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REVIEW

New antiplatelet agents in the treatment of acute coronary syndromes

Les nouveaux agents antiplaquettaires dans le traitement des syndromes coronaires aigus

Pierre Sabouret[a,*], **Magali Taiel-Sartral**[b]

[a] *Cardiovascular Prevention Institute, 14 bis, boulevard de l'Hôpital, 75005 Paris, France*
[b] *Cardiovascular Medical Unit, Lilly, Neuilly-sur-Seine, France*

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Summary Effective antagonism of the $P2Y_{12}$ platelet receptor is central to the treatment of acute coronary syndrome (ACS) patients, especially in the setting of percutaneous coronary intervention and stenting. According to consensus guidelines, early revascularization and intensive antiplatelet therapy are key to reducing the complications that arise from myocardial ischaemia and the recurrence of cardiovascular events. Until recently, clopidogrel was the key $P2Y_{12}$ antagonist advocated, but due to several limitations as an antiplatelet agent, newer drugs with more predictable, rapid and potent effects have been developed. Prasugrel and ticagrelor are now the recommended first-line agents in patients presenting with non-ST-segment elevation ACS and ST-segment elevation ACS, due to large-scale randomized trials that demonstrated net clinical benefit of these agents over clopidogrel, as stated in the European guidelines. Although no study has directly compared the two agents, analysis of the data to date suggests that certain patient types, such as diabetics, those with ST-segment elevation

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; AHA, American Heart Association; CABG, coronary artery bypass graft; CI, confidence interval; CYP, cytochrome P450; ESC, European Society of Cardiology; HPR, high on-treatment platelet reactivity; HR, hazard ratio; LD, loading dose; MD, maintenance dose; NSTEMI, non-ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STE-ACS, ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina.

* Corresponding author.
E-mail addresses: pierre.sabouret@psl.aphp.fr, pfsabouret@free.fr (P. Sabouret).

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myocardial infarction or renal failure and the elderly may have a better outcome with one agent over the other. Further studies are needed to confirm these differences and answer pending questions regarding the use of these drugs to optimize efficacy while minimizing adverse events, such as bleeding. The aim of this review is to provide an overview of the current $P2Y_{12}$ receptor antagonists in the treatment of ACS, with a focus on issues of appropriate agent selection, timing of treatment, bleeding risk and the future role of personalized treatment using platelet function and genetic testing.

MOTS CLÉS
Molécules antiplaquettaires ;
Réactivité plaquettaire ;
Antagoniste du récepteur $P2Y_{12}$

Résumé L'inhibition effective du récepteur plaquettaire $P2Y_{12}$ est primordiale dans le traitement des patients présentant un syndrome coronaire aigu (SCA), en particulier lors de l'exécution d'une intervention coronaire percutanée (ICP) avec pose de stent. Selon les recommandations, une revascularisation précoce et un traitement antiplaquettaire intensif sont clés pour réduire les complications secondaires à l'ischémie myocardique et prévenir la récurrence d'événements cardiovasculaires. Jusqu'à un passé récent, clopidogrel a été le produit de référence pour inhiber le récepteur $P2Y_{12}$, cependant, en raison d'un certain nombre de limitations de son action antiplaquettaire, de nouveaux agents, plus constants dans leur effet, plus rapides et plus puissants, ont été développés. Prasugrel et ticagrelor sont maintenant les molécules de première ligne recommandées chez les patients présentant un SCA sans sus-décalage du segment ST (NSTE-SCA) ou avec sus-décalage du segment ST (STE-SCA), en raison de l'existence de larges études randomisées ayant démontré un bénéfice clinique net de ces produits supérieur à clopidogrel, comme le mentionnent les recommandations européennes. Bien qu'aucune n'étude n'ait directement comparé les deux produits, à ce jour l'analyse des données suggère que certains profils de patients, comme les diabétiques, les patients avec un STEMI, les insuffisants rénaux ou les sujets âgés, tirent plus de bénéfice avec l'une ou l'autre des molécules. Des études supplémentaires sont nécessaires pour confirmer ces différences et répondre à des questions restées en suspens quant à l'utilisation optimale de ces produits, consistant à favoriser leur efficacité tout en réduisant leurs effets secondaires tels que les saignements. Le but de cette revue de la littérature est d'apporter une vue d'ensemble sur les molécules actuelles antagonistes du récepteur $P2Y_{12}$ dans le traitement du SCA, en insistant sur les problématiques concernant le choix approprié de la molécule, le moment de son administration, le risque de saignement et le rôle futur d'un traitement personnalisé grâce aux tests de fonction plaquettaire et génétiques.

Introduction

Acute coronary syndromes (ACSs) have a significant impact on health in the Western world, with an estimated burden of 1.5 million hospitalizations and 4.5 million emergency department visits per year attributed to ACSs in the USA [1]. Despite advances in treatment, ACSs are associated with significant morbidity and mortality.

In an ACS, acute atherosclerotic plaque rupture leads to platelet activation, adhesion and aggregation, which are vital factors in the early formation of a coronary thrombus [2]. Antiplatelet agents that inhibit agonism by adenosine diphosphate (ADP) of the $P2Y_{12}$ platelet receptor are central to the prevention of complications and recurrent cardiovascular ischaemic events in patients with ACS and also post percutaneous coronary intervention (PCI) [3—5]. Based on current European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines [6—9], the diagnosis of ACS is further substratified into ST-segment elevation ACS (STE-ACS) and non-ST segment elevation ACS (NSTE-ACS). Dual antiplatelet therapy comprising aspirin and a $P2Y_{12}$ antagonist is currently recommended for the treatment of this clinical presentation.

Clopidogrel

Clopidogrel is a second-generation thienopyridine derivative that binds specifically and irreversibly to the platelet $P2Y_{12}$ purinergic receptor, inhibiting ADP-mediated platelet activation and aggregation [10,11]. Clopidogrel is a prodrug that is metabolized to its active form in the liver. The reactive thiol group of the active metabolite of clopidogrel forms a disulphide bridge between one or more cysteine residues of the $P2Y_{12}$ receptor. This interaction is irreversible, accounting for the observation that platelets are inhibited, even if no active metabolite is detectable in plasma. Until recently, clopidogrel was the standard of care in dual antiplatelet therapy. However, clopidogrel has several limitations as an antiplatelet agent. Firstly, it has a delayed onset of action, which results in suboptimal platelet inhibition at the time of urgent or early PCI. Secondly, the platelet inhibition due to clopidogrel is irreversible and there is interindividual variability in the recovery of platelet function, leading to higher bleeding risk for patients undergoing surgery, including coronary artery bypass graft (CABG). Thirdly, there is considerable interindividual variability in the pharmacodynamic response

to the drug, with some patients being termed clopidogrel resistant or as having high on-treatment platelet reactivity (HPR). This is largely due to interindividual differences in the metabolism of the prodrug and has been correlated with increased risk of atherothrombotic events [12–15].

The CURE trial was the key landmark analysis that exemplified clopidogrel efficacy. In this study of 12,562 patients presenting with NSTE-ACS within 24 hours of symptom onset, clopidogrel 300 mg then 75 mg and aspirin was compared with aspirin alone. Clopidogrel resulted in a 20% relative risk reduction in the prevalence of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction (MI) and stroke compared with aspirin monotherapy. This clinical benefit was also shown in patients presenting with ST-segment elevation myocardial infarction (STEMI) and treated with thrombolysis in the CLARITY-TIMI 28 trial, where there was a similar reduction in the occurrence of the clinical endpoint of cardiovascular death, myocardial infarction and recurrent ischaemia [16].

A higher loading dose (LD) of clopidogrel was assessed in ACS patients in the CURRENT-OASIS 7 trial, where 600 mg were administered on day 1, 150 mg on days 2–7 and 75 mg thereafter [17]. There was overall no benefit for this strategy with respect to rate of occurrence of the primary outcome of cardiovascular death, myocardial infarction or stroke after 30 days (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.83–1.06; $P = 0.3$). There was however a significant increase in the rate of bleeding in the high double-dose group (2.5%) compared with in the low-dose group (2.0%) (HR 1.24, 95% CI 1.05–1.46; $P = 0.01$). In a subgroup analysis of 17,263 patients who underwent PCI, the high dose appeared to have benefit in moderate-to-high-risk patients undergoing PCI, significantly decreasing the occurrence of the primary composite endpoint of myocardial infarction, stroke or cardiovascular death at 30 days (3.9% vs. 4.5%; HR 0.86, 95% CI 0.74–0.99; $P = 0.039$) (Table 1). Further support for these findings was found in the COMMIT trial, which included a large number of patients with acute myocardial infarction ($n = 45,852$) and demonstrated that 75 mg without LD within 24 hours of presentation produced a 9% proportional reduction in the occurrence of death, reinfarction or stroke [4].

Newer antiplatelet agents

To overcome the sub-optimal pharmacodynamic and pharmacokinetic profile of clopidogrel, new $P2Y_{12}$ inhibitors have been developed, which are more predictable and have a faster onset of action – characteristics that make them particularly attractive for PCI. Prasugrel and ticagrelor are two agents that are now recommended for the treatment of NSTE-ACS [6] and STEMI [8] based on evidence that has demonstrated a reduction in cardiovascular events compared with clopidogrel. Intravenous agents with reversible action, such as cangrelor, have also been developed, allowing an alternative route of administration and even more rapid onset and offset of action compared with oral agents.

Prasugrel

Prasugrel is a third-generation thienopyridine that has a similar mechanism of action to clopidogrel, in that its active form binds covalently to the $P2Y_{12}$ receptor via a disulphide bond, causing irreversible blockade for ADP binding. However, it has much more rapid and consistent inhibitory effects on platelet aggregation than clopidogrel, due to more efficient in vivo generation of its active metabolite [18]. The prodrug is rapidly hydrolysed by carboxylesterases to a thiolactone, which is then efficiently converted to the active derivative via cytochrome P450 (CYP) isoenzymes (CYP3A4, CYP2B6 and CYP2C9) in a one-step process. CYP2C19 makes only a minor metabolic contribution [19]. The esterase-mediated step for prasugrel occurs mainly in the intestine, as does the CYP-mediated oxidative step leading to the active metabolite formation. However, hydrolysis of clopidogrel by esterases in the intestine and/or liver leads to formation of an inactive metabolite, and conversion of the remaining clopidogrel to its active metabolite requires two CYP-mediated steps that occur mainly in the liver. The polymorphisms in CYP2C9, CYP2C19, CYP2C17 and ABCB1 that have an effect on clopidogrel do not significantly alter prasugrel clinical efficacy, pharmacokinetics or pharmacodynamics [20,21]. The peak concentration of the active metabolite of prasugrel is achieved rapidly at 30 minutes and a maximum of 60–70% inhibition is usually achieved within 2–4 hours [20]. For the STEMI population, recent studies have shown that optimal inhibition of platelet aggregation is reached 2–6 hours after LD administration [22] and rarely before 1 hour [23].

The ACAPULCO trial specifically evaluated the pharmacodynamic effects of a 10 mg maintenance dose (MD) of prasugrel in 56 patients with unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI), compared with a high MD of clopidogrel (150 mg daily) after a high LD (900 mg). Greater platelet inhibition with prasugrel 10 mg daily was observed over 14 days compared with clopidogrel 150 mg daily [24].

The pharmacodynamic benefit of prasugrel was further demonstrated in the OPTIMUS-3 study, when prasugrel was compared with high-dose clopidogrel in 35 patients with type 2 diabetes mellitus and coronary artery disease. Prasugrel was associated with greater platelet inhibition than clopidogrel at 4 hours post LD, as assessed using the VerifyNow assay (least squares mean 89.3% vs. 27.7%; $P < 0.0001$) and this was also seen for the MD at 7 days (61.8% vs. 44.2%; $P < 0.0001$) [25].

The superior antiplatelet effect of prasugrel was further demonstrated in the phase II PRINCIPLE-TIMI (prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation – TIMI) 44 trial, which compared a 60 mg dose of prasugrel with a 600 mg LD of clopidogrel. Among patients planned for PCI, loading with prasugrel 60 mg resulted in greater platelet inhibition than a clopidogrel 600 mg LD. Daily maintenance therapy with prasugrel 10 mg resulted in a greater antiplatelet effect than clopidogrel 150 mg daily [26].

In addition, the safety of prasugrel was demonstrated in the JUMBO-TIMI (Joint Utilization of Medications to Block Platelets Optimally – Thrombolysis in Myocardial Infarction)

Table 1 Comparison of endpoints between trials.

Endpoint (percentage of events)	CURRENT-OASIS 7			TRITON-TIMI 38 (2007)			PLATO invasive (2009)		
	Clopidogrel 600 mg	Clopidogrel 300 mg	HR (95% CI)	Prasugrel	Clopidogrel 300 mg	HR (95% CI)	Ticagrelor	Clopidogrel 300 mg	HR (95% CI)
Primary endpoint[a]	3.90	4.50	0.86 (0.74—0.99)	9.90	12.10	0.81 (0.73—0.90)	9.00	10.70	0.84 (0.75—0.94)
All-cause death	1.90	2.10	0.94 (0.76—1.16)	3.00	3.20	0.95 (0.78—1.16)	3.90	5.00	0.81 (0.68—0.95)
Non-fatal myocardial infarction	2.00	2.60	0.79 (0.64—0.96)	7.30	9.50	0.76 (0.67—0.85)	5.30	6.60	0.80 (0.69—0.92)
Non-CABG-related major bleeding[b]	0.80	0.60	1.34 (0.94—1.91)	2.40	1.80	1.32 (1.03—1.68)	2.80	2.20	1.23 (0.98—1.55)

CABG: coronary artery bypass graft; CI: confidence interval; HR: hazard ratio.
[a] Death from cardiovascular causes, non-fatal MI, non-fatal stroke.
[b] According to Thrombolysis in Myocardial Infarction (TIMI) criteria.

phase II trial. This was a dose-ranging comparison of different prasugrel doses (7.5 mg, 10 mg and 15 mg) with clopidogrel [27]. At 30 days, there was a numerically higher but not statistically significant rate of bleeding events (non-CABG Thrombolysis in Myocardial Infarction [TIMI] major + minor) in the prasugrel groups than in the clopidogrel group; access site bleeding was the most common type of bleeding observed.

The superior pharmacodynamic and pharmacokinetic profile of prasugrel has translated into clinical benefit compared with clopidogrel. The TRITON-TIMI 38 trial evaluated 13,608 patients with moderate-to-high-risk ACS, including 10,074 patients with UA or NSTEMI and 3534 patients with STEMI [28], who were planned to undergo PCI. Patients were randomized to receive a prasugrel 60 mg LD followed by 10 mg/day or clopidogrel 300 mg followed by 75 mg/day; for STEMI patients, the study drug was given as soon as possible, meaning that prasugrel could be given without knowledge of the coronary anatomy; for UA/NSTEMI patients, the study drug was given when the decision for PCI was made after the coronary angiogram. Patients continued therapy for 6—15 months after enrolment. Prasugrel was associated with a 19% reduced risk of occurrence of the primary endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) compared with clopidogrel and fewer ischaemic events, which translates to a number needed to treat of 46. This ischaemic benefit was counterbalanced by an increased risk of bleeding: among patients treated with prasugrel, 146 (2.4%) had at least one TIMI major haemorrhage that was not related to CABG, compared with 111 (1.8%) patients treated with clopidogrel (hazard ratio 1.32, 95% CI 1.03—1.68; $P = 0.03$), with a number needed to harm of 167; thus, the overall net clinical benefit of prasugrel was significant. The ischaemic benefit was mainly driven by a reduction in myocardial infarction and stent thrombosis, with overall reductions of 2.3% and 1.3%, respectively. No difference was observed in mortality (Table 1).

Based mainly on the outcome of the TRITON trial, prasugrel was approved by the Food and Drug Administration (USA) in July 2009 and by the European Medicines Agency (Europe) in February 2009.

Ticagrelor

Ticagrelor (AZD6140) is the first of a new class of antiplatelet family called cyclopentyl-trazolo-pyrimidines (CPTPs) and is also the first oral reversible selective $P2Y_{12}$ receptor antagonist. Like the thienopyridines, ticagrelor binds the platelet $P2Y_{12}$ receptor to inhibit the prothrombotic effects of ADP. However, unlike the thienopyridines, this effect is non-competitive and reversible. Ticagrelor appears to act through an allosteric modulation site and exhibits a conformational change in the receptor by binding independently of ADP; it therefore does not prevent ADP binding but seems to have an effect on ADP receptor-induced signaling and platelet aggregation [29,30]. Ticagrelor is a direct-acting compound and does not require metabolic activation, thus obviating any influence of the CYP pathway on the antiplatelet response. Moreover, CYP2C19 and ABCB1 genotypes, which are known to influence the effects of clopidogrel, did not influence the effect on ischaemic outcomes in ACS patients. When administered orally, the agent displays a linear pharmacokinetic profile and has a rapid onset of action. The maximum plasma concentration and maximum platelet inhibition are reached 1—3 hours after treatment [20]. However, as with prasugrel, for the STEMI population, recent studies have shown that optimal inhibition of platelet aggregation is rarely reached before 1 hour [23] and that the effects of ticagrelor and prasugrel on inhibition of platelet aggregation are similar [31]. Ticagrelor has a relatively short half-life and an offset of action that is more rapid than clopidogrel, so it may be advantageous in clinical scenarios requiring rapid reversal of the antiplatelet effect (e.g. in patients requiring CABG). However, this pharmacodynamic profile could also put patients at risk of acute events, such as stent thrombosis, especially after drug-eluting stent implantation if they are not strictly compliant with therapy.

In a pharmacodynamics substudy of the PLATO study of 69 patients with ACS (to be discussed later), ticagrelor (180 mg LD, 90 mg twice-daily MD) exhibited greater inhibition of platelet aggregation than a standard regimen of clopidogrel (300—600 mg LD, 75 mg/day MD) within the first hours after LD and after 28 days of maintenance therapy [32].

In the RESPOND trial, ticagrelor was shown to overcome non-responsiveness to clopidogrel in patients with stable coronary artery disease. Patients who were deemed to be non-responders to clopidogrel ($n = 41$) were treated with ticagrelor (180 mg LD/90 mg twice daily MD) and high-dose clopidogrel (600 mg LD/75 mg/day MD) in a 14-day two-way crossover design [33]. Ticagrelor treatment resulted in a significantly greater reduction in platelet aggregation from baseline than high-dose clopidogrel.

Similarly to prasugrel, ticagrelor has shown clinical benefit in head-to-head phase II and III studies with clopidogrel in ACS, showing decreased incidence of adverse cardiac events with a higher rate of non-CABG related bleeding [33,34].

The PLATO study was the largest randomized study to compare ticagrelor with clopidogrel. In total 18,624 patients with ACS were included and randomized to either ticagrelor (180 mg LD, 90 mg twice daily thereafter) or clopidogrel (300—600 mg LD, 75 mg daily thereafter) [28]. Treatment began within 24 hours of symptom onset and all patients were treated with aspirin therapy.

At 12-month follow-up, there was a 16% lower rate of the primary composite endpoint of cardiovascular mortality, myocardial infarction and stent thrombosis in patients receiving ticagrelor (9.8% vs. 11.7%; $P < 0.001$), which translates to a number needed to treat of 53. This improved outcome was driven by lower cardiovascular mortality, myocardial infarction and stent thrombosis. Again, this ischaemic benefit was balanced by increased bleeding. There was no increase in overall bleeding, but there was an increase in major non-CABG related bleeding with the PLATO definition (4.5% vs. 3.8%, respectively; $P = 0.03$) and the TIMI definition (2.8% vs. 2.2%; $P = 0.025$), with a number needed to harm of 167. Although this trial was not powered for mortality, there appeared to be a mortality rate benefit (4.5% with ticagrelor vs. 5.9% with clopidogrel) [34].

There was a surprising finding of increased risk of primary endpoint in ticagrelor-treated patients in the patients enrolled in the USA, which may be related to aspirin doses of > 300 mg in this patient group [35].

In a pre-specified analysis of PLATO, ticagrelor appeared to have an even more significant impact in chronic kidney disease patients, with a 21% reduction in occurrence of the primary endpoint and a 28% reduction in mortality without a significant increase in bleeding [36].

Apart from unresolved issues regarding differences in efficacy, ticagrelor has been reported to have a propensity to elevate uric acid and creatinine concentrations, increase ventricular pauses and cause dyspnoea.

Ticagrelor received regulatory approval in Europe in December 2010 and in the USA in July 2011.

Cangrelor

Cangrelor belongs to a family of ATP analogues that are relatively resistant to the breakdown of endonucleotidases; it does not require metabolic activation and acts as a reversible competitive antagonist on the $P2Y_{12}$ receptor. Administered intravenously rather than orally, cangrelor has a short half-life of < 5 minutes, with a rapid onset of effect, inhibiting platelets to a high degree, and a quick offset of effect with resolution of normal platelet function within an hour of cessation of treatment [37—39]. With this pharmacokinetic profile, the major use for cangrelor is in the acute setting, where a rapid antiplatelet effect with minimal increase in bleeding is needed (Table 2).

While the pivotal trials to date have shown a satisfactory rate of major bleeding side effects, the highly potent cangrelor has not had a significant impact on the occurrence of adverse cardiac events. The phase III CHAMPION-PCI and CHAMPION-PLATFORM trials compared cangrelor with clopidogrel 600 mg in ACS patients scheduled for PCI, with the timing of the clopidogrel dose being the major difference between the trials [40]. Both trials were discontinued prematurely due to insufficient evidence of the clinical effectiveness of cangrelor. There were, however, reductions in stent thrombosis and death from any cause. Furthermore, the lack of overall demonstrable clinical benefit of cangrelor may be related to the definition of myocardial infarction used, which made it difficult to adjudicate early ischaemic events. This hypothesis is supported by a pooled analysis of the two trials, using the universal definition of myocardial infarction, which showed cangrelor to be associated with a significant reduction in early ischaemic events compared with clopidogrel in patients with NSTE-ACS undergoing PCI [41,42].

The definition of myocardial infarction was carefully chosen in a subsequent trial to assess cangrelor — the CHAMPION-PHOENIX study [43,44]. This was a randomized double-blind double-dummy trial that compared cangrelor with clopidogrel standard of care in 11,145 patients who had not previously received a $P2Y_{12}$ antagonist and required PCI, including patients with stable angina and ACS (with or without ST-segment elevation). The primary efficacy endpoint was a composite of death, myocardial infarction, ischaemia-driven revascularization or stent thrombosis at 48 hours after randomization.

The rate of occurrence of the primary efficacy endpoint was lower in the cangrelor group than in the clopidogrel group (4.7% vs. 5.9%; odds ratio 0.78; $P = 0.005$), driven by the reduction in the rate of acute periprocedural myocardial infarction and by a reduced rate of stent thrombosis (0.8% vs. 1.4%; $P = 0.01$). The benefit from cangrelor was consistent across several pre-specified subgroups, apart from diabetic patients, who represented 27.8% of the global population, (relative risk 0.92 [0.67—1.27]; $P = 0.26$). The rate of occurrence of the primary safety endpoint was 0.16% in the cangrelor group versus 0.11% in the clopidogrel group ($P = 0.44$).

Overall, the data suggest a promising role for cangrelor. Future studies are needed, however, to determine the optimal way to transition ACS PCI patients from cangrelor to prasugrel or ticagrelor; such patients represented only 43% of patients recruited in the CHAMPION-PHOENIX trial.

Due to its rapid on/off effect, cangrelor also has potential as a bridging agent in patients requiring surgery, by adequately preventing ischaemic events while allowing rapid restoration of platelet function on therapy discontinuation in the event of bleeding. The BRIDGE study evaluated the efficacy of this strategy for patients taking thienopyridine antiplatelet agents, such as clopidogrel, who are scheduled for surgery. A total of 210 patients taking thienopyridines for ACS or after stent placement, who were awaiting CABG, had their thienopyridine stopped and were then randomized to either cangrelor (0.75 μg/kg/min) or placebo for at least 48 hours. The study drug was discontinued 1—6 hours before CABG surgery. Patients randomized to cangrelor had lower levels of platelet reactivity throughout the treatment period compared with placebo. There was no significant difference in major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor. With the use of a surrogate endpoint — platelet reactivity as the primary endpoint — the findings of this trial must be interpreted with caution. However, it does demonstrate the potential role of cangrelor in this not uncommon setting.

Clinical implications of novel agents

The above-mentioned trials have clearly changed experts' opinions and this is reflected in both the ESC and the American College of Cardiology Foundation/AHA guidelines for both STE-ACS and NSTE-ACS [6—9]. The European guidelines for NSTE-ACS recommend that a $P2Y_{12}$ inhibitor be added as soon as possible to aspirin and treatment maintained for 12 months [6]. Ticagrelor (180 mg LD, 90 mg twice daily) is recommended for all patients (including those pretreated with clopidogrel) at moderate-to-high risk of ischaemic events (e.g. those showing elevated troponins). The guidelines advocate prasugrel (60 mg LD, 10 mg daily dose) for $P2Y_{12}$ inhibitor-naive patients, especially those with diabetes mellitus, in whom coronary anatomy is known and who are proceeding to PCI, unless the patient shows a high risk of life-threatening bleeds. The ESC NSTE-ACS guidelines recommend that either ticagrelor or prasugrel be administered in preference to clopidogrel.

Similarly, with respect to the treatment of STEMI with primary PCI, the recent 2012 ESC STE-ACS guidelines advocate prasugrel or ticagrelor over clopidogrel.

Table 2 Pharmacological properties of $P2Y_{12}$ antagonists.

$P2Y_{12}$ receptor inhibitors	Type	Administration	Action	Loading dose; maintenance dose
Clopidogrel	Thienopyridine (second generation)	Oral	Hepatic transformation in active metabolite/irreversible blockade	300—600 mg; 75 mg
Prasugrel	Thienopyridine (third generation)	Oral	Hepatic transformation in active metabolite/irreversible blockade	60 mg; 10 mg
Ticagrelor (AZD6140)	Cyclopentyl-triazolo-pyrimidine	Oral	Direct and reversible inhibition; competitive binding	180 mg; 90 mg twice daily
Cangrelor (ARC-669931MX)	ATP analogue	Intravenous	Direct and reversible inhibition; competitive binding	30 μg/kg; bolus 4 μg/kg/min for 2—4 hours

Treatment of specific subgroups

No trial has directly compared prasugrel with ticagrelor and significant differences in study design make this comparison difficult. The design of PLATO differs from TRITON-TIMI 38 in two important ways. Firstly, the proportion of patients with NSTE-ACS was less in PLATO (59.5% and 59.3% in the ticagrelor and clopidogrel arms, respectively, compared with 74% in the TRITON trial). Secondly, PLATO studied the outcome of all ACS patients, whether pretreated with clopidogrel or not and whether invasively treated by PCI or CABG or medically managed. TRITON studied the outcome of ACS patients undergoing PCI: in STEMI patients treatment was initiated as soon as possible after the index event; in NSTE-ACS patients treatment was initiated after the decision for PCI [45]. However, additional analysis of the pivotal trials is possible and may help to identify preferential targets for these drugs.

Prasugrel may be the preferred drug in patients presenting with STE-ACS undergoing PCI. In the TRITON-TIMI 38 trial, prasugrel was more effective than clopidogrel in patients presenting with STEMI (10.0% vs. 12.4%, HR 0.79, 95% CI 0.65—0.97; $P = 0.02$), with no significant difference in bleeding risk [45].

A subgroup analysis of TRITON-TIMI 38 reported that prasugrel significantly reduced the incidence of the primary endpoint compared with clopidogrel among non-diabetics (9.2% and 10.6%, respectively; HR 0.86; $P = 0.02$) and diabetes mellitus patients (12.2% and 17.0%, respectively; HR 0.70; $P < 0.001$, P interaction = 0.09), with a striking number needed to treat of 21 for all ACS PCI diabetes mellitus patients. Diabetes mellitus subjects taking insulin also had greater benefit, with a reduced incidence of the primary endpoint compared with clopidogrel (14.3% and 22.2%, respectively; HR 0.63; $P = 0.009$), than those not taking insulin (11.5% and 15.3%, respectively; HR 0.74; $P = 0.009$). Non-diabetics taking prasugrel were more likely than those receiving clopidogrel to develop major haemorrhage (2.4% vs. 1.6%, HR 1.43; $P = 0.02$). Rates of major haemorrhage with clopidogrel and prasugrel were similar in diabetes mellitus patients (2.6 and 2.5%, respectively; HR 1.06; $P = 0.81$, $P = 0.29$). Therefore, prasugrel produced a greater net clinical benefit (composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke or non-fatal TIMI major bleeding not related to CABG) than clopidogrel in diabetes mellitus patients (14.6% vs. 19.2%; HR 0.74; $P = 0.001$) than in those without diabetes mellitus (11.5% and 12.3%, respectively; HR 0.92; $P = 0.16$, $P = 0.05$).

By contrast, in the PLATO trial, the benefit of ticagrelor in diabetes mellitus patients was consistent with the overall trial results but did not reach statistical significance [46].

As discussed previously, the PLATO trial suggested that patients with chronic renal disease in particular may benefit from ticagrelor treatment [36].

Until recently there has been a lack of data on the use of $P2Y_{12}$ inhibitors in the treatment of patients presenting with NSTE-ACS who are selected for medical management without revascularization. The recently published TRILOGY trial attempted to address this issue by performing a randomized double-blind double-dummy active-control event-driven trial [47]. High-risk NSTEMI and UA patients were included and treated with either clopidogrel or prasugrel from within 10 days of presentation up to 30 months. The MD of prasugrel was 10 mg, but 5 mg in elderly patients (aged $\geq$ 75 years) who represented 23% of the total trial population. Occurrence of the primary efficacy endpoint (cardiovascular death, myocardial infarction or stroke in patients aged < 75 years) was not statistically different between the two arms of the study. Neither was statistical significance achieved for other efficacy endpoints, including cardiovascular death, myocardial infarction, stroke, all-cause death, cardiovascular death plus myocardial infarction, recurrent hospitalization for UA, all-cause death, myocardial infarction or stroke, and for the net clinical benefit endpoint, including major bleeding.

These results are in contrast with the findings of a pre-specified sub-analysis of the PLATO trial, which was performed in a population half the size of the TRILOGY-ACS population, with a shorter follow-up (median 9.2 months) [41]. Patients treated with ticagrelor had lower rates of

primary composite endpoint (12.0% vs. 14.3%; HR 0.85, 95% CI 0.73—1.00; $P = 0.04$) and mortality (6.1% vs. 8.2%; HR 0.75, 95% CI 0.61—0.93; $P = 0.01$). However, it is important to stress that there was 24% crossover to vascularization during the hospitalization phase in the PLATO substudy (versus close to 0% in TRILOGY-ACS) and 40% crossover to vascularization during the follow-up period in the PLATO substudy (versus 7.9% in TRILOGY-ACS) [48,49].

Future role for clopidogrel?

With the advent of newer $P2Y_{12}$ antagonists, the question as to the future role, if any, for clopidogrel in the acute and long-term treatment of ACS must be addressed. Indeed, the newer agents are now recommended as first line for patients presenting with moderate-to-high-risk ACS. However, there are several clinical situations where clopidogrel may be preferable to these agents. Firstly, for low-risk ischaemic patients, clopidogrel remains the preferred choice. Secondly, for patients with a high bleeding risk or on concomitant oral anticoagulant therapy, the current guidelines advocate short-duration triple therapy and that the $P2Y_{12}$ agent be clopidogrel [6,9]. Thirdly, generic clopidogrel is considerably cheaper and so may temper enthusiasm for these newer agents in real-life practice. However, in a cost analysis comparing clopidogrel with prasugrel, prasugrel remained an economically dominant strategy: if a hypothetical generic cost for clopidogrel of $1 per day is used, the incremental net cost with prasugrel is $996 per patient, yielding an incremental cost-effectiveness ratio of $9727 per life-year gained [50]. Furthermore, a group of 31 patients was switched from prasugrel 10 mg to clopidogrel 75 mg, resulting in an increased rate of HPR from 0% with prasugrel to 29% with clopidogrel. Early switching from prasugrel 10 mg to clopidogrel 75 mg reduces the number of patients with low on-treatment platelet reactivity and minor bleeding events but unmasks a group of non-responders to clopidogrel with unknown consequences for clinical outcomes [51].

Personalized treatment

The concept of personalized treatment, based on platelet reactivity assessment with bedside monitoring assays and genotyping with rapid genetic testing platforms, has been the subject of much debate recently. HPR is well established as an independent predictor of increased cardiovascular events [52]. The factors related to variability of response to clopidogrel can broadly be divided into four categories: environmental, cellular, clinical and genetic factors [53].

Genetic variability in drug absorption and metabolism is a key factor responsible for the inefficient generation of the active drug metabolite. The two-step hepatic CYP-dependent oxidative metabolism of the prodrug appears to be of particular importance. Pharmacogenomic analyses have identified loss-of-function variant alleles of *CYP2C19*, specifically the *2C19*2* allele, to be the predominant genetic mediators of the antiplatelet effect of clopidogrel [54].

Several trials have assessed whether this risk factor is modifiable to improve clinical outcome with the adjustment of $P2Y_{12}$ antagonist therapy in patients with poor metabolic response to clopidogrel. The randomized data so far have been neutral. The TRIGGER PCI trial was the first to evaluate this by randomizing stable coronary artery disease patients with HPR after undergoing PCI to either prasugrel 10 mg daily or clopidogrel 75 mg daily. The trial was discontinued due to a low event rate [55]. The GRAVITAS study followed and examined the efficacy of double-dose clopidogrel (150 mg daily) in a similar low-risk post PCI population [56]. This personalized strategy did not affect clinical outcome, which may have been related to the inadequate treatment of HPR by double-dose clopidogrel. Finally the randomized ARCTIC trial included a higher-risk population, tested for both aspirin and clopidogrel resistance and offered several alternative treatments for HPR, with follow-up platelet function testing to ensure adequate response [57]. Despite this trial design, there was no statistical difference in cardiovascular events between the monitoring versus the conventional treatment arm but there was a trend towards lower bleeding events. The conclusion that can be drawn from these trials is that platelet function monitoring cannot be recommended routinely in the general PCI population or, at least, that stable coronary patients might not benefit from a platelet function test. However, platelet function monitoring may have a role in selected groups, such as those with stent thrombosis or bleeding events, and it is needed to pursue research on platelet function testing, especially in ACS patients. In the area of ACS, we are now waiting for the results of the ANTARCTIC (NCT01538446) study, which is evaluating the value of a platelet function test in the ACS elderly population, with a focus on bleeding events.

Conclusions

Despite advances made in the treatment of ACS, a significant number of patients will have recurrent ischaemic events on current dual antiplatelet therapy, highlighting the need for improvement of current therapies. Newer agents have been developed to overcome the shortcomings of clopidogrel as a $P2Y_{12}$ antagonist and the pivotal trials to date have shown that prasugrel and ticagrelor in particular improve outcome. It is now emerging that there are differences in efficacy between these two agents, which should allow clinicians to better tailor treatment. Further studies are indicated to directly compare these agents and also to assess novel intravenously administered agents, such as cangrelor. The role of platelet function and genetic testing in subpopulations as tools to prevent bleeding events with these more potent agents is yet to be established.

Disclosure of interest

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