DURATION OF DUAL ANTIPLATELET THERAPY IN PATIENTS WITH CORONARY ARTERY DISEASE

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OBJECTIVE:

To review the optimal duration of dual antiplatelet therapy (DAPT) following elective and emergent percutaneous coronary intervention (PCI) for the treatment of chronic stable angina and acute coronary syndromes (ACS).

BACKGROUND:

The optimal duration of DAPT following PCI is influenced by patient, clinical and procedural characteristics. The benefit of DAPT for reduction in ischemic risk must be weighed against the risk of bleeding from its extended use. This document summarizes recent changes in clinical practice guidelines.

EFFICACY OF DUAL ANTIPLATELET THERAPY

The use of acetylsalicylic acid (ASA) in combination with either clopidogrel, ticagrelor, or prasugrel is indicated for the treatment of ACS to prevent future major adverse cardiovascular events (MACE). The use of ASA in combination with clopidogrel, ticagrelor or prasugrel is indicated following emergent PCI for the treatment of ACS, and the use of ASA with clopidogrel is indicated following elective PCI for the treatment of chronic stable angina.

DAPT in those with ACS who underwent revascularization

- The **PCI-CURE** study initially established the benefit of DAPT (clopidogrel with ASA) over ASA alone in patients who underwent PCI for Non-ST Elevation Acute Coronary Syndrome (NSTEACS).

- The **PLATO** trial (ticagrelor) and **TRITON-TIMI 38** trial (prasugrel) demonstrated increased efficacy of the second generation P2Y12 inhibitors over clopidogrel following PCI for an ACS indication. Ticagrelor also demonstrated efficacy amongst ACS treated with bypass surgery.

- The **ISAR-REACT 5** trial compared DAPT with ticagrelor vs DAPT with prasugrel in patients who presented with ACS and were undergoing revascularization. The prasugrel regimen demonstrated a 26% relative risk reduction over the ticagrelor regimen in a composite CV outcome, which was driven by nonfatal MI.

DAPT in those with ACS who were medically managed

Clopidogrel used in combination with ASA for the medical treatment of ACS in the CURE trial resulted in a 20% reduction in the combined endpoint of death, myocardial infarction, and stroke. The PLATO trial (ticagrelor) demonstrated increased efficacy of ticagrelor over clopidogrel amongst ACS treated with medical therapy. Prasugrel did not show additional benefit over clopidogrel when used for the treatment of ACS without revascularization in the TRILOGY trial (Table 1).

None of these trials showed an overall mortality benefit with DAPT.

TABLE 1: SELECTED TRIALS OF THE SECOND GENERATION P2Y12 INHIBITORS

Trial	Trial Population	Efficacy Endpoint	Safety Endpoint	Efficacy Results	Safety Results
PLATO (ASA + ticagrelor vs. ASA + clopidogrel)	ACS treated with PCI, CABG or medical therapy	Composite of death from vascular causes, MI, stroke at 1 year	Major bleeding Non-CABG related major bleeding	HR 0.84 (95% CI, 0.77-0.92)	HR 1.04 (95% CI 0.95-1.13) HR 1.19 (95% CI, 1.02-1.38)
TRITON (ASA + prasugrel vs. ASA + clopidogrel)	ACS treated with PCI	Composite of cardiovascular death, nonfatal MI, nonfatal stroke at 15 months	Major bleeding	HR 0.81 (95% CI, 0.73-0.90)	HR 1.32 (95% CI, 1.03-1.68)
TRILOGY (ASA + prasugrel [10 mg daily if <75 years; 5 mg daily if ≥75] vs. ASA + clopidogrel)	ACS treated medically	Composite of cardiovascular death, MI, or stroke at 30 months	Severe or life-threatening bleeding	HR overall population 0.96 (95% CI, 0.86-1.07) HR <75 years 0.91 (95% CI, 0.79-1.05)	HR overall population 0.83 (95% CI, 0.48-1.46) HR <75 years 0.94 (95% CI, 0.44-1.99)

Note: ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention

SAFETY OF DUAL ANTIPLATELET THERAPY (BLEEDING CONSIDERATIONS)

While second generation P21Y12 inhibitors (prasugrel and ticagrelor) reduce MACE rates compared to clopidogrel in patients receiving ASA in the setting of ACS and PCI, these agents are associated with increased rates of major bleeding. Compared to clopidogrel, ticagrelor was associated with an increased risk of non-CABG related bleeding in the PLATO trial, and prasugrel was similarly associated with an increased risk of major bleeding in the TRITON trial. Use of prasugrel was associated with similar rates of bleeding amongst medically treated patients in the TRILOGY trial (Table 1). As such, caution needs to be exercised when choosing to use DAPT and when selecting a second generation P2Y12 inhibitor over clopidogrel; especially in patients at increased risk of bleeding. Table 2 lists clinical variables that have been associated with increased bleeding in clinical trials and registries.

TABLE 2: VARIABLES ASSOCIATED WITH AN INCREASED RISK OF BLEEDING WITH DAPT

Need for oral anticoagulation in addition to DAPT
Advanced age (>75 years)
Frailty
Anemia with hemoglobin <110g/L
Chronic renal failure (estimated creatinine clearance [eGFR] <40mL/min)
Low body weight (<60kg)
Hospitalization for bleeding within the last year
Prior stroke/intracranial bleed
Regular need for nonsteroidal anti-inflammatory therapy or prednisone

DURATION OF DUAL ANTIPLATELET THERAPY FOLLOWING ACS

DAPT durations less than 12 months

The results of the CURE and PCI-CURE trials led to the current recommendation for 1 year of DAPT using clopidogrel and ASA for the treatment of ACS, as an adjunct to medical therapy, CABG or PCI. Amongst ACS patients treated with PCI, some trials of selected patients have suggested that DAPT may be used for as short as 3-6 months post PCI when followed by ASA monotherapy.

However, other studies have demonstrated that shorter durations of DAPT following PCI for an ACS indication have been associated with higher rates of stent thrombosis and recurrent myocardial infarction (MI). As such, it is currently suggested that DAPT be continued for at least 1 year post ACS in patients not at high risk for bleeding.

Recent studies have assessed the safety of using a regimen of DAPT for less than 12 months followed by P2Y12 inhibitor monotherapy in patients treated with PCI for both stable coronary artery disease and ACS.

- **STOP-DAPT2** investigated 1 month of DAPT, followed by clopidogrel monotherapy vs continued DAPT in patients mostly at low-to-medium thrombotic risk. Superiority was found with the clopidogrel monotherapy group in a large composite outcome of cardiovascular thrombotic and bleeding events. The major secondary endpoints suggested that 1 month of DAPT was non-inferior to 12 months of DAPT in terms of cardiovascular endpoints and superior in terms of bleeding. There was no significant subgroup interaction in patients who experienced ACS as the reason for PCI. However, there was a significant subgroup interaction those with an estimated GFR less than 30 mL/min/1.73m^2, suggesting those patients may have better outcomes with 12 months of DAPT rather than 1 month.

- **SMART-CHOICE** studied 3 months of DAPT, followed by P2Y12 monotherapy (clopidogrel used in ~75% of patients) compared with 12 months of DAPT. This study found similar outcomes to STOP-DAPT2, with noninferiority demonstrated for MACE. This was consistent in the subgroup of patients who experienced ACS. There were similar rates of major bleeding between the two groups.

- The much larger **TWILIGHT** study (about 7000 patients) assessed 3 months of DAPT with ticagrelor, followed by ticagrelor monotherapy vs continued DAPT. The trial population had at least 1 feature associated with a high risk of ischemic or bleeding events. There was a significant reduction in bleeding in those assigned to 3 months of DAPT. This study also suggested non-inferiority with 3 months of DAPT in terms of MACE. There was no significant interaction in the subgroup who underwent PCI for ACS.

DAPT durations more than 12 months

Increasing evidence has suggested that patients at high risk for MACE following PCI for ACS may derive benefit from a strategy of extended DAPT beyond 1 year. The **DAPT** trial evaluated a strategy of 30 vs 12 months of DAPT (clopidogrel or prasugrel in combination with ASA) following PCI for either stable CAD or ACS. Compared to 12 months of DAPT, 30 months of DAPT was associated with lower rates of stent thrombosis and MACE. However, extended use of DAPT was associated with higher rates of moderate to severe bleeding. No cardiovascular-related mortality difference was found. There was an unexpected exploratory finding of higher rates of all-cause mortality associated with extended DAPT.

Similar results were obtained in the **PEGASUS** trial, which enrolled stable patients who had experienced an MI within 1-3 years to one of two doses of ticagrelor (either 90mg BID or 60mg BID) or placebo in addition to ASA. The median duration of follow up was 33 months, and the median time on ticagrelor was 29 months. The composite rate of cardiovascular death, myocardial infarction and stroke was reduced by both doses of ticagrelor compared to placebo. However, both doses of ticagrelor increased the risk of TIMI major bleeding compared to placebo. There was no difference in mortality between the groups. Table 2 lists clinical variables that may help to identify those patients in whom the potential for bleeding may outweigh any efficacy gains with extended DAPT.

In summary, extended DAPT for more than 12 months decreases thrombotic outcomes at the expense of a higher risk of bleeding. There is no clear mortality benefit. The decision to extend DAPT beyond 12 months requires individualization based on thrombotic and bleeding risk factors. Figure 1 outlines the current Canadian Cardiovascular Society recommendations for DAPT for ACS patients who undergo PCI.

DURATION OF DUAL ANTIPLATELET THERAPY FOLLOWING ELECTIVE PCI FOR A NON-ACS INDICATION

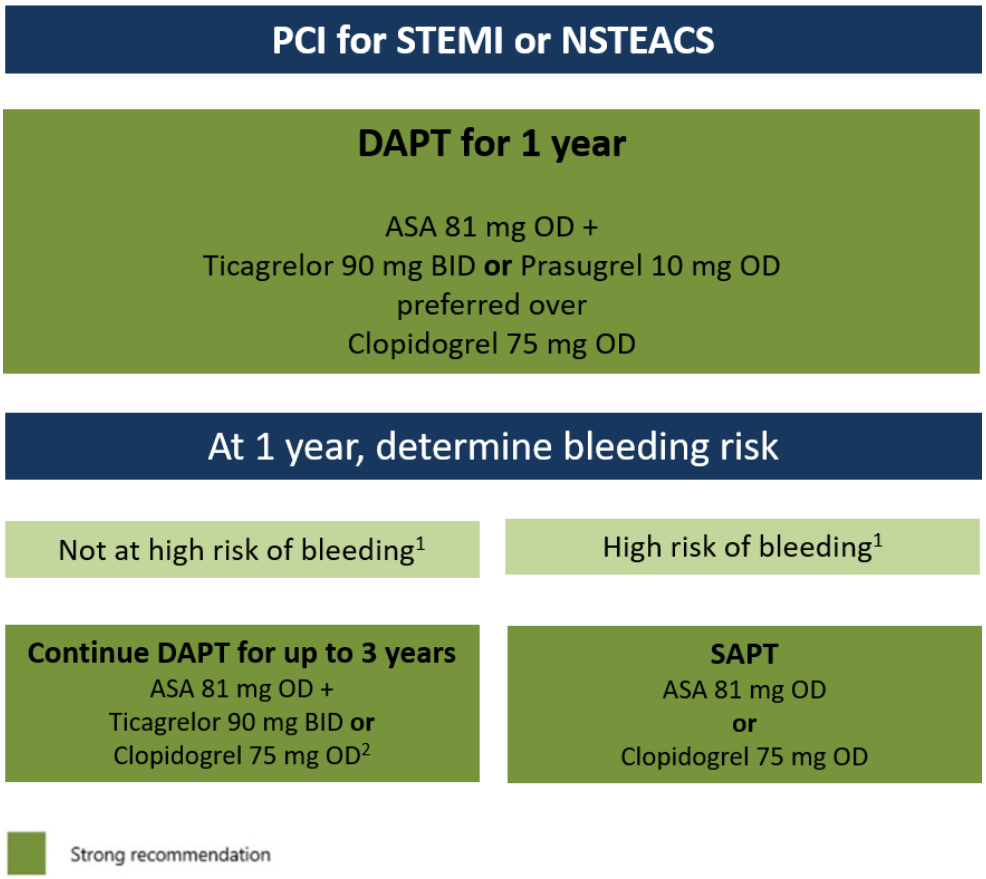
Patients who undergo elective PCI for a non-ACS indication are at inherently lower risk for long-term MACE compared to those who undergo PCI for an ACS indication. In addition, newer generation drug eluting stents (DES) have inherently lower thrombotic risk compared to older first generation sirolimus and tacrolimus DES. Several trials have demonstrated the safety of a shorter course of DAPT in this setting, although increased thrombotic risk has been associated with several angiographic and clinical variables (Table 3). As such, although DAPT is recommended for up to 1 year post elective PCI, its use may also be shortened to a total of 6 months. DAPT use beyond 1 year may be considered if a patient has additional clinical or angiographic variables that suggest an increased risk of a thrombotic event and is a low risk for bleeding (Tables 2 and 3).

Figure 1 outlines the current Canadian Cardiovascular Society recommendations for DAPT therapy for patients with stable CAD who undergo elective PCI.

TABLE 3: VARIABLES ASSOCIATED WITH A HIGHER RISK OF A THROMBOTIC EVENT POST PCI FOR ACS

Clinical Variables	Angiographic Variables
Prior MI or Troponin positive ACS	Multiple stents (≥3 stents or ≥3 lesions stented) or use of a biodegradable vascular scaffold
Diabetes mellitus (treated with oral hypoglycemics or insulin)	Long stent length (>60mm total stent length)
Chronic kidney disease (eGFR <60mL/min)	Complex lesion (bifurcation stenting using 2 stents, stenting of a chronic total occlusion)
Prior stent thrombosis	Left main or proximal LAD stenting
Current smoker	Multivessel PCI

FIGURE 1: RECOMMENDATIONS FOR DURATION OF DAPT IN PATIENTS WITH ACS (STEMI OR NSTEACS) WHO UNDERGO PCI

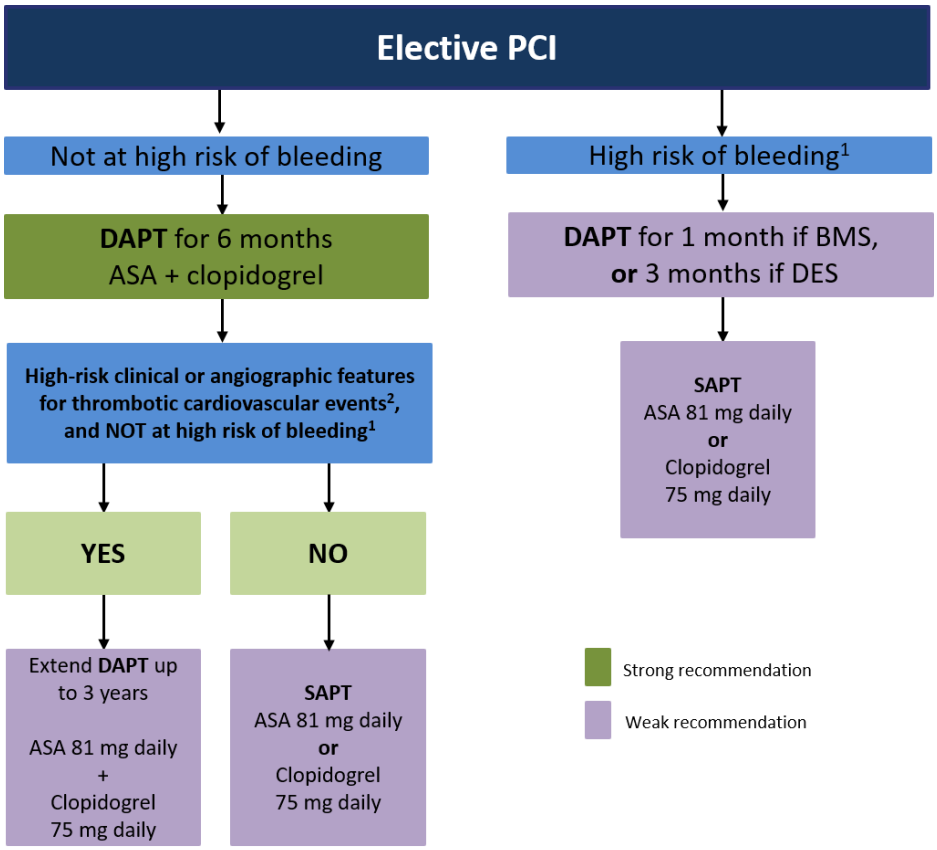


[1] Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (>75 years), frailty, anemia with hemoglobin <110 g/d, chronic renal failure (creatinine clearance <40 mL/min), low body weight (<60 kg), hospitalization for bleeding within last year, prior stroke/intracranial bleeding, regular need for NDAISs or prednisone.

[2] Instead of ticagrelor or clopidogrel, prasugrel 5-10 mg daily is also an option (weak recommendation).

BID, twice daily; DAPT, dual antiplatelet therapy; NSTEACS, non-ST segment elevation acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; OD, once daily; SAPT, single antiplatelet therapy; STEMI, ST segment elevation myocardial infarction

FIGURE 2: RECOMMENDATIONS FOR DURATION OF DAPT IN PATIENTS UNDERGOING ELECTIVE PCI



[1] Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (>75 years), frailty, anemia with hemoglobin <110 g/d, chronic renal failure (creatinine clearance <40 mL/min), low body weight (<60 kg), hospitalization for bleeding within last year, prior stroke/intracranial bleeding, regular need for NDAISs or prednisone.

[2] Clinical and angiographic features associated with increased risk of thrombotic events include: age >65, diabetes mellitus, prior myocardial infarction, chronic renal occlusion (creatinine clearance <60 mL/min), multi-vessel disease, multiple stents implanted, complex bifurcation lesions, total stent length >60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; SAPT, single antiplatelet therapy

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES

- Acetylsalicylic Acid (ASA®)
- Clopidogrel (Plavix®)
- Prasugrel (Effient®)
- Ticagrelor (Brilinta®)

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