

Dual Antiplatelet Therapy Made Practical

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Presenter Disclosure Information

Financial Disclosure: I do not have a financial relationships with any commercial entity which may represent, in perception or reality, a conflict of interest in the context of this presentation

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Objectives

- Identify patient characteristics that would lead you to select one antiplatelet agent over another as part of dual antiplatelet therapy (DAPT)
- Based on available data select an appropriate duration of DAPT
- Recommend a reasonable approach to DAPT in patients receiving oral anticoagulation



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Audience Response Question

A 64 year old male patient with new onset chest pressure and nausea presented to ER and was found to have NSTEMI which was treated 3 days ago with an everolimus drug eluting stent

- Medications on discharge include metoprolol tartrate 100mg twice daily, lisinopril 20mg once daily, atorvastatin 80mg once daily, clopidogrel 75mg once daily, aspirin 325mg once daily, ranitidine 150mg once daily

Do you agree with aspirin dose?

- A. Yes
- B. No



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2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

Updated six guidelines:

- *2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery*
- *2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention*
- *2012 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease*
- *2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction*
- *2014 ACC/AHA Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes*
- *2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery*

J Am Coll Cardiol. 2016; doi:10.1016/j.jacc.2016.03.513



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Aspirin Dosing in Patients Treated With DAPT

- Studies of nearly 200,000 patients have consistently shown that lower doses of aspirin (≤ 100 mg daily) are associated with less major bleeding and total bleeding than higher doses as monotherapy or with clopidogrel
- Studies comparing lower (75-150mg daily) with higher aspirin doses have consistently found comparable ischemic events with either dose as monotherapy or with clopidogrel
- Efficacy of ticagrelor appears decreased in patients treated with higher (≥ 300 mg daily) versus lower (≤ 100 mg daily)

COR	LOE	Recommendation
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.



P2Y₁₂ Inhibitor Selection as Part of DAPT

- Requires fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk
- Decisions regarding treatment with and duration of DAPT require a thoughtful assessment of the benefit/risk ratio, integration of study data, and patient preference



Factors Associated with Increased Ischemic Risk

- Increased ischemic risk
 - Advanced age
 - ACS presentation
 - Prior MIs
 - Extensive CAD
 - Diabetes
 - CKD
- Increased risk of stent thrombosis
 - ACS presentation
 - Diabetes
 - LVEF < 40%
 - First generation DES
 - Stent undersizing or deployment
 - Small stent diameter or greater length
 - Bifurcation stents
 - In-stent restenosis



Factors Associated with Increased Bleeding Risk

- History of prior bleeding
- Oral anticoagulant therapy
- Female sex
- Advanced age
- Low body weight
- CKD
- Diabetes
- Anemia
- Chronic steroids or NSAID therapy

J Am Coll Cardiol. 2016; doi:10.1016/j.jacc.2016.03.513



Prasugrel Considerations

- Examined in ACS patients planned for PCI
 - Therapy started AFTER coronary anatomy known
- Compared to clopidogrel, prasugrel over a median of 15 months
 - Reduced nonfatal MI (NNT 46) and probable or definite stent thrombosis (NNT 77)
 - Increased TIMI major (NNH 167) and life-threatening (NNT 200) bleeding
- Negative benefit:risk profile in patients with prior stroke/TIA (contraindicated)
- Questionable risk/benefit profile in patients aged > 75 years OR weight < 60 kg
- Used clopidogrel 300mg loading dose

N Engl J Med 2007;357:2001-15



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Ticagrelor Considerations

- Reduced wide composite of CV events including death compared to clopidogrel in ACS patients with or without PCI (NNT 53) and definite stent thrombosis (NNT 166)
- Cost of non-CABG major bleeding (NNH 143)
- Dyspnea a non-bleeding side effect (NNH 16 with NNH requiring discontinuation of 125)
- Exclusions included strong CYP3A4 mediators and those at risk for bradycardia
- Benefit seen with aspirin dose $\leq 100\text{mg/day}$

N Engl J Med 2009; 361:1045-1057



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Clopidogrel Considerations

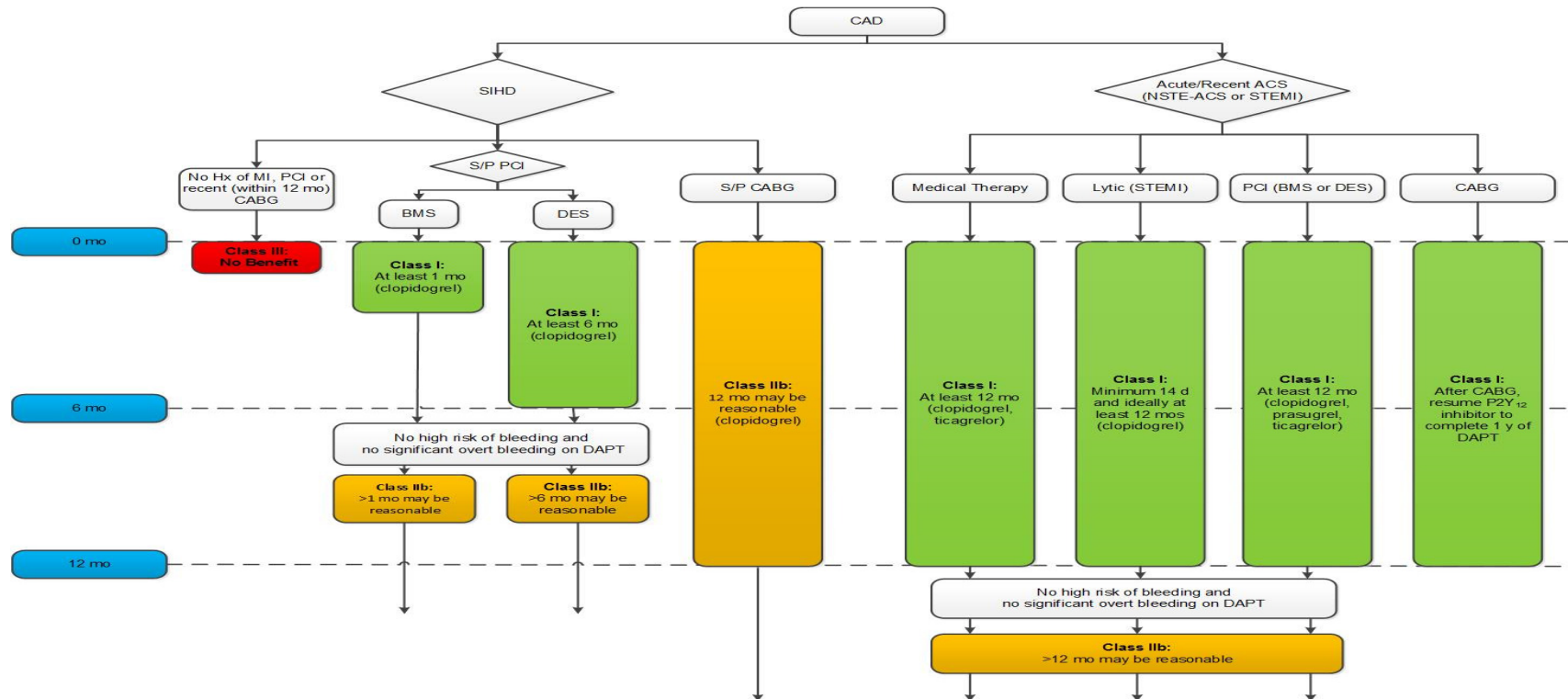
Only P2Y₁₂ inhibitor with beneficial evidence in:

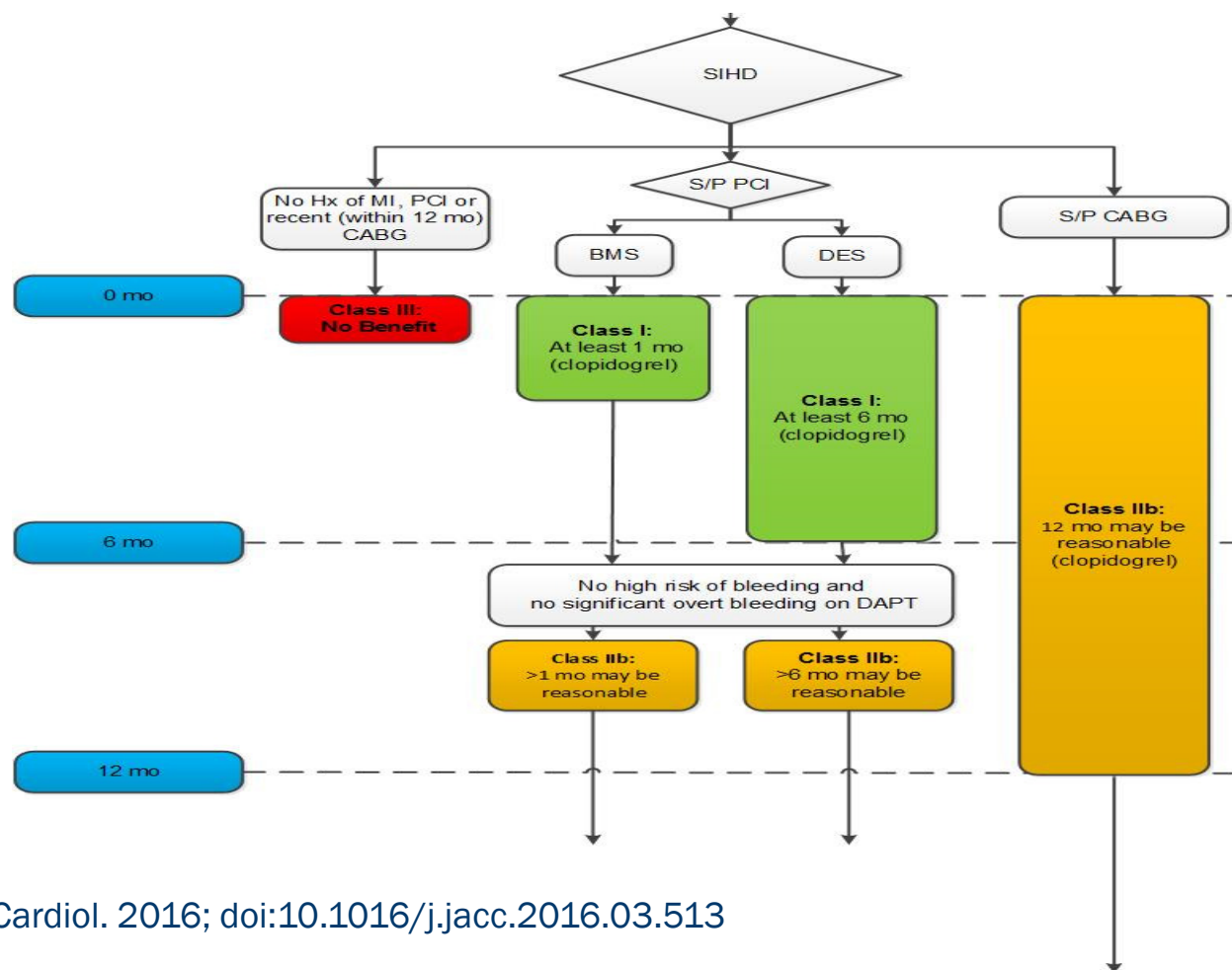
- Non-ACS stenting
- Secondary stroke prevention
- True aspirin allergy
- Non-cardiac stents
- Transcatheter aortic valve replacement



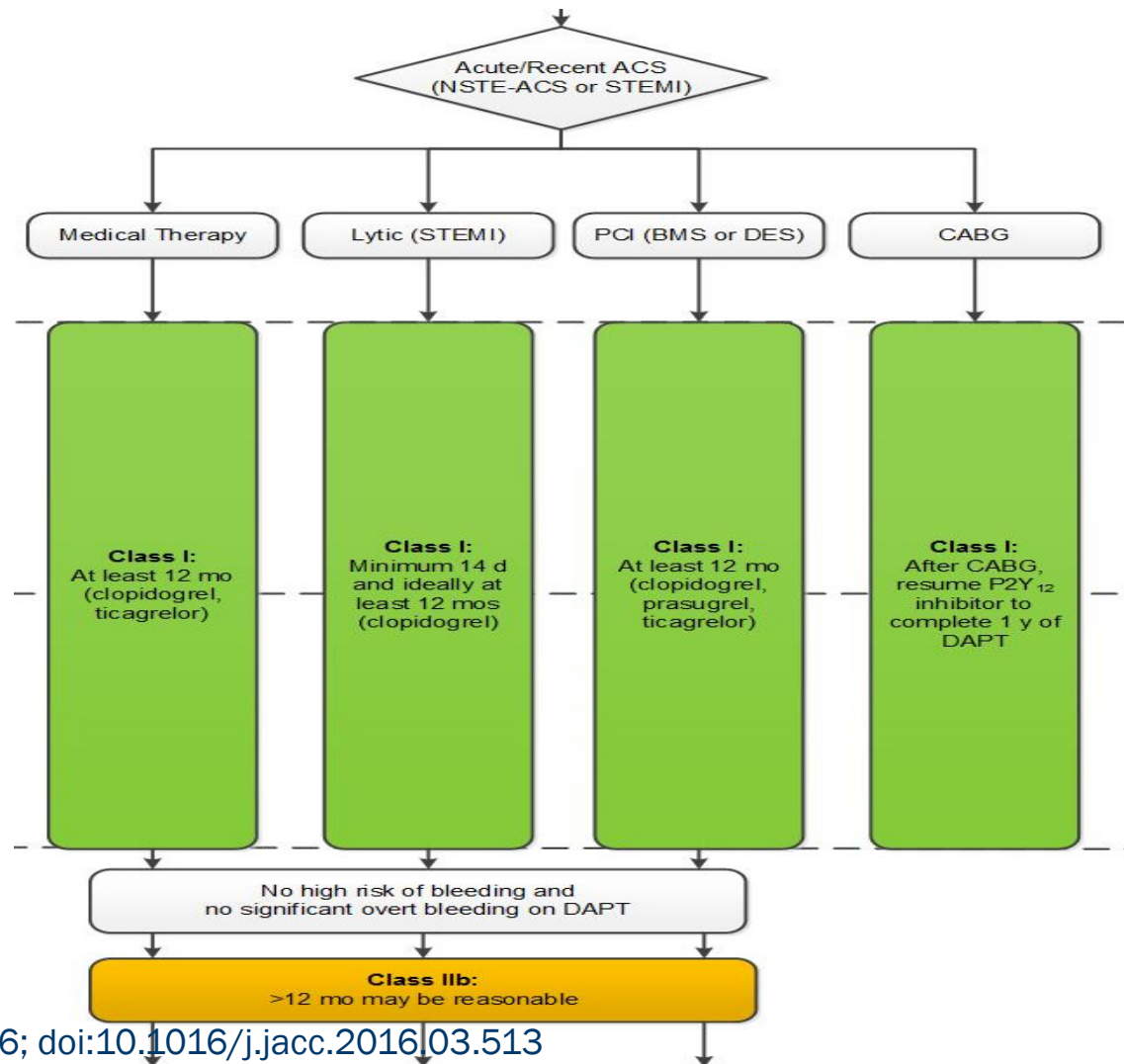
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Master Treatment Algorithm for Duration of P2Y₁₂ Inhibitor Therapy in Patients With CAD Treated With DAPT





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Selection of Specific P2Y₁₂ Inhibitors in NSTEMI-ACS or STEMI

COR	LOE	Recommendations
Ia	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTEMI-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy.
Ia	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy.
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA.

Duration of DAPT in Patients With SIHD Treated With PCI

COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month.
I	B-R ^{SR}	In patients with SIHD treated with DAPT after DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months.
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.

SR indicates systematic review.

Duration of DAPT in Patients With SIHD Treated With PCI

COR	LOE	Recommendations
IIb	A ^{SR}	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable.
IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 3 months may be reasonable.

SR indicates systematic review.

Duration of DAPT in Patients With ACS Treated With PCI

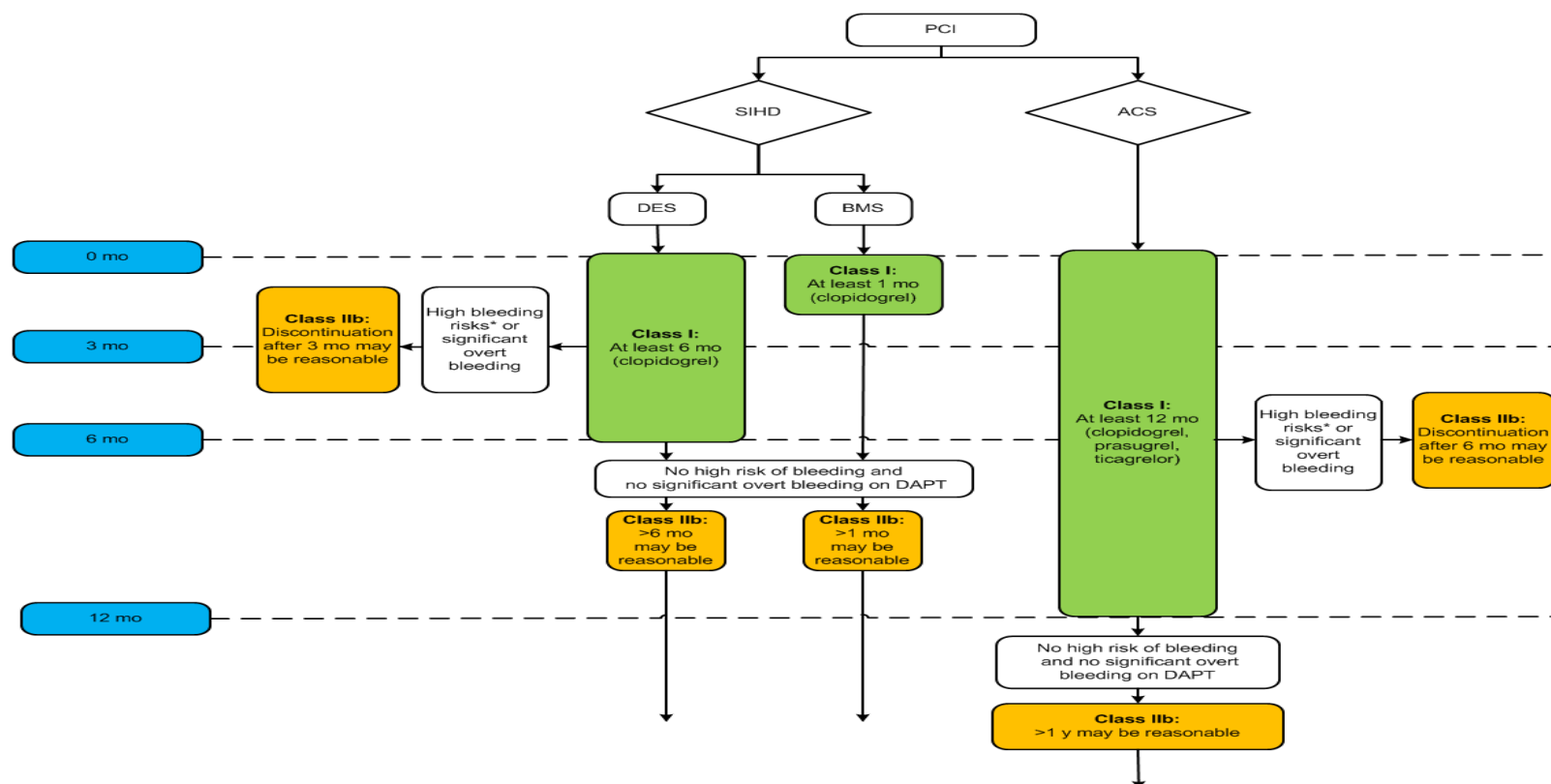
COR	LOE	Recommendations
I	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy.
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy.

Duration of DAPT in Patients With ACS Treated With PCI

COR	LOE	Recommendations
IIb	A ^{SR}	In patients with ACS (NSTEMI-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable .
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 6 months may be reasonable.
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA.

SR indicates systematic review.

Treatment Algorithm for Duration of P2Y₁₂ Inhibitor Therapy in Patients Treated With PCI



The DAPT Score

- DAPT data used to create numerical score for balancing risks of ischemic events, bleeding
 - Multivariable models to predict the composite of MI or stent thrombosis (ischemia model) and GUSTO moderate/severe bleeding (bleeding model) over time
 - Older age exclusively predicted increased bleeding risk while exclusive predictors of increased ischemic events included history of PCI or MI, stent diameter < 3 mm, chronic heart failure or LVEF < 30%, and MI at presentation
 - Further prospective evaluation required and validation in other cohorts



The DAPT Score

- The DAPT Score ranges from -2 to 10 and is made up of the following factors:
 - Age
 - Diabetes status
 - Smoking status
 - PCI or MI history
 - Presence of chronic heart failure or LVEF < 30%
 - Index procedural characteristics: MI at presentation, vein-graft PCI, stent diameter < 3mm, paclitaxel-eluting stent
- Among those receiving extended DAPT vs. placebo, patients with scores of less than 2 had a higher incidence of bleeding ($P < .001$), while those with scores of ≥ 2 had lower incidences of both combined ischemic events and death, MI, or stroke ($P < .001$ for both)
- http://www.daptstudy.org/for-clinicians/score_calculator.htm



The DAPT Score

DAPT Score Calculator

Patient Characteristics

Age

Diabetes Mellitus ☒

Cigarette Smoking Within Last Two Years ☐

Prior Myocardial Infarction or Percutaneous Coronary Intervention ☒

History of Congestive Heart Failure or Left Ventricular Ejection Fraction < 30% ☐

Index Procedure Characteristics

Myocardial Infarction at Presentation ☒

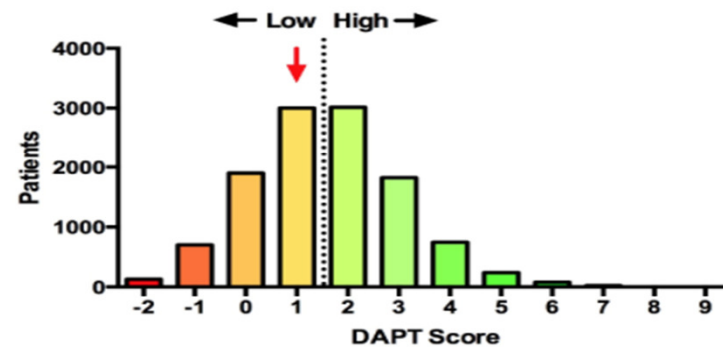
Stenting of Vein of Graft ☐

Stent Diameter < 3mm ☐

DAPT Score = 1: LOW

Calculated DAPT Score Shown by Red Arrow

Distribution of DAPT Scores in the DAPT Study



Results Observed in the DAPT Study for Patients with Low (<2) DAPT Scores Are Shown:

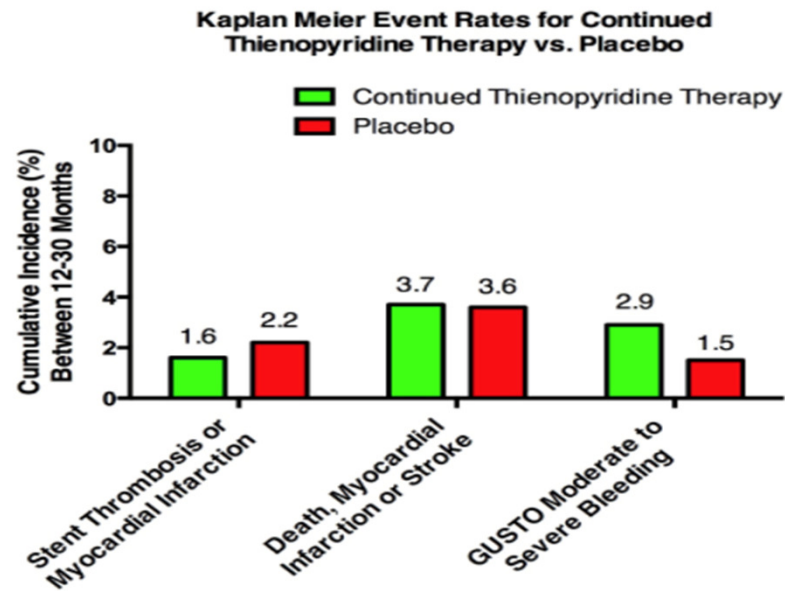
http://www.daptstudy.org/for-clinicians/score_calculator.htm



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The DAPT Score

Results Observed in the DAPT Study for Patients with Low (<2) DAPT Scores Are Shown:



http://www.daptstudy.org/for-clinicians/score_calculator.htm



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Combination Antithrombotic Therapy

- 20-30% of patients with indications for anticoagulation have ischemic heart disease that requires PCI
- Anticoagulant and antiplatelet combination therapy is associated with 4-16% risk of fatal and non-fatal bleeding
 - ~50% 6 month mortality in patients who have bled
- Atrial fibrillation patients with PCI may be at higher risk of stent thrombosis or thromboembolism if not on DAPT and oral anticoagulation respectively

The Lancet 2013;381:1107-15
CHEST 2012;141:e531S-75S
Thromb Haemost 2011;106:572-84

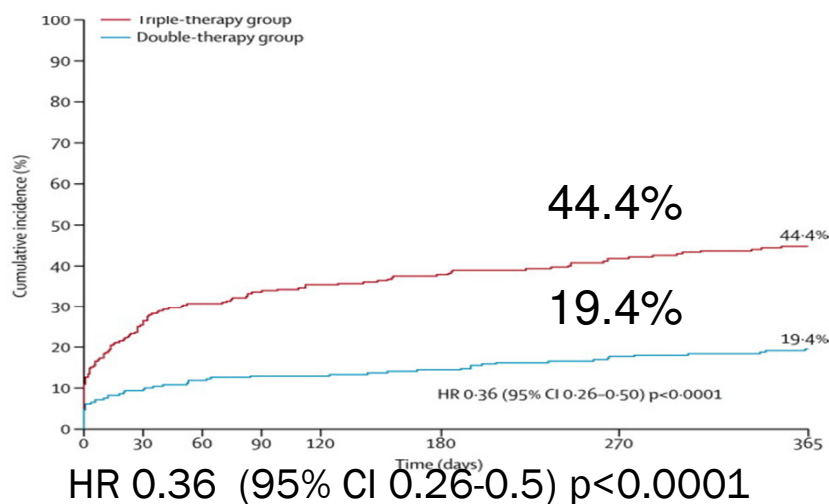


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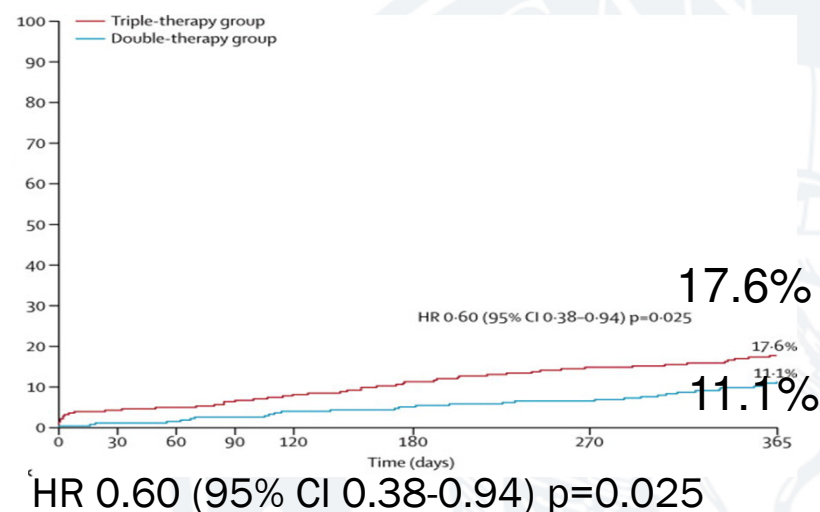
Combination Antithrombotic Therapy in NVAF and PCI: Less is More?

VKA + clopidogrel/ASA vs. VKA + clopidogrel (n = 573)

Primary Endpoint: Any Bleeding



Secondary Endpoint: Death, MI, stroke, TVR, ST



The Lancet 2013;381:1107-15

Combination Antithrombotic Therapy: Guideline Recommendations

- **AHA/ACCF STEMI Guideline 2013**
 - Anticoagulation with warfarin if Afib with CHADS₂ score of ≥ 2 , mechanical valve, VTE or hypercoagulable disorder (1, Level C)
 - Duration triple therapy should be minimized to extent possible (1, Level C)
 - Lower INR of 2-2.5 might be considered if on DAPT (IIb, Level C)
- **AHA/ACC NSTEMI ACS Guideline 2014**
 - Shorter duration of triple therapy are favored when possible
 - INR target of 2-2.5 has been recommended, but not proven to be safer
 - WOEST Trial findings require confirmation
 - Little information with prasugrel, ticagrelor or DOACs as part of combination therapy
- **AHA/ACC/HRS Atrial Fibrillation Guideline 2014**
 - Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA₂DS₂VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (IIb, Level B)



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Combination Antithrombotic Therapy: Summary and Synthesis of Recommendations

- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA₂DS₂-VASc, HAS-BLED)
- Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
- Consider a target INR of 2.0–2.5 when warfarin is used
- Clopidogrel is the P2Y₁₂ inhibitor of choice
- Use low-dose (≤ 100 mg daily) aspirin
- PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding



Summary

- Selection of oral thienopyridine must consider indication, if ACS whether invasive strategy, patient characteristics (i.e. history of TIA/stroke, weight) and timing/dose of loading dose
- While extended (beyond 1 year) DAPT reduces MACE post coronary stenting or MI it also increases risk of bleeding. Patients should be carefully selected for extended DAPT
- Triple antithrombotic therapy (NVAf with ACS/PCI) should be carefully implemented for as short of duration as determined acceptable. Little information with prasugrel, ticagrelor or DOACs as part of combination therapy



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