Glycoprotein IIb/IIIa inhibitors (GPI) are potent parenteral inhibitors of platelet aggregation. Three agents are available—abciximab, eptifibatide, and tirofiban—and have been studied across the spectrum of acute ischemic heart disease as well as for elective and primary percutaneous coronary intervention (PCI) (1–12). The use of all 3 agents in the setting of PCI has been associated with a significant reduction in both short- and long-term events compared with unfractionated or low-molecular-weight heparin alone. Indeed, a 35% to 50% reduction in major adverse cardiovascular ischemic events was reported in low-, intermediate-, and high-risk patients undergoing PCI including patients with stable coronary artery disease (CAD) (1,3,4), patients presenting with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) (5,7,8), particularly patients with elevated troponin levels (5,12), and patients presenting with ST-segment elevation myocardial infarction (STEMI) (9–11) (Tables 1, 2, and 3). Notably, this reduction in events was mainly driven by a reduction in periprocedural myocardial infarctions, including
large or Q-wave myocardial infarctions, but there was no mortality reduction. Furthermore, a meta-analysis suggested that the use of GPI in NSTE-ACS was associated with a mortality reduction in diabetic patients, but this was not confirmed in a randomized trial (13). All of these studies demonstrated that the risk of bleeding, measured in a variety of ways, was higher with the addition of GPI to standard therapy; however, the lack of other therapeutic options and the high rate of adverse outcomes in both the acute coronary syndrome (ACS) and PCI settings made for an acceptable trade-off between the benefit of reduced ischemic events and the risk of increased bleeding.

Stenting was not routinely performed in these early studies, and patients were not pre-treated with thienopyridines. As the therapeutic armamentarium of ischemic heart disease has evolved, the utility of GPI has become less clear in a variety of clinical settings. The purpose of this review is to summarize the data reducing the role of GPI to a select population in the current era, review strategies for reducing the bleeding risk associated with GPI, and develop a proposal for what role GPI should play in the modern era.

**Bleeding Risk Associated With GPI**

Whereas ischemic events were strikingly reduced with abciximab in the EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications) trial, TIMI (Thrombolysis In Myocardial Infarction) major bleeding risk was similarly increased (7% for placebo vs. 14% for abciximab, p = 0.001). However, when adjusted-dose heparin and early sheath removal were implemented, GPI use was associated with a smaller (~1%) absolute increase in major bleeding in some studies (4,5,8), and no significant increase in major bleeding in other studies (2,3,6,7). Transfusion requirements and TIMI minor bleeding remained higher with GPI. Of note, the TIMI scale may underestimate rates of clinically important bleeding complications, and TIMI minor bleeding has been associated with over a 50% increase in the adjusted rate of death or myocardial infarction (MI) (14). Thus, significant bleeding associated with GPI may be more common than reported in these early trials.

As described in many PCI trials, most major bleeding occurs at the femoral access site (1,5). In fact, groin hematoma and retroperitoneal hemorrhage constituted 60% to 80% and 5% to 10% of major bleeding events, respectively, whereas gastrointestinal bleeding and intracranial bleeding constituted ~15% and <2% of major bleeding episodes, respectively. Thus, a safer vascular access strategy will potentially attenuate the bleeding risk associated with GPI.

**Evolution of PCI Pharmacotherapy: Diminishing Role of Traditional GPI Dosing and Current Indications**

As opposed to the pivotal GPI trials (1–11), studies performed in the current era of routine stenting and thienopyridine therapy have not consistently shown a net clinical benefit with GPI, that is, a benefit on the composite of death, MI, revascularization, and major bleeding (Table 4). After pre-loading with 600 mg of clopidogrel at least 2 h before elective PCI, the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial indicated that the addition of abciximab to unfractionated heparin in low-risk patients undergoing elective PCI did not further reduce ischemic complications (15); this was further expanded to elective PCI in diabetic patients in the ISAR-SWEET (Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics) trial (16). In both studies, bleeding rates were higher with GPI, therefore shifting the traditional benefit-risk ratio away from supporting their routine use in elective PCI. Furthermore, in the case of STEMI, the BRAVE-3 (Bavarian Reperfusion Alternatives Evaluation-3) trial (17) showed that the addition of abciximab to heparin in patients undergoing primary PCI and pre-loaded with 600 mg of clopidogrel in the emergency department did not reduce infarct size or improve clinical outcomes. Previously, the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial had shown that patients presenting with STEMI and undergoing stenting did not achieve the same marked benefit with abciximab as patients undergoing angioplasty did (10). Accordingly, the above-mentioned data questioned the value of GPI in both elective PCI and primary PCI. However, in the ISAR-REACT 2 trial, the tailored use of GPI for high-risk NSTE-ACS patients, particularly patients with elevated troponin levels, was beneficial despite stenting and pre-loading with clopidogrel and provided a substantial clinical benefit without significantly increasing major or minor bleeding rates (18). Thus, this trial identified a population in which GPI use is still warranted. In addition, the use of GPI in patients undergoing an elective PCI for stable CAD, but not adequately pre-loaded with thienopyridines, still seems reasonable (19).
Newer oral antiplatelet therapies, such as prasugrel and ticagrelor, have not been studied in the setting of elective PCI, but they have shown a benefit over clopidogrel in the setting of NSTE-ACS and STEMI managed invasively (20,21). In the TRITON–TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) trial of 13,608 patients with ACS undergoing PCI, 55% of the patients received GPI. The benefit of prasugrel over clopidogrel was consistent among patients who did or did not receive GPI, and the relative increase of major or minor bleeding with prasugrel versus clopidogrel was not significantly different in patients who were or were not treated with GPI (22). This established the benefit of prasugrel even in the setting of potent platelet inhibition with GPI. Similarly, the benefit and safety of ticagrelor versus clopidogrel was not altered in patients receiving GPI (21). However, whereas the utility of adding the potent and prompt platelet inhibitors prasugrel or ticagrelor to GPI has been investigated, the benefit and safety of adding GPI therapy to prasugrel or ticagrelor have not been evaluated yet and merit investigation.

In addition to antiplatelet therapy, anticoagulants have also undergone significant evolution and available options now include low-molecular-weight heparins (both subcutaneous and intravenous), synthetic indirect factor Xa inhibitors, and direct thrombin inhibitors. The agent that has been most studied directly against a GPI-based strategy is the direct thrombin inhibitor bivalirudin. Unlike unfractionated and low-molecular-weight heparins, bivalirudin does not activate platelets. The REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial (23) compared a strategy of bivalirudin plus provisional GPI to a strategy of unfractionated heparin plus routine GPI in ~6,000 patients undergoing elective PCI. The primary end point of 30-day death, MI, target vessel revascularization, and major bleeding was similar between

<table>
<thead>
<tr>
<th>Study (Year) Ref. #</th>
<th>GPI</th>
<th>n</th>
<th>Routine Stenting in the PCI Subgroup (% Stent Use)</th>
<th>Thienopyridine Pre-Loading</th>
<th>Percent Elevated Troponin</th>
<th>Death or MI at 30 Days</th>
<th>TIMI Major Bleeding</th>
<th>TIMI Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC (1994) (1)</td>
<td>Abciximab</td>
<td>2,099</td>
<td>No (&lt;2%)</td>
<td>No</td>
<td>N/A</td>
<td>42%</td>
<td>6.6% vs. 9.6%, p = 0.01</td>
<td>14% vs. 7%, p = 0.001</td>
</tr>
<tr>
<td>EPILOG (1997) (2)</td>
<td>Abciximab</td>
<td>2,792</td>
<td>No (15%)</td>
<td>N/A</td>
<td>46%</td>
<td>4% vs. 9.1%, p &lt; 0.001</td>
<td>2% vs. 3.1%, p = NS in low-dose UFH</td>
<td>4% vs. 3.7%, p = NS in low-dose UFH</td>
</tr>
<tr>
<td>EPISTENT (1998) (3)</td>
<td>Abciximab</td>
<td>2,399</td>
<td>Yes (100%)</td>
<td>No</td>
<td>Yes</td>
<td>36%</td>
<td>5.2% vs. 10.2%, p &lt; 0.001</td>
<td>1.5% vs. 2.2%, p = NS</td>
</tr>
<tr>
<td>ESPRIT (2000) (4)</td>
<td>Eptifibatide</td>
<td>2,064</td>
<td>Yes (95%)</td>
<td>No</td>
<td>Yes</td>
<td>13%</td>
<td>6.4% vs. 10.2%, p = 0.0014</td>
<td>1% vs. 0.4%, p = 0.027</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Year) Ref. #</th>
<th>GPI</th>
<th>n</th>
<th>% Undergoing PCI</th>
<th>Routine Stenting in the PCI Subgroup (% Stent Use)</th>
<th>Thienopyridine Pre-Loading</th>
<th>Thienopyridine Therapy After PCI</th>
<th>% ACS</th>
<th>Thienopyridine Therapy After PCI</th>
<th>% ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTURE (1997) (5)</td>
<td>Abciximab</td>
<td>1,560</td>
<td>98%</td>
<td>No (&lt;2%)</td>
<td>No</td>
<td>N/A</td>
<td>31%</td>
<td>4.8% vs. 9%, p = 0.003*</td>
<td>3.8% vs. 1.9%, p = 0.04</td>
</tr>
<tr>
<td>RESTORE (1997) (6)</td>
<td>Tirofiban</td>
<td>2,212</td>
<td>100%</td>
<td>No (2.5%)</td>
<td>N/A</td>
<td>33%</td>
<td>5.1% vs. 6.3%, p = 0.1</td>
<td>2.4% vs. 2.1%, p = 0.67</td>
<td>N/A</td>
</tr>
<tr>
<td>PRISM-PLUS (1998) (7)</td>
<td>Tirofiban</td>
<td>1,560</td>
<td>30%</td>
<td>No (&lt;2%)</td>
<td>No</td>
<td>N/A</td>
<td>45%</td>
<td>8.7% vs. 12%, p = 0.004</td>
<td>1.4% vs. 0.8%, p = 0.23</td>
</tr>
<tr>
<td>PURSUIT (1998) (8)</td>
<td>Eptifibatide</td>
<td>10,948</td>
<td>24%</td>
<td>(50%)</td>
<td>No</td>
<td>N/A</td>
<td>45%</td>
<td>14.2% vs. 15.7%, p = 0.004</td>
<td>3% vs. 1.3%, p &lt; 0.001</td>
</tr>
</tbody>
</table>

*In CAPTURE trial, the benefit of GPI was limited to patients with elevated troponin (death or MI at 30 days: 5.8% with GPI vs. 19.6% with placebo if troponin elevated; 5.2% with GPI vs. 4.9% with placebo if troponin was not elevated). MI = myocardial infarction; other abbreviations as in Table 1.
the 2 strategies. This noninferiority was driven by a significant reduction in major and minor bleeding with bivalirudin that came at the expense of a slight and nonsignificant increase in periprocedural MI rate. Similarly, in the open label ACUITY (Acute Catheterization and Urgent Intervention Strategy) trial of patients with intermediate-to-high-risk NSTEMI randomized to bivalirudin alone, bivalirudin plus GPI, or heparin (either unfractionated or low-molecular-weight) plus GPI, there was a trend toward a reduction of ischemic events in the GPI arms, particularly in patients undergoing PCI with 300 to 600 mg of clopidogrel in the emergency department; patients in the bivalirudin arm had significantly less bleeding, but a significantly higher rate of acute stent thrombosis (25). Interestingly, however, in the HORIZONS-AMI trial, the rate of stent thrombosis at 30 days was not significantly different between the 2 arms and bivalirudin was associated with a lower 30-day and 1-year mortality that may have been related to the bleeding reduction (25,26). Thus, although the role of GPI has been questioned in patients presenting with STEMI and receiving heparin (17), this role is further reduced in patients receiving bivalirudin. The American College of Cardiology guidelines currently give a Class IIa recommendation for the use of GPI at the time of primary PCI in select patients with STEMI, particularly patients with a large thrombus burden or those who have not received adequate thienopyridine pre-loading (27).

<p>| Table 3. Major Studies Addressing GPI Use in Patients Undergoing Primary PCI for STEMI |
|---------------------------------|-------------------|-----------------|-------------------------|-------------------------|</p>
<table>
<thead>
<tr>
<th>Study (Year) (Ref. #)</th>
<th>GPI</th>
<th>n</th>
<th>% Stent</th>
<th>Thienopyridine Loading Before or Immediately After PCI*</th>
<th>GPI vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMIRAL (2001) (9)</td>
<td>Abciximab</td>
<td>300</td>
<td>92%</td>
<td>No</td>
<td>Death, MI, Urgent TVR at 30 Days NS† p = 0.01 Major Bleeding† p = 0.004 Minor or Moderate Bleeding† p = 0.004</td>
</tr>
<tr>
<td>CADILLAC angioplasty arms (2002) (10)</td>
<td>Abciximab</td>
<td>1,046</td>
<td>0%</td>
<td>Yes</td>
<td>4.8% vs. 8.3%, p = 0.02 0.4% vs. 0.6%, p = Ns 2.3% vs. 2.5%, p = Ns</td>
</tr>
<tr>
<td>CADILLAC stent arms (2002) (10)</td>
<td>Abciximab</td>
<td>1,036</td>
<td>100%</td>
<td>Yes</td>
<td>4.4% vs. 5.7%, p = Ns 0.8% vs. 0.2%, p = Ns 4.3% vs. 2.5%, p = Ns</td>
</tr>
<tr>
<td>ON-TIME 2 (2008) (11)</td>
<td>Tirofiban</td>
<td>984</td>
<td>90%</td>
<td>Yes</td>
<td>7% vs. 8.2%, p = Ns 4% vs. 2.9%, p = Ns 6.1% vs 4.4%, p = Ns</td>
</tr>
</tbody>
</table>

*In the ON-TIME 2 trial, patients were pre-loaded with 600 mg of clopidogrel before arrival to the cardiac catheterization laboratory. In CADILLAC trial, 300 mg of clopidogrel or 500 mg of ticlopidine were given before cardiac catheterization. No loading dose of thienopyridine was administered in the ADMIRAL trial. †TIMI criteria were used to define major and minor bleeding in ADMIRAL and ON-TIME 2 trials, and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) trial criteria were used to define major and moderate bleeding in CADILLAC trial. §In the ON-TIME 2 trial, the high-bolus dose of tirofiban reduced the primary end point of residual ST-segment deviation 1 h after PCI but did not improve TIMI flow grade or clinical outcomes.

TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

<p>| Table 4. Randomized Trials of GPI Therapy During PCI in the Context of Routine Stenting and Adequate Thienopyridine Pre-Loading |
|-----------------|-----------------|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Study (Year) (Ref. #)</th>
<th>n</th>
<th>Study Population</th>
<th>% Complex (Type B2/C) Coronary Lesions</th>
<th>% Diabetes</th>
<th>TIMI Major Bleeding*</th>
<th>TIMI Minor Bleeding*</th>
<th>% Patients Requiring Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-REACT (2004) (15)</td>
<td>2,159</td>
<td>Stable CAD</td>
<td>65%</td>
<td>21%</td>
<td>4% vs. 4%, p = Ns 1% vs. 1%, p = Ns 2% vs. 2%, p = Ns 2% vs. 1%, p = 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR-SWEET (2004) (16)</td>
<td>701</td>
<td>Stable CAD diabetes</td>
<td>68%</td>
<td>100%</td>
<td>5.7% vs. 4.3%, p = 0.39 1.1% vs. 0.9%, p = Ns 3.4% vs. 1.4%, p = 0.09 2.3% vs. 0.6%, p = 0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAVE-3 (2009) (17)</td>
<td>800</td>
<td>STEMI</td>
<td>—</td>
<td>19%</td>
<td>4.7% vs. 3.5%, p = Ns 1.8% vs. 1.8%, p = Ns 3.7% vs. 1.8%, p = 0.06 3% vs. 3.3%, p = Ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR-REACT 2 (2006) (18)</td>
<td>2,022</td>
<td>ACS † troponin in 51%</td>
<td>80%</td>
<td>25%</td>
<td>8.9% vs. 11.9%, p = 0.034 1.4% vs. 1.4%, p = Ns 4.2% vs. 3.3%, p = Ns 2.5% vs. 2%, p = Ns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See TIMI bleeding definition in Table 1. †In the BRAVE-3 trial, abciximab was not associated with a reduction in infarct size (the primary end point). Patients were pre-loaded with 600 mg of clopidogrel in the emergency department. †In patients with elevated troponin values, event rates with GPI versus placebo: 13.1% versus 18.3%, p = 0.02. In patients without troponin elevation, event rates with GPI versus placebo: 4.6% versus 4.6%, p = 0.99.

CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Tables 1, 2, and 3.
Table 5. Measures That Reduce Bleeding Risk With GPI

<table>
<thead>
<tr>
<th>Dosage and infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bolus-only strategy or reduction of infusion duration</td>
</tr>
<tr>
<td>• Careful selection of upstream therapy in acute coronary syndromes limited to patients who have not received thienopyridine loading and who are at the highest spectrum of risk</td>
</tr>
<tr>
<td>• Heparin dose adjustment to obtain ACT &lt;250 s during PCI (starting bolus ≤50 U/kg)</td>
</tr>
<tr>
<td>• EP2Y12 tirofiban infusion dose adjustment in patients with creatinine clearance ≤50 and ≥30 ml/min, respectively</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avoidance of GPI in patients older than 75 years and in patients at high bleeding risk</td>
</tr>
<tr>
<td>• Targeting patients with NSTE MI undergoing PCI (particularly if not receiving bivalirudin or if receiving bivalirudin but not adequately pre-loaded with a thienopyridine)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Access selection and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use of transradial approach</td>
</tr>
<tr>
<td>• Use of smaller sheath size</td>
</tr>
<tr>
<td>• Prompt sheath removal</td>
</tr>
<tr>
<td>• Avoidance of venous sheath placement in case of femoral access</td>
</tr>
<tr>
<td>• Use of vascular closure devices (possibly)</td>
</tr>
</tbody>
</table>

ACT = activating clotting time; abbreviations as in Tables 1, 2, 3, and 4.

Current indications for GPI use. In summary, the anti-ischemic value of GPI seems currently limited to 4 subgroups of patients: 1) patients with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI (18), particularly if they are not receiving bivalirudin, or if they are receiving bivalirudin but are not adequately pre-loaded with a thienopyridine, as recommended by the American College of Cardiology guidelines (24,28); 2) patients having thrombotic complications or large side-branch closure or unsealed dissection during any PCI performed for stable or unstable CAD, whether bivalirudin is used or not (GPI were used for bailout in 7% and 9% of patients randomized to bivalirudin in the REPLACE-2 and ACUITY trials, respectively); 3) select patients with STEMI, particularly those not pre-loaded with a thienopyridine in the emergency department or those with a large thrombus burden; 4) patients undergoing ad hoc PCI for stable or unstable CAD and not adequately pre-loaded with a thienopyridine (19). In fact, studies that did not show a benefit of GPI in elective PCI had mandated appropriate clopidogrel pre-loading and there is currently not enough evidence that supports omitting bivalirudin in patients receiving heparin and not adequately pre-loaded with a thienopyridine (15,16,19). However, if bivalirudin is the anticoagulant used in elective PCI, GPI may be omitted regardless of thienopyridine pre-loading (29); as opposed to ACS, the comparable effectiveness of bivalirudin and heparin plus GPI in elective PCI was not influenced by clopidogrel pre-treatment (29). Also, GPI may be omitted in ad hoc elective PCI if a rapid-onset and potent oral P2Y12 receptor antagonist is loaded during PCI, but this strategy has yet to be tested.

On the other hand, if hyporesponsiveness to clopidogrel or aspirin is suspected clinically or on the basis of platelet function or genetic testing, GPI may have a role even in patients undergoing PCI for stable CAD. In the 3T/2R (Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel) study, patients undergoing PCI who were poor responders to aspirin, clopidogrel, or both who were treated with tirofiban compared to placebo had a significant reduction in the 30-day risk of major adverse cardiovascular events (3.8% vs. 10.7%, p = 0.031), without an increase in bleeding (30).

With further study, expanded use of bedside and laboratory platelet function testing, and wider use of genetic testing, the role of GPI in these situations will become better defined.

Because a robust relationship between major bleeding and increased mortality and morbidity has been reported in several analyses, the reduction of bleeding risk has become a primary target for improving PCI outcomes (31,32). Therefore, it is reasonable to better define strategies of GPI administration that would reduce bleeding risk in the 4 subgroups of patients who benefit from GPI, particularly patients with NSTEMI. Several potential options are available and are discussed herein (Table 5).

Duration of Infusion of GPI After PCI: The Appropriateness of Bolus-Only or Short-Infusion Strategy

Currently, on the basis of the EPIC and ESPRIT (Novel Dosing Regimen of Epifibatide in Planned Coronary Stent Implantation) trials, it is recommended to administer a 12-h infusion of abciximab and an 18– to 24-h infusion of epifibatide, respectively, after PCI. In the EPIC trial, an abciximab bolus followed by a 12-h infusion resulted in a 35% reduction in the rate of death, MI, or unplanned revascularization at 30 days compared with unfractionated heparin alone (1). By contrast, patients receiving bolus-only were protected for the first 6 h only; end points measured at
30 days demonstrated no difference between bolus-only and placebo because of ongoing ischemic events beyond 6 h, mainly driven by acute vessel closure. However, in the EPIC trial, thienopyridine therapy was not used and only balloon angioplasty was performed. Routine stenting with optimal deployment technique and coverage of dissection planes reduces the prothrombotic stimuli and may obviate the need for prolonged GPI infusion. However, due to the concern raised by the EPIC trial, subsequent trials of abciximab in PCI generally used bolus and 12-h infusion regimens despite routine stenting and thienopyridine therapy. Similarly, large trials of eptifibatide did not attempt to reduce or eliminate the infusion.

Few studies have specifically addressed the issue of the infusion duration in the modern era (Table 6) (33–35). The BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) trial randomized patients who received eptifibatide bolus therapy and underwent successful PCI with stenting to either a standard (18 h) or shorter (≤2 h) infusion of eptifibatide (33). All patients received appropriate clopidogrel therapy before or at the conclusion of PCI. Whereas 32% of patients had ACS with elevated troponin level, most patients had stable CAD. Moreover, patients with visible thrombus, unsealed dissection, coronary slow flow, or loss of major side branches were excluded. Compared with the standard infusion, the shorter infusion was associated with a similar incidence of periprocedural myocarditis and adverse ischemic events at 30 days and a significantly lower incidence of major bleeding (1% vs. 4.2%, \( p = 0.02 \)).

In the EASY (Early Discharge After Transradial Stenting of Coronary Arteries) trial by Bertrand et al. (34), 1,005 patients who received a bolus of abciximab during an uncomplicated transradial PCI were randomly allocated to either an abciximab bolus-only strategy and same-day discharge, or to a standard 12-h abciximab infusion and overnight hospitalization. Only 20% of patients had an elevated troponin level at the time of the procedure. The bolus-only strategy was noninferior with respect to the 30-day occurrence of death or adverse ischemic events. Major bleeding was low in both groups, likely related to the use of the radial access site. Of note, more than 90% of patients in the EASY trial had received clopidogrel >12 h before the procedure.

These findings are similar to those reported in a large retrospective single-center analysis (35). A major limitation of these studies is that they compared short-length with full-length regimens of GPI, rather than a short-length regimen of GPI with placebo. Because most of these patients were undergoing elective PCI for stable CAD and because in the current era, GPI are mainly beneficial in NSTEMI, there was a questionable need for GPI in most of these patients. Thus, this strategy needs to be adequately studied in NSTEMI and potentially in patients with stable CAD undergoing ad hoc PCI without clopidogrel pre-loading, where a bolus of GPI with a truncated infusion may be enough to bridge the gap between PCI and the 2-to-8-h time it takes clopidogrel to reach an adequate antiplatelet effect (this theory is yet unproven). The newer P2Y\(_{12}\) receptor antagonists, prasugrel or ticagrelor, which induce a much higher and consistent inhibition of platelet activity coupled with a prompt onset of activity within 30 min of administration, may further influence any need for GPI, more so prolonged GPI infusions, but this needs to be tested prospectively (36,37).

### Table 6. Studies Comparing a Bolus-Only Strategy or a Short Infusion of GPI With Long Standard Infusions

<table>
<thead>
<tr>
<th>Study (Year) (Ref. #)</th>
<th>Study Type</th>
<th>GPI Type</th>
<th>Study Population</th>
<th>B(_2)/C Coronary Lesion* (%)</th>
<th>Duration of Infusion</th>
<th>Adequate Clopidogrel Load Before PCI†</th>
<th>Bolus-Only or Short Infusion vs. Prolonged Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIEF PCI (2009) (33)</td>
<td>RCT, 624 patients</td>
<td>Eptifibatide</td>
<td>ACS (53%) or stable CAD</td>
<td>≤2 h vs. 18 h</td>
<td>70%</td>
<td>4.8% vs. 4.5%, ( p = 1.0 )</td>
<td>1% vs. 4.2%, ( p = 0.02 )</td>
</tr>
<tr>
<td>EASY (2006) (34)</td>
<td>RCT, 1,005 patients</td>
<td>Abciximab</td>
<td>ACS or stable CAD</td>
<td>Bolus-only vs. 12 h</td>
<td>92%</td>
<td>1.4% vs. 1.8%, ( p = N5 )</td>
<td>0.8% vs. 0.2%, ( p = N5 )</td>
</tr>
<tr>
<td>Kini et al. (2008) (35)</td>
<td>Retrospective analysis, 2,629 patients</td>
<td>Eptifibatide</td>
<td>ACS (39%) or stable CAD</td>
<td>Bolus-only vs. 12–18 h</td>
<td>54%</td>
<td>3.2% vs. 3%, ( p = 0.73 )</td>
<td>0.8% vs. 1.6%, ( p = 0.09 )</td>
</tr>
</tbody>
</table>

*Coronary lesions defined according to lesion classification of American College of Cardiology/American Heart Association. †The definition of appropriate clopidogrel load before PCI varied between studies (600 mg ± 2 h or 300 mg ± 6 h or 75 mg ± 4 days before PCI (33); 300 mg ± 12 h before PCI (34); 300 mg ± 3 h before PCI (35)). ‡Major and minor bleeding risks were defined according to REPLACE-2 study criteria. Major bleeding = intracranial, intracocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin ≥3 g/dl; any decrease in hemoglobin ≥4 g/dl; or transfusion of at least 2 U of packed red blood cells or whole blood. Minor bleeding = clinically overt bleeding that did not meet major bleeding criteria.

RCT = randomized controlled trial; other abbreviations as in Tables 1, 2, 3, 4, and 5.
GPI Dose Adjustment

Being renally cleared, eptifibatide and tirofiban infusion rates should be reduced by 50% if creatinine clearance (CrCl) is ≤50 or ≤30 ml/min, respectively, while maintaining the same bolus dose (38). In addition, eptifibatide is contraindicated in patients on dialysis (39). By contrast, abciximab does not require dose adjustment with renal failure. Data from moderate-to high-risk PCI patients with NSTE-ACS treated with eptifibatide in the PROTECT-TIMI 30 (Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents) trial showed that the lack of adjustment of the maintenance infusion occurred in 45% of patients with CrCl ≤50 ml/min and was associated with a high rate of bleeding complications (20%); in fact, no major or minor bleeding event occurred among patients with reduced CrCl who received the reduced-dose infusion (40). Consistent with these findings, data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry showed that excess dosing of eptifibatide and tirofiban occurs in 27% of patients treated with GPI, mainly in women, older patients, small patients, or patients with renal insufficiency (38). Excess dosing was associated with a 17.5% rate of major bleeding, a 36% increase in the adjusted rate of major bleeding, and a 50% increase in mortality. Furthermore, data from the National Cardiovascular Data Registry (NCDR)–CathPCI registry indicated that the use of eptifibatide in dialysis patients was associated with increased in-hospital bleeding and mortality risk (39). By contrast, abciximab seems relatively safe in advanced renal failure (41).

In aggregate, these data suggest that the risks associated with GPI can be mitigated in patients with chronic kidney disease. All patients undergoing PCI need to have CrCl assessed, and, if eptifibatide or tirofiban are used, their dosages need to be adjusted accordingly.

Impact of age and sex. Several analyses have shown that older patients have an increased bleeding risk with GPI. In a meta-analysis by Boersma et al. (12), the benefit of GPI decreased with advancing age, with a nonsignificant treatment effect in patients ≥60 years of age. Additionally, in a pre-specified subgroup analysis of ACUITY trial, the benefit of bivalirudin monotherapy over combined therapy with GPI in terms of the number needed to treat to prevent 1 bleeding event was particularly high in patients older than 75 years of age (42). These data suggest that the risk may outweigh the benefit in most patients older than 75 years of age, and, if used, the GPI dose should be adjusted and the infusion shortened or eliminated.

Results from the CRUSADE initiative indicate that women with ACS had higher rates of major bleeding than men among patients treated with GPI (15.7% vs. 7.3%, p < 0.0001) and among patients not treated with GPI (8.5% vs. 5.4%, p < 0.0001) (43). Treated women were also more likely to receive excess dosing of GPI than men (46.4% vs. 17.2%, p < 0.0001) were, and bleeding risk attributable to excess dosing was much higher in women (25.0% vs. 4.4%).

Anticoagulation Dose Adjustment

The EPILOG (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIB/IIIa Receptor [abciximab] Blockade) trial randomly assigned 2,799 low-risk patients to placebo plus standard-dose, weight-adjusted heparin (100 U/kg); abciximab plus standard-dose, weight-adjusted heparin; or abciximab plus a reduced-dose, weight-adjusted heparin (70 U/kg bolus, activated clotting time [ACT] goal 200 to 300 s) regimens. Although rates of 30-day composite ischemic events were reduced by 56% in both abciximab groups, bleeding was increased only in the abciximab plus standard-dose heparin group (2). In the ESPRIT trial, TIMI major bleeding was overall increased with eptifibatide therapy, but not in the tertile of patients with ACT <244 s (44). Later trials using low-dose heparin, early sheath removal, avoidance of routine placement of venous sheaths, and target ACT levels of 200 to 250 s reported no difference in major or minor bleeding for patients treated with abciximab versus placebo (3,7). This highlights the efficacy and safety of GPI when used in conjunction with a reduced-dose heparin regimen and a target ACT of 200 s.

Upstream Versus Downstream Administration of GPI in ACS

Early GPI studies have suggested that the upstream use of GPI in ACS reduces the risk of MI in the pre-procedural period compared with therapy with heparin only (5,7,8). Recently, however, in the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndromes) trial, the routine upstream addition of eptifibatide to the therapy of intermediate- and high-risk NSTE-ACS patients managed with an intended invasive strategy did not prove superior to their provisional downstream addition during PCI and was associated with an increase in bleeding (45). This may be in part explained by the fact that any anti-ischemic benefit conferred during the time interval preceding PCI is offset by a 2.4% increase in TIMI major or minor bleeding, and that patients assigned an invasive strategy did not always undergo PCI. In fact, the upstream use of GPI significantly reduced the absolute risk of ischemic events by 2.4% in patients who underwent PCI. Furthermore, in the FINESSE (Facilitated
The EARLY ACS trial could help determine subgroups of patients that may benefit from upstream use of GPI.

**Radial Versus Femoral Approach: Access Management**

Femoral access site bleeding complications constitute over one-half of the major bleeding that occurs after PCI (as demonstrated in the EPIC, CAPTURE [Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment], REPLACE-2, and ACUITY trials) (1,5,23,24). Recent data from the NCDR-CathPCI registry indicates that, although used in a small minority of PCI procedures, the radial artery access site, compared with the femoral artery access site, is associated with a 58% reduction of bleeding and vascular complications (47). This benefit is more pronounced in elderly patients and in women. These findings have been replicated in several registry analyses, 1 of which suggests that the radial approach is associated with a significant reduction in mortality (48). An ongoing multicenter randomized trial that is an extension of the CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes) study is comparing the transradial and the transfemoral access sites in patients with ACS undergoing PCI.

Importantly, this reduction in access site bleeding may attenuate the increase in bleeding risk associated with GPI. A recent analysis from the ACUITY trial reported that the use of bivalirudin monotherapy was associated with significantly less 30-day major bleeding than heparin plus GPI after femoral access (3.0% vs. 5.8%, \( p < 0.0001 \)), but not...
after radial access (4.2% vs. 2.2%, p = 0.19) (49). In a large Italian registry of patients who underwent PCI for ACS utilizing GPI, the transradial approach, in comparison with the transfemoral approach, was associated with low bleeding rates and a 6.6× lower odds of major/minor bleeding (50). These results confirm the findings of an analysis of 150 patients undergoing PCI and receiving GPI: no major access site bleeding complications occurred in the radial group (51). The radial approach may be particularly useful in women or high-bleeding risk patients receiving GPI. Furthermore, as opposed to transfemoral PCI, female sex was not a predictor of adverse clinical outcomes after transradial PCI performed under maximal antiplatelet therapy, including GPI (52).

If, by contrast, transfemoral access is used, early sheath removal within 4 to 6 h of the procedure seems fundamental in reducing bleeding risk (1,2,5). Though the reduction of vascular complications with vascular closure devices remains questionable, early sheath removal allowed by these devices may prove beneficial. A multivariate analysis from the NCDR-CathPCI registry showed that closure devices were significantly associated with less bleeding and vascular access complications (53). In addition, closure devices have been reported to be safe in patients receiving GPI (54). A recent analysis of the ACUITY trial data showed that vascular closure devices independently reduce access site bleeding by 22%; this benefit extended to patients receiving GPI (55). It is important to point out that these analyses are observational and that the safety and potential benefit may be driven by the operator’s experience with these devices.

Collectively, available data support the use of the radial access site, smaller sheaths (irrespective of the access site), prompt sheath removal, and possibly vascular closure devices to minimize bleeding risk, although additional prospective and/or randomized data are needed in some of these areas.

In summary, we suggest a strategy of GPI use that takes into account the patient’s baseline ischemic and bleeding risk and the above-described measures limiting hemorrhagic events (Fig. 1). Many ischemic risk factors are also bleeding risk factors (56,57), hence the importance of a careful use of GPI with the strategies outlined in Table 5.

Conclusions and Final Recommendations

- Early studies have shown a reduction of ischemic events with GPI, yet more recent studies performed in the era of routine thienopyridine therapy show an increase in bleeding risk and a less consistent net clinical benefit of GPI administration.
- To use GPI safely, one should:
  - Target high-risk patients, particularly NSTEMI patients or patients undergoing PCI without adequate clopidogrel pre-loading.
  - Avoid the routine upstream use of GPI in ACS, particularly if thienopyridines are used early on.
  - Appropriately adjust dose for patients with renal failure.
  - Reduce or eliminate the infusion.
  - Use radial approach, particularly in patients with NSTEMI who otherwise have an indication to receive GPI.
  - Select lower bleeding risk patients, which is challenging because ACS patients who are likely to benefit from GPI have a higher bleeding risk than stable patients (56,57).

Reprint requests and correspondence: Dr. Elias B. Hanna, Department of Medicine, Cardiovascular Section, Louisiana State University, 1542 Tulane Avenue, Room 323, New Orleans, Louisiana 70112. E-mail: ehanna10@yahoo.com.

REFERENCES

43. Alexander KP, Chen AY, Newby LK, et al., for the CRUSADE Investigators. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse Outcomes


Key Words: acute coronary syndrome(s) ■ bleeding risk ■ dose adjustment ■ glycoprotein IIb/IIIa inhibitor ■ percutaneous coronary intervention.