Acute Coronary Syndromes: Unstable Angina and Myocardial Infarctions Part 4

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Treatment of ACS

1. Management of ACS S/Sx
2. Initial Management in ED
3. **Acute Therapies during hospitalization:**
    1. Non-pharmacologic Management
    2. **Pharmacologic Management**
        A. Anti-ischemic
        B. Acute Reperfusion
        C. **Anti-thrombotic**
        D. Adjunct
4. Chronic Therapies after discharge

Anti-Thrombotic Therapies for ACS/PCI

- What is the purpose of anti-thrombotic therapy in these settings?

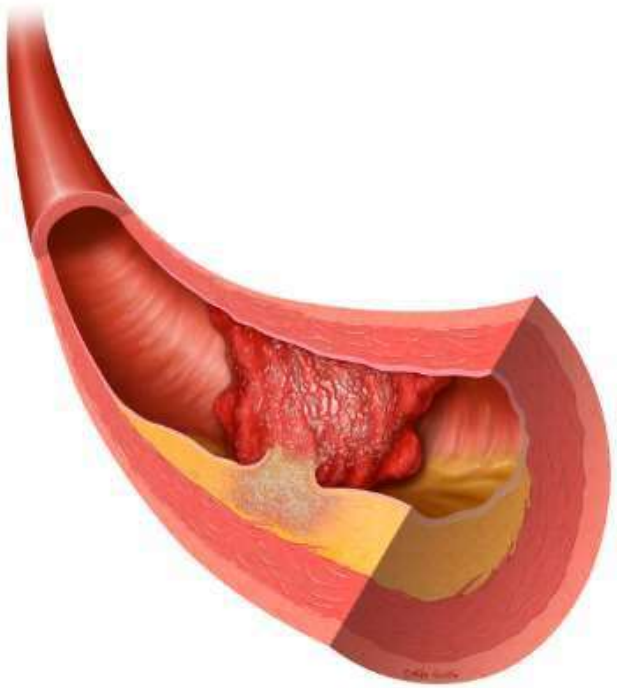
  ACS:

  PCI:

- Anti-thrombotic therapies includes:

  1.

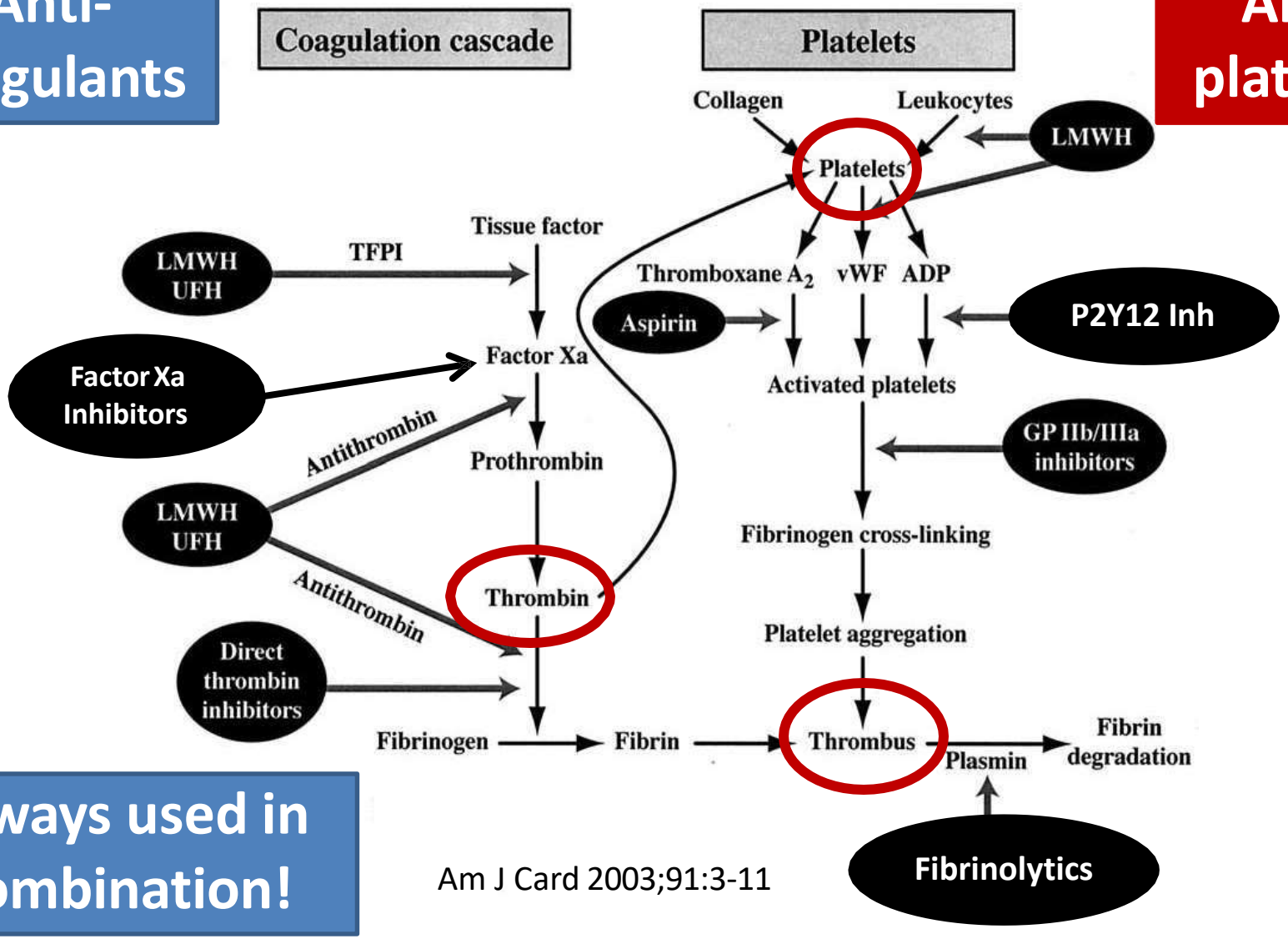
  2.



Anti-thrombotic Therapies

Anti-coagulants

Anti-platelets

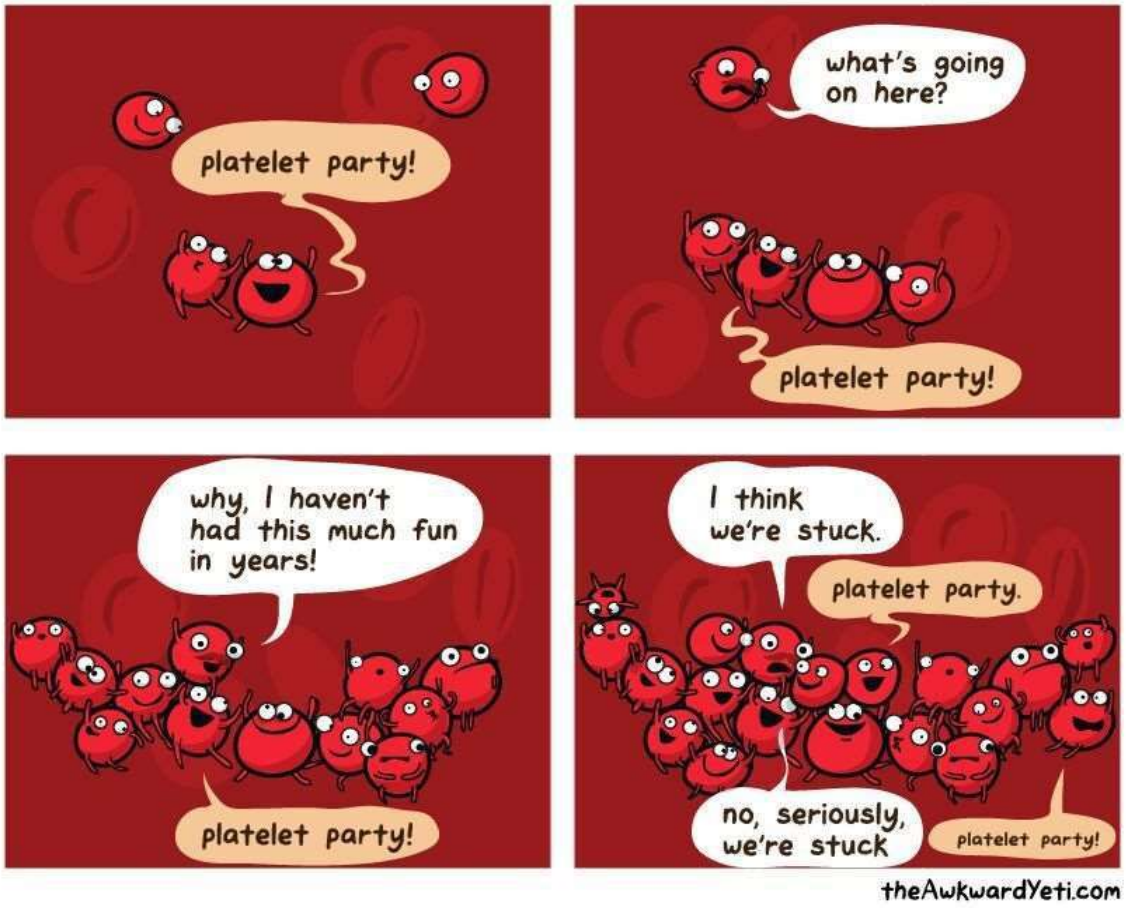


Always used in combination!

Am J Card 2003;91:3-11

Anti-Platelet Therapies in ACS

- Aspirin
- $P2Y_{12}$ Inhibitors
- DAPT (Dual antiplatelet therapy)
- GP 2b/3a Inhibitors



Anti-Platelet Therapy: Aspirin

- Outcome: 23% reduction in mortality
  - ISIS-2: One month of aspirin therapy in 1000 patients with AMI would avert 25 deaths and 10-15 non-fatal cardiac events
- MOA: Inhibition of platelet activation
- Contraindication: Consider clopidogrel if aspirin is contraindicated

2013 STEMI guidelines, 2014 NSTE ACS guidelines

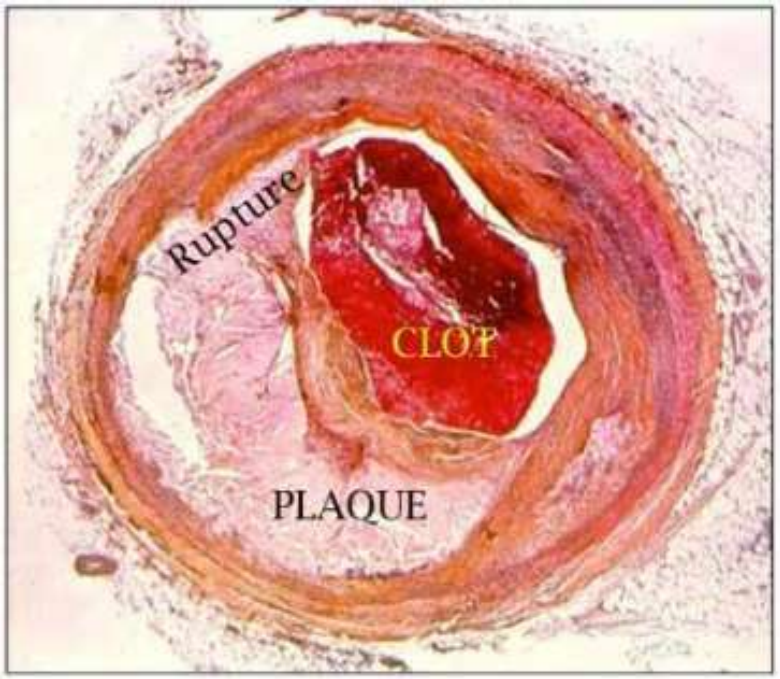
Aspirin Dosing

- Acute dose:
  - 162 - 325 mg non-EC STAT (chew & swallow) if not given prior to admission
- Chronic dose:
  - Post fibrinolytic: 81 mg daily (non-EC)
  - Post PCI/stent: 81 mg daily (non-EC)
  - Post CABG: 81 mg daily (non-EC)
  - High bleeding risk: 81 mg daily (non-EC)
    - Add proton pump inhibitor therapy to prevent GI bleeding

2013 STEMI, 2014 NSTE ACS; *2011 PCI; 2015 CABG guidelines; Xian Y et al. Circ 2016;132:174-181; 2016 DAPT in CAD Focused Update

Dual Antiplatelet Therapy

- **Why is DAPT so important after ACS or PCI?**
  - Both events are powerful activators of platelets and can lead to thrombotic coronary occlusion



$P2Y_{12}$ Receptor Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Administration	Oral	Oral	Oral	IV
Reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active drug	Active drug
Onset of Action	2-8 hours	30 min-4 hr	30 min-4 hr	2 min
Duration of Effect	7-10 days	7-10 days	3-5 days	30-60 min
Withdrawal before major surgery	5 days	7 days	5 days	~ 60 min

2011 ESC NSTEMI/UA guidelines; Franchi F, Angiolillo DJ. Nat Rev Cardiol 2015;12:30-47

Clopidogrel (Plavix®)

- MOA: Inhibition of platelet activation
- Dosing: give in combination with aspirin!
  - PCI (CCS or ACS): 600 mg prior to PCI or within 1 hour of completion, then 75mg daily
  - ACS treated medically: 300mg LD, then 75mg daily
- SE: lower bleeding risk compared to other $P2Y_{12}$ inhibitors
- Note: CABG must be postponed for 5 days if clopidogrel therapy started to minimize bleeding during surgery

2013 STEM; 2014 NSTE ACS; 2011 PCI; 2015 CABG guidelines; 2016 DAPT in CAD

Prasugrel (Effient®)

- Dosing: 60 mg load, 10mg daily in combo w/ASA
- SE: Bleeding risk higher than with clopidogrel
- Patient populations to consider use:
  - DM, ACS (not CCS)
- Patient populations to avoid use:
  - Elderly, body weight < 60kg (use 5mg), and H/O CVA/TIA (contraindicated), renal dysfunction
- Note: CABG must be postponed for 7 days if therapy started to minimize bleeding during surgery

2013 STEMI guidelines; 2014 NSTE ACS guidelines; 2011 PCI guidelines; 2016 DAPT in CAD

Ticagrelor (Brilinta®)

- Dosing: 180 mg load, 90mg BID in combo w/ASA
- Avoid using with ASA doses > 81 mg/day
- SE: Bleeding risk higher than with clopidogrel, dyspnea, bradycardia
- Patient populations to consider use:
  - DM, ACS
  - Also indicated in medically treated ACS
- Patient population to avoid use:
  - Severe bradycardia, renal dysfunction, dyspnea
- Note: CABG must be postponed for 5 days if therapy started to minimize bleeding during surgery

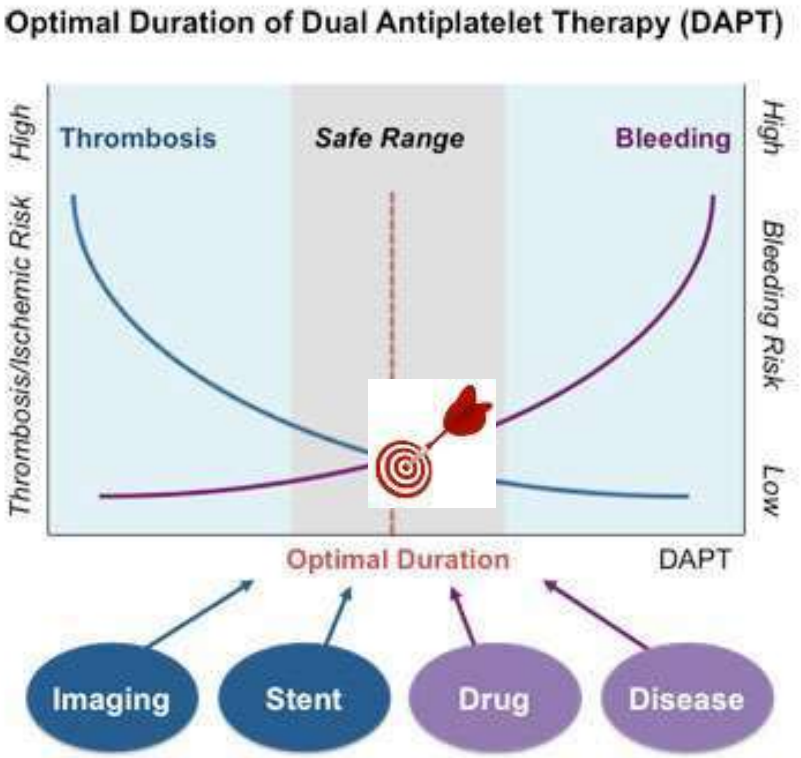
ACC/AHA 2011 PCI guidelines; 2014 NSTE ACS guidelines; 2016 DAPT in CAD

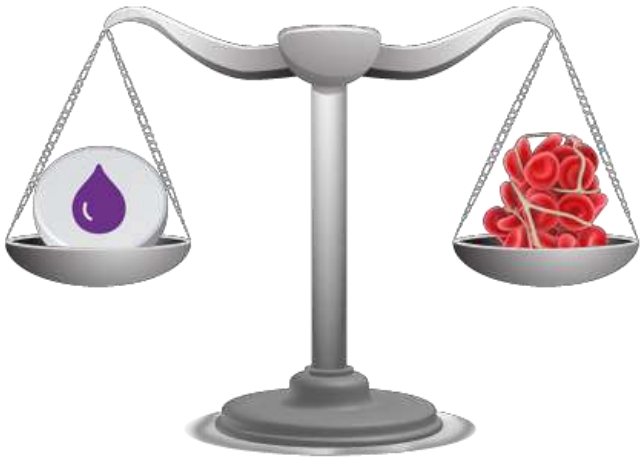
Cangrelor (Kengreal®)

- Indication: use during PCI to reduce risk of peri-procedural MI and stent thrombosis in patients not treated with a $P2Y_{12}$ inhibitor and not receiving a GP 2b/3a inhibitors
- Dose: 30 mcg/kg bolus prior to PCI, followed by 4 mcg/kg/min infusion continued for at least 2 hours or for duration of PCI
- Conversion to oral $P2Y_{12}$ inhibitor: administer oral loading dose immediately after D/C infusion

DAPT Length of Therapy

LOT should be individualized for each patient based on type of CHD, FDA approved indication, invasive treatments used, risk for clotting, and risk for bleeding.





Factors Associated with Increased Ischemic Risk (may favor longer duration DAPT)

- **Increased Ischemic Risk:**
  - Advanced age
  - ACS presentation
  - Multiple prior MI
  - Extensive CAD
  - DM
  - CKD
- **Increased Risk of Stent Thrombosis:**
  - ACS presentation
  - DM
  - LVEF < 40%
  - In-stent restenosis

2016 ACC/AHA DAPT in CAD Focused Update

Factors Associated with Increased Bleeding Risk (may favor shorter duration DAPT)

- H/O prior bleeding
- Oral anticoagulant tx
- Female
- Advanced age
- Low body weight
- CKD
- DM
- Anemia
- Chronic steroid or NSAID tx

Figure 1. Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT

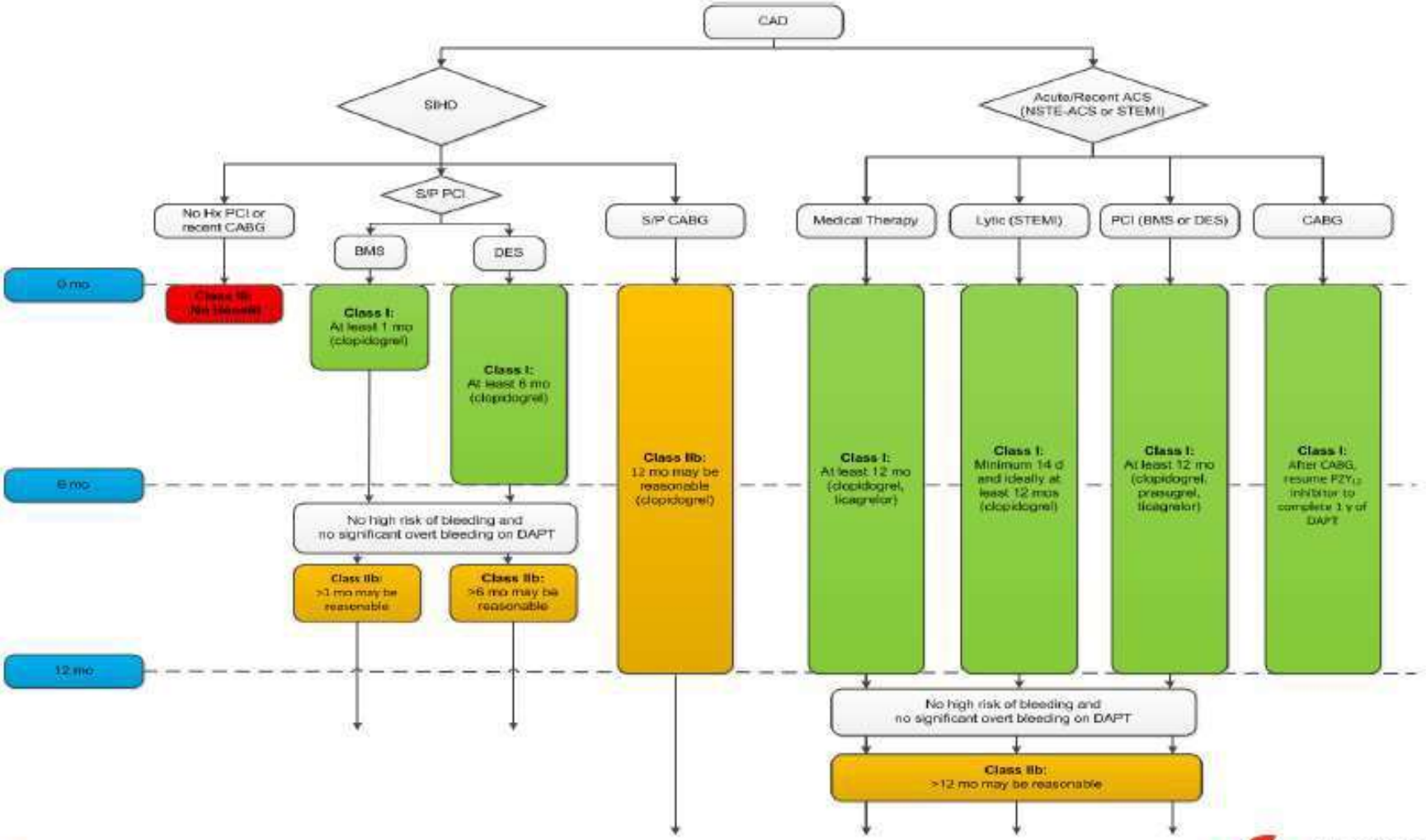


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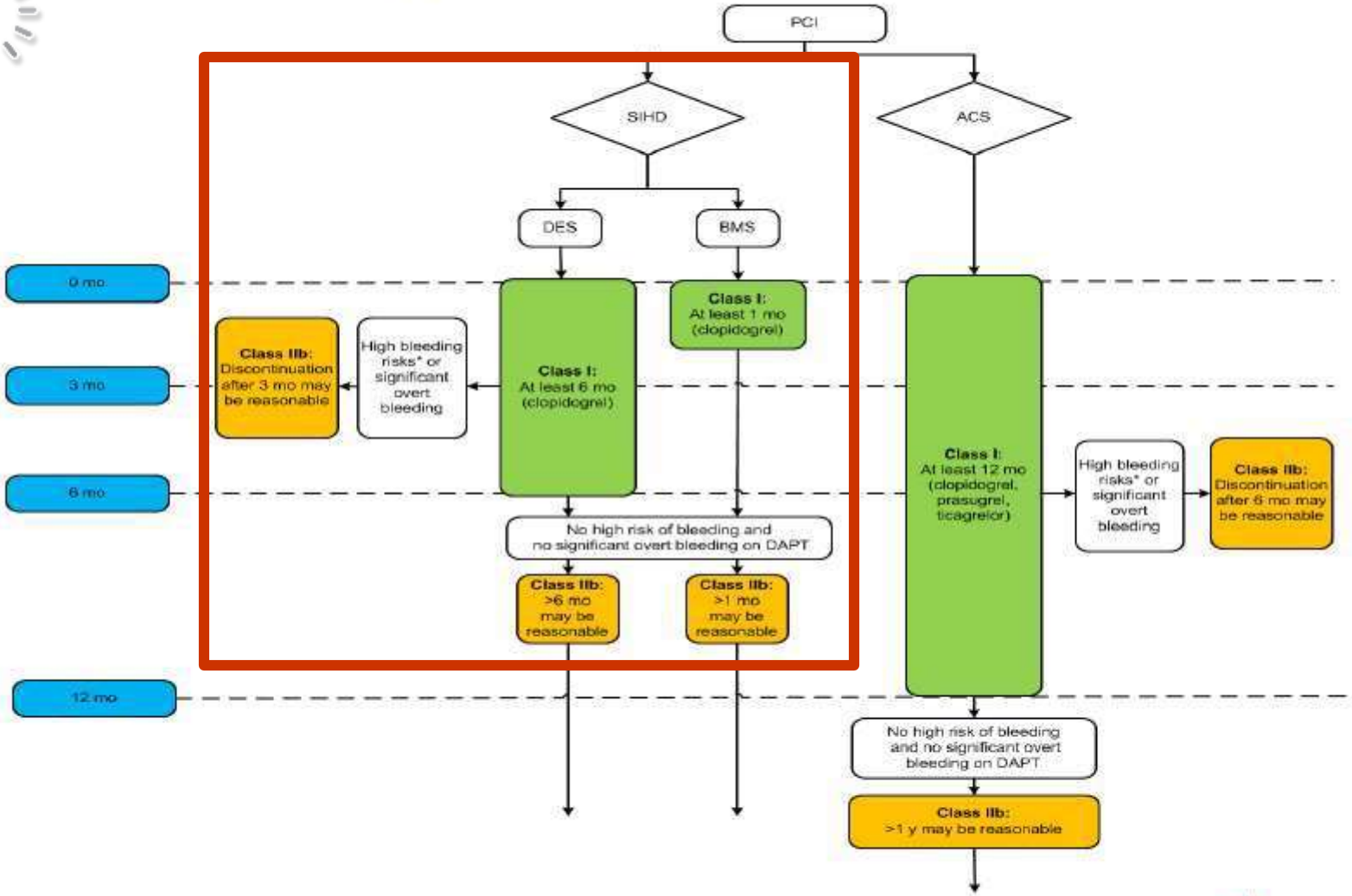
Figure 2. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI



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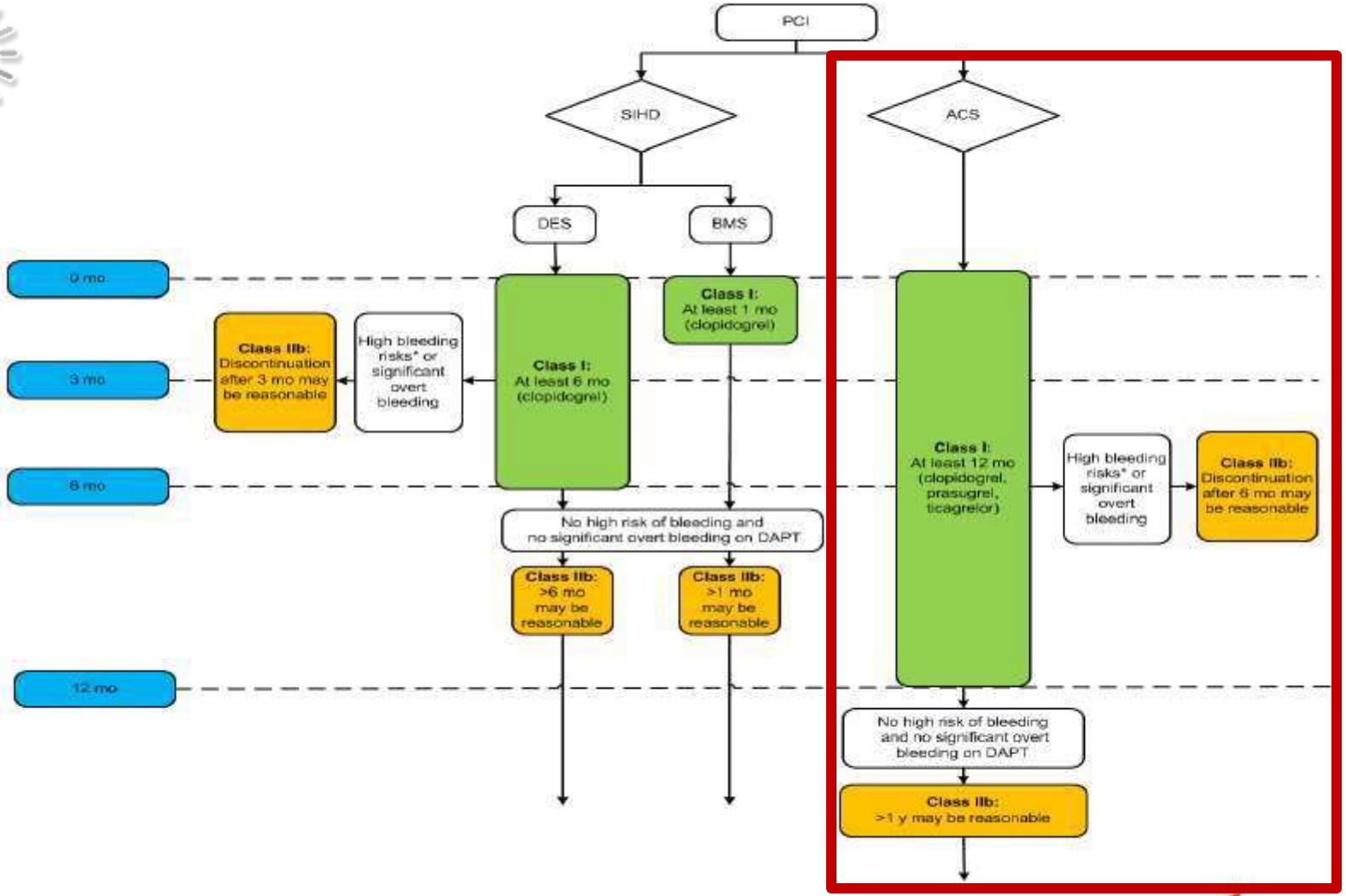
Duration of DAPT in Patients with CCS (SIHD) Treated with PCI

- **BMS: DAPT (C only) for a minimum of 1 month**
  - Reasonable to continue longer if bleeding has not occurred and is not at high risk for bleeding
- **DES: DAPT (C only) for at least 6 months**
  - If patient develops high risk of bleeding (i.e. start oral anticoagulant), at high risk of severe bleeding complication (i.e. undergo major surgery), or develops significant bleeding, stopping $P2Y_{12}$ inhibitor after 3 months is reasonable

2016 ACC/AHA DAPT in CAD Focused Update

Figure 2. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI



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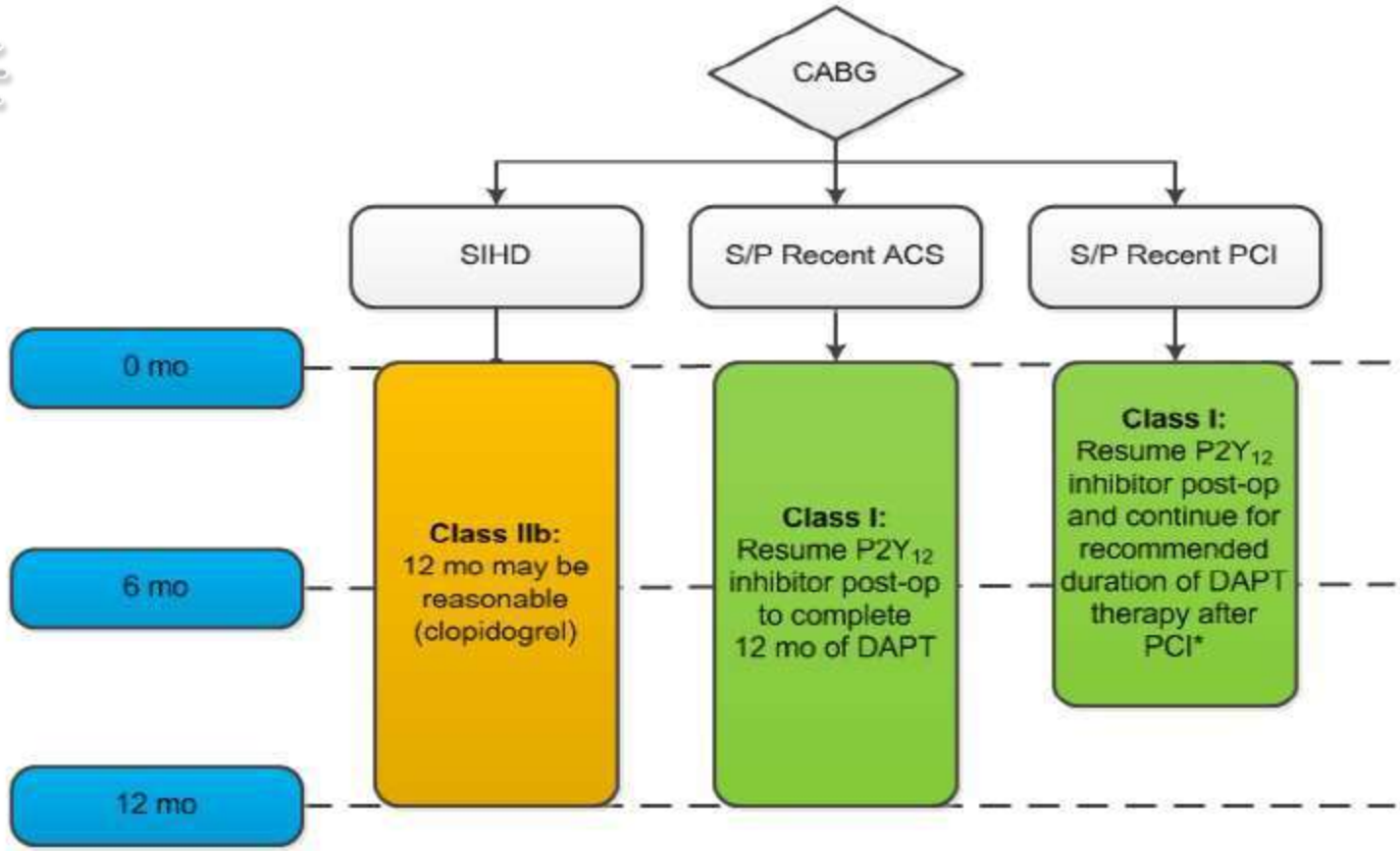
Duration of DAPT in Patients with ACS Treated with PCI

- **BMS/DES: DAPT (C, P, or T) for a minimum of 12 mo.**
  - Reasonable to choose P or T over C
  - If patient develops high risk of bleeding (i.e. start oral anticoagulant), at high risk of severe bleeding complication (i.e. major surgery), or develops significant bleeding, stopping $P2Y_{12}$ inhibitor after 6 months is reasonable

2016 ACC/AHA DAPT in CAD Focused Update

Figure 3. Treatment Algorithm for Management and Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Undergoing CABG



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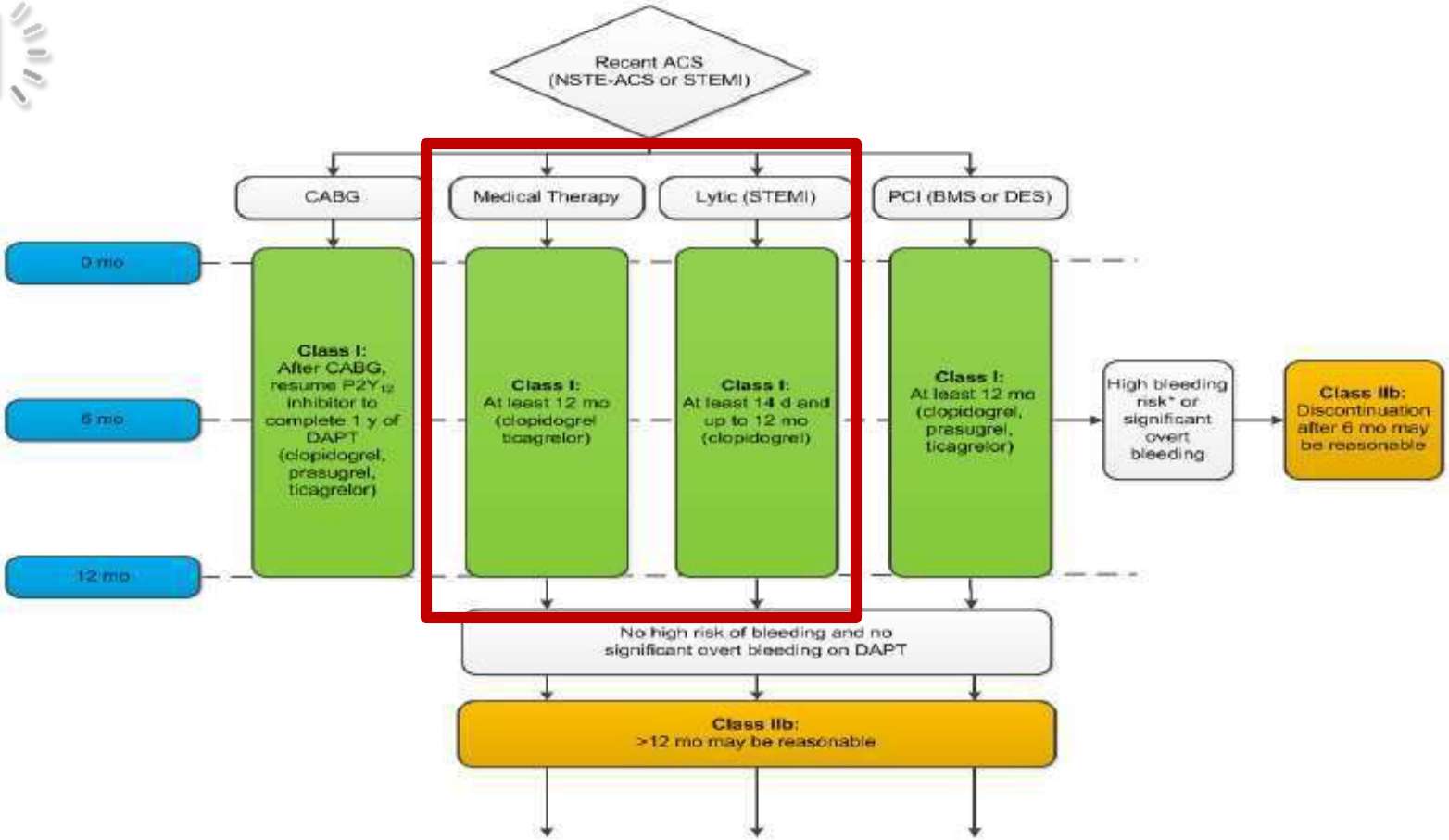
Duration of DAPT in Patients with CHD (CCS/ACS) Treated w/CABG

- Recent stent placement: resume $P2Y_{12}$ inhibitor therapy post-op and continue until recommended LOT reached
- Recent ACS: resume $P2Y_{12}$ inhibitor post-op to complete 12 months
- CCS (SIHD): 12 months DAPT (C only) is reasonable to improve vein graft patency

2016 ACC/AHA DAPT in CAD Focused Update

Figure 5. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patient With Recent ACS (NSTE-ACS or STEMI)



NSTE-ACS = NSTEMI and Unstable Angina

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Duration of DAPT in ACS

- Medically treated: DAPT (C or T) for at least 12 months
  - Reasonable to use ticagrelor over clopidogrel
  - Reasonable to continue longer if bleeding has not occurred

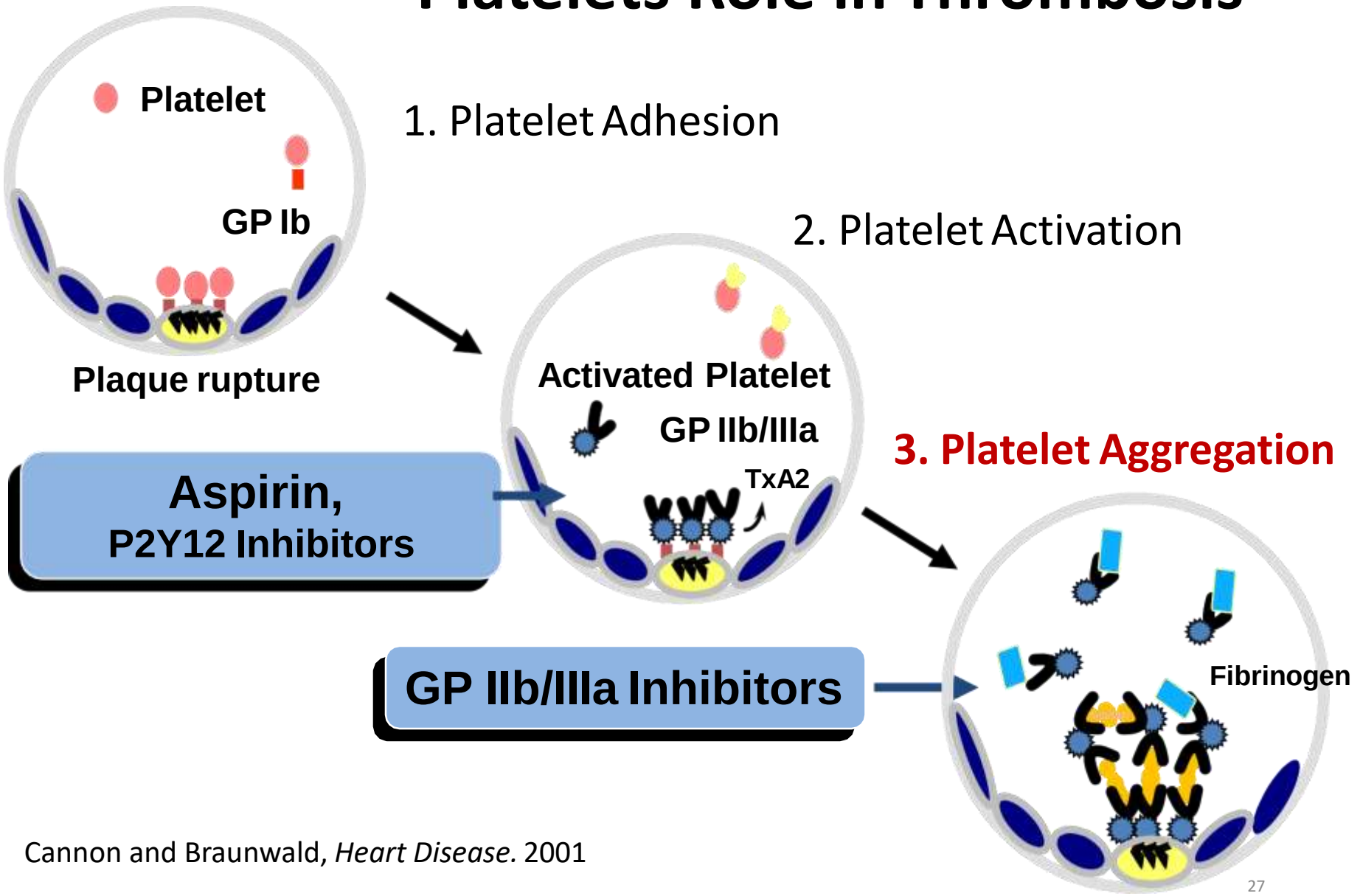
- STEMI treated w/fibrinolytics and no PCI: clopidogrel should be continued for minimum of 14 days, ideally at least 12 mo.

2016 ACC/AHA DAPT in CAD Focused Update

DAPT LOT Summary

Minimum Length of DAPT	Indications/Patient Populations and $P2Y_{12}$ Inhibitor
1 month	
3 months	
6 months	
12 months	

Platelets Role in Thrombosis



Cannon and Braunwald, *Heart Disease.* 2001

Comparison of GP IIb/IIIa Inhibitors

	Abciximab (Reopro)	Eptifibatide (Integrilin)	Tirofiban (Aggrastat)
Type	Chimeric Fab antibody fragment	Cyclic heptapeptide	Nonpeptide
GP IIb/IIIa specificity	No	Yes	Yes
Elimination half-life	30 min (unbound)	2.5 hours	2 hours
Dosage reduction for renal dysfunction	No	Yes CrCl < 50 ml/min or SCr > 2	Yes CrCl < 30 ml/min
Platelet fxn	Days (up to 15)	4-8 hours	4-8 hours

Anti-Platelet Therapy: Glycoprotein IIb/IIIa Inhibitors

- Outcome: ~20% decrease in early (and late) risk of death, MI, and urgent revascularization when used with PCI
- Dosing: time of initiation depends on indication
  - Before PCI (upstream): consider for high risk NSTE ACS patients
  - During PCI: consider for all patients (ACS, SIHD)
- MOA: Block platelet aggregation
- SE: Bleeding, thrombocytopenia, antibody formation (abciximab)
- Adjunct therapies: aspirin, UFH (LMWH), and $P2Y_{12}$ inhibitor

2011 NSTEMI/UA guideline update; 2011 PCI guidelines; 2013 STEMI guidelines

Anti-Platelet Therapy: Glycoprotein IIb/IIIa Inhibitors

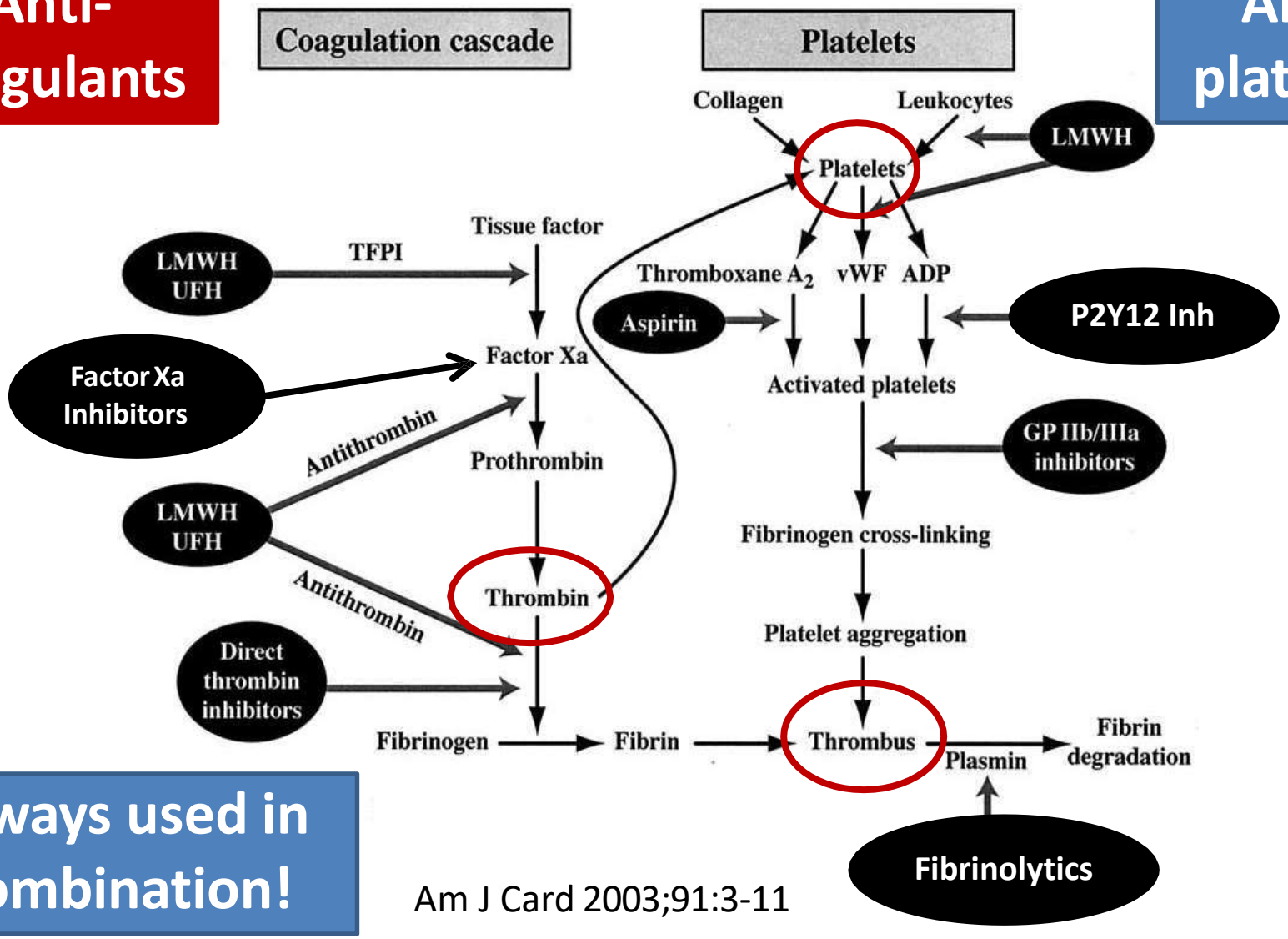
- Due to higher bleeding risk and the development of $P2Y_{12}$ inhibitors, GP 2b/3a inhibitor use is low.
- GP 2b/3a inhibitors are reserved for patients who fail traditional antiplatelet/ antithrombotic therapies during PCI.

2011 NSTEMI/UA guideline update; 2011 PCI guidelines; 2013 STEMI guidelines

Anti-thrombotic Therapies

Anti-coagulants

Anti-platelets



Always used in combination!

Am J Card 2003;91:3-11

Anti-Coagulants in ACS

- UFH
- Enoxaparin
- Fondaparinux
- Bivalirudin
- Warfarin
- DOACs

Unfractionated Heparin

- MOA: inhibition of thrombin (factor IIa) and platelet activation
- Dosing:
  - 60 units/kg bolus (max 4000 units), then 12 units/kg/hr (max 1000 units/hr), maintain aPTT 1.5-2 x control (50-70 sec)
    - Rebolus in cath lab based on ACT values:
      - Dose 70-100 units/kg
      - Target ACT values 250-350 sec
  - Continue for 48 hours or until after PCI performed
  - If therapy required >48 hours, convert to LMWH to decrease risk for HIT

2013 STEMI guidelines; 2014 NSTE ACS guidelines; 2011 PCI guidelines

Enoxaparin

- MOA: anti-Xa activity (some anti-IIa activity)
- Indication: alternative to UFH in patients undergoing revascularization (PCI, fibrinolytic)
- Side effects: Higher bleeding rate than UFH
- Monitoring: unable to measure ACT values in cath lab to assess degree of anticoagulation
- Dosing:
  - Enoxaparin 1 mg/kg SQ BID
    - CrCl< 30ml/min: 1 mg/kg SQ qday
    - Loading dose of 30mg IV in select patients
  - Continue through hospitalization or until after PCI performed

2013 STEMI guidelines; 2014 NSTE ACS guidelines

Bivalirudin

- MOA: binds reversibly to thrombin (DTI)
- Indication: Alternative to UFH for ACS, during PCI, or patients with HIT (or suspected HIT)
- Dose:
  - 0.75 mg/kg IV bolus, 1.75 mg/kg/hr infusion, and stop a completion of PCI (may be continued up to 4 hours post)
  - CrCl < 30 ml/min: decrease infusion rate to 1mg/kg/hr
- SE: Bleeding (though less than other therapies)

JAMA 2003;289:853-63; 2014 NSTE ACS guidelines

Fondaparinux (Arixtra)

- MOA: anti-Xa activity (no anti-IIa activity)
- Indication: alternative to UFH/LMWH in patients requiring revascularization (PCI, fibrinolytic); patients with thrombosis due to HIT
- Dose: 2.5 mg SQ qday
  - Administer only if SCr <3 (CrCl > 30ml/min)
  - Continue until PCI started
    - **Another anticoagulant with anti-IIa must be used during PCI**

ACC/AHA 2013 STEMI, 2014 NSTE ACS guidelines

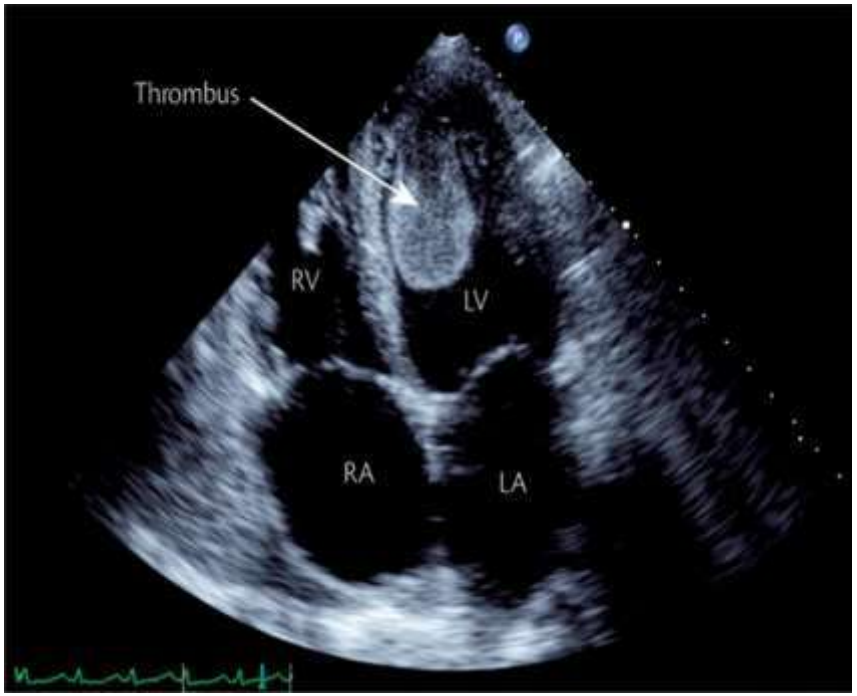
ACC/AHA Recommendations for Anti-coagulation Therapy and PCI

- For UFH: Continue through PCI then discontinue
- For bivalirudin: Continue through PCI then D/C (may stop when bag is empty or 4 hrs after PCI)
- For enoxaparin:
  - If last dose < 8 hours prior to PCI, no further dose needed
  - If last dose 8-12 hours prior to PCI, give 0.3 mg/kg IV bolus
- For fondaparinux: Because of risk for radial or femoral catheter thrombosis, fondaparinux should not be used as sole anti-coagulant during PCI

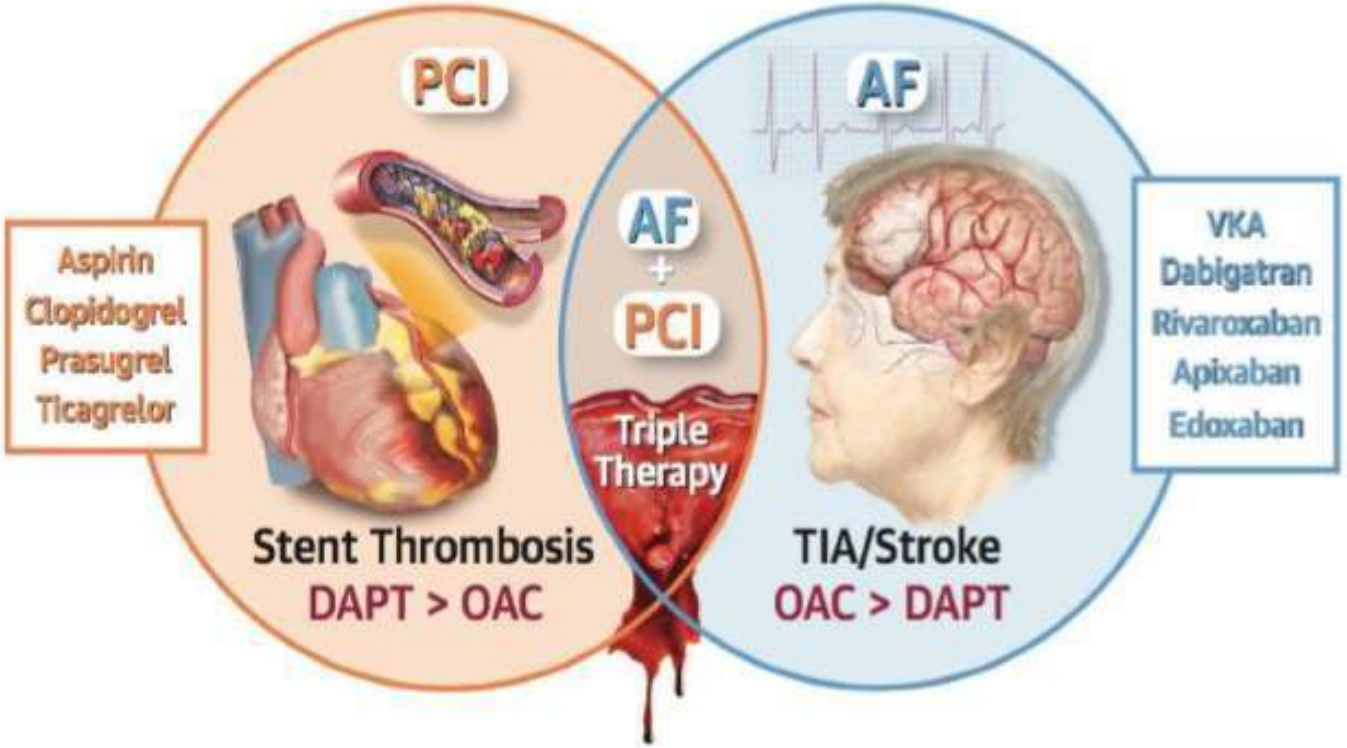
ACC/AHA 2014 NSTE ACS; 2013 STEMI guidelines; 2011 PCI guidelines

Anti-Coagulant Therapy: Warfarin (and DOACs) in ACS

- Not indicated for long term therapy unless a compelling indication present:
  - Atrial fibrillation (DOAC)
  - VTE
  - LV thrombus (warfarin)
  - Prior mechanical valve replacement

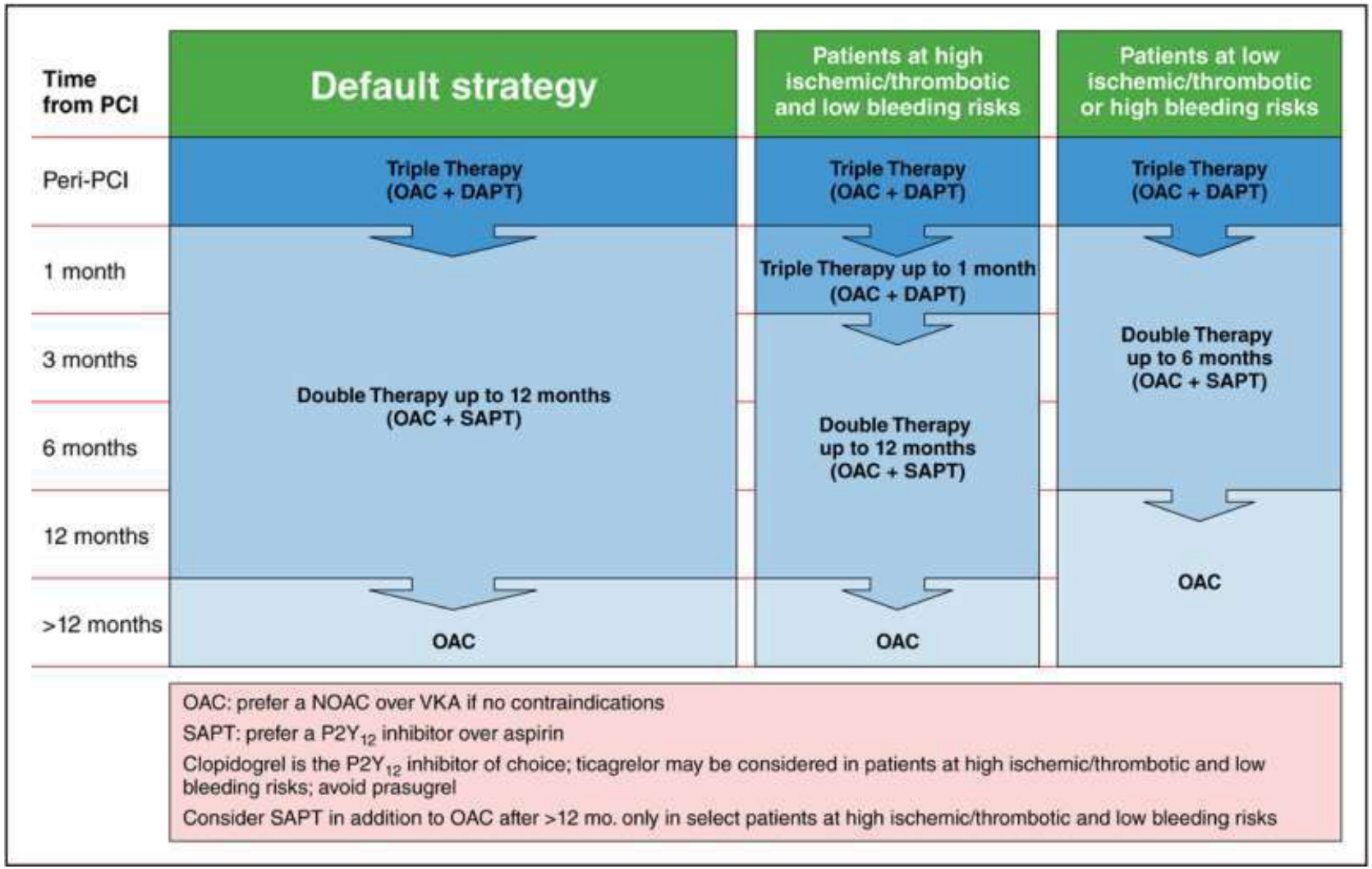


Triple Therapy vs Triple Threat



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

Management of Antiplatelet Therapy in <u>Patients with Afib Undergoing PCI</u> Treated with OAC - 2018 Expert Consensus



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

Anti-Thrombotics Summary: PCI Therapies

	Pre-PCI
1. Antiplatelet: Non-EC aspirin in combination with **second** anti-platelet drug:	Yes
a) $P2Y_{12}$ inhibitor (oral or IV)	Yes* (crushed tabs?)
2. Anticoagulant: UFH or LMWH or DTI	Yes

*** Oral loading dose may be held until CABG ruled out**

Anti-Thrombotics Summary: PCI Therapies

	During PCI
1. Antiplatelet: Non-EC aspirin in combination with second anti-platelet drug:	No- already given pre-PCI
a) $P2Y_{12}$ inhibitor	IV- continued Oral (crushed?) - Yes*
2. Anticoagulant: UFH or LMWH or DTI	Continued

*** Oral loading dose should be given within 1 hour of PCI if not given pre-PCI**

Anti-Thrombotics Summary: PCI Therapies

	Post-PCI
1. Antiplatelet: Non-EC aspirin in combination with second anti-platelet drug	Yes, life long
a) $P2Y_{12}$ inhibitor (oral only)	**Yes**, LOT depends on SIHD (CCS) vs ACS and procedure
2. Anticoagulant: UFH or LMWH or DTI	**No**, unless indicated for other conditions (i.e. LV thrombus, Afib)

Thank-you!