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Research Article

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Long Term Efficacy of Prasugrel versus Clopidogrel in Patients undergoing Percutaneous Coronary Intervention and Anticoagulated with Bivalirudin

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Abstract

Aim: Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention. We studied the long term efficacy of prasugrel compared with clopidogrel loading in patients undergoing percutaneous coronary intervention (PCI), electively or emergently, who were anticoagulated with bivalirudin during the procedure.

Methods and Results: This retrospective cohort study included 296 patients (153 prasugrel and 143 clopidogrel) who underwent PCI at our institution from January 2009-December 2012. Time to stroke, non-fatal MI, PCI, CABG, or death (MACE) was assessed in all patients. The mean follow-up was 1198 days (1284 ± 599 days for clopidogrel patients vs. 1119 ± 423 days for prasugrel patients), first MACE occurred in 26 (18.2%) clopidogrel patients vs 17 (11.1%) prasugrel patients (p=0.085). The propensity-adjusted (for key clinical and non-clinical risk factors) Cox model showed no significant difference to time to the first MACE event (Hazard ratio for clopidogrel versus prasugrel [HR]=1.06; 95% confidence interval [CI]: 0.54 to 2.04; p=0.860). Likewise the conditional survival model revealed no differences between clopidogrel patients and prasugrel patients in terms of repeated MACE or repeated MI (Repeated MACE: HR=1.37; 95%CI: 0.74, 2.52 and Repeated MI: HR=1.32; 95%CI: 0.71, 2.45).

Conclusion: On the long term, there were no significant differences in MACE between patients anticoagulated with bivalirudin and given either clopidogrel or prasugrel during PCI.

Keywords

Prasugrel; Clopidogrel; Percutaneous coronary intervention; Coronary artery disease

Introduction

Between 2009 and 2014, the Food and Drug Administration approved 6 new anticoagulant or antithrombotic drugs [1]. While this represents valuable innovation in a clinically important area of care, it creates a need for the comparative effectiveness evidence showing which drugs – and which combinations of drugs – lead to optimal outcomes, in which patient population, to enable informed decision-making at the point of care. Current clinical practice guidelines for percutaneous coronary intervention (PCI) with stenting include dual antiplatelet therapy with aspirin plus a loading dose of a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor), as well as an anticoagulant, either unfractionated heparin (with a glycoprotein IIb/IIIa inhibitor in the case of patients undergoing primary PCI for an ST-elevation myocardial infarction and other patients with high risk features) or bivalirudin [2]. In 2003/2004, the REPLACE-2 trial demonstrated that bivalirudin with provisional administration of a glycoprotein IIb/IIIa inhibitor produced non-inferior outcomes compared to heparin plus routine administration of a glycoprotein IIb/IIIa inhibitor and carried a reduced risk of major bleeding [3,4]. Use of bivalirudin in clinical practice steadily increased, and was reported to be the anticoagulant of choice in almost 40% of PCI procedures as early as 2006 [5].

Novel antiplatelet drugs, such as prasugrel, have been tested in study samples in which the majority of patients received heparin and a glycoprotein IIb/IIIa inhibitor [6]. Especially given evidence that bivalirudin has a significantly different impact on platelet aggregation than unfractionated heparin [7,8], this leaves important questions, about the relative safety and efficacy of the different antiplatelet therapies in the context of bivalirudin use, unanswered. Other important questions for which evidence remains sparse or lacking, include the safety and efficacy of prasugrel in patients undergoing elective PCI [2], and the long-term outcomes of patients undergoing PCI treated with the different P2Y12 receptor inhibitors. To help address these gaps, we report long-term safety and effectiveness outcomes for prasugrel vs. clopidogrel among patients who underwent PCI, for various indications, and received bivalirudin during the procedure.

Methods

The study cohort included 296 patients who underwent PCI at Baylor University Medical Center (Dallas, TX) between January 2009 and December 2012. Clinical, non-clinical, and procedural data were collected by utilizing the Cath PCI registry (http://cvquality.acc.org/en/NCDR-Home/Registries/Hospital-Registries.aspx) and the Baylor University Medical Center institutional database. Time (in days) to a major adverse event (stroke, non-fatal MI, PCI, CABG, or death) (MACE) or last follow-up (12/31/2014) was assessed for all patients from date of surgery or intervention by using data from the Dallas-Fort Worth Hospital Council (DFWHC) regional database –a hospital trade association, with 75 member institutions (>140 hospitals). This study was approved by the Baylor Research Institute IRB.

The study cohort was described by computing means, standard deviations (SDs), and percentages while differences in demographic and clinical details were tested with a Wilcoxon (for continuous factors) or a chi-square (for categorical factors) test. A Bonferroni correction was employed to account for multiplicity.

A propensity-adjusted Cox proportional hazards model was developed to assess the association between patients' medical management (clopidogrel vs prasugrel) and first MACE. The

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propensity model, which we have described previously [9], was developed using recognized clinical and non-clinical risk factors [10] (Table 1) in a logistic regression model with medication management as the outcome and the risk factors as covariates. Multiple imputations using Markov Chain Monte Carlo simulation was used to address missing data (creatinine 22.7%, renal failure 14.5%, and smoking history 10.5%). The propensity score was then fitted as a 5-knot restricted cubic spline [11] in the Cox model, along with medication type, to model time to MACE.

Additionally, repeated MACE and repeated MI were modeled separately using conditional, propensity-adjusted Cox models to test whether repeated MACE or MI events were associated with medication type –this survival model employed Prentice, Williams, and Peterson correction for the condition that a patient cannot be considered at risk for a second (third and so on) event unless they have already experienced the previous one [12]. In all models all continuous variables were fitted using restricted cubic splines with 5 knots [11,13].

Results

Nearly all baseline demographic and clinical characteristics were similar between the clopidogrel (n=143) and prasugrel (n=153) study groups (Table 1), although patients in the clopidogrel group had slightly greater pre-existing renal failure (8.7% vs. 1.3%; p=0.07). Procedural characteristics by medication are presented in Table 2.

The mean follow-up was 1198 days (1284 ± 599 days for clopidogrel patients vs. 1119 ± 423 days for prasugrel patients, p=0.126), first MACE occurred in 26 (18.2%) clopidogrel patients vs. 17 (11.1%) prasugrel patients (p=0.085). The propensity-adjusted Cox model showed no significant difference to time to the first MACE event (Hazard ratio for clopidogrel versus prasugrel [HR]=1.06; 95% confidence interval [CI]: 0.54 to 2.04; p=0.860).

The results of the conditional analyses of repeated MACE events and repeated MI are presented in Table 3. Of note, the unadjusted analyses indicated a greater number of total MACE events and total MI events in the clopidogrel group versus the prasugrel group. However, when adjusted for key case-mix risk factors, these differences were not statistically significant (Repeated MACE: HR=1.37; 95%CI: 0.74, 2.52; p=0.377 and Repeated MI: HR=1.32; 95%CI: 0.71, 2.45; p=0.377) (Table 3).

Discussion

The TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) clinical trial enrolled 13,608 moderate-to-high-risk patients with ACS (with or without ST-segment elevation) undergoing percutaneus coronary intervention. Patients were randomized to compare prasugrel with clopidogrel with a median follow-up time of 14.5 months. Prasugrel use was associated with fewer ischemic events as well as urgent target vessel revascularization than was clopidogrel. Prasugrel use was, however, associated with a small, but statistically significant, increased risk of major bleeding. The decrease in ischemic events occurred both in the first 3 days post-PCI and from 3 days post-PCI to the study end while the excess major bleeding observed was predominantly during the maintenance phase [14]. Of note that TRITON-TIMI 38 was limited to patients with acute coronary syndrome undergoing PCI. Only 3% of each study arm received bivalirudin [6].

Other observational studies have compared clopidogrel and prasugrel in context of bivalirudin as the procedural anticoagulant. Laynez et al reported the results of 692 patients with acute coronary syndrome undergoing PCI with stent implantation, 96 received prasugrel either during or just after PCI. There was no significant difference in in-hospital bleeding and ischemic events, nor any significant difference in ischemic events at 30 days. The study did not report any risk adjusted comparisons. Also, only 56.4% of the patients who received prasugrel were discharged with this among their prescription medications; the others were switched to clopidogrel [15]. Diaz et al. reported the results of 168 consecutive STEMI patients treated by primary angioplasty and receiving bivalirudin + either clopidogrel or prasugrel, and compared safety and efficacy outcomes in 70 propensity-matched pairs. There were no mortalities or major bleeding episodes in either group at 30 days, but higher rate of acute and sub-acute thrombosis in the clopidogrel group which approached statistical significance (4.3% vs. 0%, p=0.08). The total number of events i.e. stroke, thrombosis, reinfarction within 30 days, death within 30 days, hematomas and transfusion, were significantly higher in clopidogrel group (5.7% vs. 0%, p=0.042) [16].

The Swedish Coronary Angiography and Angioplast Registry, compared patients (with or without ACS) who underwent PCI and were treated with prasugrel for maintenance therapy -with or without clopidogrel loading dose- (n=2,142) or clopidogrel (n=23,994). In patients with ACS, there was lower 30 day mortality, as well as, lower in-hospital bleeding in the prasugrel group. In elective patients, there

Table 1: STS risk factors and patient characteristics.

Characteristic	Clopidogrel (n=143, 48.3%)	Prasugrel (n=153, 51.7%)	p-value
Age, years	65.9 ± 11.8	63.2 ± 10.5	0.67
Body mass index, kg/m^2	29.1 ± 5.5	30.0 ± 6.7	>0.99
Female gender	33.1%	28.3%	>0.99
Race			
White	74.7%	78.3%	>0.99
Black	10.6%	11.2%	
Hispanic	7.8%	9.2%	
Other/Unknown	7.0%	1.3%	
Diabetes mellitus	32.4%	32.9%	>0.99
Renal failure	8.7	1.3	0.07
Creatinine, mg/dL	1.5 ± 1.9	1.2 ± 0.8	>0.99
Hypertension	81.0%	82.7%	>0.99
Peripheral vascular disease	17.6%	10.0%	>0.99
Cerebrovascular disease	11.3%	4.7%	0.62
Current smoker	23.5%	30.7%	>0.99
Congestive Heart Failure	12.7%	19.1%	>0.99
Previous PCI	31.0%	25.7%	>0.99
Previous CABG	17.6%	15.1%	>0.99
Previous MI	21.1%	21.7%	>0.99
Stable or unstable angina	62.2%	71.2%	>0.99
Operative Status			
Elective	63.4%	69.3%	>0.99
Urgent	27.5%	25.3%	
Emergency	9.2%	5.3%	

Abbreviations: STS=Society of Thoracic Surgeons; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MI=myocardial infarction;

[1]p-values using Bonferroni correction

Table 2: Procedural characteristics.

Characteristic	Clopidogrel (n=143, 48.3%)	Prasugrel (n=153, 51.7%)	p-value
Target coronary vessel			
Left main	5 (3.5%)	4 (2.6%)	0.659
Left anterior descending	67 (46.9%)	68 (44.4%)	0.678
Left circumflex	45 (31.5%)	22 (14.4%)	<0.001
Right	62 (43.4%)	46 (30.1%)	0.018
Saphenous vein graft	15 (10.5%)	8 (5.2%)	0.091
Procedural characteristic			
Access radial			
Glycoprotein IIb/IIa inhibitor	6 (4.2%)	4 (2.6%)	0.214
Type A or B1/B2 lesion	103 (72.0%)	87 (56.9%)	0.007
Type C lesion	40 (28.0%)	66 (43.1%)	0.036
Drug-eluting stent	111 (77.6%)	133 (86.9%)	0.009
Bare metal stent	27 (18.9%)	13 (8.5%)	
Complications			
Bleeding from entry site	0 (0%)	0 (0%)	>0.99
Access site hematoma	0 (0%)	1 (0.7%)	0.333
Discharge medications			
Aspirin	139 (97.2%)	149 (97.4%)	0.923
Beta-blocker	109 (76.2%)	113 (73.9%)	0.638
Angiotensin converting enzyme inhibitor	70 (49.0%)	76 (49.7%)	0.901
Angiotensin receptor blocker	26 (18.2%)	22 (14.4%)	0.375

Table 3: Conditional survival analysis for repeated MACE events.

Characteristic	Clopidogrel (n=143, 48.3%)	Prasugrel (n=153, 51.7%)	p-value
Number of MACE events per patient			
0	117 (81.8%)	136 (88.9%)	
1	16 (11.2%)	14 (9.2%)	0.139*
2	8 (5.6%)	3 (2.0%)	
3	2 (1.4%)	0 (0.0%)	
Total MACE events	38	20	0.027**
Total MI	36	19	0.035**
Total stroke	1	1	a
Total deaths	1	0	a
Hazard Ratio, repeated MACE	1.37 (95%CI: 0.74, 2.52)	Reference	0.319***
Hazard Ratio, repeated MI only	1.32 (95%CI: 0.71, 2.45)	Reference	0.377***

*Unadjusted chi-squared test; **Unadjusted repeated events Cox proportional hazards model;

***Propensity-adjusted (variables in Table 1) repeated events Cox proportional hazards model; 95%CI=95% confidence intervals

[a]The outcomes of stroke and death contained inadequate sample sizes to perform meaningful analyses.

Abbreviations: MACE=Major Adverse Cardiac Event; MI=myocardial infarction

was comparable mortality but reduced in-hospital bleeding with prasugrel. The authors concluded that these differences were probably due to patient selection as patients treated with prasugrel generally had lower frequency of ischemic and hemorrhagic risk factors [17].

Bivalirudin results in significant additional suppression of platelet aggregation, over and above that achieved with 600 mg clopidogrel loading dose, which unfractionated heparin does not [8].

Prasugrel achieves greater and more rapid platelet inhibition than clopidogrel, likely because of more efficient generation of the active metabolite [18]. The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction44 (PRINCIPLE-TIMI 44) trial found that in patients undergoing elective PCI, prasugrel achieved greater platelet inhibition than did clopidogrel after a loading dose and during maintenance treatment [19]. Also, genetic difference impacts the efficacy of clopidogrel. Carriers of the CYP2C19 allele receive a 32.4 percentage point lower exposure to the active metabolite than people without this allele. The results for this subgroup in TRITON-TIMI 38 showed a similar, or slightly greater, lowering in the endpoint of cardiovascular death, MI and stroke, and in stent thrombosis with prasugrel as in the overall study population [20].

The ACCF/AHA/SCAI guidelines recommend 600 mg loading dose but do not specify the timing [2]. While the European guidelines recommend a 3

00 mg more than 6 hours pre-PCI, or 600 mg at least 2 hours before PCI if that is not possible [21].

However, in the daily practice, the antiplatelet drug and dose is frequently administered a few minutes before PCI [22,23]. This allows for diagnostic angiography before the dose is administered, to rule out the need for CABG which carries increased risk of bleeding if performed after loading dose [1,23]. Prasugrel achieves greater and more rapid platelet inhibition than clopidogrel [18]. The time taken to reach, at least, 20% inhibition of platelet aggregation is 30 minutes for prasugrel vs. 1.5 hours for clopidogrel [24]. So, prasugrel may be a better choice when waiting until just before PCI to administer the antiplatelet dose.

In the present study, there were no statistically significant differences between both groups in terms of ischemic complications with a tendency towards more myocardial infarctions in the clopidogrel group, which did not reach statistical significance after adjusting for cardiovascular risk factors. Although it has been previously established that the use of prasugrel is more cost-effective than clopidogrel in patients with acute coronary syndrome undergoing elective PCI, (10) clopidogrel is now available as a generic and is available at a lower price.

Study Limitations: The generalizability of our results is limited because of the observational, retrospective, single-center nature of our study. Although the 2 groups had minor differences (Tables 1 and 2), important factors influencing the operating physician's choice of antiplatelet agent might not have been identified.

Conclusions

In this retrospective analysis, after a mean follow up of 40 months, there were no significant differences in the incidence of MACE between patients' anticoagulated with bivalirudin and given either clopidogrel and prasugrel during PCI.

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