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P2Y12 platelet inhibition in clinical practice

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Abstract Platelet adhesion, activation and aggregation play a pivotal role in atherothrombosis. Intracoronary atherothrombosis is the most common cause of the development of acute coronary syndrome (ACS), and plays a central role in complications occurring around percutaneous coronary intervention (PCI) including recurrent ACS, procedure-related myocardial infarction or stent thrombosis. Inhibition of platelet aggregation by medical treatment impairs formation and progression of thrombotic processes and is therefore of great importance in the prevention of complications after an ACS or around PCI. An essential part in the platelet activation process is the interaction of adenosine diphosphate (ADP) with the platelet P2Y12 receptor. The P2Y12 receptor is the predominant receptor involved in the ADP-stimulated activation of the glycoprotein IIb/IIIa receptor. Activation of the glycoprotein IIb/IIIa receptor results in enhanced platelet degranulation and thromboxane production, and prolonged platelet aggregation. The objectives of this review are to discuss the pharmacological limitations of the P2Y12 inhibitor clopidogrel, and describe the novel alternative P2Y12 inhibitors prasugrel and ticagrelor and the clinical implications of the introduction of these new medicines.

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Introduction

Platelet adhesion, activation and aggregation play a pivotal role in atherothrombosis. Intracoronary atherothrombosis is the most common cause of the development of acute coronary syndrome (ACS), and plays a central role in complications occurring around percutaneous coronary intervention (PCI) including recurrent ACS, procedure-related myocardial infarction (MI) or stent thrombosis [1]. Inhibition of platelet aggregation by medical treatment impairs formation and progression of thrombotic processes and is therefore of great importance in the prevention of complications after an ACS or around PCI [2, 3]. Platelet inhibitors include thromboxane inhibitors (aspirin); adenosine diphosphate (ADP) receptor antagonists (or P2Y12 inhibitors) such as the thienopyridines (clopidogrel and prasugrel) and the nonthienopyridines (elinogrel, ticagrelor and cangrelor); the glycoprotein IIb/IIIa inhibitors; and medication working through other pathways and include dipyridamole, cilostazol, protease-activated receptor antagonists and the platelet adhesion antagonists [4].

The platelet inhibitor of choice, the optimal time of initiation and the duration of treatment depend on the indication for therapy and patient characteristics. In recent years, bleeding has been identified as an important risk factor for adverse outcomes and has led to a renewed emphasis on individual bleeding risk in choosing appropriate therapy [5]. Current European treatment guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for patients with ACS and patients who undergo PCI with stent placement [2]. The efficacy of this

combination in patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina has been shown in multiple large clinical trials [6–8]. Despite the efficacy of the aforementioned combination, there are important pharmacological limitations associated with clopidogrel use. Newly developed P2Y12 inhibitors such as prasugrel, ticagrelor and cangrelor, are more potent and have a faster onset of action than clopidogrel. The objectives of this review are to discuss the limitations of clopidogrel, and describe alternative P2Y12 inhibitors and the clinical implications of the introduction of these new medicines.

Pharmacology of P2Y12 inhibitors

An essential part in the platelet activation process is the interaction of ADP with the platelet P2Y12 receptor [9]. The P2Y12 receptor is the predominant receptor involved in the ADP-stimulated activation of the glycoprotein IIb/IIIa receptor [10]. Activation of the glycoprotein IIb/IIIa receptor results in enhanced platelet degranulation and thromboxane production, and prolonged platelet aggregation [11]. Thienopyridines inhibit the platelet activation and aggregation by antagonizing the platelet P2Y12 receptor. This prevents the binding of ADP to the receptor which attenuates platelet aggregation and reaction of platelets to stimuli of thrombus aggregation such as thrombin [4].

Pharmacological limitations of clopidogrel

Despite proven clinical efficacy of clopidogrel in patients with an ACS or after PCI, either as monotherapy or in combination with aspirin, pharmacological limitations of clopidogrel prevent this medication from always being fully effective [12]. Clopidogrel, a prodrug, requires a 2-step hepatic cytochrome P450 (CYP) metabolic activation to produce the active metabolite that inhibits the platelet P2Y12 receptor [13]. Before intestinal absorption, 85% of the pro-drug is hydrolyzed by esterases to an inactive carboxylic acid derivate. Because of these pharmacodynamic characteristics of clopidogrel, several hours pass between ingestion and reaching therapeutic levels. This results in suboptimal platelet aggregation inhibition during acute PCI for ACS and a higher risk for acute stent thrombosis. Moreover, the longer period up to therapeutic levels may raise the bleeding risk during acute coronary artery bypass grafting (CABG) if necessary based on coronary anatomy. Second, there is a substantial variability in clopidogrel response between patients. Accumulating evidence shows that a suboptimal response to clopidogrel is associated with worse clinical outcomes such as coronary ischemia or stent thrombosis [14–17]. This suboptimal therapeutic response is a consequence of the variation in the CYP gene [18]. This gene codes for the CYP-450 enzymes involved in the biotransformation of the prodrug clopidopgrel to the active metabolite. Particularly polymorphisms in the CYP2C19 allele are associated with a reduced activity of clopidogrel. Three large studies have shown that clopidogrel users who are carrier of the loss-of-function CYP2C19 allele endure more ischemic events compared with patients without this mutation, with the genetic substudy of the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial showing that these were mainly early events (within 30 days) [19–21]. Treatment strategies tailored to the heterogeneity in clopidogrel response were investigated in the GRAVITAS (Gauging Responsiveness with A VerifyNow Assay—Impact on Thrombosis and Safety) trial [22]. This trial analyzed whether tailored platelet aggregation inhibition on the basis of platelet function testing using a point-of-care assay (VerifyNow, Accumetrics Inc, San Diego, CA, USA) improved cardiovascular outcomes after drug-eluting stent placement during urgent or elective PCI. However, in patients with a high residual platelet activity, a higher clopidogrel dosing (loading dosis 600 mg post-PCI, followed by 150 mg daily) did not reduce the incidence of ischemic outcomes compared with a lower clopidogrel dosing (loading doses 150 mg post-PCI, followed by 75 mg daily). In order to overcome the described limitations of clopidogrel, alternative antiplatelet treatments have been developed.

Pharmacology of prasugrel

Prasugrel is a third generation thienopyridine. Rapidly after ingestion, prasugrel is hydrolyzed in the gastro-intestinal system into an intermediary metabolite. This intermediary metabolite is hepatically activated in a single-step and forms an active metabolite that binds to the P2Y12 receptor on the platelet. This irreversible bond with the receptor inhibits activation and aggregation of the platelet [18]. The peak concentration of the active metabolite of prasugrel is reached after 30 min, and the final concentration is linearly dependent on the prasugrel dose which varies between 5 and 60 mg. If not bound to the receptor, active metabolites have a half life of approximately 7 h [18]. A maximum of 60–70% platelet inhibition is usually achieved within 2–4 h [11]. There are important differences in the metabolic process between prasugrel and clopidogrel. First, with the initial hydrolization of clopidogrel, a substantial fraction is inactivated. Second, the activation of clopidogrel involves two CYP dependent steps, in contrast to a single CYP-dependent step with prasugrel [23]. This results in a

more rapid and consistent activation of prasugrel, with more receptor blocking active metabolite [24]. Third, genetic CYP variants do not have a significant influence on the active metabolites of prasugrel, subsequent platelet aggregation and clinical outcomes [25].

As a consequence, more effective platelet aggregation is achieved with prasugrel compared with clopidogrel both after the loading dose and with maintenance dose, as shown by research in patients with stable coronary disease [25] and elective PCI [26].

Pharmacology of the direct-acting P2Y12 inhibitors ticagrelor and cangrelor

Ticagrelor is a compound that directly and reversibly binds to and inhibits the P2Y12 receptor at a site distinct from the ADP binding site [11]. The compound is orally active without the requirement of metabolic activation [27]. It undergoes enzymatic degradation to at least one active metabolite which is approximately as potent as its parent compound [27]. The maximum plasma concentration and maximum platelet inhibition is reached 1–3 h after treatment, and the plasma half-life is 6–13 h [11]. In patients with ACS, ticagrelor exhibited greater inhibition of platelet aggregation than a standard regimen of clopidogrel [28]. Moreover, CYP2C19 and ABCB1 genotypes, known to influence the effects of clopidogrel, did not influence the effect on ischemic outcomes in ACS patients [20].

Much like to ticagrelor, the intravenous agent cangrelor directly and reversibly antagonizes ADP binding to the P2Y12 receptor. Cangrelor rapidly reaches steady state plasma levels and platelet aggregation inhibition within 30 min of onset of infusion without the need for a bolus dose, and the plasma half-life is short, being approximately less than 9 min [29]. Maximal platelet inhibition is achieved within 15 min. In patients with ischemic heart disease a substantially greater P2Y12 receptor blockade was achieved with cangrelor compared with clopidogrel [30].

Clinical trials

Prasugrel

The more effective platelet inhibition with the new P2Y12 inhibitors potentially results in a reduction of ischemic events and, the downside, more bleeding events. The safety and antiplatelet effects of prasugrel were investigated in two phase II studies, the JUMBO-TIMI 26 [31] and the PRINCIPLE-TIMI 44 [26]. The JUMBO-TIMI (Joint Utilization of Medications to Block Platelets Optimally—Thrombolysis in Myocardial Infarction) 26 was a dose-ranging safety trial comparing different prasugrel doses with clopidogrel (loading dose 300 mg, maintenance dose 75 mg) in patients undergoing PCI [31]. At 30 days after PCI, no statistical difference was observed in non-CABG-related (TIMI major plus minor) bleeding events when comparing prasugrel with clopidogrel. However, bleeding events were numerically higher with prasugrel use. Access site bleeding occurred most frequently. Importantly, because of evidence available at the time of enrolment in JUMBO-TIMI 26, there was an increased use of higher-than-approved doses of clopidogrel (loading dose 600 mg) in clinical practice. In the second phase II study involving prasugrel, the PRINCIPLE-TIMI (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—TIMI) 44, a 60 mg prasugrel dose was compared with a 600 mg loading dose of clopidogrel [26]. Among patients planned for PCI, loading with 60 mg prasugrel resulted in greater platelet inhibition than a 600 mg clopidogrel loading dose. Daily maintenance therapy with prasugrel 10 mg resulted in a greater antiplatelet effect than 150 mg daily clopidogrel.

As in the previous investigation, numerically higher bleeding was observed with prasugrel, although this difference did not reach statistical significance. The overall positive results from the JUMBO-TIMI 26 trial resulted in a large phase III efficacy and safety trial, the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—TIMI) 38 [32]. In this trial, 13,608 patients with moderate and high-risk ACS were randomized to prasugrel (60 mg loading dose and 10 mg daily maintenance dose) or clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) for 6–15 months (median 14.5 months). Randomization took place after coronary angiography and before PCI. The main efficacy endpoint was cardiovascular death, nonfatal MI, or nonfatal stroke. Major bleeding (definition: TIMI major bleeding not related to CABG), was included as the key safety endpoint. The use of prasugrel was associated with a significant reduction of the main efficacy endpoint, with an event rate of 12.1% in the clopidogrel group versus 9.9% in the prasugrel group ($P < 0.001$). This was mainly driven by a reduction in MI and stent thrombosis, no difference was observed in mortality. However, the reduction in ischemic endpoints with prasugrel was accompanied by a higher incidence of TIMI defined major bleeding, occurring in 1.8% of the patients in the clopidogrel group versus 2.4% in the prasugrel group. This translates into a risk of three extra major bleeds per 1,000 patients with prasugrel use, keeping in mind that patients at high risk for bleeding were excluded. As a consequence the bleeding risk with prasugrel could be potentially higher in clinical practice, although the same is true for the benefits [33]. This balance

has received increasing attention as many of the established risk factors for ischemic events are also suggestive of higher bleeding risk [34]. Especially noteworthy in this regard are the higher incidence of fatal and CABG-related bleeding observed with prasugrel. In an exploratory analysis, three subgroups of interest were identified that had less clinical efficacy and greater absolute levels of bleeding than the overall cohort, resulting in less net clinical benefit or in clinical harm. These included patients with a history of stroke or transient ischemic attack, patients aged 75 years and older, and patients with a body weight of less than 60 kg. Subanalyses from the TRITON-TIMI 38 are summarized in Table 1.

Ticagrelor

The safety, tolerability and efficacy of ticagrelor were investigated in the DISPERSE-2 (Dose confirmation study assessing anti-platelet effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction) phase II trial [35]. In this trial patients with a NSTE-ACS were randomized to receive ticagrelor 90 or 180 mg twice a day, or clopidogrel 75 mg once a day for up to 12 weeks. At 4-week follow-up, no difference was observed in major bleeding although an increase in minor bleeding was observed at the higher ticagrelor dose. On the other side, encouraging results were observed on the secondary end point of MI. Both doses of ticagrelor achieved a greater mean inhibition of platelet aggregation than clopidogrel in the ACS patients [28]. Ticagrelor was compared with clopidogrel in 18,624 patients with ACS in the multicenter randomized PLATO (Study of Platelet Inhibition and Patient Outcomes) [36]. Patients on maintenance treatment or who had received loading doses of clopidogrel were accepted. After randomization, the patients received ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300–600 mg loading dose, 75 mg daily thereafter). Patient randomization took place as early as possible after the index event. The main outcome at 12-month follow-up was the composite of cardiovascular death, MI or stroke which occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel ($P < 0.001$). This significantly lower event rate was driven by lower cardiovascular mortality, MI and stent thrombosis rates. The mortality benefit (4.5% with ticagrelor vs. 5.9% with clopidogrel) contrasts with the TRITON-TIMI 38 trial, were no differences in mortality were observed. Mechanisms for the reduction in mortality potentially include the favourable balance between the atherothrombotic effect and bleeding risk due to the faster speed of action or the higher potency of platelet inhibition with ticagrelor, or mechanisms beyond pure P2Y12 receptor inhibition [37]. It might be directly related to the metabolism of adenosine. In addition to causing reversible platelet inhibition, adenosine is involved in numerous biological activities including cardioprotection from reperfusion injury, apoptosis, myocyte regeneration, improved myocardial contractility, and electrical stability. Another explanation might be the small difference in bleeding. Major bleeding, according to the PLATO study definition, occurred in 11.6% of the patients in the clopidogrel group versus 11.2% in the ticagrelor group (2.2 vs. 2.8 if the TIMI non-CABG-related major bleeding definition is used). In contrast to the use of prasugrel in TRITON-TIMI 38, there was no increased risk of CABG-related bleeding with ticagrelor. Comparable with prasugrel, non-procedure-related bleeding, including gastrointestinal and intracranial bleeding, were numerically higher with ticagrelor than with clopidogrel, although not statistically significant different. The prevention of ischemic events with ticagrelor is achieved by a greater anti-platelet effect in the first hours of treatment and during maintenance therapy [38]. Notably, ticagrelor was associated with dyspnea resulting discontinuation in 0.9% of the patients. Finally, ventricular pauses were observed more frequently in the ticagrelor group. In 3,000 patients with available continuous ECG monitoring, these were predominantly asymptomatic pauses, sinoatrial nodal in origin, and nocturnal that occurred most frequently in the acute phase of the index ACS. There were no clinical consequences related to the excess of these ventricular pauses in patients assigned to ticagrelor [39]. Subanalyses from the PLATO trial are summarized in Table 1.

Cangrelor

The comparison between cangrelor and clopidogrel have been described in the large phase III CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PCI and CHAMPION PLATFORM trials [40, 41]. The major difference between the two trials was the timing of the administration of the study drugs. In the CHAMPION PCI trial, cangrelor or clopidogrel (600 mg) was started within 30 min before PCI. In the CHAMPION PLATFORM trial, cangrelor was started at the beginning of PCI, while clopidogrel (600 mg) was administered at the end of PCI. In the 8,877 patients enrolled in CHAMPION PCI and 2655 enrolled in CHAMPION PLATFORM, no reduction in ischemic outcomes was observed at 48 h when comparing cangrelor with clopidogrel. In CHAMPION PLATFORM, cangrelor use was associated with reductions in the prespecified secondary outcomes stent thrombosis and death. Similar to the observation in PLATO, transient dyspnea occurred more often with cangrelor use.

Table 1 Overview of subgroups from TRITON-TIMI 38 and PLATO

Study	Subgroup	*n*	Outcome	Follow-up	Definition	Prasugrel (%)	Clopidogrel (%)	*P* value
TRITON-TIMI 38	STEMI undergoing PCI [43]	3534	CV death, MI or stroke	15 months		10.0	12.4	0.0221
			Bleeding	15 months	Non-CABG TIMI major or minor	5.1	4.7	0.6494
					Non-CABG TIMI major	2.4	2.1	0.6451
	ACS and diabetes [55]	3146 (776 insulin-dependent)	CV death, MI or stroke	15 months		12.2	17.0	<0.001
			Bleeding	15 months	Non-CABG TIMI major or minor	5.3	4.3	0.13
					Non-CABG TIMI major	2.5	2.6	0.81
	ACS and PCI with stent [62]	12844	CV death, MI or stroke	15 months		10	12	0.0001
			Bleeding	15 months	Non-CABG TIMI major or minor	–	–	–
					Non-CABG TIMI major	2	2	0.06
	ACS and PCI without stent [63]	569	CV death, MI or stroke	15 months		14.2	17.1	0.27
			Bleeding	15 months	Non-CABG TIMI major or minor	4.3	2.2	0.25
					Non-CABG TIMI major	2.1	0	0.03
	ACS and GP IIb/IIIa inhibitor [64]	7414	CV death, MI or stroke	30 days		6.5	8.5	<0.05*
			Bleeding	30 days	Non-CABG TIMI major or minor	3.3	2.9	NS*
					Non-CABG TIMI major	1.2	1.1	NS*
	ACS without GP IIb/IIIa inhibitor [64]	6194	CV death, MI or stroke	30 days		4.8	6.1	<0.05*
			Bleeding	30 days	Non-CABG TIMI major or minor	1.2	1.1	<0.05*
					Non-CABG TIMI major	0.9	0.6	<0.05*

Study	Subgroup	*n*	Outcome	Follow-up	Definition	Ticagrelor (%)	Clopidogrel (%)	*P* value
PLATO	STEMI undergoing PPCI [42]	7544	CV death, MI or stroke	360 days		9.4	10.8	0.07
			Bleeding	360 days	PLATO major	9.0	9.2	0.76
					TIMI major	6.1	6.4	0.66
					Non-CABG TIMI major	2.5	2.2	0.60
	ACS and planned invasive strategy [48]	13408	CV death, MI or stroke	360 days		9.0	10.7	0.0025
			Bleeding	360 days	PLATO major	11.5	11.6	0.8803
					TIMI major	7.9	7.9	1.0000
					Non-CABG TIMI major	2.8	2.2	0.0814

Table 1 continued

Study	Subgroup	*n*	Outcome	Follow-up	Definition	Ticagrelor (%)	Clopidogrel (%)	*P* value
	ACS and planned non-invasive strategy [49]	5216	CV death, MI or stroke	360 days		12.0	14.3	0.045
			Bleeding	360 days	PLATO major	11.9	10.3	0.079
					TIMI major	7.9	7.2	0.270
					Non-CABG TIMI major	2.8	2.2	0.142
	ACS and diabetes [54]	4662 (1036 insulin-dependent)	CV death, MI or stroke	360 days		14.1	16.2	<0.0001
			Bleeding	360 days	PLATO major	14.1	14.8	<0.0001
					TIMI major	7.6	7.0	NS*
					Non-CABG TIMI major	–	–	–
	ACS and renal dysfunction CrCl (<60 ml/min) [57]	3237	CV death, MI or stroke	360 days		17.3	22.0	<0.05*
			Bleeding	360 days	PLATO major	15.1	14.3	NS*
					TIMI major	–	–	–
					Non-CABG TIMI major	4.8	3.9	NS*
	ACS undergoing CABG [65]	1899	CV death, MI or stroke	360 days		10.6	13.1	0.2862
			Bleeding	360 days	PLATO major	81.2	80.1	0.6691
					TIMI major	59.3	57.6	0.5300
					Non-CABG TIMI major	–	–	–

ACS acute coronary syndrome, *CABG* coronary artery bypass grafting, *CrCl* creatinin clearance, *CV* cardiovascular, *MI* myocardial infarction, *PPCI* primary percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction, *TIMI* Thrombolysis In Myocardial Infarction

* Derived from manuscript

Clinical practice

The choice of drug, initiation, and duration of P2Y12 inhibition depend on the clinical setting (urgent or elective intervention) and patient-related factors such as the ischemic risk, bleeding risk and other baseline clinical characteristics. The levels of recommendation regarding P2Y12 inhibition are according to the European Society of Cardiology 2010 guidelines on myocardial revascularization.

STEMI

The preferred treatment for patients with STEMI is mechanical reperfusion by primary PCI. Thus fast acting P2Y12 inhibitors are of paramount importance in these high-risk patients who require urgent intervention. In STEMI patients, prasugrel (60 mg loading dose, followed by 10 mg daily) or ticagrelor (180 mg loading dose, followed by 90 mg twice daily) are recommended as P2Y12 inhibitors (both class I, level B). Both agents have been shown to reduce ischemic outcomes in STEMI patients, without increasing the bleeding risk significantly [42, 43]. Clopidogrel (600 mg loading dose, followed by 75 mg daily) should be used primarily if the more effective ADP receptor blockers are contraindicated or unavailable (class I, level C).

NSTE-ACS

The choice of P2Y12 inhibition in patients presenting with NSTE-ACS depends on the chosen treatment strategy. Presently, there are three trials with long-term follow-up after a routine or selective invasive management in these patients [44–46]. Based on these clinical trial results and a large patient-pooled meta-analysis, current guidelines recommend a routine invasive strategy, consisting of routine coronary angiography and PCI if suitable, in high-risk NSTE-ACS patients [2, 47].

High risk of ischemic heart disease is associated with ST-segment changes, elevated troponin, diabetes, and a GRACE risk score of more than 140. ACS patients undergoing a routine invasive management have been analyzed in subgroup analyses from PLATO and TRITON-TIMI 38. In PLATO, NSTE-ACS patients comprised around 50% of the ACS population, while around 75% were NSTE-ACS patients in TRITON-TIMI 38 [26, 48]. Compared to clopidogrel, ticagrelor or prasugrel reduced ischemic outcomes in these patients. For prasugrel and ticagrelor, there is respectively a class IIa, level B and class I, level B recommendation. However, in patients with a history of stroke and TIA, or prasugrel is contraindicated and in patients with a body weight of less than 60 kg, and patients aged $\geq$75 years, prasugrel should be used with caution with a 5 mg dose because of an increased bleeding risk. Prasugrel should also be avoided in patients referred for CABG. If prasugrel is used, it should be administered after coronary angiography.

Patients triaged to the selective invasive strategy undergo coronary angiography only in case of hemodynamic or electrical instability, or a positive ischemia detection test. With the latest trials focusing mainly on patients undergoing invasive management, less data is available on conservatively managed patients. However a substudy from PLATO in ACS patients intended for non-invasive management showed that the benefits of ticagrelor over clopidogrel are consistent, and with a greater absolute benefit with those from the overall PLATO results [49]. This indicates that ticagrelor can be recommended unless there are contra-indications to this agent.

Regardless of the intended treatment strategy in NSTE-ACS, a large proportion of the patients do not undergo revascularization during initial hospitalization. Because the optimal approach to antiplatelet therapy for high-risk, medically managed NSTE-ACS patients remains uncertain, the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial currently enrols medically managed NSTE-ACS patients who are randomized to prasugrel and aspirin versus clopidogrel and aspirin for a median duration of 18 months [50]. Regarding ticagrelor, the abovementioned PLATO substudy in ACS patients intended for a non-invasive management showed a consistent benefit of ticagrelor regardless of revascularization.

Elective PCI

After diagnostic coronary angiography, the majority of PCI procedures ultimately result in stent placement. The current European guidelines for myocardial revascularization recommend a clopidogrel loading dose of 300 mg administered at least 6 h before the procedure (class I, level c) [2]. A 600 mg loading dose may be preferred if given within 6 hours. If no intervention is planned after coronary angiography, clopidogrel can be stopped. In patients with a high thrombotic risk (diabetics, patients after recurrent MI, after stent thrombosis, complex lesions such as left main stenting, or in life threatening situations should an occlusion occur) or patients with a high on treatment platelet reactivity, clopidogrel might not optimally protect against thrombotic complications. However, the role of currently available platelet reactivity assays are unclear as the predictive accuracy of platelet function tests for ischemic outcomes is only modest [51]. This point was made clear in the aforementioned GRAVITAS trial, showing a higher clopidogrel dosing in patients with a high residual platelet activity did not reduce ischemic outcomes. In addition, the

Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) trial (ClinicalTrials.gov identifier: NCT00910299) was recently terminated because of low event (6 month cardiovascular death or MI) rates. Although these trials question the use of routine platelet testing in elective PCI, it must first be mentioned that it has been shown that the predictive accuracy of platelet function tests for ischemic outcomes is only modest. Moreover, no test is able to identify patients at high risk for bleeding. Second, no data is available in the abovementioned patients at high risk for ischemic events, including comparisons between prasugrel and ticagrelor with clopidogrel. Third, although genotyping might assist in identifying patients with a low response to clopidogrel, CYP2C19 polymorphisms explain around 5.2% of the antiplatelet response [52]. No data is currently available regarding ticagrelor, prasugrel, or a high dose clopidogrel after platelet function testing in patients at high risk for ischemic events.

Other clinical considerations in the choice of P2Y12 inhibition

Diabetic patients, especially those with an ACS, are at a high risk for (recurrent) ischemic events. This can partly be attributed to increased platelet reactivity [53]. Substudies of PLATO and TRITON-TIMI 38 in diabetic patients confirmed this higher risk in diabetic patients. Ticagrelor reduced ischemic outcomes in ACS patients, irrespective of the diabetic status, when compared to clopidogrel but numerically more in patients with poor metabolic control (HbA1c >6%) [54]. Total major bleeding events were similar, but non-CABG related major bleeding events were numerically more frequent with ticagrelor. When comparing prasugrel with clopidogrel in diabetic patients, a lower number of ischemic and similar bleeding events were observed [55]. Possible explanations for the similar bleeding rates remain speculative, but have been ascribe by investigators as possibly due to higher body weight or greater baseline platelet reactivity among diabetics, or simply the play of chance. The latter explanation is supported by the similar relative increase in the combination of major or minor bleeding among diabetics and nondiabetics and the higher major bleeding rate among diabetics compared with nondiabetics on clopidogrel. These findings were not expected if related to platelet reactivity only. Moreover, there was no significant interaction regarding the main outcome.

A high risk subgroup for bleeding events, often excluded from major clinical trials, are patients with an impaired renal function. The extent of renal dysfunction is related to cardiovascular outcomes, as illustrated in patients with renal dysfunction who presented with a MI [56]. Importantly, the initial dose of an antithrombotic drug does not add to the risk of bleeding in cases of renal dysfunction [2]. In contrast, repeated dosing results in accumulation of drugs and its associated increased bleeding risk. Dose reductions could potentially mitigate the accumulation of drugs. However, in patients with a glomerular filtration rate (GFR) of 30–60 ml/min/1.73 m^2, no information is available about dose reductions for prasugrel. Moreover, prasugrel is contraindicated in patients with severe renal dysfunction (GFR of less than 30 ml/min/1.73 m^2). Regarding clopidogrel, no information is available about dose reductions in patients with renal dysfunction. Finally, for ticagrelor no reduction is required in patients with a GFR of less than 60 ml/min/1.73 m^2 and the benefit was sustained and in fact numerically enhanced in this high risk subset of patients [57].

Ticagrelor is dosed twice daily which requires good adherence to medical therapy to ensure a reduction in risk of ischemic events, although this might also be true for the other medication required once daily. Treatment with any of the more potent P2Y12 inhibitors results in higher risk for spontaneous bleeding events, accumulating over time which should be considered in frail patients.

In patients with ACS, in which an invasive management is planned, the presence of shock, vomiting or sedation might prevent oral intake of P2Y12 inhibitors. In these patients, intravenous cangrelor might prove to be an alternative for the oral agents. However, cangrelor is currently not approved for clinical practice.

Conclusions and remaining questions

New P2Y12 inhibitors have decreased ischemic events after PCI compared with clopidogrel [58]. On the horizon is elinogrel, a novel P2Y12 inhibitor that has passed the dose-escalation study ERASE MI (Early Rapid Reversal of Platelet Thrombosis with Intravenous Elinogrel before PCI to Optimize Reperfusion in Acute Myocardial Infarction) [59]. Results of ERASE MI were incorporated into the design of the phase II nonurgent INNOVATE PCI trial (INtraveNous and Oral administration of elinogrel, a selective and reversible P2Y [12]-receptor inhibitor, versus clopidogrel to eVAluate Tolerability and Efficacy in nonurgent Percutaneous Coronary Interventions; ClinicalTrials.gov identifier: NCT00751231) were both IV and oral dosing of elinogrel are compared with clopidogrel (presented by Rao SV et al., at European Society of Cardiology Conference 2010). Patients treated with elinogrel, a reversible and competitive P2Y12-receptor antagonist which requires no metabolic activation, had greater inhibition of platelet aggregation than those treated with

clopidogrel. At 120 days, there was no difference in major bleeding, minor bleeding, or bleeding requiring medical attention among those treated with elinogrel and those treated with clopidogrel. Currently, a phase III trial is planned.

Despite the improvement in clinical outcomes with the new P2Y12 inhibitors, remaining questions are the possibility to switch drugs, different doses, duration of therapy, optimal time of initiation (in NSTE-ACS), and cost-effectiveness.

Regarding the duration of therapy, current clinical practice guidelines recommend 12-month treatment with dual antiplatelet therapy in the setting of ACS. However, the optimal duration after PCI and the extent to which dual antiplatelet therapy confers benefit against ischemic events (including stent thrombosis) beyond 12 months is not known. The DAPT study is currently enrolling patients to assess the impact of 30 versus 12 months of dual antiplatelet therapy in patients undergoing PCI with stent placement [60].

Cost-effectiveness of the novel agents ticagrelor and prasugrel have been recently described. From the US healthcare perspective, treatment with prasugrel versus clopidogrel for a median of 14.7 months appeared to be an economically dominant treatment strategy, resulting in both lower costs and greater life expectancy [61]. The lower costs were mainly due to a reduction in the costs of repeat PCIs. A cost effectiveness study of ticagrelor from PLATO showed that treating ACS patients with ticagrelor for 12 months is associated with a gain in 0.13 quality-adjusted life year in a lifetime perspective compared with generic clopidogrel (presented by Henriksson M et al. at the International Society for Pharmacoeconomics and Outcomes Research Conference 2011). Regarding the cost per quality-adjusted life year gained, ticagrelor was highly cost-effective applying conventional thresholds of cost-effectiveness.

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