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

Benjamin MM1, Filardo G2,3, Pollock BD2, Sass DM1 and Schussler JM4*

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 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
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. 1119 ± 423 days for prasugrel patients, HR=0.74, 2.52; p=0.377 and Repeated MI: HR=1.32; 95%CI: 0.71, 2.45; p=0.377 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].

**Discussion**

The TTRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitorN 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 percutaneous 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 Angioplasty 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>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel (n=143, 48.3%)</th>
<th>Prasugrel (n=153, 51.7%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.9 ± 11.8</td>
<td>63.2 ± 10.5</td>
<td>0.67</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.1 ± 5.5</td>
<td>30.0 ± 6.7</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Female gender</td>
<td>33.1%</td>
<td>28.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>White</td>
<td>74.7%</td>
<td>78.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Black</td>
<td>70.6%</td>
<td>72.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hispanic</td>
<td>67.8%</td>
<td>72.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>7.0%</td>
<td>1.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32.4%</td>
<td>32.9%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8.7</td>
<td>1.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.5 ± 1.9</td>
<td>1.2 ± 0.8</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81.0%</td>
<td>82.7%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>17.6%</td>
<td>10.0%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11.3%</td>
<td>4.7%</td>
<td>0.62</td>
</tr>
<tr>
<td>Current smoker</td>
<td>23.5%</td>
<td>30.7%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>12.7%</td>
<td>19.1%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>31.0%</td>
<td>25.7%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>17.6%</td>
<td>15.1%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Previous MI</td>
<td>21.1%</td>
<td>21.7%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Stable or unstable angina</td>
<td>62.2%</td>
<td>71.2%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Operative Status</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Elective</td>
<td>63.4%</td>
<td>69.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Urgent</td>
<td>27.5%</td>
<td>25.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Emergency</td>
<td>9.2%</td>
<td>5.3%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Abbreviations: STS=Society of Thoracic Surgeons; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; MI=myocardial infarction; "p-values using Bonferroni correction
had lower frequency of ischemic and hemorrhagic risk factors [17].

due to patient selection as patients treated with prasugrel generally
was comparable mortality but reduced in-hospital bleeding with
vasculitis, over and above that achieved with 600 mg clopidogrel
aggregation, over and above that achieved with 600 mg clopidogrel
loading dose, which unfracthionated 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 Infarction 44 (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
vascular 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 [1,2]. 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.

Bivalirudin results in significant additional suppression of platelet

Table 2: Procedural characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel (n=143, 46.3%)</th>
<th>Prasugrel (n=153, 51.7%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target coronary vessel</td>
<td>Left main</td>
<td>5 (3.5%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>Left anterior descending</td>
<td>67 (46.9%)</td>
<td>68 (44.4%)</td>
</tr>
<tr>
<td></td>
<td>Left circumflex</td>
<td>45 (31.5%)</td>
<td>22 (14.4%)</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>62 (43.4%)</td>
<td>46 (30.1%)</td>
</tr>
<tr>
<td></td>
<td>Saphenous vein graft</td>
<td>15 (10.5%)</td>
<td>8 (5.2%)</td>
</tr>
</tbody>
</table>

Procedural characteristic

Access radial

Glycoprotein IIb/IIIa inhibitor

Type A or B1/B2 lesion

Type C lesion

Drug-eluting stent

Bare metal stent

Complications

Bleeding from entry site

Access site hematoma

Discharge medications

Aspirin

Beta-blocker

Angiotensin converting enzyme inhibitor

Angiotensin receptor blocker

Table 3: Conditional survival analysis for repeated MACE events.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel (n=143, 46.3%)</th>
<th>Prasugrel (n=153, 51.7%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MACE events per patient</td>
<td>0</td>
<td>117 (81.8%)</td>
<td>136 (88.9%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>16 (11.2%)</td>
<td>14 (9.2%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8 (5.6%)</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 (1.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total MACE events</td>
<td>38</td>
<td>20</td>
<td>0.027**</td>
</tr>
<tr>
<td>Total MI</td>
<td>36</td>
<td>19</td>
<td>0.035**</td>
</tr>
<tr>
<td>Total stroke</td>
<td>1</td>
<td>1</td>
<td>a</td>
</tr>
<tr>
<td>Total deaths</td>
<td>1</td>
<td>0</td>
<td>a</td>
</tr>
<tr>
<td>Hazard Ratio, repeated MACE</td>
<td>1.37 (95% CI: 0.74, 2.52)</td>
<td>Reference</td>
<td>0.319***</td>
</tr>
<tr>
<td>Hazard Ratio, repeated MI only</td>
<td>1.52 (95% CI: 0.71, 2.45)</td>
<td>Reference</td>
<td>0.377***</td>
</tr>
</tbody>
</table>

*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

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

References


doi:http://dx.doi.org/10.4172/2324-8602.1000271


