Review

Current status and prospects of antiplatelet therapy in percutaneous coronary intervention in Japan: Focus on adenosine diphosphate receptor inhibitors

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Summary Dual antiplatelet therapy with aspirin and clopidogrel is routinely used to prevent thrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) in Japan. However, these agents have various limitations and some patients will experience further cardiovascular events. The purpose of this article is to review the antiplatelet agents currently used in patients undergoing PCI in Japan, to discuss the issues and limitations associated with these antiplatelet agents, and to characterize new antiplatelet agents currently under investigation in Japan. Particular emphasis is placed on the novel thienopyridine prasugrel, and the potential this drug has for overcoming the issues associated with other antiplatelet agents.

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Introduction

When ruptured, coronary artery plaques release thrombogenic substances into the circulation, stimulating platelet activation and aggregation [1]. Patients undergoing percutaneous coronary intervention (PCI) are at particular risk of thrombotic events, particularly when stents are placed. PCI is conducted in approximately two-thirds of patients with myocardial infarction (MI) in Japan, and is much more frequently performed in Japan than in the USA or Europe [2].

Antiplatelet agents play a key role in preventing thrombosis in patients undergoing PCI [3]. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial [4] showed a greater reduction in stent thrombosis following treatment with aspirin in combination with clopidogrel as compared with aspirin alone. Therefore, dual antiplatelet therapy is now the standard of care for the prevention of ischemic events in such patients [1,3]. However, some patients remain at increased risk of ischemic events following successful PCI and treatment with the currently available antiplatelet agents [1,3].

This article reviews the antiplatelet agents currently used to prevent thrombosis in patients undergoing PCI, the issues associated with such agents, and the characteristics of the novel antiplatelet agent prasugrel, including the potential that this agent may have in overcoming the issues associated with other agents. Furthermore, we discuss the current situation in Japan, and steps being taken to overcome the limitations associated with current therapies for Japanese patients.

ADP receptor inhibitors

Adenosine diphosphate (ADP), a nucleotide found in platelets, is the product of adenosine triphosphate (ATP) dephosphorylation. ADP binds to purinergic receptors (principally P2Y1 and P2Y12) expressed on the platelet membrane to mediate platelet activation and aggregation (reviewed by Angiolillo et al. [5]). The P2Y1 receptor is a G_{i/q11} coupled G-protein receptor that plays an important role in responses to shear stress by mobilizing intracellular calcium [6]. The P2Y12 receptor is a G_{i/q11} coupled G-protein receptor that plays similar roles to P2Y1, but is also important in the potentiation of platelet activation mediated by physiological agonists, such as collagen, von Willebrand factor and thromboxane A2, and is essential for aggregation [6–8]. Activation of P2Y12 reduces adenylyl cyclase activity, which ultimately leads to platelet aggregation and fibrinogen-mediated platelet crosslinking [9]. Clopidogrel and ticlopidine are thienopyridines that preferentially inhibit the P2Y12 receptor and prevent ADP-mediated inhibition of adenylyl cyclase activity, thus reducing platelet aggregation [7,8,10].

Ticlopidine

Ticlopidine is a first-generation thienopyridine that, in Japan, is used after PCI for the "treatment of thrombosis and embolism in association with vascular surgery and blood circulation outside the body as well as the improvement of blood circulation disorders” [11].

In early clinical studies, ticlopidine alone or in combination with aspirin was shown to be more effective than other anticoagulants in preventing stent thrombosis after coronary artery stenting [12,13], and more effective than aspirin [14] or a placebo [15] in the prevention of recurrent stroke in patients who had recently experienced a thromboembolic stroke [15], or an episode of transient or mild persistent focal cerebral or retinal ischemia [14]. Ticlopidine was also more effective than a placebo in reducing the incidence of vascular surgery in patients with intermittent claudication [16].

However, ticlopidine is associated with a risk of potentially life-threatening hematologic adverse events (e.g. neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura, and aplastic anemia). In addition to the less favorable safety profile of ticlopidine compared with clopidogrel or prasugrel, ticlopidine also has a slower onset of action than prasugrel, but one that is similar to that of clopidogrel (reviewed by Angiolillo [3]). As a consequence of these limitations, ticlopidine is used less frequently than clopidogrel in many countries [3]. Nevertheless, ticlopidine is still widely used in Japan partly because of the more limited indication for clopidogrel.

Clopidogrel

In Japan, clopidogrel, a second-generation thienopyridine, is approved for use in patients with acute coronary syndrome (ACS) [either non-ST-elevation myocardial infarction (STEMI) or unstable angina] undergoing PCI, and for the prevention of recurrent ischemic cerebrovascular disorder (except cardioembolic stroke) [17].

In large (n = 3491–45,852), randomized, double-blind trials, clopidogrel alone or in combination with aspirin was more effective than aspirin alone in reducing major cardio-
vascular events in patients with recent non-STEMI, STEMI, stroke, or symptomatic peripheral artery disease [18]; in decreasing the incidence of death, reinfarction, or stroke in post-STEMI patients [19]; and in reducing the risk of an occluded infarct-related artery on angiography, death, or recurrent MI before angiography in acute STEMI patients scheduled to undergo angiography [20].

In addition, in two [21,22] of three [21–23] studies comparing clopidogrel with ticlopidine, clopidogrel plus aspirin demonstrated a more favorable tolerability/safety profile than ticlopidine plus aspirin in patients undergoing coronary stent placement. In the third study [23], the two drugs appeared to have similar tolerability profiles, although clopidogrel was associated with fewer non-cardiac events than ticlopidine. Furthermore, in an analysis of two Japanese studies conducted in patients with prior stroke, the safety profile of clopidogrel was significantly better than that of ticlopidine [24]. In all of these studies, the two drugs had a similar efficacy with regard to prevention of cardiovascular events.

Based on the results of large trials, clopidogrel has become the antiplatelet agent of choice to prevent thrombotic events [3]. Current US-based guidelines recommend antiplatelet therapy with a combination of aspirin and clopidogrel for patients who are undergoing PCI or who have ACS [25,26]. Although Japanese guidelines state that ticlopidine plus aspirin is the antiplatelet regimen of choice in patients undergoing coronary artery stenting, ticlopidine is expected to be replaced by clopidogrel because of the more favorable tolerability profile associated with the latter drug [27]. However, clopidogrel has limitations that should be discussed.

Issues associated with clopidogrel

Clopidogrel is an inactive prodrug that is converted into its active form via hepatic cytochrome-mediated biotransformation in the liver (reviewed by Angiolillo et al. [1]). Activation of clopidogrel is inefficient, with as little as 10–15% of the prodrug becoming active and the remaining being hydrolyzed into an inactive form [28]. Clopidogrel also has a slow onset of action, reaching steady-state in 3–7 days at a dose of 75 mg [29]. However, this can be shortened by the administration of a loading dose (300–600 mg), which can reduce the time to reach inhibitory levels close to steady-state to approximately 2 h [29]. Clopidogrel is also associated with a delayed cessation of action, which may be problematic in patients requiring CABG or other surgery. In addition, the patient responses to clopidogrel show great inter-individual variability [30]. Furthermore, the drug has been associated with incomplete platelet inhibition or poor responsiveness [1,10].

Poor responsiveness to clopidogrel

Poor response to clopidogrel may be divided into the following categories: clinical response (occurrence of cardiovascular events while taking antiplatelet agents) and laboratory response (incomplete blocking of platelet activity in vitro) [31]. However, the poor response determined by laboratory tests of platelet function shows low sensitivity and specificity for identifying thrombotic risk [31].

The frequency of poor response to clopidogrel varies greatly because of differences in a variety of factors, such as the definition of response used, the laboratory test employed, the patient population studied, and the drug dosing regimen administered (reviewed by Kuliczkowski et al. [32]). For example, when platelet aggregation induced by ADP was assessed by optical transmittance, poor response ranged from 5 to 44%; in a meta-analysis, incomplete inhibition of platelets was seen in about 21% of patients undergoing PCI; and using cytometric analysis with vasodilator-stimulated phosphoprotein (VASP), the prevalence was around 30% [32]. Poor response to clopidogrel has also been reported in several studies in Japan, with approximately 14% of patients undergoing PCI being non-responders to clopidogrel [33].

The causes of poor responsiveness to clopidogrel are likely multifactorial and may be divided into genetic, clinical, and cellular factors (Fig. 1) (reviewed by Angiolillo et al. [1] and Sweeney et al. [34]). Examples of contributing factors include: poor drug compliance/underdosing; poor drug bioavailability/absorption; the influence of metabolizing enzyme cytochrome P450 subtypes; the influence of CYP2C19 genetic variants; and possible drug-to-drug interactions with other commonly used medications, such as statins and proton pump inhibitors [1,34].

CYP2C19 is an important enzyme involved in the altered pharmacokinetic profiles of a number of drugs [35]. On the basis of their ability to metabolize various CYP2C19 substrates, patients can be classified as extensive, intermediate, or poor metabolizers [35]. More Asians than Caucasians (12–23% vs. 1–6%) carry genetic polymorphisms causing them to be poor metabolizers of CYP2C19 substrates [35]. A significantly higher incidence of cardiovascular adverse events was reported after acute MI in clopidogrel-treated patients with CYP2C19 loss-of-function alleles than in those with functional alleles [36]. In addition, the CYP2C19*2 genetic variant was a major determinant of prognosis in young patients treated with clopidogrel after MI [37]. Furthermore, among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did non-carriers [38]. In contrast, in patients with ACS or atrial fibrillation, clopidogrel was more effective than placebo in reducing the rate of cardiovascular events, irrespective of CYP2C19 loss-of-function allele status; however, patients carrying CYP2C19 gain-of-function alleles appeared to benefit more from clopidogrel than did non-carriers [39].

The prevalence of polymorphisms in CYP2C19 is relatively high in Japanese patients [40], and these polymorphisms were shown to have marked effects on the response to clopidogrel. Indeed, we recently reported the impact of the CYP2C19 genotype on platelet activity in 201 Japanese patients with stable coronary heart disease (CHD) during antiplatelet therapy. In these patients, the distribution of the CYP2C19*1/*1, *1/*2, *1/*3, *2/*2, *2/*3 and *3/*3 genotypes was 37%, 33%, 11%, 11%, 7%, and 1%, respectively (Fig. 2). Among those treated with dual antiplatelet therapy, platelet reactivity was most significantly decreased in wild-type homozygotes (CYP2C19*1/*1), followed by the *2 and *3 heterozygotes (*1/*2, *1/*3), but was poorly inhibited in
Clinical factors
- Failure to prescribe/poor compliance
- Underdosing
- Poor absorption
- Drug–drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Increased body mass index

Cellular factors
- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Upregulation of the P2Y12 pathway
- Upregulation of the P2Y13 pathway
- Upregulation of P2Y-independent pathways (collagen, epinephrine, TXA2, thrombin)

Figure 1 Variability in the response to clopidogrel [1]. Reprinted with permission from Elsevier.

*2/*2, *2/*3, and *3/*3 individuals. However, when patients carrying the variant allele were classified into two groups based on the duration of dual antiplatelet therapy, platelet reactivity was significantly decreased in those treated for >7 days compared with those treated for <7 days (Fig. 3). Moreover, the incidence of cardiovascular events was higher in patients carrying at least one variant allele than in wild-type homozygotes [41]. In that study, we also investigated the relationship between CYP2C19 polymorphisms and cardiovascular events in 98 patients. As shown in Fig. 4, the prevalence of subsequent cardiovascular events was significantly higher in carriers than in non-carriers, despite treatment with clopidogrel.

Poor metabolism of clopidogrel in some patients has resulted in the addition of a ‘boxed warning’ by the US Food and Drug Administration [42]. This warns clinicians of the possibility of reduced effectiveness in patients who are poor metabolizers of clopidogrel. Increasing the dosage of clopidogrel might be expected to overcome poor clinical response. However, this is not uniformly supported by results of clinical trials indicating that targeting an independent pathway may offer a more effective approach than attempting to overload an ineffective system [43].

Three-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) are widely used among patients with cardiovascular disease. Several studies have suggested that some statins, including simvastatin and fluvastatin, may reduce the bioactivity of clopidogrel, although this was not a class effect, and other studies showed no effect of concomitant statin use on clopidogrel [44]. Nevertheless, clinicians should be aware of possible interactions between these drugs.

Proton pump inhibitors (PPI) are often needed in patients given antithrombotic agents because of the increased risk of gastrointestinal bleeding [37,45,46]. Concomitant use of clopidogrel and PPI after hospital discharge for ACS was associated with an increased risk of adverse outcomes compared with the use of clopidogrel without PPI, suggesting that the use of PPI may be associated with an attenuation of the benefits of clopidogrel after ACS [47–49]. How-

Figure 2 Distribution of CYP2C19 phenotypes and genotypes in 201 Japanese patients with stable coronary heart disease on antiplatelet therapy [41]. EM, extensive metabolizers; IM, intermediate metabolizers; PM, poor metabolizers. Reprinted with permission from Elsevier.
ever, these findings are equivocal, as a sub-analysis [50] of TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) found no association between PPI use and the primary endpoint (composite of cardiovascular death, MI, or stroke) in patients treated with clopidogrel [hazard ratio (HR) = 0.94; 95% confidence interval (CI) = 0.80–1.11].

Overcoming poor responsiveness to clopidogrel

Although there are no formal recommendations for “treating” incomplete responses, a number of approaches have been proposed (reviewed by Kuliczkowski et al. [32]). These include the use of glycoprotein IIb/IIIa during elective angioplasty [51,52]; increasing the clopidogrel dose, particularly in patients with diabetes [53]; adding in a third antiplatelet drug (e.g. cilostazol) [54,55]; switching to ticlopidine [56]; and switching to one of the newer antiplatelet agents, such as prasugrel or ticagrelor [57].

In the next section, we wish to focus on the opportunities provided by newer antiplatelet agents and the possible implications for the treatment and prevention of thrombosis in Japan.

ADP receptor inhibitors in development in Japan

To date, much of our knowledge regarding the prevention of cardiovascular disease has been derived from studies conducted largely in European populations [2,58]. Moreover,
Antiplatelet populations large, reported, countries on or cated events Prasugrel vascular patients (STEMI) from two so that cardiovascular patients treated Kaplan—Meier the with cardiovascular prasugrel. Reprinted A, B from Wolters Kluwer.

Japanese cardiovascular prevention guidelines are based on results of such studies [58]. However, because geographic differences in cardiovascular risk factors have been reported, particularly in Asian countries, it is important that large, well-designed clinical trials are conducted in these countries so that evidence-based guidelines specific to Asian populations can be prepared [2,58]. The following sections discuss two of the drugs for which these studies are being performed, with particular focus on prasugrel.

Prasugrel

Prasugrel is a third-generation thienopyridine that is indicated for the prevention of thrombotic cardiovascular events in patients with ACS (unstable angina, non-STEMI, or STEMI) who are to be managed with PCI [59]. Compared with clopidogrel, this drug has a faster onset of action, greater inhibition of platelet aggregation at clinical doses, less between-patient variability, and a more efficient metabolism (i.e. more efficient absorption and conversion to the active metabolite) (reviewed by Angiolillo [3]).

In addition, prasugrel appears to be effective in clopidogrel poor responders and in CYP2C19 genetic variant carriers. For example, Brandt et al. [60] conducted a randomized crossover trial of healthy volunteers to compare the effects of 60 mg prasugrel and 300 mg clopidogrel on platelet aggregation in response to ADP. They found that inhibition of platelet aggregation in response to 5 and 20 μmol/L ADP was significantly greater after prasugrel than after clopidogrel (5 μmol/L ADP: 84.1 ± 9.5% vs. 48.9 ± 27.0%, respectively; 20 μmol/L ADP: 78.8 ± 9.2% vs. 35.0 ± 24.5%, respectively; both, p < 0.001). Prasugrel was also effective in subjects with poor responsiveness to clopidogrel (Fig. 5), which was defined as inhibition of platelet aggregation of <25% at 4 h and 24 h. Similarly, in stable aspirin-treated patients with stable coronary artery disease, Jernberg et al. [61] reported that prasugrel achieved greater inhibition of platelet aggregation than clopidogrel. Moreover, even though variation in the gene encoding CYP2C19 contributed to reduced exposure to clopidogrel’s active metabolite and a corresponding reduction in PZY(12) inhibition in patients with stable CHD, it did not significantly influence the response to prasugrel [62]. Similarly, common functional CYP genetic variants did not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with prasugrel. Overall, the pharmacokinetic and pharmacodynamic characteristics of prasugrel are independent of CYP2C19 status, which is in contrast to observations with clopidogrel, and this may partly explain the different pharmacological and clinical responses to the two medications [63] (Figs. 3 and 4).

However, because of its mechanism of action, prasugrel has the same limitations as clopidogrel when used preoperatively, including the risk of major bleeding. To determine ways to maximize the clinical benefits of prasugrel and to limit bleeding and risk, future studies should investigate individualized antiplatelet therapy regimens based on point-of-care platelet function tests [64]. This would be similar to the situation for patients receiving warfarin who undergo monitoring of prothrombin times.

The efficacy of prasugrel in preventing major cardiovascular events in patients with ACS undergoing PCI was investigated in the large (n = 13,608), double-blind, double-dummy, multicenter, TRITON-TIMI 38 study [57]. Patients in this study were randomized to receive prasugrel (60 mg loading dose, then 10 mg/day) or clopidogrel (300 mg loading dose, then 75 mg/day) for up to 15 months. The primary composite endpoint was the combined incidence of cardiovascular death, nonfatal MI, and nonfatal stroke.

In TRITON-TIMI 38, the incidence of cardiovascular events after stent implantation was 19% lower in the group receiving prasugrel once daily than in the group receiving clopidogrel once daily (Table 1) [57]. In addition, the incidence of post-stent thrombosis in the prasugrel group was about one-half of that in the clopidogrel group (Table 1). The advantages of prasugrel over clopidogrel were seen early and later on in the trial [65], and did not differ with stent type (i.e. drug-eluting or bare metal) [66]. In addition, a

![Cumulative cardiovascular event rate (%) vs. Follow-up duration (days)](image)

**Figure 4** Kaplan–Meier analysis of the occurrence of cardiovascular events in patients treated with clopidogrel (A) [41]. Reprinted with permission from Elsevier. A composite of cardiovascular death (CVD), myocardial infarction (MI), or stroke in patients treated with prasugrel (B) [63]. Reprinted with permission from Wolters Kluwer.
sub-analysis of the study results showed that PPI use was not associated with the risk of the primary endpoint in patients treated with either agent [50].

In terms of safety, among patients with STEMI who had undergone coronary artery bypass grafting (CABG), the incidence of thrombolysis in myocardial infarction (TIMI) major or minor bleeding was significantly ($p=0.0032$) higher in those who received prasugrel than in those who received clopidogrel (Table 2) [67], while the incidence of major safety endpoints, including TIMI major bleeding in non-CABG patients and fatal TIMI major bleeding in non-CABG patients, was similar in both groups (Table 2) [67]. In contrast, the

<p>| Table 1 | Efficacy of prasugrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Results of the large, double-blind, double-dummy, multicenter TRITON-TIMI 38 trial in which patients were randomized to receive prasugrel or clopidogrel for up to 15 months [57]. |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Major efficacy endpoints in the overall cohort at 15 months</th>
<th>$n$ (%)</th>
<th>Hazard ratio for prasugrel (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel ($N=6813$)</td>
<td>Clopidogrel ($N=6795$)</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>643 (9.9)</td>
<td>781 (12.1)</td>
</tr>
<tr>
<td>Nonfatal MI, or nonfatal stroke (primary endpoint)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>133 (2.1)</td>
<td>150 (2.4)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>475 (7.3)</td>
<td>620 (9.5)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>61 (1.0)</td>
<td>60 (1.0)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization</td>
<td>188 (3.0)</td>
<td>197 (3.2)</td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI, or nonfatal stroke</td>
<td>652 (10.0)</td>
<td>798 (12.3)</td>
</tr>
<tr>
<td>Urgent target-vessel revascularization</td>
<td>692 (10.7)</td>
<td>822 (12.7)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia</td>
<td>156 (2.5)</td>
<td>233 (3.7)</td>
</tr>
<tr>
<td>Stent thrombosis†</td>
<td>797 (12.3)</td>
<td>938 (14.6)</td>
</tr>
<tr>
<td>Stent thrombosis†</td>
<td>68 (1.1)</td>
<td>142 (2.4)</td>
</tr>
</tbody>
</table>

Reprinted from [57], with permission from the Massachusetts Medical Society. MI, myocardial infarction.

* $p=0.001$.
† Stent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium; the numbers of patients at risk were all patients whose index procedure included at least one intracoronary stent: 6422 patients in each of the two treatment groups.
incidence of cardiovascular death or non-fatal myocardial infarction was significantly lower with prasugrel than with clopidogrel [67]. A subsequent analysis of the TRITON-TIMI 38 study results showed that the mortality rate was significantly lower in patients undergoing isolated CABG treated with prasugrel than in patients treated with clopidogrel, despite the higher incidence of bleeding with prasugrel [68].

In the TRITON-TIMI 38 study, which was performed predominantly in Caucasian patients, prasugrel was also significantly more effective than clopidogrel in terms of the net clinical-benefit endpoints of death, MI, stroke, and TIMI major bleeding unrelated to CABG (12.2% vs. 14.6%; \( p = 0.0218 \)), and death, MI, stroke, and TIMI major bleeding either related or unrelated to CABG (12.5% vs. 14.7%; \( p = 0.0412 \)) [67].

The pharmacokinetic and pharmacodynamic characteristics of prasugrel have been assessed in Chinese, Japanese, and Korean subjects, as compared with white volunteers [69,70]. In the first study [69], platelet inhibition was significantly higher in Chinese than in white volunteers up to 2 h after a single 30-mg dose of prasugrel, and at all times after a 30-mg dose of prasugrel than after a 300-mg dose of clopidogrel. In the second study [70], mean exposure to the active metabolite of prasugrel after a 60-mg loading dose and with 10-mg or 5-mg maintenance doses was higher in Chinese, Japanese, and Korean volunteers than in Caucasian volunteers, resulting in greater platelet inhibition. Taken together, these results suggest that prasugrel may be as effective as clopidogrel in Asian patients after appropriate dose adjustments. Longer randomized studies are now needed to confirm the clinical efficacy and safety of prasugrel in Japanese and other Asian patients.

**Ticagrelor**

Ticagrelor is a reversible ADP receptor antagonist that was recently approved in the EU for the prevention of major cardiovascular events in patients with ACS. In the pivotal PLATO (PLA T elet inhibition and patient Outcomes) study [71], the group receiving ticagrelor twice daily showed a 16% decrease in the cardiovascular composite endpoint compared with the group receiving clopidogrel once daily. Although there was no increase in the incidence of CABG-related major bleeding, the incidence of non-CABG-related major bleeding was significantly higher in the ticagrelor groups, as was the incidence of dyspnea. A phase II study is now underway to determine the pharmacokinetic and pharmacodynamic profiles of two doses of ticagrelor plus low-dose aspirin in Japanese and Asian patients with stable CHD (clinicaltrials.gov registration number: NCT01118325). The results of this study are eagerly awaited to determine the relative efficacy of ticagrelor in this patient population.

**Thienopyridines and liver dysfunction**

Both clopidogrel and ticlopidine have been associated with hepatotoxicity, such as hepatitis and cholestatic jaundice. These associations have been reported in case reports [72–74] and as adverse events in clinical trials [24,75], and the rates of these events seem to be higher in Asian patients.
than in Western patients [76]. The reason for this is unclear, but it has been suggested to be related to human leucocyte antigen genomic subtypes [77]. At this stage, it is not possible to determine whether hepatotoxicity is a cause for concern with the newer thienopyridines, as no data have been reported in this setting. Nevertheless, clinicians should be aware of the possibility of hepatotoxicity when treating patients with these drugs.

Summary and future prospects

Clopidogrel is the antiplatelet drug of choice for use in combination with aspirin to prevent atherothrombotic events in patients with ACS undergoing PCI. However, some patients remain at increased risk of subsequent cardiovascular events despite treatment with clopidogrel. As such, novel agents that provide further risk reductions for cardiovascular events are required. Prasugrel and ticagrelor are antiplatelet agents that have shown promise in clinical trials. Prasugrel is already approved for use in the prevention of thrombotic cardiovascular events in patients with ACS undergoing PCI, and ticagrelor is in preregistration for a similar indication in patients with ACS. Both drugs are under development in Japan, and a new indication for prasugrel is currently being explored. Because ethnic differences in cardiovascular risk factors exist (e.g. lipid control, abdominal/visceral obesity, insulin resistance), and because Japanese guidelines on the prevention of cardiovascular disease are largely based on studies in European populations, large cardiovascular prevention studies in Japanese patients with carefully titrated doses are essential, as are studies to assess the safety and efficacy of the newer agents such as prasugrel and ticagrelor. This is particularly important considering the studies showing more effective inhibition of platelet aggregation in phase II studies of prasugrel in Asian than in white/Caucasian populations [69,70]. Japanese-specific guidelines based on findings from such studies are greatly anticipated.

Conflict of interest

HO has received speakers’ fees from Astellas, AstraZeneca, Banyu, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Eisai, Japan Lifeline, Kowa, Kyowa HakkoKirin, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Schering-Plough, and Takeda.

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