Ticagrelor in the treatment of coronary artery disease patients

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Practice Points

- Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor blocker is a major therapeutic option to treat patients with coronary artery diseases.
- Clopidogrel, a widely used $P2Y_{12}$ receptor blocker is associated with limitations such as delayed onset of action, wide response variability with a substantial percentage of patients exhibiting high on-treatment platelet reactivity.
- Prasugrel is a third-generation thienopyridne and is associated with faster onset of action, greater platelet inhibition and reduced ischemic event occurrence and stent thrombosis compared to clopidogrel therapy in patients with acute coronary artery syndrome (ACS) undergoing PCI. But it is associated with more bleeding.
- Ticagrelor is a direct acting, reversibly binding, noncompetitive $P2Y_{12}$ receptor blocker and is associated with rapid onset and greater platelet inhibition compared to clopidogrel.
- In the PLATO trial, ticagrelor therapy was associated with reduced ischemic event occurrence than clopidogrel in ACS patients.
- Lower mortality and no significant differences in coronary artery bypass graft-related bleeding compared to clopidogrel therapy are major advantages associated with ticagrelor therapy.
- Transient and non-severe dyspnea related events and interaction with high aspirin dose are major concerns.
- Based on the favorable results observed in the PLATO trial, both American and European guidelines recommend ticagrelor in patients with ACS.

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SUMMARY Clopidogrel is a major $P2Y_{12}$ receptor blocker administered in addition to aspirin to reduce the ischemic event occurrence in a wide range of patients with arterial diseases particularly in patients treated with percutaneous coronary intervention (PCI). However, pharmacodynamic studies have disputed the 'one size fits all' dosing of clopidogrel therapy and highlighted its limitations such as delayed onset of action; wide response variability with a substantial percentage of patients exhibiting high on-treatment platelet reactivity, which has been linked to worsened post-PCI ischemic outcomes; and irreversible inhibition, which is a concern in patients needing urgent surgery. The recently approved third-generation thienopyridine, prasugrel is associated with a faster onset of action, greater platelet inhibition, with less response variability and reduced ischemic event occurrence, and stent thrombosis compared with clopidogrel therapy in patients with acute coronary artery syndrome undergoing PCI. However, greater life-threatening risks and fatal bleeding associated with prasugrel therapy are major concerns. Ticagrelor is a direct-acting, reversibly binding and noncompetitive $P2Y_{12}$ receptor blocker that is associated with faster onset of action and greater inhibition. In the PLATO trial, ticagrelor therapy was associated with reduced ischemic event occurrence than clopidogrel in acute coronary artery syndrome patients. Lower mortality and similar coronary artery bypass graft-related bleeding compared to clopidogrel are major advantages with ticagrelor therapy. Ticagrelor is recommended for patients with acute coronary syndrome treated with and without PCI. However, transient and nonsevere dyspnea and interaction with high aspirin dose are major concerns.

Patients with acute coronary syndromes and patients treated with percutaneous intervention are at an increased risk for ischemic/thrombotic event occurrence, particularly myocardial infarction (MI) and stent thrombosis. The current major pharmacological interventions in these patients involve inhibition of COX-1-mediated thromboxane A_2 generation by aspirin, and blockade of the ADP–$P2Y_{12}$ receptor interaction by $P2Y_{12}$ receptor inhibitors. Simultaneous inhibition of these two important pathways is more effective in attenuating recurrent event occurrence than aspirin therapy alone [1]. Ticlopidine, a first-generation thienopyridine, added to aspirin was more effective than aspirin therapy alone or aspirin plus an oral anticoagulant (warfarin) in reducing stent thrombosis. However, primarily due to unfavorable side effects, ticlopidine was largely replaced by the second-generation thienopyridine clopidogrel [1]. It is interesting to note that these two thienopyridines were widely used in clinical practice before their target (the $P2Y_{12}$ receptor) was clearly characterized. In 1991, the $P2Y_{12}$ receptor was cloned and subsequent studies analyzed the pharmacodynamic effect of $P2Y_{12}$ receptor blockers in more detail [1,2]. Prasugrel, a third-generation thienopyridine prasugrel, is associated with faster onset of action, greater platelet inhibition with less response variability and reduced ischemic event occurrence and stent thrombosis compared with clopidogrel therapy in patients with acute coronary artery syndrome (ACS) undergoing percutaneous coronary intervention (PCI). No significant drug–drug interactions and also influence of single nucleotide polymorphisms have been reported [3]. In the TRITON-TIMI-38 trial, prasugrel was associated with better protection against ischemic event occurrence compared with clopidogrel, but more bleeding occurred. In patients with diabetes or ST-segment elevation MI (STEMI), the anti-ischemic benefit of prasugrel outweighs the risk of bleeding [4]. However, patients with a history of stroke or transient ischemic attack should continue to be treated with clopidogrel due to an increased risk of cerebral hemorrhage. Patients aged ≥75 years

or those who weigh <60 kg need to continue clopidogrel therapy until further studies reveal a net benefit with an alternate lower prasugrel maintenance dose (5 mg/day) as noted in the boxed warning [101]. The irreversible inhibition of platelet aggregation that lasts up to 7 days to recover is another important limitation of prasugrel therapy in patients who need immediate surgery [3]. Ticagrelor, a potent, oral, nonthienopyridine drug, was recently approved in Europe and the USA for the treatment of patients with acute coronary syndromes.

Central role of ADP–$P2Y_{12}$ interaction

Platelet adhesion to the subendothelial matrix exposed at the site of endothelial erosion and plaque rupture results in platelet activation and the release of important secondary agonists. Thromboxane A_2 is produced from platelet membrane phospholipids in a cascade that first involves the production of intermediates (prostaglandin (PG)G_2 and PGH_2) by COX and conversion of PGH_2 by thromboxane synthase to thromboxane A_2. ADP is released from dense granules. Although these two agonists exhibit complementary effects by their autocrine and paracrine functions, continuous downstream signaling from the $P2Y_{12}$ receptor is essential for stable thrombus generation [1]. In animal experiments using an *ex vivo* perfusion chamber, it was clearly demonstrated that treatment with clopidogrel added to aspirin was more effective than aspirin alone in attenuating thrombus formation. These findings were corroborated by the demonstration of enhanced inhibition of *ex vivo* ADP-induced platelet aggregation [5]. It was further demonstrated that combined treatment with clopidogrel (even at low doses) and aspirin produced near complete (~98%) inhibition of stent thrombosis in a porcine model. There was also a significant prolongation of bleeding time and enhanced inhibition of *ex vivo* ADP-induced platelet aggregation [6].

Subsequently, in clinical trials involving high-risk patients with a wide range of coronary artery disease, clopidogrel plus aspirin therapy was associated with significant reductions in ischemic event occurrences, particularly MI. These studies collectively indicated that the higher the level of platelet inhibition, the greater the attenuation of ischemic events occurring in the coronary arterial bed. Greater platelet inhibition was also accompanied by increased bleeding [7].

Limitations of thienopyridines: the rationale for ticagrelor

Despite clinical efficacy in a wide range of coronary artery disease patients, pharmacodynamic studies conducted in patients undergoing stenting indicated that clopidogrel therapy was associated with variable and moderate platelet inhibition (~50% inhibition at steady state as demonstrated by *ex-vivo* ADP-induced platelet aggregation), a delayed onset of pharmacodynamic effect (up to 8 h after a 600-mg loading dose and 5 days of a 75-mg daily maintenance dose to achieve maximum steady state inhibition) and irreversible platelet inhibition. The wide antiplatelet response variability was characterized by a substantial percentage of patients (approximately one in three patients) exhibiting high on-treatment platelet reactivity that was subsequently strongly linked to recurrent ischemic event occurrence in PCI patients [8,9].

Moreover, clopidogrel metabolism is influenced by single nucleotide polymorphisms (SNPs) of genes encoding cytochrome P450 (CYP) isoenzymes. CYP2C19 is a particularly important isoenzyme that participates in the conversion to the active metabolite. In addition, concomitant administration of drugs that either compete or inhibit CYP isoenzymes associated with clopidogrel metabolism and also other factors, such as smoking, bodyweight, renal function and diabetes, influence the pharmacodynamic effect of clopidogrel [10]. By contrast, prasugrel, a third-generation thienopyridine, is associated with a more rapid onset of action (~2 h to reach steady state ~70% inhibition), a more consistent pharmacodynamic effect and an effect that is not significantly influenced by SNPs or drug–drug interactions [3]. These pharmacodynamic characteristics were mirrored by the significant reduction in composite primary end point of nonfatal MI, cardiovascular (CV) death and nonfatal stroke compared with clopidogrel when administered on top of aspirin observed in the TRITON TIMI-38 trial in moderate- to high-risk ACS patients undergoing PCI [4].

Ticagrelor: preclinical studies

Ticagrelor (previously known as AZD 6140) belongs to the cyclopentyl-triazolo-pyrimidine (CPTP) class of antiplatelet agents and is structurally different to thienopyridines and ATP analogs. The chemical name of

ticagrelor is [(1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl]amino}-5-(propylthio)-3H-(1,2,3)-triazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol] [11].

Ticagrelor is a reversibly binding, orally administered agent that selectively and potently blocks ADP-induced $P2Y_{12}$ receptor signaling [11,12]. In *in vitro* binding studies using human washed platelets, ticagrelor exhibited an apparent noncompetitive inhibition of ADP-induced aggregation with slow receptor kinetics ($t_{1/2}$ for binding = 3.5 min). In an experiment conducted with Chinese hamster ovarian cells transfected with the rh-$P2Y_{12}$ receptor, ticagrelor was associated with potent, rapid and reversible binding properties, with a K_d =10.5 nM, an association constant (k_{on})= 0.00011/nM/s, a dissociation constant (k_{off}) = 0.00087 s, and half-life values of 4 min for binding and 14 min for unbinding. It was also demonstrated that ADP was capable of displacing [^{33}P]2MeS-ADP but not the $P2Y_{12}$-selective CPTP [^{125}I]AZ11931285. Thus, the mode of inhibition by ticagrelor depended on the agonist used, with classic competitive antagonism versus 2MeS-ADP and apparent noncompetitive antagonism versus ADP. These data indicated that ticagrelor did not prevent ADP binding, but reversibly inhibited the ADP-induced receptor conformational change and G-protein activation by binding to a site distinct from the ADP-binding site. These characteristics keep the receptor in an inactive state and following ticagrelor unbinding, the receptor can be reactivated by ADP. Based on preliminary modeling data, it was suggested that owing to its bulky 7-[2-(3,4-difluoro-phenyl)-cyclopropylamino] and 5-propylsulfanyl substituents, ticagrelor cannot be accommodated in the center of the transmembrane cage but rather binds to a second pocket consisting of the upper transmembrane domains (domains 1, 2 and 7), extracellular loop 2 and the N-terminal domain of $P2Y_{12}$. ADP binds to the core of the transmembrane domain via electrostatic interactions with histidine 253 and arginine 256, and the 3-hydroxyl group forming a hydrogen bond with serine 282 [13].

In *in vitro* studies, ticagrelor exhibited an approximately 100-fold higher affinity for the $P2Y_{12}$ receptor and rapid achievement of equilibrium within 15 min as compared with no equilibrium reached with compound '105', a compound indistinguishable from the active metabolite of prasugrel. Furthermore, ticagrelor was 48-fold more potent in inhibiting 2-Mes-ADP-induced $P2Y_{12}$ receptor activation and 63-fold more potent than compound '105' in inhibiting ADP-induced aggregation in washed human platelets [14].

In animal studies, ticagrelor administration produced greater dose-dependent antithrombotic effects than thienopyridines without an equivalent increase in bleeding time. Ticagrelor administration was associated with a significant inhibition of platelet aggregation and P-selectin expression in mice in a dose-dependent fashion. In mice experiments, the rapid metabolism of ticagrelor was associated with marked reversibility of effect where a 10-mg/kg dose was associated with a peak inhibition of platelet function achieved at 1–2 h and substantial recovery of platelet function was observed by 4 h after dosing, reflecting the fall in plasma ticagrelor levels. Laser injury studies using the mouse cremasteric model indicated that ticagrelor administration was associated with a significantly reduced thrombus burden compared with untreated mice and there was no additional suppression of thrombus formation in $P2Y_{12}$ null mice treated with ticagrelor [15].

In *in vitro* experiments, ticagrelor but not clopidogrel, inhibited 2-MeSADP-induced contraction of mice thoracic aorta ring segments both in the clopidogrel-treated and in the untreated group. 2-MeSADP induced contractions in human internal mammary arteries and small arteries were also inhibited by ticagrelor [16].

Metabolism & potential drug interactions

A multiple dose escalating study in healthy volunteers showed that ticagrelor was extensively absorbed with a mean C_{max} achieved at 1.5 h. Ticagrelor is metabolized rapidly by hepatic CYP3A4/5 to produce AR-C124910xx with a T_{max} of 2 h. AR-C124910xx is the main metabolite of ticagrelor and is equipotent in inhibiting the $P2Y_{12}$ receptor. The terminal pharmacokinetic half-life of ticagrelor is approximately 8 h. Ticagrelor is mainly eliminated in feces and <1% is excreted in urine. There was no effect of food on ticagrelor absorption [17,18].

In *in vitro* experiments using human liver microsomes, ticagrelor moderately inhibited CYP2C9 activity with an IC_{50} of 10.5 M but little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1

activity was observed. Ticagrelor at concentrations of up to 20 M was not an inducer of CYP1A2 or CYP3A4 in fresh human hepatocytes. Although ticagrelor exhibited a tendency for CYP2B6 and CYP2C9 induction, its potential to cause drug interactions via the induction of these enzymes is low at a therapeutic dose. Finally, ticagrelor metabolism may be inhibited when coadministered with potent CYP3A4/5 inhibitors such as ketoconazole, dexamethazone, rifampin, carbamazepine, phenytoin and phenobarbital and coadministration of these drugs are discouraged. For example, after coadministration with ketoconazole, there were 2.4- and 7.3-fold increases in ticagrelor C_{max} and AUC values and correspondingly 89 and 56% decreases in AR-C124910xx C_{max} and AUC values, respectively. Although there was increased ticagrelor exposure with moderate CYP3A4 inhibitors such as dilitiazem, amprenavir, fluconazole, erythromycin and aprepitant, these agents can be coadministered with ticagrelor [19,20].

Not only is ticagrelor metabolized by CYP3A4, it is also a mild inhibitor of CYP3A4. Therefore, it is not recommended that ticagrelor be coadministered with ergot alkaloids and cisapride, which have narrow therapeutic indices. Similarly, coadministration of simvastatin or lovastatin at doses >40 mg, but not atorvastatin, was not recommended since plasma levels of the former statins were found to be elevated with coadministration of ticagrelor. Since ticagrelor has no effect on CYP2C9, it has no influence on the metabolism of tolbutamide and warfarin [20,102].

Ticagrelor is a substrate as well as a weak inhibitor of the transporter protein, ABCB1 (p-glycoprotein). Coadministration of ticagrelor is associated with increased digoxin but not ticagrelor exposure and appropriate monitoring of drugs with narrow therapeutic indices such as digoxin and cyclosporine when coadministered with ticagrelor is recommended. Similarly, ticagrelor exposure may be increased when coadministered with strong ABCB1 inhibitors such as verapamil. In the absence of current data, caution is advised during coadministration of the latter drugs. Although exposure of ethinylestradiol was increased by approximately 20%, the efficacy of oral contraceptives is not expected to change when coadministered with ticagrelor [20,102].

Caution is advised with concomitant use of drugs that induce bradycardia since ticagrelor therapy itself was associated with bradycardia and ventricular pauses. Also, concomitant therapy with selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding. Although ticagrelor therapy has not been demonstrated to influence coagulation parameters, caution is advised because of potential interactions affecting hemostasis during coadministration of ticagrelor with other antithrombotic agents such as heparin or enoxaparin [102].

In a PLATO pharmacodynamic substudy, proton pump inhibitor use was associated with higher platelet reactivity with clopidogrel but not ticagrelor therapy. Recently, it was reported that among patients enrolled in the PLATO trial, a higher rate of primary end point was observed with PPI therapy in both the clopidogrel (13.0 vs 10.9%; adjusted hazard ratio [HR]: 1.20; 95% CI: 1.04–1.38) and ticagrelor (11.0 vs 9.2%; HR: 1.24; 95% CI: 1.07–1.45) groups. Interestingly, patients on non-PPI gastrointestinal (GI) drugs had similar primary end point rates compared with those on PPI therapy (PPI vs non-PPI GI treatment: clopidogrel HR: 0.98; 95% CI: 0.79–1.23; ticagrelor HR: 0.89; 95% CI: 0.73–1.10). By contrast, patients on no gastric protection therapy had a significantly lower primary end point rate (PPI vs no GI treatment: clopidogrel HR: 1.29; 95% CI: 1.12–1.49; ticagrelor HR: 1.30; 95% CI: 1.14–1.49). Since higher primary events rates were observed with both clopidogrel and ticagrelor therapy treated with gastric protection therapy, the authors concluded that the association between PPI use and adverse events may be due to confounding, with PPI use more of a marker for rather than a cause of higher rates of CV events [20].

Pharmacokinetic properties

In clopidogrel-naive ACS patients, administration of a ticagrelor 180-mg dose was associated with C_{max} values of 931 and 275 mg/ml for ticagrelor and AR-C124910xx, respectively and mean area under the plasma concentration–time curve (AUC) values of 6104 and 1584 ng/h/ml. After 4 weeks of a twice-daily (b.i.d.) ticagrelor 90-mg dose, the mean C_{max} values at 3 h were 770 ng/ml for ticagrelor and 257 ng/ml for AR-C124910xx. The mean AUC values for ticagrelor and AR-C124910xx were 4752 and 1961 ng/h/ml, respectively and these parameters were not significantly changed after 8 or 12 weeks of ticagrelor 90 mg b.i.d. therapy.

These results indicate that ticagrelor administration was associated with a comparatively stable plasma ticagrelor or ARC-C124910XX levels over 12 weeks [21].

The pharmacokinetic data of the ONSET-OFFSET study demonstrated that C_{max}, T_{max} and AUC from time 0 to 8 h (AUC_{0-8h}) for ticagrelor were 733 ng/ml, 2.0 h, 4130 ng/h/ml, respectively; and for AR-C124910xx were: 210 ng/ml, 2.1 h, 1325 ng/h/ml, respectively. Trough plasma ticagrelor (305 ng/ml) and AR-C124910xx (121 ng/ml) concentrations were 5.2- and 7.7-times higher than respective concentrations producing 50% maximum effect (EC_{50}). In the RESPOND study, ticagrelor mean C_{max} and AUC_{0-8h} following 2-week dosing were comparable between clopidogrel responders (724 ng/ml, 3983 ng/h/ml) and nonresponders (764 ng/ml, 3986 ng/h/ml). Pharmacokinetics of ticagrelor were unaffected by prior clopidogrel dosing. E_{max} estimates were IPA >96% for both responders and nonresponders. Trough plasma levels were sufficient to achieve high IPA. These results indicate that at current recommended doses, ticagrelor therapy is associated with significant inhibition of platelet aggregation that is similar in both clopidogrel responders and nonresponders and trough plasma levels of ticagrelor and its active metabolite are sufficient to achieve high levels of inhibition of platelet aggregation in stable CAD patients [22].

There were no differences in the pharmacokinetics of ticagrelor or its metabolite AR-C124910xx after a loading dose or during maintenance dosing in stable CAD patients with or without dyspeoea [23]. In one study there were approximately 20% lower exposure to ticagrelor and no significant differences in platelet inhibition in patients with severe renal insufficiency (creatinine clearance <20 ml/min) as compared with patients with normal renal function. However, no dose adjustments for renal insufficiency are recommended. There are insufficient data on ticagrelor pharmacokinetics, pharmacodynamics and clinical efficacy in patients on hemodialysis [24]. In patients with mild hepatic impairment, there was 12 and 23% higher C_{max} and AUC values, respectively, compared with healthy volunteers [25]. In ACS patients aged ≥75 years old, there was approximately 25% higher exposure of ticagrelor and its metabolite than in younger patients; however, this was not considered clinically relevant based on pharmacokinetic population analysis and dosage adjustments are not necessary. Similarly, women also may have higher exposure to ticagrelor but not clinically significant enough to adjust the doses. Regarding ethnic differences, African–Americans have 18% lower ticagrelor bioavailability whereas Asians have a higher mean of 39% [102].

Antiplatelet efficacy in humans

In a randomized study involving healthy volunteers, >90% inhibition of platelet aggregation was observed with b.i.d. doses of 50–300 mg of ticagrelor that was more consistently sustained at 24 h compared with once-daily doses of 50–600 mg. A once-daily ≥300-mg dose and ≥100-mg b.i.d. doses of ticagrelor were associated with more consistent inhibition than a 300-mg loading followed by a 75-mg once-daily dose of clopidogrel [26].

In the ONSET-OFFSET study, an investigation conducted in patients with stable coronary artery disease, ticagrelor was dosed the same as in the PLATO study and as recommended in the guidelines (180-mg loading and 90-mg b.i.d. maintenance dose). This dose was associated with a faster onset following loading, greater and more consistent platelet inhibition during maintenance (6 weeks), and an earlier offset following the last maintenance dose as compared with a 300-mg clopidogrel loading dose followed by 75-mg daily maintenance dose **(Figure 1)** [27]. Similarly, superior platelet inhibition was observed during ticagrelor compared with clopidogrel therapy in a substudy of patients in the PLATO study [28].

In the RESPOND study, ticagrelor was associated with superior platelet inhibition in both clopidogrel responders and nonresponders. Ticagrelor produced a rapid increase in platelet inhibition in both clopidogrel responders and nonresponders following switching from clopidogrel therapy, whereas changing to clopidogrel from ticagrelor was associated with a reduction in platelet inhibition [29]. Finally, platelet reactivity was below the cutoff points previously associated with ischemic risk as measured by light transmittance aggregometry, VerifyNow® $P2Y_{12}$ assay and vasodilator-stimulated phosphoprotein phosphorylation in 98–100% of patients after ticagrelor therapy versus 44–76% of patients after clopidogrel therapy [30].

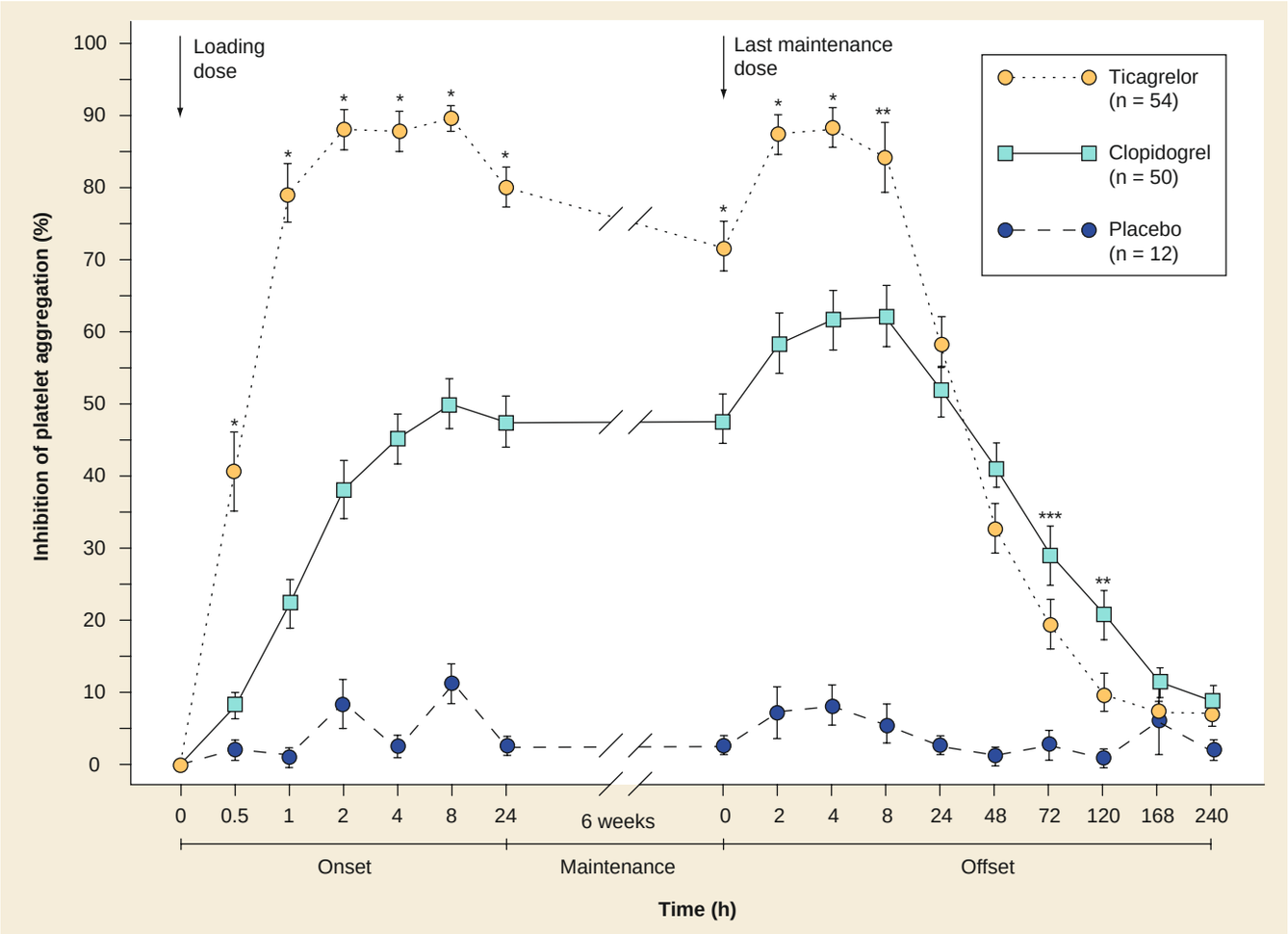


Figure 1. Inhibition of platelet aggregation (%; 20 µmol/l ADP, final extent) by protocol time and treatment. Data are expressed as mean ± standard error of the mean.
*p < 0.0001, **p < 0.005, ***p < 0.05, ticagrelor versus clopidogrel.
Reproduced with permission from [27].

In a pooled analysis of patients treated with ticagrelor and clopidogrel therapy, it was demonstrated that ticagrelor therapy was associated with rapid inhibition of platelet aggregation. Ticagrelor therapy was associated with a significantly lower prevalence of high on-treatment platelet reactivity (0–8%) compared with a 600-mg load followed by a 75-mg maintenance dose of clopidogrel (21–81%) at 2, 4, 8 and 24 h and ≥2 weeks after dosing [30]. In another subanalysis of the ONSET-OFFSET and RESPOND studies, *CYP2C19* (**1*, **2*, **3*, **4*, **5*, **6*, **7*, **8* and **17*) genotyping was performed. There was no statistically significant influence of genotype on platelet function during aspirin therapy alone. Ticagrelor therapy was associated with significantly lower platelet reactivity than clopidogrel by all assays irrespective of *CYP2C19* genotype or genetically predicted metabolizer status, including patients with ultra-metabolizer status. During clopidogrel therapy loss-of-function carriers had greater platelet reactivity compared with non-carriers. The influence of genotype on platelet reactivity during clopidogrel therapy was greatest during the maintenance phase and was best demonstrated by the VerifyNow $P2Y_{12}$ assay [31].

Ticagrelor: clinical efficacy

In the Phase I DISPERSE trial, ticagrelor treatment (≥100 mg b.i.d.) was associated with more rapid and greater platelet inhibition than clopidogrel (300-mg loading dose/75-mg maintenance dose) and was well tolerated across all

doses. However, there was an increased dose-independent bleeding time and a dose-dependent 10–20% incidence of nonserious dyspnea [32].

In the DISPERSE-2 trial involving 990 patients with non-ST segment elevation acute coronary syndrome, major or minor bleeding at 4 weeks was similar between the three treatment groups (clopidogrel group = 8.1%; ticagrelor 90 mg or 180 mg b.i.d. groups = 8.0%) and dose-dependent minor bleeding was observed [33]. 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 (2.4% 180 mg; 3.6% 90 mg) compared with clopidogrel (4.6%) and an increased incidence of dose-dependent dyspnea (9.6% 90 mg; 15.9% 180 mg) compared with clopidogrel (6.4%). Most episodes of dyspnea were mild or moderate in severity [33]. These studies provided the foundation for a 180-mg loading dose and 90 mg b.i.d. dose for maintenance dose for ticagrelor therapy for the Phase III PLATO trial.

The PLATO trial enrolled 18,624 patients with ACS (including STEMI) to evaluate the comparative efficacy of ticagrelor versus clopidogrel treatment for the prevention of vascular events and death **(Figure 2)**. Among the 18,624 patients enrolled, 43% of patients had non-STEMI, 38% had STEMI and 17% had unstable angina. During the trial, 61% of patients underwent PCI and 10% had CABG. The mean duration of time from chest pain onset to study drug administration was 11.3 h (interquartile range: 4.8–19.8). In both groups, 46% of patients received clopidogrel treatment in hospital before randomization. Among the patients treated with ticagrelor, 21 and 14% received ≥300 and ≥600 mg of clopidogrel, respectively. In the clopidogrel group, 60% received ≥300 mg, 20% received ≥600 mg within 24 h before or after randomization. Therapy with GPIIb/IIIa inhibitors was administered in approximately 27%, unfractionated heparin in approximately

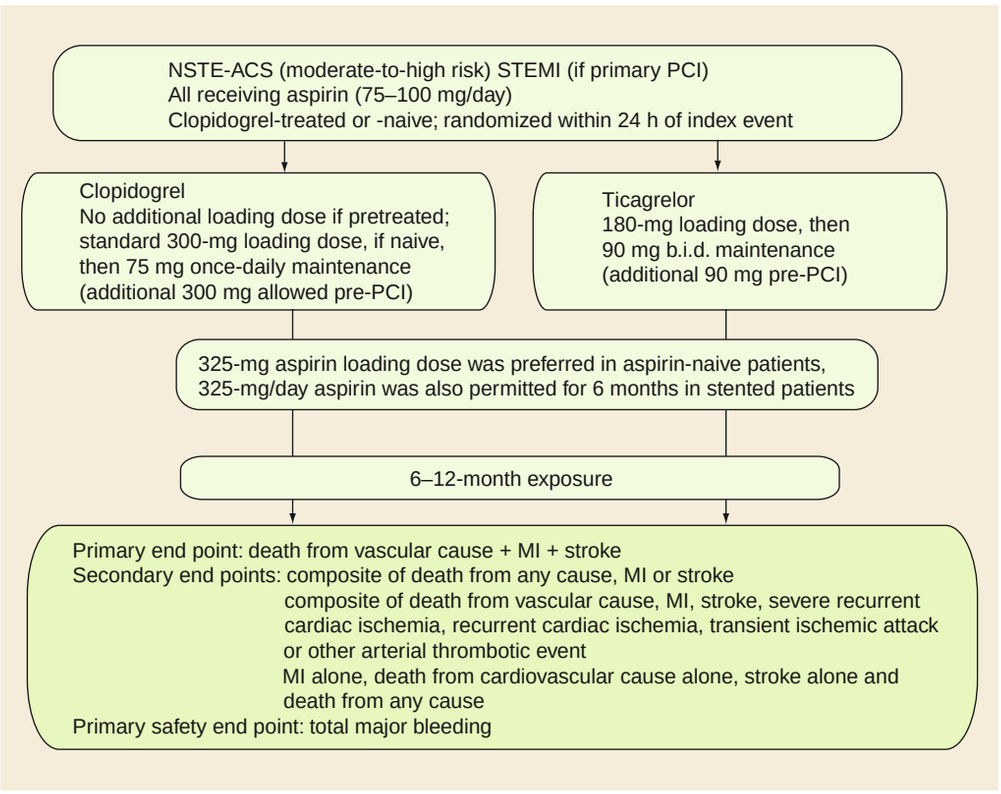


Figure 2. PLATO trial design.
b.i.d.: Twice daily; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

57%, low-molecular-weight heparin in approximately 52% and proton pump inhibitors in approximately 45% of patients in both groups. Among 64% of patients who underwent PCI, a bare-metal stent was used in approximately 42% of patients in each group. Overall adherence was 83% and patients were exposed to drugs for a median duration of 277 days (Table 1) [34].

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 (Table 1). At 30 days, ticagrelor was associated with a 12% reduction in the occurrence of the primary end point. The Kaplan–Meier curve continued to diverge throughout the treatment period with a 16% relative risk (RR) reduction observed at 12 months. These findings indicate that ticagrelor was associated with increasing efficacy over time compared with clopidogrel therapy. Importantly, ticagrelor treatment was also associated with a significant 22% reduction in all-cause mortality including CV death and a 26% reduction in MI but 17% nonsignificant increase in stroke compared with clopidogrel treatment. There was a 33% reduction in definite stent thrombosis, 25% reduction in probable or definite stent thrombosis and 23% reduction in possible, probable or definite stent thrombosis with ticagrelor therapy (Figure 3).

With respect to patient characteristics, region of enrollment and treatment factors, the primary composite end point outcomes were generally consistent across most patient groups. Heterogeneity was reported in three subgroups out of 33 predefined subgroups:

- Ticagrelor therapy was associated with a 20% reduction in the primary end point outcome in patients from Europe, Middle East, Africa and Asia/Australia and a 14% reduction in Central and South American patients. However, in North Americans, there was 25% increase in the primary end point in the ticagrelor treated group (p = 0.045 for the interaction);
- Ticagrelor therapy was associated with a 24% reduction in the primary end point in patients whose bodyweight was at least the median for their gender and there was only 9% reduction in those whose bodyweight was below the median for their gender (p = 0.04 for interaction);
- There was 20% reduction in the primary end point in ticagrelor-treated patients who were receiving lipid-lowering agents but a 2% increase in the primary end point was observed in patients who were not receiving lipid lowering agents at randomization (p = 0.04 for interaction).

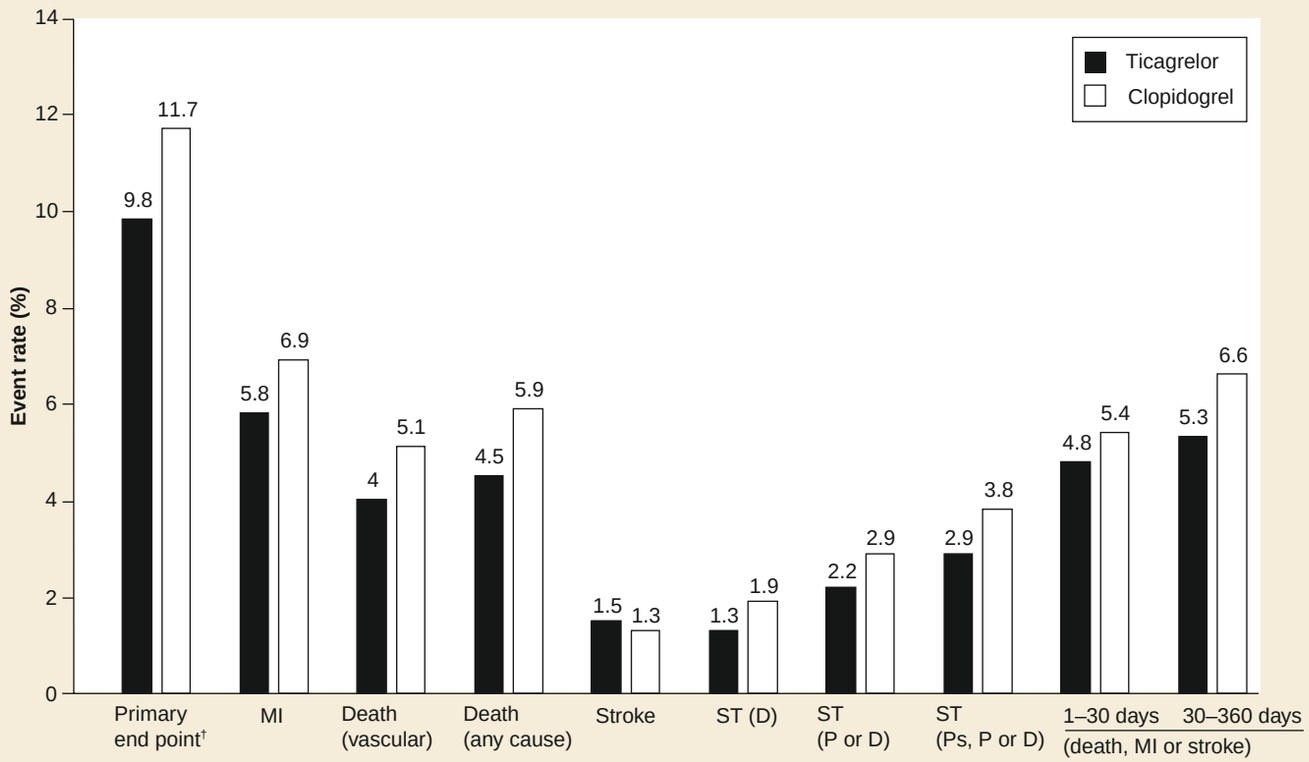
Another interesting observation is that although in STEMI and non-STEMI patients, a significant reduction (~16%) in primary end point was observed, no benefit was observed in patients diagnosed with unstable angina (HR: 0.96; 95% CI: 0.75–1.22). Similarly, only a 6% reduction in primary end point occurrence was observed in patients who were ≥75 years old compared with an 18% reduction in patients <75 years old (p =0.22 for interaction) [34].

Regarding primary safety end points, there were no significant differences in the rates of major bleeding as defined by protocol (p = 0.43), which was consistent in all predefined subgroups except for BMI (p = 0.05). In addition, there were no differences in major bleeding as defined by the TIMI criteria (p = 0.57) or life-threatening or fatal bleeding according to study criteria (5.8% in both groups; p = 0.7). The secondary efficacy end point of non-CABG-related

Table 1. PLATO trial characteristics.

	Ticagrelor (n; %)	Clopidogrel (n; %)	p-value
Key baseline characteristics			
MI	1900 (20.4)	1924 (20.7)	–
PCI	1272 (13.6)	1220 (13.1)	–
CABG	532 (5.7)	574 (6.2)	–
Dyspnea	1412 (15.1)	1358 (14.6)	–
Positive troponin	7965 (85.3)	7999 (86.1)	–
STEMI	3496 (37.5)	3511 (37.8)	–
Non-STEMI	4005 (42.9)	3950 (42.5)	–
Unstable angina	1549 (16.6)	1563 (16.8)	–
Other characteristics			
Premature discontinuation of the drug	23.4	21.5	0.002
– Due to adverse event	7.4	6.0	<0.001
Clopidogrel administered before randomization	46	46.1	0.91
No LD or missing information	52.9	1.0	–
300–375 mg	20.6	59.5	–
600–675 mg	13.7	19.6	–
GPIIb/IIIa inhibitor	26.4	26.8	0.62
Proton pump inhibitor	45.4	44.4	0.21
Planned invasive treatment	72.1	71.9	0.68

CABG: Coronary artery bypass grafting; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.



HR (95% CI)	0.84 (0.77–0.92)	0.84 (0.75–0.91)	0.79 (0.69–0.91)	0.78 (0.69–0.81)	1.17 (0.91–1.52)	0.67 (0.50–0.95)	0.75 (0.59–0.95)	0.77 (0.62–0.95)	0.88 (0.77–1.00)	0.80 (0.70–0.91)
p-value	<0.001	0.005	0.001	<0.001	0.22	0.009	0.02	0.01	0.045	<0.001

Figure 3. Primary analysis of the PLATO trial: efficacy end points.
†Composite of cardiovascular death, nonfatal MI and nonfatal stroke.
D: Definite; HR: Hazard ratio; MI: Myocardial infarction; P: Probable; Ps: Possible; ST: Stent thrombosis.

major bleeding according to study criteria or TIMI criteria was higher in the ticagrelor group (p = 0.03 for both). However, no difference in CABG-related bleeding was observed between groups according to both bleeding criteria (p = 0.32 for both). Ticagrelor therapy was associated with numerically more fatal intracranial hemorrhages compared with clopidogrel-treated patients (0.1 vs 0.01%, respectively; p = 0.02) whereas excess extracranial bleeding events were associated with clopidogrel treatment (0.3 vs 0.1%, respectively; p = 0.03) **(Figure 4)** [34].

The incidence of any dyspnea was nearly two-times higher (HR: 1.84; 95% CI: 1.68–2.02; p > 0.001) in the ticagrelor group. However, the incidence of dyspnea requiring discontinuation of study treatment was minimal in both groups but significantly higher in the ticagrelor group compared with the clopidogrel group (0.9 vs 0.1%; HR: 6.12; p < 0.001). There were no differences in the incidence of bradycardia or neoplasm arising during treatment but the incidence of ventricular pauses ≥3 s observed by Holter monitoring was higher in patients treated with ticagrelor (5.8 vs 3.6%; p = 0.01) during the first week. There were no differences in the incidence of ventricular pauses ≥5 s during the first week or ventricular pauses ≥3 or ≥5 s at 30 days **(Figure 5)**. Both serum creatinine and uric acid levels were higher in patients treated with ticagrelor during the whole treatment period (p < 0.001 at 1 and 12 months for both) **(Figure 6)** [34].

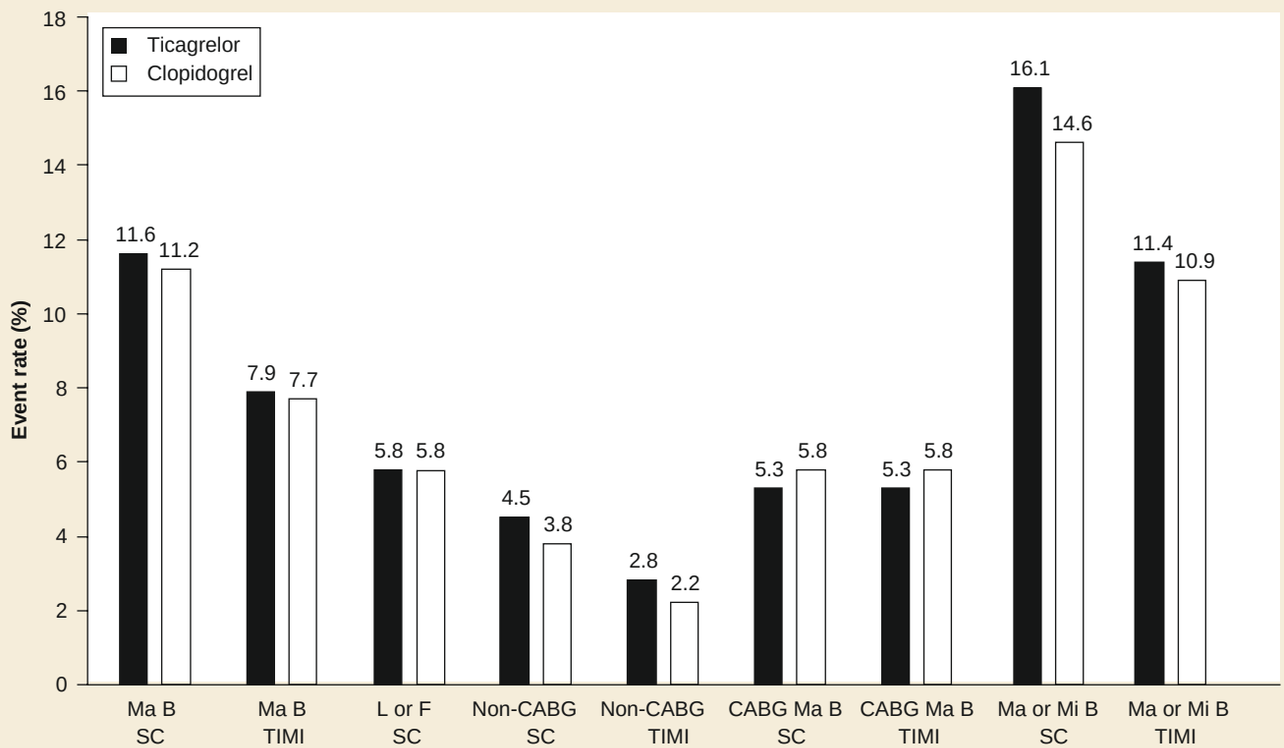
In summary, in the PLATO trial, for every 1000 patients admitted for ACS, replacing clopidogrel with ticagrelor for 12 months resulted in 14 fewer deaths, 11 fewer MIs and six to eight fewer cases of stent thrombosis without

an increase in bleeding requiring transfusion. Moreover, based on the PLATO data, it can be estimated that treating 54 patients with ticagrelor instead of clopidogrel for 1 year will prevent one event of CV death, MI or stroke [35].

Additional analyses

Invasive management

At the time of randomization, invasive management was planned in 13,408 (72%) patients, however, only 82% of this group were treated invasively (~75% underwent PCI during the study and an additional 5–6% underwent CABG). Similar to the primary analysis, in patients who underwent a planned invasive strategy, ticagrelor therapy was associated with a significant reduction in the occurrence of the primary end point (16% reduction; p = 0.0025), MI (20% reduction; p = 0.0023) and all-cause mortality (19% reduction; p = 0.0103). However, there was no difference in stroke (1.2 vs 1.1%, respectively; p = 0.646). In addition, there was a significant decrease in stent thrombosis (definite, definite or probable, and total) that was confined to patients treated with bare-metal stents. Finally, the ticagrelor benefit remained significant irrespective of the total clopidogrel loading dose received either prior to randomization or at 24 h following study enrollment. Both primary efficacy end point events as well as stent thrombosis were significantly reduced by ticagrelor versus clopidogrel therapy whether subjects received a



HR	1.04	1.03	1.03	1.19	1.25	0.95	0.94	1.11	1.05
(95% CI)	(0.95–1.13)	(0.93–1.15)	(0.90–1.16)	(1.02–1.38)	(0.3–1.53)	(0.85–1.06)	(0.82–1.07)	(1.03–1.20)	(0.96–1.15)
p-value	0.43	0.57	0.70	0.03	0.03	0.32	0.32	0.008	0.33

Figure 4. Primary analysis of the PLATO trial: safety end points.
CABG: Coronary artery bypass grafting; HR: Hazard ratio; L or F: Life-threatening or fatal bleeding; Ma B: Major bleeding; Mi B: Minor bleeding; SC: Study criteria; TIMI: Thrombolysis in myocardial infarction.

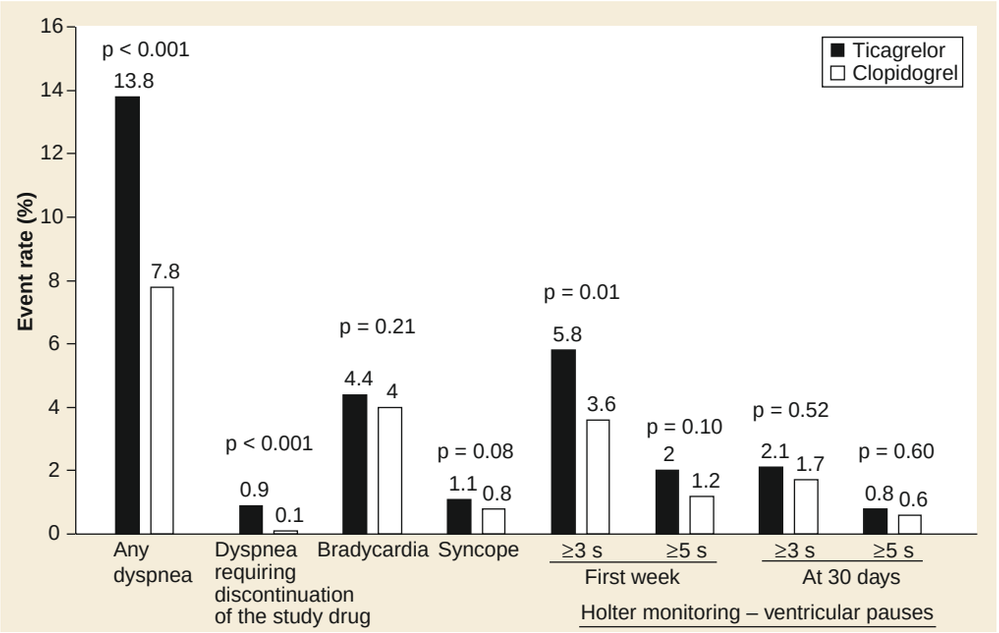


Figure 5. Major adverse events in the PLATO trial.

≥600-mg or a <600-mg clopidogrel loading dose within 24 h pre- or post-study enrollment [35].

Noninvasive management

In the PLATO trial, out of 5216 patients admitted to hospital for ACS who were specified as planned for noninvasive strategy, 3143 (60%) patients were managed with a noninvasive strategy by the end of the follow-up. Among these patients, there was 15% reduction in the primary end point (p = 0.04), a 25% reduction in total mortality (p = 0.01), a 17% increase in major bleeding (protocol defined; p = 0.08) and a numerically increased rate of non-CABG-related bleeding (p = 0.10) that occurred in patients treated with ticagrelor compared with clopidogrel therapy. There was numerically higher rate of intracranial bleeding associated with ticagrelor therapy (total incidences were very small). This analysis indicates that the potential benefit of more potent $P2Y_{12}$ receptor inhibitors is confined to high-risk patients [36].

Coronary artery bypass graft surgery

In an analysis of patients who underwent CABG (n = 1261) with last intake of study drug within 7 days, there were no significant differences between ticagrelor and clopidogrel therapies with respect to the primary end point outcome. However, a 51% reduction in total mortality (4.7 vs 9.7%; p<0.01), and a 48% reduction in CV mortality (p = 0.07) after CABG was observed in the ticagrelor group. Similar rates of CABG-related major bleeding were observed between treatment groups (81.2 vs 80.1%; HR: 1.07; p = 0.67) [23]. Finally, ticagrelor therapy was associated with a 5.0% per year absolute reduction in total mortality and 3.8% per year absolute reduction in CV mortality [37].

An earlier offset of pharmacodynamic effects during ticagrelor therapy compared with clopidogrel therapy was demonstrated in the ONSET-OFFSET study. At 48 h after the last maintenance dose, ticagrelor-treated patients had numerically lower IPA and at 72 h this difference became significant such that the IPA at 72 h in the ticagrelor group was similar to the IPA at 120 h in the clopidogrel group. These pharmacodynamic findings suggested that ticagrelor-treated patients would have the same CABG-related bleeding risk at 72 h after last maintenance dose as a clopidogrel-treated patient at 120 h after last maintenance dose. However, the recommendation of the US FDA were: "when possible, discontinue BRILINTA [USA] at least 5 days prior to any surgery" [102]. The latter recommendation was based on the analysis from the PLATO trial in patients who underwent CABG that showed similar incidences in both groups of CABG-related life-threatening/fatal bleeding in patients who had discontinued the study drug up to 4–5 days before CABG [37]. However,

in the EMA product information for ticagrelor (Brilique™, Europe), it was mentioned that "if a patient is to undergo elective surgery and antiplatelet effect is not desired, Brilique should be discontinued 7 days prior to surgery" [103].

ST-segment elevation MI

Among 7544 patients with STEMI or left-bundle-branch block for whom primary PCI was intended, there were no significant differences in the primary composite end point of MI, death or stroke (9.4 vs 10.8%; HR: 0.87; 95% CI: 0.75–1.01; p = 0.07) and major bleeding (HR: 0.98; p = 0.76) between the ticagrelor and clopidogrel groups. Regarding secondary end points, ticagrelor therapy was associated with a significant reduction in MI alone (HR: 0.80; p = 0.03), total mortality (HR: 0.82; p = 0.05) and definite stent thrombosis (HR: 0.66; p = 0.03). There was a significantly increased risk of stroke associated with ticagrelor therapy (HR: 1.63; p = 0.02). No interaction was observed between presentation with STEMI or left-bundle-branch block with respect to ticagrelor efficacy. A similar reduction in absolute mortality was observed with ticagrelor therapy in patients coadministered plasminogen activator inhibitor or streptokinase [38].

In a prespecified ECG analysis of STEMI patients (n = 6206) with at least 1-mm ST-segment elevation in two contiguous leads, a higher rates of vascular death/MI within 1 year was observed in patients with a greater ST-segment shift at baseline. The clinical benefit of ticagrelor versus clopidogrel was consistent irrespective of baseline total ST-deviation and these benefits may be related to the prevention of recurrent vascular events overtime rather than related to the rapidity or the completeness of acute reperfusion. The authors suggested that these benefits of ticagrelor were related to the greater antithrombotic effects of ticagrelor and the inhibition of adenosine reuptake by red blood cells that are favorably influencing myocardial reperfusion [39].

Renal insufficiency

It is well known that renal dysfunction is an important risk factor for ischemic and bleeding event occurrence in patients with ACS. Ticagrelor therapy was associated with 23% reduction in the primary end point (17.3 vs 22.0%; HR: 0.77; 95% CI: 0.65–0.90) compared with clopidogrel in patients with renal dysfunction (creatinine clearance <60 ml/min, n = 3237) whereas there was only a 10% RR reduction in patients with normal renal function (7.9 vs 8.9%; HR: 0.90;

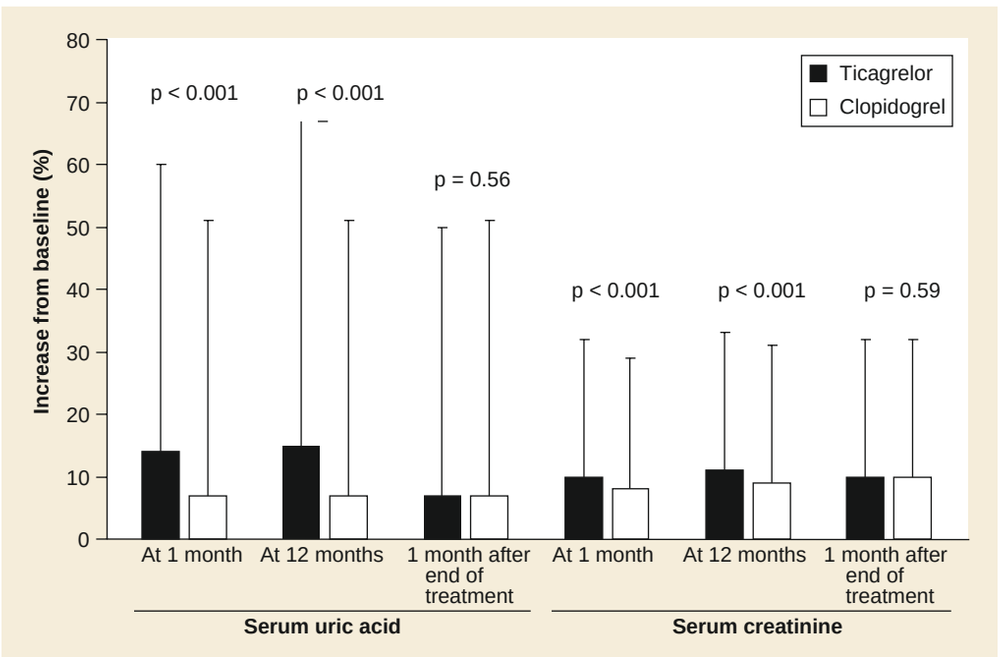


Figure 6. Effect of ticagrelor and clopidogrel treatments on serum uric acid and creatinine levels in the PLATO trial.

95% CI: 0.79–1.02). Similar to the primary analysis, in patients with renal insufficiency, a 28% reduction in total mortality (10.0 vs 14.0%; HR: 0.72; 95% CI: 0.58–0.89) but no significant differences in major bleeding, fatal bleeding and non-CABG-related bleeding were observed during ticagrelor therapy compared with clopidogrel therapy. These results are in line with the previously mentioned pharmacokinetic and pharmacodynamic study results where ticagrelor therapy was not significantly influenced by renal dysfunction. However, a significant p-value for interaction (p = 0.03) in the primary end point analysis based on Modification of Diet in Renal Disease (MDRD) formula may suggest a similar efficacy of ticagrelor compared with clopidogrel in patients with normal renal function [40].

Diabetes

In the prespecified diabetes substudy of the PLATO trial, based on admission levels of hemoglobin A1c, ticagrelor treatment was associated with a 12% reduction in primary composite end point occurrence (HR: 0.88; 95% CI: 0.76–1.03), an 18% reduction in all-cause mortality (HR: 0.82; 95% CI: 0.66–1.01) and a 35% reduction in 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 seen irrespective of diabetic status, insulin treatment and glycemic control. However, the reduction in primary end point occurrence was more pronounced in mainly patients with a HbA1c level above the median (HR: 0.80; 95% CI: 0.70–0.91) [41].

Dyspnea & pulmonary function

In PLATO, 14.5% of patients (n = 1339) during ticagrelor therapy and 8.7% (n = 798) patients during clopidogrel therapy had dyspnea. Most of the dyspnea events occurred during the first 30 days of treatment and were mild or moderate in intensity. Only 39 dyspnea related events (0.4%) during ticagrelor therapy and 24 dyspnea related events events (0.3%) during clopidogrel in the trial were considered severe. There were no specific causes for dyspnea such as prior history of congestive heart failure, chronic obstructive pulmonary disease or others. There was a 66% lower risk of CV death in ticagrelor-treated patients with dyspnea compared with clopidogrel suggesting that there were no increased risk of mortality associated with dyspnea. Thus, dyspnea events that occurred during ticagrelor treatment were usually mild or moderate in intensity, resolved spontaneously or upon discontinuation of medication in the majority of patients, and did not appear to be associated with any differences in any efficacy or other safety outcomes compared with clopidogrel therapy [42].

Various pulmonary function measurements such as pulse oximetry, spirometry, lung volumes and diffusion capacity were made at 30 days following the administration of the study drug, at the end of the study drug administration (mean: 211 days) and also at approximately 30 days after the discontinuation of the study drug in 199 patients enrolled in the PLATO study. There were no differences between ticagrelor- and clopidogrel-treated groups in pulmonary function at all time points measured [43].

ECG analysis

In 2908 patients, a continuous ECG assessment was performed. Among these patients, 98.5, 68.4 and 67.0% of patients had 1-week, 1-month and both recordings, respectively. More frequent ventricular pauses of ≥3 s occurred during the first week of ticagrelor therapy than clopidogrel therapy (5.8 vs 3.6%; RR: 1.61; p = 0.006). These events occurred less frequently and to a similar extent with both drugs at 30 days (2.1 vs 1.7%). Most of the ticagrelor-related ventricular pauses were asymptomatic, sinoatrial nodal in origin (66%) and nocturnal. No differences were observed between ticagrelor and clopidogrel treatments in the incidence of clinically reported bradycardiac adverse events, including syncope, pacemaker placement and cardiac arrest [44].

In *in vitro* experiments, ticagrelor has been shown to interfere with adenosine metabolism and increase adenosine concentrations by inhibiting adenosine uptake by erythrocytes, which may be attributed to the inhibition of the sodium-independent equilibrative nucleoside transporters. Similar to another adenosine uptake inhibitor dipyridamole, ticagrelor was shown to augment cardiac blood flow in a canine model of reactive hypoxia [45]. Similarly, using a luciferase-based bioluminescence assay, Ohman *et al.* demonstrated that ticagrelor can release large amounts of ATP in a dose-dependent manner from erythrocyte and suggested that this can rapidly be converted to adenosine by ectonucleotidases present in endothelial cells, white blood cells and erythrocytes [46].

In a fibrinolytic-treated canine infarct model, despite similar levels of platelet inhibition, ticagrelor treatment was associated with improved reperfusion times, lower reocclusion rates and more rapid restoration of myocardium tissue perfusion compared with clopidogrel [47,48]. Therefore, ticagrelor-induced increases in tissue concentration of adenosine at the sinoatrial and atrioventricular nodes is a plausible explanation for the increased bradycardia events observed in DIPSERSE-2 and PLATO trials; however, the precise mechanism is not known at this time [35–37]. Recently, ticagrelor oral administration, but not clopidogrel and prasugrel, prevented ADP-induced contraction of vascular smooth muscle cells in a rat model [49].

Geographic region

Patients from the USA comprised only 7.5% of the total population in the PLATO trial. However, the trend in clinical outcomes observed in US patients was opposite to other demographic regions. Among demographic characteristics, US patients had greater bodyweight compared with patients from the rest of the world (87 vs 80 kg), and higher rates of dyslipidemia (68 vs 45%), prior PCI (29 vs 12%, prior CABG (17 vs 5%), chronic obstructive pulmonary disease (13 vs 5%), diabetes (33 vs 24%), history of dyspnea (25 vs 14%), and family history of CV disease (53 vs 30%). However, US patients had a lower rate of STEMI (16 vs 39%), persistent ST-segment elevation (15 vs 40%) and ST-segment depression (15 vs 40%). Finally, the time from index event to study drug administration was longer in US patients compared with patients from the rest of the world (16.7 vs 10.8 h) [50].

Compared with a 19% RR reduction in the rest of the world, there was 27% relative increase in the occurrence of the combined primary end point rate in the US population. Interestingly, among the primary efficacy end points, MI was a major event and was numerically higher among US patients treated with ticagrelor (9.1 vs 5.1%). Moreover, in patients treated with clopidogrel, the incidences of CV death, stroke and all cause mortality were less in the American population (2.7 vs 4.9%, 0.6 vs 1.2% and 3.4 vs 5.6%, respectively). There were no major differences in the safety end points. Regarding treatment strategies, more American patients were treated with drug-eluting stents and received a higher aspirin dose. Moreover, adherence to the study drug (defined as >80% compliance at each visit) was lower and also there was greater overall study drug discontinuation in the American population compared with the rest of the world (62 vs 85% and 31 vs 22%, respectively) [101]. Two independent groups performed statistical analyses of the PLATO data in order to address the 'North American paradox' and proposed a higher aspirin maintenance dose as a potential explanation for the regional differences although the play of chance remains another very likely explanation. Concerns about the potential risk of high-dose aspirin and ticagrelor were addressed in the guidelines as well as a FDA boxed warning as follows: "after initial dosing, clinicians should use aspirin doses of 75–100 mg/day". Although *in vitro* studies tried to explain this interaction as being related to off-target actions of ticagrelor, a plausible explanation remains elusive at this time.

Bleeding

No significant interactions were observed for major bleeding or combined minor plus major bleeding between treatment groups and age ≥75 years, weight <60 kg, region, chronic kidney disease, creatinine clearance <60 ml/min and aspirin dose >325 mg on the day of randomization, prerandomization clopidogrel administration or clopidogrel loading dose. Independent predictors for non-CABG-related major bleeding include increasing age, decreasing creatinine clearance, low admission hemoglobin, female gender, prior GI bleeding, glycoprotein IIb/IIIa inhibitor use and randomization to ticagrelor. Similarly, an interaction for region was not observed [102].

Fatal bleeding events were uncommon in the PLATO study and did not differ between the treatment groups. Net clinical benefit, adjusted for patient-related, clinical and laboratory variables, including region, age, final diagnosis, history of TIA or stroke, aspirin on the day of randomization, creatinine clearance, baseline hemoglobin and Killip classification, favored ticagrelor throughout the study, particularly after 30 days on treatment. Although incidences of fatal bleeding events were low (20 vs 23 events), most of the fatal bleeding events in ticagrelor therapy were related to intracranial hemorrhage (11 out of 20 events) [51].

In a recent meta-analysis of randomized trials involving patients undergoing PCI, a

significant reduction in mortality (OR: 0.87; 95% CI: 0.79–0.95; p = 0.002), recurrent MI (OR: 0.80; 95% CI: 0.74–0.87; p < 0.0001), definite in-stent thrombosis (OR: 0.52; 95% CI: 0.43–0.63; p < 0.0001) were observed in patients treated with new $P2Y_{12}$ blockers (ticagrelor/prasugrel) compared with high-dose clopidogrel (600 mg). In addition, there were no significant differences in major bleeding complications with new $P2Y_{12}$ blockers compared with standard-dose clopidogrel (OR: 1.06; 95% CI: 0.96–1.17; p = 0.25) [52].

Conclusion

The pharmacodynamic properties such as rapid onset and greater platelet inhibition and similar bleeding outcome compared with clopidogrel observed in the PLATO trial make ticagrelor a preferable antiplatelet agent in the setting of ACS and *ad hoc* PCI. A reduction in mortality in the ACS patient is a major advantage in treatment with ticagrelor. However, b.i.d. administration, occurrence of dyspnea, elevated uric acid and creatinine levels and increase in ventricular pauses are important concerns. These latter effects are minor and do not appear to be associated with significant clinical issues. Based on the favorable results observed in the PLATO trial, both American and European guidelines recommend ticagrelor in patients with ACS. Due to potential interaction between high-dose aspirin and ticagrelor, American guidelines recommend ticagrelor with low maintenance dose aspirin for long-term therapy.

Financial & competing interests disclosure

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