Reduction in Recurrent Cardiovascular Events with Prasugrel Compared with Clopidogrel in Patients with Acute Coronary Syndromes from the TRITON-TIMI 38 Trial

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Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial

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Aims In the TRITON-TIMI 38 trial, greater platelet inhibition with prasugrel reduced the first occurrence of the primary endpoint (cardiovascular death, MI, or stroke) compared with clopidogrel in patients with an acute coronary syndrome (ACS) undergoing planned percutaneous coronary intervention. We hypothesized that prasugrel would reduce not only first events but also recurrent primary endpoint events and therefore total events compared with clopidogrel.

Methods and results Poisson regression analysis was performed to compare the number of occurrences of the primary endpoint between prasugrel and clopidogrel in TRITON-TIMI 38. Landmark analytic methods were used to evaluate the risk of a recurrent primary endpoint event following an initial non-fatal endpoint event. Among patients with an initial non-fatal event, second events were significantly reduced with prasugrel compared to clopidogrel (10.8 vs. 15.4%, HR 0.65, 95% CI 0.46–0.92; $P = 0.016$), as was CV death following the non-fatal event (3.7 vs. 7.1%, HR 0.46, 95% CI 0.25–0.82; $P = 0.008$). Overall there was a reduction of 195 total primary efficacy events with prasugrel vs. clopidogrel (rate ratio 0.79, 95% CI 0.71–0.87; $P < 0.001$). Recurrent bleeding events occurred infrequently (TIMI major non-CABG bleeds: four with prasugrel and two with clopidogrel). Study drug discontinuation was frequent following the initial major bleeding event (42% of patients discontinued study drug).

Conclusion While standard statistical analytic techniques for clinical trials censor patients who experience a component of the primary composite endpoint, total cardiovascular events remain important to both patients and clinicians. Prasugrel, a more potent anti-platelet agent, reduced both first and subsequent cardiovascular events compared with clopidogrel in patients with ACS.

Keywords Acute coronary syndrome • Percutaneous coronary intervention • Prasugrel • Clopidogrel

Introduction

In standard statistical analysis of clinical outcomes trial data using survival methodology, patients who experience a component of a primary composite endpoint are censored from the analysis following the initial event. Such patients continue to be followed during the trial and are at risk for the occurrence of additional events, but second and third order events are generally not considered in a primary endpoint efficacy analysis. However, in a real-world clinical setting, both patients and clinicians are concerned

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not only with the initial event a patient may experience but with subsequent events as well. Additionally, patients who experience multiple events may be a subset of subjects who are poor responders to therapy. Identification of baseline characteristics, including platelet response measures in the setting of an acute coronary syndrome, among such subjects may allow modifications of the clinical management strategy prior to the occurrence of subsequent events, such as providing more intensive or additional therapy.

As previously reported,[1] The TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel (TRITON)-TIMI 38 showed an overall reduction in the composite endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke over a median duration of therapy of 14.5 months (interquartile range 8.8 months, 15.1 months) with intensive dual antiplatelet therapy with prasugrel compared to the approved regimen of clopidogrel in patients with ACS undergoing percutaneous coronary intervention (PCI). These benefits of prasugrel over clopidogrel in preventing events were achieved at the cost of an increased rate of TIMI major non-CABG-related bleeding.[1] We hypothesized that not only first events but subsequent events would also be reduced with greater platelet inhibition using prasugrel when compared with standard therapy with clopidogrel. We also sought to evaluate whether repeated bleeding events occurred more frequently with prasugrel.

Methods

The study design and primary results of the TRITON-TIMI 38 trial have been published previously.[1,2] A total of 13 608 patients with an acute coronary syndrome (both UA/NSTEMI and STEMI) for whom a PCI was planned were enrolled in TRITON-TIMI 38 and were randomized to prasugrel (loading dose of 60 mg and daily maintenance dose of 10 mg) or the approved regimen of clopidogrel (300 mg loading dose and 75 mg daily maintenance dose).[1] Randomization was to occur prior to the onset of PCI and blinded study drug administration was to be administered as soon as possible after randomization. During the maintenance phase, patients were to receive blinded study drug and aspirin (suggested dose of 75–162 mg). After hospital discharge, follow-up visits were conducted at 30 days, 90 days, and at 3 month intervals thereafter for a minimum of 6 months and maximum of 15 months.

All endpoints used in the analyses in the initial[1] as well as this report were adjudicated by members of an independent clinical events committee who were blinded to the treatment assignment.[2] Fatal events were counted as a single event, not as two separate events. For example, if a patient experienced an MI and then had cardiovascular death with the cause of death adjudicated as due to the MI, the event was considered one fatal MI event and was not counted as both an MI and cardiovascular death. Patients were to remain on study drug even if the subject experienced one of the efficacy endpoints of the study. If a subject experienced a bleeding event, study drug could be continued or discontinued at the treating physician's discretion.

Efficacy comparisons were performed according to the intention-to-treat principle. A sensitivity analysis was performed that included only efficacy events that occurred during the 'at-risk' period, defined as on study drug or within 7 days after permanent study drug discontinuation. The analysis of bleeding events was also restricted to the 'at-risk' period.

Baseline clinical characteristics are presented as frequencies for categorical variables and medians and interquartile ranges for continuous variables. Comparisons between baseline characteristics for patients with no events, a single event, or multiple events (*Table 1*), as well as for the comparison of prasugrel with clopidogrel in the cohort of

Table 1 Baseline characteristics in patients with no events, single event, or multiple events

	No events (n = 12 184)	Single event (n = 1284)	Multiple events (n = 140)	P-value
Age ≥75 years	1511 (12.4%)	256 (19.9%)	42 (30.0%)	<0.001
Age (years)	60 (52, 69)	63 (55, 72)	69 (60, 78)	<0.001
Gender (male)	9054 (74.3%)	939 (73.1%)	92 (65.7%)	0.05
White race	11236 (92.6%)	1174 (91.6%)	127 (90.7%)	0.29
History of hypertension	7735 (63.5%)	893 (69.5%)	113 (80.7%)	<0.001
History of hypercholesterolaemia	6778 (55.6%)	721 (56.2%)	81 (57.9%)	0.82
History of diabetes	2718 (22.3%)	371 (28.9%)	57 (40.7%)	<0.001
Current tobacco use	4706 (38.6%)	462 (36.0%)	27 (19.3%)	<0.001
Prior MI	2072 (17.0%)	308 (24.0%)	54 (38.6%)	<0.001
Prior CABG	862 (7.1%)	145 (11.3%)	31 (22.1%)	<0.001
Creatinine clearance (mL/min)	100.2 (77.8, 126.8)	92.5 (69.4, 120.6)	74.0 (55.5, 101.5)	<0.001
CrCl <60 mL/min	1260 (10.5%)	186 (15.0%)	44 (32.1%)	<0.001
Stent used for index PCI	11517 (94.5%)	1195 (93.1%)	132 (94.3%)	0.10
BMS used for index PCI	5772 (47.4%)	619 (48.2%)	70 (50.0%)	0.71
DES used for index PCI	5745 (47.2%)	576 (44.9%)	62 (44.3%)	0.24
Multivessel PCI	1670 (14.0%)	195 (15.6%)	31 (22.8%)	0.006
NSTEMI/UA	9040 (74.2%)	934 (72.7%)	100 (71.4%)	0.41
Randomization				<0.001
Prasugrel	6170 (50.6%)	595 (46.3%)	48 (34.3%)	
Clopidogrel	6014 (49.4%)	689 (53.7%)	92 (65.7%)	

Table 2 Baseline characteristics for prasugrel vs. clopidogrel among patients with at least one non-fatal event

	Prasugrel (n = 529)	Clopidogrel (n = 674)	P-value
Age ≥75 years	107 (20.2%)	117 (17.4%)	0.20
Age (years)	63 (55, 72)	62 (54, 71)	0.06
Gender (male)	387 (73.2%)	496 (73.6%)	0.87
White race	486 (91.9%)	623 (92.7%)	0.59
Region			0.80
North America	171 (32.3%)	227 (33.7%)	
South America	23 (4.3%)	36 (5.3%)	
Western Europe	141 (26.7%)	163 (24.2%)	
Eastern Europe	117 (22.1%)	145 (21.5%)	
Rest of World	77 (14.6%)	103 (15.3%)	
History hypertension	382 (72.2%)	471 (69.9%)	0.38
History hypercholesterolaemia	296 (56.0%)	398 (59.1%)	0.28
History of diabetes	137 (25.9%)	210 (31.2%)	0.05
Current tobacco use	184 (34.8%)	242 (35.9%)	0.69
Prior MI	126 (23.8%)	177 (26.3%)	0.33
Prior CABG	67 (12.7%)	82 (12.2%)	0.79
Creatinine clearance (mL/min)	92.2 (69.9, 118.4)	94.6 (70.7, 125.8)	0.13
CrCl <60 mL/min	77 (14.7%)	99 (14.9%)	0.95
PCI performed	525 (99.2%)	669 (99.3%)	0.98
CABG performed during index hospitalization	7 (1.3%)	16 (2.4%)	0.19
Stent used for index PCI	498 (94.1%)	633 (93.9%)	0.87
BMS used for index PCI	252 (47.6%)	319 (47.3%)	0.92
DES used for index PCI	246 (46.5%)	314 (46.6%)	0.98
Anti-thrombin			0.27
UFH	353 (68.5%)	413 (63.1%)	
LMWH	38 (7.4%)	59 (9.0%)	
Bivalirudin	15 (2.9%)	23 (3.5%)	
Other/combo	109 (21.2%)	160 (24.4%)	
GP2b3a inhibitor used during index hospitalization	302 (57.1%)	401 (59.5%)	0.40
SBP (mm Hg)	132 (120, 150)	135 (120, 151)	0.31
Heart rate (b.p.m.)	71 (62, 80)	71 (62, 80)	0.76
NSTEMI/UA	390 (73.7%)	503 (74.6%)	0.72
MV PCI	94 (18.2%)	92 (13.9%)	0.04

patients with at least one non-fatal event (*Table 2*), were made using χ^2 test for categorical variables and Wilcoxon rank for continuous variables. Poisson regression analysis was performed to compare the total number of occurrences of the primary endpoint between all patients in the prasugrel and clopidogrel groups. Poisson regression is a generalized linear model applied when analysing multiple discrete counts (i.e. number of occurrences of an event) over a period of time (i.e. duration of follow-up in the trial). Landmark analytic methods were used to evaluate the risk of a second event following the initial event, with entry time into the analysis being set at the time of the first event. The landmark method of survival analysis utilizes a fixed timepoint from which patients were entered into the analysis and considered at risk (in this case, after the occurrence of an initial primary endpoint event) to assess the subsequent response in the treatment groups. Landmark event rates were presented as Kaplan–Meier failure estimates and were compared using the log rank test. Hazard ratios for the landmark analyses were calculated using Cox proportional hazard models. All tests were two-sided with a P-value <0.05 considered to be significant. Due to the exploratory nature of the analysis, no adjustments were made to thresholds for significance for multiple testing. Analyses were performed using Stata/SE 9.2 (Stata Corp., College Station, TX, USA).

Results

Among patients with no events, the median length of follow-up was 14.8 months (25th/75th percentile, 11.5 and 15.2 months overall; same for both prasugrel and clopidogrel); among patients experiencing at least one event, the median length of follow-up was 14.3 months (25th/75th percentile 7.0 and 15.1 months). Patients with multiple events were older, had more comorbidities at study entry including hypertension and diabetes, and tended more frequently to be females (*Table 1*). Baseline characteristics

among patients experiencing at least one non-fatal event comparing those randomized to prasugrel vs. clopidogrel are shown in *Table 2*. While most baseline characteristics were similar between the prasugrel and clopidogrel groups, those randomized to prasugrel were slightly older, less likely to have a history of diabetes, and more likely to have undergone multivessel PCI (*Table 2*).

Efficacy

As previously reported,[1] the primary endpoint of first occurrence of CV death, MI, or stroke was significantly reduced in the prasugrel group when compared with the clopidogrel group (9.9%, $n = 643$ vs. 12.1%, $n = 781$, HR 0.81, 95% CI 0.73–0.90; $P < 0.001$). In addition to the reduction in first events, subsequent events were also reduced in the prasugrel group ($n = 58$ in the prasugrel group vs. $n = 115$ in the clopidogrel group, $P < 0.001$, *Figure 1*), resulting in 195 fewer total primary events during follow-up (total events $n = 701$ vs. $n = 896$, rate ratio 0.79, 95% CI 0.71–0.87; $P < 0.001$). Results were consistent when using all-cause mortality instead of CV death in the composite endpoint, with significantly fewer total events with prasugrel compared with clopidogrel ($n = 750$ with prasugrel vs. $n = 937$ with clopidogrel, rate ratio 0.80, 95% CI 0.73–0.89; $P < 0.001$). In a sensitivity analysis that included only primary endpoint events that occurred while on study drug or within 7 days after the study drug was discontinued, prasugrel was associated with a reduction in first events (9.7% in the prasugrel group vs. 11.4% in the clopidogrel group, HR 0.84, 95% CI 0.76–0.94; $P = 0.002$), subsequent events ($n = 51$ vs. $n = 98$, $P < 0.001$), and total events (rate ratio 0.81, 95% CI 0.73–0.90, $n = 657$ vs. $n = 811$; $P < 0.001$).

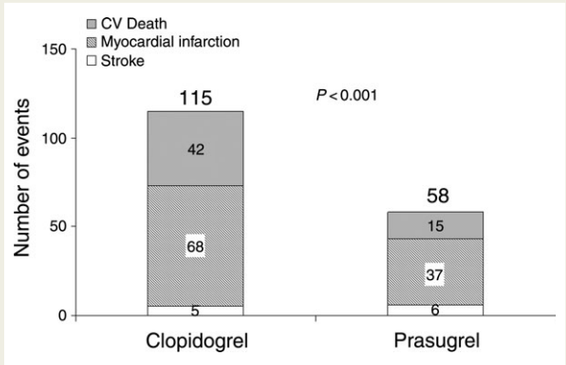

Figure 1 Additional primary endpoint events by randomized therapy. The prasugrel group had a lower number of both first events ($P < 0.001$), additional events ($P < 0.001$), and total events ($P < 0.001$).

In a landmark analysis from the time of the first event to recurrent event or last follow-up, a second primary endpoint event occurred in 10.8% of the prasugrel group and 15.4% of the clopidogrel group (HR 0.65, 95% CI 0.46–0.92; $P = 0.016$) (*Figure 2A*). After adjusting for covariates that were associated with the occurrence of an additional event (age, gender, history of hypertension, history of diabetes, non-use of tobacco products, prior MI, creatinine clearance <60 mL/min, and multivessel PCI), the adjusted HR is 0.66 (95% CI 0.46–0.95; $P = 0.024$). Cardiovascular death following a non-fatal MI or stroke was also significantly reduced in the prasugrel group compared with the clopidogrel group (3.7 vs. 7.1%, HR 0.46, 95% CI 0.25–0.82; $P = 0.008$) (*Figure 2B*). Results were similar when adjusting for multivessel PCI, which was not balanced between treatment groups in this cohort, as well as covariates that were associated with the occurrence of cardiovascular death following an initial non-fatal event (age, history of hypercholesterolaemia, history of diabetes, non-use of tobacco products, prior MI, and creatinine clearance <60 mL/min) (HR 0.49, 95% CI 0.26–0.91; $P = 0.023$).

The reduction in second events with prasugrel was consistent in several key subgroups, including the elderly, gender, stent type, index event, and creatinine clearance (*Figure 3*). A significant interaction was observed between history of diabetes and treatment on

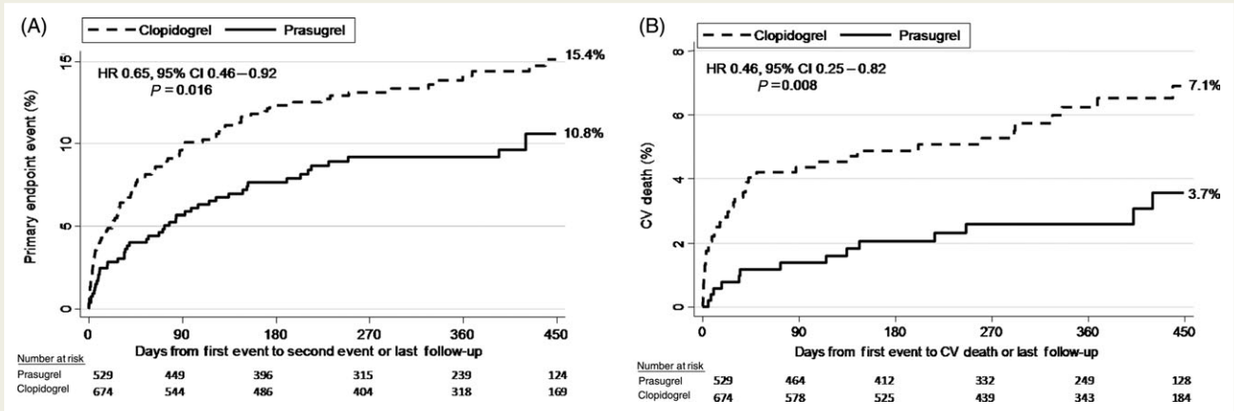

Figure 2 (A) Landmark analysis of time from first event to second event by randomized therapy. The occurrence of a subsequent ischaemic event was significantly reduced in the prasugrel group (HR 0.65, 95% CI 0.46–0.92; $P = 0.016$). (*B*) Landmark analysis of time from first event to cardiovascular death by randomized therapy. Cardiovascular mortality following a non-fatal ischaemic event occurred significantly less frequently among patients treated with prasugrel (HR 0.46, 95% CI 0.25–0.82).

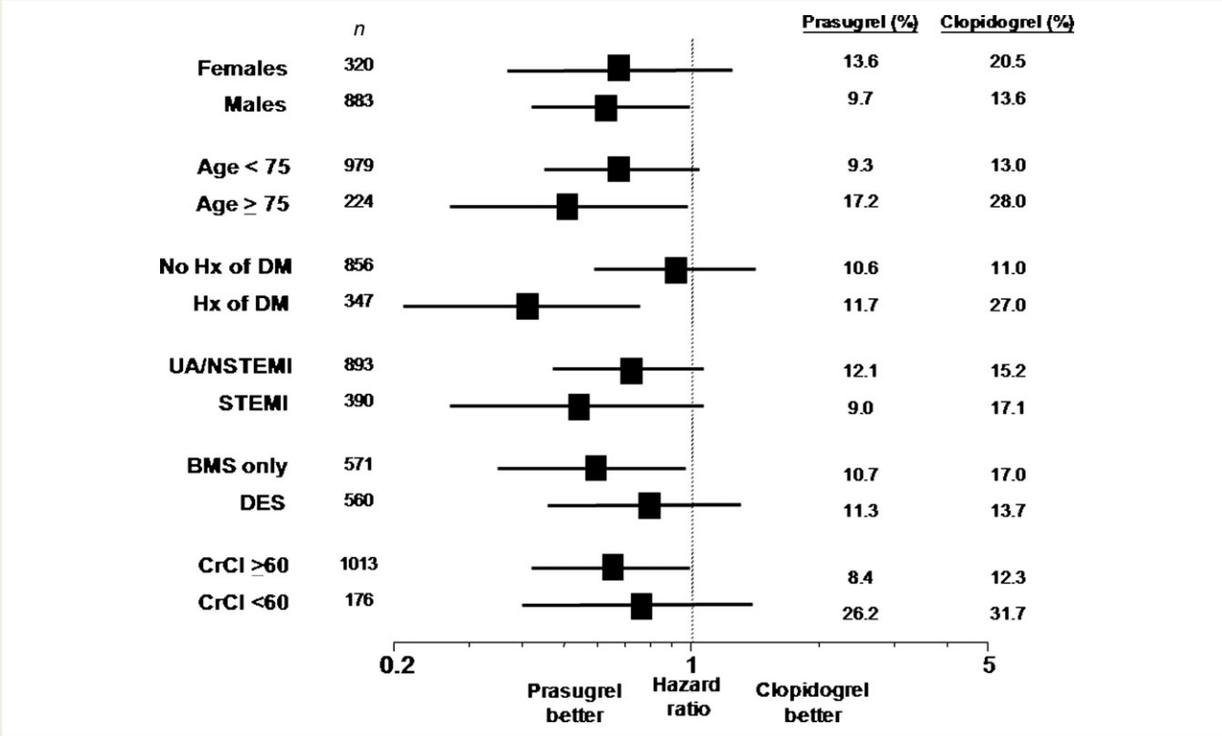

Figure 3 Subsequent primary events during follow-up by randomized therapy among subgroups. Among patients with a first, non-fatal ischaemic event, second events were directionally lower with prasugrel in all subgroups (i.e. point estimate falls to the left of the line of unity). With the exception of history of diabetes (interaction $P = 0.036$), there were no other significant interactions by subgroup. Rates are Kaplan–Meier failure rates at 15 months.

the risk of a second event ($P_{interaction} = 0.036$), with a large risk reduction in subsequent events in diabetics treated with prasugrel (HR 0.40, 95% CI 0.21–0.75, $P = 0.003$).

Bleeding

Initial TIMI major non-CABG bleeding events were more frequent in the prasugrel group (2.4 vs. 1.8%, HR 1.32, 95% CI 1.03–1.68, $P = 0.03$),[1] as were TIMI minor non-CABG bleeding events (2.7 vs. 2.0%, HR 1.31, 95% CI 1.04–1.66; $P = 0.02$). Recurrent bleeding events during the at-risk period occurred infrequently in both arms, due to a high rate of study drug discontinuation following the initial bleeding event (overall 42% of patients who had an initial TIMI major non-CABG bleeding event discontinued study drug; 42% for prasugrel vs. 43% for clopidogrel, P = NS). The frequency of such recurrent events was similar between the treatment arms, with four repeat TIMI major non-CABG bleeds in the prasugrel group and two in the clopidogrel group. There were five repeat TIMI minor non-CABG bleeds in each treatment group. Likewise, among patients with at least one TIMI non-CABG major or minor bleed, there were 17 recurrent non-CABG TIMI major or minor bleeding events in the prasugrel group and 13 in the clopidogrel group.

Of the 26 patients with a TIMI non-CABG fatal bleed, three patients in the prasugrel group had experienced an adjudicated bleeding event by TIMI criteria prior to the fatal bleed, one of which was a TIMI non-CABG major bleed 4 months prior to the fatal bleed and two of which were TIMI non-CABG minor bleeds, one 2 days prior to the fatal bleed, and one 4 days prior to the fatal bleed. None of the patients with a TIMI non-CABG fatal bleed in the clopidogrel group had experienced a prior TIMI major or minor bleeding event.

Discussion

This analysis from the TRITON-TIMI 38 trial demonstrates that randomization to prasugrel, a drug that results in greater platelet inhibition when compared with clopidogrel, prevented not only the first primary endpoint event but also reduced subsequent and therefore the total number of primary endpoint events among patients with an ACS undergoing PCI. While the early benefit of prasugrel was evident in the primary analysis in the report of the main results as shown by the immediate separation of the Kaplan–Meier curves,[1] our findings suggest that continued therapy with a regimen that provides higher levels of IPA remains important, even after an ischaemic event has occurred. Indeed, intensive anti-platelet therapy seems to be of added benefit to those who have already had such an event, an observation evident in both the intent-to-treat and on-treatment analyses.

Despite the practice of censoring patients who experience a component of the primary composite endpoint in standard

statistical analysis of clinical outcomes trial data when applying survival methods, what is of importance to patients and from a healthcare resource utilization perspective are the outcomes for a patient during the course of the entire trial.[3] Multiple events experienced by a given patient require more hospitalizations, tests, treatments, and physician visits, resulting in increased costs. From a patient perspective, additional ischaemic events result in a higher mortality as well as an impaired quality of life.[4]

Several validated scoring systems accurately predict those at an increased risk of events following an ACS based on baseline characteristics and index presentation.[5–9] While risk scores were higher and baseline clinical risk factors (e.g. older age, more frequent diabetes, hypertension, and prior MI) were more frequent among patients with multiple events than those with a single event, other unidentified factors also influence the risk of recurrent ischaemic events. Based on the observation that total events in this study were higher with clopidogrel, it is possible that those patients with recurrent events may be more resistant to anti-platelet therapy, and/or more likely to be hyporesponders to platelet inhibition, a concept previously reported to be associated with an increased risk of thrombotic events.[10–14] Several studies have shown that prasugrel produces higher and more consistent levels of the active metabolite that binds to the platelet P2Y12 receptor than clopidogrel, both at the approved dose used in the current study as well as at higher doses.[15,16]

Patients with diabetes experiencing ACS are of particular interest since they are known to have an increased rate of cardiovascular events and more aggregable platelets[17–19] and the primary analysis of TRITON-TIMI 38 showed that they responded particularly well to prasugrel. In this analysis, we observed that a significant interaction occurred between diabetes and randomized therapy on the risk of a recurrent primary endpoint event, with a hazard ratio of 0.40 favouring prasugrel in patients with diabetes.

There was no difference between treatment groups in the risk of recurrent bleeding events, although such events were rare due to a high rate (42%) of study drug discontinuation following the initial bleeding event. As per the protocol, if a subject experienced a bleeding event during the trial, the investigator was permitted to discontinue study drug therapy and restart study drug after the bleeding event had subsided. However, a large number of patients in both arms who experienced a major bleeding event permanently discontinued study drug.

Limitations

It should be noted that with landmark analyses comparing two therapies within a trial, the original randomization assigned at study entry is subject to survivor bias and study drug discontinuation. However, among patients with a non-fatal ischaemic event who comprised the landmark analysis cohort, there were few significant differences in evaluated baseline characteristics between the prasugrel and clopidogrel groups (age, history of diabetes, and multivessel PCI). When the landmark analysis for a second event was adjusted for these imbalanced covariates, as well as covariates associated with the occurrence of an additional event, prasugrel remained associated with a lower risk of additional events compared with clopidogrel (univariate HR 0.65; adjusted HR 0.66, $P = 0.024$). Additionally, there was no difference in mortality between treatment groups overall in the TRITON-TIMI 38 trial (3.0 vs. 3.2%, HR 0.95, $P = 0.64$). The impact that continued therapy with prasugrel compared with clopidogrel could have had on recurrent bleeding events may not be fully assessed due to the high rate of study drug discontinuation (in both treatment arms) following the initial bleeding event and the infrequent nature of repeat bleeding events.

Clinical implications

Prasugrel, a more potent thienopyridine than clopidogrel, reduced not only the first but also subsequent occurrences of primary endpoint events compared with the approved dose of clopidogrel. This observation emphasizes the need for continued high levels of platelet inhibition following an acute coronary syndrome. Patients who experience an ischaemic event despite treatment with clopidogrel may be hyporesponders to this drug and may require more intensive platelet P2Y12 inhibition to prevent the occurrence of subsequent adverse thrombotic complications. Patients at greatest risk for events, such as those who have already experienced an event while on clopidogrel (especially diabetic patients) may experience especially salutary effects when treated with a drug that provides more intensive inhibition of the platelet P2Y12 receptor.

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References

1. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
2. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, Winters KJ, Warmke JW, McCabe CH, Braunwald E. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006;**152**:627–635.
3. Gold M, Siegel J, Russel L, Weinstein M. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
4. Spertus JA, Radford MJ, Every NR, Ellerbeck EF, Peterson ED, Krumholz HM. Challenges and opportunities in quantifying the quality of care for acute myocardial infarction: summary from the Acute Myocardial Infarction Working Group of

the American Heart Association/American College of Cardiology First Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. *Circulation* 2003;**107**:1681–1691.
5. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–842.
6. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–2567.
7. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353.
8. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;**102**:2031–2037.
9. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, de Lemos JA, McCabe CH, Braunwald E. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet* 2001;**358**:1571–1575.
10. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Paniccia R, Moschi G, Gori AM, Abbate R, Antoniucci D. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;**49**:2312–2317.
11. Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissha MZ, Tantry US. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005;**46**:1827–1832.
12. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, Novikov I, Pres H, Savion N, Varon D, Hod H. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;**109**:3171–3175.
13. 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**:246–251.
14. Gurbel PA, Bliden KP. Durability of platelet inhibition by clopidogrel. *Am J Cardiol* 2003;**91**:1123–1125.
15. Brandt JT, Payne CD, Wiviott SD, Weerakkody G, Farid NA, Small DS, Jakubowski JA, Naganuma H, Winters KJ. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007;**153**:66 e9–66 e16.
16. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;**116**:2923–2932.
17. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes* 2005;**54**:2430–2435.
18. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007;**298**:765–775.
19. Vinik AI, Erbas T, Park TS, Nolan R, Pittenger GL. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001;**24**:1476–1485.

The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.