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Review

An evidence-based review of current anti-platelet options for STEMI patients

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ABSTRACT

Drug-eluting stents are the default treatment for acute coronary syndromes, unless concerns or contraindications preclude dual antiplatelet therapy (DAPT). Platelet microemboli and mediators from activated platelets can undermine the restoration of perfusion. Therefore, ST-segment elevation MI (STEMI) patients should receive antiplatelet treatments regardless of reperfusion strategy. This review offers an evidence-based comparison of the $P2Y_{12}$ antagonists that have been evaluated in STEMI.

While several studies support clopidogrel in STEMI, the benefits emerge several hours after administration and vary considerably reflecting genetic, cellular and clinical inter-individual differences. Although higher clopidogrel loading doses may improve outcomes, ticagrelor and prasugrel are more potent, produce less inter-individual variability, and show a faster onset of action. Ticagrelor and prasugrel improve outcomes compared to clopidogrel, with manageable bleeding risks, although further studies with a longer follow up are needed.

Studies directly comparing ticagrelor and prasugrel are now needed. In the meantime, most current guidelines focus on clopidogrel and, therefore, need revision. While several polymorphisms influence platelet activity, CYP2C19 variants are the most consistently linked to clopidogrel responsiveness. Consensus groups should consider the studies needed to allow routine pharmacogenomic testing. The evidence-based use of $P2Y_{12}$ antagonists in DAPT should further reduce the morbidity and mortality associated with STEMI.

1. Introduction

Declines in the prevalence of several modifiable risk factors (including untreated hypertension and dyslipidaemias, and smoking), greater uptake of primary and secondary prevention, and growing implementation of reperfusion strategies contributed to the decrease in cardiovascular (CV) mortality across the developed world in recent years. In the United Kingdom, CV deaths among people under 75 years of age declined by 44% in the last decade [1]. In the USA, in-hospital mortality following myocardial infarction (MI) declined between 1997 and 2006 in all groups, except among men <55 years of age [2]. Overall, average in-patient mortality among patients with ST segment elevation MI (STEMI) declined from 25% to 30% in the 1960s (before the advent of coronary care units) to around 16% in the mid-1980s (before the introduction of reperfusion strategies). One-month in-patient mortality is now around 4–6%. Nevertheless, community studies suggest that overall 1-month mortality is about 50% among people with presumed MI or acute coronary syndromes (ACS). About half of these deaths occur within 2 hours of the onset of MI or ACS. This early mortality has shown little improvement in recent years [3].

Against this background, reperfusion aims to restore flow through infarcted arteries as quickly and completely as possible and then maintain vessel patency and improve perfusion to the infarcted myocardium [4]. Stents reduced the risk of dissection-related acute vessel closure and late restenosis among STEMI patients undergoing angioplasty [5]. A meta-analysis of 13 randomised trials encompassing 7352 patients found that compared with bare metal stents (BMS), drug-eluting stents (DES) reduced the risk of target vessel revascularisation (TVR) (relative risk [RR]: 0.44; 95% confidence interval [CI]: 0.35 to 0.55). DES did not increase mortality (RR: 0.89; 0.70 to 1.14), MI (RR: 0.82; 0.64 to 1.05) or stent thrombosis (RR: 0.97; 0.73 to 1.28) compared with BMS. The differences between DES and BMS persisted over the 2 years after implantation. An analysis of data collected from 26,521 patients enrolled in 18 registries showed that DES significantly reduced TVR (RR: 0.54; 0.40 to 0.74) without increasing MI risk (RR: 0.87; 0.62 to 1.23). DES implantation reduced mortality risk during the year following implantation (RR 0.68; 0.54–0.86) but not after 2 years (RR 0.89; 0.64–1.22). Registries probably include a broader, more complex, and heterogeneous population of STEMI patients than randomised studies, which may account for these differences [6]. Indeed, guidelines published by the European Society of Cardiology (ESC) suggest that DES are the default treatment in almost all ACS cases and lesion subsets, unless concerns or

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Table 1
Comparison of the characteristics of clopidogrel, prasugrel and ticagrelor (Eshaghian).

Type	Clopidogrel Thienopyridine	Prasugrel Thienopyridine	Ticagrelor Cyclopetyltriazolopyrimidine
Prodrug	Yes	Yes	No
Oral administration	Yes	Yes	Yes
Loading dose (mg)	300	60	180
Maintenance dose (mg)	75	10	90
Frequency of administration	Once daily	Once daily	Twice daily
Onset of action	Delayed	Rapid	Rapid
Offset of action	Delayed	Delayed	Rapid
Individual variability	Large	Small	Small
CYP-450 activation	Yes (twice)	Yes	No
Irreversible $P2Y_{12}$ inhibition	Yes	Yes	No
Relative potency	Low	High	High
Mean platelet inhibition	~50%	~70%	~95%
Time to peak inhibition (h)	~12*	2	2
Half-life	Life of platelet	Life of platelet	7–12 h
Days to hold before CABG surgery	>5	>7	>3

*With 300 mg loading dose.

contraindications preclude prolonged dual antiplatelet therapy (DAPT) [7], the focus of this review.

Bare metal stents and DES delay endoluminal healing at the angioplasty site, which predisposes to stent thrombosis—a complication associated with a considerable risk of mortality (approximately 20% to 40%), MI (around 50% to 70%) and repeat revascularization [5]. Therefore, BMS and DES implantation necessitates reliable and effective DAPT (aspirin plus one of the following: clopidogrel, ticagrelor or prasugrel) [3,4,7,8]. Indeed, antiplatelet therapy is so important to successful outcomes with stents that patients likely to comply poorly with DAPT, including those with multiple co-morbidities or using polypharmacy, represent a relative contraindication to DES [7]. Furthermore, microvascular damage caused by microemboli and mediators released from activated platelets that promote occlusion or spasm undermine the restoration of perfusion. Therefore, STEMI patients should receive antiplatelet and antithrombotic treatments regardless of reperfusion strategy [4].

Several other agents—such as low molecular weight heparin and glycoprotein IIb/IIIa inhibitors (GPI)—also improve outcomes in the STEMI setting. However, these tend to be used alongside DAPT to maximise reperfusion. For example, during the On-TIME 2 study, pre-hospital initiation of high-dose bolus tirofiban and high-dose clopidogrel improved residual ST deviation compared with placebo before (10.9 ± 9.2 and 12.1 ± 9.4 mm respectively, $p = 0.028$) and 1 hour after (3.6 ± 4.6 and 4.8 ± 6.3 mm; $p = 0.003$) percutaneous coronary intervention (PCI) [9]. Tirofiban reduced major adverse cardiac events (MACE) at 30 days compared with placebo (5.8% and 8.6% respectively; $p = 0.043$). A strong trend suggested that tirofiban decreased mortality after 30 days (2.2% and 4.1% respectively; $p = 0.051$) and 1 year (3.7% and 5.8% respectively; $p = 0.08$) [10]. In STEMI patients receiving fibrinolysis, enoxaparin's net benefit is similar in patients who are and are not treated with clopidogrel (risk reduction 2.4% [95% CI −0.5 to 5.3%]; and 1.7% [95% CI 0.5% to 3.0%] respectively). Overall, combining a fibrinolytic, aspirin, clopidogrel and enoxaparin is an effective reperfusion strategy in STEMI [11]. In the CICERO trial, the benefit of systemic versus intracoronary administration of abciximab in addition to pretreatment with aspirin, heparin and clopidogrel was investigated [12]. The incidence of complete ST-segment resolution was similar in both groups (64% vs 62% for intracoronary and systemic respectively). However, the incidence of myocardial blush grade 2/3 was significantly higher (76% vs 67%; $p = 0.022$) and the size of enzymatic infarct significantly lower (5.5 vs 6.1%; $p = 0.008$) in the intracoronary group than the systemic group, indicating an improvement in myocardial reperfusion with the intracoronary administration of abciximab. The incidence of MACE was not different between the two groups [12]. However, recent data from the AIDA STEMI trial showed no benefit of intracoronary application of abciximab over intravenous administration for ST-segment resolution, or for the composite end point of death, reinfarction or new heart failure at 90 days [13].

DAPT's efficacy reflects the complementary mechanisms of the component drugs. Aspirin permanently acetylates cyclooxygenase 1 (COX-1), inhibiting conversion of arachidonic acid to thromboxane A2 (TxA2). Clopidogrel, ticagrelor and prasugrel antagonise platelet $P2Y_{12}$ receptors, a COX-1-independent pathway, thereby inhibiting aggregation induced by several mediators including ADP, collagen, thrombin, serotonin, epinephrine and TxA2. Pathways associated with $P2Y_{12}$ also amplify certain downstream effects triggered by platelet activation, including granule release, TxA_2 formation, inflammation and coagulation [14]. This review offers an evidence-based comparison of the antiplatelet agents that antagonise $P2Y_{12}$ receptors—clopidogrel, ticagrelor and prasugrel (Table 1)—that have been evaluated in STEMI patients [1,15].

A summary of the main randomised studies of antiplatelet agents in the setting of ACS and STEMI, which will be described in further detail below, can be found in Table 2.

Table 2
Summary of the main randomised studies of antiplatelet agents in the setting of ACS and STEMI.

Study (year)	Patients (*n*)	Duration of follow-up	Intervention	Primary endpoint	Results
CLARITY-TIMI 28	STEMI and fibrinolysis ($n = 3491$)	30 days	Clopidogrel 300 mg LD + 75 mg MD	TIMI flow 0–1, death or recurrent MI before angiography	21.7% vs 15% ($p < 0.001$)
TRITON TIMI 38	ACS ($n = 13608$)	15 months	Clopidogrel 300 mg/75 mg vs Prasugrel 60/10 mg	CV death, MI or stroke	12.1% vs 9.9% ($p < 0.001$)
TRITON TIMI 38 STEMI	STEMI ($n = 3534$)	15 months	Clopidogrel 300 mg/75 mg vs Prasugrel 60/10 mg	CV death, MI or stroke	12.4% vs 10% ($p = 0.0221$)
PLATO	ACS ($n = 18624$)	12 months	Clopidogrel 300/600 mg/ 75 mg vs Ticagrelor 180 mg LD/90 mg bid	CV death, MI or stroke	11.7% vs 9.8% ($p < 0.001$)
PLATO STEMI	STEMI ($n = 7544$)	12 months	Clopidogrel 300/600 mg/ 75 mg vs Ticagrelor 180 mg LD/90 mg bid	CV death, MI or stroke	10.8% vs 9.4% ($p = 0.07$)