Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 6, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.10.029

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery

Results From the PLATO (Platelet Inhibition and Patient Outcomes) Trial

Claes Held, MD, PhD,* Nils Åsenblad, MSc, PhLic,* Jean Pierre Bassand, MD,† Richard C. Becker, MD,‡ Christopher P. Cannon, MD,§ Marc J. Claeys, MD, PhD,‖ Robert A. Harrington, MD,‡ Jay Horrow, MD,¶ Steen Husted, MD, DSc,# Stefan K. James, MD, PhD,* Kenneth W. Mahaffey, MD,‡ José C. Nicolau, MD, PhD,** Benjamin M. Scirica, MD, MPH,§ Robert F. Storey, MD, DM,†† Marius Vintila, MD, PhD,‡‡ Joseph Ycas, PhD,¶ Lars Wallentin, MD, PhD*

Uppsala, Sweden; Besancon, France; Durham, North Carolina; Boston, Massachusetts; Edegem, Belgium; Wilmington, Delaware; Århus, Denmark; São Paolo, Brazil; Sheffield, United Kingdom; and Bucharest, Romania

Objectives The purpose of this study is to evaluate the efficacy and safety of ticagrelor and clopidogrel in patients with acute coronary syndrome undergoing coronary artery bypass graft surgery (CABG), as a post-randomization strategy.

Background Ticagrelor is a novel, reversibly binding, oral, direct-acting $P2Y_{12}$-receptor antagonist. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, which randomized 18,624 patients with acute coronary syndromes, ticagrelor compared with clopidogrel significantly reduced the risk of the primary composite end point of cardiovascular (CV) death, myocardial infarction, or stroke (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.77 to 0.92; $p < 0.001$). This report investigated the outcomes of patients treated with CABG during the trial.

Methods In total, 1,899 patients underwent CABG post-randomization. The protocol recommended ticagrelor/placebo to be withheld for 24 to 72 h and clopidogrel/placebo for 5 days preoperatively. In all, 1,261 patients underwent CABG and were receiving study drug treatment <7 days before surgery. The statistical analysis was based on events occurring from the CABG procedure until the end of the study, excluding 3 patients with CABG after study end.

Results In the 1,261 patient cohort, the relative reduction of primary composite end point at 12 months (10.6% [66 of 629] with ticagrelor versus 13.1% [79 of 629] with clopidogrel; HR: 0.84; 95% CI: 0.60 to 1.16; $p = 0.29$) was consistent with the results of the whole trial. Total mortality was reduced from 9.7% (58 of 629) to 4.7% (29 of 629; HR: 0.49; 95% CI: 0.32 to 0.77; $p < 0.01$), CV death from 7.9% (47 of 629) to 4.1% (25 of 629; HR: 0.52; 95% CI: 0.32 to 0.85; $p < 0.01$), and non-CV death numerically from 2.0% to 0.7% ($p = 0.07$). There was no significant difference in CABG-related major bleeding between the randomized treatments.

Conclusions In the subgroup of patients undergoing CABG within 7 days after the last study drug intake, ticagrelor compared with clopidogrel was associated with a substantial reduction in total and CV mortality without excess risk of CABG-related bleeding. (J Am Coll Cardiol 2011;57:672–84) © 2011 by the American College of Cardiology Foundation

The currently recommended dual antiplatelet treatment of patients with acute coronary syndrome (ACS) or stenting reduces the risk of major adverse ischemic cardiovascular events (1–3) but simultaneously increases the risk of bleeding complications at interventional procedures, for example, coronary artery bypass graft surgery (CABG) (4,5). Al-

From the *Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; †University of Besancon, Besancon, France; ‡Duke Clinical Research Institute, Durham, North Carolina; §TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts; ‖University Hospital Antwerp, Edegem, Belgium; ¶AstraZeneca Research and Development, Wilmington, Delaware; #Århus University Hospital, Århus, Denmark; **University of São Paolo Medical School, São Paolo, Brazil; ††University of Sheffield, Sheffield, United Kingdom; and the ‡‡Carol Davila University of Medicine Bucharest, Bucharest, Romania. The PLATO study was funded by AstraZeneca. For full author disclosures, please see the end of this article.

Manuscript received July 29, 2010; revised manuscript received October 11, 2010, accepted October 12, 2010.

though recent international guidelines recommend the early start of dual antiplatelet therapy with aspirin and a thienopyridine for patients with acute coronary syndromes, this strategy is controversial because of the excess risk of bleeding complications in patients undergoing urgent bypass surgery (6,7). The currently used combination of aspirin and thienopyridine (clopidogrel or prasugrel) provides irreversible platelet inhibition with recovery of platelet function after 5 to 7 days by the production of new platelets. Ticagrelor, the first reversibly binding, direct-acting oral $P2Y_{12}$ receptor antagonist leads to greater and more consistent $P2Y_{12}$ inhibition than clopidogrel, with more rapid onset and offset of $P2Y_{12}$ inhibition than clopidogrel (8–12). For patients with a need of CABG surgery, the interval after cessation of $P2Y_{12}$ inhibition might therefore be shortened to 2 to 3 days with ticagrelor rather than the 5 to 7 days recommended with clopidogrel and/or prasugrel. The PLATO (Platelet Inhibition and Patient Outcomes) trial found that ticagrelor was superior to clopidogrel for the prevention of cardiovascular and total death, myocardial infarction (MI), and stent thrombosis without an increase in major bleeding in a population with ACS (13). Among the 18,624 patients included in the main PLATO trial, 10.2% (n = 1,899) underwent CABG at any time during the trial after randomization, and 6.8% (n = 1,261) had CABG within 7 days after discontinuation of study treatment. The objective of this post-randomization analysis was to investigate the efficacy and safety outcome in this subgroup of PLATO study.

See page 685

Methods

The PLATO trial (NCT00391872) was an international, prospective, randomized, double-blind, double-dummy, event-driven study of 18,624 patients hospitalized for either acute ST-segment elevation ACS with an intention for primary percutaneous coronary intervention (PCI) or non–ST-segment elevation ACS, managed invasively or medically. Details of the study design, population, and outcomes have been published previously (14). In brief, patients were randomly assigned to treatment with either ticagrelor or clopidogrel within 24 h of onset of the most recent cardiac ischemic symptoms and before PCI. Ticagrelor-assigned patients received a 180-mg loading dose followed by a maintenance dose of 90 mg twice daily (bid). Clopidogrel-treated patients not already receiving a loading dose of open-label clopidogrel or who had not been taking clopidogrel or ticlopidine for ≥5 days before randomization, received a loading dose of 300 mg, followed by a maintenance dose of 75 mg once daily. The remaining patients received the 75-mg daily maintenance dose of clopidogrel as their first dose. Patients undergoing PCI received 1) an additional 90-mg dose of ticagrelor/placebo at procedures >24 h after randomization, and 2) at the discretion of the investigator, an additional 300 mg clopidogrel/placebo at any time relative to randomization. All patients received a dose of acetylsalicylic acid (ASA) 75 to 100 mg per day unless intolerant. For patients not previously receiving ASA, a loading dose of 325 mg was preferred (although a dose of 160 to 500 mg was allowed). After stent placement, an ASA dose up to 325 mg daily was allowed for as long as 6 months, and the low dose used thereafter. Randomized treatment continued for 6 to 12 months.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft surgery
CI = confidence interval
CK-MB = creatine kinase-myocardial band
CV = cardiovascular
HR = hazard ratio
PCI = percutaneous coronary intervention
ULN = upper limit of normal

For patients undergoing coronary artery bypass graft surgery (CABG), it was recommended that the study drugs would be withheld before surgery, 5 days for clopidogrel study drug and 24 to 72 h for ticagrelor study drug, while maintaining study blind. It was also recommended that the study drug be restarted as soon as possible after surgery and before discharge.

Events. The detailed definitions of efficacy and safety outcome events have been previously presented (14). Death from vascular causes included cardiovascular death, cerebrovascular death, and any death without noncardiovascular cause. Myocardial infarction was defined in accordance with the recently proposed universal definition (15). Periprocedural MI within 24 h after CABG was defined as either: 1) creatine kinase–myocardial band (CK-MB) ≥5 times local or central laboratory upper limit of normal (ULN), and, if the pre-CABG CK-MB was more than the ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI and development of new pathological Q waves on the electrocardiogram (no symptoms are required); or 2) CK-MB ≥10 times local or central laboratory ULN and, if the pre-CABG CK-MB was more than the ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI (with or without Q waves; no symptoms are required). Stroke was defined as focal loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms lasting at least 24 h or leading to death.

The primary safety end point was PLATO study defined total major bleeding (13,14). Major life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding requiring pressors or surgery, a fall in hemoglobin of 50 g/l (3.1 mmol/l) or greater, or need for transfusion of at least 4 units of red blood cells. We defined other major bleeding as significantly disabling (such as intraocular bleeding with

JACC Vol. 57, No. 6, 2011
February 8, 2011:672–84

permanent vision loss), a drop in hemoglobin of at least 30 g/l (1.9 mmol/l) but <50 g/l (3.1 mmol/l) or requiring transfusion of 2 to 3 units of red blood cells. The TIMI (Thrombolysis In Myocardial Infarction) criterion for major bleeding was programmed from the electronic case record form (eCRF), using a cut-point of ≥50 g of hemoglobin per liter, but did not necessarily require clinical evidence of excessive bleeding post-CABG. The GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) study definition of severe bleeding was derived from eCRF specific questions and was defined as fatal, intracranial, intrapericardial bleed with cardiac tamponade, or development of hypovolemic shock or severe hypotension due to bleeding requiring pressor support or surgery; and each of these items was specified by the investigators on the bleeding event form. Minor bleeding was defined as any bleeding requiring medical intervention but not meeting the criteria for major bleeding.

An independent central adjudication committee adjudicated all suspected primary and secondary efficacy end points as well as major and minor bleeding events, and in addition, all patients with CABG were adjudicated concerning occurrence of any of these outcome events.

Statistics. The primary efficacy end point was time from CABG to first occurrence of any event from the composite of death from vascular causes, MI, or stroke. Other efficacy end points were the individual components of the primary end point, all-cause mortality, and CABG-related mortality. The primary safety end point was time from CABG to the first occurrence of any major bleeding event. The efficacy analyses comprised all patients who were randomized to study treatment and underwent a CABG with last intake of study drug within 7 days before surgery; events occurring after end of trial, withdrawal of consent, or last contact with the patient were censored. The safety analyses on bleeding comprised all patients who were randomized to study treatment and underwent CABG with intake of study drug within 7 days before surgery, with censoring of events occurring >7 days after permanently stopping study medication. Baseline characteristics and procedures in hospital or at discharge were compared between treatment groups with the use of either Fisher's exact (categorical variables) or Wilcoxon rank-sum test (continuous variables). A Cox proportional hazards model, with a factor for treatment group, was used to analyze time-to-event end points. Fisher's exact test was used to analyze binary end points. The consistency of effects with regard to the timing of stop of study drug before CABG was analyzed with an interaction effect model based on either Cox proportional hazards model (time-to-event outcomes) or a logistic regression model (binary outcomes). A p value <0.05 was regarded as statistically significant. No adjustment for multiplicity was performed. All analyses were done with SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Overall, 18 624 patients with ACS from 862 centers in 43 countries between October 2006 and July 2008 were randomized in the trial. Of these, 1,899 (10.2%) patients underwent CABG during the trial, 1,849 (9.9%) received at least 1 dose of study drug, and 1,584 (8.5%) had CABG between first and last intake of study drug (study drug stopped at any time before CABG, even remotely). A total of 1,261 (6.8%) patients underwent CABG with last intake of study drug within 7 days before surgery (Fig. 1), of which 632 patients received ticagrelor and 629 patients received clopidogrel and constituted the patient population in this study. Three ticagrelor patients were excluded as they had missing values for the efficacy end points because the CABG was performed after the censoring date at 12 months.

The 2 treatment groups were balanced with regard to baseline characteristics, in-hospital treatments, and procedures (Tables 1 and 2). Median age was 64 years, and 21% were women. Previous PCI and CABG was noted in 10.4% and 1.5%, respectively. Chronic renal disease occurred in 4.8%. Almost all patients (94%) were receiving aspirin before randomization. Open-label clopidogrel pre-randomization

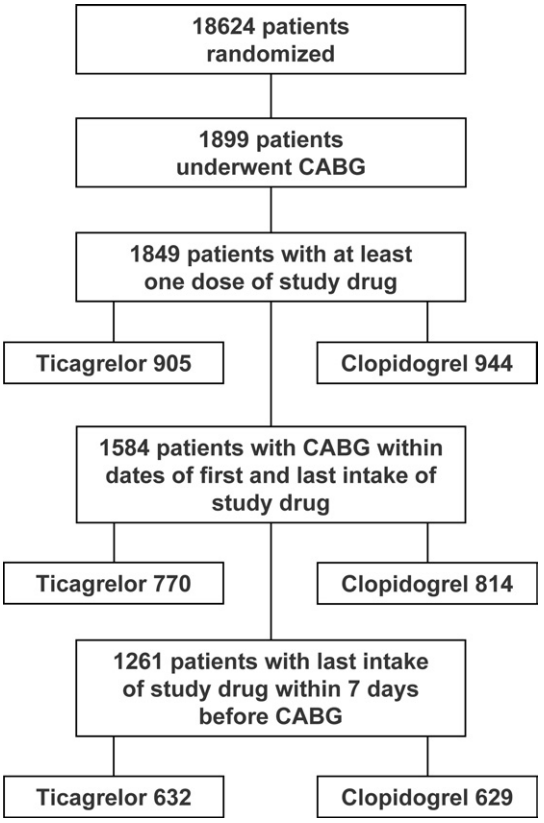

Figure 1 Study Population Undergoing CABG by Randomized Treatment Assignment

Study population undergoing coronary artery bypass graft surgery (CABG) by randomized treatment assignment.

Table 1 Baseline Characteristics in the Study Population at Randomization

Characteristic	Ticagrelor (n = 632)	Clopidogrel (n = 629)	p Value*
Age, yrs	64 (56–71)	64 (56–71)	0.3067
Age >75 yrs	86 (13.6)	99 (15.7)	0.3013
Women	121 (19.1)	145 (23.1)	0.0976
Weight, kg	70 (64–80)	71 (63–80)	0.8035
Weight <60 kg	16 (13.2)	23 (15.9)	0.6038
Height, cm	162 (158–165)	160 (156–165)	0.5386
BMI, kg/m^2	26.8 (24.8–31.3)	27.1 (24.6–30.9)	0.9528
Waist circumference, cm	98 (89–109)	97 (90–107)	0.8978
Men	511 (80.9)	484 (76.9)	0.0976
Weight, kg	82 (73–92)	81 (72–90)	0.2584
Weight <60 kg	15 (2.9)	16 (3.3)	0.8227
Height, cm	172 (168–177)	173 (168–178)	0.2792
BMI, kg/m^2	27.6 (25.0–30.5)	26.9 (24.6–29.4)	0.0450
Waist circumference, cm	99 (91–108)	99 (91–107)	0.7374
Race			
White	588 (93.0)	588 (93.5)	0.9697
Black	8 (1.3)	9 (1.4)	
Oriental	26 (4.1)	23 (3.7)	
Other	10 (1.6)	9 (1.4)	
CV risk factors			
Smoker	208 (32.9)	185 (29.4)	0.1837
Hypertension	433 (68.5)	422 (67.1)	0.6297
Dyslipidemia	356 (56.3)	328 (52.1)	0.1419
Diabetes mellitus	193 (30.5)	207 (32.9)	0.3969
History			
Angina pectoris	344 (54.4)	327 (52.0)	0.3975
Myocardial infarction	124 (19.6)	131 (20.8)	0.6238
Congestive heart failure	30 (4.7)	22 (3.5)	0.3216
Percutaneous coronary intervention	58 (9.2)	73 (11.6)	0.1669
Coronary artery bypass graft	5 (0.8)	14 (2.2)	0.0395
Transient ischemic attack	21 (3.3)	18 (2.9)	0.7454
Nonhemorrhagic stroke	24 (3.8)	25 (4.0)	0.8853
Peripheral arterial disease	43 (6.8)	53 (8.4)	0.2899
Chronic renal disease	33 (5.2)	27 (4.3)	0.5087

Values are median (25th–75th percentiles) or n (%). *The p values were calculated with Fisher's exact test (categorical variables) or Wilcoxon's rank sum test (continuous variables).

BMI = body mass index; CV = cardiovascular.

(any dose) had been used in 46.5% of ticagrelor-treated patients and in 44.2% of clopidogrel-treated patients (Table 3). Of patients receiving both open-label clopidogrel and clopidogrel/placebo, 82% had received 300 mg and 18%, 600 mg, respectively. The randomized treatment was given for a median duration of 224 days.

A majority of the CABG procedures (57%) were performed during the initial hospitalization. As illustrated in Figure 2, most procedures were undertaken within the first 60 days. When invasive treatment was planned at study entry, CABG was performed earlier. However, across the whole study period, at least as many patients in the group with "planned noninvasive strategy" as with "planned invasive strategy" ultimately underwent CABG. The time to CABG after randomization did not differ between ticagrelor- and clopidogrel-treated patients (hazard ratio [HR]: 0.96; 95% confidence interval [CI]: 0.87 to 1.05; p = 0.36). Of all CABG procedures, 95% were without valve replacement and 91% included the target vessel of index event. The number of grafts were 0 in 3 (0.2%), 1 or 2 in 391 (31%), 3 or 4 in 754 (60%), and ≥5 in 100 (8%) patients. In the ticagrelor group, investigational treatment was discontinued within the first 2 days in 190 (30.1%) patients, within 3 to 5 days in 277 (43.8%), and for >5 days in 165 (26.1%), before surgery. Corresponding numbers for patients in the clopidogrel group were 174 (27.7%), 338 (37.9%), and 217 (34.5%). Study drugs were restarted within 7 days in 57% and in 84% within 14 days post-CABG, with no difference between the treatment groups.

Efficacy outcomes among patients undergoing CABG. The occurrence of the primary end point (CV death, MI, or stroke) with ticagrelor compared with clopidogrel from CABG and onward was 10.6% versus 13.1% (HR: 0.84; 95% CI: 0.60 to 1.16; p = 0.29) (Table 4) and was consistent with the results in the whole trial. The rate of MI

JACC Vol. 57, No. 6, 2011
February 8, 2011:672–84

Table 2 CABG Evaluations, Treatments, and Procedures in Hospital or at Discharge for Index Event (n = 1,261)

Characteristic	Ticagrelor (n = 632)	Clopidogrel (n = 629)	p Value*
Abnormal physical findings	108 (17.1)	107 (17.0)	0.1896
Heart rate, beats/min	72 (64–82)	73 (65–84)	0.2016
Systolic blood pressure, mm Hg	131 (120–150)	132 (120–150)	0.6035
Diastolic blood pressure, mm Hg	80 (70–89)	80 (70–87)	0.3708
Killip class >2	9 (1.4)	11 (1.8)	0.6604
Persistent ST-segment elevation >1 mm/LBBB/final diagnosis STEMI	206 (32.6)	210 (33.4)	0.8107
TIMI STEMI risk score >2†	122 (59.2)	116 (55.2)	0.4291
Antithrombotic treatment in hospital			
Aspirin before randomization	597 (94.5)	587 (93.3)	0.4127
Aspirin after randomization	614 (97.2)	611 (97.1)	1.0000
Unfractionated heparin	356 (56.3)	355 (56.4)	1.0000
Low-molecular-weight heparin	393 (62.2)	381 (60.6)	0.5635
Fondaparinux	20 (3.2)	18 (2.9)	0.8694
Bivalirudin	2 (0.3)	5 (0.8)	0.2867
Glycoprotein IIb/IIIa inhibitor	134 (21.2)	141 (22.4)	0.6332
Other medication in hospital			
Beta-blocker	578 (91.5)	563 (89.5)	0.2505
ACE inhibitor and/or ARB	521 (82.4)	532 (84.6)	0.3243
Cholesterol lowering (statin)	612 (96.8)	613 (97.5)	0.6126
Calcium-channel inhibitor	181 (28.6)	189 (30.0)	0.6208
Diuretics	370 (58.5)	369 (58.7)	1.0000
Proton-pump inhibitor	345 (54.6)	376 (59.8)	0.0686
Invasive procedures in hospital			
Coronary angiography	564 (89.2)	567 (90.1)	0.6436
PCI within 24 h of randomization	112 (17.7)	126 (20.0)	0.3139
Any PCI pre-discharge	130 (20.6)	135 (21.5)	0.7298
Any CABG pre-discharge	352 (55.7)	368 (58.5)	0.3335

Values are median (25th–75th percentiles) or n (%). *The p values were calculated with Fisher's exact test (categorical variables) or Wilcoxon's rank sum test (continuous variables). †The TIMI (Thrombolysis In Myocardial Infarction) study ST-segment elevation myocardial infarction (STEMI) risk score >2 in percentage of patients with persistent ST-segment elevation >1 mm or left bundle branch block (LBBB) or final diagnosis STEMI.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

or stroke at or after CABG did not differ between the 2 treatment groups. The difference in the composite outcome was driven by a reduction in CV death from 7.9% (47 of 629) for clopidogrel, to 4.1% (25 of 631) for ticagrelor (HR: 0.52; 95% CI: 0.32 to 0.85; p < 0.01) (Table 4, Fig. 3B). Total mortality in association with or after CABG was reduced from 9.7% (58 of 629) to 4.7% (29 of 629; HR: 0.49; 95% CI: 0.32 to 0.77; p < 0.01) (Table 4, Fig. 3A). Also non-CV death was numerically reduced from 2.0% to 0.7% (HR: 0.35; 95% CI: 0.11 to 1.11; p = 0.07). There was no significant treatment by subgroup interaction for the outcomes of: 1) the primary efficacy composite; and 2) total; or 3) CV mortality for the following subgroups: open-label clopidogrel before randomization, hypertension, diabetes mellitus, smoking, dyslipidemia, or age >75 years or <75 years, weight >60 or <60 kg or <80 or >80 kg, or waist >100 cm or <100 cm. For sex, p values for interaction were <0.01 for total mortality and <0.05 for CV mortality, but not significant for the primary composite. The hazard ratios for total mortality were 0.29 (95% CI: 0.16 to 0.55) and 1.16 (95% CI: 0.59 to 2.31) for males and females, respectively. The hazard ratios for CV mortality were 0.32 (95% CI: 0.16 to 0.63) and 1.15 (95% CI: 0.56 to 2.39) for males and females, respectively.

A sensitivity analysis of the total CABG population (n = 1,899), showed consistent results with the study population. The reduction in total mortality in association with or after CABG, was reduced from 8.4% to 5.0% (HR: 0.60; 95% CI: 0.42 to 0.87; p < 0.01), and CV death was decreased from 6.8% to 4.1% (HR: 0.61; 95% CI: 0.41 to 0.92; p < 0.05).

Post-CABG mortality in relation to time from last study drug before surgery. In a further exploratory hypothesis-generating analysis, total and CV mortality post-CABG were analyzed in relation to days from last intake of study drugs before CABG surgery, as shown in Figure 4. The p value for interaction was of borderline significance (p = 0.06) for total mortality overall. There was no mortality difference between ticagrelor and clopidogrel when last intake was 1 day or less. However, if last intake of study drug was 2, 3, or 4 days before surgery, there were significant reductions in total mortality. When grouping into time intervals of last intake of study drugs, stopping 1 to 4 days before CABG, total mortality was 3.4% versus 15.5% (HR: 0.21; 95% CI: 0.10 to 0.42; p < 0.01 for

Table 3 Detailed Information on the Randomized Treatment

Characteristic	Ticagrelor (n = 632)	Clopidogrel (n = 629)	p Value*
Treatment duration, days	226 (24–364)	223 (28–363)	0.9186
Delay from start of pain, h	14.4 (6.9–20.4)	13.5 (6.7–20.8)	0.6007
Delay from hospital admission, h	9.0 (2.3–17.0)	6.8 (2.2–15.7)	0.0932
OL+IP/placebo			0.3376
300 mg	527 (83.4)	511 (81.2)	
600 mg	105 (16.6)	118 (18.8)	
OL clopidogrel pre-randomization			0.0462
None	338 (53.5)	351 (55.8)	
75 mg (50–150 mg)	94 (14.9)	66 (10.5)	
300 mg (151–449 mg)	142 (22.5)	135 (21.5)	
600 mg (≥450 mg)	58 (9.2)	77 (12.2)	
Study drug stopped before CABG			0.0012
1 day before CABG	84 (13.3)	88 (14.0)	
2 days before CABG	106 (16.8)	86 (13.7)	
3 days before CABG	114 (18.0)	73 (11.6)	
4 days before CABG	84 (13.3)	69 (11.0)	
5 days before CABG	79 (12.5)	96 (15.3)	
6 days before CABG	91 (14.4)	110 (17.5)	
7 days before CABG	74 (11.7)	107 (17.0)	
Restarted drug after CABG			0.8267
Did not restart	234 (37.0)	238 (37.8)	
<7 days	227 (35.9)	225 (35.8)	
7–14 days	111 (17.6)	100 (15.9)	
>14 days	60 (9.5)	66 (10.5)	

Values are median (25th–75th percentiles) or n (%). *The p values were calculated with Fisher's exact test (categorical variables) or Wilcoxon's rank sum test (continuous variables).

CABG = coronary artery bypass graft surgery; IP = investigational product (blinded); OL = open label.

interaction), and corresponding CV mortality was 3.1% versus 11.8% (HR: 0.25; 95% CI: 0.12 to 0.53; $p < 0.05$ for interaction), in the ticagrelor-treated patients compared with clopidogrel-treated patients. When last study drug intake was >4 days before CABG, there was no difference in mortality between the study drugs.

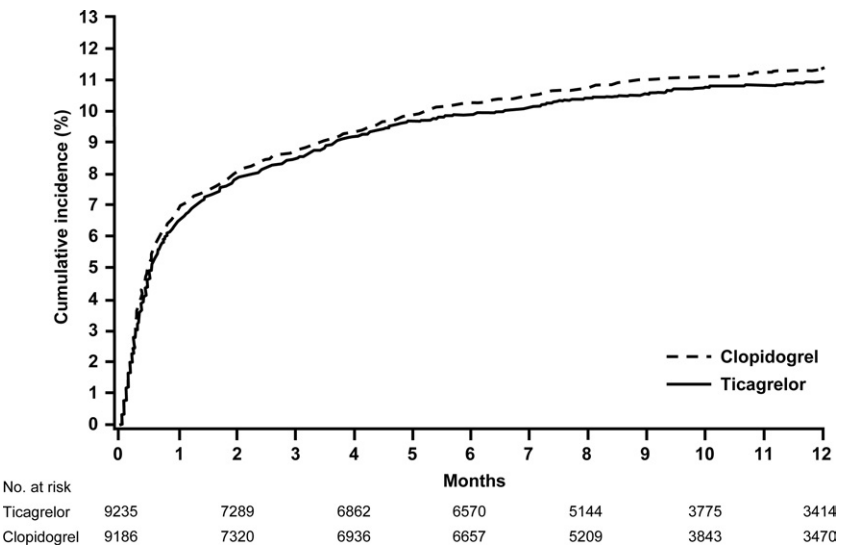

Figure 2 Timing of CABG From Randomization

Kaplan-Meier curve illustrating time from randomization to coronary artery bypass graft surgery (CABG) by ticagrelor **(solid line)** and clopidogrel **(dashed line)** in the total study population.

Table 4 Outcome After Coronary Artery Bypass Graft Surgery in the Study Population

End Point	Ticagrelor* (n = 629)	Clopidogrel* (n = 629)	HR (95% CI)	p Value†
Primary objective CV death/MI/stroke	66 (10.6)	79 (13.1)	0.84 (0.60–1.16)	0.2862
MI, excluding silent	37 (6.0)	35 (5.7)	1.06 (0.66–1.68)	0.8193
All-cause mortality	29 (4.7)	58 (9.7)	0.49 (0.32–0.77)	0.0018
CV death	25 (4.1)	47 (7.9)	0.52 (0.32–0.85)	0.0092
Non-CV death	4 (0.7)	11 (2.0)	0.35 (0.11–1.11)	0.0748
Stroke	13 (2.1)	11 (2.1)	1.17 (0.53–2.62)	0.6967
Hemorrhagic stroke	0 (0.0)	1 (0.2)		
Nonhemorrhagic/unknown stroke	13 (2.1)	10 (1.9)	1.29 (0.57–2.95)	0.5430

Values are number of events (%). *The percentage is the Kaplan-Meier estimate of the rate of the end point at 12 months post-CABG. †The p values were calculated by means of Cox regression analysis.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

Bleeding among patients undergoing CABG. Nearly all bleeding events occurred within 24 h post-CABG. Overall, according to the PLATO study definitions, major CABG-related bleeding occurred in 81.3% versus 80.1% (HR: 1.01; 95% CI: 0.90 to 1.15; p = 0.84) of the ticagrelor- and clopidogrel-assigned patients, respectively (Table 5). Correspondingly, life-threatening/fatal CABG-related bleeds occurred in 42.6% versus 43.7% (HR: 1.02; 95% CI: 0.87 to 1.21; p = 0.77). Bleeding according to TIMI major criteria occurred in 57.6% versus 59.3% (HR: 1.03; 95% CI: 0.89 to 1.19; p = 0.68) and TIMI minor criteria in 21.6% versus 21.1% (HR: 0.97; 95% CI: 0.77 to 1.24; p = 0.82), in the respective clopidogrel and ticagrelor groups. Similarly, the GUSTO study severe bleeding rates were 10.6% versus 12.2% (HR: 0.87; 95% CI: 0.62 to 1.20; p = 0.39). Fatal bleeds were uncommon: 5 in the ticagrelor group and 6 in the clopidogrel group. There were 2 intracranial bleeds, 1 in each treatment group.

There was no difference in CABG-related hemoglobin drop >50 g/l occurring in 228 (36%) in the respective clopidogrel group versus 241 (38%) in the ticagrelor group, nor in any transfusion within 7 days of the CABG that was given in 351 (56%) patients versus 349 (55%) patients, respectively. Neither was there any difference in CABG-related bleeds leading to transfusion of >4 U of blood as noted in, respectively, 102 (16.2%) patients versus 113 (17.9%) patients. Furthermore, there was no difference in transfusion of platelets or fresh frozen plasma observed. Reoperation due to bleeding was infrequent and occurred in 21 (3.3%) patients assigned to clopidogrel and in 25 (4.0%) patients receiving ticagrelor. Chest tube drainage of >2 l was also rare but did not differ between the treatment groups (Table 5). None of the various bleeding definition rates differed between the ticagrelor group and the clopidogrel group regardless of intake of open-label clopidogrel pre-randomization (p = 0.80 for interaction).

Sensitivity analyses of the safety population (n = 1,584) found consistent results, with no difference in bleeding rate between ticagrelor and clopidogrel for any of the life-threatening/major or minor bleeding definitions.

Post-CABG bleeding in relation to time from last study drug before surgery. There was no difference in PLATO study major/fatal/life-threatening CABG-related bleeding or GUSTO study severe bleeds between ticagrelor and clopidogrel, with respect to time from last intake of study drug before surgery, not even when the drug was stopped 1 day before surgery (Table 6) (p = 0.76 for interaction). Chest tube drainage measured over 24 h did not differ between treatment groups for any of 7 intervals between cessation of study drug and CABG (Fig. 5), either by total milliliters of drainage or by percentage of patients with at least 500 ml of drainage. Treatment groups also did not differ in the decrease in hemoglobin concentration adjusted for red cell transfusion for any of the 7 intervals (Fig. 6). Figure 6 indicates less impact of perioperative bleeding on hemoglobin concentration when the interval is at least 5 days.

Discussion

The current analysis showed that among patients initially treated for ACS and subsequently undergoing CABG with last intake of study drug within 7 days before surgery, ticagrelor compared with clopidogrel was associated with around a halving in total and CV mortality without any change in the risk of CABG-related bleeding. The absolute reduction in total mortality was 5.0% per year, and for CV mortality, 3.8% per year.

In the total PLATO trial, there was a significant 22% relative and 1.4% per year absolute reduction in total mortality. Thus, the lower mortality for patients treated with CABG is consistent with the overall trial results, although more pronounced. The current analysis also indicated a relationship between CABG mortality and the time of last intake of study drug before surgery. Thus, there might be a special hazard associated with a remaining effect of clopidogrel in association with surgery. The reasons for the higher mortality in the clopidogrel group were, however, not related to bleeding complications. This lack of relationship might be in accordance with a recent registry study in which there was no significant increase in risk of bleeds or reopera-

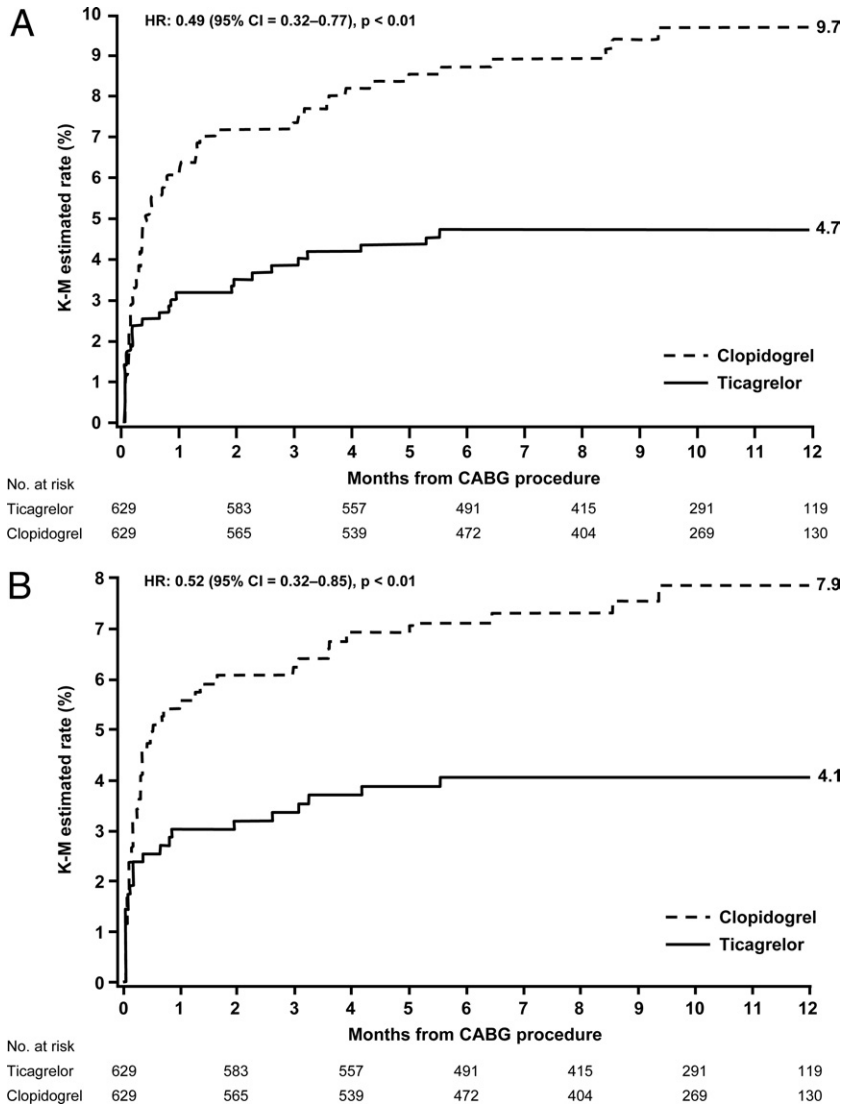

Figure 3 **Cumulative Risk of Any Death or CV Death**

Kaplan-Meier (K-M) curve showing **(A)** time from coronary artery bypass graft surgery (CABG) to any death or **(B)** or time to cardiovascular (CV) death, independent of the duration of randomized study treatment before CABG. **Solid line** = ticagrelor; **dashed line** = clopidogrel. CI = confidence interval; HR = hazard ratio.

tions when clopidogrel treatment was stopped <5 days before CABG (16). Also, the findings from the CABG subgroup in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial are consistent, with lack of increase in bleeding regardless of upstream clopidogrel, although the transfusion rate was higher among patients whose clopidogrel was stopped <5 days before CABG (17). In our study, the time of stopping ticagrelor and clopidogrel before surgery affected the mortality rate, and especially in the time window between 1 and 4 days. The excess of fatalities in the current study may have been caused by other cardiovascular events, for example, arrhythmia/sudden death and heart failure, and also by noncardiovascular events, such as infections or sepsis. The more frequent occurrence of sepsis at surgery in clopidogrel-treated patients has previously been reported (18) as a potential hazard that might be contributing to worsening in outcomes also at CABG.

CABG differs from other major surgery in that it includes full heparinization therapy, platelet dysfunction from the pump, and fibrinolysis, factors that all impact the risk of bleeding (19). It is therefore not possible to extrapolate bleeding risk to other forms of major surgery. Despite the more intense platelet inhibition by ticagrelor and the shorter treatment-free interval before CABG, there was no significant difference in the rate of major/life-threatening bleeding/fatal bleeding at surgery, or in chest tube drainage, reoperation due to bleeding, or hemoglobin concentrations adjusted for red cell transfu-

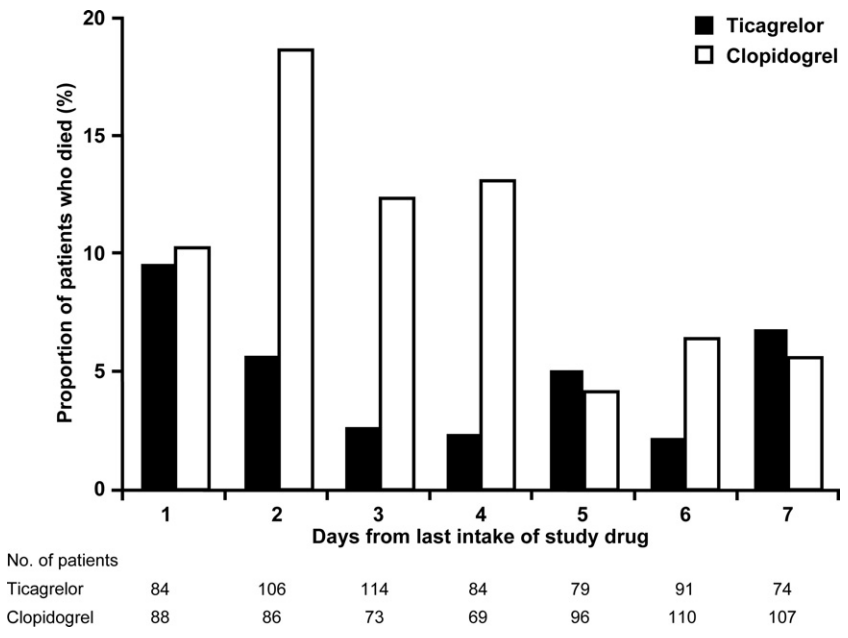

Figure 4 Cumulative Risk of Any Death by Last Intake of Study Drug

Total mortality among ticagrelor-treated patients **(solid bars)** and clopidogrel-treated patients **(open bars)** by days from last intake of study drug before coronary artery bypass graft surgery.

Table 5 Bleeding Complications During and After CABG

End Point	Ticagrelor* (n = 632)	Clopidogrel* (n = 629)	OR/HR (95% CI)	p Value†
Major CABG bleeds‡	513 (81.2)	504 (80.1)	1.07 (0.80–1.43)	0.6691
CABG-related life-threatening/fatal‡	276 (43.7)	268 (42.6)	1.04 (0.83–1.31)	0.7330
Fatal CABG bleeds‡	5 (0.8)	6 (1.0)	0.83 (0.20–3.28)	0.7730
CABG-related intracranial bleeding‡	0 (0.0)	0 (0.0)		
All intracranial bleedings after CABG	1 (0.2)	1 (0.2)	1.01 (0.06–16.09)	0.9967
CABG TIMI, all major‡	375 (59.3)	362 (57.6)	1.08 (0.85–1.36)	0.5300
CABG TIMI, minor‡	133 (21.0)	136 (21.6)	0.97 (0.73–1.28)	0.8367
CABG-related GUSTO severe bleed‡	67 (10.6)	77 (12.2)	0.85 (0.59–1.22)	0.3768
Any transfusion within 7 days after CABG	349 (55.7)	351 (56.5)	0.98 (0.85–1.14)	0.8336
PRBC or whole blood within 7 days after CABG	333 (53.2)	322 (51.9)	1.03 (0.88–1.20)	0.6948
Total blood transfusion within 7 days after CABG, no. of units§	4.0 (2.0–9.0)	4.0 (2.0–8.0)		0.7616
PRBC or whole blood within 7 days after CABG, no. of units§	3.0 (2.0–4.0)	3.0 (2.0–4.0)		0.8598
Platelets within 7 days after CABG	97 (15.4)	109 (17.5)	0.88 (0.67–1.16)	0.3705
Fresh frozen plasma within 7 days after CABG	159 (25.3)	151 (24.1)	1.05 (0.84–1.31)	0.6749
CABG-related bleed resulting in Hb decrease >50 g/l‡	241 (38.1)	228 (36.2)	1.08 (0.86–1.37)	0.5216
CABG-related bleed resulting in Hb decrease >30 g/l‡	442 (69.9)	425 (67.6)	1.12 (0.87–1.43)	0.3950
Major/life-threatening CABG-related bleeding resulting in death within 7 days after CABG	8 (1.3)	18 (3.0)	0.44 (0.19–1.01)	0.0524
Reoperation due to bleeding‡	25 (4.0)	21 (3.3)	1.19 (0.63–2.27)	0.6528
CABG-related bleed resulting in transfusion >4‡	113 (17.9)	102 (16.2)	1.12 (0.83–1.53)	0.4544
Transfusion whole blood/PRBC >5 U within 2 days after CABG‡	31 (4.9)	25 (4.0)	1.25 (0.70–2.23)	0.4947
Chest tube output >2 l within 24 h‡	21 (3.3)	17 (2.7)	1.24 (0.61–2.52)	0.6218
Chest tube output, ml, within 24 h§	575 (300–950)	540 (320–810)		0.2447

Values are number of events (%). *For time-to-event outcomes, percent (%) is the Kaplan-Meier estimate of the rate of the end point at 12 months post-CABG. †The p values are from Cox regression analysis (time-to-event outcomes) or Fisher's exact test (binary outcomes). ‡Binary outcome with odds ratio (OR). §Median (25th–75th percentiles) and p value from Wilcoxon rank-sum test.
GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries study; Hb = hemoglobin; PRBC = packed red blood cells; other abbreviations as in Tables 2 and 4.

Table 6 Bleeding Outcomes in Subgroups With Different Intervals Between Cessation of Study Treatment and CABG (n = 1,261)

End Point	Characteristic*	Total, n	Ticagrelor† (n = 632)	Clopidogrel† (n = 629)	OR (95% CI)‡	p Value Interaction‡
CABG-related life-threatening/fatal bleed	Study drug stop before CABG					0.7613
	≤1 day	172	55 (65.5)	52 (59.1)	1.31 (0.71–2.44)	
	1–2 days	192	50 (47.2)	42 (48.8)	0.94 (0.53–1.65)	
	2–3 days	187	56 (49.1)	33 (45.2)	1.17 (0.65–2.11)	
	3–4 days	153	39 (46.4)	29 (42.0)	1.20 (0.63–2.27)	
	4–5 days	175	22 (27.8)	27 (28.1)	0.99 (0.51–1.91)	
	5–6 days	201	29 (31.9)	45 (40.9)	0.68 (0.38–1.21)	
	>6 days	181	25 (33.8)	40 (37.4)	0.85 (0.46–1.59)	
CABG-related GUSTO severe bleed	Study drug stop before CABG					0.4400
	≤1 day	172	12 (14.3)	17 (19.3)	0.70 (0.31–1.56)	
	1–2 days	192	11 (10.4)	16 (18.6)	0.51 (0.22–1.16)	
	2–3 days	187	16 (14.0)	10 (13.7)	1.03 (0.44–2.41)	
	3–4 days	153	10 (11.9)	8 (11.6)	1.03 (0.38–2.77)	
	4–5 days	175	7 (8.9)	5 (5.2)	1.77 (0.54–5.81)	
	5–6 days	201	4 (4.4)	12 (10.9)	0.38 (0.12–1.21)	
	>6 days	181	7 (9.5)	9 (8.4)	1.14 (0.40–3.20)	

Values are number of events (%). *Percent (%) is the rate of the end point: (number of events divided by n of group per level of characteristic) times 100%. †Characteristic: ≤1 day is 0 to ≤24 h, 1 to 2 days is >24 h to ≤48 h, and so forth. ‡Odds ratio and p value from logistic regression.

Abbreviations as in Tables 2, 4, and 5.

sions. Bleeding around CABG is frequent, and a decrease in hemoglobin >30 g/l or blood transfusions commonly occur. Because of the rigorous application of the bleeding definitions in the PLATO study, the criteria for major bleeding were fulfilled in >80% of the CABG-treated patients. However, despite thorough analyses of the occurrence of bleeding by a vast number of bleeding definitions, there appeared no significant difference in rate of CABG-associated bleeding between clopidogrel and ticagrelor. Also, the reoperation rates were similar.

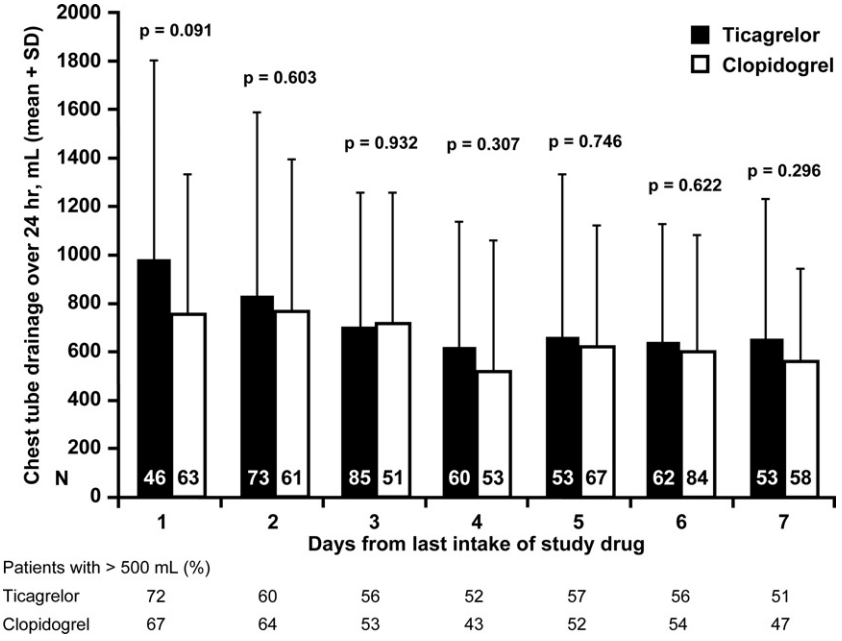

Figure 5 Chest Tube Drainage by Days From Last Intake of Study Drug

Chest tube drainage during 24 h, in milliliters (mean ± SD, vertical axis), according to the interval in days (horizontal axis) from cessation of study drug to coronary artery bypass graft surgery for ticagrelor **(solid bars)** and clopidogrel **(open bars)**. The N denotes the number of patients, and the p value indicates nominal significance levels for the comparison between treatment groups by Student's *t* test. Below the horizontal axis appear the percentages of patients with >500 ml for ticagrelor/clopidogrel.

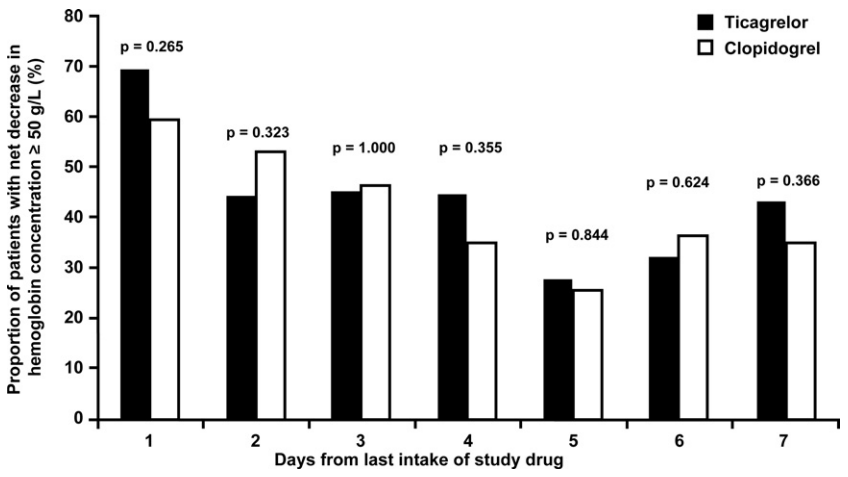

Figure 6 **Proportion of Patients With Decrease in Hemoglobin >50 g/l by Days From Last Intake of Study Drug**

Percentage of patients (vertical axis) with net decrease in hemoglobin concentration, adjusted by red cell transfusions, of 50 g/l or more according to the interval in days (horizontal axis) from cessation of study drug to coronary artery bypass graft surgery for ticagrelor **(solid bars)** and clopidogrel **(open bars)**. The p value denotes nominal significance levels for the comparison between treatment groups by the Fisher exact test.

The lack of difference in bleeding, when using the more potent direct and reversible $P2Y_{12}$ inhibitor ticagrelor as compared with clopidogrel, still might indicate a relatively lower risk of bleeding in relation to platelet activity at CABG. This is in contrast to the comparison of prasugrel, the indirect and potent $P2Y_{12}$ inhibitor, with clopidogrel in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) study (20), inducing a fourfold higher rate of major bleeding among patients undergoing CABG. However, also in the TRITON trial, there were more fatalities after CABG in patients assigned to clopidogrel than to prasugrel.

The PLATO trial allowed patients already on treatment with clopidogrel to be randomized into the trial, leading to that almost one-half of patients in both groups were pre-treated with clopidogrel at entry in the trial. However, open-label clopidogrel did not affect the efficacy or safety results, since no significant interaction was observed. The halving in mortality by using ticagrelor instead of clopidogrel in association with CABG was striking and also explained about a quarter of the mortality reduction in the whole trial. The finding that the excess mortality with clopidogrel was unrelated to differences in the rates of bleeding raises the suspicion that clopidogrel treatment might be associated with other specific risks in association with major surgery. These observations might have relations to the lack of any significant mortality benefits despite striking reductions in the rate of myocardial infarction in the major studies comparing clopidogrel with placebo in ACS (20–22).

Study limitations. The current study is a retrospective analysis of a nonrandomized subgroup of a large prospective randomized trial, and therefore provides exploratory information concerning the findings. The formal adjudication of causes of deaths in the main study distinguished between death from vascular and nonvascular causes, but a further subcategorization was not performed.

Conclusions

In ACS patients needing CABG during dual antiplatelet treatment, ticagrelor as compared with clopidogrel reduces CV and total death without an increase in major bleeding.

Author Disclosures

Claes Held has received institutional grants from Schering-Plough, GlaxoSmithKline, Bristol-Myers Squibb, and AstraZeneca; has advisory board membership with AstraZeneca and Pfizer; and has received a scholarship from Pfizer. Nils Åsenblad has ownership equity in AstraZeneca. Jean Pierre Bassand is a consultant to Sanofi-Aventis; has stock ownership in Sanofi-Aventis, GlaxoSmithKline, and Eli Lilly; and is on the speaker's bureau of AstraZeneca, Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, and Servier. Richard C. Becker receives research support from Regado Biosciences, Johnson and Johnson, and Bayer; is an advisory consultant to AstraZeneca, Regado Biosciences, and Bristol-Myers Squibb; and receives research support to the Duke Clinical Research Institute from AstraZeneca. Christopher P. Cannon receives research/grants from Accumetrics, AstraZeneca, GlaxoSmithKline, Intekrin Therapeutics, Merck, and Takeda; is on the advisory board of Bristol-Myers Squibb, Sanofi-Aventis, Novartis, and Alnyam; receives honorarium for development of independent educational symposia from Pfizer and AstraZeneca; and is a clinical advisor/equity for Automedics Medical Systems. Marc J. Claeys is on the advisory board and receives honoraria from AstraZeneca and Eli Lilly. Robert A. Harrington receives

lecture/honoraria fees from Eli Lilly and The Medicines Company; consultant fees from AstraZeneca, Merck, Novartis, Portola, Sanofi-Aventis, and Schering-Plough; and grant support from AstraZeneca, Bristol-Myers Squibb, Merck, Portola, Schering-Plough, and The Medicines Company. Jay Horrow is an employee and has equity ownership in AstraZeneca. Steen Husted receives research grants from AstraZeneca, Bristol-Myers Squibb, Pfizer, and Bayer; and consultant fees from Sanofi-Aventis, Pfizer, and AstraZeneca. Stefan K. James receives research grants and honoraria from AstraZeneca. Kenneth W. Mahaffey receives grant support from Amgen, Amylin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CardioKinetix, Cierra, Cordis, Edwards Lifesciences, Eli Lilly, GlaxoSmithKline, Guidant, Innocoll Pharmaceuticals, Johnson and Johnson, KCI Medical, Luitpold Pharmaceutical, Medtronic, Merck, Momenta Pharmaceutical, Novartis, Portola Pharmaceutical, Pozen, Regado Biotechnologies, Sanofi-Aventis, Schering-Plough, and The Medicine Company; and consulting fees from Adolor, Alexion, Amgen, Argolyn Bioscience, AstraZeneca, Bayer, Boehringer Ingelheim, Brigham and Women's Hospital, Bristol-Myers Squibb, Daiichi Sankyo, Duke University School of Medicine, Eli Lilly, Elsevier, Forest Labs, Genetech, GlaxoSmithKline, Guidant, Johnson and Johnson, Merck, Novartis, Pfizer, Proctor and Gamble, Sanofi-Aventis, Schering-Plough, Scios, WebMD, and Williams Beaumont hospital. José C. Nicolau is a consultant to and receives advisory board fees from AstraZeneca, Sanofi-Aventis, and Merck; and lecture fees from AstraZeneca, Sanofi-Aventis, Merck, and Eli Lilly. Benjamin M. Scirica receives consulting fees from AstraZeneca, Cogentus Pharmaceuticals, Merck, Daiichi Sankyo, and Novartis; and research grant support from AstraZeneca, Johnson and Johnson, Bayer Healthcare, Merck, Daiichi Sankyo, and Novartis. Robert F. Storey receives research grants/honoraria and/or consultancy fees from AstraZeneca, Eli Lilly, Daiichi Sankyo, Novartis, Eisai, The Medicine Company, Schering-Plough, Merck, GlaxoSmithKline, Sanofi-Aventis, Bristol-Myers Squibb, Medscape, Dynabyte, and Teva. Marius Vintila receives research grants from Sanofi-Aventis and Servier; consultant fees from Pfizer and Sanofi-Aventis; speaker fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Menamni, Merck, Novartis, Pfizer, Sanofi-Aventis, and Servier; and has advisory board membership with AstraZeneca, Novartis, Pfizer, Sanofi-Aventis, and Servier. Joseph Ycas is an employee of AstraZeneca and has equity in AstraZeneca and Bristol-Myers Squibb. Lars Wallentin receives research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough; honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough; consultant fees from Regado Athera, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Eli Lilly; and lecture fees from AstraZeneca, Boehringer Ingelheim, and Eli Lilly.

Acknowledgments

The authors thank all investigators and study participants for making the study come true. They also thank Sylvia Olofsson at UCR (Uppsala Clinical Research Center) and Karen Pieper at DCRI (Duke Clinical Research Institute) for their excellent supportive statistical work, and Håkan Emanuelsson at AstraZeneca for his leadership during the trial. Ebba Bergman at UCR has provided professional help in communication between the coauthors.

Reprint requests and correspondence: Dr. Claes Held, Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Department of Cardiology, Dag Hammarskjölds v 14B, Uppsala 75185, Sweden. E-mail: claes.held@ucr.uu.se.

REFERENCES

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:652–726.
2. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598–660.
3. Van de Werf, F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909–45.
4. Fox KA, Mehta SR, Peters R, 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.
5. Mehta S, Yusuf S, Peters RJ, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
6. Kulik A, Chan V, Ruel M. Antiplatelet therapy and coronary artery bypass graft surgery: perioperative safety and efficacy. Expert Opin Drug Saf 2009;8:169–82.
7. Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy 2008;28:376–92.
8. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
9. Gurbel PA, Bliden KP, Butler K, 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.
10. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038–47.
11. L'Allier PL, Ducrocq G, Pranno N, et al. Clopidogrel 600-mg double loading dose achieves stronger platelet inhibition than conventional regimens: results from the PREPAIR randomized study. J Am Coll Cardiol 2008;51:1066–72.

12. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. J Am Coll Cardiol 2006;48:931–8.
13. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
14. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the Platelet Inhibition and Patient Outcomes (PLATO) trial. Am Heart J 2009;157:599–605.
15. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
16. Kim JH, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. Am Heart J 2008;156:886–92.
17. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following preoperative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol 2009;53:1965–72.
18. Blasco-Colmenares E, Perl TM, Guallar E, et al. Aspirin plus clopidogrel and risk of infection after coronary artery bypass surgery. Arch Intern Med 2009;169:788–96.
19. Karkouti K, McCluskey SA, Syed S, Pazaratz C, Poonawala H, Crowther MA. The influence of perioperative coagulation status on postoperative blood loss in complex cardiac surgery: a prospective observational study. Anesth Analg 2010;110:1533–40.
20. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
21. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
22. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

Key Words: acute coronary syndromes ■ clopidogrel ■ coronary artery bypass grafting ■ ticagrelor.