An Overview of Antiplatelets for Acute Coronary Syndromes

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Introduction

Dual antiplatelet therapies have consistently been shown to improve outcomes in patients with acute coronary syndromes. Over the past decade there have been significant advances with the development of antiplatelets that have shown to be effective in reducing mortality rates but at the expense of higher bleeding events. This article describes the properties of current antiplatelet therapies used in clinical practice, recommendations for use and how to switch to an alternative antiplatelet drug. One of the controversies encountered on a daily basis is the management of patients who are on dual antiplatelet therapy and require surgical procedures after an acute coronary event. The risk of bleeding with the prospect of further ischaemic events needs to be assessed. As such no clear guidelines exist due to the lack of clinical trial data and each case needs to be individualized.

Keywords: Antiplatelet therapy; Percutaneous coronary intervention; Drug eluting stents; Bare metal stents

Discussion

Dual antiplatelet therapy is the most effective treatment for Acute Coronary Syndromes (ACS). The discovery of aspirin in 1974 for the secondary prevention after a myocardial infarction (MI) [1] demonstrated significant reductions in the rates of recurrent MI and death. Aspirin inhibits thomboxane A2 production by irreversibly inactivating cyclooxygenase 1 and hence inhibits platelet aggregation. A loading dose of 150-300 mg is recommended once the diagnosis of acute coronary syndrome (ACS) has been made followed by aspirin 75-81 mg once daily long term [2]. Aspirin should be combined with a P2Y12 inhibitor for a minimum of 12 months [2,3].

Currently there are three P2Y12 receptor inhibitor drugs that are commonly prescribed in the United Kingdom; clopidogrel, prasugrel and ticagrelor. Clopidogrel and prasugrel are categorised as thienopyradines and irreversibly bind to the P2Y12 receptor on the platelet, hence preventing platelet aggregation. They are pro drugs and require conversion to their active forms. Several cytochrome P450 enzymes are required to convert clopidogrel to its active form. In patients with ACS, the CURE trial (effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation) showed a significant reduction in death from cardiovascular causes, non fatal MI or stroke when aspirin and clopidogrel was combined versus aspirin and placebo [4]. In those undergoing percutaneous coronary intervention (PCI), there were lower rates of cardiovascular death, MI and revascularisation [5]. The combination of aspirin and clopidogrel however, was associated with increased bleeding rates [4]. Despite the positive results with clopidogrel,

approximately 4-30% of patients have inadequate platelet inhibition hence, up to 10% having higher thrombotic events [2]. Inadequate platelet inhibition with clopidogrel may occur due to non compliance, inappropriate dosing, defects of the P2Y12 gene or increased number of P2Y12 receptors [6]. Clopidogrel 300-600 mg is recommended as a loading dose followed by 75 mg daily [2,3]. Prasugrel unlike clopidogrel requires one step for conversion to its active form and subsequently is available in a higher concentration. A loading dose of 60 mg is required followed by 10 mg daily. The TRITON TIMI 38 trial (prasugrel versus clopidogrel in patients with acute coronary syndromes) demonstrated the superiority of the combination of aspirin and prasugrel over aspirin and clopidogrel with a reduction in death from cardiovascular causes, non fatal MI and non fatal stroke. Stent thrombosis was also lower in the prasugrel group. However, there was a higher incidence of major, life threatening and fatal bleeding with prasugrel when compared to clopidogrel [7]. Prasugrel should be avoided in patients >75 years or <60 kg in body weight due to a lack of benefit. It is also contraindicated in patients who have had a history of cerebrovascular events due to evidence suggesting harm in this patient group [7]. Intracranial haemorrhage rates are higher with prasugrel when compared to the other antiplatelets. The annual risk of intracranial haemorrhage has been reported as 0.4% with prasugrel which is higher when aspirin is combined with clopidogrel (0.3%) [8].

The use of clopidogrel and prasugrel has largely been superseded by ticagrelor based on compelling evidence from the PLATO study (ticagrelor versus clopidogrel in patients with acute coronary syndromes). Unlike clopidogrel and prasugrel, ticagrelor binds reversibly to the P2Y12 receptor in its active form. A loading dose of 180 mg is prescribed followed by 90 mg twice daily. In the PLATO trial there were lower death rates from vascular causes, MI or stroke with ticagrelor and aspirin when compared to clopidogrel and aspirin. However, major bleeding unrelated to coronary artery bypass grafting was higher with ticagrelor. Therefore in patients with a history of gastrointestinal bleeding it is preferable to use clopidogrel. Side effects of ticagrelor include dysponea and bradyarrhythmias. Dysponea tends to be mild has been reported in up to 14.2% of patients due to higher levels of adenosine since adenosine deaminase is inhibited. There is however no compromise in pulmonary function and symptoms tend to subside with continuation. Patients should attempt to persevere with symptoms but if intolerable it is feasible to switch to an alternative anti platelet. Ventricular pauses have been documented with ticagrelor and generally resolve within 30 days of drug commencement [9]. Other antiplatelets include ticlopidine and cangrelor. Ticlopidine was the first P2Y12 receptor inhibitor for ACS patients but is obsolete due to serious haematological side effects. Cangrelor has recently been approved and provides immediate inhibition of P2Y12 receptor

inhibition as it is administered intravenously in patients who are undergoing PCI. Taking into account the available evidence, prasurel or ticagrelor is preferred over clopidogrel for ACS patients [2].

Aspirin should be combined with a P2Y12 receptor inhibitor as soon as the diagnosis of ACS is made regardless of management strategy [2,3]. DAPT is recommended for 1 year followed by long term aspirin [2,3]. According to the National Institute of Clinical Excellence (NICE) 2015 guidelines for patients who have has an ST elevation myocardial infarction the minimum duration for clopidogrel should be one month followed by long term aspirin. The basis for this is unclear.

A shorter duration of DAPT is associated with lower major bleeding rates. Longer duration of DAPT beyond 12 months resulted in lower MI and stent thrombosis but increased rates of major bleeding [10]. In the PEGASUS-TIMI 54 trial (long term use of ticagrelor in patients with prior myocardial infarction) the benefit of aspirin and ticagrelor beyond 1 year after an acute coronary event was compared with monotherapy alone. There was a 1.2-1.3% absolute reduction in the risk of cardiovascular death, myocardial infarction or stroke but at the expense of increased bleeding rates [11].

Based on trial data the American College of Cardiology (ACC) guidelines have given a class IIb ("maybe considered") recommendation to the use of extended DAPT in patients with higher ischemic risk with lower bleeding risk (Table 1) [3].

	Aspirin	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of action	Inhibits thomboxane A2 production by irreversibly inactivating cyclooxygenase 1	Irreversibly binds to the P2Y12 receptor	Irreversibly binds to the P2Y12 receptor	Irreversibly binds to the P2Y12 receptor	Reversibly binds to the P2Y12 receptor
Daily regime	A loading dose of 150-300 mg, followed by 75-81 mg once daily	500 mg loading dose followed by 250 mg twice daily	300-600 mg loading dose followed by 75 mg daily	60 mg loading dose followed by 10 mg daily	180 mg loading followed by 90 mg twice daily
Duration of treatment after acute coronary event	Lifelong	6 months	12 months	12 months	12 months
Side effects	Gastric bleeding, Haemorrhagic stroke	Diarrhea, Nausea, Vomiting, Neutropenia	Haemorrhagic stroke	Bleeding	Dysponea
	Bleeding	Bleeding	Bleeding	Avoid in patients > 75 years, <60 kg in body weight or history of cerebrovascular disease	Bradyarrhythmias
					Bleeding
Absolute annual Intracranial haemorrhage risk (Indian journal ICH)	0.03%		0.33%	0.40%	0.30%

Table 1: Antiplatelet therapies past and present.

Due to the side effect profile, safety, costing and efficacy of anti platelets it may be necessary to switch between antiplatelets. Ticagrelor is reversibly binding with plasma half life of 8-12 hours therefore requiring twice daily dosing. A loading dose is advised when switching from ticagrelor to prasugrel/clopidogrel to avoid a gap in anti-platelet coverage. Clopidogrel and prasugrel are irreversibly binding; hence a loading dose may not be essential. However based on the current available data a loading dose is recommended when switching between antiplatelets [12].

Approximately 5-15% of patients who have had a PCI procedure will require a surgical procedure within 2 years [13]. Complexities surrounding the management of DAPT prevails since there is no clear guidance due to the paucity of data from clinical trials. Therefore decision making needs to be individualised. The type and urgency of surgery needs consideration and if possible should be delayed for at least 1 year after an ACS. If surgery cannot be postponed then the risk of bleeding with continuation of DAPT and the risk of ischemic events needs to be assessed particularly in patients who have had PCI. Early discontinuation of DAPT increases the risk of stent thrombosis especially if there is a history of recent PCI, >1 stent, long stents, bifurcation stenting, left main stem stenting, incomplete revascularisation, diabetes and heart failure.

Predictors of bleeding risk in ACS patients include female sex, renal dysfunction, and history of bleeding and advanced age. This is therefore complicated in surgical patients who have increased risk of MI if DAPT is discontinued and increased bleeding risk if DAPT is continued. The incidence of adverse ischaemic events has been reported as 20% at 30 days when the timing between stent insertion and surgery was <45 days. When the interval exceeded 6 months adverse ischaemic events were much lower at 1.2%. It is unclear if the reported findings were due to discontinuation of DAPT or P2Y12 receptor inhibitor alone [14]. If the duration of DAPT therapy needs to be reduced for ACS patients who have had PCI and are undergoing surgical procedures it is compulsory that a minimum of 1 month of DAPT is completed for those who have had a bare metal stent and 6 months for drug eluting stents [2].

Depending on the type of surgery to be performed some recommendations exist regarding antiplatelet therapy. For endoscopic

procedures P2Y12 receptor inhibitors should be discontinued for 7-10 days if a polypectomy, gastrostomy or biliary sphincterectomy is planned [15]. DAPT can be continued for dental procedures as there is a low risk of bleeding associated with such procedures. Aspirin can be continued for dermatologic procedures, ophthalmic surgery and carotid endarterctomy. There is little evidence regarding P2Y12 receptor inhibitors in patients undergoing dermatological procedures and ideally should be stopped in ophthalmic procedures if on DAPT [16]. In general P2Y12 receptor inhibitors should be discontinued 5 days before a surgical procedure if required and reinstituted thereafter when feasible [16,17]. Due to the complexities surrounding the management of DAPT in ACS patients undergoing surgical procedures, each case must be individualised and should be discussed with a specialist.

Conclusion

DAPT has consistently been shown to be efficacious in reducing mortality rates in patients with ACS. The major side effects encountered with antiplatelets is bleeding and thus it may become necessary to switch to an alternative antiplatelet. Patients should be prescribed a loading dose when switching between antiplatelets to allow sufficient antiplatelet coverage. The management of patients who are on DAPT for an ACS and require surgery is often challenging as the risk of bleeding versus further ischaemic events needs to be assessed. No clear guidelines exist due to the lack of clinical data but if possible surgery should be delayed until DAPT treatment has been completed. In more complex cases a discussion with a specialist needs to be sought.

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