RESEARCH

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

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Abstract

Objective To evaluate efficacy and safety outcomes in patients in the PLATelet inhibition and patient Outcomes (PLATO) trial who at randomisation were planned for a non-invasive treatment strategy.

Design Pre-specified analysis of pre-randomisation defined subgroup of prospective randomised clinical trial.

Setting 862 centres in 43 countries.

Participants 5216 (28%) of 18 624 patients admitted to hospital for acute coronary syndrome who were specified as planned for non-invasive management.

Interventions Randomised treatment with ticagrelor (n=2601) versus clopidogrel (2615).

Main outcome measurements Primary composite end point of cardiovascular death, myocardial infarction, and stroke; their individual components; and PLATO defined major bleeding during one year.

Results 2183 (41.9%) patients had coronary angiography during their initial hospital admission, 1065 (20.4%) had percutaneous coronary intervention, and 208 (4.0%) had coronary artery bypass surgery. Cumulatively, 3143 (60.3%) patients had been managed non-invasively by the end of follow-up. The incidence of the primary end point was lower with ticagrelor than with clopidogrel (12.0% (n=295) *v* 14.3% (346); hazard ratio 0.85, 95% confidence interval 0.73 to 1.00; P=0.04). Overall

mortality was also lower (6.1% (147) *v* 8.2% (195); 0.75, 0.61 to 0.93; P=0.01). The incidence of total major bleeding (11.9% (272) *v* 10.3% (238); 1.17, 0.98 to 1.39; P=0.08) and non-coronary artery bypass grafting related major bleeding (4.0% (90) *v* 3.1% (71); 1.30, 0.95 to 1.77; P=0.10) was numerically higher with ticagrelor than with clopidogrel.

Conclusions In patients with acute coronary syndrome initially intended for non-invasive management, the benefits of ticagrelor over clopidogrel were consistent with those from the overall PLATO results, indicating the broad benefits of P2Y12 inhibition with ticagrelor regardless of intended management strategy.

Trial registration Clinical trials NCT00391872.

Introduction

In patients with non-ST elevation acute coronary syndrome with moderate to high risk characteristics, current guidelines recommend an invasive strategy with angiography followed by percutaneous coronary intervention or coronary artery bypass grafting if appropriate.[1 2] However, the Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial supports a conservative, non-invasive strategy with intensive medical treatment and invasive procedures only in case of signs or symptoms of ischaemia,[3] and this is

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considered an appropriate treatment strategy for non-ST elevation acute coronary syndrome in patients at lower risk.[1] A considerable proportion of patients do not have angiography or revascularisation during the initial hospital admission.[4 5] However, dual antiplatelet treatment with aspirin and the P2Y12 inhibitor clopidogrel is recommended for 12 months in all patients with non-ST elevation acute coronary syndrome, as both patients who had revascularisation and those managed medically derived benefit in post hoc analyses from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.[6 7] No clinical trial has prospectively evaluated P2Y12 inhibitors in patients intended for an initial non-invasive management strategy.

The PLATelet inhibition and patient Outcomes (PLATO) trial found that the reversibly binding oral P2Y12-inhibitor ticagrelor was superior to clopidogrel for the prevention of the composite end point of death from vascular causes, myocardial infarction, and stroke, as well as vascular death in itself and total death, without an increase in major bleeding, in a broad population of patients with acute coronary syndromes starting treatment as soon as possible after hospital admission.[8] A pre-specified objective of the PLATO trial was to compare ticagrelor and clopidogrel in the stratum of patients with non-ST elevation acute coronary syndrome whom, at randomisation, the treating physician stated as planned for a non-invasive treatment strategy.[9] Selection of a strategy before randomisation provides the opportunity to do a proper statistical comparison between the groups.[10]

Methods

Design overview

The PLATO trial enrolled 18 624 patients from 43 countries between October 2006 and July 2008. Details of the design, patients, outcome definitions, and results have been published.[8 9] Patients were included if they were admitted to hospital with ST segment elevation acute coronary syndrome scheduled for primary percutaneous coronary intervention or non-ST segment elevation acute coronary syndrome, with onset of symptoms during the previous 24 hours. For non-ST segment elevation acute coronary syndrome, at least two of the following three criteria were required: ST segment depression or transient elevation of at least 1 mm in two or more contiguous leads; a positive biomarker indicating myocardial necrosis; and one additional risk indicator, including age over 60 years, previous myocardial infarction or coronary artery bypass grafting, carotid artery disease, previous ischaemic stroke, transient ischaemic attack, carotid stenosis, cerebral revascularisation, diabetes mellitus, peripheral artery disease, or chronic renal dysfunction (creatinine clearance <60 mL/min). The most important exclusion criteria included contraindication to clopidogrel, fibrinolytic treatment within 24 hours, need for oral anticoagulation treatment, need for dialysis, and clinically important anaemia or thrombocytopenia.

Setting and participants

At the time of randomisation, the treating physician designated patients as planned for initial invasive management or initial conservative management in the interactive voice randomisation system. The investigator answered the following question just before randomisation: "Concerning this patient, do you intend to use an invasive strategy, with coronary angiography followed by revascularisation based on the coronary anatomy, or a non-invasive strategy?" These designations were considered to be non-binding but created statistically proper pre hoc subgroups

for this analysis. After randomisation, subsequent decisions to do angiography and revascularisation based on changes in the patients' clinical statuses were not restricted.

Randomisation and interventions

Patients were randomly assigned to ticagrelor or clopidogrel. Ticagrelor was given in a loading dose of 180 mg followed by 90 mg twice daily. Patients randomised to clopidogrel who had not received an open label loading dose and had not been taking clopidogrel for at least five days before randomisation received a 300 mg loading dose of clopidogrel study drug followed by 75 mg daily. Others continued a maintenance dose of 75 mg clopidogrel daily. All patients received acetylsalicylic acid (aspirin) unless they were intolerant of it. The randomised treatment continued for a minimum of six months and a maximum of 12 months; the median length of study treatment in the overall population was 9.1 months.

Outcomes and follow-up

The primary efficacy end point was the composite of death from vascular causes, myocardial infarction, or stroke.[8 9] Secondary end points included the individual components of the primary end point; all cause mortality; non-vascular mortality; death from vascular causes or myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, or other arterial thrombotic event; stroke subclassified as ischaemic, haemorrhagic, and unknown. Death from vascular causes included cardiovascular deaths, cerebrovascular deaths, or any other death for which no non-vascular cause was clearly documented.

The primary safety end point was PLATO defined total major bleeding. Definitions of bleeding used in the trial have been previously published.[9] An independent central adjudication committee, unaware of the group assignments, adjudicated all primary and secondary end points and major and minor bleeding events. TIMI major bleeding was programmed from the electronic case report form, using a cut-off point of ≥5 g/dL haemoglobin, but did not necessarily require clinical evidence of excessive bleeding after coronary artery bypass grafting.

Statistical analysis

The analysis was a pre-specified stratum of the total trial. We used univariable Cox proportional hazards models to analyse the primary and secondary end point results. We present Kaplan-Meier curves for each treatment group for selected end points and procedures. We present estimates of the end points for each treatment group as the Kaplan-Meier rates at 360 days and total number of events during follow-up. When we analysed subgroups, we derived the P value for interaction from a Cox model containing subgroup membership, treatment, and the subgroup by treatment interaction. We used the intention to treat principle and SAS version 9.2 for all analyses. We used a P value of 0.05 as a critical value determining statistical significance of the overall treatment differences.

Results

Patients

The PLATO trial recruited 18 624 patients with acute coronary syndrome (with or without ST elevation) from 862 centres in 43 countries between October 2006 and July 2008. At the time of randomisation, 5216 (28%) patients were specified by the investigator as being intended for a non-invasive treatment strategy (fig 1). Of these, 2601 patients were randomised to

ticagrelor and 2615 to clopidogrel. The median age was 65 years, and 36.5% were women (table 1). The median time from onset of symptoms to randomisation was 16.6 (interquartile range 9.1-22.0) hours, and the duration of the randomised treatment was 276 (175-365) days. Despite the initial intent for a non-invasive approach, 2183 (41.9%) patients had coronary angiography during the initial hospital admission, at a median of 51 hours to in-hospital angiography; 1065 (20.4%) had in-hospital percutaneous coronary intervention, at a median of 70 hours; and 208 (4.0%) had in-hospital coronary artery bypass grafting at a median of 12 days (table 2). At the end of follow-up, 2040 (40%) of the patients had had a revascularisation procedure; 1514 (72.6%) of these had percutaneous coronary intervention only, 559 (25.8%) had coronary artery bypass grafting only, and 33 (1.6%) had both (fig 2). Most patients were diagnosed as having non-ST elevation myocardial infarction and unstable angina at discharge, but 451 patients (218 patients in the ticagrelor group and 233 in the clopidogrel group) had ST elevation myocardial infarction as their final diagnosis (table 2 and fig 1).

Compared with patients with intended invasive management, patients with intended non-invasive management were older, were more often women, and more often had cardiovascular risk factors such as diabetes, previous myocardial infarction, heart failure, stroke, and renal and peripheral artery disease (table 1).[11] Furthermore, they had a higher average Thrombolysis In Myocardial Infarction (TIMI) non ST-elevation myocardial infarction risk score but less often had a positive troponin test (table 1). On the basis of the intended non-invasive management, unfractionated heparin, glycoprotein IIb/IIIa inhibitors, and bivalirudin were used less often but fondaparinux and low molecular weight heparin were used more often. During hospital admission, the proportion of patients who had coronary angiography was less than half, percutaneous coronary intervention about a quarter, and coronary artery bypass grafting slightly more than two thirds those of the invasive cohort (table 2).

Outcomes

The incidence of the primary composite end point was significantly lower with ticagrelor than with clopidogrel (14.3% *v* 12.0%; hazard ratio 0.85, 95% confidence interval 0.73 to 1.00; P=0.04). All cause mortality was reduced from 8.2% to 6.1% (hazard ratio 0.75, 0.61 to 0.93; P=0.01) and cardiovascular mortality from 7.2% to 5.5% (0.76, 0.61 to 0.96; P=0.02) with use of ticagrelor rather than clopidogrel. The rate of myocardial infarction and the composite of cardiovascular death and other thromboembolic events did not differ significantly between the groups. Rates of stroke were not significantly different, although numerically more haemorrhagic strokes occurred in the ticagrelor group (table 3).

Compared with patients with intended invasive treatment, patients with intended non-invasive management had an initially lower primary event rate, but the event curves crossed at approximately 30 days and increased more over time (fig 3). The benefit for ticagrelor compared with clopidogrel was consistent between the two cohorts; the hazard ratio was 0.85 (0.85 to 1.00) in the non-invasive cohort and 0.84 (0.75 to 0.94) in the invasive cohort (P for interaction=0.89). The total mortality was higher in the intended non-invasive cohort than in the intended invasive cohort during the entire course of the study (fig 4), but the relative benefit with ticagrelor was consistent (hazard ratio 0.75 (0.61 to 0.93) *v* 0.80 (0.61 to 0.93): P for interaction=0.64).

Bleeding

We found no statistically significant difference in the rates of PLATO defined total major bleeding: 11.9% for ticagrelor treated patients and 10.3% for clopidogrel treated patients (hazard ratio 1.17, 0.98 to 1.39; P=0.08) (fig 5, table 3). Nor did we find any significant difference between the randomised groups when we used the TIMI definition of major bleeding. The incidence of life threatening or fatal major bleedings did not differ between the groups. Numerically more intracranial bleedings occurred in the ticagrelor group, but the difference was not statistically significant. We found a significantly higher incidence of PLATO defined other major bleedings and of the composite of major and minor bleedings in the ticagrelor group owing to a higher incidence of bleedings related to non-coronary artery bypass grafting during long term treatment.

Outcome in subgroups

In the overall PLATO population, 7955 patients had non-ST elevation acute coronary artery syndrome as their final diagnosis. Among these, 2910 (36.6%) patients were intended for non-invasive management at the time of randomisation. The result for ticagrelor compared with clopidogrel in this subgroup was consistent with the overall results in the non-invasive cohort, with non-significant diagnosis by treatment interactions for the primary outcome (P=0.58), mortality (P=0.91), and major bleeding (P=0.90). Among the intended non-invasively managed patients, 87 patients in the ticagrelor group were admitted without persistent ST elevation or new left bundle branch block but had ST elevation myocardial infarction as their final diagnosis compared with 103 patients in the clopidogrel group. Also, among 3948 patients who did not actually have revascularisation during their hospital admission despite the initially intended management strategy (as a post-randomisation decision), ticagrelor reduced the primary outcome compared with clopidogrel, consistent with the overall results, from 15.2% (726) to 12.2% (224) (hazard ratio 0.81, 0.68 to 0.97).

Significant versus insignificant coronary disease among patients who had in-hospital angiography

Of all patients (intended invasive and non-invasive) who had coronary angiography during hospital admission, significant coronary disease, defined as at least one stenosis greater than 50%, was found in 10 755/11 503 (94%) of those who were intended for invasive management and in 596/674 (89%) of those who were initially intended for non-invasive management. Patients with no significant disease had numerically lower event rates compared with those who were discovered to have significant disease. The primary composite event rate and mortality were consistently numerically lower in the ticagrelor group compared with the clopidogrel group, with no increase in major bleeding, independent of angiographic findings.

Discussion

This substudy of the PLATO trial indicates that treatment with ticagrelor compared with clopidogrel reduces major ischaemic events without significantly increasing major bleeding across the spectrum of management strategies for acute coronary syndrome. The unique design of the trial, with collection of information about the intended management strategy at the time of randomisation, allowed us to investigate the outcome of the randomised treatments in patients with an intended non-invasive treatment strategy without interference from post-randomisation treatment selections. This patient population has been

under-represented in most clinical trials, and no other oral platelet inhibitor has been prospectively investigated in the setting of a primary non-invasive management strategy.

Comparison with other studies

The Global Utilisation of Strategies To prevent Occluded arteries IV (GUSTO IV) trial prospectively showed a high level of platelet inhibition achieved with the glycoprotein IIb/IIIa receptor inhibitor abciximab during 24 or 48 hours compared with placebo in patients with non-ST elevation acute coronary syndrome who were intended for initial medical management.[12] However, in contrast to the significant benefit of abciximab that has been shown in patients with acute coronary syndrome having percutaneous coronary intervention, abciximab increased the incidence of bleeding and did not reduce ischaemic end points in this trial that encouraged an early non-invasive management strategy.[13] Clopidogrel versus placebo in addition to aspirin for acute coronary syndrome has not been evaluated prospectively in patients not intended for invasive management. However, the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial showed consistent benefit whether or not revascularisation was actually done.[14] The ongoing TRILOGY (NCT00699998) trial is investigating the efficacy and safety of the thienopyridine prasugrel compared with clopidogrel in patients at high risk selected for medical management of acute coronary syndrome.

In the PLATO trial, 28% of the total patient population and 37% of the patients with a final diagnosis of non-ST elevation acute coronary artery syndrome were designated as planned for initial non-invasive management by the treating physician. Several registries and clinical trials have shown that 30-60% of patients admitted with non-ST elevation acute coronary syndrome in the Western world do not actually have cardiac catheterisation during hospital admission and 45-80% of patients do not have revascularisation.[4 5 15 16] The patients in PLATO intended for non-invasive management had a higher long term event rate than did those intended for invasive management,[11] probably related in part to their high risk profile at baseline. These findings are consistent with registry data and post hoc analyses from clinical trials showing an up to twofold higher event rate compared with patients who have revascularisation.[17] The shape of the event curves for the primary outcome differed between the invasive and non-invasive cohorts, with a higher early event rate in the invasive cohort and crossing event curves reflecting the different distributions of ST elevation and non-ST elevation acute coronary syndrome in the two cohorts and peri-procedural events.

Invasive management

Despite an intended non-invasive strategy at the time of randomisation, approximately half of the patients had coronary angiography, a third had percutaneous coronary intervention, and one tenth had coronary artery bypass grafting during the course of the study for emerging clinical indications. The relative reduction of the primary ischaemic end point and mortality by ticagrelor compared with clopidogrel was independent of the initial pre-randomisation treatment strategy, without any significant increase in major bleeding. Although the results in subgroups based on post-randomisation clinical data and treatment options have to be interpreted with caution, the benefit of ticagrelor compared with clopidogrel was consistent with the overall trial results. Thus, the results were in favour of ticagrelor whether or not revascularisation was actually done post-randomisation and whether or not significant coronary disease was found at any angiography during hospital admission.

Safety

Although rates of PLATO defined overall major bleeding did not differ significantly between the randomised groups, an excess of minor bleedings occurred, particularly of those not related to coronary artery bypass grafting during long term treatment. We also found a numerical increase in intracerebral bleedings, although the numbers were very small. The higher incidence of minor bleedings should be taken into consideration in patients at low risk not intended for invasive treatment, as patients at low risk of thromboembolic events have a low potential benefit from more extensive antithrombotic treatment and bleeding complications tend to accrue over time.

Conclusion and implications

In a population of patients with acute coronary syndrome managed with a planned non-invasive treatment strategy, more intense P2Y12 receptor inhibition with ticagrelor achieved a clinically important reduction in ischaemic events and mortality, but without increasing major bleeding, compared with clopidogrel. These results indicate the broad benefits of intensified P2Y12 inhibition for patients with acute coronary syndrome across management strategies.

What is already known on this topic

Ticagrelor reduced ischaemic events and mortality compared with clopidogrel, with similar major bleeding rates, through 12 months in the PLATO trial

30-60% of patients admitted with non-ST elevation acute coronary syndrome in the Western world do not have cardiac catheterisation during hospital admission, and 45-80% do not have revascularisation

No clinical trial has prospectively reported outcomes with P2Y12 inhibitors among patients intended for initial non-invasive management

What this study adds

In acute coronary syndrome patients initially intended for non-invasive management, ticagrelor achieved a clinically important reduction in ischaemic events and mortality compared with clopidogrel, without increasing major bleeding

The reduction of ischaemic events and mortality by ticagrelor over clopidogrel was consistent in acute coronary syndrome patients with non-ST elevation who did not actually have revascularisation

The benefits of intensified P2Y12 inhibition apply across different management strategies

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Tables

Table 1| Patients' characteristics. Values are percentages (numbers) unless stated otherwise

	Planned non-invasive			
	Ticagrelor (n=2601)	Clopidogrel (n=2615)	Total (n=5216)	Planned invasive (n=13 408)
Demographics				
Median (IQR) age (years)	66 (57-73)	65 (57-73)	65 (57-73)	61 (53-69) (n=13 406)
Age ≥75 years	21.3 (553)	21.2 (555)	21.2 (1108)	13.2 (1770)
Women	36.9 (961)	36.1 (945)	36.5 (1906)	25.2 (3382)
Median (IQR) weight (kg)	78 (69-88) (n=2597)	78 (69-88) (n=2608)	78 (69-88) (n=5205)	80 (70-90) (n=133 63)
Median (IQR) body mass index (kg/m^2)	27.3 (24.6-30.4) (n=2592)	27.4 (24.6-30.4) (n=2603)	27.3 (24.6-30.4) (n=5195)	27.4 (24.8-30.4) (n=133 37)
Cardiovascular risk factors				
Habitual smoker	25.2 (654/2600)	25.8 (675/2614)	25.5 (1329/5214)	39.9 (5349/13 396)
Hypertension	71.8 (1868/2600)	72.4 (1893)	72.1 (3761/5215)	62.9 (8422/13 398)
Dyslipidaemia	47.0 (1223/2600)	45.5 (1191)	46.3 (2414/5215)	46.8 (6275/13 397)
Diabetes mellitus	30.6 (796/2600)	28.9 (757)	29.8 (1553/5215)	23.2 (3109/13 398)
Medical history				
Angina pectoris	59.5 (1547/2600)	58.7 (1536)	59.1 (3083/5215)	39.4 (5275/13 398)
Myocardial infarction	28.9 (752/2600)	30.3 (793)	29.6 (1545/5215)	17.0 (2279/13 398)
Congestive heart failure	11.2 (290/2600)	12.4 (324)	11.8 (614/5215)	3.3 (436/13 398)
Percutaneous coronary intervention	12.5 (325/2600)	12.8 (335)	12.7 (660/5215)	13.7 (1832/13 397)
Coronary artery bypass graft	6.7 (175/2600)	7.4 (194)	7.1 (369/5215)	5.5 (737/13 398)
Transient ischaemic attack	3.9 (101/2600)	4.2 (110)	4.0 (211/5215)	2.1 (288/13 398)
Non-haemorrhagic stroke	5.5 (144/2600)	5.8 (151/2614)	5.7 (295/5214)	3.2 (427/13 398)
Peripheral arterial disease	7.3 (191/2600)	8.0 (210)	7.7 (401/5215)	5.5 (743/13 398)
Chronic renal disease	5.0 (131/2600)	5.5 (143)	5.3 (274/5215)	3.8 (511/13 398)
Physical findings				
Median (IQR) heart rate	72 (64-82) (n=2584)	73 (65-82) (n=2601)	72 (64-82) (n=5185)	74 (64-84) (n=13 231)
Median (IQR) systolic blood pressure	130 (120-150) (n=2584)	130 (120-150) (n=2601)	130 (120-150) (n=5185)	133 (120-150) (n=13 231)
Median (IQR) diastolic blood pressure	80 (70-88) (n=2584)	80 (70-86) (n=2601)	80 (70-87) (n=5185)	80 (70-90) (n=13 231)
Risk indicators				
Troponin positive*	74.5 (1860/2495)	75.4 (1900/2520)	75.0 (3760/5015)	86.9 (11 329/13 042)
ST depression (≥1 mm)	61.7 (1602/2597)	64.0 (1673/2613)	62.9 (3275/5210)	46.4 (6211/13 380)
TIMI NSTE-ACS risk score >2	89.2 (2259/2532)	88.5 (2261/2555)	88.9 (4520/5087)	68.8 (8954/13 006)

IQR=interquartile range; TIMI NSTE-ACS=Thrombolysis In Myocardial Infarction non-ST elevation acute coronary syndrome.

*Positive result on testing for troponin I consisted of troponin I concentration ≥0.08 µg/L for first sample taken, as measured at central laboratory with use of Advia Centaur TnI-Ultra Immunoassay (Siemens).

Table 2| Treatments and procedures during hospital admission. Values are percentages (numbers) unless stated otherwise

	Planned non-invasive			Planned invasive (n=13 408)
	Ticagrelor (n=2601)	Clopidogrel (n=2615)	Total (n=5216)	
Type of acute coronary syndrome* at discharge				
STEMI	8.4 (218/2594)	8.9 (233/2608)	8.7 (451/5202)	49.1 (6575/13 380)
NSTEMI	55.6 (1441/2594)	56.3 (1469/2608)	55.9 (2910/5202)	37.7 (5045/13 380)
Unstable angina pectoris or other	36.0 (935/2594)	34.7 (906/2608)	35.4 (1841/5202)	13.2 (1760/13 380)
Antithrombotic treatment during initial hospital admission				
Aspirin	95.2 (2475/2600)	94.7 (2472/2611)	94.9 (4947/5211)	98.0 (13 128/13 390)
Unfractionated heparin	37.5 (975)	36.7 (959)	37.1 (1934)	66.0 (8844)
Low molecular weight heparin	64.1 (1668)	63.6 (1663)	63.9 (3331)	47.1 (6318)
Fondaparinux	5.0 (131)	4.8 (125)	4.9 (256)	1.9 (253)
Bivalirudin	0.3 (8)	0.4 (10)	0.3 (18)	2.7 (356)
Glycoprotein IIb/IIIa inhibitor	5.6 (145)	6.2 (162)	5.9 (307)	35.3 (4730)
Other drug from randomisation to end of study				
β blocker	85.0 (2212)	83.9 (2194)	84.5 (4406)	85.7 (11 489)
ACE inhibitor/angiotensin receptor blocker	83.2 (2162/2600)	82.8 (2162/2611)	83.0 (4324/5211)	86.9 (11 637/13 390)
Cholesterol lowering drug (statin)	89.9 (2337)	89.7 (2345)	89.8 (4682)	95.3 (12 778)
Calcium antagonist	29.5 (767)	30.1 (786)	29.8 (1553)	21.7 (2905)
Diuretic	48.9 (1272/2600)	46.8 (1222/2611)	47.9 (2494/5211)	38.9 (5213/13 390)
Proton pump inhibitor	39.9 (1038)	39.0 (1020)	39.5 (2058)	54.0 (7237)
Invasive procedures				
Coronary angiography:				
Before discharge	41.8 (1088)	41.9 (1095)	41.9 (2183)	96.9 (12 987)
Any time during follow-up	55.6 (1447)	55.4 (1448)	55.5 (2895)	97.6 (13 085)
Median (IQR) time to angiography (hours)	89 (26-266) (n=1445)	92 (26-235) (n=1446)	91 (26-240) (n=2891)	0.6 (0.1-3.8) (n=13 083)
Percutaneous coronary intervention (PCI):				
Before discharge	20.3 (528)	20.5 (537)	20.4 (1065)	76.8 (10 298)
Any time during follow-up	28.4 (738)	29.7 (776)	29.0 (1514)	78.0 (10 463)
Median (IQR) time to PCI (hours)	136 (40-379) (n=738)	144 (42-391) (n=776)	141 (41-383) (n=1514)	0.8 (0.3-3.0) (n=10 462)
Coronary artery bypass grafting (CABG):				
Before discharge	4.2 (108)	3.8 (100)	4.0 (208)	5.7 (762)
Any time during follow-up	11.0 (287)	10.4 (272)	10.7 (559)	10.0 (1340)
Median (IQR) time to CABG (hours)	609 (306-1682) (n=287)	642 (308-1852) (n=272)	623 (307-1742) (n=559)	240 (92-1145) (n=1340)

ACE=angiotensin converting enzyme; IQR=interquartile range; NSTEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction.

*Defined by final diagnosis of index event.

Table 3| Efficacy and safety of treatment. Values are Kaplan-Meier estimates of percentage rate of end point (numbers) at 12 months

	Ticagrelor (n=2601)	Clopidogrel (n=2615)	Hazard ratio (95% CI)	P value*
Primary objective				
Cardiovascular death + myocardial infarction (excluding silent) + stroke	12.0 (295)	14.3 (346)	0.85 (0.73 to1.00)	0.045
Secondary objectives				
Myocardial infarction	7.2 (176)	7.8 (187)	0.94 (0.77 to 1.15)	0.555
Cardiovascular death	5.5 (132)	7.2 (173)	0.76 (0.61 to 0.96)	0.019
All cause death	6.1 (147)	8.2 (195)	0.75 (0.61 to 0.93)	0.010
Non-cardiovascular death	0.6 (15)	1.0 (22)	0.68 (0.35 to 1.31)	0.252
Stroke:	2.1 (50)	1.7 (37)	1.35 (0.89 to 2.07)	0.162
Ischaemic	1.5 (37)	1.4 (32)		0.530
Haemorrhagic	0.5 (11)	0.2 (4)		0.069
Unknown	0.2 (5)	0.06 (1)		0.124
Cardiovascular death + myocardial infarction + stroke + composite ischaemic events† + other arterial thrombotic events	18.6 (460)	20.3 (492)	0.94 (0.82 to 1.06)	0.309
Primary safety objective				
Total major bleeding	11.9 (272)	10.3 (238)	1.17 (0.98 to 1.39)	0.079
Life threatening or fatal bleeding	5.5 (125)	5.6 (129)	0.99 (0.77 to 1.26)	0.911
Intracranial bleeding	0.5 (11)	0.2 (4)	2.83 (0.90 to 8.90)	0.075
Other major bleeding	6.8 (154)	4.9 (114)	1.38 (1.09 to 1.76)	0.009
Secondary safety objectives—components of major bleeding events				
Non-CABG related	4.0 (90)	3.1 (71)	1.30 (0.95 to 1.77)	0.103
CABG related	8.3 (189)	7.5 (174)	1.11 (0.90 to 1.36)	0.335
Coronary procedure related	9.2 (211)	8.2 (191)	1.13 (0.93 to 1.37)	0.231
Non-coronary procedure related	0.04 (1)	0.4 (7)	0.15 (0.02 to 1.19)	0.072
Secondary safety objectives—major or minor bleeding events				
Total	16.4 (378)	14.4 (332)	1.17 (1.01 to 1.36)	0.0358
Non-CABG related	8.3 (190)	6.7 (151)	1.29 (1.04 to 1.60)	0.0182
CABG related	8.9 (202)	8.5 (196)	1.05 (0.86 to 1.28)	0.6341
Coronary procedure related	10.8 (250)	10.0 (235)	1.09 (0.91 to 1.30)	0.3657
Non-coronary procedure related	0.5 (11)	0.8 (16)	0.70 (0.33 to 1.51)	0.3632
Other safety objectives				
TIMI defined cut-off point for major bleeding:				
Total	7.9 (181)	7.2 (164)	1.13 (0.91 to 1.39)	0.270
Non-CABG related	2.8 (61)	2.2 (47)	1.33 (0.91 to 1.94)	0.142
CABG related	5.4 (124)	5.3 (122)	1.03 (0.80 to 1.33)	0.799
Transfusion of blood products:				
PRBCs or whole blood	7.6 (174)	7.2 (172)	1.03 (0.83 to 1.27)	0.804
Platelets	1.3 (30)	1.2 (27)	1.13 (0.67 to 1.90)	0.645
Fresh frozen plasma	2.4 (55)	2.2 (50)	1.12 (0.76 to 1.64)	0.565

CABG=coronary artery bypass grafting; PRBC=packed red blood cells; TIMI=Thrombolysis In Myocardial Infarction.

*From univariate Cox model.

†Severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, and transitory ischaemic attack.
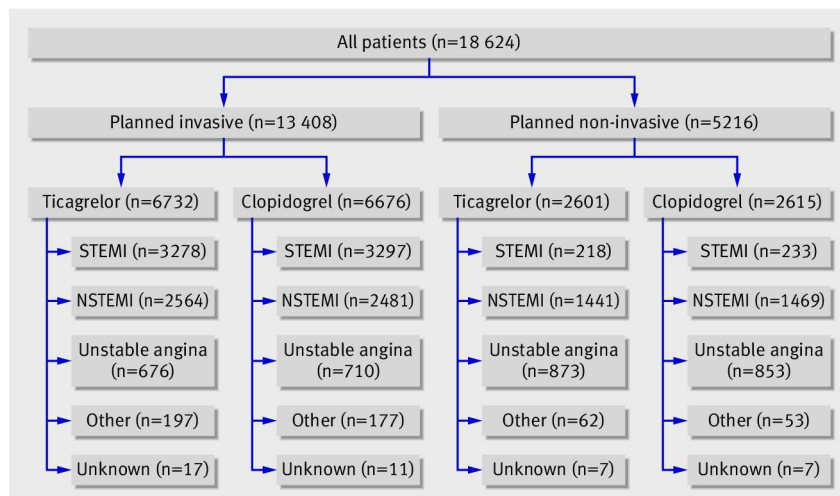
Figures

Fig 1 Flowchart showing number of patients intended for invasive and non-invasive management at time of randomisation, randomised to ticagrelor or clopidogrel, and final diagnosis at discharge. NSTEMI=non-ST segment myocardial infarction; STEMI=ST segment myocardial infarction
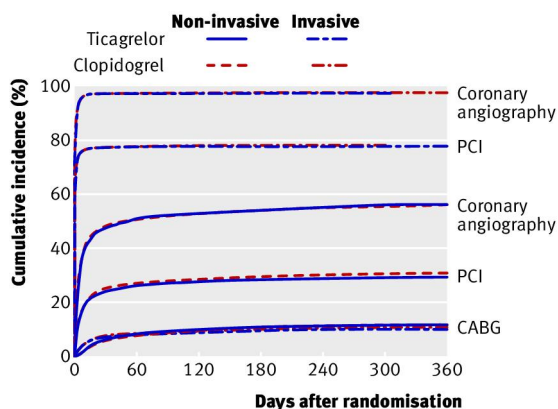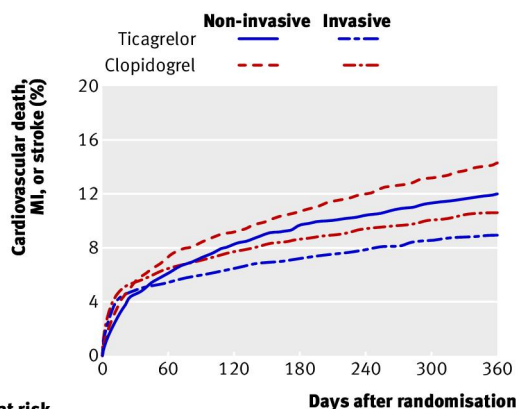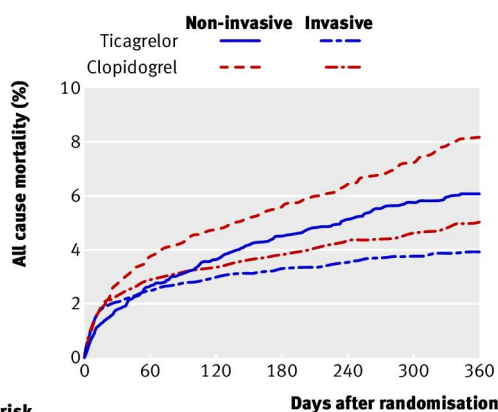

Fig 2 Cumulative incidence of cardiac catheterisation, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients intended for non-invasive management and randomised to ticagrelor or clopidogrel

Fig 3 Cumulative incidence of primary composite of cardiovascular death, myocardial infarction (MI), and stroke in ticagrelor and clopidogrel groups in patients intended for invasive and non-invasive management at time of randomisation

Fig 4 Cumulative incidence of total mortality in ticagrelor and clopidogrel groups in patients intended for invasive and non-invasive management at time of randomisation

Fig 5 Cumulative incidence of major bleeding in ticagrelor and clopidogrel groups in patients intended for invasive and non-invasive management at time of randomisation