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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...
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, the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitoR 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. 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. 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). 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 as well as this report were adjudicated by members of an independent clinical events committee who were blinded to the treatment assignment. 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%)        |                   |
patients with at least one non-fatal event (Table 2), were made using χ² 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

| Table 2 Baseline characteristics for prasugrel vs. clopidogrel among patients with at least one non-fatal event |
|--------------------------------------------------|--------------------------------------------------|----------------|
| Age ≥75 years                                     | Prasugrel (n = 529)                              | Clopidogrel (n = 674) |
| Age (years)                                       | 107 (20.2%)                                     | 117 (17.4%)         | 0.20 |
| Gender (male)                                     | 63 (55.72)                                      | 62 (54.71)          | 0.06 |
| White race                                        | 387 (73.2%)                                     | 496 (73.6%)         | 0.87 |
| Region                                            | 486 (91.9%)                                     | 623 (92.7%)         | 0.59 |
| North America                                     | 171 (32.3%)                                     | 227 (33.7%)         | 0.80 |
| South America                                     | 23 (4.3%)                                       | 36 (5.3%)           | 0.69 |
| Western Europe                                    | 141 (26.7%)                                     | 163 (24.2%)         | 0.33 |
| Eastern Europe                                    | 117 (22.1%)                                     | 145 (21.5%)         | 0.33 |
| Rest of World                                     | 77 (14.6%)                                      | 103 (15.3%)         | 0.33 |
| 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                                      | 353 (68.5%)                                     | 413 (63.1%)         | 0.27 |
| UFH                                               | 38 (7.4%)                                       | 59 (9.0%)           | 0.87 |
| LMWH                                              | 15 (2.9%)                                       | 23 (3.5%)           | 0.87 |
| Bivalirudin                                       | 109 (21.2%)                                     | 160 (24.4%)         | 0.87 |
|OTHER/combo                                       | 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 |
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, 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, 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).

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
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, $P = 0.03$) 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, 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. 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.

Several validated scoring systems accurately predict those at an increased risk of events following an ACS based on baseline characteristics and index presentation. 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. 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.

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 and the primary characteristics and index presentation. While risk scores were higher 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. 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.

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