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Review

Perioperative management of dual anti-platelet therapy

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Abstract

Dual anti-platelet therapy denotes a regimen of aspirin plus a P2Y₁₂ receptor inhibitor, clopidogrel, prasugrel, or ticagrelor. Such therapy is a cornerstone of medical management following acute coronary syndromes and is imperative following percutaneous coronary interventions. While there is uncertainty about the optimal duration of dual antiplatelet therapy following percutaneous coronary intervention, the new 2016 American College of Cardiology/American Heart Association Guidelines suggest that for patients with stable ischemic heart disease at least six months of such therapy following a drug eluting stent and one month following a bare metal stent should be implemented. In patients with acute coronary syndrome including non-ST elevation and ST elevation myocardial infarction it is recommended to extend dual antiplatelet therapy treatment to one year in both drug eluting stent and bare metal stent groups. There may be latitude for earlier discontinuation in appropriately selected patients; extended dual antiplatelet therapy beyond one year may be beneficial in others. Herein, we describe current guidelines and evidence supporting if and when dual antiplatelet therapy should be interrupted for surgery for patients who have undergone percutaneous coronary intervention.

Keywords:

Dual-Antiplatelet Therapy, DAPT, Perioperative, Surgery, Aspirin, Clopidogrel, Bridging, PCI, Discontinuation.

1. Introduction:

The advent of the coronary stent revolutionized percutaneous coronary intervention (PCI), as prior to its introduction, percutaneous transluminal coronary angioplasty (PTCA) conferred a restenosis rate of 44 to 77% with reocclusion in 14-40% of patients¹. Bare metal stents and drug eluting stent (DES) are associated with a lower risk of re-stenosis, however, stent thrombosis (ST) remains a possible complication of stent placement with an incidence of about 3% to 20% of DES implantations depending upon lesion type and patient population². The majority of these events occur within 35 days of stent deployment³. Dual anti-platelet therapy (DAPT) with aspirin plus clopidogrel, prasugrel, or ticagrelor serves to reduce the rate of stent thrombosis and major adverse cardiovascular outcomes following acute coronary syndromes (ACS) and PCI⁴. While DAPT is a cornerstone of therapy in patients with CAD, there is uncertainty about the optimal duration of DAPT. Extended duration of DAPT may be associated with excess bleeding, a risk that may be balanced by the benefits of less stent thrombosis⁵.

The duration of DAPT and the need to potentially interrupt such therapy is of particular concern in the perioperative setting. Elective surgeries and procedures are best postponed until the “mandatory” period of DAPT has passed following PCI (i.e. 1 month and 6 months respectively in bare metal stent and DES patients with stable ischemic heart disease (SIHD), and 1 year in

both groups after acute coronary syndrome)⁴. Interruption of DAPT outside of this window may be associated with a higher risk of stent thrombosis, MI, or death⁵. Recommendations notwithstanding, the rate of nonemergent noncardiac surgery within the first year after coronary artery stent placement has been reported to occur between 5 and 7%, of which many were marked as urgent or semi-urgent⁶. Given relative uncertainty that physicians have in managing DAPT in the perioperative setting, this article delineates current guidelines and evidence to inform decision-making. The article will define dual antiplatelet therapy and discuss current 2016 ACC/AHA guidelines for the perioperative management of DAPT. We will also share best practices for interruption of DAPT, when it is necessary, and offer a commentary on suggestions for its re-initiation in the post-operative setting.

2. Antiplatelet Therapies

Aspirin

Aspirin irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) via acetylation, which irreversibly inhibits formation of the prostaglandin derivative thromboxane A₂, inhibiting platelet aggregation⁷. This effect has had many major cardiac implications over the decades. It was first shown to reduce the risk of death or MI at 12 weeks by 50% among patients w/ unstable angina, and its uses have extended into primary prevention in select circumstances⁸. Along with statins, aspirin constitutes the cornerstone of secondary prevention of coronary artery disease. As discussed below, general recommendations are to continue aspirin perioperatively. Important to this discussion is the POISE-2 trial, which was a randomized controlled trial, published in 2014, which studied aspirin versus placebo in patients in the perioperative setting of noncardiac surgery. Patients in two strata, either already on ASA or initiated during the study were randomized to either continue ASA during surgery or switched to placebo. The trial showed no increase in composite death or non-fatal MI, but was associated with an increase in bleeding. However, this study was not powered to speak to the higher risk of thrombosis and unique pathophysiology that

exists in patients who have undergone recent PCI. Only 2.6% and 1.1% of patients had ever undergone PCI with bare metal stents or DES respectively in the aspirin arm out of 4998 patients⁹. In our experience, the risks of bleeding may outweigh the expected benefits in some cases, such as neurosurgery, spinal surgery, or non-cataract ophthalmological procedures. But, save these circumstances, aspirin should generally be continued perioperatively. The 2016 ACC/AHA guidelines explicitly recommends continuation of aspirin in the perioperative period if possible⁴.

Clopidogrel

The active metabolite of clopidogrel irreversibly blocks the P2Y₁₂ segment of the ADP receptor on the platelet surface, which prevents activation of the GPIIb/IIIa complex, reducing platelet aggregation for the duration of the lifespan of the platelet (7-10 days)¹⁰. The efficacy of clopidogrel was first seen in the CAPRIE study, in which it was shown to be somewhat more effective than aspirin alone in reducing ischemic stroke, MI, or vascular death in patients with previous atherothrombotic event¹¹. It was later shown that combination aspirin and clopidogrel resulted in a 2% absolute risk reduction of cardiovascular death, MI and stroke in patients with acute coronary syndrome (ACS) with a 1% increase in bleeding risk¹². Substudy analysis revealed that adding DAPT with clopidogrel reduced composite cardiovascular death, MI and revascularization within 30 days of PCI placement with BMS. Thus aspirin and clopidogrel became standard of care after ACS and stent placement, with continued controversy over the length of treatment¹³.

Prasugrel

A thienopyridine like clopidogrel, prasugrel is also an inhibitor of platelet activation and aggregation being metabolized to active R-128727 which irreversibly blocks P2Y₁₂ of ADP receptors on the platelet surface¹⁴. The TRITON-TIMI 38 randomized ACS patients awaiting PCI

with usual care including aspirin to either clopidogrel or prasugrel. The primary endpoint of death from cardiovascular causes, non-fatal MI, and non-fatal stroke occurred in 12.1 versus 9.9 percent of patients in the clopidogrel and prasugrel groups, respectively. This was at the expense of increased major bleeding, 2.4% in the prasugrel group versus 1.1% in the clopidogrel group¹⁵.

Ticagrelor

Ticagrelor is a cyclopentyltriazolopyrimidine, which unlike the thienopyridines, reversibly and noncompetitively binds the ADP P2Y₁₂ receptor on the platelet surface reducing platelet aggregation, thus making reactivation of platelets possible after serum concentrations of the drug have dropped¹⁶. The 2009 Platelet Inhibitions and Patient Outcomes (PLATO) trial established ticagrelor as an option in DAPT as it showed a significant reduction of CV death, MI or stroke (9.8% versus 11.7%, ticagrelor versus clopidogrel) without an increase in the rate of overall major bleeding in the ticagrelor group versus clopidogrel¹⁷. Currently American guidelines indicate that Clopidogrel, Prasugrel or Ticagrelor are all acceptable choices post-PCI with prasugrel contraindicated in patients with history of TIA or CVA¹⁸. European guidelines indicate that ticagrelor or prasugrel should be used preferentially, with clopidogrel use limited to those who cannot tolerate the aforementioned two¹⁹. ACC/AHA guidelines this year recommend that in patients with ACS with or without PCI, ticagrelor particularly is a reasonable in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy⁴.

3. Timing of Elective Surgery after Percutaneous Coronary Intervention

Surgery may induce a prothrombotic state and thus the risk of premature discontinuation of DAPT following a PCI for the purposes of an elective surgery or procedure should be considered carefully²⁰. General consensus is that elective surgery should be delayed until after the appropriate window of DAPT post-PCI: 6 months following DES and 1 month following BMS in SIHD and 1 year for both groups after ACS⁴. While guidelines suggest that DAPT not be

interrupted for one month after bare metal stent implantation or 6 months following DES implantation, some have demonstrated that adverse outcomes are related to the circumstances in which DAPT interruption occurs. Evidence shows that physician-guided interruption of therapy, or scheduled interruption has overall better outcomes as opposed to spontaneous discontinuation by the patient. This is best illustrated in the PARIS Registry, a prospective observational study of adult patients in Europe and the United States who underwent successful PCI and were discharged on DAPT. The patients were followed at 1, 6, 12 and 24 months post-implantation. During these periods, the effects of cessation of DAPT were examined in terms of major adverse events (composite of cardiac death, definite or probable stent thrombosis, MI, or target-lesion revascularization). At 2 years, major adverse events were seen in 11.5% of patients, 74% of which occurred while patients were on DAPT. Compared to those on DAPT, the hazard ratio for MACE in those with interruption of DAPT (temporary cessation of DAPT due to surgical procedure, less than 14 days) was 1.41 (95% CI 0.94-2.12). Disruption of DAPT (due to bleeding or non-compliance) had an HR of 1.50 (95% CI 1.14-1.97), further stratified by time period (HRs of 7.04 within 7 days; 2.17 between 8-30 days; and 1.3 at more than 30 days). Those who remained on DAPT had lower MACE risk²¹. This study highlights the importance of physician-guided discontinuation and reinitiation of DAPT as opposed to patient interruption of therapy. Thus, if DAPT must be stopped, it is best done so under close physician/cardiologist guidance and for the shortest amount of time possible.

A related but somewhat distinct issue, some have examined extending DAPT duration for longer than 12 months post-DES, calling into question the current time window prior to elective surgery. In the DAPT trial, in particular, extending ASA+clopidogrel or ASA+prasugrel versus continuing ASA alone beyond 12 months showed that continuation of DAPT significantly reduced the risk of stent thrombosis (0.4% vs. 1.4%; hazard ratio, 0.29) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio 0.71), but at the expense of increased bleeding (2.5% vs. 1.6%, P=0.001). There was, however, an increased risk of ST and MI within 3

months of stopping the thienopyridine⁵. Even the one-year proposal of DAPT continuation after DES placement, may be conservative in certain patients warranting even a longer needed window in the future. On one hand, evidence suggests that premature discontinuation of DAPT prior to the aforementioned windows established by stent type can cause harm, which could potentially be reduced by physician-guided or scheduled discontinuation. On the other hand, there is some evidence that extending the period of DAPT for DES beyond one year may have efficacy in terms of preventing poor outcomes. 2016 ACC/AHA guidelines speak specifically to extending the period past their own established windows in patients without bleeding complication or increased bleeding risk stating it may be reasonable to continue past the mandatory period in both SIHD and ACS patients⁴. It is therefore paramount to consider each patient, their respective risks, and comorbidities in determining the exact timing of surgery if it can indeed be delayed.

To summarize current guidelines (also see Figure 1):

- Patients undergoing urgent noncardiac surgery during first 4 to 6 weeks after BMS or one year after DES implantation should continue DAPT unless risk of bleeding outweighs risk of ST.
- If the decision is made to suspend P2Y₁₂ receptor inhibitor therapy, ASA alone should be continued if it is determined that thrombotic risk outweighs bleeding risk (i.e. caution with high bleeding risk procedures such as neurosurgery).
- Perioperative management of DAPT should be a consensus decision between the surgeon, cardiologist, anesthesiologist and patient.
- Elective noncardiac surgery should be delayed 30 days after BMS implantation.
- Elective noncardiac surgery should be delayed 6 months after DES implantation.

4. Management of DAPT if Surgery is Indicated Prior to the End of Recommended Intervals

ACC/AHA guidelines are clear that if possible, stopping DAPT prior to aforementioned time marks should be avoided to reduce the risk of complications of ST, ischemic events, and death. Even so, a large number of patients who have undergone stent must, for many reasons, undergo surgery or procedures prior to the end of the recommended DAPT window⁶. If surgery must proceed, and an increased bleeding risk is acceptable to the care team and patient, then ideally DAPT should be continued perioperatively. The evidence is not robust, but according to many case studies and an extrapolation of patients undergoing CABG in the CURE trial, continuing clopidogrel in the perioperative period confers a higher risk of minor bleeding without significant impact on major morbidity or mortality⁵. If it is the opinion of the care team that continuing dual antiplatelet therapy confers too high of a bleeding risk, the P2Y₁₂ inhibitor should be stopped 5 days prior to scheduled surgery to avoid irreversible potent inhibition of platelet aggregation and ASA should be continued if possible¹². This 5 day stop time was formulated based on the pharmacokinetics of clopidogrel and cannot necessarily be extrapolated to the other agents. The ACC/AHA guidelines note DAPT should be reinitiated as soon as possible after surgery⁴. European Society of Cardiology Guidelines on Myocardial Revascularization discusses the option of platelet function testing at bedside to guide interruption of treatment instead of using an arbitrary time period. The guidelines cite that high platelet reactivity is often the culprit of 30-day post-PCI stent thrombosis. Thus, bedside testing of platelet reactivity is encouraged by the European Society of Cardiology in clinical research, but the role of testing in clinical practice is promising but not yet validated²².

It is widely recommended that aspirin be continued in the perioperative period, especially in those patients where the second agent is discontinued, to ensure continued reduction in the risk of ST. Exceptions to this exist, such as patients undergoing surgery of high bleeding risk like intracranial surgery⁴. As previously mentioned, POISE-2 noted no increased composite death, non-fatal MI, or non-fatal stroke in those with aspirin stopped perioperatively (7.0% in ASA group versus 7.1% in placebo group; P=0.92), but increased bleeding was noted. However this study was not

powered to provide information among those patients with higher risk of stent thrombosis such as recent PCI, as only 4.7% of both the aspirin and placebo group having had a history of PCI¹¹. Thus, general consensus recommends continuation of ASA in patients with a recent PCI and or ACS. It is important to note that some studies examining shorter periods of DAPT less than the aforementioned windows show no increase in adverse clinical or cerebral events. One such study, Feres et al., showed that after PCI with zotarolimus-eluting stents, patients with low risk ACS or SIDH who received aspirin and clopidogrel at 3 months versus 12 months had no significant difference in net adverse clinical and cerebral events, 6.0% at 3 months and 5.8% at 12 months ($p=0.002$). Thus, in the event that DAPT must be stopped before the suggested windows, there is some evidence that there is no difference in major events even at 3 months²³.

5. A Word on Bridging Therapy

Bridging therapy in the perioperative period refers to initiation of an alternative therapy up to the point of surgery to bolster an antithrombotic affect while an agent such as clopidogrel has been discontinued for several days. Generally, data are lacking, and currently there is no consensus to provide bridging therapy to these high-risk patients. One phase II study of patients with recently deployed DES and on clopidogrel requiring interruption of DAPT placed patients on the short-acting glycoprotein IIb/IIIa receptor inhibitor tirofiban as a bridge to coronary artery bypass grafting or other invasive surgery. In thirty patients with a recently implanted DES (median 4 months), clopidogrel was stopped 5 days before surgery with tirofiban started 24 hours later and continued until 4 hours prior to surgery. ASA continuation was at the discretion of the surgeon. There were no cardiac events during the index hospitalization²⁴. No randomized controlled trials adequately powered have supported this. The drug Cangrelor, a short acting IV reversible P2Y₁₂ inhibitor has also been considered for the purposes of bridging given its half-life of 2-3 minutes. A randomized controlled trial published in JAMA evaluated the use of cangrelor in patients undergoing CABG. Two hundred ten patients w/ recent initiation of clopidogrel for ACS or

recent stent were randomized to cangrelor or placebo prior to undergoing CABG surgery. The primary endpoint was platelet inhibition after clopidogrel discontinuation measured by platelet reactivity units (PRUs), the cut-off for adequate inhibition being 240 PRUs. The study found that 98.8% of patients receiving cangrelor had PRU of 240 up to the procedure compared to 19% in the placebo group with no difference in bleeding²⁵. This trial appears promising, but did not examine important clinical end points. For now, the general consensus favors no bridging therapy.

6. Conclusions

Dual anti-platelet therapy is a cornerstone treatment following acute coronary syndromes and percutaneous coronary interventions. Guidelines recommend that patients remain on DAPT for 1 month following BMS and for 6 months following DES in patients with SIHD and 1 year for bare metal stent and DES patients with ACS. While interruption of DAPT before these time intervals should be avoided, if possible, for elective surgeries or procedures, there is equipoise about the optimal duration of DAPT with evidence supporting both extended and shorter durations of treatment. New ACC/AHA guidelines do recommend extending DAPT beyond the aforementioned periods in patients without bleeding complication or increased bleeding risk. For non-elective surgeries or procedures and in appropriately selected patients, DAPT may be interrupted after 6 months of treatment⁴. The decision to proceed with a surgery or procedure requires a careful discussion between all team members, and considering for the risks of bleeding on DAPT balanced against the risks of thrombosis without DAPT. If possible, DAPT should be continued perioperatively. In most circumstances, aspirin should not be interrupted. There is no established role for bridging therapies at the present time. Future research may further refine strategies for best practice of continuing DAPT in the perioperative setting.

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Declaration of Interest

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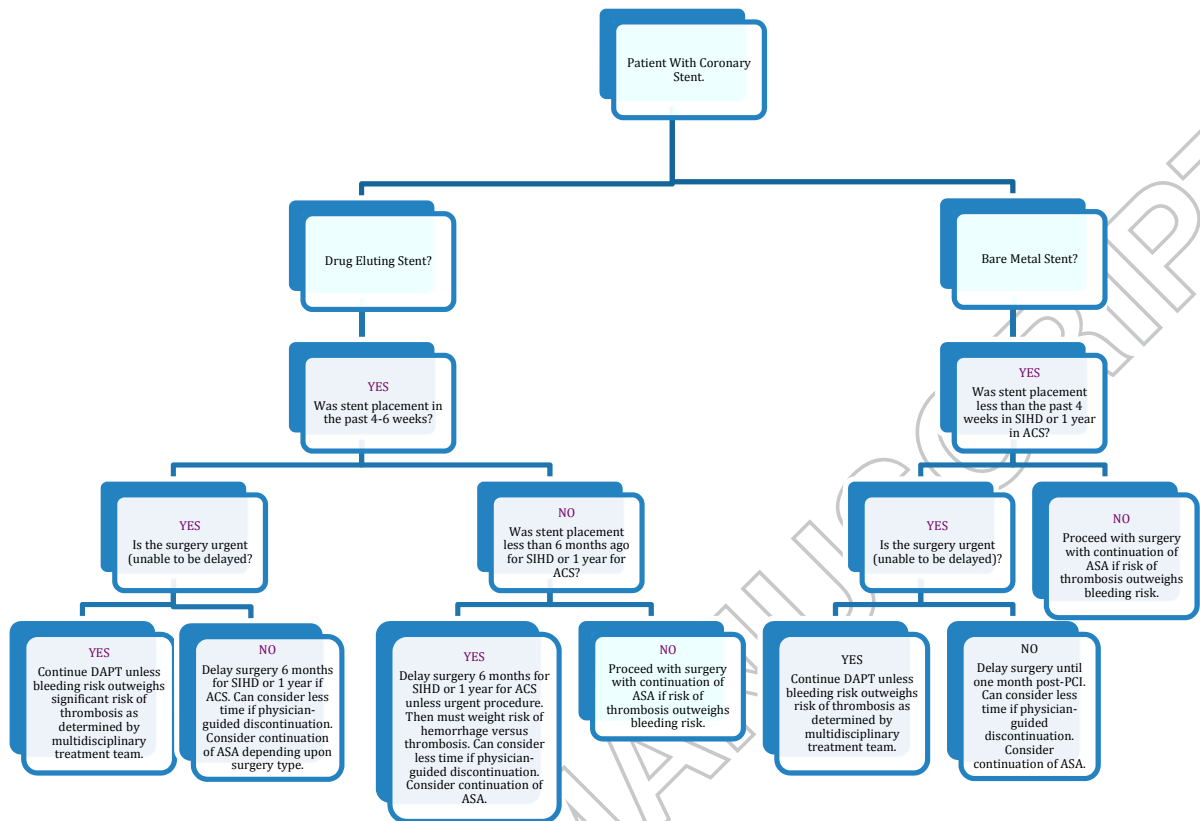


Figure 1. Algorithm for Management of DAPT in the Perioperative Period.

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