Contemporary Use of Prasugrel in Clinical Practice
Insights From the Blue Cross Blue Shield of Michigan Cardiovascular Consortium

Amneet Sandhu, MD; Milan Seth, MS; Simon Dixon, MD; David Share, MD, MPH; David Wohns, MD; Thomas LaLonde, MD; Mauro Moscucci, MD, MBA; Arthur L. Riba, MD; Michael Grossman, MD; Hitinder S. Gurm, MBBS

Background—Prasugrel is a recently approved thienopyridine for use in patients with acute coronary syndromes undergoing percutaneous coronary intervention. There are no data on contemporary use of prasugrel in routine clinical practice.

Methods and Results—We assessed the patterns of prasugrel use among 55,821 patients who underwent percutaneous coronary intervention and were discharged alive from January 2010 to December 2011 at 44 hospitals participating in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Potential inappropriate therapy was defined as use in patients who had a history of cerebrovascular disease, weighed <60 kg, or were aged ≥75 years old. Clopidogrel was prescribed to 83% (n = 46,574) and 17% (n = 9,247) of patients received prasugrel on hospital discharge. A steady, linear increase in prasugrel use was seen during the study period, with discharge prescription increasing from 8.4% in quarter 1 of 2010 to 22.3% in quarter 4 of 2011. Of the total cohort, 69.1% of patients presented with acute coronary syndrome, and in this group, 17.2% received prasugrel. Among patients prescribed prasugrel, 28.3% (n = 2,614) received the medication for indications outside of acute coronary syndromes. One or more known contraindications to the drug were present in 6% to 10% of patients discharged on this agent.

Conclusions—There has been a steady increase in the use of prasugrel with the drug being used in ≈22% of patients undergoing percutaneous coronary intervention by study end. Prasugrel use in patients with known contraindications is not uncommon and may be a suitable target for focused quality improvement efforts.

Key Words: acute coronary syndromes ■ coronary revascularization ■ stents

Prasugrel is a novel thienopyridine approved by the Food and Drug Administration in July 2009 for use in patients undergoing percutaneous coronary intervention (PCI) in the setting of acute coronary syndrome (ACS).1 Relative to clopidogrel, prasugrel offers more consistent and faster acting platelet inhibition.2 In patients undergoing PCI for ACS, compared with clopidogrel, prasugrel has superior anti-ischemic efficacy at the cost of a higher risk of bleeding complications. Subgroup analysis from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON TIMI) 38 trial showed that patients with low body weight (<60 kg), prior history of a cerebrovascular event, and age ≥75 years are at a greater risk of bleeding complications without suggestion of clinical benefit in these groups.1 Accordingly, the Food and Drug Administration, manufacturer, and the present American College of Cardiology/American Heart Association guidelines recommend against the use of prasugrel in these patient subgroups.3,4

There is a paucity of data on contemporary prasugrel use in clinical practice. The purpose of this study was to evaluate patterns of prasugrel use among all patients undergoing PCI in Michigan across 44 hospitals participating in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2).

Methods

BMC2-PCI Database

The BMC2-PCI is a prospective, multicenter registry that represents a regional collaborative effort to assess and improve quality of care and outcomes of patients with coronary disease who undergo PCI. In use since 1998, this registry now encompasses all nonfederal hospitals in Michigan and has been approved by the institutional review boards of all participating hospitals. A standardized data collection tool was used to collect baseline clinical, demographic, procedural, angiographic, and medication data, as well as procedural
WHAT IS KNOWN

• Prasugrel is a novel medication available for use in patients undergoing percutaneous coronary intervention in the setting of acute coronary syndromes.
• This medication offers more consistent, faster platelet inhibition and has superior anti-ischemic efficacy at the cost of a higher risk of bleeding complications compared with clopidogrel.

WHAT THE STUDY ADDS

• A steady increase in the use of prasugrel, from 8.4% to 22.5% during the study period, demonstrates a cautionary uptake of this medication since drug approval.
• The leading reason for prescription of this drug is unstable angina/non–ST-segment-elevation myocardial infarction, although one third of patients receiving prasugrel did so for reasons other than acute coronary syndrome.
• A significant portion of patients are prescribed this medication in the setting of known contraindications.

Data Collection and Statistical Analysis

A total of 65,175 patients underwent PCI at 44 hospitals from January 2010 to December 2011. Exclusion criteria included death before discharge (n=896), balloon only PCI or unknown stent placement (n=6,460), concurrent use of clopidogrel and prasugrel at discharge (n=1,071), use of neither clopidogrel nor prasugrel at discharge (n=1,613), documented contraindication to clopidogrel (n=255), or documented contraindication to prasugrel (n=23). After exclusion, 55,821 patients were included in this analysis. The choice of pharmacotherapy was at the discretion of the operating physician within the dictates of the individual hospital policy. Continuous variables are expressed as mean±SD, and discrete variables are expressed as frequency counts and percentages. R version 2.14 was used for all analysis.

Results

Of 65,175 patients who underwent PCI, 55,821 fit the inclusion criteria at 44 hospitals between January 2010 and December 2011 throughout the state of Michigan. Of the study population, 83% (n=46,574) were prescribed clopidogrel and 17% (n=9,247) were prescribed prasugrel at hospital discharge. The Table displays patient demographics, preprocedural medications, and historical clinical data of the cohort. Age distribution and in-hospital outcomes. The registry does not specifically record history of transient ischemic attack (TIA) or stroke but does track prior history of cerebrovascular disease (CVD) defined as prior stroke or TIA, as well as significant carotid disease. CVD was used as a surrogate for patients with a history of stroke or TIA for this analysis. Details of the data collection are described in previous publications.

A dedicated staff member collected the data and forwarded them to the coordinating center. Medical records of all patients undergoing coronary artery bypass grafting as well as those patients who died in the hospital were reviewed by auditors from the coordinating center. Medical records of all patients undergoing PCI at each participating institution ranging from 0% to 40%.

Table. Patient Demographics, Preprocedural Medications, and Historical Clinical Data for the Cohorts Receiving Prasugrel and Clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N (%)</td>
<td>9,247 (16.6%)</td>
<td>46,574 (83.4%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age, y</td>
<td>59±9.7</td>
<td>66±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>73.7</td>
<td>64.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.5±7.6</td>
<td>30.5±7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>35.8</td>
<td>28.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>78.5</td>
<td>85.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>34.6</td>
<td>37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline GFR, mL/min</td>
<td>92.2±30.5</td>
<td>76.7±32.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF, %</td>
<td>7</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>28.3</td>
<td>34.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>11.8</td>
<td>19.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>36.7</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Significant valve disease, %</td>
<td>2.9</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>5</td>
<td>11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding, %</td>
<td>0.3</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline hemoglobin, mg/dL</td>
<td>14.1±1.7</td>
<td>13.4±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid, %</td>
<td>6.7</td>
<td>10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uninsured, %</td>
<td>7.8</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>93.7</td>
<td>95.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heparin, %</td>
<td>67.5</td>
<td>70.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LMWH, %</td>
<td>7.1</td>
<td>5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa inhibitor, %</td>
<td>39.5</td>
<td>33.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bivalirudin, %</td>
<td>33.5</td>
<td>38.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Total fluoroscopy time, min</td>
<td>12.9±9.7</td>
<td>14.5±11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total contrast, mL</td>
<td>198.7±76.8</td>
<td>193.5±78.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bare metal stent, %</td>
<td>15.9</td>
<td>25.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-eluting stent, %</td>
<td>85.7</td>
<td>75.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CHF, congestive heart failure; GFR, glomerular filtration rate; LMWH, low molecular weight heparin; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

for clopidogrel was evenly spread while the majority of those receiving prasugrel were <60 years old. Women constituted 35.1% and 26.3% of those receiving clopidogrel and prasugrel, respectively. Current smoking was significantly more common among the prasugrel group. Multiple statistically significant differences were noted in patient comorbidities between the 2 groups. Patients in the clopidogrel group were more likely to have hypertension, congestive heart failure, extracardiac vascular disease, diabetes mellitus, a history of myocardial infarction, atrial fibrillation, a history of coronary artery bypass grafting, and prior PCI. Figure 1 shows prasugrel use per quarter for the total cohort during the time period studied. A linear trend is noted indicating an increase in clinical use of prasugrel from 8.4% in quarter 1 of 2010 to 22.3% in quarter 4 of 2011. Figure 2 displays the considerable variation of prasugrel use across participating institutions ranging from 0% to 40%.

Figure 3 exhibits prasugrel use by indication for patients with and without known contraindications. Of the total cohort,
69.1% (n=38,589) presented with ACS and 17.2% (n=6633) were prescribed prasugrel. Among patients with ACS presenting with acute ST-elevation–myocardial infarction (STEMI), 20.7% were discharged on this medication. A total of 4471 (23%) of 19,569 patients presenting with unstable angina or non-STEMI (NSTEMI) for whom prasugrel was not contraindicated received this medication. Among patients prescribed prasugrel, the presenting diagnosis in 54.2% was unstable angina/NSTEMI, whereas 17.5% received the medication for STEMI. ACS was not present among 28.3% of patients who were discharged on prasugrel. Of the total cohort, 30.9% (n=17,232) presented with non-ACS conditions, and 15.2% (n=2614) of patients in this group were treated with prasugrel. Figure 4 displays trends in prasugrel use during the study period for ACS and non-ACS indications.

In total, among patients presenting with ACS (n=38,589, 69% of total), ≥1 contraindications to prasugrel were present in 34% (n=13,069) of patients. Nine hundred fifty-three patients had ≥1 known contraindications to the drug as defined in our study. Among this group, 52% (n=498) had a history of CVD, 35% (n=335) were >75 years of age, and 22% (n=208) weighed <60 kg. Figure 5 exhibits trends in use of prasugrel among patients with known contraindications. To account for the inclusion of carotid disease as part of our study’s definition of CVD, cases with mutually exclusive contraindications based on age and weight were isolated. Of the patients discharged on prasugrel in this study, we estimate 6% to 10% had 1 or more known contraindications, including weight <65 kg, age >75, and history of stroke or TIA.

The rate of a composite end point of bleeding requiring transfusion and vascular complications was significantly higher for patients who received prasugrel with a contraindication compared with patients without contraindications receiving the drug (transfusions: 2.4% versus 0.7%, vascular complications: 2.3% versus 1.7%, combined: 3.8% versus 2.1%; P<0.001). No major difference was found in other in-hospital outcomes, including the need for coronary artery bypass grafting, stroke or TIA, or periprocedural myocardial infarction in patients receiving prasugrel with and without contraindications.
Discussion

Our data provide an overview of the contemporary use of prasugrel among almost all patients undergoing PCI in Michigan. From quarter 1 of 2010 to quarter 4 of 2011, an \( \approx 3 \)-fold increase in the percentage of patients discharged on prasugrel after PCI is evident. It has been demonstrated that the interventional cardiology community changes its practice rapidly in response to the emergence of new data.\(^8\) In contrast, a slow and steady increase in the overall use of prasugrel was seen during our study period, likely demonstrating a cautionary uptake of this medication. Despite increasing use since Food and Drug Administration approval, the slow adoption of prasugrel may be related to a lack of perceived dramatic clinical benefit or concerns about higher risk of bleeding and cost. In addition, there is a considerable variation in use across institutions; this potentially could be a result of drug accessibility, familiarity with clopidogrel, systems practice, or patient/clinician preference.

Although the leading reason for prescription of this drug is unstable angina/NSTEMI, one third of patients receiving prasugrel did so for non-ACS conditions. Recent data demonstrate a lack of benefit of prasugrel over clopidogrel in nonvascularized patients with ACS. This would suggest that the benefit of prasugrel over clopidogrel may be specific to the indications that were studied, and extrapolation to patients who were not enrolled in TRITON TIMI 38 trial may not be justified. Further studies are therefore warranted to define the use of this agent in other patient populations, including the significant portion receiving it for non-ACS conditions.\(^9,10\)

Of concern, we found that a significant portion of patients receive prasugrel in the setting of known contraindications. Known relative contraindications to prasugrel include age >75 years and weight <60 kg with an absolute contraindication of prior history of stroke/cerebrovascular accident or TIA. Although we were unable to specifically assess how many patients with CVD had a prior TIA or stroke in our study population, between 6\% and 10\% of patients receiving this drug do so with a known contraindication. With an increase in overall use of this medication during the study period, a concerning increase in use is also evident in patients with contraindications. Of note, a large difference in bleeding requiring transfusion was apparent between the indicated and contraindicated group of patients who were treated with prasugrel, thus highlighting these patients’ propensity for a greater risk of bleeding. Given the previously demonstrated increased long-term risk of bleeding in these patients, physicians need to be cognizant of these concerns when prescribing this drug.\(^1,11\) Further study is required for analysis of potential adverse, long-term outcomes in this increasing subset of patients.

Study Limitations

Hospitals participating in the BMC2 registry are actively involved in ongoing collaborative quality improvement efforts, and these data may not represent practice patterns at other institutions. It is possible that our practice patterns are different from other regions, which may limit the generalizability of our findings. Additionally, our study was limited by the retrospective nature of the data and the absence of information on patient-specific factors such as severity of disease, comorbidities, and procedural success. Despite these limitations, our study provides valuable insights into the contemporary use of prasugrel in Michigan and highlights the need for further research to understand the implications of these findings for patient care and quality improvement.
hospitals. However, these data are generalizable in that they reflect the outcomes of almost all patients undergoing PCI in Michigan. Given variables recorded in our database, we could not isolate a history of stroke or TIA and used CVD as a surrogate for these conditions. Other limitations include data collection on drug prescription at hospital discharge without knowledge of actual dosage prescribed and use of prescription or compliance with medication(s). In addition, data collected in this study are limited to in-hospital outcomes and revolve around a single, procedurally oriented patient admission. As a result, our study was not designed to define the long-term impact of use of therapy in this patient population. Finally, no data on platelet aggregation studies were collected, and we are unable to evaluate whether prasugrel use was influenced by the results of platelet function testing.

Conclusions
Our study provides an analysis of contemporary use of prasugrel and trends in its clinical prescribing practices since drug approval. There has been a steady increase in the overall use of this medication during the study period, with a significant portion of patients receiving the medication for off-label indications. More importantly, this agent is used in a substantial number of patients with known contraindications. Further work is warranted to understand and reduce the use of this drug in this subset of patients who are at higher risk of complications.

Acknowledgments
We are indebted to all the study coordinators, investigators, and patients who participated in BMC2. H.S. Gurm had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis.

Reproducible research statement
Protocol: Data Dictionary available on request by contacting H.S. Gurm at hgurm@med.umich.edu.
Statistical code: Available to interested readers by contacting Milan Seth at msseth@med.umich.edu.
Data: Not available.

Sources of Funding
The BMC2 registry is funded by Blue Cross Blue Shield of Michigan. The sponsor had no role in analysis, study design, or decision to publish these results.

Disclosures
H.S. Gurm receives research funding from Blue Cross Blue Shield of Michigan, the National Institutes of Health, and the Agency for Healthcare Research and Quality. Dr Grossman receives research funding from Blue Cross Blue Shield of Michigan and the National Institutes of Health. Dr Share is employed part-time by Blue Cross Blue Shield of Michigan. The other authors report no conflicts.

References


Contemporary Use of Prasugrel in Clinical Practice: Insights From the Blue Cross Blue Shield of Michigan Cardiovascular Consortium
Amneet Sandhu, Milan Seth, Simon Dixon, David Share, David Wohns, Thomas LaLonde, Mauro Moscucci, Arthur L. Riba, Michael Grossman and Hitinder S. Gurm

Circ Cardiovasc Qual Outcomes. published online May 14, 2013;
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/early/2013/05/14/CIRCOUTCOMES.111.000060

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org/subscriptions/