Antiplatelet therapy and the anaesthetist

Sian I. Jaggar

Royal Brompton Hospital, Sydney Street, London, Great Britain

Correspondence to Dr. Sian I Jaggar, MBBS, BSc, FRCA, FFPMRCA, CertMedEd, MD, Royal Brompton Hospital, Sydney Street, London SW3 6NP, Great Britain.
e-mail: s.jaggar@rbht.nhs.uk

Received 18 December 2018
Accepted 10 January 2019

The Egyptian Journal of Cardiothoracic Anesthesia 2019, 13:6–9

Increasing numbers of patients internationally are taking dual antiplatelet therapy (DAPT). Both continuing and stopping this treatment may be risky for the patient. It is vital to consider the competing thrombotic and bleeding risks in the perioperative period. It is incumbent upon anaesthetists to maintain their knowledge base in this rapidly developing area. This article provides information to support practice as.

Keywords:
antiplatelet agents, bleeding, thrombosis

Egypt J Cardiothorac Anesth 13:6–9

1687-9090

Increasing numbers of patients are now taking antiplatelet therapeutic agents for the prevention of arterial thrombus [1]. Such patients provide anesthetists with challenging decisions; both continuing and stopping the agents may be fraught with problems. The aim of the study is to provide general anesthetists with tools to support them in their discussions with surgeons, physicians, and patients as to the 'least worst' option for perioperative management.

In contrast to venous thrombi, which have low platelet concentrations, arterial thrombi have a high platelet concentration [2]. This reflects the process of primary hemostasis, which consists of three processes: adhesion, activation, and aggregation (see Fig. 1).

Conventional and newer anticoagulant agents are likely to be of little help alone in avoiding disease associated with arterial thrombi, where antiplatelet agents are the treatment of choice [3]. Currently, these agents are primarily indicated for the secondary prevention of ischemia in patients with prior coronary, cerebral, or peripheral events [4]. Indeed, due to the risk of bleeding (and all-cause mortality) and limited evidence of benefit, these agents should not be prescribed routinely for primary prevention. Their therapeutic place lies in the on-going management of patients with evidence of:

(1) Myocardial disease – angina, acute coronary syndrome, or myocardial infarction [5].
(2) Cerebrovascular disease – transient ischemic attack or ischemic cerebrovascular accident [6].
(3) Peripheral artery disease – following bypass surgery [7].
(4) Medical intervention to arterial tree – insertion of stents to coronary or cerebral circulations, or post-coronary arterial bypass grafts [8].

Between 2010 and 2015 ~100 000 coronary stents per year were inserted in Egypt [9]. Should such patients present for further surgery they are potentially at risk of excessive bleeding (if antiplatelet agents continued perioperatively) or further ischemic damage to vital organs (if agents are stopped). Both adverse impacts will need to be managed by the anesthetist.

Antiplatelet agents in current use

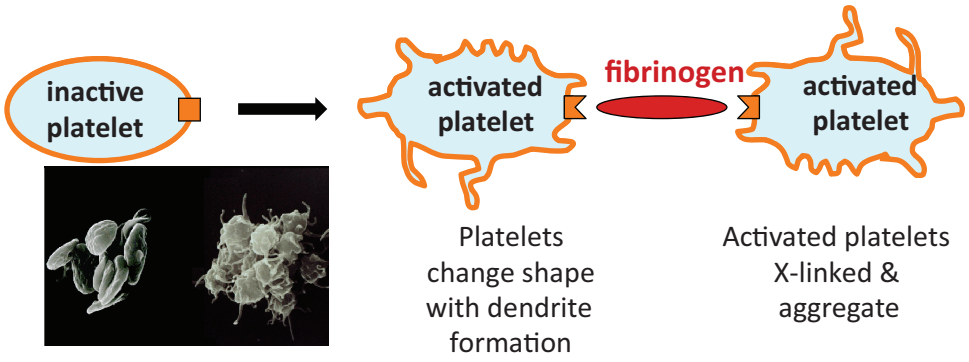
A wide range of agents are in current use [10]:

(1) Cyclooxygenase (COX) inhibitors – aspirin.
(2) ADP receptor ($P2Y_{12}$) inhibitors – clopidogrel, prasugrel, and ticagrelor.
(3) Glycoprotein IIb/IIIa (GIIb/IIIa) inhibitors – abciximab, tirofiban, and eptifibatide.
(4) Phosphodiesterase (PDE) inhibitors – cilostazol.
(5) Adenosine reuptake inhibitors – dipyridamole.
(6) Thromboxane synthase inhibitors – ifetroban.
(7) Thromboxane receptor antagonists – picotamide.
(8) Thrombin receptor (PAR-1) antagonists – vorapaxar.

However, strong evidence for their use is limited to the first three groups of agents. Thus, other agents should be stopped perioperatively, and their long-term use reviewed by physicians in consultation with the patient.

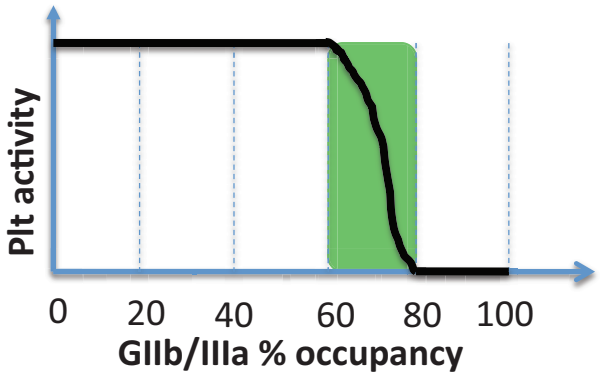
COX and $P2Y_{12}$ inhibitors inhibit the activation of platelets, while glycoprotein IIb/IIIa inhibitors inhibit aggregation (the final common pathway).

Figure 1



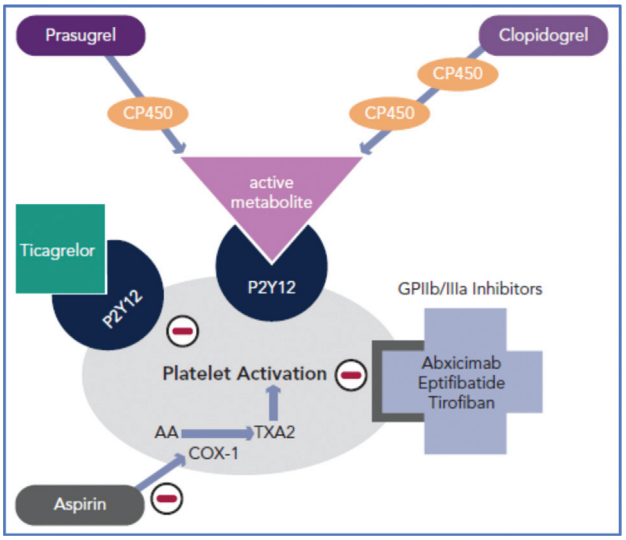
Platelets undergo conformational change on activation. These more amorphous platelets aggregate under the influence of fibrinogen.

Figure 2



Degree of platelet activity is dependent on the degree of occupancy of the glycoprotein IIb/IIIa receptor by platelet-blocking agents.

Figure 3



Agents that inhibit platelet activity act at a variety of different sites and may therefore have additive actions.

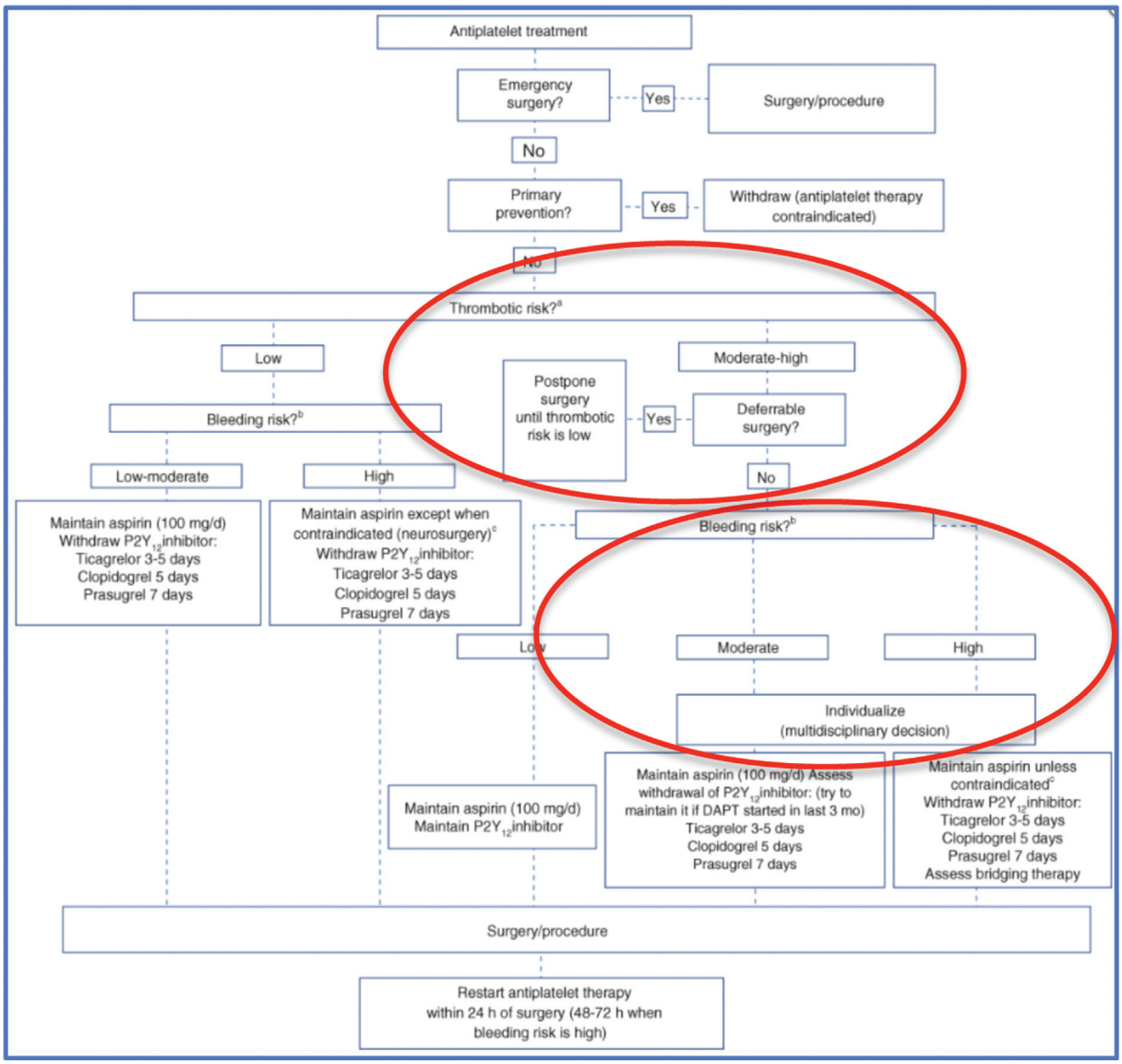
Antiaggregant agents (abciximab, tirofiban, and eptifibatide) are mainly used when patients are undergoing acute coronary percutaneous interventions when profound antiplatelet activity is required. Such patients are of extremely high risk for surgery and should only be accepted for acute life-saving interventions. Unfortunately, platelet transfusions are only likely to be of help if the agent used was the irreversible agent abciximab. Unfortunately, in patients who have received tirofiban or eptifibatide, routine platelet transfusions will be of no help. These agents bind reversibly to GIIb/IIIa and will redistribute to block the receptor on any transfused platelets, thus rendering them useless. For patients who received abciximab, platelet transfusions should be administered, aiming for 60–80% GIIb/IIIa occupancy (see Fig. 2). This will provide new, active platelets and will enhance the patient's own platelet activity.

Withdrawal of antiplatelet agents

Both COX and $P2Y_{12}$ inhibitors act to inhibit activation of platelets (see Fig. 3) and for most indications dual antiplatelet treatment (DAPT) is suggested. Both American and European Specialist Cardiology bodies (AHA, ESC) suggest that aspirin should be continued perioperatively and surgery avoided within 1 month of starting DAPT [8,11]. Where the stent inserted is drug eluting (as a pose to bare metal) this advice extends to avoiding surgery for at least 4 months – and thus it is important to elicit the type of stent that a patient has been treated with. Indeed, where drug-eluting stents have been inserted, knowledge of the particular type of stent used is helpful [12]. Third-generation stents may be less crucially dependent on longer-term DAPT treatment, and in the future, bioabsorbable stents may change guidance entirely [21].

Where withdrawal of $P2Y_{12}$ inhibitors is suggested, the time required will vary with the agent. Ticagrelor can be continued longest (withdraw 5

Figure 4



The European Specialist Cardiology 2018 guidelines state that where both thrombotic risk and bleeding risk are moderate to high, and surgery is deferrable, then treatment should be individualized by a multidisciplinary team.

days prior to surgery), while clopidogrel (withdraw for 7 days) and prasugrel (withdraw for 10 days) require longer [13]. If the patient is on $P2Y_{12}$ inhibitor monotherapy (not recommended), this should be replaced by aspirin.

Advice regarding delay is helpful where surgery is elective, but the anesthetist may well be faced with managing patients for urgent or emergent conditions. In these circumstances, where surgery poses a moderate/high risk of bleeding, the guidance is: 'individualized treatment following a multidisciplinary team discussion' (see Fig. 4). So what help is there to guide this discussion?

A DAPT risk score has been devised that is a moderately accurate prediction tool as regards the competing risks of cardiovascular and bleeding events when surgery is not contemplated [14]. The scores require information regarding:

(1) Patient characteristics – age, hypertension, diabetes mellitus, previous myocardial infarction/percutaneous interventions, heart failure, cigarette smoking, peripheral artery disease, renal insufficiency, full blood count.
(2) Stent characteristics – stent diameter and stent position (in vein graft?).

On-line calculation tools are freely available, and are useful for quantifying relative risks [15,16]. Such evidence should be shared with the wider multidisciplinary team – including the patient (and where the patient agrees, the family).

Where there is a high risk of thrombotic cardiovascular events if DAPT is withdrawn the MDT may question whether 'bridging' is necessary. Unfortunately, there is little evidence to aid this decision, or the choice of the bridging agent. However, it is clear that heparin should not be used for bridging as it increases platelet aggregation (via the IIb/IIIa receptor) despite decreasing the platelet numbers [17]. The availability of intravenous agents such as cangrelor has renewed interest in bridging [13], and the use of antiaggregant agents (such as abciximab) 72 h after withdrawal of $P2Y_{12}$ inhibitors has also been suggested. This, like triple therapy [18,19] (DAPT+oral anticoagulant – where both venous and arterial thrombus are a risk) increases the risk of bleeding further.

Conclusion

Increasing numbers of patients are taking DAPT. Continuing and stopping this treatment perioperatively provide competing risks to the patient (thrombotic versus bleeding risk). Anesthetists must be intimately involved in multidisciplinary discussions regarding which risk is greater, as they will be the acute physician called upon to manage the consequences. Any discussions should include an understanding of the appropriateness of treatment, and the relative risks of each choice [20]. The use of validated prediction tools is to be encouraged.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 NICE clinical knowledge summery: antiplatelet treatment. Available at: https://cks.nice.org.uk/antiplatelet-treatment#!topicsummary [Last revised December 2018].

2 Koupenova M, Kehrel BE, Corkrey HA, Freedman JE. Thrombosis and platelets: an update. Eur Heart J 2016; 38:785–791.

3 Phillips DR, Conley PB, Sinha U, Andre P. Therapeutic approaches in arterial thrombosis. J Thromb Haemost 2005; 3:1577–1589.

4 Piepoli MF, Hoes AW, Agewall S, Albus S, Brotons C, Catapona AL, *et al.* 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016; 37:2315–2381.

5 Wilson SJ, Newby DE, Dawson D, Irving J, Berry C. Duration of dual antiplatelet therapy in acute coronary syndrome. Heart 2017; 103:573–580.

6 Jing J, Meng X, Zhao X. Dual antiplatelet therapy in transient ischaemic attack and minor stroke with different infarction patterns. Subgroup analysis of the CHANCE randomized clinical trial. JAMA Neurol 2018; 75:711–719.

7 Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass. Cochrane Database Syst Rev 2015; 19:CD000535.

8 Bitti JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of antiplatelet therapy in patients with coronary artery disease. Circulation 2016; 134:e156–e178.

9 Magdy A, Shawky A, Mohanad A, Shaheen S. Egypt: coronary and structural heart interventions from2010 to 2015. Eurointervention 2017; 13:Z21–Z24.

10 Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collett JP, *et al.* Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J 2011; 32:2922–2932.

11 Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, *et al.* 2017 ESC focused update on dual antip;atelet therapy in coronary artery disease developed in collaboration with EACTS. EJCTS 2018; 53:34–78.

12 Schmidt T, Abbott JD. Coronary stents: history, design and construction. J Clin Med 2018; 7:126.

13 Koenig-Oberhuber V, Filipovic M. New antiplatelet drugs and new anticoagulants. BJA 2016; 117 (S2):ii74–ii84.

14 Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen 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; 315:1735–1749.

15 American College of Cardiology. Online DAPT risk calculator. Available at: https://tools.acc.org/DAPTriskapp/?_ga=2.222097944.1818735717.1544613814-543758694.1533140907#!/content/calculator/ [Accessed 15 December 2018]. [Accessed on 2019 Feb 6]

16 PRECISEDAPT. Online risk calculator. Available at: http://www.precisedaptscore.com/predapt/webcalculator.html [Accessed on 2019 Feb 6].

17 Gao C, Boylan B, Fang J, Wilcox DA, Newman DK, Newman PJ. Heparin promotes platelet responsiveness by potentiating αIIbβ3-mediated outside-in signalling. Blood 2011; 117:4946–4952.

18 Esmonde S, Sharma D, Peace A. Antiplatelet agents in uncertain clinical scenarios – a bleeding nightmare. Cardiovasc Diagn Ther 2018; 8:647–662.

19 Gong X, Tang S, Li J, Zhang X, Tian X, Ma S. Antithrombotic therapy strategies for atrial fibrillation patients undergoing percutaneous coronary intervention: a systematic review and network meta-analysis. PLoS One 2017; 12:e0186449.

20 Banerjee S, Angiolilo DJ, Boden WE, Murphy JG, Khalili H, Hasan AA, *et al.* Use of antiplatelet/DAPT for post-PCI patients undergoing noncardiac surgery. J Am Coll Cardiol 2017; 69:1861–1870.

21 Capodanno D, Angiolili DJ. Antiplatelet therapy after implantation of bioresorbable vascular scaffolds: a review of the published data, practical recommendations, and future directions. JACC Cardiovasc Interv 2017; 10:425–437.