Q J Med 2013; **106**:105–115
doi:10.1093/qjmed/hcs187 Advance Access Publication 24 October 2012

Review

QJM

A critical overview on ticagrelor in acute coronary syndromes

E.P. NAVARESE[1], A. BUFFON[2], M. KOZINSKI[1], K. OBONSKA[1], M. RYCHTER[1], V. KUNADIAN[3], D. AUSTIN[3], S. DE SERVI[4], A. SUKIENNIK[1] and J. KUBICA[1]

From the [1]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Skłodowskiej-Curie Street No 9, 85-094 Bydgoszcz, Poland, [2]Department of Cardiology, Catholic University of Sacred Heart, Rome, Largo A. Gemelli, 8, 800168 Rome, Italy, [3]Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Road, High Heaton, Newcastle upon Tyne NE2 4HH, Newcastle, UK and [4]Department of Cardiovascular Disease, Civic Hospital, Via Cesare Candiani 2, 20025 Legnano, Italy

Address correspondence to Dr E.P. Navarese, Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Skłodowskiej-Curie Street No 9, 85-094 Bydgoszcz, Poland. email: eliano.navarese@alice.it

Summary

Until a few years ago, the mainstay of anti-platelet therapy in patients with acute coronary syndrome (ACS) was the combination of aspirin and clopidogrel, a P2Y12 receptor inhibitor. However, current clinical practice has now changed with the introduction of ticagrelor, a more potent cardiovascular drug than clopidogrel, without the limitations related to clopidogrel therapy. In this review, we provide a critical overview of ticagrelor in ACS, highlight the results with ticagrelor in several subgroups of patients and discuss the future trials.

Introduction

The pathophysiology of acute coronary syndrome (ACS) is characterized by the rupture of an atherosclerotic plaque within the coronary artery, with subsequent platelet aggregation, thrombus formation and ischaemia. Before platelets aggregate, they must first be activated to express activated glycoprotein IIb/IIIa receptors on the cell surface. This activation is the result of stimulation from endogenous platelet agonists, such as thromboxane A2 and adenosine diphosphate (ADP). ADP activates platelets by binding to P2Y12 receptors on the cell surface.

P2Y12 receptors are irreversibly antagonized by clopidogrel, a P2Y12 receptor inhibitor. However, clopidogrel therapy is flawed by several limitations; this fact prompted the research for new drugs that are able to overcome clopidogrel limitations**.**

In this review, we critically discuss the limitations of clopidogrel therapy, the pharmacologic properties of the new cardiovascular drug ticagrelor, the main findings of the randomized clinical studies and of their subgroup analyses comparing ticagrelor to clopidogrel therapy in the ACS setting.

Limitations of clopidogrel: why is ticagrelor needed?

Clopidogrel as an anti-platelet agent has shown several limitations. The first drawback is related to the metabolism of clopidogrel, which is a prodrug

requiring two-step activation involving several hepatic cytochrome P (CYP) isoenzymes to convert prodrug to the active metabolite. This results in a delayed onset of action (6–8 h after a 300 mg loading dose).

The second limitation of clopidogrel is related to its irreversible binding to P2Y12 receptors, leading to a gradual recovery of platelet function after drug withdrawal; patients who need urgent surgical revascularization are therefore, at increased risk of bleeding within 5–7 days after cessation of clopidogrel. In the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) study, among patients undergoing coronary artery bypass grafting (CABG), bleeding tended to be more common if CABG was performed within 5 days of clopidogrel administration (8.5% with clopidogrel vs. 5.7% with placebo).[1]

Despite clinical efficacy in a broad range of coronary artery disease patients, pharmacodynamic studies conducted in patients undergoing stenting showed 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) as well.[2,3] Additionally, moderate platelet inhibition by clopidogrel is insufficient to suppress an increase in ADP-induced platelet aggregation in the mid-morning, in the period when myocardial infarction, stroke and sudden cardiac death occur the most frequently.[4] The wide anti-platelet response variability was characterized by a consistent percentage of patients (approximately one in three patients) exhibiting high on-treatment platelet reactivity (HPR) that was subsequently strongly linked to recurrent ischaemic event occurrence in patients undergoing percutaneous coronary intervention (PCI).[5]

Moreover, clopidogrel metabolism is influenced by single nucleotide polymorphisms of genes encoding cytochrome P450 isoenzymes. CYP2C19 is a particularly important isoenzyme that participates in the conversion to the active metabolite.[6] Mega *et al.*[7] showed that carriers of at least one CYP2C19 reduced-function allele had relative reductions of 32.4 and 9% in plasma concentration of the active metabolite of clopidogrel and absolute decrease in maximal platelet aggregation 4 h after pretreatment with a 600 mg loading dose of clopidogrel, respectively, as compared with non-carriers. The pharmacokinetic and pharmacodynamic effects of CYP2C19 reduced-function allele on the response to clopidogrel were observed after a loading dose and during the administration of a maintenance dose. Carriers of a reduced-function CYP2B6 allele also tended to have a lower pharmacokinetic and pharmacodynamic response to clopidogrel.

Finally, it is well known that multi-drug therapy increases the risk of drug–drug interactions and this holds true specifically for clopidogrel; clopidogrel, a prodrug, requires hepatic CYP450 metabolic activation to produce the active metabolite that inhibits the platelet P2Y12 receptor, decreasing platelet activation and aggregation processes. Atorvastatin, omeprazole and several other drugs have been shown in pharmacodynamic studies to competitively inhibit CYP activation of clopidogrel, eventually reducing clopidogrel responsiveness.[8]

Chemical properties of ticagrelor

Ticagrelor, a cyclopentyl-triazolo-pyrimidine acting as an analogue of adenosine triphosphate (ATP), constitutes a first non-thienopyridine direct platelet P2Y12 receptor blocker.

Recognition of the fact that ATP competitively inhibits ADP-induced platelet aggregation encouraged attempts to identify its stable and potent analogue. Differences between the structures of ticagrelor and ATP consist of inclusion of a nitrogen atom in the purine-like moiety of ATP and omission of an oxygen atom in the sugar-like moiety of the molecule.[9] As a result of these changes, ticagrelor and ATP exert opposed electrostatic properties: ticagrelor is lipophilic, whereas ATP is highly hydrophilic. Ticagrelor possesses nanomolar affinity for the P2Y12 receptor and remains highly selective for this receptor when compared with other adenosine receptors. As ticagrelor binds to the P2Y12 receptor on a distinct site than thienopyridines, there is no competition between them.

Another main difference between these platelet ADP antagonists is related to the type of bond linking ticagrelor or thienopyridines with the P2Y12 receptor. Ticagrelor only forms a hydrogen bond and there is no S-S covalent bond formation as with clopidogrel or prasugrel.[10] This could be the reason for the reversible anti-platelet effect played by ticagrelor since hydrogen bonding is weaker than covalent bonding.

Pharmacology of ticagrelor

Pharmacological properties of ticagrelor vs. clopidogrel are summarized in Table 1. Ticagrelor is rapidly absorbed and has a half-life of 7–12 h, thus requiring twice-daily dosing. Ticagrelor is directly active following oral administration. In addition, ticagrelor is a reversible inhibitor, in contrast to clopidogrel, which irreversibly blocks the P2Y12 receptor. Due to the reversibility of ticagrelor binding to the P2Y12

Table 1 Main pharmacologic characteristics of clopidogrel and ticagrelor

	Clopidogrel	Ticagrelor
Dose in ACS	600 mg loading dose, then 75 mg/die	180 mg loading dose, then 90 mg × 2/die
Route of administration	Per os	Per os
Mechanism of action	Prodrug, irreversible	Active drug, reversible
IPA (%)	40–60	85–95
Time to maximal IPA (h)	4–8	2–4
End of anti-platelet effect (days)	5–7	3–5
Half-life	~11 days	7–12 h
Administration	QD	BID
Time to steady state (days)	3–7	2–3
Pharmacologic interactions	Several, most important with omeprazol	Rifampicin, ketoconazol, diltiazem

IPA (%), percentage of inhibition of platelet aggregation; QD, once daily; BID, twice daily.

receptor, its inhibitory effect is directly dependent on plasma drug concentration. Although a fast offset of ticagrelor action related to its reversibility remains beneficial in patients requiring urgent CABG, it theoretically could expose non-adherent patients to increased risk for coronary artery stent thrombosis if they missed one or two doses. Therefore, similar to thienopyridines, it is crucial to inform the patients undergoing coronary stenting about to be strictly adherent to the anti-platelet therapy with ticagrelor.

Ticagrelor has one known active metabolite (AR-C124910XX), which is also rapidly formed. The pharmacokinetics of ticagrelor and AR-C124910XX are predictable, with dose-proportional plasma concentrations after administration that are stable at steady state. Ticagrelor and AR-C124910XX are extensively metabolized into an inactive metabolite (AR-C133913XX) and its glucoronide conjugate before being eliminated in urine. Ticagrelor exerts its platelet-inhibitory effects through an apparent antagonism of ADP activation of the P2Y12 receptor, which in turn blocks its intraplatelet signalling sequence. This antagonistic effect is non-competitive, suggesting that there are distinct binding sites on human P2Y12 receptors.

The pharmacokinetic data of the study of the ONSET and OFFSET of antiplatelet effects comparing ticagrelor, clopidogrel and placebo with aspirin (ONSET-OFFSET)[11] demonstrated that maximum plasma concentration (Cmax), time to Cmax (tmax) and area under the plasma concentration–time curve from time 0–8 h (AUC0-8h) 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.

In the response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies study (RESPOND),[12] ticagrelor mean Cmax and AUC0-8h following 2-week dosage were comparable between clopidogrel responders (724 ng/ml and 3983 ng•h/ml) and non-responders (764 ng/ml and 3986 ng•h/ml). Pharmacokinetics of ticagrelor were unaffected by prior clopidogrel dosing; these results indicate that at current recommended doses, ticagrelor therapy can provide significant inhibition of platelet aggregation that is similar in both clopidogrel responders and non-responders.

Metabolism and potential drug interactions

In *in vitro* experiments with 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. 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 co-administrated with potent CYP3A4/5 inhibitors such as ketaconalzole, dexametahzone, rifampin, carbamazepine, phenytoin and phenobarbital and co-administration of these drugs are discouraged. Although there was increased ticagrelor exposure with moderate CYP3A4 inhibitors such as dilitiazem, amprenavir, fluconazole, erythromycin and aprepitant, these agents can be co-administered with ticagrelor.

Off-target effects of ticagrelor

Unexpected mortality benefits present in the PLATelet inhibition and patient Outcomes trial (PLATO), a landmark phase III study comparing ticagrelor with clopidogrel in a broad spectrum of

ACS patients, despite only a moderate decrease in the risk of subsequent myocardial infarction, led to a speculation that advantages of ticagrelor therapy may exceed its anti-platelet properties and may be, at least partially, attributed to its off-target effects.[13–16]

Since P2Y12 receptors were identified on vascular smooth muscle cells,[17] we and others have demonstrated in animal and human models that ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced vascular smooth muscle cells contraction.[18,19] Lack of impact of thienopyridines on vessel reactivity may be explained by high instability of their active metabolites that do not reach the systemic circulation in sufficient concentrations.[18] Although the clinical relevance of the vasorelaxant effect of ticagrelor is yet to be determined, coronary vasospasm is generally accepted to frequently superimpose atherosclerotic plaque instability and thrombus formation while ADP constitutes a powerful platelet agonist being released from activated platelets.

Additionally, investigating pleiotropic effects of ticagrelor, other groups proved that ticagrelor not only inhibits the uptake of adenosine by human erythrocytes,[20] but also induces release of ATP from human erythrocytes, followed by its subsequent degradation to adenosine.[21] The former mechanism was also demonstrated to significantly enhance the adenosine-induced increase in coronary blood flow in a canine model.[22] Furthermore, Serebruany[21] believes that ticagrelor may be transformed to adenosine by degrading oxygenases and/or cyclopropylcarbonyl radical fragmentation pathways Numerous features related to inhibition of adenosine uptake by ticagrelor and probably chronically increasing adenosine blood levels on ticagrelor therapy, such as promotion of pre-conditioning, prevention of sudden cardiac death, reduction of infarct size, inhibition of tumour growth, bronchoconstriction, neurocardiogenic syncope and upregulation of purine metabolism, were postulated.[21] Due to its adenosine-like effects, ticagrelor has the potential to induce dyspnoea and to trigger ventricular pauses. Similarly, transient elevations in uric acid and creatinine concentrations were observed during ticagrelor therapy.[13] These adverse events were usually mild and self-limiting in clinical trials,[13,23,24] but patients will need to be monitored closely when starting ticagrelor therapy.

Randomized studies of ticagrelor vs. clopidogrel in ACS

The randomized, double-blind, double-dummy Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-St-segment Elevation myocardial infarction-2 (DISPERSE-2) trial[25] evaluated the safety, tolerability and initial efficacy of either ticagrelor or clopidogrel added to aspirin in 990 patients with non-ST-segment elevation ACS. The patients were randomized in a 1:1:1 fashion to receive ticagrelor 90 mg twice a day, ticagrelor 180 mg twice a day or a clopidogrel 300 mg loading dose plus 75 mg a day for up to 12 weeks. Patients in the ticagrelor group were further randomized to receive or not receive the 270 mg loading dose of the drug. The primary endpoint, Kaplan–Meier rate of protocol-defined major or minor bleeding over 4 weeks, did not differ between the three groups (9.8, 8.0 and 8.1%, respectively). Rates of major bleeding were also similar (7.1, 5.1 and 6.9%, respectively). Notably, the bleeding rates were not different regardless of previous treatment with clopidogrel, or administration of a loading dose of ticagrelor or platelet glycoprotein IIb/IIIa inhibitors. Asymptomatic ventricular pauses longer than 2.5 s were more common with ticagrelor, particularly at 180 mg twice a day (5.5, 9.9 and 4.3%, respectively; $P = 0.58$ and $P = 0.01$, respectively, vs. clopidogrel). Remarkably, the study highlighted for the first time that among patients undergoing CABG 1–5 days after stopping the drug, treatment with ticagrelor as opposed to clopidogrel was associated with a numerically lower incidence of major bleeding, a finding consistent with the reversible inhibition of the P2Y12 receptor provided with AZD6140.

The ONSET/OFFSET study[11] was a multi-centre, randomized, double-blind, double-dummy, parallel-group study of the onset and offset of antiplatelet effects of ticagrelor (180 mg loading dose and 90 mg daily maintenance dose) vs. high loading-dose clopidogrel (600 mg loading dose followed by 75 mg daily maintenance dose) in 123 patients with stable coronary artery disease. Following the loading dose, a more rapid onset of inhibition of platelet aggregation (IPA) was seen with ticagrelor compared with clopidogrel either at 30 min ($41 \pm 33\%$ vs. $8 \pm 10\%$; $P < 0.0001$), 1 h ($79 \pm 25\%$ vs. $23 \pm 26\%$; $P < 0.0001$) and 2 h ($88 \pm 15\%$ vs. $38 \pm 32\%$; $P < 0.0001$). Higher IPA for ticagrelor was also observed in the maintenance therapy phase. A faster offset rate for IPA was observed after the last dose of ticagrelor than for clopidogrel from 4 to 72 h. In addition, ticagrelor was shown to be associated with low prevalence of high platelet reactivity at 2, 8 and 24 h, and 6 weeks compared with clopidogrel according to multiple established platelet function assays.

The RESPOND study[12] was a randomized, double-blind, double-dummy, crossover trial that

examined the use of ticagrelor in 98 patients with stable coronary artery disease as a function of responsiveness to clopidogrel. Non-responsiveness to clopidogrel was defined as a <10% absolute change in 20 µmol/l ADP-induced platelet aggregation between the baseline value and at 6–8 h after the 300 mg clopidogrel loading dose. In a two-way crossover design, non-responders and responders were randomly assigned to receive clopidogrel (600 mg loading dose, then 75 mg once daily) or ticagrelor (180 mg loading dose, then 90 mg twice daily) for 14 days (period 1). Thereafter, all non-responders switched treatment, with half of the responders continuing the previous treatment, and half switching treatment. The use of ticagrelor among non-responders resulted in a 0.10, 0.30 and 0.50% decrease in platelet aggregation from baseline in 100, 75 and 13% of the patients, respectively. In addition, there was a significant ($P = 0.0001$) decrease in platelet aggregation from a mean 59% to 35% in patients who switched from clopidogrel to ticagrelor and an increase in platelet aggregation from mean 36% to 56% in patients switched from ticagrelor to clopidogrel. These results indicated that the anti-platelet effect of ticagrelor is consistent regardless of responsiveness to clopidogrel, that ticagrelor may represent a logical substitute for clopidogrel non-responders, and that platelet inhibition in patients responsive to clopidogrel may be significantly augmented by switching to ticagrelor without reduction in anti-platelet effect.

Findings of the PLATO trial

The PLATO study[13] was a multi-centre, randomized, double-blind, phase III trial that compared ticagrelor with clopidogrel. The study included over 18 000 patients who were admitted to hospital for an ACS, with or without ST-segment elevation. Patients in the ticagrelor group were given a loading dose of 180 mg, followed by a dose of 90 mg twice daily. Patients in the clopidogrel group received a 300 mg loading dose followed by 75 mg daily. Patients undergoing PCI received an additional dose of their study drug at the time of PCI: 300 mg clopidogrel at the investigator's discretion or 90 mg ticagrelor for patients who were undergoing PCI more than 24 h after randomization. In patients undergoing CABG, it was recommended that the study drug be withheld for 5 days in the clopidogrel group and for 24–72 h in the ticagrelor group. All patients received 75–100 mg aspirin daily. The primary efficacy endpoint was the composite of vascular death, myocardial infarction (MI) and stroke, whereas the primary safety endpoint included major bleedings defined according to the study criteria.

The findings for the efficacy and safety endpoint in the PLATO trial are summarized in Table 2. The primary efficacy endpoint occurred significantly less frequently in the ticagrelor group than in the clopidogrel group [9.8 vs. 11.7% at 12 months; hazard ratio (HR) 0.84, 95% confidence interval (95% CI) 0.77–0.92; $P < 0.001$]. This difference was apparent as early as 30 days after the start of treatment and was driven by statistically significant reductions in both vascular death and MI ($P < 0.01$ for both).

The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major bleeding as defined in the trial (11.6 and 11.2%, respectively; $P = 0.43$). There was also no difference in life-threatening or fatal bleeding (5.8% in each group, $P = 0.7$). The two treatment groups also did not differ significantly in the rates of CABG-related major bleedings according to and the thrombolysis in myocardial infarction (TIMI) criteria, despite the fact that ticagrelor was only withheld for 24–72 h before surgery, whereas clopidogrel was withheld for 5 days. However, there was a higher rate of non-CABG-related major bleeding with ticagrelor compared with clopidogrel, according to the study criteria (4.5 vs. 3.8%, $P = 0.03$) and TIMI criteria (2.8 vs. 2.2%, $P = 0.03$). There were also more episodes of intra-cranial bleeding [26 (0.3%) vs. 14 (0.2%), $P = 0.06$), including fatal intra-cranial bleeding [11 (0.1%) vs. 1 (0.01%), $P = 0.02$].

Based on the results of the PLATO study, treating 1000 patients who have ACS with ticagrelor instead of clopidogrel would prevent 11 vascular deaths and 11 MIs at the cost of 6 non-CABG-related major bleeding episodes. The overall results of this study demonstrated that in patients who had ACS, treatment with ticagrelor significantly reduced the primary endpoint of death from vascular causes, MI and stroke, driven by a statistically significant reduction in death from vascular causes and MI, without an increase in the rate of overall major bleeding, but with an increase in the rate of non-procedure-related bleeding.

Subgroups from the PLATO trial

Invasive management

Similar to the primary analysis, in ACS patients who underwent an invasive strategy (72%, $n = 13\,408$), ticagrelor therapy was associated with a significant reduction in the occurrence of the primary endpoint (16% reduction, $P = 0.0025$), MI (20% reduction, $P = 0.0023$), and all cause morality (19% reduction, $P = 0.0103$).[26] However, there was a non-significant

Table 2 Results for efficacy and safety endpoints in the PLATO trial

Efficacy endpoints					Safety endpoints				
	Ticagrelor (%)	Clopidogrel (%)	HR (95% CI)	*P*-value		Ticagrelor (%)	Clopidogrel (%)	HR (95% CI)	*P*-value
Primary endpoint	9.8	11.7	0.84 (0.77–0.92)	<0.001	Primary endpoint	11.6	11.2	1.04 (0.95–1.13)	0.43
MI	5.8	6.9	0.84 (0.75–0.95)	0.005	MB-SC	7.9	7.7	1.03 (0.93–1.15)	0.57
Death from vascular causes	4.0	5.1	0.79 (0.69–0.91)	0.001	MB-TIMI	8.9	8.8	1.00 (0.91–1.11)	0.96
Death from any cause	4.5	5.9	0.78 (0.69–0.89)	<0.001	Life threatening or fatal bleeding, SC	5.8	5.8	1.03 (0.90–1.16)	0.70
Stroke	1.5	1.3	1.17 (0.91–1.52)	0.22	Secondary efficacy endpoint				
Definite ST	1.3	1.9	0.67 (0.50–0.95)	0.009	Non-CABG MB, SC	4.5	3.8	1.19 (1.02–1.38)	0.03
Probable or definite ST	2.2	2.9	0.75 (0.59–0.95)	0.02	Non-CABG MB, TIMI	2.8	2.2	1.25 (0.3–1.53)	0.03
Possible, probable or definite ST	2.9	3.8	0.77 (0.62–0.95)	0.01	CABG MB, SC	5.3	5.8	0.95 (0.85–1.06)	0.32

SC, study criteria; MB, major bleeding.

increase in stroke (8% increase, $P=0.646$). 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 enrolment. Both primary efficacy endpoint events and stent thrombosis were significantly reduced by ticagrelor vs. clopidogrel therapy whether subjects received a $\geqslant$600 mg or a <600 mg clopidogrel loading dose within 24 h pre- or post-study enrolment.[26]

Non-invasive management

Of 18 624 participants in the PLATO trial, 5216 (28%) were specified as planned for non-invasive management.[27] The majority of these patients (60%) were treated with only medical therapy throughout the study period. They were older, more frequently of female gender with diabetes and hypertension than patients undergoing a planned invasive strategy. The high risk profile of conservatively treated patients is confirmed by the higher overall mortality observed in such patients than in those treated invasively (Figure 1). Ticagrelor was very effective in reducing overall mortality in such population with 2.1% absolute risk reduction (6.1 vs. 8.2%, HR 0.75, 95% CI 0.61–0.93).[27]

Patients undergoing CABG

In the PLATO trial, 1899 patients (10%) underwent CABG. Cardiac surgery was performed in 782 patients for whom an initial invasive strategy was planned during admission. The recently published results in this population however, refer to 1261 patients with the last intake of study drug within 7 days before surgery.[28] Median age was 64 years and 79% were men. The primary endpoint was 10.6% in the ticagrelor arm and 13.1% in the clopidogrel arm patients (HR 0.84, 95% CI 0.60–1.16). Cardiovascular death was significantly reduced in ticagrelor-treated, as compared with clopidogrel-treated patients (4.1 vs. 7.9%, $P=0.01$), as well as all-cause death (4.7 vs. 9.7%, $P=0.01$). Interestingly, the mortality reduction was evident for patients with last intake of study drug from 2 to 5 days before surgery. Bleedings were similar in the two groups, whatever definition was used.

Diabetes

In the pre-specified diabetes substudy of the PLATO trial, based on admission levels of haemoglobin A1c, ticagrelor treatment was associated with a

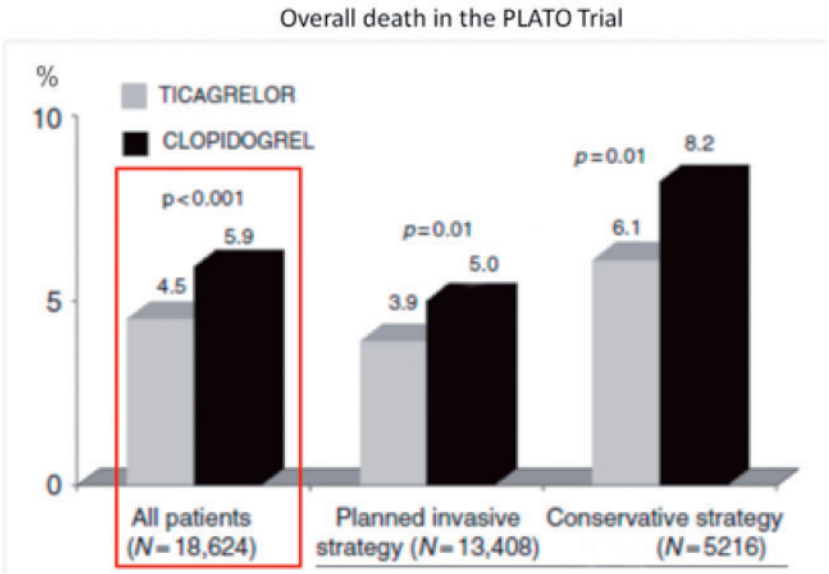

Figure 1. All-cause death in the ticagrelor and clopidogrel arms of the PLATO trial. Percentages are Kaplan–Meier estimates of the rate of the endpoint at 12 months. Mortality rates are reported in the overall population, in subgroups of patients undergoing either planned invasive or conservative strategy, adapted from De Servi *et al.*[33]

12% reduction in the primary composite endpoint 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 bleedings (HR 0.95, 95% CI 0.81–1.12). These benefits were seen irrespective of diabetic status, insulin treatment and glycaemic control. However, the reduction in primary end point occurrence was more pronounced in patients with a HbA1c level above the median (HR 0.80, 95% CI 0.70–0.91).[29]

Renal insufficiency

Ticagrelor therapy was associated with 23% reduction in the primary endpoint (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% relative risk reduction in patients with normal renal function (7.9 vs. 8.9%, HR 0.90; 95% CI 0.79–1.02).[30] 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.

Geographic region

Ruff *et al.*[31] found a consistent reduction in ischaemic events, increased bleeding and a favourable net clinical outcome with prasugrel, another more potent anti-platelet agent, compared with clopidogrel throughout the regions of the world and in both developed and developing countries, despite differences in patient demographics, procedural techniques, medical device use, and adjunctive medications. On the contrary, a significant interaction was observed between treatment and region ($P = 0.045$) in the PLATO trial, with less effect in North America than in the rest of the world.[32] Although a play of chance could not be excluded, only aspirin dose, that was higher in USA than in the other countries, explained a substantial fraction of the regional interaction. Moreover, high dosage ($\geqslant 300$ mg/day) was associated with a higher hazard ratio for the primary endpoint with ticagrelor as compared with clopidogrel in both the USA and the rest of the world. Although other pre-randomization or post-randomization factors were excluded as explanations, it must be noticed that there were profound differences in patient characteristics and modality of treatment between USA and non-US countries.[33] The great majority of enrolled patients in the USA were non-ST-elevation MI (NSTEMI) patients, with a lower representation of ST-elevation MI (STEMI) than in non-US countries. Concerns about the potential risk of high dose aspirin and ticagrelor are addressed in a Food and Drug Administration (FDA) boxed warning for ticagrelor which states: 'after initial dosing, clinicians should use aspirin doses of 75–100 mg/day'.

Ongoing trials

Several unanswered questions regarding ticagrelor therapy are addressed in the ongoing clinical studies.

The PrEvention with ticaGrelor of secondAry thrombotic events in high-riSk patients with prior acUte coronary Syndrome-thrombolysis in myocardial infarction 54 trial (PEGASUS-TIMI 54) investigated the effectiveness of ticagrelor in comparison with placebo on a background of aspirin therapy in preventing cardiovascular events in 21 000 patients with history of MI between 1 and 3 years ago with at least one additional risk factor, including age $\geqslant$65 years old, diabetes requiring medication, documented history of second prior myocardial infarction (>1 year ago), angiographic evidence of multi-vessel coronary artery disease and/or chronic, non-end stage renal dysfunction.[34] In this randomized, double-blind, three-arm, parallel-group, international, multi-centre study patients will be assigned to either ticagrelor 60 or 90 mg twice daily or placebo. The primary efficacy endpoint for the Pegasus-TIMI 54 study is the composite of cardiovascular death, non-fatal MI or non-fatal stroke.

The Administration of Ticagrelor in the cardiac catheterization Laboratory or in the Ambulance for New sT-elevation myocardial Infarction to open the Coronary artery trial (ATLANTIC) evaluates 30-day efficacy and safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in 1770 patients with ST-segment elevation MI planned for PCI.[35] According to the study hypothesis, initiation of ticagrelor as early as in the ambulance setting leads to a rapid reperfusion of the infarct-related artery therefore, facilitating PCI and optimizing the outcome for the patient. The ATLANTIC trial is designed as a randomized, parallel-group, double-blind, placebo-controlled study. Based on the result of randomization, patients receive a loading dose of 180 mg ticagrelor for the pre-hospital administration and placebo for in-hospital administration or a placebo for pre-hospital administration and 180 mg ticagrelor loading dose for in-hospital administration. All study participants continue on ticagrelor 90 mg twice daily (BID) and are followed in study for 30 days post-randomization. TIMI flow grade 3 of MI culprit vessel at initial angiography and ST-segment resolution up to pre-PCI $\geqslant$70% were selected as primary study endpoints.

The Ticagrelor and Aspirin for the Prevention of cardiovascular events after Coronary Artery Bypass Surgery trial (TAP-CABG) is a randomized, double-blind, parallel-group, single-centre study aimed to assess safety and efficacy of ticagrelor co-administered with aspirin for the prevention of cardiovascular events after CABG.[36] In this study, 244 patients will be assigned to receive either ticagrelor 90 mg BID or placebo BID starting within 48 h of surgery. The primary efficacy endpoint is the composite of all-cause mortality, MI, stroke or repeat revascularization within 1 year following CABG, whereas secondary endpoints include the individual endpoints of all-cause mortality, cardiovascular death, MI, stroke, repeat revascularization.

The most burning, still open, question is a direct comparison of clinical outcomes in ACS patients treated with either ticagrelor or prasugrel. Furthermore, future studies are warranted to assess the benefits of ticagrelor in older patients being at high risk for bleeding and often under-represented in clinical trials. Furthermore, the exact duration of dual anti-platelet therapy with aspirin and ticagrelor in patients undergoing invasive management with coronary stent implantation and the optimal anti-coagulant regimens in combination with aspirin and ticagrelor deserve further investigation as well. Therapy with ticagrelor and bivalirudin in patients treated with PCI may appear an appealing strategy with maintained protection from ischaemic events and potentially lower risk of bleeding complications in comparison with the combination of clopidogrel, unfractionated heparin and glycoprotein IIb/IIIa inhibitor.

Optimal anti-platelet drug in ACS: conclusive comments

New platelet adenosine P2Y12 antagonists have successfully overcome many limitations of clopidogrel and have further improved prognosis of ACS patients. Therefore, both ticagrelor and prasugrel were approved in Europe and in the USA and their use in the setting of ACS is currently recommended by international guidelines.[37–39] Such recommendations correspond with the results of meta-analysis by Navarese *et al.*[40] assessing ischaemic and bleeding complications with new, compared with standard, ADP-antagonist regimens in the ACS setting. Navarese and colleagues observed significant reductions in mortality [odds ratio (OR) 0.87; 95% CI 0.79–0.95; $P=0.002$] (Figure 2), recurrent MI (OR 0.80; 95% CI 0.74–0.87; $P<0.0001$) and definite in-stent thrombosis (OR 0.52; 95% CI 0.43–0.63; $P<0.0001$) attributed to therapy with new oral anti-platelet regimens. In addition, there were no significant differences in major bleeding complications with new platelet P2Y12 blockers as compared with standard-dose clopidogrel (OR 1.06; 95% CI 0.96–1.17; $P=0.25$).[40]

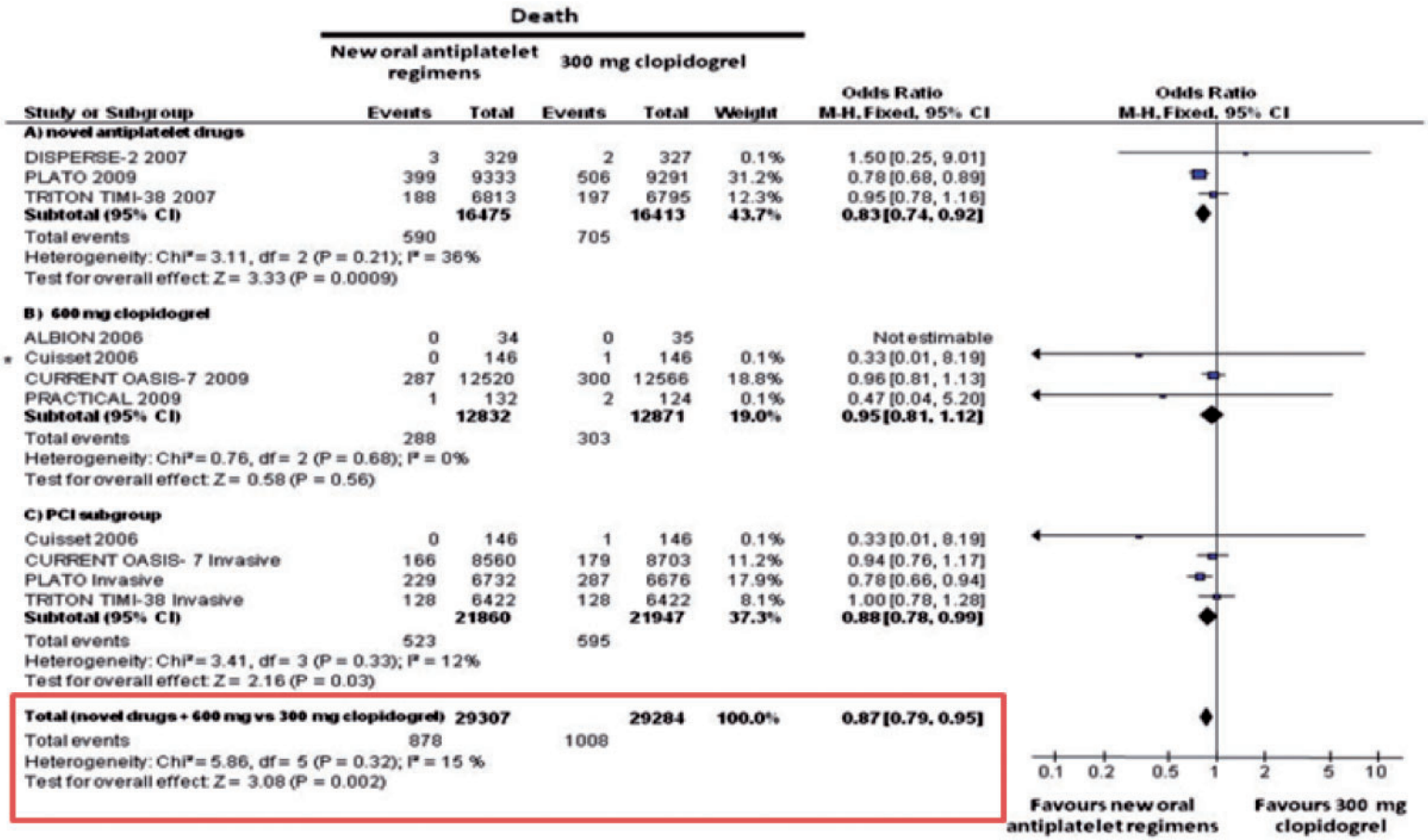

Figure 2. Pre-specified meta-analysis for overall mortality in the group of novel anti-platelet drugs ticagrelor and prasugrel (**A**), 600 mg of clopidogrel (**B**) and PCI subgroup (**C**); ORs and 95% CI are reported. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; *cardiovascular mortality, adapted from Navarese *et al.*[40]

The favourable outcomes of ticagrelor in the PLATO trial were seen in a wide range of patients, including those managed invasively and conservatively and those with and without ST-segment elevation ACS. The ability of ticagrelor to reduce both vascular death and MI is noteworthy, because neither high-dose clopidogrel nor prasugrel have demonstrated vascular mortality reduction in the management of ACS patients. Additionally, prasugrel is contra-indicated in patients with a history of stroke or transient ischaemic attack, as there was an increased risk of major bleeding in this population.

To sum up, ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) is now recommended for all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy and including those pre-treated with clopidogrel, whereas prasugrel (60 mg loading dose, 10 mg daily maintenance dose) is advised only for P2Y12-inhibitor-naive patients in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.

Acknowledgements

The present contribution is a project of Systematic Investigation and Research on Interventions and Outcomes (SIRIO)-MEDICINE, a group of senior scientists and fellows collaborating world-wide to pursue research and innovation in medicine.

Conflict of interest: E.P.N. and M.K. received honoraria from Astra Zeneca not related to the present contribution.

References

1. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, *et al.* Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. *Circulation* 2004; **110**:1202–8.
2. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; **107**:2908–13.
3. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol* 2005; **45**:246–51.
4. Kozinski M, Bielis L, Wisniewska-Szmyt J, Boinska J, Stolarek W, Marciniak A, *et al.* Diurnal variation in platelet inhibition by clopidogrel. *Platelets* 2011; **22**:579–87.
5. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tokés-Füzesi M, Magyarlaki T, *et al.* Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. *Am Heart J* 2010; **160**:543–51.
6. Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese EP, Goch A. Genetic determinants of platelet response to clopidogrel. *J Thromb Thrombolysis* 2011; **32**:459–66.
7. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, *et al.* Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009; **360**:354–62.
8. Bates ER, Lau WC, Angiolillo DJ. Clopidogrel-drug interactions. *J Am Coll Cardiol* 2011; **57**:1251–63.
9. van Giezen JJJ. Optimizing platelet inhibition. *Eur Heart J Suppl* 2008; **10(Suppl. D)**:D23–9.
10. Ramaraj R, Movahed MR, Hashemzadeh M. Novel antiplatelet agent ticagrelor in the management of acute coronary syndrome. *J Interv Cardiol* 2011; **24**:199–207.
11. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, *et al.* Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009; **120**:2577–85.
12. Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, *et al.* Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation* 2010; **121**:1188–99.
13. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**:1045–57.
14. Serebruany VL. Mortality benefit in PLATO cannot be explained by antiplatelet properties of ticagrelor. *Cardiology* 2010; **117**:231–3.
15. Serebruany VL. The TRITON versus PLATO trials: differences beyond platelet inhibition. *Thromb Haemost* 2010; **103**:259–61.
16. Serebruany VL, Atar D. The PLATO trial: do you believe in magic? *Eur Heart J* 2010; **31**:764–7.
17. Wihlborg AK, Wang L, Braun OO, Eyjolfsson A, Gustafsson R, Gudbjartsson T, *et al.* ADP receptor P2Y12 is expressed in vascular smooth muscle cells and stimulates contraction in human blood vessels. *Arterioscler Thromb Vasc Biol* 2004; **24**:1810–15.
18. Grzesk G, Kozinski M, Navarese EP, Krzyzanowski M, Grzesk E, Kubica A, *et al.* Ticagrelor, but not clopidogrel and prasugrel, prevents ADP-induced vascular smooth muscle cell contraction: a placebo-controlled study in rats. *Thromb Res* 2012; **130**:65–9.
19. Högberg C, Svensson H, Gustafsson R, Eyjolfsson A, Erlinge D. The reversible oral P2Y12 antagonist AZD6140 inhibits ADP-induced contractions in murine and human vasculature. *Int J Cardiol* 2010; **142**:187–92.
20. Ohman J, Kudira R, Albinsson S, Olde B, Erlinge D. Ticagrelor induces adenosine triphosphate release from human red blood cells. *Biochem Biophys Res Commun* 2012; **418**:754–8.
21. Serebruany VL. Adenosine release: a potential explanation for the benefits of ticagrelor in the PLATelet inhibition and clinical outcomes trial? *Am Heart J* 2011; **161**:1–4.

22. van Giezen JJ, Sidaway J, Glaves P, Kirk I, Björkman JA. Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. *J Cardiovasc Pharmacol Ther* 2012; **17**:164–72.

23. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, *et al.* Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the Platelet Inhibition and Patient Outcomes [PLATO] pulmonary function substudy). *Am J Cardiol* 2011; **108**:1542–6.

24. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, *et al.* Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011; **32**:2945–53.

25. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, *et al.* Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007; **50**:1844–51.

26. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, *et al.* Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010; **375**:283–93.

27. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011; **342**:d3527.

28. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol* 2011; **57**:672–84.

29. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, *et al.* Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the Platelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2010; **31**:3006–16.

30. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, *et al.* Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2010; **122**:1056–67.

31. Ruff CT, Giugliano RP, Antman EM, Murphy SA, Lotan C, Heuer H, *et al.* For the TRITON–TIMI 38 Investigators. Safety and efficacy of prasugrel compared with clopidogrel indifferent regions of the world. *Int J Cardiol* 2012; **155**:424–9.

32. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, *et al.* Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011; **124**:544–54.

33. De Servi S, Navarese EP, D'Urbano M, Savonitto S. Treating acute coronary sindromes with new antiplatelet drugs: the mortality issue with prasugrel and ticagrelor. *Curr Med Res Opin* 2011; **27**:2117–22.

34. *Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS)*. http://clinicaltrials.gov/ct2/show/NCT01225562 (30 September 2012, date last accessed).

35. *A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention (PCI) (ATLANTIC)*. http://clinicaltrials.gov/ct2/show/NCT01347580?term=ticagrelor&rank=5 (30 September 2012, date last accessed).

36. *Ticagrelor and Aspirin for the Prevention of Cardiovascular Events After Coronary Artery Bypass Surgery (TAP-CABG)*. http://clinicaltrials.gov/ct2/show/NCT01373411?term=ticagrelor&rank=16 (30 September 2012, date last accessed).

37. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, *et al.* ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**:2999–3054.

38. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, *et al.* Guidelines on myocardial revascularization. *Eur Heart J* 2010; **31**:2501–55.

39. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE , Jr *et al.* 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (Updating the 2007 guideline and replacing the 2011 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012; **60**:645–81.

40. Navarese EP, Verdoia M, Schaffer A, Suriano P, Kozinski M, Castriota F, *et al.* Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials. *QJM* 2011; **104**:561–9.