CLINICAL INVESTIGATION

Role of ticagrelor in the treatment of coronary artery disease

Clin. Invest. (2011) 1(3), 429–437

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Ticagrelor is a reversibly binding, noncompetitive, direct-acting, orally administered $P2Y_{12}$-receptor antagonist and is a credible alternative to clopidogrel in the treatment of patients with acute coronary syndrome. Ticagrelor therapy has been associated with rapid onset and faster offset of actions and greater and consistent platelet inhibition. In the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor significantly reduced the rate of the combined end point of cardiovascular death, myocardial infarction or stroke in acute coronary syndrome patients compared with clopidogrel. A major potential benefit of ticagrelor is the unprecedented reduction in mortality among acute coronary syndrome patients. An additional important observation was similar CABG-related bleeding events in ticagrelor (vs clopidogrel)-treated patients despite the fact that ticagrelor provides more potent $P2Y_{12}$-receptor blockade.

Keywords: acute coronary syndrome • $P2Y_{12}$ receptor • platelets • reversibly bound inhibitor • thrombosis • ticagrelor

Ischemic complications of coronary arterial disease are mainly attributed to platelet-rich thrombus generation at the site of vascular injury [1]. Adenosine diphosphate (ADP) is an important secondary agonist released from platelet dense granules in response to multiple stimuli such as thromboxane A2, collagen, thrombin and shear. Continuous and amplified ADP-mediated $P2Y_{12}$-receptor signaling results in persistent activation of the glycoprotein (GP)IIb/IIIa receptor and subsequent stable thrombus generation [2,3]. In addition, activation of the ADP receptor is also implicated in the expression of platelet membrane-bound p-selectin and CD-40L ligand leading to platelet–leukocyte interactions and enhanced inflammation. Moreover, platelet activation is associated with the development of a procoagulant surface where multiple coagulation processes occur that greatly amplify thrombin generation. In this scenario, the addition of thienopyridines (irreversible platelet ADP-receptor antagonists) to aspirin (platelet cyclooxygenase-1 inhibitor) has been shown to attenuate arterial ischemic event occurrence, inflammation and procoagulant activities [3–5].

Clopidogrel (a second-generation thienopyridine), has been adopted as a mainstay of antiplatelet therapy in addition to aspirin to reduce the incidence of ischemic events in a wide range of patients with arterial diseases, including stable coronary artery disease undergoing percutaneous coronary intervention (PCI) with stents and acute coronary syndrome (ACS) patients treated with and without PCI. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, the suggestion of benefit of clopidogrel when added to aspirin was demonstrated in patients with a history of atherothrombosis [6]. Recently, pharmacokinetic, pharmacodynamic and pharmacogenomic studies have disputed the 'one size fits all' dosing of clopidogrel. Clopidogrel is a prodrug that must undergo a two-step hepatic conversion to an active metabolite in order to inhibit the $P2Y_{12}$ receptor and block ADP-induced platelet activation and

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aggregation. This conversion process is associated with variable and at times suboptimal generation of active metabolite compared with the relatively fast and efficient metabolism of the third-generation thienopyridine, prasugrel. Therefore, clopidogrel treatment has been associated with a delayed onset of action, variable response and an overall modest degree of platelet inhibition. Lower levels of active metabolite generation may be secondary to limited intestinal absorption (due to drug–drug interactions or single nucleotide polymorphisms [SNPs] of the *ABCB1* gene) as well as functional variability in hepatic cytochrome (CYP) P450 isoenzymes activity (due to drug–drug interactions and SNPs of genes encoding CYP450 isoenzymes) [7]. A substantial percentage of patients treated with clopidogrel (even the 600 mg load and 150 mg maintenance doses) exhibit either absence or limited inhibition of platelet aggregation as measured by *ex vivo* assays. The latter phenomenon has been described as clopidogrel 'resistance', 'nonresponsiveness' or 'hyporesponsiveness'. Multiple prospective studies have conclusively demonstrated the relation between high on-treatment platelet reactivity to ADP to the occurrence of ischemic events in the PCI population. Finally, irreversible inhibition of the $P2Y_{12}$ receptor is associated with two important limitations; delayed recovery of platelet function and a narrow therapeutic window. Delayed or slow recovery of platelet function is an important clinical problem in patients who require urgent surgery. A relatively narrow therapeutic window may, in part, explain why bleeding is a frequent complication, even in the context of recurrent adverse ischemic events [8].

The third-generation thienopyridine prasugrel has a faster onset of action and provides greater platelet inhibition throughout the loading and maintenance phases (vs clopidogrel). In addition, prasugrel metabolism is not affected by SNPs and appears to be less affected by drug–drug interactions involving the hepatic CYP450 system than has been demonstrated for clopidogrel [9]. It has been shown that the combination of prasugrel with aspirin compared with clopidogrel with aspirin therapy is associated with significantly improved clinical outcomes (20% relative decrease in major cardiovascular [CV] events) among ACS patients undergoing PCI in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) study [10]. However, the higher level of irreversible platelet inhibition by prasugrel may have also accounted for an increased incidence of both coronary artery bypass grafting (CABG)- and non-CABG-related major bleeding events with prasugrel treatment. The antithrombotic benefit of prasugrel is mainly attributed to reduction of myocardial infarction (MI) and stent thrombosis in ACS patients undergoing planned primary PCI for ST-segment elevation MI (STEMI), or in unstable angina (UA)/non-STEMI (NSTEMI) patients in whom the coronary anatomy is known to be suitable for PCI [11]. Prasugrel treatment is contraindicated in patients with active pathological bleeding or a history of transient ischemic attack or stroke and should be used with caution in selected patients who weigh <60 kg or are ≥75 years old. Furthermore, prasugrel therapy should be discontinued at least 7 days prior to any surgery if possible [10].

Ticagrelor

Preclinical studies

Ticagrelor (previously known as AZD 6140) is a reversibly binding, oral, $P2Y_{12}$-receptor blocker belonging to the cyclopentyl-triazolo-pyrimidine (CPTP) class of antiplatelet agents [12]. It has been developed to address the various limitations of treatment with the irreversible thienopyridines clopidogrel and prasugrel. Preclinical studies have demonstrated that ticagrelor selectively and potently blocks the $P2Y_{12}$ receptor [12,13]. The reversible nature of ticagrelor binding demonstrated a half-life of approximately 4 min for binding and 14 min for unbinding [12]. It was demonstrated that ticagrelor does not prevent ADP binding, but reversibly inhibits receptor conformational change and G-protein activation induced by ADP coupling by binding to a site distinct from the ADP-binding site [13,14]. In animal studies, ticagrelor administration produced greater dose-dependent antithrombotic effects than thienopyridines without an equivalent increase in bleeding time, resulting in a 'wider therapeutic window' [15]. A multiple dose escalating study in healthy volunteers showed that ticagrelor was extensively absorbed with a median t_{max} of 1.5–3 h and >99% bound to plasma proteins. The maximum mean concentration in plasma was reached at 1.5 h. Ticagrelor is metabolized rapidly by hepatic CYP3A4/5 to produce R-C124910XX with a mean t_{max} of 2 h. AR-C124910XX is the main metabolite of ticagrelor and is equipotent in inhibiting the $P2Y_{12}$ receptor. The terminal half-life of ticagrelor is approximately 8 h. Ticagrelor is mainly eliminated in feces and <1% is excreted in urine. More consistent and greater platelet inhibition was observed after a twice-daily dose of ≥100 mg dose compared with a once-daily dose of <300 mg [16,17].

Clinical studies

The Phase I Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in NSTEMI (DISPERSE) trial was a dose-escalation study performed in patients with atherosclerotic disease (n = 200). In this study, ticagrelor treatment (≥100 mg

twice daily [b.i.d.]) was associated with more rapid and greater platelet inhibition (>90–95% inhibition at steady state) than clopidogrel 75 mg daily (once daily [q.d.]; ~60% inhibition at steady state). Ticagrelor treatment was well tolerated across all doses and was associated with an increased dose-independent bleeding time compared with clopidogrel. However, a dose-dependent incidence of dyspnea (10–20%) was observed that was not associated with congestive heart failure or bronchospasm [18].

To compare the safety, tolerability and efficacy of ticagrelor and clopidogrel therapies, patients with NSTEMI acute coronary syndrome (n = 900) were randomly treated with either ticagrelor 90 or 180 mg b.i.d. (50% of ticagrelor-treated patients received a 270 mg loading dose [LD]) or clopidogrel 75 mg q.d. for 12 weeks in the DISPERSE-2 trial. Major or minor bleeding at 4 weeks (primary end point of the study) was similar between the three treatment groups (clopidogrel = 8.1%, ticagrelor 90 mg b.i.d. = 9.8% and 180 mg b.i.d. = 8.0%). There were two fatal bleeding events in the ticagrelor 90 mg b.i.d. group [18]. Major bleeding occurred less frequently among ticagrelor-treated patients (36%) compared with clopidogrel-treated patients (64%) when CABG was performed between 1 and 5 days after the last dose. Ticagrelor was associated with a lower incidence of MI (2.5% 180 mg b.i.d.; 3.8% 90 mg b.i.d.) compared with clopidogrel (5.6%) and an increased incidence of dyspnea that was dose-dependent (1.5% 90 mg b.i.d.; 15.8% 180 mg b.i.d.) as compared with clopidogrel (6.4%) was observed. Most episodes of dyspnea were mild or moderate in severity [19].

The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial was a Phase III, randomized, multicenter, double-blind study designed to evaluate superiority of ticagrelor (180 mg [LD]/90 mg b.i.d.) compared with clopidogrel (300–600 mg LD/75 mg q.d.) for the prevention of vascular events and death in patients with ACS (including STEMI) [20]. Among the 18,624 patients enrolled, 43% had NSTEMI, 38% STEMI and 17% UA. During the trial, 61% of patients underwent PCI and 10% had CABG. Before randomization, 46% of patients were treated with clopidogrel [20]. The primary efficacy end point of the trial (composite of CV death, nonfatal MI and nonfatal stroke) was significantly reduced by ticagrelor compared with clopidogrel at 30 days (4.8 vs 5.4%; p = 0.045) and the superiority of ticagrelor was maintained throughout 12 months with 16% relative risk reduction (9.8 vs 11.7%, respectively; p < 0.001) (Figure 1). CV death (5.1% clopidogrel; 4.0% ticagrelor; p = 0.001) and MI (6.9% clopidogrel; 5.8% ticagrelor; p = 0.005) but not stroke (1.5 vs 1.3%; p = 0.22) were reduced by ticagrelor treatment (Figure 2). The clinical benefit associated with ticagrelor treatment was attenuated in patients weighing less than the gender-specific median (p = 0.04 for interaction), those not taking lipid-lowering drugs at randomization (p = 0.04 for the interaction), and subjects enrolled in North America (p = 0.045 for the interaction). Despite greater platelet inhibition demonstrated with ticagrelor as compared with clopidogrel in Phase II studies, the reduction in the prevalence of stent thrombosis was not as great as observed in TRITON-TIMI 38 trial with prasugrel therapy. Moreover, the risk reduction was consistent with ticagrelor therapy in patients who were managed medically or with invasive therapy. Importantly, among patients with UA either treated with invasive or medical treatment, ticagrelor was not associated with a significant risk reduction [20,21]. The benefits of ticagrelor treatment were more pronounced in patients who needed a subsequent PCI within 2–7 days of randomization compared with the absence of short-term and limited long-term benefit associated with ticagrelor treatment in patients who did not have a subsequent PCI [101].

Between ticagrelor- and clopidogrel-treated patients, there were no differences in the primary safety end point of major bleeding rate as defined by either the study protocol (ticagrelor 11.6% vs clopidogrel 11.2%; p = 0.43) or TIMI criteria (7.9 vs 7.7%; p = 0.57) (Figure 3). The incidences of life-threatening and fatal bleeding as well as the requirement for red cell transfusion were similar between treatment groups. Despite the fact that patients in the ticagrelor treatment group were allowed

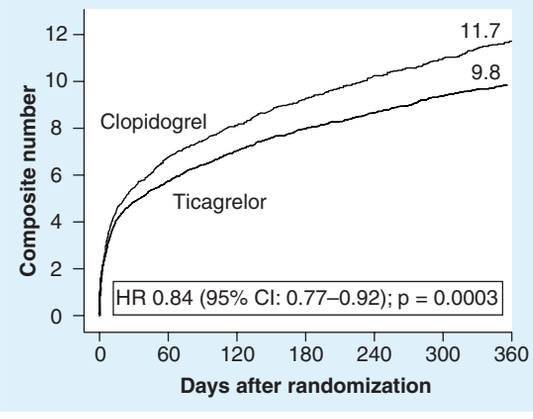


Figure 1. Study of Platelet Inhibition and Patient Outcomes (PLATO) trial: primary outcome (cardiovascular death + myocardial infarction + stroke). In 1000 acute coronary syndrome patients, replacing clopidogrel with ticagrelor for 12 months resulted in 14 fewer deaths, 11 fewer myocardial infarctions, six to nine fewer cases of ST and no increase in bleeding requiring transfusion.

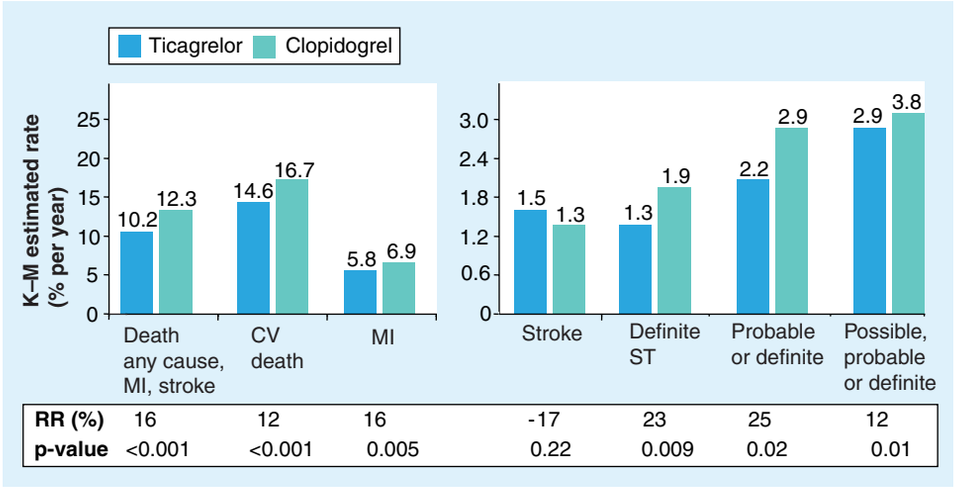


Figure 2. Study of Platelet Inhibition and Patient Outcomes (PLATO) trial: major efficacy end points.

CV: Cardiovascular; K–M: Kaplan–Meier; MI: Myocardial infarction; RR: Risk reduction.

event rates, were higher following ticagrelor treatment (4.5 vs 3.8%; p = 0.026, and 2.8 vs 2.2%; p = 0.025 for protocol and TIMI study group defined bleeding events, respectively). Ticagrelor therapy was associated with numerically more fatal intracranial hemorrhages compared with clopidogrel-treated patients, whereas excess extracranial bleeding events were associated with clopidogrel treatment [20].

Dyspnea was more common following ticagrelor (13.8 vs 7.8%; p < 0.001), but infrequently (0.9%) required discontinuation of therapy. Most reports of dyspnea were mild-to-moderate, occurred earlier and lasted <20 days with ticagrelor therapy. However, two thirds of the dyspnea-related events in the study resolved indicating that ticagrelor-related dyspnea unlikely causes chronic pulmonary changes. A higher frequency of ventricular pause (≥3 s) determined by Holter monitoring was observed during ticagrelor treatment during the first week of therapy (5.8 vs 3.8% clopidogrel; p = 0.01), but was no longer evident at 30 days. Both serum creatinine and uric acid levels were increased in ticagrelor-treated patients at 1 and 12 months of treatment. Although no clinical sequelae were attributable to these asymptomatic laboratory aberrations, concerns have been expressed that sustained elevations in these

to undergo CABG within 24–72 h following discontinuation of study medication (compared with 5 days in the clopidogrel group), CABG-related bleeding event rates were similar between the two groups (numerically less in ticagrelor-treated patients). Another interesting observation is that although numerically greater bleeding was observed with ticagrelor treatment compared with clopidogrel until day 5 after stopping the drug, lesser all-cause mortality following CABG was observed with ticagrelor treatment compared with clopidogrel treatment (US FDA evaluation). Non-CABG-related major bleeding, including nonprocedural bleeding

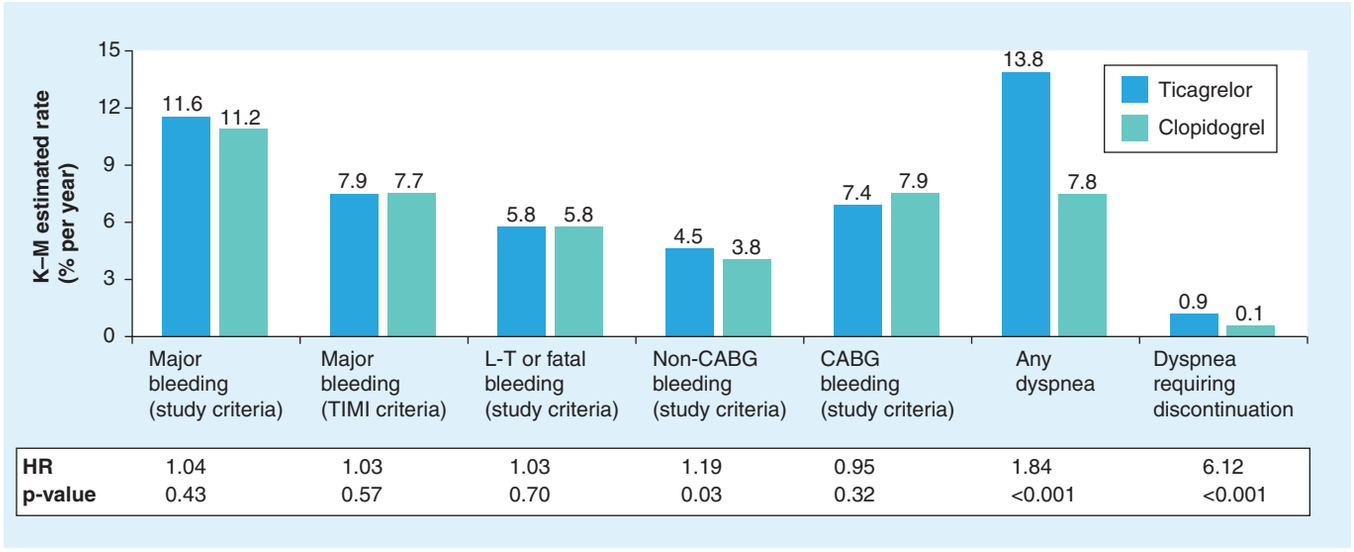


Figure 3. Study of Platelet Inhibition and Patient Outcomes (PLATO) trial: major safety end points.

CABG: Coronary artery bypass grafting; HR: Hazard ratio; K–M: Kaplan–Meier; L-T: Life threatening; TIMI: Thrombolysis in myocardial infarction.

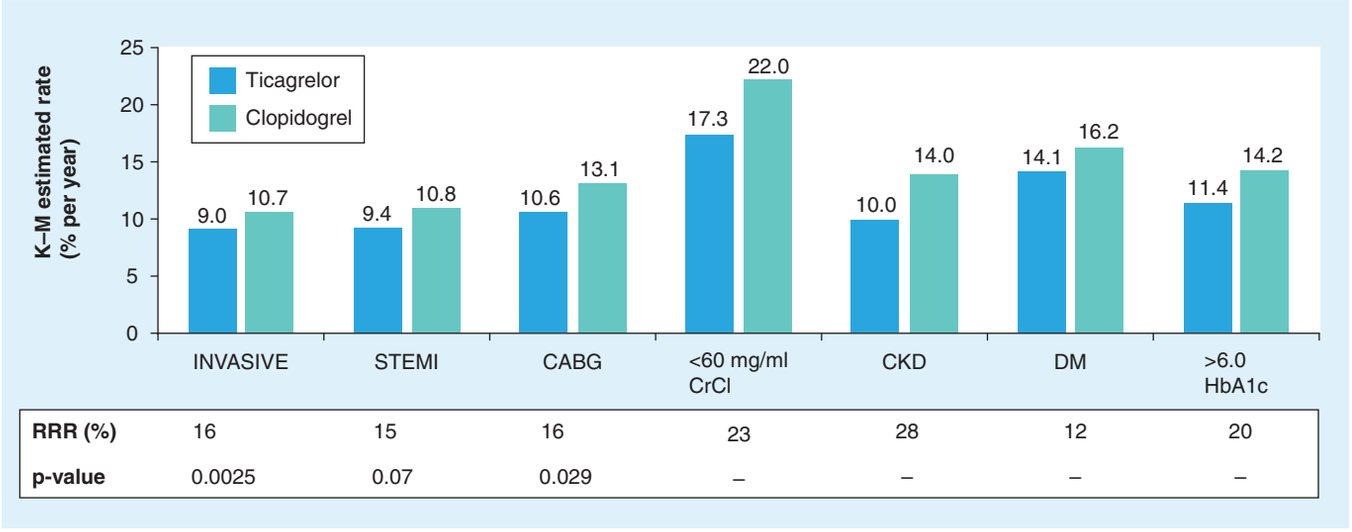
levels may have deleterious consequences in long-term follow-up [101]. Finally, ticagrelor treatment was associated with a nonsignificant increased risk for stroke (1.5 vs 1.3%), an earlier time to overall stroke, nonsignificantly more intracranial hemorrhagic bleeding events and also a higher rate of death from stroke (11 vs two in clopidogrel group) [20].

The most remarkable observation of the PLATO trial was a significant and consistent reduction in mortality (4.5% ticagrelor vs 5.9% clopidogrel; RR = 0.78) that has not previously been observed with other antiplatelet agents added to aspirin therapy. The most prominent cause of death (~95%) was vascular death, including CV deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. An additional important observation was similar CABG-related bleeding events in ticagrelor (vs clopidogrel)-treated patients, despite the fact that ticagrelor provides more potent $P2Y_{12}$-receptor blockade and that patients treated with ticagrelor were permitted to undergo CABG in an earlier time-frame than clopidogrel-treated patients. Finally, the PLATO trial demonstrated that in 1000 patients admitted for ACS, replacing clopidogrel with ticagrelor for 12 months will result in 14 fewer deaths, 11 fewer MIs and six to nine fewer cases of stent thrombosis without increased bleeding requiring transfusion. Moreover, treating 54 patients with ticagrelor instead of clopidogrel for 1 year prevented one event of CV death, MI or stroke [20].

Despite superior benefits associated with ticagrelor therapy among various categories of ACS patients, when the efficacy of ticagrelor therapy was evaluated across geographic regions, a lack of benefit was observed in patients from North America. The significance of the latter was a matter of debate during a recent FDA advisory committee meeting and may be a reason for postponing the FDA's decision on approval. Various analyses were performed by a team from AstraZeneca as well as the FDA to address the statistically significant difference in the efficacy of ticagrelor relative to clopidogrel. The primary outcome was unfavorable for ticagrelor therapy in patients recruited from the USA (n = 1413) and Canada (n = 401) with HR = 1.27; 95% CI: 0.92, 1.75 and HR = 1.17; 95% CI: 0.59, 2.31, respectively. Moreover, in the US patients, the HR for MI was 1.38 (95% CI: 0.95–2.01), for CV death was 1.26 (95% CI: 0.69, 2.31), and for stroke was 1.75 (95% CI: 0.51, 5.97). Different baseline characteristics at the time of enrollment, subsequent treatment strategies among the US population compared with non-US population and importantly, higher doses of long-term aspirin treatment (average ~220 mg q.d. vs ~100 mg q.d., HR = 1.62 compared with 1.23 in non-US population patients treated with ≥300 mg aspirin) prescribed among US patients have been attributed to the latter observations in the US population. The potential mechanistic explanation for the aspirin–ticagrelor interaction remains elusive and it was concluded to be an 'unresolvable issue' at the FDA meeting [101].

The prespecified analysis of patients who underwent a planned invasive treatment strategy (72%; n = 13,408) in the PLATO trial demonstrated that ticagrelor therapy was associated with a significant reduction in the primary efficacy end point of CV death, MI or stroke (9.0 vs 10.7% clopidogrel; p = 0.0025) as well as the key secondary end point of all-cause death plus MI plus stroke (9.4 vs 11.2% clopidogrel; p = 0.0016) **(Figure 4)**. Furthermore, all-cause mortality (3.9 vs 5.0%; p = 0.013) and MI (5.3 vs 6.6%; p = 0.0023) were also reduced in ticagrelor-treated patients. Finally, the ticagrelor benefit remained significant (vs clopidogrel) irrespective of the total clopidogrel LD received either prior to randomization or up to 24 h following study enrollment. Both primary efficacy end point events as well as stent thrombosis were significantly reduced by ticagrelor (vs clopidogrel) whether subjects received ≥600 or <600 mg clopidogrel LD within 24 h pre- or post-study enrollment. In addition, no differences in major bleeding (11.6 vs 11.5%) or severe bleeding (3.2 vs 2.9%) were observed in ticagrelor-treated patients compared with clopidogrel-treated patients [22].

A retrospective analysis of the nonrandomized subgroup of 1261 patients who underwent CABG in the PLATO trial with last intake of study drug within 7 days was performed. Ticagrelor therapy was associated with a significantly reduced primary efficacy end point (10.6 vs 13.1%; HR = 0.84; 95% CI: 0.60–1.16; p = 0.029), and with significantly lower total mortality (4.7 vs 9.7%; HR = 0.49, 95% CI: 0.32–0.77; p < 0.01) and CV mortality (4.1 vs 7.9%; HR = 0.52; 95% CI: 0.32–0.85; p = 0.0092) after CABG, and a similar rate of CABG-related major bleeding (81.3 vs 80.1%, HR = 1.01; 95% CI: 0.90–1.15; p = 0.84) [23]. A higher frequency of both major and fatal/life-threatening bleeds were observed with ticagrelor treatment compared with clopidogrel treatment when CABG was performed between 24 and 96 h after stopping study drug, and the higher bleeding rate was associated with a larger volume of chest tube drainage and transfusions. However, when CABG was performed after 96 h of stopping study drug, the ticagrelor-treated patients experienced less bleeding compared with clopidogrel-treated patients. Moreover, the p-value for an interaction at different time intervals was not significant. Finally, despite higher bleeding associated with early CABG in ticagrelor-treated patients, all-cause mortality rate was lower in the ticagrelor group when



RRR (%)	16	15	16	23	28	12	20
p-value	0.0025	0.07	0.029	–	–	–	–

Figure 4. Study of Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis: primary outcome (CV death + MI + stroke).

CABG: Coronary artery bypass grafting; CKD: Chronic kidney disease; CrCl: Creatinine clearance; CV: Cardiovascular; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; K–M: Kaplan–Meier; RR: Relative risk reduction; STEMI: ST-segment elevation myocardial infarction.

considering any time interval between last dose of study treatment and beginning of CABG [23].

In another subanalysis of 8340 patients with STEMI in the PLATO trial, ticagrelor therapy was associated with reduced primary end point events (9.4 vs 10.8%; HR = 0.87; 95% CI: 0.75–1.01; p = 0.07) compared with clopidogrel. Moreover, in this subgroup of STEMI patients, there was a statistically significant reduction in definite stent thrombosis (HR = 0.66; p = 0.03) and no difference in major bleeding with ticagrelor compared with clopidogrel therapy. However, there was a higher risk of stroke with ticagrelor compared with clopidogrel therapy (1.7 vs 1.0%; HR = 1.63; 95% CI: 1.07–2.48; p = 0.02), although the overall risk of stroke was low in both groups. Thus, ticagrelor may be a major alternative to clopidogrel in the treatment of patients with STEMI intended for primary PCI [24].

The superior efficacy of ticagrelor therapy reducing primary end points was also observed in patients with chronic kidney disease with a creatinine clearance of <60ml/min (n = 3237) compared with clopidogrel (17.3 vs 22%; HR = 0.77; 95% CI: 0.65–0.90). Interestingly, in patients with normal renal function (n = 11,965), the benefit of ticagrelor therapy was not as great as that observed in patients with chronic renal disease (7.9% vs 8.9%; HR = 0.90; 95% CI: 0.79–1.02). The benefit of ticagrelor therapy in patients with chronic kidney diseases was evident in reducing total mortality with no significant differences in major bleeding rates, fatal bleeding, and non-CABG bleeding compared with clopidogrel [25].

In the prespecified diabetes substudy of the PLATO trial, based on admission levels of hemoglobin A1c (n = 15,150), ticagrelor treatment was associated with reduced primary composite end points (HR = 0.88; 95% CI: 0.76–1.03), all-cause mortality (HR = 0.82; 95% CI: 0.66–1.01) and stent thrombosis (HR = 0.65; 95% CI: 0.36–1.17) with no increase in major bleeding (HR = 0.95; 95% CI: 0.81–1.12). These benefits were observed irrespective of diabetic status, insulin treatment and glycemic control, but the benefit in reduction of primary end point events was more pronounced in patients with HbA1c above the median (HR = 0.80, 95% CI: 0.70–0.91) [26].

Thus, ticagrelor is an effective adjunctive pharmacotherapy in both early invasive as well as long-term management of a wide range of ACS patients by reducing all-cause mortality, stent thrombosis and MI without a significant difference in total major bleeding events when compared with clopidogrel therapy. The pharmacodynamic basis for these clinical observations was, in part, explained by the Randomized Double-Blind Assessment of the Onset and Offset of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients with Stable Coronary Artery Disease (ONSET/OFFSET) and Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) studies [27,28]. In the ONSET/OFFSET study, ticagrelor therapy was associated with rapid onset; at 1 h following oral loading ticagrelor platelet inhibition was 1.6-times greater than the maximal platelet inhibition observed following clopidogrel

treatment that occurred 7.8 h after 600 mg LD, the increased magnitude of platelet inhibition associated with ticagrelor was sustained during the maintenance phase and more rapid recovery in platelet aggregation following discontinuation of ticagrelor compared with clopidogrel (4-to-72-h slope [% IPA/h], -1.04 vs -0.48; $p < 0.0001$) [27]. In the RESPOND study, ticagrelor therapy provided a greater level of platelet inhibition (compared with clopidogrel) in both clopidogrel responders and nonresponders. In subjects who switched therapies, switching to ticagrelor was associated with rapid enhancement of platelet inhibition in both clopidogrel responders as well as nonresponders whereas switching to clopidogrel was associated with a reduction in measured platelet inhibition. Finally, ticagrelor was effective in reducing the prevalence of high platelet reactivity (HPR) in nearly all ticagrelor-treated patients (irrespective of clopidogrel response status) as measured by all assays, and this effect was evident within 1 h. The extremely low prevalence of HPR in patients treated with ticagrelor provides a plausible mechanism to explain the clinical benefit associated with of ticagrelor therapy in the PLATO trial [28].

In a genetic substudy of the PLATO trial, 10,285 patients' DNA samples were genotyped for SNPs of *2C19* (*2–*8 [loss-of-function (LOF) alleles], and *17[gain-of-function allele]) as well as *ABCB1* [29]. In this analysis, the primary outcome was less frequent in ticagrelor-treated patients compared with clopidogrel-treated patients irrespective of 2C19 genotype; 8.6 versus 11.2% (HR = 0.77; 95% CI: 0.60–0.99; p = 0.0380) in LOF carriers; and 8.8 versus 10·0% (HR = 0.86; 95% CI: 0.74–1.01; p = 0.0608) in LOF noncarriers (interaction p = 0.46). Moreover, the primary outcome was less frequent in ticagrelor-treated patients irrespective of ABCB1 genotype (interaction p = 0.46), but a numerically higher rate was observed in clopidogrel-treated patients with increased expression ABCB1 (TT) genotype (11.8%) compared with intermediate and lower expression (9.8 and 10.5%, respectively). Finally, 30 day higher events rates were observed in clopidogrel-treated patients who were LOF allele carriers compared with noncarriers (5.7 vs 3.8%; p = 0.028) and gain-of-function carriers had a nonsignificantly higher frequency of major bleeding events than either noncarriers or LOF carriers (11.9 vs 9.5%; p = 0.022) [29].

The influence of SNPs of *2C19* and *ABCB1* gene on platelet function following LDs and during maintenance doses were evaluated in the ONSET/OFFSET and RESPOND genotype studies. In these studies, no statistically significant influence of the latter genotypes on platelet function during aspirin therapy alone and during ticagrelor therapy was observed. Ticagrelor exhibited lower platelet reactivity than clopidogrel by all assays irrespective of *2C19* genotype or metabolizer status ($p \leq 0.01$). A greater platelet reactivity during clopidogrel therapy was observed in the LOF carriers compared with noncarriers. Finally, the influence of genotype on platelet reactivity was greatest during clopidogrel maintenance and best demonstrated by the VerifyNow $P2Y_{12}$ assay [30].

Off-target effects

In a dog thrombosis model, ticagrelor has been to shown to inhibit ADP-induced platelet activation and aggregation and to prevent platelet-mediated thrombosis. These latter characteristics have been associated with a prolonged reperfusion time, reduce re-occlusion and cyclic flow variation. Finally, there was a significantly decreased infarct size and rapidly restoration of myocardial tissue perfusion associated with ticagrelor therapy [31]. Ticagrelor has been associated with a platelet unrelated 'off-target' effect on adenosine metabolism that may, in part, contribute to the mortality reduction [32]. In contrast to clopidogrel, there are no known influences of specific genetic polymorphisms on the antiplatelet effects or clinical benefits of ticagrelor.

Future perspective

The rapid onset of platelet inhibition induced by ticagrelor makes this agent a desirable antiplatelet strategy in the setting of ACS and *ad hoc* PCI. Insufficient and delayed platelet inhibition in the latter clinical situations with clopidogrel therapy have been clearly associated with poorer clinical outcomes with respect to the occurrence of ischemic events. Moreover, the greater inhibition sustained in the maintenance phase of therapy makes ticagrelor an attractive alternative to clopidogrel. The effect of ticagrelor in reducing stent thrombosis as compared with clopidogrel should also be considered in the treatment of patients with complex and high-risk coronary anatomy undergoing PCI. A major potential benefit of ticagrelor is the unprecedented reduction in mortality among ACS patients.

Ticagrelor is the first reversibly binding direct inhibitor of the $P2Y_{12}$ receptor and is associated with more rapid onset and offset pharmacodynamics than clopidogrel. The latter property may explain the lower prevalence of CABG-related bleeding observed in the PLATO trial following ticagrelor (vs clopidogrel) and may afford greater flexibility in the timing of surgery for ticagrelor-treated patients. Ticagrelor provides potent, predictable and reliable $P2Y_{12}$ receptor inhibition as it does not require metabolic conversion to active metabolite and is not influenced by genotypic variants in hepatic cytochrome P450 isoenzymes or drug–drug interactions that influence hepatic enzyme activity. The b.i.d. dosing regimen currently approved

for ticagrelor use may be less attractive (vs q.d. for thienopyridine therapies) in the noncompliant patient and, thus, patient education regarding the importance of medication compliance is essential.

Financial & competing interests disclosure

Paul A Gurbel has received research grants from: Astra Zeneca, Portola, Pozen and Sanofi/Aventis. Consultant/Honoraria: Astra Zeneca, Portola, Pozen, Sanofi/Aventis, Bayer, Lilly, Daiichi Sankyo and Schering-Plough. Dean K Kereiakes has received research grants from Daiichi Sankyo, Inc. Consultant/Honoraria: Eli Lilly & Co. Udaya S Tantry reports no conflicts of interest. 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 manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Continuous and amplified ADP-mediated $P2Y_{12}$-receptor signaling is critical for the generation of arterial thrombosis.
- $P2Y_{12}$-receptor blockade by thienopyridine is associated with numerous limitations, such as wide response variability and nonresponsiveness (clopidogrel), irreversible inhibition (clopidogrel and prasugrel), and increased bleeding events (prasugrel).
- Ticagrelor is a reversibly binding, noncompetitive, direct-acting, orally administered $P2Y_{12}$-receptor antagonist.
- Ticagrelor therapy has been associated with rapid onset and faster early offset of actions and greater and consistent platelet inhibition.
- The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated that in 1000 patients admitted for acute coronary syndrome, replacing clopidogrel with ticagrelor for up to 12 months will result in 14 fewer deaths, 11 fewer myocardial infarctions and six to nine fewer cases of stent thrombosis without an increased number of major bleeding events requiring transfusion.
- A major potential benefit of ticagrelor is the unprecedented reduction in mortality among acute coronary syndrome patients.

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