

CHAPTER 4

Antiplatelet Strategies in Percutaneous Coronary Interventions: Selection, Duration and Considerations

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1. Introduction

Antiplatelet agents are a central component of therapy in the management of patients undergoing percutaneous coronary interventions (PCI). Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor has been the cornerstone of treatment in both the peri-procedural and post-stent time periods in the efforts to reduce stent thrombosis. Increased potency of anti-platelet agents has expanded the options for therapy in PCI while guidelines regarding optimal DAPT duration have undergone considerable evolution. Improved stent design has significantly reduced the incidence of stent thrombosis leading to a reduction in the necessary duration of dual antiplatelet therapy. Indications for extending DAPT duration have expanded to long-term secondary prevention of atherothrombosis beyond stented lesions in selected high-risk patients, at the expense of higher rates of bleeding. The range of options for antiplatelet therapy in PCI necessitates that clinicians be comfortable with current knowledge on available drugs and strategies for use. This chapter will review the optimal approach in selecting antiplatelet agents, timing of administration, and methods to identify optimal duration of use for individual patients.

2. Antiplatelet Selection

Aspirin

Mechanism of action: Irreversible inactivation of cyclooxygenase (COX) enzymes, leading to the decrease in the production of thromboxane-2, a key mediator of platelet aggregation.

Role in PCI: The mainstay of antiplatelet therapy in PCI, aspirin provides significant reductions in cardiovascular events in the setting of secondary prevention of atherothrombosis.

Dose: Aspirin is provided as an oral loading dose of 162-325 mg prior to PCI. Maintenance low dose (75-100 mg) aspirin provides similar reductions in long term cardiovascular morbidity as compared to the high dose, while reducing the rates of bleeding.

Caution: The risk of gastrointestinal bleeding is increased with the use of aspirin especially when used in DAPT.

P2Y12 inhibitors

The P2Y12 receptor is the predominant G-coupled protein that interacts with Adenosine diphosphate (ADP). This interaction activates the GP IIb/IIIa receptor resulting in the stimulation of platelet aggregation. The addition of a P2Y12 inhibitor to aspirin reduces the risk of stent thrombosis after PCI and provides long-term secondary prevention of ischemia related to acute coronary syndromes. Each of the drugs in this class of antiplatelet has unique properties in its P2Y12 blockade, lending them to be preferred in specific populations/clinical scenarios (**Figure 1**).

Clopidogrel

Role in PCI: Clopidogrel, a thienopyridine, is converted to its active metabolite via CYP enzyme. In addition to reducing the risk of stent thrombosis, long term benefit in acute coronary syndrome (ACS) was seen in the PCI-CURE (sub-study of the CURE trial) where the addition of clopidogrel to ASA in patients undergoing PCI provided a reduction in cardiovascular death, non-fatal MI and stroke over a mean follow-up of 8 months compared to placebo.¹ While the development of more

potent P2Y₁₂ inhibitors may be preferred for the initial treatment of ACS, clopidogrel continues to play a role in initial and maintenance therapy in stable ischemic heart disease (SIHD) as well as in ACS for patients with elevated bleeding risk.

Dose: The loading dose of clopidogrel in the CURE trial was 300 mg followed by 75 mg daily.² However, a higher loading dose of 600 mg provides more rapid time to maximum platelet inhibition. Subsequent trials evaluating loading and maintenance strategies for clopidogrel in PCI (ARMYDA-2 and CURRENT-OASIS 7) have showed improved ischemic outcomes including a reduction in stent thrombosis on the higher loading dose of 600 mg. While rates of bleeding were increased in CURRENT-OASIS 7 for the 600 mg dose, ARMYDA-2 showed similar safety profiles for both doses.

Caution: There is a significant variation in response to clopidogrel as measured by ADP platelet aggregation, which has been linked to increase risk of thrombotic events. The variation has been in large part attributed to gene polymorphisms of CYP2C19 (enzyme responsible for clopidogrel's active metabolite). However, screening patients by either testing for platelet reactivity or gene polymorphisms remains controversial and lacks sufficient data to recommend routine use. Drug interactions with clopidogrel, most prominently proton pump inhibitors (PPI), have also been associated with variations in pharmacokinetics, but has not been shown in randomized trials to be harmful.³ As such, addition of a PPI to DAPT after PCI continues to be the strategy of choice to reduce gastrointestinal bleeding.

Prasugrel

Role in PCI: Another thienopyridine and irreversible inhibitor of P2Y₁₂, prasugrel is converted to its active metabolite in a single step, and its antiplatelet activities are not altered by polymorphisms of the CYP enzyme. This provides a more rapid, reliable and potent antiplatelet effect as compared to clopidogrel. These enhanced antiplatelet properties were demonstrated in the TRITON-TIMI 38 trial, where in patients with ACS undergoing PCI, those receiving prasugrel had improved ischemic outcomes

as compared with patients receiving clopidogrel, at the cost a significant increase in major bleeding. Its potent antiplatelet activity makes it suitable for patients with ACS scheduled to undergo PCI. However, careful attention must be made to individual bleeding risk.

Dose: The loading dose of prasugrel is 60 mg with maintenance dose of 10 mg daily.

Caution: Prasugrel should be avoided in patients who are > 75 years of age, have a body weight of <60 kg, history of TIA/CVA, severe liver dysfunction or have conditions predisposing them to high risk of bleeding (i.e renal dysfunction, concomitant anticoagulant use etc.) as these groups of patients have the greatest risk of major bleeding episodes. Prasugrel typically is not given prior to defining coronary anatomy (can be considered in STEMI where likelihood of PCI is significant), to reduce the risk of surgical bleeding for those patients needing CABG.⁴ Furthermore, pretreatment with prasugrel in ACS failed to improve ischemic outcomes while increasing bleeding complications.⁵

Ticagrelor

Role in PCI: Ticagrelor is a direct acting P2Y₁₂ inhibitor, having the advantage of not needing metabolic conversion to an active form. This provides a quicker, more reliable and sustained platelet inhibition as compared to clopidogrel. When compared with clopidogrel in the ACS population undergoing PCI in the PLATO trial, ticagrelor reduced cardiovascular death, MI and stroke without a significant increase in the rate of major bleeding.⁶ Given its more potent antiplatelet action, it is preferred over clopidogrel in patients with ACS according to guidelines.

Dose: The loading dose of ticagrelor is 180 mg followed by 90 mg twice daily.

Caution: Dyspnea, ventricular pauses, bradycardia and high grade AV block are associated with ticagrelor use.

Cangrelor

Role in PCI: Another direct acting P2Y12 inhibitor and the only intravenous option, cangrelor provides an option for rapid onset of action (within a few minutes) and potent antiplatelet effects. Cangrelor has been shown to reduce the rates of ischemic events compared to clopidogrel in patients undergoing PCI. However, its place in therapy for patients undergoing PCI is controversial, as it has not been studied in comparison to more potent antiplatelet therapy currently available. Nevertheless, being the only IV P2Y12 inhibitor, it fills an important need for reliable platelet inhibition in patients unable to take oral medication or who may require a drug with rapid offset (e.g. patients scheduled for surgery).

Dose: Bolus of 30 mcg/kg; infusion of 4 mcg/kg/min for duration of PCI or 2 hours (the longer duration of the two).

Caution: The adverse events associated with cangrelor use are primarily limited to bleeding.

3. GPIIb/IIIa inhibitors

Mechanism of action: Platelet activation induces a conformational change in the GPIIb/IIIa receptor leading to the binding of fibrinogen and Von Willenbrand factor. This results in enhanced platelet aggregation. Given the GPIIb/IIIa inhibitors act on a final common pathway for platelet aggregation, they provide a potent inhibition of platelet activity.

Role in PCI: The administration of GPIIb/IIIa inhibitors was previously favored during PCI due to its IV formulation rapid and potent antiplatelet activity, and observed reduction in markers of myocardial necrosis following PCI. However, its widespread use has gone out of favor with the advent of more potent oral P2Y12 inhibitors and improved stent designs. Although variable based on geographic location and operator preference, its place in therapy is reserved for cases of PCI with high thrombus burden. Some operators have also favored intracoronary administration to localize its effects.

Dose: Abciximab: 0.25 mg/kg IV; 0.125 µg/kg/min IV for 12 hours (max 10 µg/min) ; Eptifibatide: 180 µg/kg IV bolus; 2 µg/kg/min for 18 to 24 hours; Tirofiban: 0.4 µg/kg IV bolus; 0.1µg/kg/min for 18 to 24 hours.

Caution: Although rare, severe thrombocytopenia can lead to life threatening bleeding complications.

4. Timing of P2Y12 inhibitor administration

Stable ischemic heart disease

While the loading dose of ASA should be administered prior to coronary angiography, the addition of P2Y12 inhibitor can be administered once the decision is made to proceed to PCI. This is to avoid use in patient's not needing revascularization or the 10-15% of patients who will end up needing CABG, placing them at a higher risk of bleeding and potentially delaying revascularization. Among patients undergoing PCI, there is no strong evidence that loading P2Y12 inhibitors before versus after the procedure strongly influences outcomes.

Acute coronary syndrome

The optimal timing of P2Y12 administration in ACS has been a source of debate. While early data from the PCI-CURE study favored pre-loading patients on a P2Y12 who are scheduled for coronary angiography, this strategy came at a time when there was significant time between diagnosis and angiography (mean 6 days).¹ In the era of early invasive therapy for high-risk patients, the data for benefit of pre-loading is less clear whereas the risk of bleeding increases significantly. While it is preferable to administer a P2Y12 inhibitor as early as possible in STEMI given the high likelihood of PCI, the decision to pre-load in ACS should take into consideration patient bleeding risks and likelihood of

finding surgical disease. Furthermore, preloading specifically with prasugrel is relatively contraindicated given no proven ischemic benefit over clopidogrel and higher rate of bleeding complications.⁵

5. Minimum duration of DAPT

Stable Ischemic Heart Disease

The combination of ASA and a P2Y12 inhibitor significantly reduces the risk of stent thrombosis, a dreaded complication with high mortality. Early studies suggested increased risk of this event with discontinuation of the P2Y12 inhibitor in the use of drug eluting stents (DES), leading to a recommendation of 12 months of DAPT after stent placement. This recommendation was largely based on observational data and expert opinion. Rapid changes in DES design and material however, led to a reduction in the risk of stent thrombosis in 2nd generation stents. Several randomized control studies compared 12 month vs. 6 month DAPT in newer generation stents. A meta-analysis of 6 large randomized control studies showed similar rates of ischemic events with reduced rates of major bleeding in the shortened DAPT arm. The 2016 ACC/AHA Update on DAPT gives a class I recommendation for a minimum of 6 months of DAPT after DES placement in SIHD.⁴

Acute coronary syndrome

Patients with ACS represent a high-risk sub group for future thrombotic events. The importance of DAPT in enhanced antiplatelet action in these patients was highlighted in the CURE study (see P2Y12 inhibitors). The PCI-CURE sub-study and the CREDO trial showed similar reductions in cardiovascular events with prolonging DAPT (clopidogrel and ASA) duration up to a year vs short term DAPT (1 month) after BMS placement. Given the increased thrombotic risk in patients with ACS and benefit seen in extending DAPT up to a year, the 2016 ACC/AHA update on DAPT gives a class I recommendation a minimum of 12 months of DAPT in ACS regardless of revascularization strategy.⁴

6. Prolonged DAPT

Improved DES stent design has shortened the minimum duration of DAPT necessary to reduce the risk of stent thrombosis. However, very late (≥ 12 months) events are still of concern with the use of DES. Several randomized control studies failed to show reduction in cardiovascular events or mortality with prolonging DAPT beyond 12 months, while showing increased risk of major bleeding with extended therapy. These trials however, lacked significant power to detect differences in ischemic outcomes.

The DAPT trial sought to overcome this limitation by randomizing 9,961 patients to 12 months vs. 30 months of DAPT.⁷ Rates of major cardiovascular and cerebrovascular events, including stent thrombosis, were lower in the extended therapy arm. Importantly, non-stent related ischemic events were also reduced, suggesting a role for DAPT in secondary prevention of atherothrombotic events. The improved ischemic outcomes of prolonged DAPT did come at the cost of increased moderate to severe bleeding. A meta-analysis of randomized control studies comparing short term (6-12 months) vs. prolonged DAPT (≥ 18 months) similarly showed a reduction in ischemic events including MI and stent thrombosis in the extended therapy group while increasing the rate of major bleeding. The 2016 ACC/AHA update on DAPT gives a class IIb recommendation for the continuation of DAPT beyond the minimum recommendation of 6-12 months after DES placement based on indication (SIHD vs. ACS, respectively) among patients who have been able to tolerate therapy without significant bleeding events and who are not at risk for major bleeding (i.e oral anticoagulant use).⁴

7. Patient selection for prolonged DAPT

While prolonging DAPT therapy beyond the currently recommended minimum durations appears to improve ischemic outcomes, the increased risk of major bleeding gives pause for concern. Patient characteristics including prior MI or diabetes increases the risk of future thrombotic events while

others such as advanced age increase the risk of major bleeding. Thus, the decision on the optimal duration of DAPT after PCI should be a personalized one.

Clinical risk tools can aid in the decision-making process and offers clinicians the ability of communicating individualized risk assessments for therapy with their patients (**Figure 2**). The DAPT score (derived from the DAPT trial) is comprised of both clinical characteristics that increase risk of ischemia and bleeding (**Table 1**) when prolonging DAPT ≥ 12 months.⁸ Individuals with a DAPT score ≥ 2 who receive prolonged DAPT derive a greater benefit from extending therapy in reducing MACE than those with scores < 2 [Number needed to treat to benefit 33 vs. 167, respectively], while seeing a decreased risk of major bleeding [Number needed to treat to harm 250 vs. 63, respectively]. Applying the DAPT score to high-risk patient populations such as those with an MI history can also help further risk stratify these patients and potentially avoid bleeding in those that do not stand to benefit.⁹ The DAPT score is a valuable tool that considers both risks and benefits of prolonged DAPT in one composite score, helping both clinicians and patients understand the utility of extending therapy.

The PARIS risk scores was developed from a registry of patients undergoing PCI and receiving DAPT over a follow up of up to 2 years.¹⁰ The PARIS risk scores have the advantage of representing “real world” data, including patients with a history of bleeding or those on chronic oral anticoagulation. Separate prediction models of clinical variables were made for ischemic and bleeding events and an integer-based system was developed for those at low, intermediate and high risk (**Table 1**). The PARIS score offers a more comprehensive review of individual ischemic and bleeding risk.

The PRECISE-DAPT risk score was developed to identify individuals at high bleeding risk with prolonged DAPT. The score was developed from 8 randomized control studies comparing short term DAPT (3-6 month) vs. prolonged DAPT (≥ 12 months) after PCI.¹¹ The clinical variables in the score are from the index hospitalization of PCI (**Table 1**). A score ≥ 25 identified individuals at high bleeding risk with prolonged therapy. These patients also failed to derive an ischemic benefit. A score < 25 identified

patients whose bleeding risk was unchanged from prolonged therapy, while also reducing risk of ischemic events. The PRECISE-DAPT score offers the advantage of helping to establish DAPT durations upfront, limiting those at high bleeding risk to the guideline recommended minimum 6-month therapy in SIHD. While the PRECISE-DAPT score was developed with the inclusion of patients with ACS, shortened DAPT durations might pose increased risk of ischemic events.¹² This high-risk subgroup should continue to receive the guideline recommended minimum of 12 months of DAPT, unless a major bleeding event or high-risk procedure precludes it.

These clinical risk tools should help clinicians and patients make personalized decisions for DAPT durations after PCI. However, it must be kept in mind, they only have a moderate discriminative ability to predict future events and should serve as a guide to clinical decision-making. In fact, the risks for ischemia and bleeding are dynamic over time and decisions to continue DAPT beyond the minimum durations should be continually evaluated.

8. Atrial fibrillation and DAPT

The management of patients with atrial fibrillation who undergo PCI is challenging. These patients are at risk of stroke requiring oral anticoagulation, making them particularly high risk of major bleeding with DAPT after stent placement. Strategies to reduce the risk of bleeding after PCI in these patients has involved shortening DAPT duration to 6 weeks with continuation of warfarin and ASA thereafter in ISAR-TRIPLE or eliminating ASA altogether, in the WOEST trial. These strategies have shown similar rates of cardiovascular and cerebrovascular events with reduced major bleeding vs. the conventional triple antithrombotic therapy.

Recently, randomized studies have examined alternative strategies to triple antithrombotic therapy with the use of novel oral anticoagulants. The PIONEER-AF trial showed reduced major bleeding events and similar rates of MACCE with the use of 12 months of rivoroxaban and a P2Y12 inhibitor vs.

triple antithrombotic therapy (warfarin + DAPT) for a duration of 1, 6 or 12 months (left to discretion of treating physician).¹³ The REDUAL PCI trial showed reduced rates of major bleeding with dabigatran and a P2Y12 inhibitor vs. triple antithrombotic therapy with warfarin for 1-3 months.¹⁴ Therapy with dual antithrombotic regimen with dabigatran was also non-inferior to triple therapy in respects to thromboembolic risk. Dual anti-thrombotic therapy or shortened durations of DAPT with anticoagulation is an effective alternative to reducing risk of bleeding compared to the conventional triple anti-thrombotic therapy after PCI in patients with atrial fibrillation.

9. Non-cardiac surgery and DAPT

While previous data from observational studies indicated increased rates of stent thrombosis with DES up to a year post implantation, more recent randomized control trials with newer generation DES show reduced duration of risk post PCI. Data also suggests the risks of stopping P2Y12 inhibitor therapy for stent thrombosis after DES placement may be similar at 3 vs. 6 months. As such, the 2016 ACC/AHA updated guidelines on DAPT duration provide a class IIb recommendation for stopping DAPT 3 months post DES placement for an elective non-cardiac surgery, acknowledging improved ischemic complications with newer generation stents.⁴ Decisions regarding optimal duration of DAPT in this setting should be made with consideration for urgency of surgery and ischemic risk as guided by risk scores.

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Figure 1: Algorithm for P2Y12 selection for DES placement in PCI

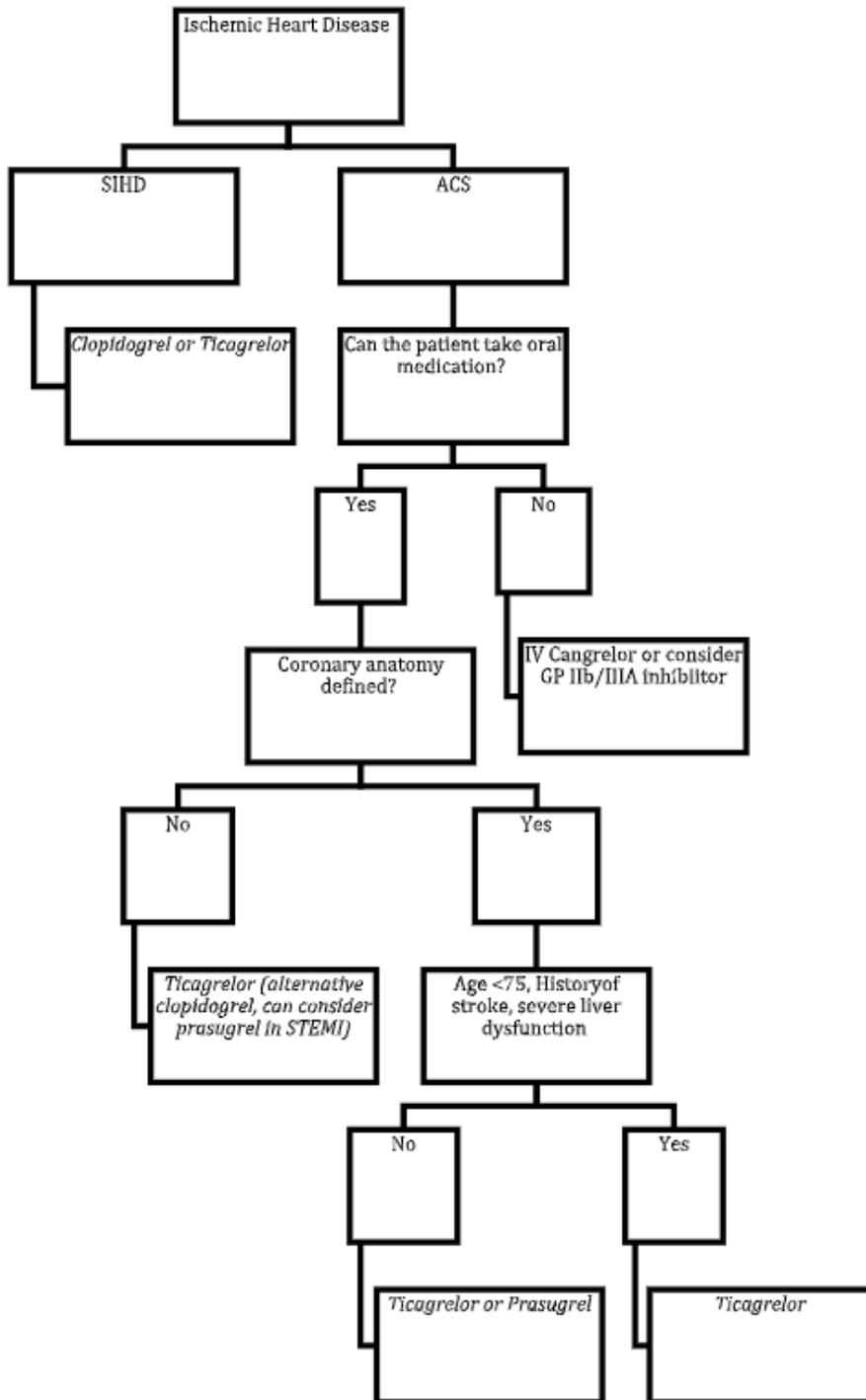
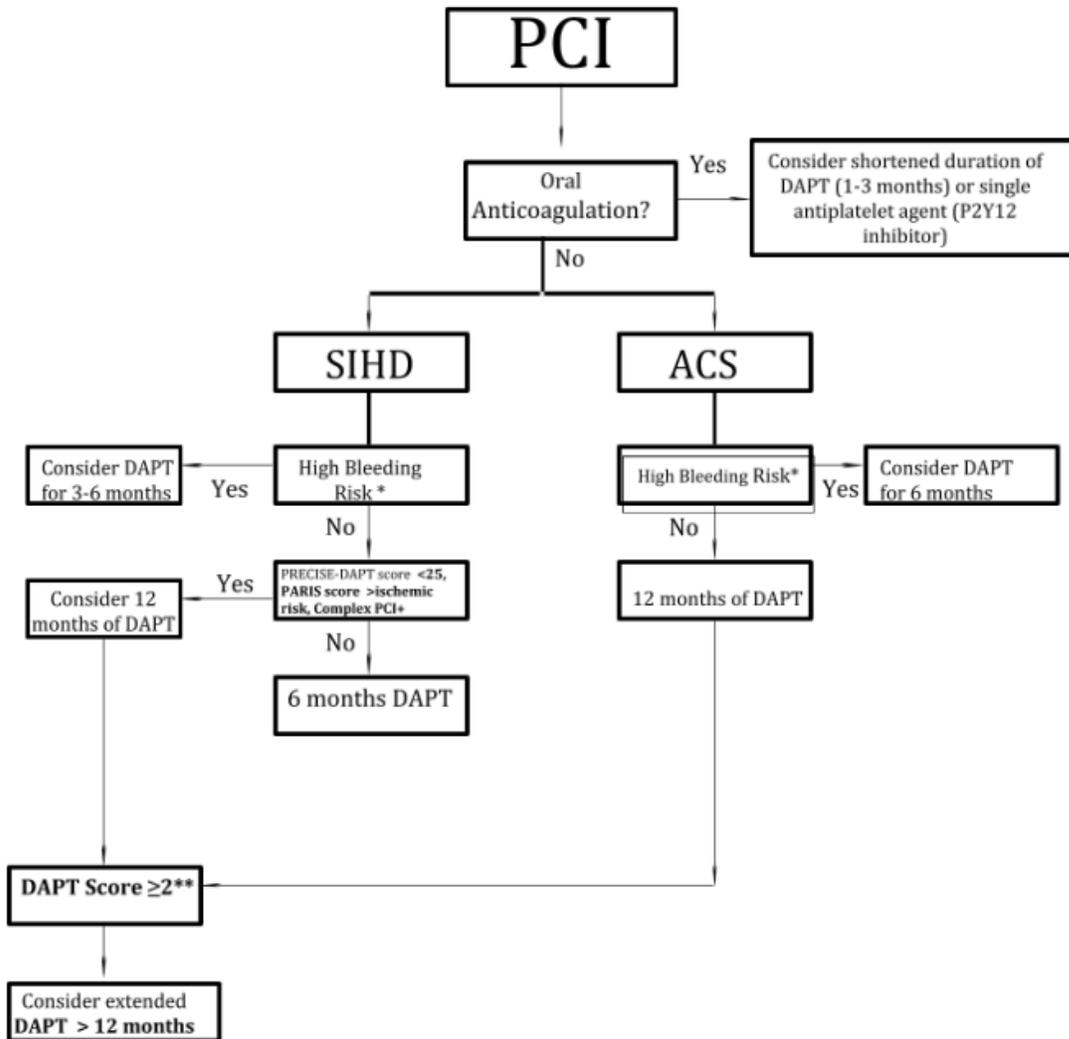


Figure 2: Algorithm for duration of DAPT after DES placement



*High bleeding risk: Significant overt major bleeding episode or high bleeding risk surgical procedure

**Assessment after completion of 12 months of therapy without major bleeding event

+Complex PCI: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion

Table 1: Risk scores for extended DAPT after PCI

Risk Score	Risk Assessment	Scoring System	Clinical Variables	DAPT Cessation (months)	Risk Score	Decision-Making Tool
DAPT	Bleeding and ischemic (combined)	Integer Based	Age (65-74: -1, 75+: -2), DM (+1), Prior MI/PCI (+1), ACS (+1), stent diameter <3mm (+1), LVEF <30% (+2), Vein graft stent (+2), tobacco use (+1)	12 vs. 30	<2: Low risk ≥2: High risk	Available online: http://tools.acc.org/DAPT_riskapp/#!/content/calculator/
PARIS	Bleeding and ischemic (separate)	Integer Based	Ischemia: Prior revascularization (+2), ACS [(TnT + : +2), TnT - : +1], IDDM (+3), NIDDM (+1), CrCL <60 (+2), tobacco use (+1) Bleeding: Age (50-59: +1, 60-69: +2, 70-79: +3, ≥80: +4), BMI (<25: +2, 25-34: 0, ≥35: +2), TTT (+2), anemia (+2), CrCl <60 (+2), tobacco use (+2)	Up to 24	Ischemic risk: 0-2: low; 3-4: intermediate; ≥5: High Bleeding risk: 0-3 low; 4-7: intermediate; ≥8 High	N/A
PRECIS E-DAPT	Bleeding only	Numerical	Hemoglobin, WBC, age, previous bleed, CrCl	6 vs. 12-24	≥25: High bleeding risk <25: Low to intermediate bleeding risk	Available online: www.precisedaptscore.com

Wbc: white blood cell count; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; CHF: Congestive heart failure; BMI: Body mass index; TTT: Triple antithrombotic therapy

References:

1. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
2. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
3. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. *N Engl J Med* 2010;363:1909-17.
4. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS 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 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134:123-155.
5. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013;369:999-1010.
6. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009;361:1045-57.

7. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66.
8. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA* 2016;315:1735-49.
9. Kereiakes DJ, Yeh RW, Massaro JM, et al. DAPT Score Utility for Risk Prediction in Patients With or Without Previous Myocardial Infarction. [J Am Coll Cardiol 2016;67:2492-502.](#)
10. Baber U, Mehran R, Giustino G, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. [J Am Coll Cardiol 2016;67:2224-34.](#)
11. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *The Lancet* 2017;389:1025-34.
12. Hahn JY, Song YB, Oh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *The Lancet* 2018;391:1274-84.
13. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med* 2016;375:2423-34.
14. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med* 2017;377:1513-24.