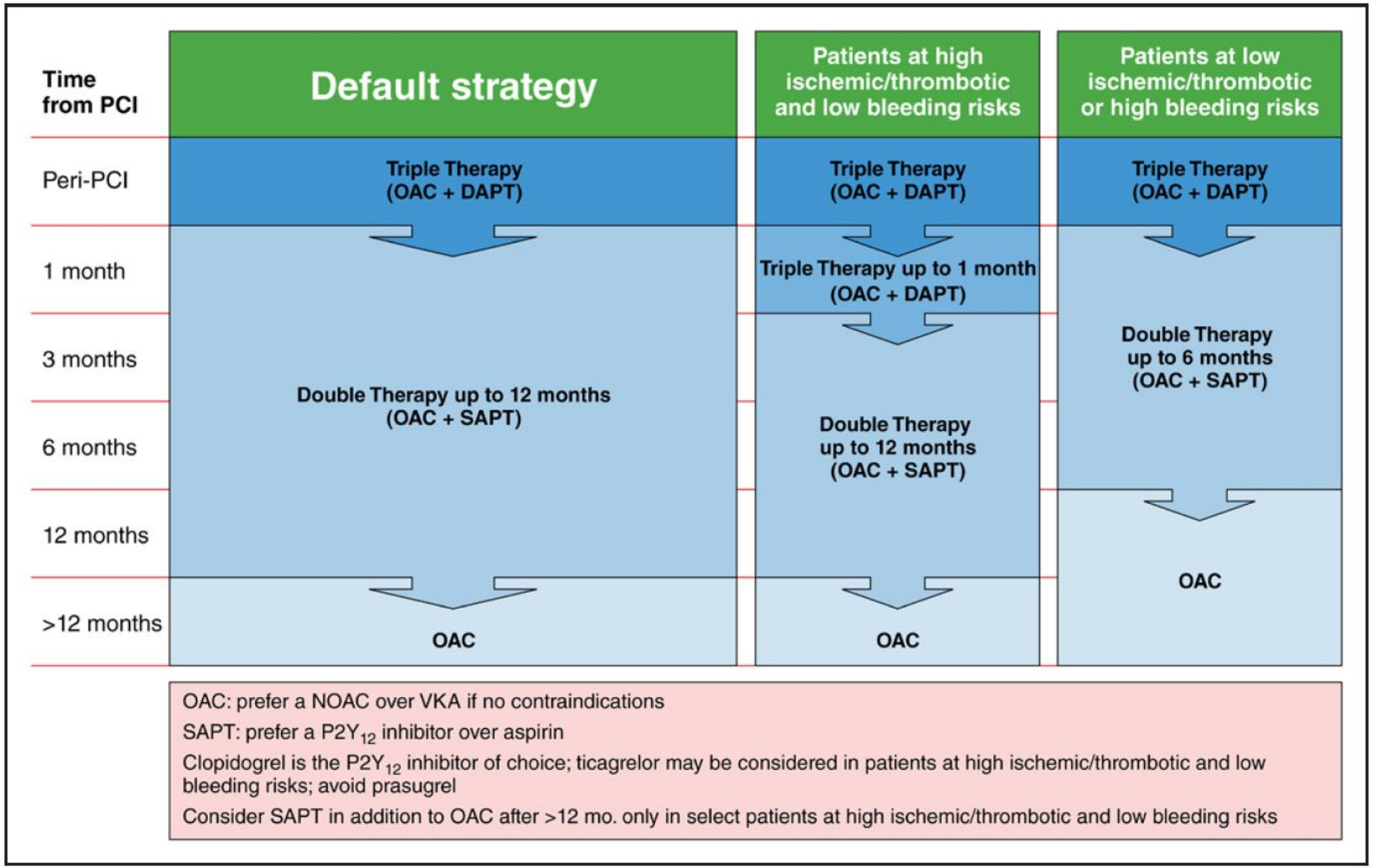
AUGUSTUS

- Apixaban 5mg BID + P2Y12
- Warfarin + P2Y12
- +/- ASA

ENTRUST-AF PCI

- Edoxaban 60mg daily + P2Y12
- Warfarin + DAPT


I. Pre-procedural Considerations
Define appropriateness of PCI procedure
Ischemic/thrombotic and bleeding risk stratification
II. Procedural Considerations
Vascular access (i.e., radial)
Stent selection (i.e., new-generation DES)
III. Post-procedural Considerations
Close monitoring with re-assessment of risk profile
Recommend use of PPIs and avoid NSAIDs
Antithrombotic Management
OAC:
• A NOAC should be preferred in most patients and used at established stroke prevention doses; lower doses are not recommended unless specifically tested.
• If VKA is chosen, maintain INR at the lower end of the therapeutic range (e.g., 2.0 – 2.5).
• Maintain OAC life-long.
APT:
• Aspirin in the peri-PCI phase and continued through hospital discharge.
• Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be a reasonable alternative in high ischemic and low bleeding risk patients; avoid prasugrel.
• Discontinue SAPT at 1 year in most patients; consider earlier SAPT discontinuation (e.g., 6 months) in patients at low ischemic or high bleeding risks and prolonging SAPT (>1 year) for select patients with high ischemic and low bleeding risks.
Strategy (double vs triple therapy):
• A double-therapy regimen (OAC plus P2Y12 inhibitor) immediately after hospital discharge for most patients.
• Consider triple-therapy by extending aspirin use for a limited period of time (e.g., 1 month) only in patients at high ischemic and low bleeding risks.


Time from PCI
Default strategy
Patients at high ischemic/thrombotic and low bleeding risks
Patients at low ischemic/thrombotic or high bleeding risks
Peri-PCI
Triple Therapy (OAC + DAPT)
Triple Therapy (OAC + DAPT)
Triple Therapy (OAC + DAPT)
1 month
Triple Therapy up to 1 month (OAC + DAPT)
3 months
Double Therapy up to 6 months (OAC + SAPT)
Double Therapy up to 12 months (OAC + SAPT)
Double Therapy up to 12 months (OAC + SAPT)
6 months
12 months
OAC
>12 months
OAC
OAC
OAC: prefer a NOAC over VKA if no contraindications
SAPT: prefer a P2Y12 inhibitor over aspirin
Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel
Consider SAPT in addition to OAC after >12 mo. only in select patients at high ischemic/thrombotic and low bleeding risks

Thrombotic vs Bleeding Risk

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)	Increased Bleeding Risk (may favor shorter-duration DAPT)
Increased ischemic risk	History of prior bleeding
Advanced age	Oral anticoagulant therapy
ACS presentation	Female sex
Multiple prior MIs	Advanced age
Extensive CAD	Low body weight
Diabetes mellitus	CKD
CKD	Diabetes mellitus
Increased risk of stent thrombosis	Anemia
ACS presentation	Chronic steroid or NSAID therapy
Diabetes mellitus	
Left ventricular ejection fraction <40%	
First-generation drug-eluting stent	
Stent undersizing	
Stent underdeployment	
Small stent diameter	
Greater stent length	
Bifurcation stents	
In-stent restenosis	

Patient with atrial fibrillation on warfarin admitted for NSTEMI now s/p PCI

What anticoagulation and antiplatelet therapy would you start this patient on in the immediate perioperative period?

a. Rivaroxaban 15mg daily + prasugrel 10mg daily + ASA 81mg daily
b. Apixaban 5mg BID + clopidogrel 75mg daily + ASA 81mg daily
c. Rivaroxaban 2.5mg BID + clopidogrel 75mg daily
d. Apixaban 5mg BID + prasugrel 10mg daily
e. Warfarin INR goal 2-3 + clopidogrel 75mg daily + ASA 81mg daily
f. Something else

60yo male patient with AF s/p PCI with prior history of stroke, MI, DMII, HTN, HF (LVEF 30%)

Patient is started on apixaban 5mg BID + clopidogrel 75mg daily + ASA 81mg daily immediately after PCI. How would you manage this patient's antithrombotic therapy moving forward?

a. Apixaban 5mg BID + clopidogrel 75mg daily + ASA 81mg x1 month
b. Apixaban 5mg BID + clopidogrel 75mg daily + ASA 81mg x6 months
c. Apixaban 5mg BID + discontinue clopidogrel + ASA 81mg indefinitely
d. Apixaban 5mg BID + clopidogrel 75mg daily + discontinue ASA immediately

Key Points

- Significant differences exist amongst $P2Y_{12}$ Inhibitors
  - Ticagrelor/Prasugrel → Superior efficacy and potentially more bleeding
  - Ticagrelor → do not use aspirin doses >100mg daily
  - Prasugrel → BBW for history of TIA or stroke
  - Prasugrel → Not recommended for patients >75yo and dose reduction for patients <60kg
- DAPT reduces the risk of stent thrombosis and recurrent MI in extended durations
  - Duration of DAPT should be individualized based on patient characteristics to maximize benefit (reduce ischemic risk) and minimize risk (bleeding)
- Validated scoring tools can be used to assess patient bleeding risk to determine length of DAPT therapy
  - DAPT Score – Bleeding AND Ischemic risk; used at 12 months to determine extended duration
  - PRECISE DAPT Score – Bleeding risk only; used immediately to determine short vs standard/extended duration
- Patients with atrial fibrillation present an added layer of management
  - Balance thrombotic vs bleeding risk to determine duration of aspirin therapy
  - AF related stroke or systemic embolism risk with reduced doses of DOACs unknown

Thank You

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