Role Of Clinical Pharmacist In

(DAPT Regimens Choice in ACS)

Dr / Rasha Wafaie Mahmoud El-Sorady

PharmD , MBA Hospital Management candidate , Head of Clinical Pharmacy Internal Medicine and Cardiology department at AMUH

Agenda :

- Introduction and Case study
- Types of antiplatelets oral , IV
- ACS management
- DAPT combinations
- DAPT duration decision making & regimens
- Oral switching

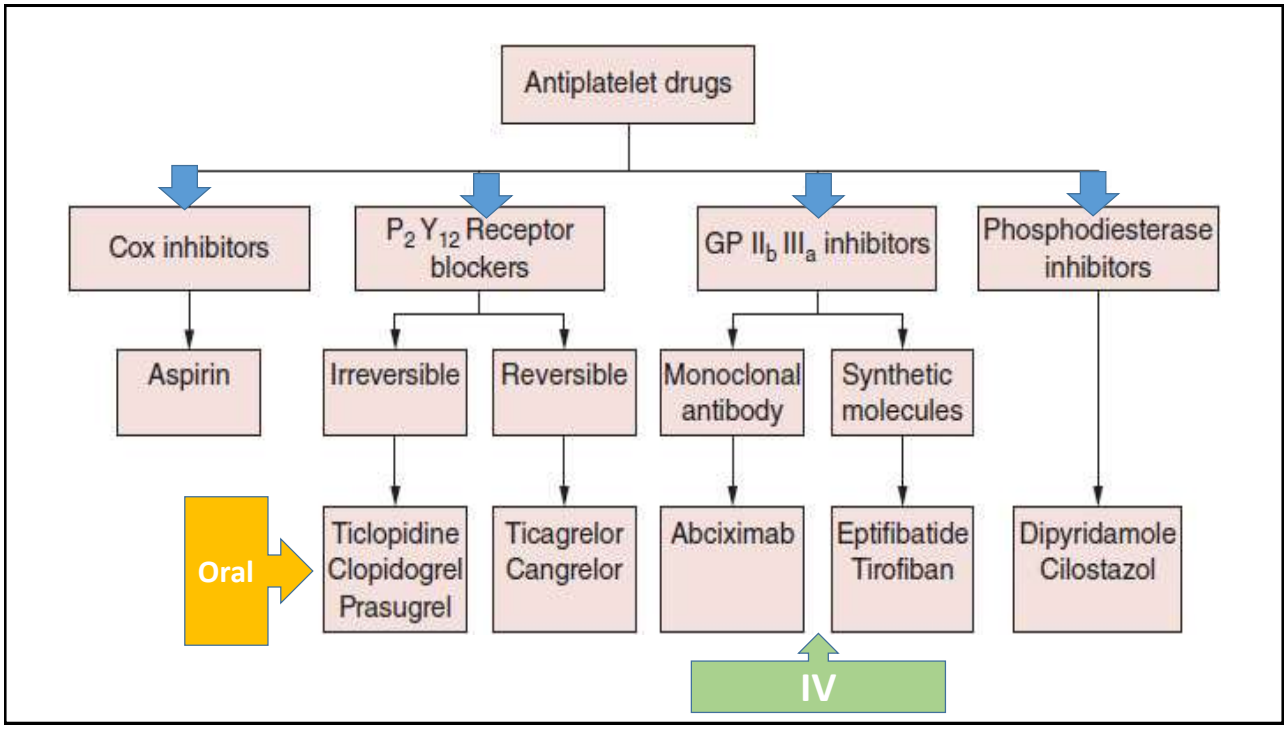
- Triple therapy management
- Bleeding management DAPT +/- OAC
- DAPT & elective non cardiac surgery

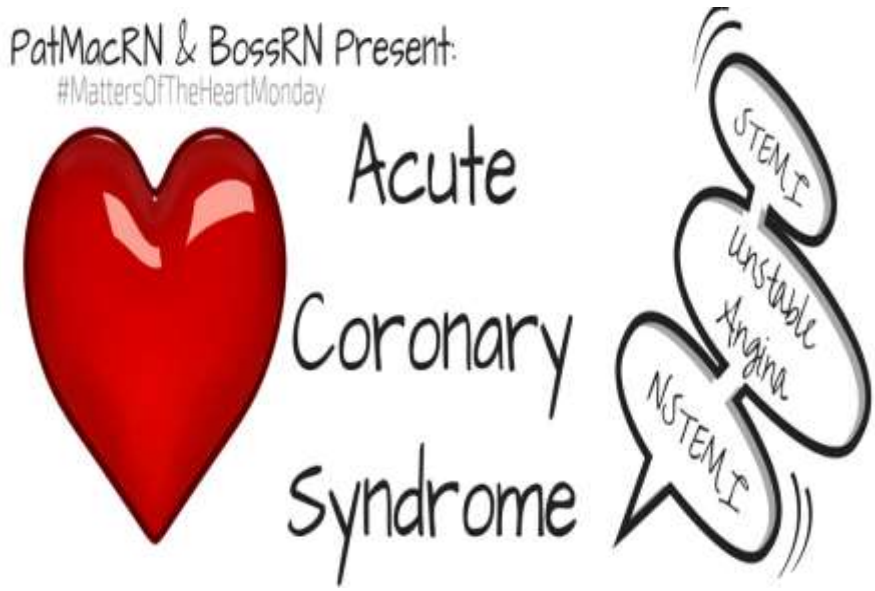
Case scenario

A 60-year-old man (weight 75 kg) presents to the ED with crushing substernal chest pain and ST-segment elevations on ECG. He has a medical history of diabetes and a 40 pack-year history of smoking. He is taken immediately to the catheterization laboratory for primary PCI, and a drug eluting stent (DES)is placed in his left anterior descending artery . In addition to aspirin, which regimen would best maintain this patient's stent patency?

- A. Clopidogrel 300-mg LD, followed by 75 mg daily for 12 months.
- B. Prasugrel 60-mg LD, followed by 10 mg daily for 12 months.
- C. Ticagrelor 180-mg LD, followed by 90 mg daily for 6 months.
- D. Clopidogrel 600-mg LD, followed by 75 mg daily for 6 months.

As an expert clinical pharmacist in cardiology department we have to provide an up-to-date overview of available data and clinical considerations to aid in decision making





ACS management

Pharmacological Conventional therapy :

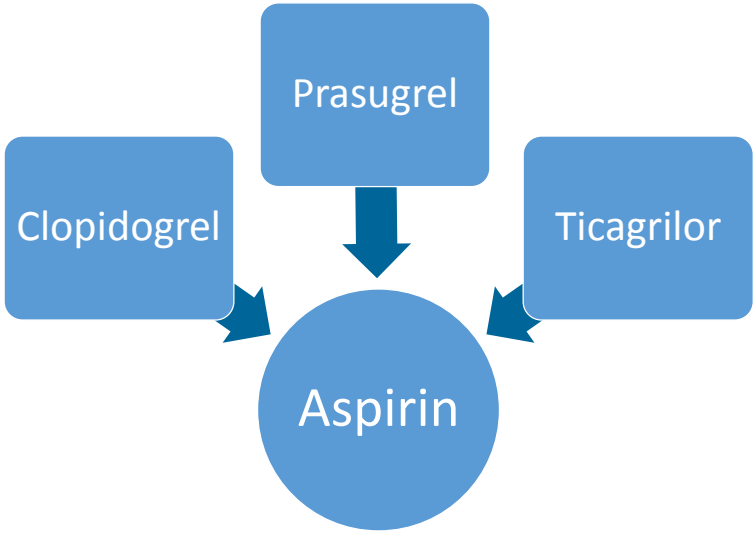
DAPT , Statins , Nitrates , B-blockers +/-ACEIs , Anticoagulant

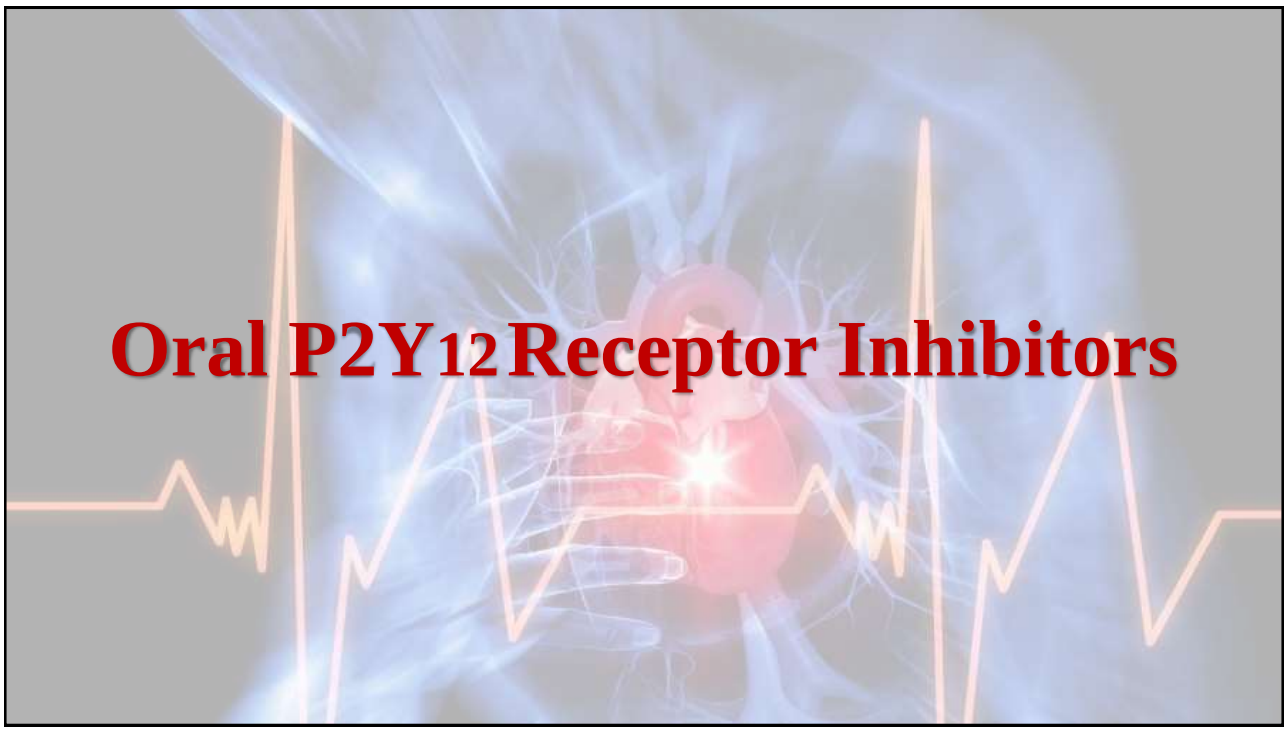
+/-

Interventional : The best PCI within 90 minutes

ACCP Updates in Therapeutics® 2019: The Pharmacotherapy Preparatory Review and Recertification Course

DAPT Combinations



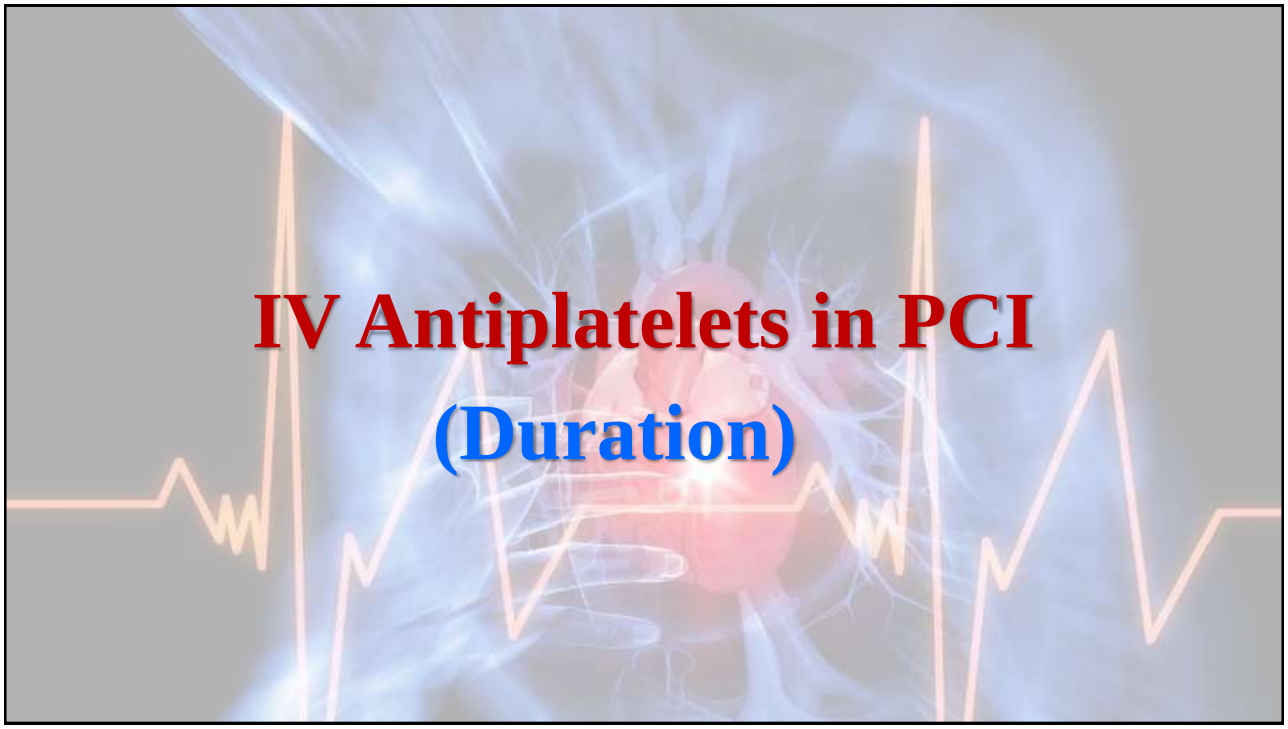


Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Mechanism of action	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor
Peak platelet inhibition	300-mg LD ~6 hr 600-mg LD ~2 hr	60-mg LD ~30 min[d]	180 mg LD ~30 min[d]
% Platelet inhibition	30%–40%	60%–70%	60%–70%
LD	300–600 mg[e]	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily; (5 mg if < 60 kg, BW ≥ 75 yr)[f]	90 mg BID[g]
Metabolism	Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes	Prodrug; converted by one step to active metabolite by several CYP pathways	Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor
Reversible platelet binding	No	No	Yes
Half-life	8 hr (metabolite)	3.7 hr (metabolite, range 2–15 hr)	7 hr (parent), 9 hr (active metabolite)
Nonresponders	Exposure to active drug affected by *CYP2C19* genetic polymorphisms	No known issues	No known issues

ACCP Updates in Therapeutics® 2019: The Pharmacotherapy

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Drug-drug interactions, drug-disease interactions, and common nonbleeding-related AEs	PPIs inhibit *CYP2C19* (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs	No clinically significant drug interactions; more bleeding with NSAIDs, OACs	Careful with asthma owing to dyspnea (up to 15%) and bradycardia (can cause ventricular pauses); More bleeding with NSAIDs, OACs Strong 3A4 inhibitors increase TIC concentrations; strong 3A4 inducers decrease TIC concentrations; do not exceed 40 mg of simvastatin or lovastatin Limit aspirin to < 100 mg; monitor digoxin concentrations
Surgery hold time[h]	5 days	7 days	5 days
Bleeding risk	Less than PRA and TIC with standard dosing	Risk of non-CABG, spontaneous, and fatal bleeds higher than with standard-dose clopidogrel	Risk of non-CABG bleeds higher than with standard-dose clopidogrel
Box warning	*CYP2C19* polymorphisms	Age-related bleeding CVA/TIA	Aspirin dosing > 100 mg
Contraindications	Active bleeding	Active bleeding TIA, CVA	Active bleeding ICH, severe hepatic disease
Supporting trials	CREDO, CURE, PCI-CURE, CLARITY, COMMIT	TRITON-TIMI 38, TRILOGY	PLATO, PEGASUS
FDA indication	ACS managed medically or with PCI	ACS with PCI	ACS managed medically or with PCI

ACCP Updates in Therapeutics® 2019: The Pharmacotherapy



IV Antiplatelets in PCI (Duration)

Agent	Dosing	Renal Adjustments
Abciximab (ReoPro)[c]	PCI: 0.25 mg/kg IVB; then 0.125 mcg/kg/min (max 10 mcg/kg) for 12 hr; ACS without PCI: Not recommended	Not necessary
Eptifibatide (Integrilin)	PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr; ACS without PCI: Of uncertain benefit in patients adequately pretreated with a $P2Y_{12}$ receptor inhibitor; single bolus used as above	If CrCl < 50 mL/min/1.73 m^2, reduce infusion by 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr	If CrCl ≤ 60 mL/min/1.73 m^2, reduce infusion by 50%

ACCP Updates in Therapeutics® 2019: The Pharmacotherapy Preparatory Review and Recertification Course

DAPT duration decision making

DAPT score

Precise DAPT score

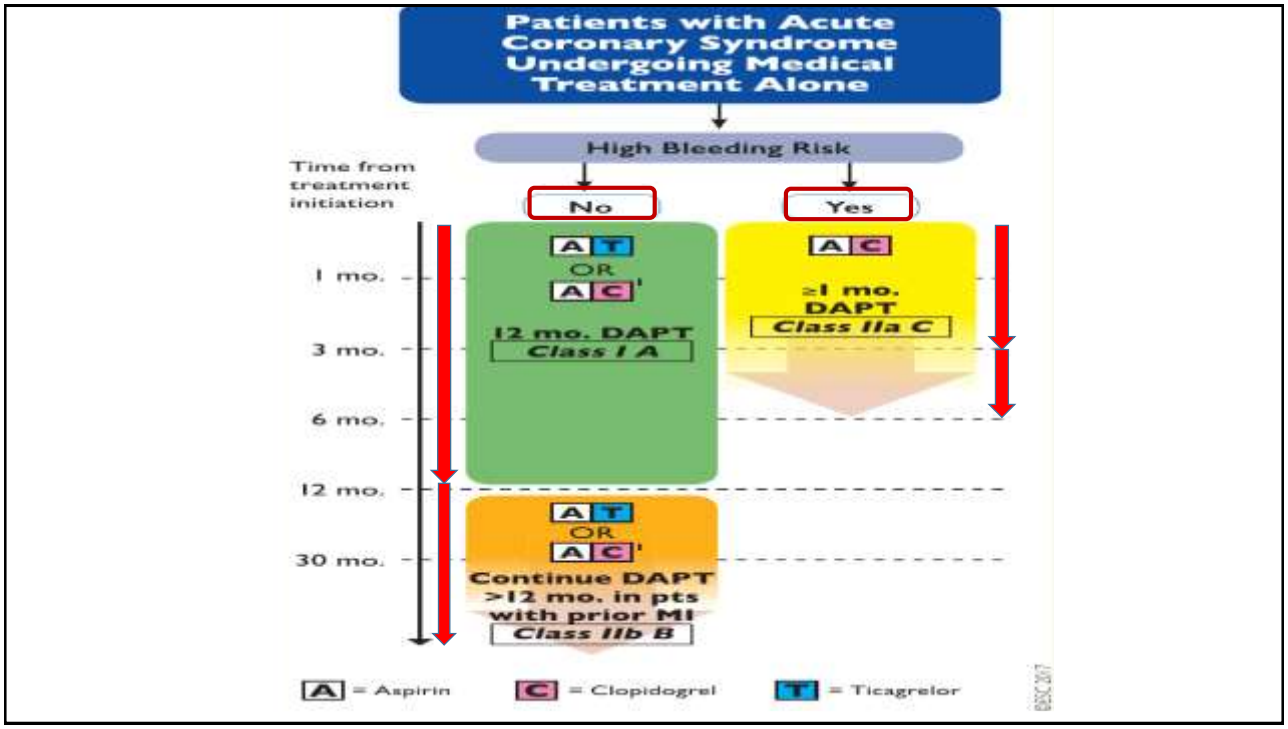
Table 3 Risk scores validated for dual antiplatelet therapy duration decision-making

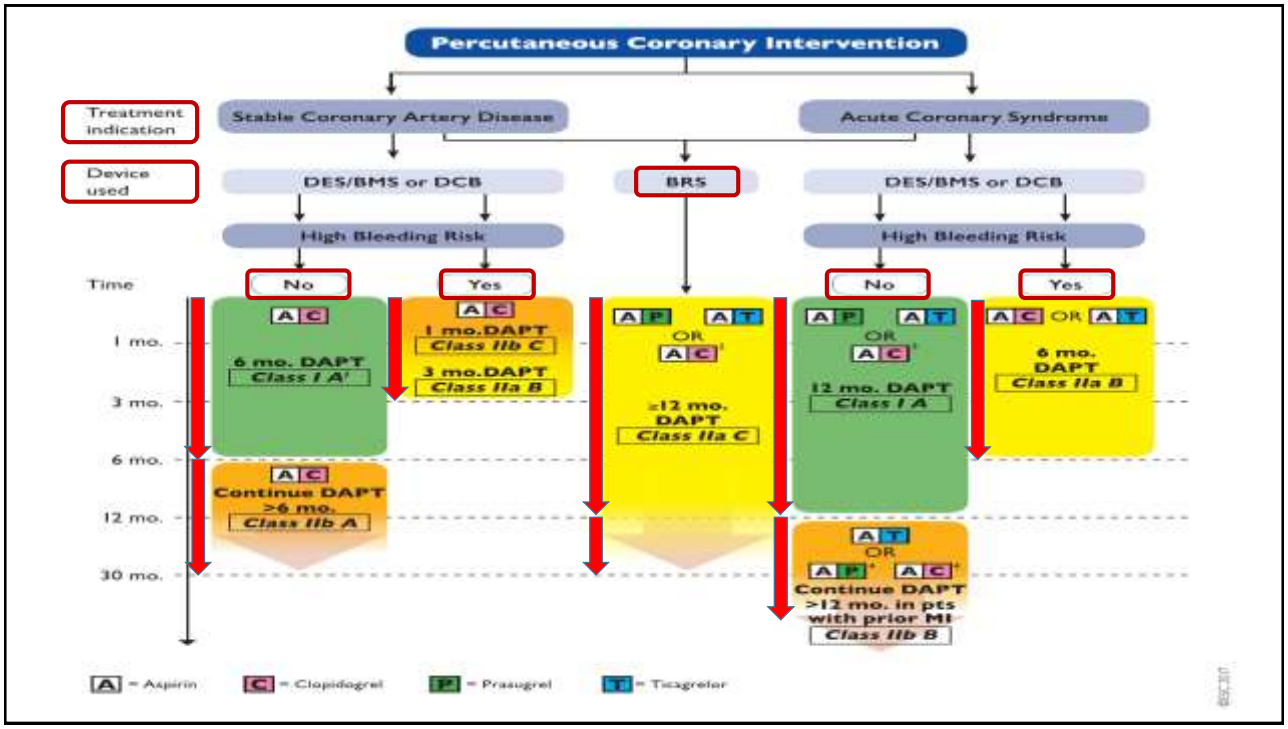
	PRECISE-DAPT score[18]	DAPT score[19]
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
Score calculation[a]	HB WBC Age CrCl Prior Bleeding Score Points	Age ≥75 −2 pt 65 to <75 −1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +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

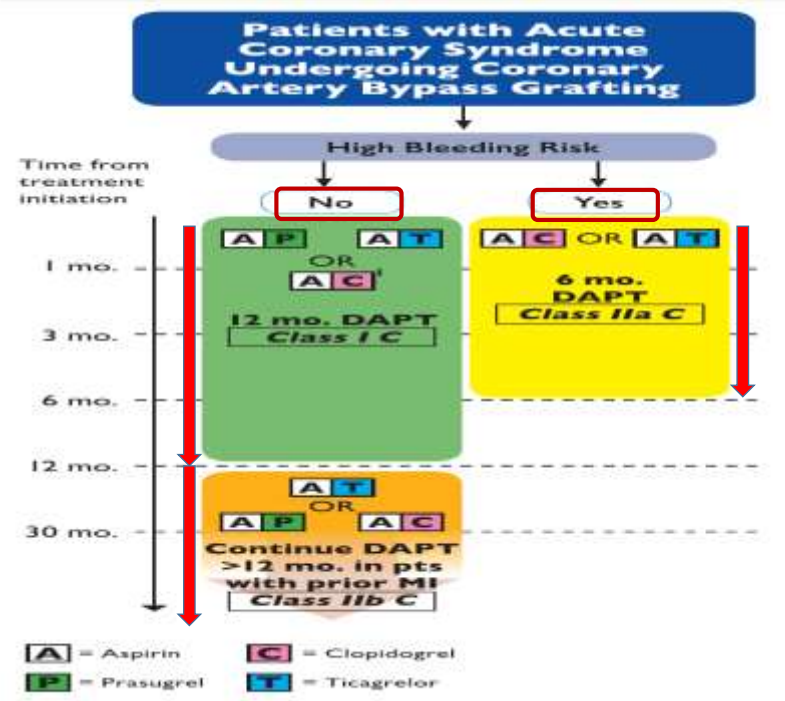
DAPT regimens

Medical treatment only
PCI
CABG

European Heart Journal (2018)




Percutaneous Coronary Intervention
Treatment indication
Stable Coronary Artery Disease
Acute Coronary Syndrome
Device used
DES/BMS or DCB
BRS
DES/BMS or DCB
High Bleeding Risk
High Bleeding Risk
Time
No
Yes
No
Yes
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A C
6 mo. DAPT
Class I A'
A C
1 mo.DAPT
Class IIb C
3 mo.DAPT
Class IIa B
A C
Continue DAPT
>6 mo.
Class IIb A
A P A T
OR
A C'
≥12 mo.
DAPT
Class IIa C
A P A T
OR
A C'
12 mo. DAPT
Class I A
A C OR A T
6 mo.
DAPT
Class IIa B
A T
OR
A P' A C'
Continue DAPT
>12 mo. in pts
with prior MI
Class IIb B
A = Aspirin
C = Clopidogrel
P = Prasugrel
T = Ticagrelor


Patients with Acute Coronary Syndrome Undergoing Coronary Artery Bypass Grafting
High Bleeding Risk
Time from treatment initiation
No
Yes
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A P A T
OR
A C'
12 mo. DAPT
Class I C
A C OR A T
6 mo.
DAPT
Class IIa C
A T
OR
A P A C
Continue DAPT
>12 mo. in pts
with prior MI
Class IIb C
A = Aspirin
C = Clopidogrel
P = Prasugrel
T = Ticagrelor

Prasugrel is superior to ticagrelor for reducing ischaemic events in patients with acute coronary syndrome and a planned invasive strategy.

BMC Cardiovascular Disorders

BMC

Compared efficacy of clopidogrel and ticagrelor in treating acute cor syndrome: a meta-analysis

Dong Wang, Xiao-Hong Yang, [...], and Xia

An electronic search of literature using Embase, PubMed, and the Cochrane Library was conducted by two reviewers separately up to June 2018. All

Conclusions

Our present findings suggest similar efficacy and safety profiles for clopidogrel and ticagrelor Ticagrelor should be considered as a valuable option to reduce the risk of bleeding, MI and stroke, whereas potentially increases the incidence of dyspnea. Given the metabolic process, ticagrelor may be a valid and even more potent antiplatelet drug than clopidogrel, as an alternative strategy in treating patients with clopidogrel

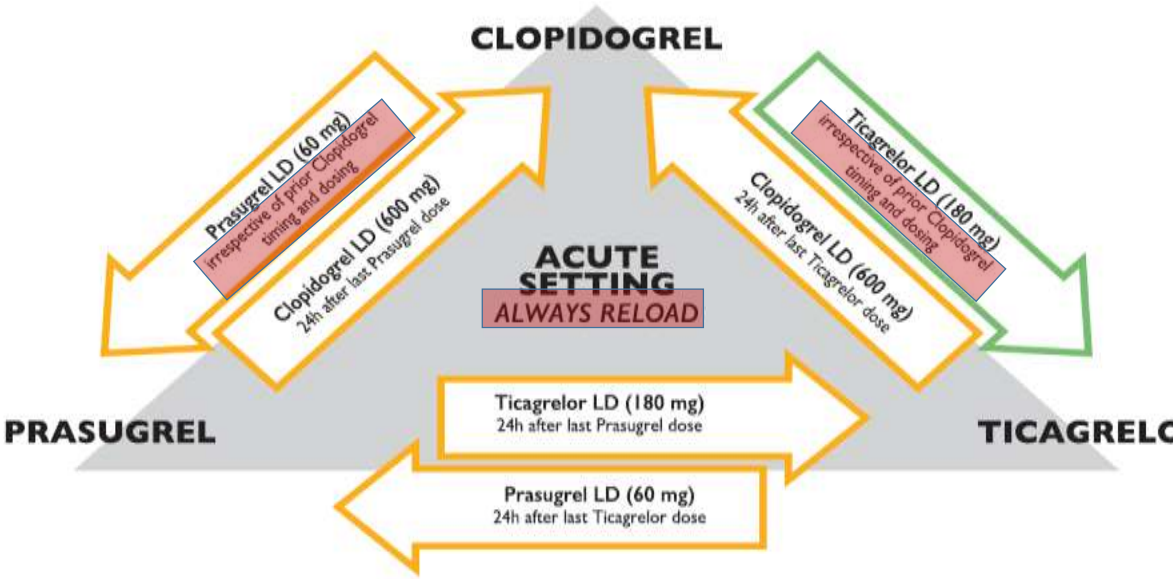
A 60-year-old man (weight 75 kg) presents to the ED with crushing substernal chest pain and ST-segment elevations on ECG. He has a medical history of diabetes and a 40 pack-year history of smoking. He is taken immediately to the catheterization laboratory for primary PCI, and a drug eluting stent (DES)is placed in his left anterior descending C.artery. In addition to aspirin, which regimen would best maintain this patient's stent patency?

- Drug of choice= Prasugrel
  - Dose= LD=60mg
  - MD=10mg twice daily
- DAPT score= 2.5

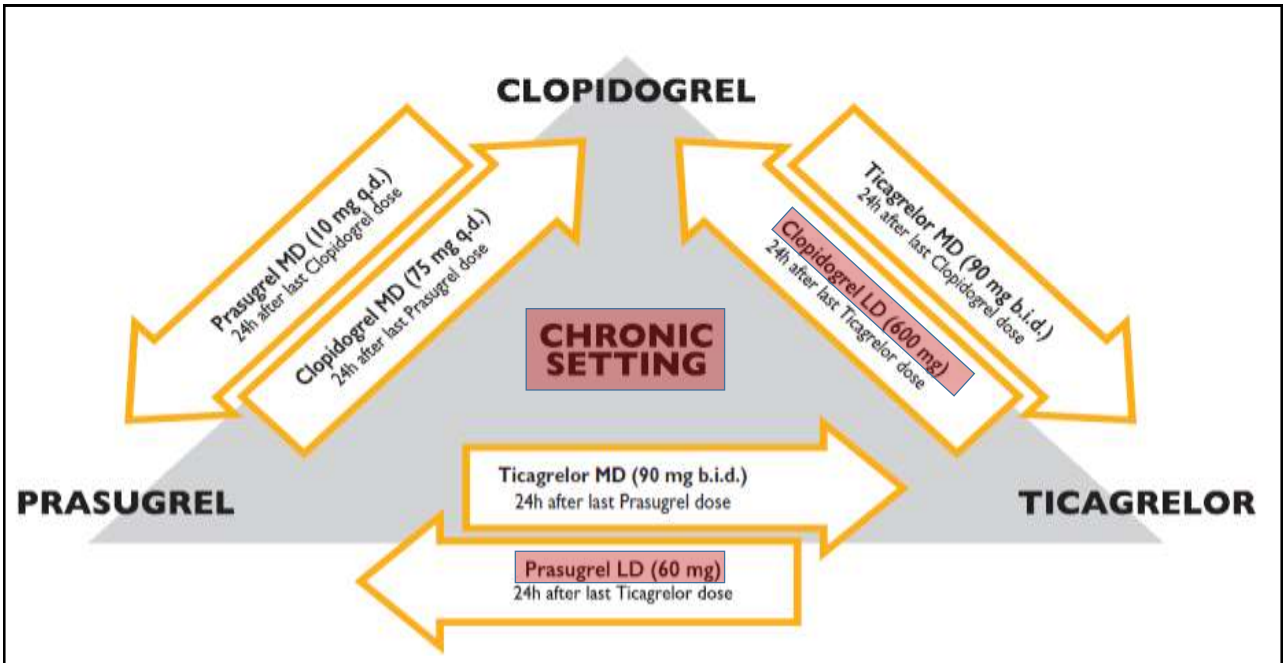
Precise DAPT= 22

so duration (12 months)

Oral P2Y12 Inhibitors Switching



European Heart Journal (2018)



European Heart Journal (2018)

DAPT & OAC

Ischemic risk **Bleeding risk**

High ischemic risk is considered as an acute clinical presentation or anatomical / procedural features

Bleeding risk can be estimated by HAS-BLED or ABC bleeding score .

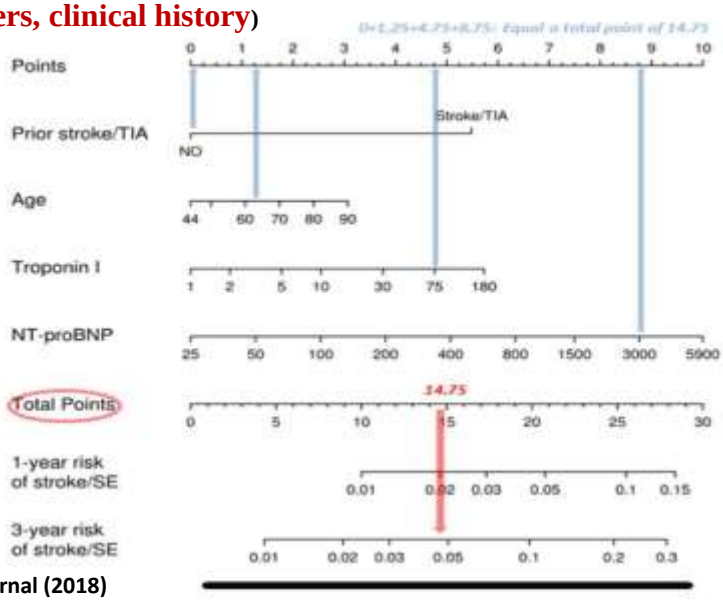
High-risk features of stent-driven recurrent ischaemic events

- Prior stent thrombosis on adequate antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease especially in diabetic patients
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
- At least three stents implanted
- At least three lesions treated
- Bifurcation with two stents implanted
- Total stent length >60 mm
- Treatment of a chronic total occlusion

European Heart Journal (2018)

ABC-Stroke and ABC-Bleeding Scores

(age, biomarkers, clinical history)

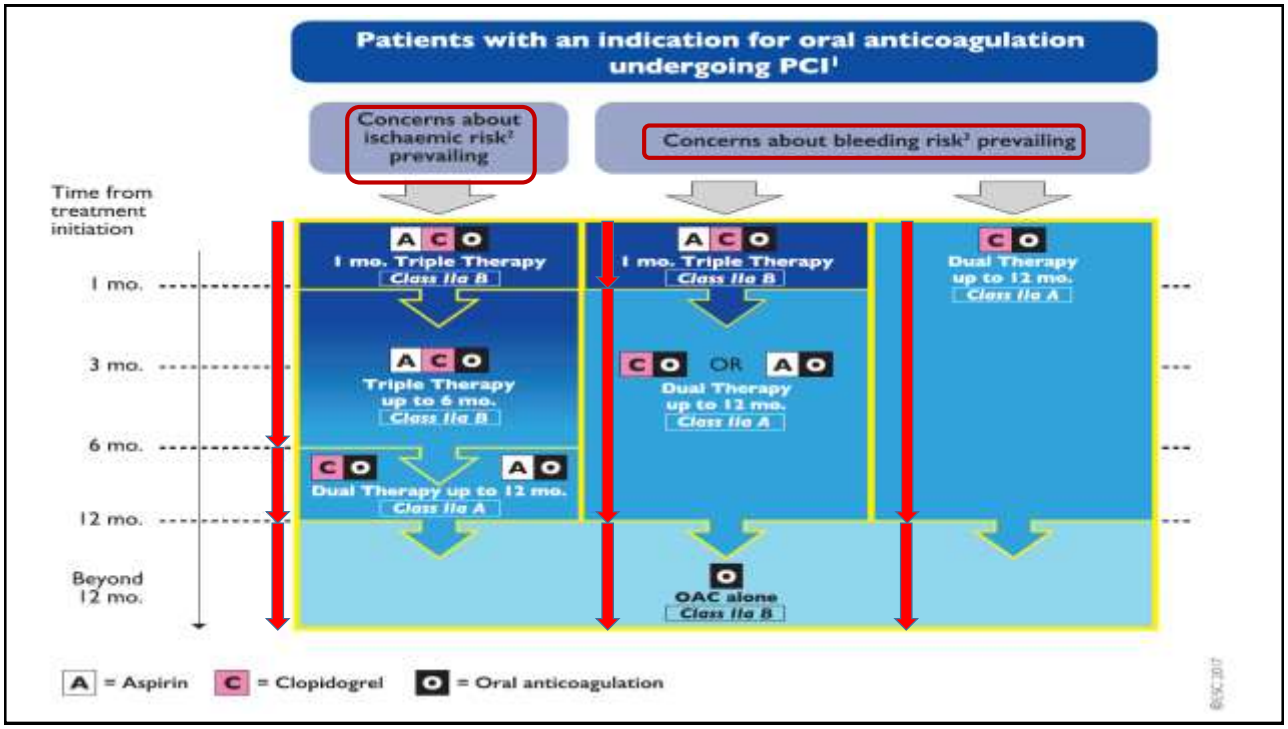


European Heart Journal (2018)

CHA2DS2-VASc / HAS-BLED scores

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**

European Heart Journal (2018)



Strategies to avoid bleeding complications + OAC

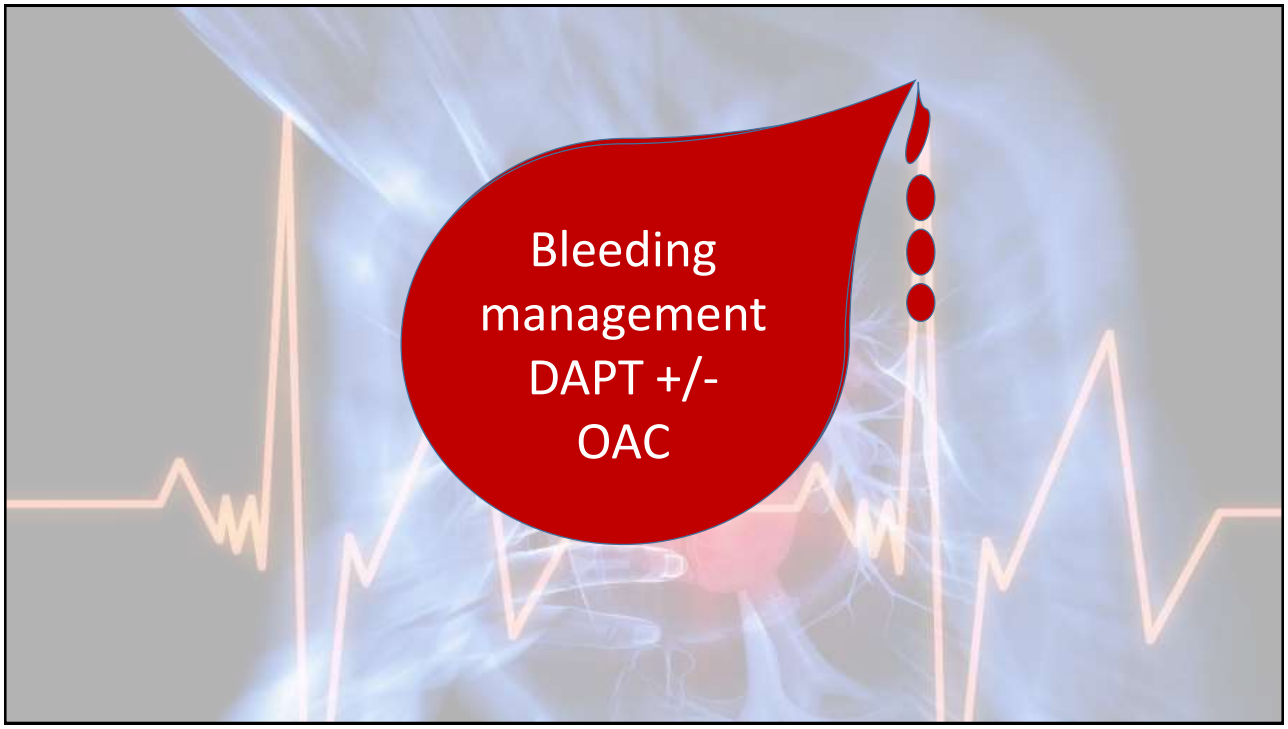
- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
- Consider the use of NOACs instead of VKA.
- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.
- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
- Use low-dose (≤ 100 mg daily) aspirin.
- Routine use of PPIs.

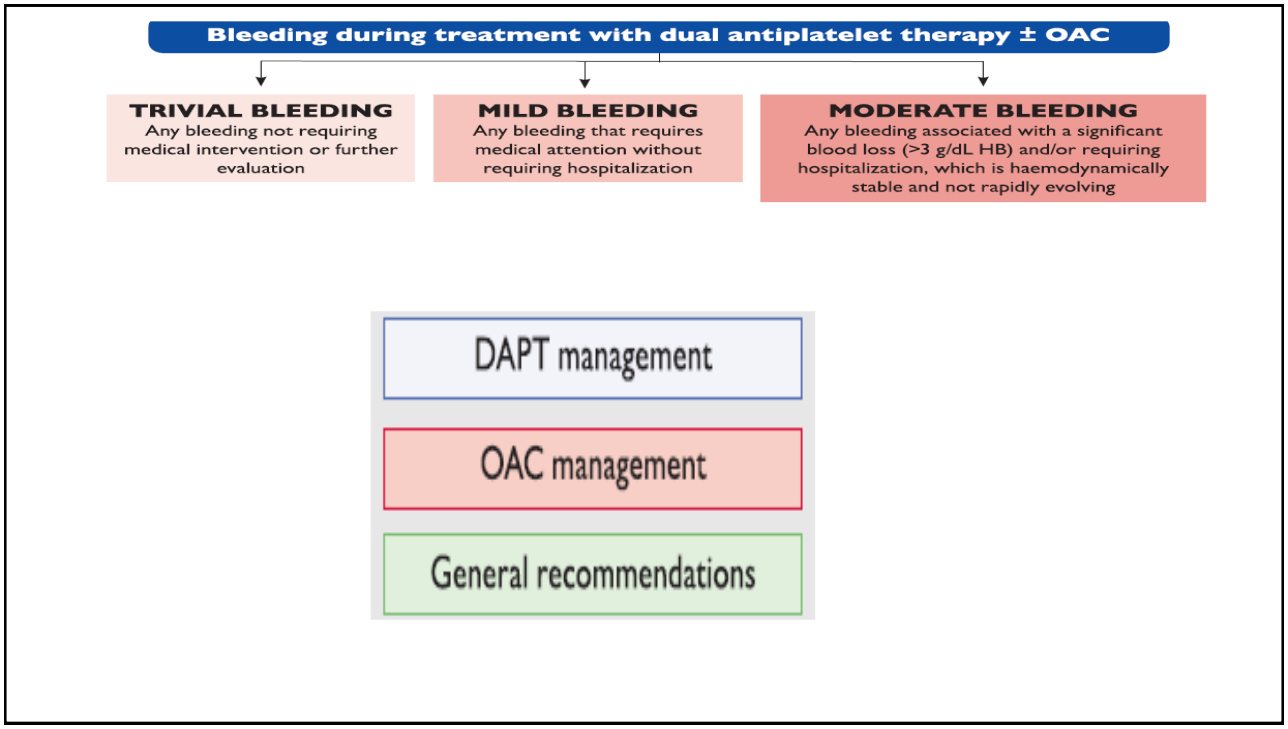
European Heart Journal (2018)

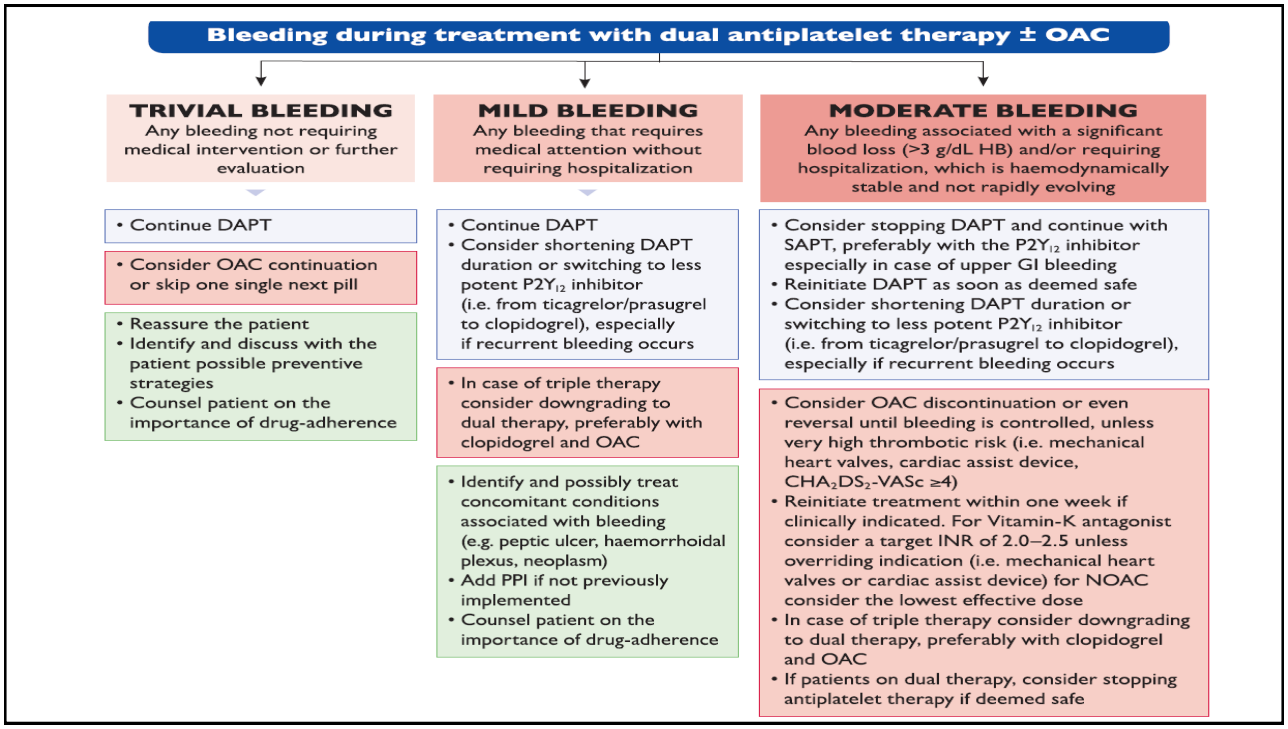
Un favourable patient profile for a combination OAC+ DAPT

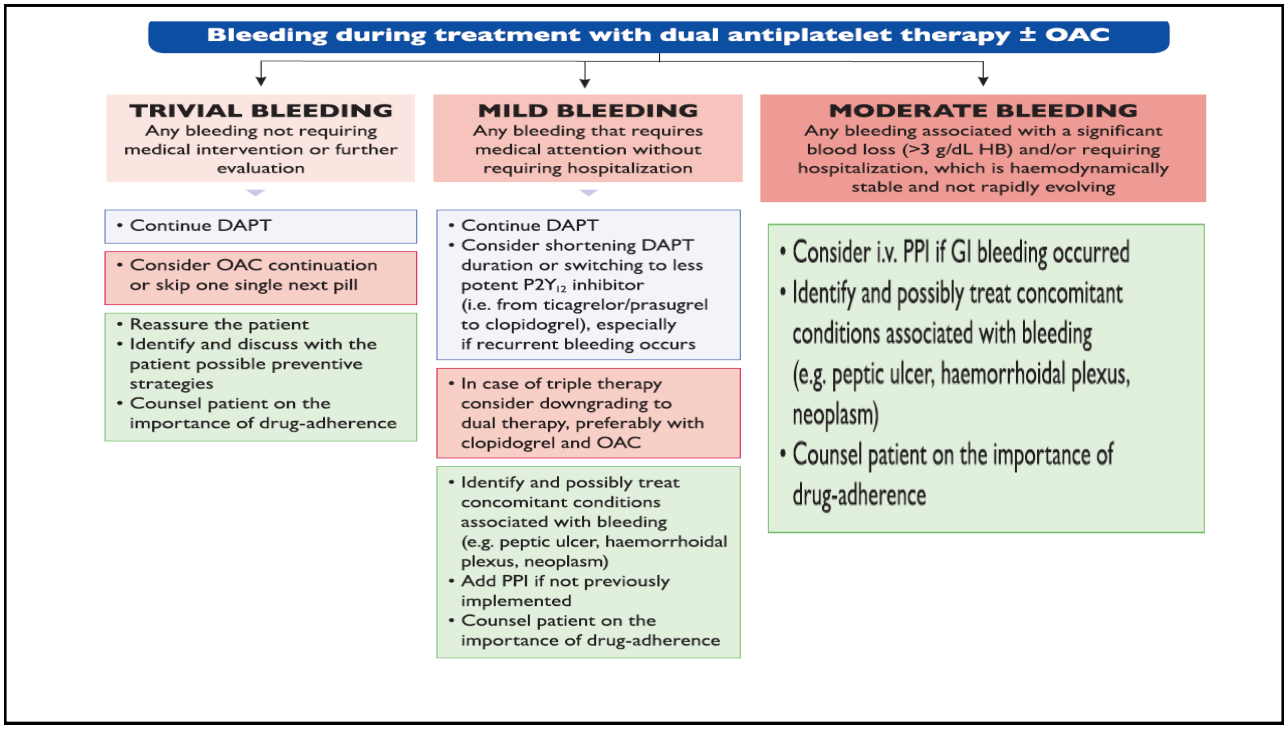
- Short life expectancy
- Ongoing malignancy
- Poor expected adherence
- Poor mental status
- End stage renal failure
- Advanced age
- Prior major bleeding/prior haemorrhagic stroke
- Chronic alcohol abuse
- Anaemia
- Clinically significant bleeding on dual antithrombotic therapy

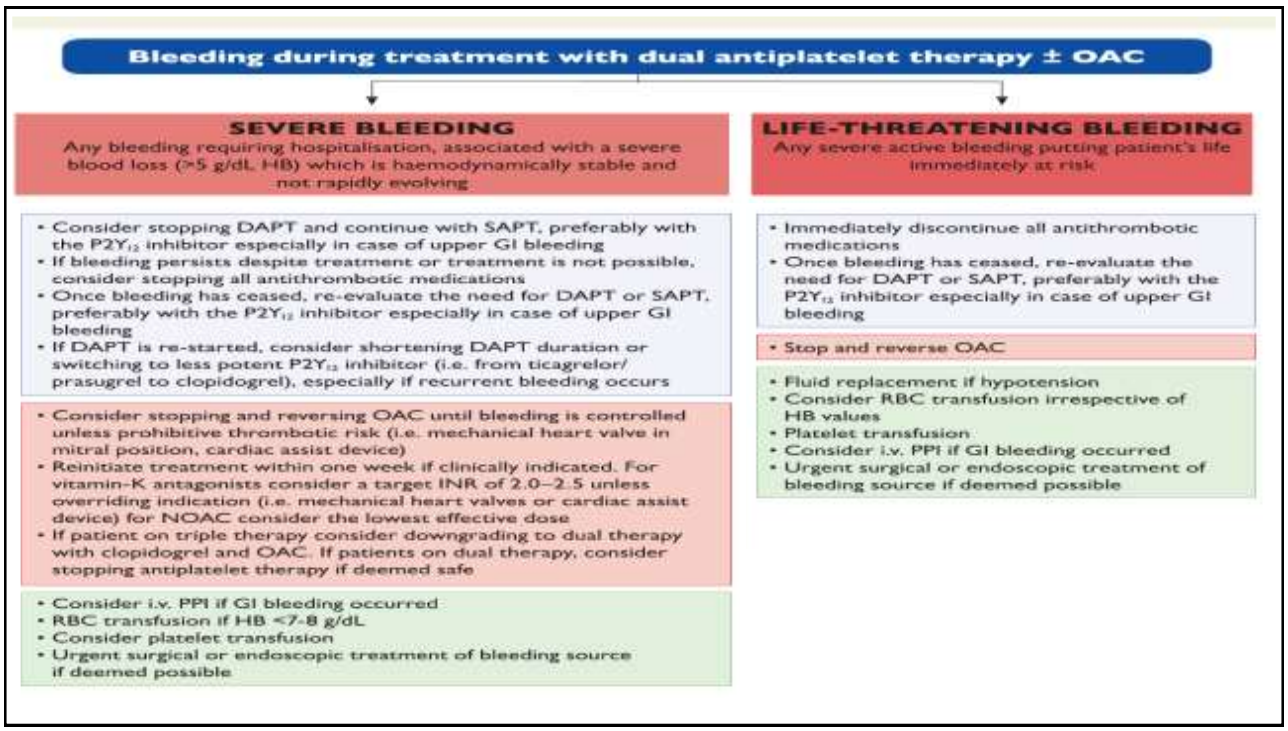
European Heart Journal (2018)




Bleeding during treatment with dual antiplatelet therapy ± OAC
TRIVIAL BLEEDING
Any bleeding not requiring medical intervention or further evaluation
MILD BLEEDING
Any bleeding that requires medical attention without requiring hospitalization
MODERATE BLEEDING
Any bleeding associated with a significant blood loss (>3 g/dL HB) and/or requiring hospitalization, which is haemodynamically stable and not rapidly evolving
DAPT management
OAC management
General recommendations


Bleeding during treatment with dual antiplatelet therapy ± OAC
TRIVIAL BLEEDING
Any bleeding not requiring medical intervention or further evaluation
MILD BLEEDING
Any bleeding that requires medical attention without requiring hospitalization
MODERATE BLEEDING
Any bleeding associated with a significant blood loss (>3 g/dL HB) and/or requiring hospitalization, which is haemodynamically stable and not rapidly evolving
• Continue DAPT
• Consider OAC continuation or skip one single next pill
• Reassure the patient
• Identify and discuss with the patient possible preventive strategies
• Counsel patient on the importance of drug-adherence
• Continue DAPT
• Consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC
• Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm)
• Add PPI if not previously implemented
• Counsel patient on the importance of drug-adherence
• Consider stopping DAPT and continue with SAPT, preferably with the P2Y12 inhibitor especially in case of upper GI bleeding
• Reinitiate DAPT as soon as deemed safe
• Consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• Consider OAC discontinuation or even reversal until bleeding is controlled, unless very high thrombotic risk (i.e. mechanical heart valves, cardiac assist device, CHA2DS2-VASc ≥4)
• Reinitiate treatment within one week if clinically indicated. For Vitamin-K antagonist consider a target INR of 2.0–2.5 unless overriding indication (i.e. mechanical heart valves or cardiac assist device) for NOAC consider the lowest effective dose
• In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC
• If patients on dual therapy, consider stopping antiplatelet therapy if deemed safe

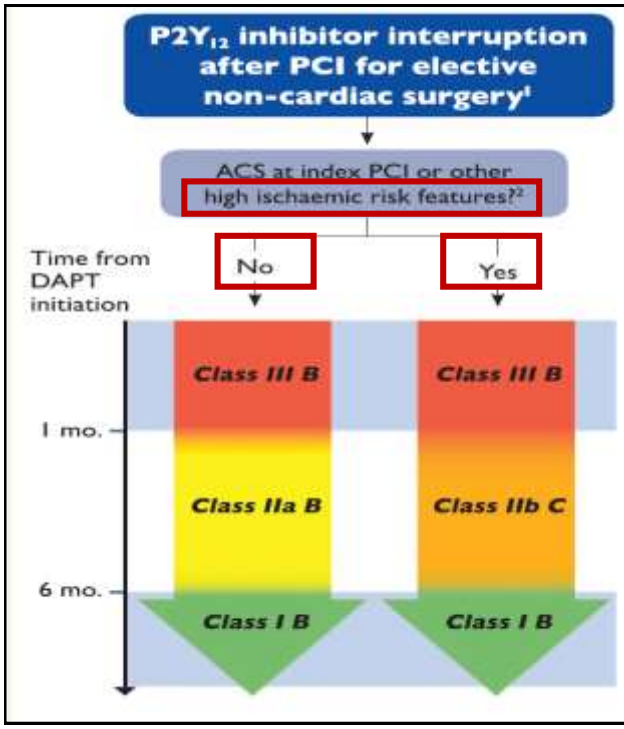

Bleeding during treatment with dual antiplatelet therapy ± OAC
TRIVIAL BLEEDING
Any bleeding not requiring medical intervention or further evaluation
• Continue DAPT
• Consider OAC continuation or skip one single next pill
• Reassure the patient
• Identify and discuss with the patient possible preventive strategies
• Counsel patient on the importance of drug-adherence
MILD BLEEDING
Any bleeding that requires medical attention without requiring hospitalization
• Continue DAPT
• Consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC
• Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm)
• Add PPI if not previously implemented
• Counsel patient on the importance of drug-adherence
MODERATE BLEEDING
Any bleeding associated with a significant blood loss (>3 g/dL HB) and/or requiring hospitalization, which is haemodynamically stable and not rapidly evolving
• Consider i.v. PPI if GI bleeding occurred
• Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm)
• Counsel patient on the importance of drug-adherence


Bleeding during treatment with dual antiplatelet therapy ± OAC
SEVERE BLEEDING
Any bleeding requiring hospitalisation, associated with a severe blood loss (>5 g/dL HB) which is haemodynamically stable and not rapidly evolving
• Consider stopping DAPT and continue with SAPT, preferably with the P2Y12 inhibitor especially in case of upper GI bleeding
• If bleeding persists despite treatment or treatment is not possible, consider stopping all antithrombotic medications
• Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the P2Y12 inhibitor especially in case of upper GI bleeding
• If DAPT is re-started, consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• Consider stopping and reversing OAC until bleeding is controlled unless prohibitive thrombotic risk (i.e. mechanical heart valve in mitral position, cardiac assist device)
• Reinitiate treatment within one week if clinically indicated. For vitamin-K antagonists consider a target INR of 2.0–2.5 unless overriding indication (i.e. mechanical heart valves or cardiac assist device) for NOAC consider the lowest effective dose
• If patient on triple therapy consider downgrading to dual therapy with clopidogrel and OAC. If patients on dual therapy, consider stopping antiplatelet therapy if deemed safe
• Consider i.v. PPI if GI bleeding occurred
• RBC transfusion if HB <7-8 g/dL
• Consider platelet transfusion
• Urgent surgical or endoscopic treatment of bleeding source if deemed possible
LIFE-THREATENING BLEEDING
Any severe active bleeding putting patient's life immediately at risk
• Immediately discontinue all antithrombotic medications
• Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the P2Y12 inhibitor especially in case of upper GI bleeding
• Stop and reverse OAC
• Fluid replacement if hypotension
• Consider RBC transfusion irrespective of HB values
• Platelet transfusion
• Consider i.v. PPI if GI bleeding occurred
• Urgent surgical or endoscopic treatment of bleeding source if deemed possible

DAPT

&

Elective non cardiac surgery



After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period.[227]	IIa	B
In patients with recent MI or other high ischaemic risk features[c] requiring DAPT, elective surgery may be postponed for up to 6 months.[17,214,215,234]	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.[229,237–239]	IIb	C

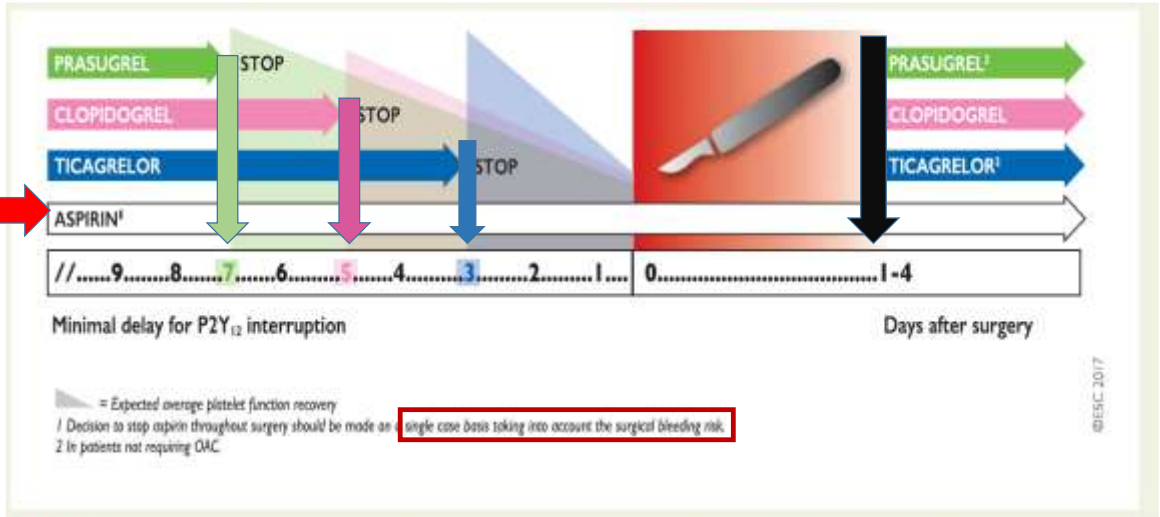


Figure 9 Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery
OAC = oral anticoagulant.

European Heart Journal (2018)

THE TAKE HOME MESSAGE

The Clinical pharmacist play an effective & efficient role in ensuring safe and optimal use of DAPT +/- anticoagulants regimens for best medical care patient achievements

In Summary

1. Pre-treatment with a P2Y12 inhibitor is generally recommended in patients in whom coronary anatomy is known
2. In (ACS) ticagrelor on top of aspirin is recommended, even in pre-treated with clopidogrel (contraindications)
3. In (ACS) undergoing PCI, prasugrel on top of aspirin is recommended (contraindications)

4. Clopidogrel on top of aspirin for:
   - Stable CAD for elective invasive procedures
   - ACS CI to ticagrelor or prasugrel
   - Indicated for OAC or thrombolysis

5. (In ACS +/-PCI), DAPT is recommended for 12 months unless the risk of bleeding (e.g. PRECISE-DAPT ≥25)

6. Switching P2Y12 inhibitor , chronic setting or acute setting (last dose timing , re loading , MD)

7. DAPT in elective cardiac and non-cardiac surgery continue aspirin and hold P2Y12 reinitiate it as soon as possible post-operatively

8. Not discontinue DAPT within the first month to patient who is planned to elective non-cardiac surgery

9. Minimize bleeding with DAPT;
   - Aspirin dose of 75 - 100 mg
   - PPI is recommended

ESC
European Society of Cardiology

STS/EACTS Latin America Cardiovascular Surgery Conference

The Society of Thoracic Surgeons

EACTS
European Association for Cardio-Thoracic Surgery

2017

American Heart Association.

2019

AMERICAN COLLEGE of CARDIOLOGY

ACCA
Acute Cardiovascular Care Association

European Heart Journal (2018)

ESC
European Society of Cardiology

Webinar

Dual Anti Platelet Therapy in 2019 - current recommendations

Tuesday 09 April 2019 from 18:00 to 19:00 CEST


Thank
you