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REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of Approved and Investigational P2Y12 Receptor Antagonists

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Abstract

Coronary artery disease remains the major cause of mortality worldwide. Antiplatelet drugs such as acetylsalicylic acid and P2Y12 receptor antagonists are cornerstone treatments for the prevention of thrombotic events in patients with coronary artery disease. Clopidogrel has long been the gold standard but has major pharmacological limitations such as a slow onset and long duration of effect, as well as weak platelet inhibition with high inter-individual pharmacokinetic and pharmacodynamic variability. There has been a strong need to develop potent P2Y12 receptor antagonists with more favorable pharmacological properties. Prasugrel and ticagrelor are more potent and have a faster onset of action; however, they have shown an increased bleeding risk compared with clopidogrel. Cangrelor is highly potent and has a very rapid onset and offset of effect; however, its indication is limited to P2Y12 antagonist-naïve patients undergoing percutaneous coronary intervention. Two novel P2Y12 receptor antagonists are currently in clinical development, namely vicagrel and selatogrel. Vicagrel is an analog of clopidogrel with enhanced and more efficient formation of its active metabolite. Selatogrel is characterized by a rapid onset of action following subcutaneous administration and developed for early treatment of a suspected acute myocardial infarction. This review article describes the clinical pharmacology profile of marketed P2Y12 receptor antagonists and those under development focusing on pharmacokinetic, pharmacodynamic, and drug–drug interaction liability.

Key Points

Overview and comparison of the clinical pharmacology profiles of marketed as well as investigational P2Y12 receptor antagonists.

Update on the P2Y12 receptor antagonist landscape including new developments.

1 Introduction

Cardiovascular disease remains the leading cause of mortality accounting for approximately 17 million deaths worldwide in 2016 [1]. Of these, 9 million deaths were due to coronary artery disease (CAD)-related ischemic events in the context of acute coronary syndrome (ACS). These are mainly caused by the rupture of atherosclerotic plaques triggering a cascade of processes involving platelet aggregation and thrombus formation, ultimately leading to the occlusion of coronary arteries. The sudden lack of oxygen supply to the myocardium manifests itself as acute myocardial infarction (AMI) with (STEMI) or without ST-segment elevation (non-STEMI).

Inhibition of platelet aggregation has been recognized as an important element in the short-term treatment as well as for the long-term prevention of thrombotic events in patients with CAD and can be achieved by targeting the purinergic G-protein-coupled P2Y12 receptor that is expressed on the membrane of human thrombocytes [2, 3]. Physiologically, platelet activation and aggregation are mediated by ADP being released upon vessel damage and binding to the P2Y12 receptor [4, 5].

P2Y12 receptor antagonists inhibit platelet aggregation by preventing ADP from binding to the P2Y12 receptor and can be broadly classified into two classes based on their chemical structure, namely thienopyridines and non-thienopyridines. Thienopyridines (i.e., ticlopidine, clopidogrel, prasugrel, and vicagrel) are prodrugs whose active metabolite covalently

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binds to the ADP-binding site of the P2Y12 receptor leading to an irreversible platelet inhibition. Non-thienopyridines (i.e., ticagrelor, cangrelor, and selatogrel), on the contrary, do not require bioactivation and reversibly bind to the P2Y12 receptor.

Ticlopidine was the first P2Y12 receptor antagonist in clinical use, but because of its less favorable pharmacokinetics, pharmacodynamics, and, most importantly, safety profile compared with the newer P2Y12 antagonists [8], it disappeared from European Union (EU) and US guidelines [6, 7]. Therefore, it will not be covered in this review.

Dual antiplatelet therapy with clopidogrel and acetylsalicylic acid has long been the gold standard of treatment. However, there has been a need to develop more potent and reliable P2Y12 receptor antagonists with a shorter onset of action. According to the 'time is muscle' concept, early intervention is crucial in the treatment of AMI.

Prasugrel and ticagrelor are more potent and yield stronger and more reliable platelet inhibition than clopidogrel, but come with the pitfall of an increased bleeding risk compared with clopidogrel [9–12]. In addition, oral absorption and hence the onset of effect of oral P2Y12 receptor antagonists is delayed in patients with ACS.

Cangrelor is the first intravenous (i.v.) P2Y12 receptor antagonist with very fast on- and offset of action for the management of patients undergoing percutaneous coronary intervention (PCI). Although with the four available P2Y12 receptor antagonists treatment options have improved, the optimal P2Y12 receptor antagonist remains to be found.

Two P2Y12 receptor antagonists are currently in phase II clinical development. Vicagrel is a novel clopidogrel analog that aims to achieve a stronger and more reliable platelet inhibition than clopidogrel. Selatogrel is a potent reversible P2Y12 receptor antagonist with a fast onset of action and is developed for subcutaneous self-administration by patients in the case of suspected AMI to allow treatment intervention at the earliest possible stage. This review focuses on the pharmacokinetic and pharmacodynamic properties (including the effect of intrinsic and extrinsic factors) of the approved P2Y12 receptor antagonists and also introduces both P2Y12 receptor antagonists in development.

2 Indication

Currently, there are four P2Y12 receptor antagonists available on the market for antiplatelet therapy that differ in their approved indications:

- Clopidogrel has been and still remains the most widely used P2Y12 receptor antagonist [13]. It is indicated for the short-term treatment and secondary prevention of atherothrombotic events in patients with ACS presenting with NSTEMI or STEMI. In addition, it is indicated in patients with recent myocardial infarction, recent stroke, or established peripheral arterial disease [14, 15].
- Prasugrel is indicated for the prevention of atherothrombotic events in patients with ACS (STEMI or NSTEMI) when undergoing primary or delayed PCI [16]. Because of an increased bleeding risk, it is not recommended in patients aged ≥ 75 years or in the presence of additional risk factors for bleeding (e.g., weight < 60 kg) [16].
- Ticagrelor is indicated for the treatment of patients with ACS or a history of myocardial infarction to "reduce the rate of cardiovascular death, myocardial infarction, and stroke" [17]. According to the US Food and Drug Administration (FDA) label, it is superior to clopidogrel for at least the first 12 months following ACS [17]. There has been an increasing trend in the use of ticagrelor over recent years in Western countries [18–21].
- Cangrelor is the most recently approved P2Y12 receptor antagonist. It is administered as an i.v. infusion and "indicated for reduction of thrombotic cardiovascular events in adult patients with CAD undergoing PCI who have not received an oral P2Y12 inhibitor prior to the PCI procedure" [22, 23].

As per the labels, the oral P2Y12 receptor antagonists clopidogrel, prasugrel, and ticagrelor should be administered in combination with acetylsalicylic acid.

3 Pharmacokinetics and Pharmacodynamics

3.1 Clopidogrel

Clopidogrel is a prodrug that requires complex bioactivation via hepatic metabolism involving different drug-metabolizing enzymes (Table 1) [24]. After oral administration, it is rapidly absorbed from the intestine. It has been shown that absorption by the intestinal epithelial cells is limited depending on P-glycoprotein (P-gp) efflux transporter expression [25]. Clopidogrel is extensively metabolized, mainly (approximately 85%) by carboxylesterase 1 (CES1) to an inactive carboxylic acid derivative representing the most abundant metabolite in blood [26–28]. Only about 15% of the absorbed clopidogrel is biotransformed to its active metabolite involving a two-step enzymatic process. In the first step, clopidogrel is converted into the inactive intermediate, 2-oxo-clopidogrel, and subsequently in the second step transformed into the active thiol metabolite (Fig. 1) [29]. This thiol metabolite consists of four diastereoisomers, of which the only pharmacologically active isomer of clinical relevance is H4 [30, 31].

Table 1 Clinical pharmacology profiles of P2Y12 receptor antagonists

Parameter	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Vicagrel	Selatogrel
Route of administration	Oral	Oral	Oral	Intravenous	Oral	Subcutaneous
Dose	300–600 mg (LD) 75 mg qd (MD)	60 mg (LD) 10 mg qd (MD)	180 mg (LD) 90 mg bid (MD)	15–30 µg/kg (i.v. bolus) 2–4 µg/kg/min (i.v. infusion)	TBD	TBD
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible	Irreversible	Reversible
Type of binding	Competitive	Competitive	Noncompetitive	Undetermined	Competitive	Competitive
Prodrug	Yes	Yes	No	No	Yes	No
Time to peak effect	2–6 h	2–4 h	2 h	2 min	4 h	15–30 min
Offset of effect	5–10 days	7–10 days	3–5 days	~1 h	5–10 days	~24 h
t_{max}	AM: 0.5–1 h	AM: 30 min	Parent: 1.5–2 h AM: 2–3 h	NA	AM: 0.5 h	30–45 min
$t_{1/2}$	AM: 30 min Parent: ~6 h	AM: ~7 h	AM: ~9–12 h Parent: 8 h	3–5 min	AM: ~45 min	~4–7 h

AM active metabolite, *bid* twice daily, *i.v.* intravenous, *LD* loading dose, *MD* maintenance dose, *NA* not applicable, *qd* once daily, *TBD* to be determined, $t_{1/2}$ half-life, t_{max} time to maximum concentration

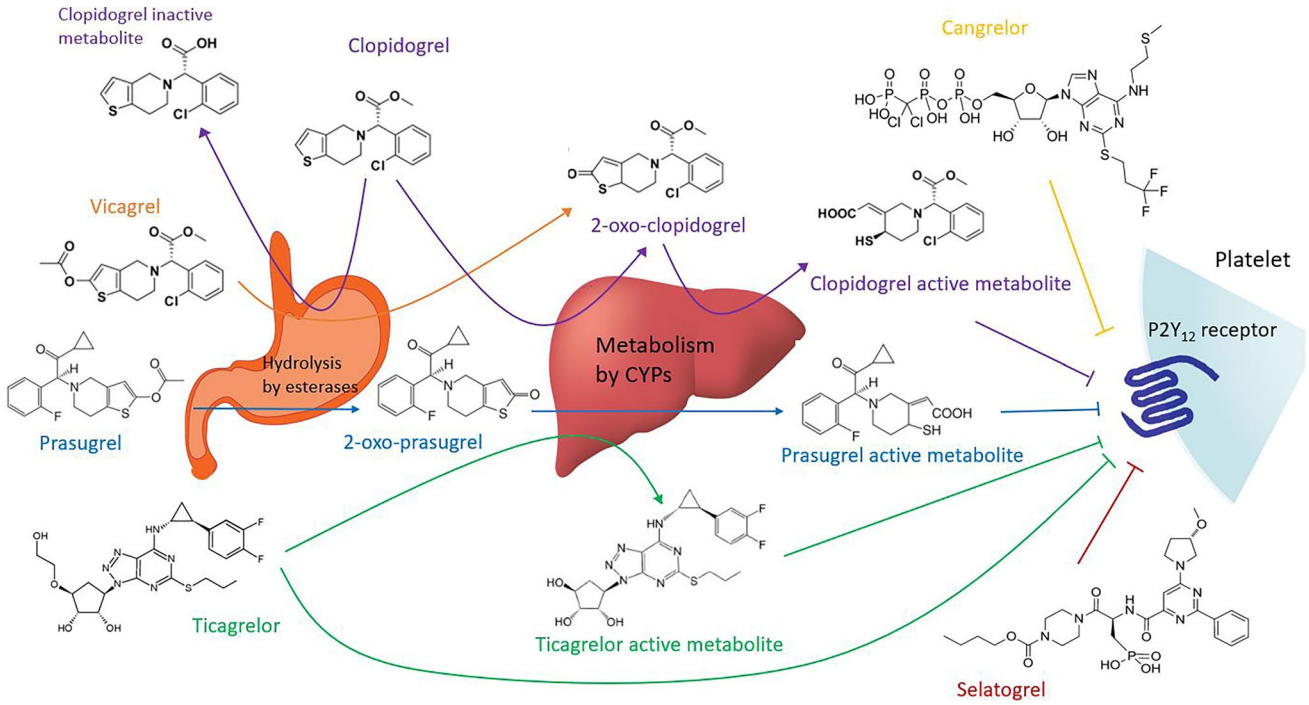

Fig. 1 Chemical structures and schematic bioactivation of P2Y12 receptor antagonists: this scheme has been modified from [217]. *CYP* cytochrome P450

Controversial data exist regarding the enzymes catalyzing the formation of the active metabolite. Several in vitro and in vivo studies have indicated cytochrome P450 (CYP)2C19 as the major enzyme responsible for the bioactivation of clopidogrel with CYP1A2, CYP2B6, CYP2C9, and CYP3A4/5 playing a minor role [32–36]. However, others suggest that 2-oxo-clopidogrel is primarily formed via intestinal CYP3A4/5 and further metabolized to the active form by paraoxonase 1 [37–39].

The pharmacokinetics (PK) of clopidogrel was described by one- or two-compartment models (Fig. 2) [40–43]. Maximum plasma concentrations (C_{max}) of the active metabolite were observed approximately 1 h after administration of a loading dose of 600 mg [44, 45].

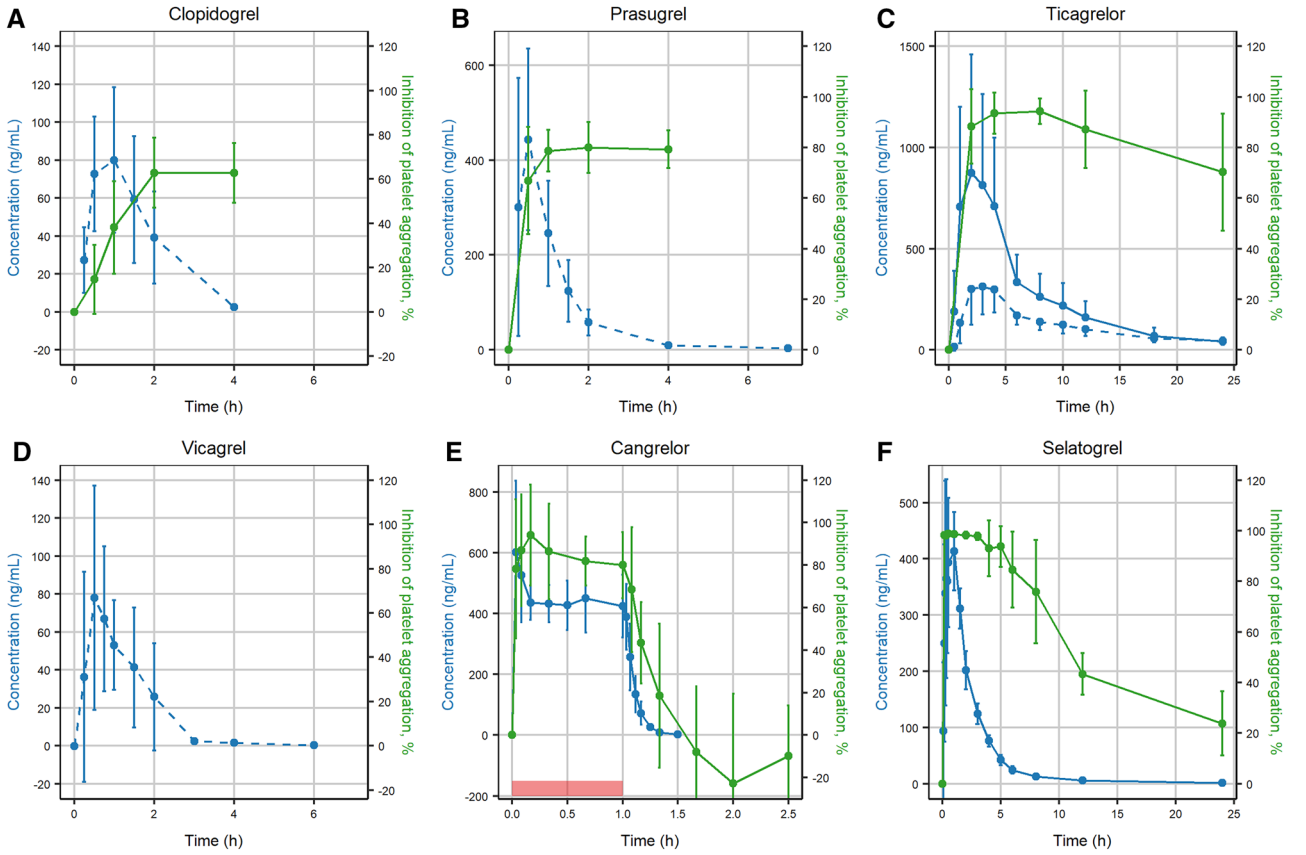

Fig. 2 Data are displayed as mean plasma concentration (blue lines) and inhibition of platelet aggregation (IPA) [green lines] over time in healthy subjects. Error bars represent the standard deviation. Plasma concentration data are provided for the parent drug (straight line) and/or active metabolite (dashed line) as appropriate. For vicagrel, no IPA data have been reported at the dose shown. The data were digitalized from publications except for selatogrel of which original data have been used. A limitation of this comparison stems from the fact that different pharmacodynamic assays were used for the respective compounds, namely light transmission aggregometry (clopidogrel, prasugrel, and ticagrelor), flow cytometry (cangrelor), and VerifyNow® (selatogrel). However, the same ADP concentration (20 µM) has been used in all assays to induce platelet aggregation. Data visualization was achieved using R (version 3.5.1) and ggplot. **a** Clopidogrel 600 mg single dose (sd.) orally (p.o.) [45]. **b** Prasugrel 60 mg sd. p.o. [45]. **c** Ticagrelor 180 mg sd. p.o. [80]. **d** Vicagrel 40 mg sd. p.o. [208]. **e** Cangrelor 30 µg/kg intravenous (i.v.) bolus followed by a 4 µg/kg/min i.v. infusion for 1 h (marked in red) [86]. **f** Selatogrel 16 mg sd. Subcutaneous (s.c.)

Interindividual variability in the plasma concentrations of the clopidogrel active metabolite is high owing to both genetic and environmental factors [44, 46–48].

The active metabolite has a short half-life of approximately 30 min, whereas the half-life of the inactive parent drug is about 6 h [14]. After an oral radiolabeled dose, about 50% of total radioactivity was found in the urine and feces, respectively [49]. Clopidogrel and its active metabolite do not show dose-proportional PK [41, 47, 50–52]. At a supratherapeutic loading dose of 900 mg, plasma concentrations of clopidogrel and the active metabolite differed only marginally from those following the therapeutic loading dose of 600 mg, suggesting saturable absorption and/or metabolism [50]. Consequently, no increase in pharmacodynamic response was observed at the 900-mg dose.

Upon binding of the active metabolite, the P2Y12 receptor is irreversibly blocked for the life span of the platelet (7–10 days) [39]. After a loading dose of 300 mg or 600 mg of clopidogrel, maximum inhibition of platelet aggregation (IPA) levels of about 40–50% and 60–70%, respectively, are reached within approximately 2–6 h [53]. Extent of IPA and onset time are dose dependent up to a loading dose of 600 mg [54]. The approved loading dose is 300 mg, but 600 mg is recommended by current guidelines because of a more favorable PD response [7, 55]. With a maintenance dose of 75 mg once daily, approximately 50% IPA is reached that is, however, highly variable between individuals [56]. Notably, up to 40% of the population do not show an adequate response to clopidogrel treatment as defined by a relative change in IPA < 10%, possibly due to insufficient metabolite generation [57, 58].

3.2 Prasugrel

Like clopidogrel, prasugrel is a prodrug administered orally. It is completely and rapidly absorbed and extensively metabolized (Table 1) [59].

Bioactivation of prasugrel also involves two metabolic steps. However, in contrast to clopidogrel, the first step is a rapid hydrolysis of prasugrel to the thiolactone 2-oxo-prasugrel (R-95913) by esterases found in the plasma, liver, and intestine [60, 61]. The active metabolite (R-138727) is formed in a second step via oxidation of 2-oxo-prasugrel by intestinal and hepatic CYP2B6 and CYP3A isoenzymes with smaller contributions of CYP2C9 and CYP2C19 (Fig. 1) [62].

Peak concentrations of the active metabolite were measured at 30 min after dosing, whereas the parent compound was not detectable in plasma, feces, or urine at any time owing to its rapid hydrolysis [45, 59, 63]. Prasugrel metabolites are mainly excreted renally as about 70% of the radioactivity after administration of a 15-mg radiolabeled dose was found in urine [59].

The PK of the prasugrel active metabolite shows a biphasic elimination (Fig. 2) [41]. The elimination half-life of the prasugrel active metabolite was reported to be 7.4 h after a loading dose of 60 mg of prasugrel [63]. The PK of prasugrel metabolites was reported to be dose proportional for doses up to 75 mg in healthy subjects [64].

Its active metabolite is equipotent to that of clopidogrel in vitro and inhibits platelet aggregation irreversibly [65]. However, compared to clopidogrel, a loading dose of 60 mg of prasugrel provides a faster onset time of 2–4 h and substantially greater IPA of approximately 80–90% both in healthy subjects and patients with CAD [47, 53, 66, 67], most likely owing to the faster and more efficient formation of its active metabolite [67]. In addition, response variability was significantly lower for prasugrel compared with clopidogrel [47, 53]. At a maintenance dose of 10 mg once daily, approximately 70% IPA is achieved. The degree of IPA is dose dependent for single and multiple doses of 20–60 mg and 5–15 mg once daily, respectively [68].

3.3 Ticagrelor

Ticagrelor was the first oral P2Y12 receptor antagonist binding reversibly and non-competitively to the receptor [69, 70]. Ticagrelor is rapidly absorbed. It does not require bioactivation as it binds to the P2Y12 receptor directly (Table 1) [71]. However, it also has a major active metabolite AR-C124910XX with about the same potency whose overall exposure is about 30–40% of that to ticagrelor in healthy subjects and about 20% in patients with AMI [72–74]. This metabolite AR-C124910XX is formed via O-desalkylation by CYP3A4 and CYP3A5 [75]. Ticagrelor also undergoes biotransformation to other metabolites through extensive metabolism in the liver by CYP3A enzymes. A total of ten metabolites have been identified, with AR-C124910XX being the major and only active metabolite (Fig. 1) [72].

In population pharmacokinetic models, ticagrelor and AR-C124910XX have each been described by one- [76, 77] or two-compartment models (Fig. 2) [78, 79]. In healthy subjects, C_{max} of ticagrelor and AR-C124910XX were reached at 1.5–2.0 h and 2.0–3.0 h after dosing, respectively [71, 72, 80]. In patients with ACS, the absorption was delayed by 1 h [81] and bioavailability reduced by 21% [77]. Ticagrelor and its active metabolite are mainly excreted via feces with renal elimination only playing a minor role [72]. The plasma half-life of ticagrelor and AR-C124910XX is approximately 8 h and 9–12 h, respectively [72, 73, 80]. Both ticagrelor and AR-C124910XX show dose-proportional PK in healthy subjects and in patients over a dose range of 30–400 mg [73, 77].

Ticagrelor inhibits platelet aggregation dose dependently up to 100 mg at which almost complete IPA is achieved [82]. Accordingly, higher doses up to 400 mg yielded only a small further increase in IPA [73, 83]. Ticagrelor is more potent than clopidogrel [81, 83, 84] and has similar or greater potency compared to prasugrel [85]. The maximum IPA level (~90%) after a loading dose of 180 mg is reached after 2 h and lasts for at least 6 h [84]. The time of maximum effect corresponds with the time to maximum concentration (t_{max}), and with decreasing plasma concentrations the extent of IPA also declines in line with the reversible mode of action [73]. Hence, a twice-daily maintenance dose of 90 mg is needed to maintain sufficient IPA.

3.4 Cangrelor

Cangrelor is administered intravenously and therapeutic plasma concentrations can be achieved almost immediately when given as an i.v. bolus. It binds to the P2Y12 receptor directly and hence does not require any bioactivation (Table 1) [86].

It has a short plasma half-life of 3–5 min as it is rapidly inactivated via dephosphorylation by nucleotidases in the blood [87, 88]. The metabolism of cangrelor is independent of hepatic CYP enzymes. The major metabolite AR-C69712 is considered inactive (Fig. 1) [89]. The distribution was described by a two-compartment model and the PK was dose proportional up to the maximum tested dose of 4 µg/kg/min (Fig. 2) [90].

Cangrelor binds reversibly to the P2Y12 receptor and has an extremely fast onset and offset of action. When

administered as an i.v. bolus (15–30 µg/kg) followed by a continuous infusion (2–4 µg/kg/min), almost complete platelet inhibition is achieved within 2 min and platelet activity recovers to baseline values within 60–90 min after termination of the infusion [86].

4 Effect of Intrinsic Factors on Pharmacokinetics and Pharmacodynamics

The effect of intrinsic factors on the PK and pharmacodynamics (PD) of marketed oral P2Y12 receptor antagonists is summarized in Table 2.

4.1 Body Weight

4.1.1 Clopidogrel

Body weight has been shown to affect the PK and PD of clopidogrel, although it is not mentioned in the label as a relevant covariate [14, 15]. In patients with stable CAD, high body weight (≥ 60 kg) resulted in an approximately 30% lower exposure to the active metabolite and lower IPA compared to patients with a low body weight (< 60 kg) [91]. Accordingly, non-response to clopidogrel defined as < 40% IPA was reported to be more frequent in overweight (body mass index ≥ 25 kg/m^2) compared with healthy patients (body mass index < 25 kg/m^2) as indicated by an incidence of 60% vs. 25% [92].

4.1.2 Prasugrel

Body weight has been shown to be the most influential covariate affecting the PK of prasugrel [93]. The label recommends a lower dose (5 mg instead of 10 mg once daily) in patients with body weight < 60 kg [16, 94] because of a higher risk of bleeding [11]. Exposure to the active metabolite was approximately 40% and 30% higher in healthy subjects and in patients with ACS, respectively, with low (< 60 kg) vs high body weight (≥ 60 kg) [63, 95]. However, a similar degree of IPA has been reported for healthy subjects and patients with CAD with low (60 kg) vs high body weight (90 kg) [53].

4.1.3 Ticagrelor

Body weight was not identified as a relevant covariate affecting the PK of ticagrelor or its active metabolite in patients with ACS [74, 77]. Hence, ticagrelor is dosed independently of body weight as per the label [17, 96]. The clearance of ticagrelor and its active metabolite was reduced by 11% and 36%, respectively, in patients with low vs high body weight having a history of AMI [76].

4.1.4 Cangrelor

Body weight was identified as a significant covariate using allometric scaling and was associated with a higher clearance and a higher volume of distribution according to a population pharmacokinetic analysis [90]. However, this is accounted for by body weight-adjusted i.v. dosing [23].

4.2 Sex

4.2.1 Clopidogrel

Exposure to the active metabolite was not significantly different between male and female healthy subjects and patients undergoing PCI [42, 46]. Accordingly, no effect of sex on the PD has been reported [97, 98].

4.2.2 Prasugrel

In healthy subjects, there was no effect of sex on the PK of the active metabolite [63]. In male and female patients with ACS, body weight-adjusted exposure to the active metabolite was also similar [95]. Accordingly, a meta-analysis of 24 phase I studies reported a similar degree of IPA in male and female subjects [53]. Hence, sex does not appear to have a relevant effect on the PK and PD of prasugrel.

4.2.3 Ticagrelor

Area under the curve from time zero to infinity ($AUC_{0-\infty}$) and C_{max} of ticagrelor were approximately 40% and 50% higher, respectively, in healthy female vs male subjects [99]. In atherosclerotic patients, no effect of sex on the PK of ticagrelor and its active metabolite has been determined [83]. However, an approximately 30% lower clearance of the active metabolite in female than in male patients with ACS or prior AMI has been reported based on two large population pharmacokinetic analyses [76, 77]. Overall, sex does not appear to have a clinically relevant impact on the PK of ticagrelor.

4.2.4 Cangrelor

In phase I and phase II studies, no impact of sex on the PK of cangrelor has been reported [100]. A meta-analysis using data from phase III and IV studies also concluded no difference in the safety and efficacy of prasugrel, ticagrelor, and cangrelor between male and female patients [101].

Table 2 Effect of intrinsic factors on the pharmacokinetics and pharmacodynamics of marketed oral P2Y12 receptor antagonists

Intrinsic factors	Clopidogrel	Prasugrel	Ticagrelor
Low body weight	Increased AM exposure in patients with stable CAD Increased IPA Not clinically significant	Increased AM exposure Increased IPA Clinically significant because of increased bleeding risk	Similar exposure in ACS Not clinically significant
Sex (female vs male)	Similar exposure in healthy subjects and patients with CAD (PCI) Not clinically significant	Similar exposure in healthy subjects Similar exposure in patients with ACS Similar IPA in healthy subjects Not clinically significant	Increased exposure in healthy female patients Similar exposure in patients with stable CAD Decreased clearance in patients with ACS Not clinically significant
Age	Similar exposure in healthy subjects across age range Similar exposure in patients with stable CAD (aged ≥ 65 years, aged < 65 years) Not clinically significant	Similar exposure in healthy subjects and patients with stable CAD across age range Similar IPA in healthy subjects across age range Increased exposure in patients with ACS aged ≥ 75 years Clinically significant because of increased bleeding risk	Increased exposure in healthy elderly patients (aged ≥ 65 years) Similar exposure in patients with stable CAD (aged ≥ 65 years, aged < 65 years) Similar exposure in patients with ACS across age range Decreased clearance of AM in patients aged > 75 years with prior MI Not clinically significant
Race			
Asian vs Caucasian	Decreased IPA Clinical significance unclear	Increased exposure and IPA Lower dose approved in Japan	Increased exposure and IPA Not clinically significant
Black vs Caucasian		Similar exposure	Similar exposure
Hispanic vs Caucasian		Similar exposure	Similar exposure
Genetic polymorphism	CYP2C19: impaired AM formation and reduced PD effects with LOF allele Clinically significant CES1: reduced function associated with increased AM exposure and higher IPA in healthy subjects and patients with CAD ABCB1: decreased exposure to AM and lower IPA in patients with stable CAD and ACS, no impact on IPA and safety in patients undergoing PCI CYP1A2*1F: associated with enhanced PD response in smokers P2Y12 receptor: C34T and G52T are associated with poor PD response	No impact of CYP2C19, CYP2C9, CYP2B6, CYP3A, and CYP1A2 on exposure and IPA Not clinically significant	No impact of CYP2C19 and ABCB1 on IPA Increased exposure and IPA associated with CYP3A4 reduced function variant
Renal impairment	Moderate and severe: decreased exposure and lower IPA Clinical relevance unclear	Moderate: similar exposure and IPA Severe: decreased exposure but similar IPA No dose adjustment needed	Severe: decreased ticagrelor and increased AM exposure, but unchanged IPA No dose adjustment needed
Hepatic impairment	Severe: similar IPA No dose adjustment needed	Moderate: similar exposure and IPA Severe: increased bleeding risk Clinically significant	Mild: increased exposure (parent and active), similar IPA Severe: not studied, but exposure likely to be increased Contraindication
Diabetes mellitus	Impaired bioactivation and reduced antiplatelet effects	No relevant impact	No relevant impact

ACS acute coronary syndrome, *AM* active metabolite, *CAD* coronary artery disease, *CES1* carboxylesterase 1, *CYP* cytochrome P450, *IPA* inhibition of platelet aggregation, *LOF* loss-of-function, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PD* pharmacodynamic

4.3 Age

4.3.1 Clopidogrel

In healthy subjects, exposure to the active metabolite was essentially independent of age [46]. In patients with cardiovascular disease aged < 65 years vs ≥ 65 years, no statistically significant pharmacokinetic difference was determined [102]. In patients undergoing PCI, no significant effect of age on the PK of the active metabolite was reported applying a population pharmacokinetic model [42].

4.3.2 Prasugrel

In healthy subjects aged 20–80 years, age did not significantly affect the PK or PD of prasugrel [103]. In patients with stable CAD, age was also not determined as significant covariate in a population pharmacokinetic model [41]. In patients with ACS aged > 75 years, exposure to the active metabolite was 19% and 25% higher than in patients aged 60–75 years or < 60 years, respectively. As elderly patients had an increased bleeding risk in the TRITON TIMI 38 trial, prasugrel is not recommended in patients aged > 75 years as per the label [16, 94]. The reasons for this increased bleeding risk are not fully clear, but may be owing to age-related changes in hemostasis [103].

4.3.3 Ticagrelor

In healthy elderly subjects aged ≥ 65 years, the C_{max} and $AUC_{0-\infty}$ of ticagrelor and its active metabolite were approximately 60% and 50% higher, respectively, compared with young subjects (aged 18–45 years) [99]. However, in 200 atherosclerotic patients, no effect of age on the PK of ticagrelor and its active metabolite has been determined [83]. In patients with ACS, the exposure ratio between the active metabolite and ticagrelor did not correlate with age based on linear regression [74]. Those findings were confirmed by a population pharmacokinetic model covariate analysis using data from > 6000 patients with ACS [77]. In patients with prior AMI aged > 75 years, the active metabolite clearance was decreased by 26% compared to patients aged < 65 years, but no clinical relevance was concluded [76]. Accordingly, no dose adjustment is recommended for elderly patients as per the label [17].

4.3.4 Cangrelor

In phase I and II studies, no impact of age on the PK of cangrelor has been reported [100] and hence no dose adjustment is required as per the label [23].

4.4 Race

4.4.1 Clopidogrel

An ethnic sensitivity study assessing the effect of race on the PK of clopidogrel has not yet been reported. However, with regard to the PD, on-treatment platelet reactivity has been more commonly observed in Asian individuals compared with White individuals and is associated with the higher prevalence of the CYP2C19 loss-of-function (LOF) allele in Asian individuals [104, 105]. Approximately 50% of Asian individuals are carriers of at least one CYP2C19 LOF allele compared with approximately 20% of the Caucasian, African–American, and Hispanic populations [106].

4.4.2 Prasugrel

No pharmacokinetic difference has been observed for African or Hispanic subjects as compared to Caucasian individuals [63]. In Asian individuals (Chinese, Japanese, Korean), active metabolite exposure was 19% higher compared with Caucasian individuals after adjusting for body weight based on a meta-analysis including 16 phase I studies [63]. In healthy White and Chinese subjects, maximum IPA after a loading dose of 30 mg of prasugrel was similar (i.e., 78% vs 87%) [107]. Despite the limited impact of race on the PK and PD of prasugrel, approximately threefold lower loading and maintenance doses of prasugrel are approved in Japan than in Europe or the USA (loading dose: 20 mg vs 60 mg; maintenance dose: 3.75 vs 10 mg once daily), probably mainly because the registration trials in Japan had been conducted with these lower doses [108].

4.4.3 Ticagrelor

Several studies and population pharmacokinetic analyses indicated that Asian individuals show an approximately 30–50% higher exposure to ticagrelor and its active metabolite compared with Caucasian individuals and consequently also an increased pharmacodynamic response [77, 109]. In contrast, the PK and PD of ticagrelor were not significantly different between Black, Hispanic, and Caucasian individuals [76, 77, 110, 111]. No dose adjustment based on race is recommended as per the label [17].

4.4.4 Cangrelor

Race was not identified to impact the PK of cangrelor [112].

4.5 Genetic Polymorphisms

Many clinically relevant genetic polymorphisms of drug-metabolizing enzymes, transporters, or receptors have been reported [113]. Among those, the functional and clinical relevance has been best characterized for polymorphisms of CYP enzymes leading to increased (i.e., rapid metabolizers) vs decreased or even lacking enzyme activity (i.e., poor metabolizers), hence contributing greatly to inter-individual pharmacokinetic and pharmacodynamic variability of many drugs including P2Y12 receptor antagonists [114].

4.5.1 Clopidogrel

The LOF CYP2C19*2 and *3 alleles are highly associated with non-responsiveness to clopidogrel and worse clinical outcome. In healthy subjects and patients with ACS, plasma concentrations of the active metabolite were significantly lower and the PD response decreased in carriers of reduced function alleles compared with wild-type subjects [36, 115, 116]. In healthy subjects and patients with CAD, the AUC of the active metabolite was also about 30–40% lower in subjects carrying at least one CYP2C19*2 allele [40, 42]. Accordingly, higher platelet reactivity has been determined in patients undergoing PCI carrying at least one LOF CYP2C19 allele [115]. With regard to the clinical impact, an increased risk of adverse cardiovascular events (e.g., stent thrombosis, myocardial infarction, ischemic stroke, and death) due to reduced CYP2C19 function has been reported for patients with CAD and ACS based on multiple studies and meta-analyses. Interestingly, the gain-of-function allele (*17) was also associated with an increased risk of major bleedings [36, 117–119]. The polymorphism of CYP1A2*1F might affect the enzyme inducibility and was associated with an enhanced PD response to clopidogrel in smokers [120, 121].

Genetic polymorphisms of CYP2C9, CYP2B6, and CYP3A4 were not clearly associated with clopidogrel response [105]. However, genetic variation in the *CES1* gene might also be of relevance for the PK/PD of clopidogrel. In healthy subjects, the reduced function allele CES1 c.428G > A (p.G143E) was associated with impaired clopidogrel hydrolysis by CES1, resulting in increased exposure to the active metabolite and greater pharmacodynamic response [28, 40]. Furthermore, patients with CAD with this genetic variant had significantly greater plasma concentrations of the clopidogrel active metabolite and consequently achieved greater IPA [122]. In addition, a study in Chinese patients with ACS indicates an effect of CES1 c.224G > A (p.S75N) on clopidogrel therapy [123].

The polymorphism (c.3435C > T variant) of the ABCB1 gene, encoding for the P-gp efflux transporter, has been shown to reduce intestinal absorption resulting in reduced active metabolite exposure and pharmacodynamic response [25, 116]. Another study concluded no effect of the ABCB1 polymorphism on the antiplatelet response in patients undergoing PCI and also no difference in the risk of stent thrombosis [124]. Furthermore, two meta-analyses indicate that this polymorphism is unlikely to have a major effect on adverse cardiovascular events [125, 126].

Polymorphisms of the P2Y12 receptor gene have also been investigated as sources of high variability and poor pharmacodynamic response but results are contradictory. A recent meta-analysis concluded that C34T and G52T polymorphisms might be associated with poor PD response in patients treated with clopidogrel [127]. The relevance of P2Y12 receptor gene polymorphisms to other P2Y12 receptor antagonists seems small, as potent and less variable IPA is achieved.

4.5.2 Prasugrel

Common functional genetic polymorphisms of CYP2C19, CYP2C9, CYP2B6, CYP3A5, and CYP1A2 did not impact the plasma concentrations of the active metabolite nor the degree of IPA in healthy subjects [128]. In patients with ACS undergoing PCI, no association between common functional CYP polymorphisms and an increased risk of cardiovascular events has been determined [128].

4.5.3 Ticagrelor

Genetic polymorphism in the *CYP3A4* gene has been shown to affect the PK and PD of the CYP3A4 substrate ticagrelor. In healthy subjects, the reduced function allele *CYP3A4*22* was associated with increased exposure to both ticagrelor and its active metabolite (89% and 30% increase in AUC $_{0\text{-}\infty}$, respectively) as well as higher IPA [129]. In healthy Chinese subjects, the clearance of the active metabolite was decreased by approximately 30% in carriers of the CYP3A4*1G allele [79]. The CYP2C19 or ABCB1 genotype had no impact on the pharmacodynamic response to ticagrelor [130].

4.5.4 Cangrelor

The impact of genetic polymorphisms of CYP enzymes on the PK or PD of cangrelor has not been investigated because its metabolism is CYP enzyme independent.

4.6 Renal Impairment

4.6.1 Clopidogrel

In patients with ACS with moderate and severe renal impairment, approximately 20% lower exposure to the active

metabolite and lower IPA has recently been reported [131]. Consistently, creatinine clearance was found as a significant covariate for the PK of the active metabolite [43]. A low degree of IPA (i.e., approximately 25%) has been determined in patients with moderate and severe renal impairment receiving 75 mg of clopidogrel once daily [132]. The label informs about these findings; however, it does not include any recommendation for dose adjustment [14, 15].

4.6.2 Prasugrel

There was no difference in active metabolite exposure or IPA between subjects with moderate renal impairment and healthy subjects. However, in subjects with end-stage renal disease, C_{max} and $AUC_{0\text{-}t}$ were 51% and 42% lower, respectively, compared with healthy subjects, but without impact on the pharmacodynamic response [133]. Hence, no dose adjustment is mandated in patients with renal disease according to the label [16].

4.6.3 Ticagrelor

In patients with severe renal impairment, exposure to ticagrelor was reduced by 20% while active metabolite exposure was 17% higher than in healthy subjects [134]. As this difference did not translate into changes in the pharmacodynamic profile, no dose adjustment is required for patients with renal impairment as per the label [17]. Those findings have recently been confirmed in patients with ACS with moderate and severe chronic kidney disease as the PK of ticagrelor and its active metabolite were unaffected and approximately 80% IPA was reached with the standard loading and maintenance dose [131].

4.6.4 Cangrelor

Renal impairment has been shown not to significantly affect the PK of cangrelor. Therefore, no dose adjustment in patients with mild, moderate, or severe renal impairment is required as per the label [22, 23].

4.7 Hepatic Impairment

4.7.1 Clopidogrel

In patients with severe hepatic impairment, platelet inhibition was comparable to that observed in healthy subjects [14]. Accordingly, the label does not recommend a dose adjustment in hepatically impaired patients [14].

4.7.2 Prasugrel

There was no relevant pharmacokinetic or pharmacodynamic difference between subjects with moderate hepatic impairment and healthy subjects [135]. However, the label contains a warning that patients with severe hepatic impairment may have a higher risk of bleeding [16].

4.7.3 Ticagrelor

In patients with mild hepatic impairment, the AUC of ticagrelor and its active metabolite were increased by 23% and 66%, respectively, compared with healthy subjects. However, this increase was not considered clinically significant, as it did not affect the pharmacodynamic response [136]. The impact of moderate and severe hepatic impairment has not been studied and hence the US label contains a warning for patients with severe hepatic impairment, indicating that plasma concentrations are likely to be increased [17]. In Europe, ticagrelor is even contraindicated in this patient population [96].

4.7.4 Cangrelor

As the metabolism of cangrelor is independent of the liver, no study in patients with hepatic impairment was performed and cangrelor can be administered irrespective of hepatic function according to the label [22, 23].

4.8 Diabetes Mellitus

Diabetes mellitus is a well-known risk factor for cardiovascular events and is associated with increased platelet reactivity [137]. This is likely caused by multiple factors such as changes in endothelial cell function, platelet signaling, platelet formation, and platelet receptor expression due to the biochemical changes associated with diabetes (e.g., hyperglycemia, insulin resistance) [138–141].

4.8.1 Clopidogrel

It has been shown that clopidogrel-induced antiplatelet effects are reduced in patients with diabetes [142]. The reason for this is not only the above-mentioned changes related to platelet reactivity, but the bioactivation of clopidogrel is also impaired in patients with diabetes potentially caused by changes in absorption and metabolism processes [143].

4.8.2 Prasugrel

In diabetic patients, prasugrel showed greater platelet inhibition and a lower incidence of non-responders compared with clopidogrel [144].

4.8.3 Ticagrelor

No significant difference in platelet inhibition has been reported for patients with or without diabetes when treated with ticagrelor [138]. In addition, antiplatelet effects of ticagrelor were consistently higher compared with clopidogrel and similar or higher compared to prasugrel in diabetic patients [145–147].

4.8.4 Cangrelor

In vitro studies using platelets from patients with and without diabetes concluded no difference in the antiplatelet effects of cangrelor [148].

5 Effect of Extrinsic Factors on the Pharmacokinetics and Pharmacodynamics

The effect of drug–drug interactions on the PK and PD of P2Y12 receptor antagonists is summarized in Table 3.

5.1 Clopidogrel

5.1.1 Victim Potential

The impact of CYP2C19 inhibition on the PK and PD of clopidogrel has been investigated with several proton pump inhibitors. In healthy subjects, the potent CYP2C19 inhibitor omeprazole reduced C_{max} and AUC of the active metabolite by approximately 40% and 30%, respectively [149]. Lansoprazole and dexlansoprazole also reduced exposure to the active metabolite, but to a lesser extent than omeprazole and esomeprazole [149]. In patients with stable CAD, exposure to the active metabolite was also reduced upon concomitant use of omeprazole or esomeprazole [150].

Accordingly, IPA was significantly lower when clopidogrel was co-administered with omeprazole and esomeprazole, while there was no IPA change observed for lansoprazole and dexlansoprazole. In patients with CAD, the antiplatelet effect of clopidogrel was also reduced upon co-administration of omeprazole [151]. Interestingly, the degree of clopidogrel-mediated IPA was still reduced when omeprazole was administered 8–12 h apart from clopidogrel [152]. Hence, concomitant use of omeprazole or esomeprazole and of moderate and strong CYP2C19 inhibitors is not advised as per the label [14, 15].

Concomitant administration of the potent CYP3A4 inhibitor ketoconazole reduced C_{max} and AUC of the clopidogrel active metabolite by approximately 20–30% and 40–50%, respectively [153]. This translated into significantly reduced IPA levels upon co-administration of ketoconazole. Lower clopidogrel-mediated IPA has also been reported for other CYP3A4 inhibitors, i.e., erythromycin and troleandomycin [154].

Accordingly, concomitant administration of the potent CYP3A4 inducer rifampicin resulted in an approximate fourfold increase in C_{max} and AUC of the active metabolite in healthy subjects [155]. This also led to approximately 20% higher IPA. Interestingly, the label does, however, not mention this interaction between clopidogrel and CYP3A4 inhibitors or inducers [14, 15].

Table 3 Clinically relevant pharmacokinetic drug–drug interactions of marketed P2Y12 receptor antagonists

Pharmacokinetic drug–drug interactions	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Victim potential	Potent CYP2C19 inhibitors (e.g., omeprazole) Potent CYP3A4 inhibitors and inducers	Strong CYP3A4 inhibitors (e.g., ritonavir; clinical relevance not clear)	Strong and moderate CYP3A4 inhibitors (e.g., ketoconazole) Strong CYP3A4 inducers (e.g., rifampicin) Strong P-gp inhibitors (e.g., cyclosporine)	None
Perpetrator potential	CYP2C8 inhibition	None	Mild CYP3A4 induction Mild P-gp inhibition Increases exposure to simvastatin and lovastatin	Potentially BCRP inhibition (in vitro; clinical relevance not clear)
Other	Opioids Smoking	Opioids	Opioids	None

BCRP breast cancer resistance protein, *CYP* cytochrome P450, *P-gp* P-glycoprotein

Morphine is commonly used as an analgesic in patients presenting with symptoms of AMI [156]. In healthy subjects, clopidogrel absorption was delayed upon co-administration of morphine presumably because of reduced gastrointestinal motility, and exposure to the active metabolite of clopidogrel was reduced by approximately 30% [157]. In patients with STEMI, an approximately 10% higher incidence of platelet reactivity has been reported upon morphine treatment [158]. Hence, treatment with a parenteral P2Y12 receptor antagonist (i.e., cangrelor) should be considered in patients requiring treatment with opioids as per the label [14, 15].

Conflicting data exist regarding the effects of statins on the PK and PD of clopidogrel. Atorvastatin, a CYP3A4 substrate, has been shown to inhibit the metabolism of clopidogrel in vitro [159] and reduced clopidogrel-mediated IPA has accordingly been reported in patients with CAD [154]. However, in healthy subjects, the PK and PD of clopidogrel were unchanged if given as a single dose and exposure was slightly increased in the context of multiple dosing upon co-administration of atorvastatin [160]. Several studies in patients with CAD reported that the PK and PD of clopidogrel were not significantly affected by concomitant use of atorvastatin [161–165]. In contrast, rosuvastatin was associated with attenuated clopidogrel-mediated IPA [164–166]. In view of these seemingly controversial data, the label interestingly does not mention any interaction with statins [14, 15]. Acetylsalicylic acid at different doses (81 mg, 100 mg, and 325 mg) did not impact the formation of the clopidogrel active metabolite in patients and healthy subjects [167, 168].

It has been shown that smoking enhances the bioactivation of clopidogrel, likely owing to CYP1A2 and to a lesser extent CYP2B6 induction. In smokers, exposure to the clopidogrel active metabolite was approximately 20% higher and CYP1A2 activity was increased compared with nonsmokers [169]. This was also reflected in the PD, as smokers showed a greater platelet inhibition, which might explain the better clinical efficacy reported for clopidogrel-treated smokers in large clinical trials. This is called the 'smokers paradox' owing to this counterintuitive effect as smoking is generally associated with an increased risk of cardiovascular events [170].

5.1.2 Perpetrator Potential

Clopidogrel has in vitro been shown to inhibit CYP3A4 and OATP1B1. However, it had no impact on the PK of the CYP3A4 and OATP1B1 substrate simvastatin in healthy subjects [171].

One of the clopidogrel metabolites, namely acyl-β-D-glucuronide, has in vitro been identified as a potent inhibitor of CYP2C8. Accordingly, clopidogrel increased the plasma exposure to the CYP2C8 probe substrate repaglinide by approximately four- to fivefold [172] and to the active metabolite of selexipag by approximately 2.7-fold [173]. Hence, the label cautions against concomitant use of clopidogrel with CYP2C8 substrates [14, 15].

5.2 Prasugrel

5.2.1 Victim Potential

Co-administration of the strong CYP3A inhibitor ketoconazole reduced C_{max} of the prasugrel active metabolite by approximately 40% but not its AUC [153]. In addition, there was no significant effect on the PD response reported. Ritonavir, another potent CYP3A inhibitor, reduced both C_{max} and $AUC_{0–6h}$ of the prasugrel active metabolite by approximately 40% [174]. Concomitant use of the strong CYP3A inducer rifampicin did not significantly affect the PK or PD of prasugrel in healthy subjects [175]. The CYP3A4 substrate atorvastatin had no significant impact on the PK and PD of prasugrel [160]. The label does not contain any warning or restrictions regarding concomitant use of CYP3A substrates, inhibitors, or inducers [16, 94].

Because prasugrel absorption from the gastrointestinal tract is pH dependent, the effect of drugs increasing the gastric pH was also investigated [93]. The proton pump inhibitor lansoprazole decreased C_{max} and AUC by 29% and 13%, respectively, while PD was unchanged [176]. The H_2 blocker ranitidine had no significant impact on the PK or PD of prasugrel [45]. Hence, prasugrel can be administered with drugs that increase gastric pH as per the label [16, 94].

In healthy subjects, co-administration of morphine had no relevant impact on the AUC of prasugrel, onset time, or degree of IPA [177]. However, in patients with STEMI, morphine treatment was associated with a delayed and reduced IPA in multiple studies [178–180].

No pharmacodynamic interaction has been reported with acetylsalicylic acid (325 mg) [68]. In contrast to clopidogrel, smoking does not affect the PK and PD of prasugrel to a relevant extent [169].

5.2.2 Perpetrator Potential

Prasugrel had no effect on the PK of the CYP2C9 substrate warfarin, but the bleeding time was prolonged. Hence, concomitant use of prasugrel and warfarin is not recommended as per the label [16, 94]. Prasugrel did not significantly alter the PK of the P-gp substrate digoxin and therefore, no effect of prasugrel on P-gp activity was concluded [93].

5.3 Ticagrelor

5.3.1 Victim Potential

Concomitant administration of the strong CYP3A inhibitor ketoconazole increased the exposure to ticagrelor markedly by approximately seven-fold, whereas the exposure to the active metabolite was decreased by approximately 60% [181]. This was also observed with the moderate CYP3A4 inhibitor diltiazem, but here the effects were less pronounced [181]. Therefore, concomitant use of strong CYP3A inhibitors is not advised as per the FDA label [17] and even contraindicated in the EU [96].

Upon co-administration of the strong CYP3A4 inducer rifampin, exposure to ticagrelor and its active metabolite was reduced by approximately 90% and 50%, respectively [80]. The pharmacodynamic response was similar up to 8 h post-dose, but declined rapidly to a mean IPA of 15% at 24 h compared to 70% at 24 h with ticagrelor alone [80]. Hence, concomitant use of strong CYP3A inducers is also not recommended as per the label [17, 96].

Exposure to ticagrelor and its active metabolite was increased by approximately 180% and 30%, respectively, upon cyclosporine-mediated inhibition of P-gp [182]. Hence, concomitant use of strong P-gp inhibitors is not advised as per the label [96].

Upon co-administration of morphine, delayed absorption and reduced ticagrelor exposure by approximately 20% has been reported in healthy subjects that, however, did not translate into any relevant IPA difference [183]. In patients with AMI, morphine reduced the AUC of ticagrelor and its active metabolite by approximately 40% and t_{max} was delayed by approximately 2 h [184]. In addition, the PD response was delayed and impaired. Similar effects on the PD have been reported for patients with STEMI upon co-administration of morphine [178, 185] and for patients with ACS upon co-administration of fentanyl [186]. According to the label, the use of a parenteral P2Y12 receptor antagonist (i.e., cangrelor) should be considered when opioid treatment is required [17, 96].

In healthy subjects, high-dose acetylsalicylic acid at 300 mg once daily had no effect on the PK or the PD of ticagrelor [187]. However, in the PLATO trial, acetylsalicylic acid at doses > 100 mg was associated with reduced effectiveness of ticagrelor and the FDA label contains a black-box warning in this regard [17] that has been challenged as there is no biological explanation and a chance finding cannot be excluded [188, 189]. The EU label is less stringent and states that co-administration of acetylsalicylic acid at doses > 300 mg is not recommended [96].

Smoking is unlikely to affect the PK and PD of ticagrelor as it is primarily metabolized via CYP3A4. Enhanced metabolism of ticagrelor in smokers has been suggested by a study in patients with ACS; however, in a large clinical trial, no effect of smoking status was found on cardiovascular events [74].

5.3.2 Perpetrator Potential

Ticagrelor has been reported to be a mild CYP3A inducer as it reduced the exposure to the CYP3A4 substrate midazolam [190]. Maximum concentration and AUC of the P-gp probe substrate digoxin were increased by 75% and 28%, respectively, upon co-administration of ticagrelor [191]. This indicates ticagrelor as a mild P-gp inhibitor and monitoring of digoxin plasma concentrations is recommended upon initiation of ticagrelor therapy [17].

Upon co-administration of ticagrelor, exposure to simvastatin (by approximately 80% for C_{max} and 60% for AUC) and atorvastatin (by approximately 40% for C_{max} and 20% for AUC) was increased [192]. It has been hypothesized that this poses an increased risk for statin-induced rhabdomyolysis [193]. However, a recent review did not conclude major safety concerns regarding concomitant use of statins and ticagrelor with respect to rhabdomyolysis and myopathy [194]. Nevertheless, use of simvastatin or lovastatin at doses greater than 40 mg is not recommended because of potential adverse reactions as per the label [17, 96].

5.4 Cangrelor

5.4.1 Victim Potential

Cangrelor has a low interaction potential with substrates or inhibitors of hepatic CYP enzymes as it is not metabolized via the liver. The concomitant use of cangrelor with commonly administered drugs in ACS (acetylsalicylic acid, unfractioned heparin, and nitroglycerin) has been investigated and showed no effect on the PK/PD of cangrelor [22].

5.4.2 Perpetrator Potential

Cangrelor or its metabolites did not inhibit or induce CYP enzymes in vitro [90]. However, breast cancer resistance protein (BCRP) was inhibited by one of the cangrelor metabolites at clinically significant doses [22].

The effects of clopidogrel and prasugrel are essentially diminished when administered during cangrelor infusion [195–197]. Mechanistically, this has been explained by the inability of the short-lived active metabolites of clopidogrel and prasugrel to bind to the P2Y12 receptor while occupied by cangrelor [198]. Hence, clopidogrel and prasugrel should not be administered during cangrelor infusion as per the label [22, 23]. In contrast, the PD of ticagrelor when given during cangrelor infusion was not significantly changed [196].

6 Potential New Treatments in Development

6.1 Current Unmet Medical Needs

6.1.1 Acute Setting

In patients with ACS, early intervention is crucial to reduce mortality as highlighted in the guidelines of the European Society of Cardiology [6] and the American Heart Association/American College of Cardiology [7]. The first 1–3 h after symptom onset have been identified to be most critical in the treatment of AMI and, in particular, in patients with STEMI [199]. Reperfusion of the occluded artery as early as possible is critical to reduce ischemic time and thereby prevent permanent damage of the myocardial tissue and death. This is commonly referred to as the 'time is muscle' concept [200]. There is, however, a relevant time gap from the onset of symptoms to treatment in the hospital [201, 202]. In addition, oral P2Y12 receptor antagonists need a considerable time of at least 2–6 h to reach their peak effect, which is even more delayed in ACS, e.g., because of limited absorption [203]. As platelets play a crucial role especially in the initial phase of thrombus formation [204], potent P2Y12 receptor antagonists with a rapid onset of action are desired.

6.1.2 Chronic Setting

Dual antiplatelet therapy with clopidogrel and acetylsalicylic acid has long been the gold standard of treatment. However, the response to clopidogrel is highly variable and unpredictable in addition to a weak platelet inhibition and slow onset. In 2010, the FDA has also issued a black-box warning for clopidogrel regarding reduced effectiveness in CYP2C19 poor metabolizers [205]. The poor response to clopidogrel seen in about 40% of subjects is multifactorial (e.g., 'smokers paradox', diabetes) and only 6–12% is explained by genetic factors. However, platelet function monitoring to adjust treatment is not recommended by current guidelines as its usefulness is unclear. One of the main limitations is the lack of a threshold that defines the optimal window of IPA [206]. Because of its well-known safety profile, clopidogrel is preferred in patients in whom ticagrelor or prasugrel is contraindicated (i.e., patients with a high bleeding risk). These patients would benefit from novel P2Y12 receptor antagonists with a low bleeding risk and improved pharmacokinetic and pharmacodynamic properties (e.g., lower non-responder rate and CYP-independent metabolism).

6.2 Vicagrel

Vicagrel is currently in phase II clinical development in China (NCT03599284) for the treatment of ACS [207, 208]. It is a clopidogrel analog and was designed to yield a stronger and more reliable IPA than clopidogrel. Vicagrel is converted via 2-oxo-clopidogrel to the same active thiol metabolite as clopidogrel [209]. However, this conversion occurs in CYP independently through hydrolysis catalyzed by esterases and is more efficient compared with clopidogrel [207, 210]. The second bioactivation step from 2-oxo-clopidogrel to the active thiol metabolite is identical to clopidogrel [210]. Formation of the active thiol metabolite is slightly faster for vicagrel than for clopidogrel with a t_{max} of 0.5 h (Table 1) [208].

The exposure to the active thiol metabolite after oral administration of 5 mg of vicagrel was comparable to 75 mg of clopidogrel and 29% higher when comparing a loading dose of 20 mg of vicagrel to 300 mg of clopidogrel in healthy Chinese subjects [208, 211]. Vicagrel showed dose-proportional PK over a dose range of 5–75 mg [208]. A similar half-life of the active metabolite was observed following 5 mg of vicagrel (0.79 h) or 75 mg of clopidogrel (0.73 h) (Fig. 2) [208].

A single loading dose of 30 mg of vicagrel resulted in a peak IPA of approximately 70% at 2 h after dosing [208]. The degree of IPA dose dependently ranged within approximately 30–80% for doses of 5–15 mg once daily, indicating greater IPA at the top dose compared with clopidogrel [211]. As for clopidogrel, the receptor inhibition is irreversible leading to a duration of IPA of 5–8 days after discontinuation of vicagrel. Both the PK and PD of vicagrel were unaffected by concomitant administration of acetylsalicylic acid 100 mg daily [211].

In a multiple-ascending dose study, no effect of the CYP2C19 phenotype on the PD of vicagrel was found [211]; however, the findings need to be confirmed by a dedicated study (NCT03942458) that was recently completed. Vicagrel may yield stronger and less variable platelet inhibition based on less CYP-dependent bioactivation compared with clopidogrel; however, larger studies in patients are needed to provide better evidence for the pharmacokinetic and pharmacodynamic claims and to establish its safety profile in a larger population.

6.3 Selatogrel

Selatogrel (ACT-246475) is currently under global clinical development for subcutaneous self-administration as early pre-hospital treatment of AMI. It is a 2-phenyl-pyrimidine derivative, that, like ticagrelor and cangrelor, reversibly and directly blocks the P2Y12 receptor [212].

Selatogrel is rapidly absorbed after subcutaneous administration with a median t_{max} between 0.50 and 0.75 h (Table 1) and achieves maximum IPA levels ≥ 85% within approximately 15–30 min after dosing [213]. In healthy

subjects, selatogrel showed dose-proportional exposure from 1 to 32 mg and was quickly eliminated with a geometric mean half-life range of 4–7 h at phase II doses of 8 mg and 16 mg (Fig. 2) [213].

Selatogrel does not undergo extensive metabolism and is mainly eliminated unchanged via the biliary route [214]. Its elimination is independent of CYP enzymes and only to a minor extent impacted by inhibition of OATP1B1 and 1B3 transporters [214, 215]. Hence, common functional genetic polymorphisms of metabolic enzymes and transporters as well as transporter- or enzyme-mediated drug–drug interactions are unlikely to affect the PK/PD of selatogrel. In addition, selatogrel has not been identified as an inhibitor or inducer of CYP enzymes or drug transporters in vitro (Idorsia Pharmaceuticals Ltd, data on file).

In 345 patients with stable CAD, selatogrel achieved prompt, consistent, and potent platelet inhibition for up to 8 h, which was reversible within 24 h [216]. A phase II study investigating the PK and PD in 47 patients with AMI has also recently been completed (NCT03487445) and confirmed the results of the study in patients with stable CAD. In addition, the concept of self-administration is expected to save valuable time in treatment initiation. Therefore, selatogrel has the potential to fill an unmet clinical need by providing rapid and potent platelet inhibition in the critical early phase of an AMI.

7 Conclusions

Inhibition of platelet aggregation mediated by P2Y12 receptor antagonists is an important element in the short-term treatment of myocardial infarction as well as for the secondary prevention of thrombotic events in patients with a history of AMI. Clopidogrel is globally still most widely used for secondary prevention of thrombotic events. Its safety profile is based on two decades of clinical experience and it is available as a generic drug in several countries worldwide. However, its PK and PD are highly variable because of an often insufficient CYP-dependent bioactivation leading to a low degree of IPA and a high proportion of non-responders. The clopidogrel-analog vicagrel is currently in phase II development in China and expected to provide greater IPA owing to an essentially CYP-independent bioactivation.

Prasugrel like clopidogrel is a prodrug requiring bioactivation catalyzed by esterases and different CYP enzymes. However, the degree of IPA achieved is much greater than with clopidogrel. On the flip side, this has been shown to be associated with an increased bleeding risk in patient studies and triggered a black-box warning in its label. It is indicated for the prevention of thrombotic events in patients with ACS undergoing PCI.

Among the oral P2Y12 receptor antagonists, ticagrelor is the most recently approved drug for secondary prevention of thrombotic events in patients with ACS post-AMI. It reliably achieves a much greater degree of IPA than clopidogrel. However, as it is mainly metabolized by CYP3A4, it has a higher potential to elicit CYP3A4-mediated drug–drug interactions.

While the oral P2Y12 receptor antagonists are effective in the long-term prevention of thrombotic events, their pitfall is the slow onset of effect due to delayed absorption in the short-term treatment of AMI. Cangrelor has a much faster onset of action than the oral P2Y12 antagonists and has been approved for the reduction of thrombotic events during PCI. It achieves almost complete IPA within minutes during an i.v. infusion that rapidly resolves when the infusion is terminated. As the use of cangrelor is restricted to the hospital setting, the well-established issue of delayed intervention is, however, also applicable to cangrelor. Selatogrel may address this unmet clinical need, as it also has a rapid onset of action similar to cangrelor after subcutaneous administration and is envisioned for self-administration by patients at the time of a suspected AMI.

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Compliance with Ethical Standards

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Conflict of interest Uta Schilling is a full-time employee of Idorsia Pharmaceuticals Ltd. Mike Ufer and Jasper fDingemanse are full-time employees of Idorsia Pharmaceuticals Ltd and owners of stocks/ stock options. Selatogrel is currently in development by Idorsia Pharmaceuticals Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article.

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