OBJECTIVES

This study was designed to evaluate the safety profile of glycoprotein IIb/IIIa receptor inhibitors (GPI) in octogenarians undergoing percutaneous coronary intervention (PCI).

BACKGROUND

Patients ≥80 years old constitute the fastest growing segment of the U.S. population and have a high prevalence of coronary artery disease. Few data exist regarding the use of GPI during PCI in octogenarians, as these patients have been excluded from randomized clinical trials of GPI.

METHODS

Consecutive patients ≥80 years old undergoing PCI between January 1998 and June 2001 were evaluated for clinical outcomes and bleeding complications.

RESULTS

One thousand three hundred and ninety two of 14,308 patients (9.7%) undergoing PCI were ≥80 years old. Of these, 459 of 1,392 (33%) of the patients were treated with GPI. Octogenarians treated with GPI were more likely to present with acute coronary syndrome or infarction, receive stents, require an intra-aortic balloon pump, or undergo multi-vessel PCI. Glycoprotein receptor inhibitor use was associated with a higher rate of bleeding, but the transfusion rate was similar to that in patients who did not receive GPI (9.8% vs. 8.6%, p = NS). No cases of intracranial hemorrhage were observed. By multivariate analysis, GPI treatment was associated with longer hospitalization but did not independently predict the need for transfusion or affect mortality.

CONCLUSIONS

Octogenarians have a high incidence of bleeding and need for transfusion after PCI. Although the use of GPI was associated with more access and non-access site bleeding and longer hospital stay, GPI treatment does not significantly increase the risk of transfusion or intracranial hemorrhage in this non-randomized cohort. (J Am Coll Cardiol 2003;42:428–32) © 2003 by the American College of Cardiology Foundation

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Patients older than 80 years of age constitute the fastest growing segment of the U.S. population and have a high prevalence of coronary artery disease (1,2). In the era of the dramatic growth of percutaneous coronary intervention (PCI), octogenarians’ cardiac and non-cardiac comorbidities are likely to be associated with higher complication rates during PCI (3–7). Although glycoprotein IIb/IIIa receptor inhibitors (GPI) are increasingly used in accordance to American College of Cardiology/American Heart Association guidelines (8) to reduce the incidence of ischemic complications in patients presenting with acute coronary syndrome (ACS) and also during PCI, few efficacy and safety data exist regarding the use of GPI in octogenarian patients. Randomized clinical trials have routinely enrolled patients younger than 75 to 80 years old. Limited data on elderly patients (generally younger than 80 years) showed that the relative benefits of GPI in older patients are similar to those of younger patients, but this may even translate into a greater absolute benefit in light of higher event rates (9–11). Nonetheless, a major concern with octogenarians and nonagenarians is the risk of bleeding—especially of intracranial hemorrhage. The purpose of this study was to assess the safety profile of GPI treatment in octogenarians undergoing PCI.

METHODS

Study population. All patients ≥80 years old undergoing elective or emergency PCI at William Beaumont Hospital between January 1998 and June 2001 were included in the study. Patients were stratified according to GPI treatment. Percutaneous intervention. Balloon angioplasty, atherectomy (rotational or extraction), or stent implantation, either alone or in combination were performed at the operators’ discretion. The activated clotting time was maintained at ≥250 to 300 s during the procedure, depending on whether or not a GPI was used. Early sheath removal and avoidance of post-intervention heparin were encouraged. All patients
Abbreviations and Acronyms

ACS = acute coronary syndrome
CK-MB = creatine kinase-MB fraction
GPI = glycoprotein IIb/IIIa receptor inhibitor
IABP = intra-aortic balloon pump
LOS = length of stay after PCI
MI = myocardial infarction
PCI = percutaneous coronary intervention

were taking aspirin, and patients received either ticlopidine or clopidogrel for two to four weeks if they received a stent. Individual operators dictated other medications.

Data collection and definitions. Baseline clinical and catheterization data were obtained prospectively at the time of the procedure by research nurses and entered into a computerized database. Clinical outcomes and any adverse events were reported by operators and confirmed by dedicated research nurses. At least one creatine kinase-MB fraction (CK-MB) assay was obtained 8 to 12 h after PCI. Non-Q-wave myocardial infarction (MI) was defined as a single CK-MB ≥3 upper limit of normal (or 50% rise if abnormal baseline value) in the absence of pathologic Q waves. Serum creatinine was routinely measured at 24 h, with additional measurements in patients with baseline renal insufficiency or those hospitalized longer. Acute renal failure was defined as 1.0 mg/dl serum creatinine rise from baseline levels. Creatinine clearance was calculated using the Cockcroft-Gault formula (12). Access site bleeding was defined as a hematoma ≥3 cm.

Statistical analysis. Data analysis was performed using SAS software (version 8.0, SAS Inc., Cary, North Carolina). Results are expressed as percentages, mean ± SD, or median (25th, 75th percentile). The Fisher exact or chi-square test (when expected frequency <5) was used to compare categorical variables. Continuous variables were compared using the Student two-sided t test, but creatinine, creatinine clearance, contrast amount, and length of stay (LOS) were compared using the Wilcoxon rank test because of their non-normal distribution. Independent predictors of LOS and transfusion requirement were determined by stepdown multivariate analysis of variance model and logistic regression analysis, respectively. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Between January 1998 and June 2001, 14,308 patients underwent PCI at William Beaumont Hospital. One thousand three hundred and ninety two (9.7%) patients were ≥80 years of age (range 80 to 98 years; 25% >85 years). Of these, 459 (33%) received a GPI at the operators’ discretion. Baseline characteristics for octogenarians are shown in Table 1. Most received epifibatide (73%), which was infused for 12 to 18 h. Abciximab (27%) was infused for 12 h. Glycoprotein inhibitor treatment was stopped early if bleeding occurred. Patients treated with GPI were more likely to be male and to present with an ACS or acute MI and were less likely to have peripheral vascular disease (19% vs. 25%, p<0.05) or peptic ulcer disease (14% vs. 18%, p=0.049).

Table 2. Procedural Data in Octogenarians Undergoing PCI

<table>
<thead>
<tr>
<th>Variables</th>
<th>No GPI (n = 933)</th>
<th>GPI (n = 459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycoprotein receptor inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab (%)</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>Eptifibatide (%)</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>Number of vessels treated†</td>
<td>1 (1, 1)</td>
<td>1 (1, 1)</td>
</tr>
<tr>
<td>One vessel (%)</td>
<td>83</td>
<td>77†</td>
</tr>
<tr>
<td>Two vessels (%)</td>
<td>16</td>
<td>20†</td>
</tr>
<tr>
<td>≥3 vessels (%)</td>
<td>1</td>
<td>3†</td>
</tr>
<tr>
<td>Patients with venous sheaths (%)</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Venous sheath size (Ff)†</td>
<td>6.0 (6.0, 7.0)</td>
<td>7.0 (6.0, 7.0)</td>
</tr>
<tr>
<td>Arterial sheath size (Ff)†</td>
<td>7.0 (6.0, 8.0)</td>
<td>7.0 (6.0, 7.0)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump (%)</td>
<td>1.7</td>
<td>5.5†</td>
</tr>
<tr>
<td>Stents (%)</td>
<td>69</td>
<td>77†</td>
</tr>
<tr>
<td>Debubbling devices (%)</td>
<td>5</td>
<td>9†</td>
</tr>
<tr>
<td>Total contrast amount (cc)</td>
<td>197 ± 83</td>
<td>215 ± 84†</td>
</tr>
<tr>
<td>Peak activated clotting time (s)</td>
<td>344 ± 79</td>
<td>336 ± 73</td>
</tr>
<tr>
<td>Heparin dose (U)</td>
<td>7,687 ± 3,998</td>
<td>5,693 ± 4,494†</td>
</tr>
<tr>
<td>Heparin infusion post-PCI (%)</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

*p < 0.05. †Values in parentheses represent 25th and 75th percentiles.
Abbreviations as in Table 1.
(IABPs) were required more frequently in patients treated with GPI (5.5% vs. 1.7%, p < 0.01). The peak cath-lab activated clotting time was slightly lower (p = 0.054) in the GPI group. All patients received a thienopyridine after stenting.

**Bleeding complications.** Table 3 shows the incidence of bleeding complications. Glycoprotein inhibitor use was associated with a higher incidence of access site and non-access site bleeding. There was no difference in the incidence of retroperitoneal hemorrhage between groups, but gastro-intestinal bleeding was more frequent after GPI use. Upper airway bleeding was almost always related to trauma from endotracheal intubation or other instrumentation. There were no cases of pulmonary or intracranial hemorrhage in either group. Overall, the rate of transfusion was similar in both groups. Transfusion requirements and the number of red-cell units given to each patient (range 1 to 11 U) were similar. The proportion of patients in each group who required >3 U of red-cell transfusion was similar (1.0% to 1.5%).

**Clinical outcomes.** Patients with ST-segment elevation infarctions or no post-intervention CK-MB value were excluded from non-Q-wave MI analysis (11%). After PCI, non-Q-wave MI was more prevalent in the GPI group, whereas in-hospital mortality rates were similar between the two groups (Table 4). Length of stay was longer in the GPI group (p < 0.05). Median and 90th percentile LOS were one day longer for the GPI group.

**Multivariate analysis.** GPI treatment was not a significant predictor of transfusion requirement but was associated with longer LOS. Transfusion requirement was best predicted by non-access site bleeds and IABP requirement (odds ratio [OR] = 11.1 [4.7 to 26.1] and OR = 15.4 [6.7 to 35.1, respectively, p < 0.0001]). Length of stay was best predicted by male gender, creatinine clearance, peak creatinine, recent infarction, new stroke, and transfusion (p < 0.0001) as well as GPI use (p = 0.01).

**DISCUSSION**

Octogenarians represent an increasing proportion of patients presenting to cardiac catheterization laboratories around the country (2,13). Previous studies have reported a higher rate of ischemic complications after PCI in older patients (6). This is presumably a manifestation of associated comorbidities (14), including peripheral vascular disease, renal insufficiency, and anemia. In this study, 23%, 16%, and 6% of patients had peripheral vascular disease, severe renal insufficiency (creatinine clearance ≤30 cc/min), and severe anemia (hematocrit ≤30%), respectively. In addition to the higher prevalence of comorbidities in the elderly, arteries are prone to age-related changes such as medial calcification, more extensive atherosclerosis, dilation, tortuosity, and impairment of endothelial function. These factors contribute to a decline in procedural success and higher ischemic and bleeding complications with PCI in the elderly.

Glycoprotein inhibitor treatment plays a key role in the contemporary management of patients undergoing PCI. Several large-scale randomized clinical trials have noted GPI’s ability to reduce ischemic complications (namely, peri-procedural cardiac enzyme elevations) (9,15–19). On the basis of these data, GPI are now widely used to minimize ischemic complications during PCI. Glycoprotein inhibitor use has extended to octogenarians despite their exclusion from most randomized clinical trials (20).

This study evaluated the safety profile of GPI treatment (73% eptifibatide) in an unselected cohort of octogenarians undergoing elective and emergency PCI. Octogenarians treated with GPI had a higher incidence of bleeding and longer hospital stay. Access site bleeds were increased in the GPI group, which is consistent with observations from randomized clinical trials (9,11,17). Severe vascular access bleeding associated with a ≥10% hematocrit decline was nearly twice as likely with GPI treatment. Non-access site bleeds, mainly gastrointestinal bleeds, were also more frequent with GPI use. However, there was no increase in the risk of intracranial, pulmonary, or retroperitoneal hemor-
rhage. The overall rate of transfusion was similar in both patient groups. Furthermore, patients treated with GPI had higher rates of stenting, which can potentially confound comparison of ischemic events and bleeding complications between the two groups. Higher rate of thienopyridine use can increase the risk of bleeding and the need for transfusion (21,22). By multivariate analysis, non-access site bleeding and IABP use, but not GPI treatment, were independently associated with a requirement for transfusion.

In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, the use of abciximab was associated with major and minor bleeding rates of 1.5% and 2.9%, respectively (17). In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, major, minor bleeding, and transfusion rates were seen in 1.0%, 2.8%, and 1.0% of patients treated with eptifibatide, respectively (9). In our study, the incidence of bleeding complications in octogenarians was higher than the rates from randomized trials. However, the GPI trials represent a select population and did not enroll octogenarians. In our experience, transfusion requirements with GPI treatment for patients <75 years old are comparable to the results of recent randomized trials.

In our study, there was a higher incidence of post-procedural MI in the GPI group. However, patients treated with GPI were more likely to have presented with an ACS and have multi-vessel PCI performed, thus suggesting that operators selected ‘higher-risk’ patients for adjunctive GPI therapy. The in-hospital mortality in this cohort was 3%, which is higher than in recent reports (5). This reflects the higher-risk profile of octogenarian patients being referred for PCI in the present era. In this non-randomized comparison, no difference in in-hospital mortality or other clinical outcomes was observed in either patient group.

Length of stay after PCI can be used as a surrogate marker for procedural complications and adverse events. For instance, LOS has been demonstrated to increase with bleeding complications in previous GPI trials, with an increase in median LOS from one to four days with minor and major bleeds, respectively (23,24). The median LOS was one day longer for the GPI group and was best predicted by male gender, creatinine clearance, recent MI, new stroke, and transfusion requirement by multivariate analysis. Longer LOS was also independently associated with GPI use (p = 0.01).

**Study limitations.** Our study represents an observational study where patient data were retrieved from the William Beaumont Hospital database after it had been obtained and recorded prospectively. It has limitations that are associated with a single-center, non-randomized study, but it represents a large “real-life” experience of PCI in octogenarians. Selection criteria for GPI treatment were not prospectively defined, limiting the application of our findings. Clinical outcomes and adverse events were either reported by operators or recorded from chart review by dedicated research nurses without an adjudication process. Bleeding complications were not reported according to Thrombolysis In Myocardial Infarction criteria (25), which makes it more difficult to compare our cohort’s bleeding complications with previously reported randomized trials’ results. Furthermore, few data exist regarding the appropriate indications for blood transfusion in patients with coronary artery disease (26,27); as a result, transfusion requirement is at the discretion of clinicians.

**Conclusions.** Octogenarians have a relatively high risk of procedural mortality and bleeding complications related to their increased comorbidities, which include a higher incidence of cardiovascular disease, atherosclerosis burden, peripheral vascular disease, renal insufficiency, and anemia. Although octogenarians have greater bleeding and longer hospitalizations after GPI treatment, GPI therapy did not portend any additional and independent risk of transfusion after PCI and may be used cautiously in selected octogenarians. Percutaneous coronary intervention is associated with a higher risk of acute morbidity in octogenarians despite improved outcomes using modern interventional techniques, and it should be considered in the context of a critical and conservative assessment. Randomized trials would be required to definitively establish and confirm the efficacy and safety of GPI treatment in this population.

**Acknowledgments**

We appreciate the assistance of the William Beaumont Hospital research nursing staff who are responsible for maintaining our database.

**Reprint requests and correspondence:** Dr. Cindy L. Grines, Director, Cardiac Catheterization Laboratories, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, Michigan 48073. E-mail: cgrines@beaumont.edu.

**REFERENCES**


