# Routine Upstream Initiation vs Deferred Selective Use of Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes

## The ACUITY Timing Trial

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**Context** In patients with moderate- and high-risk acute coronary syndromes (ACS) who undergo an early, invasive treatment strategy, current guidelines recommend administration of platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors, either upstream to all patients prior to angiography or deferred for selective use in the catheterization laboratory just prior to angioplasty. The preferred approach is undetermined.

**Objective** To determine the optimal strategy for the use of Gp IIb/IIIa inhibitors in patients with moderate- and high-risk ACS undergoing an early, invasive treatment strategy.

**Design** Prospective, randomized, open-label trial with 30-day clinical follow-up.

**Setting** Four hundred fifty academic and community-based institutions in 17 countries.

**Patients** A total of 9207 patients with moderate- and high-risk ACS undergoing an invasive treatment strategy.

**Interventions** Patients were randomly assigned to receive either routine upstream (n=4605) or deferred selective (n=4602) Gp IIb/IIIa inhibitor administration, respectively.

**Main Outcome Measures** The primary outcome was assessment of noninferiority of deferred Gp IIb/IIIa inhibitor use compared with upstream administration for the prevention of composite ischemic events (death, myocardial infarction, or unplanned revascularization for ischemia) at 30 days, using a 1-sided $\alpha$ level of .025. Major secondary end points included noninferiority or superiority of major bleeding and net clinical outcomes (composite ischemia or major bleeding).

**Results** Glycoprotein IIb/IIIa inhibitors were used more frequently (98.3% vs 55.7%, respectively) and for a significantly longer duration (median, 18.3 vs 13.1 hours; $P<.001$) in patients in the upstream group compared with the deferred group. Composite ischemia at 30 days occurred in 7.9% of patients assigned to deferred use compared with 7.1% of patients assigned to upstream administration (relative risk, 1.12; 95% confidence interval, 0.97-1.29; $P=.044$ for noninferiority; $P=.13$ for superiority); as such, the criterion for noninferiority was not met. Deferred use compared with upstream use resulted in reduced 30-day rates of major bleeding (4.9% vs 6.1%, respectively; $P<.001$ for noninferiority; $P=.009$ for superiority) and similar rates of net clinical outcomes (11.7% vs 11.7%; $P<.001$ for noninferiority; $P=.93$ for superiority).

**Conclusions** Among patients with moderate- and high-risk ACS undergoing an invasive treatment strategy, deferring the routine upstream use of Gp IIb/IIIa inhibitors for selective administration in the cardiac catheterization laboratory only to patients undergoing percutaneous coronary intervention resulted in a numerical increase in composite ischemia that, while not statistically significant, did not meet the criterion for noninferiority. This finding was offset by a significant reduction in major bleeding.

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In patients with acute coronary syndromes (ACS; unstable angina or non–ST-segment elevation myocardial infarction [MI]), an early invasive strategy, consisting of angiography with subsequent triage to either percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or medical management, results in reduced rates of death and MI com-

**For editorial comment see p 636.**

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**A complete list of the ACUITY Investigators** was published previously as an online appendix to *N Engl J Med*. 2006;355:2203-2216.

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pared with conservative care.[1] Furthermore, the upstream use of platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors (tirofiban or eptifibatide) prior to angiography in patients with ACS further reduces the occurrence of death and MI at 30 days, although at the expense of increased major and minor bleeding complications.[2,3] Most of the benefit from Gp IIb/IIIa inhibition in earlier studies was confined to patients undergoing PCI, with lesser effects present in those in whom revascularization was not performed,[4] although death and MI also occurred less frequently during the interval prior to angiography in patients receiving upstream treatment.[5] Other trials have also shown that Gp IIb/IIIa inhibitors (abciximab or eptifibatide) significantly reduce periprocedural ischemic complications in ACS patients when administered in the cardiac catheterization laboratory just prior to PCI.[6-9]

Thus, current guidelines from the American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC) recommend use of Gp IIb/IIIa inhibitors with class I evidence in patients with ACS undergoing an invasive strategy, either administered upstream prior to angiography in all patients or initiated in the catheterization laboratory selectively to patients undergoing PCI.[10-12] It is not known whether the reduction in hemorrhagic complications by deferring Gp IIb/IIIa inhibitor administration (for selective use during PCI only) is sufficient to warrant the potential increase in adverse ischemic events by not treating all patients with Gp IIb/IIIa inhibitors upstream (prior to angiography). Moreover, these 2 strategies have never been studied in a large-scale contemporary ACS population in which delays to catheterization are discouraged, resulting in median times from admission to angiography of less than 24 hours.[13,14]

We therefore performed the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Timing trial, a large-scale, multicenter, open-label randomized trial examining the optimal use strategy of Gp IIb/IIIa inhibitors in patients with moderate- and high-risk ACS undergoing an early, invasive treatment strategy.

## METHODS

### Patient Population

Entry criteria have been previously described in detail.[15] In brief, to recruit a moderate- and high-risk ACS population, patients older than 18 years with symptoms of unstable angina lasting 10 minutes or longer within the preceding 24 hours were eligible for enrollment if 1 or more of the following criteria were met: new ST-segment depression or transient elevation of 1 mm or more; troponin I or T or creatine kinase–MB elevation; known coronary artery disease; or all 4 other TIMI (Thrombosis in Myocardial Infarction) unstable angina risk criteria[16] positive.

Major exclusion criteria included acute ST-segment elevation MI or shock; bleeding diathesis or major bleeding within 2 weeks; thrombocytopenia; calculated creatinine clearance less than 30 mL/min; administration of abciximab or fibrinolytic therapy within 24 hours; use of warfarin unless it could be safely discontinued and the international normalized ratio was verified to be 1.5 or lower; concomitant use of fondaparinux; administration of bivalirudin within 6 hours of randomization or 2 or more doses of low-molecular-weight heparin prior to randomization; or allergy to study drugs or iodinated contrast that could not be premedicated. Enrollment was permitted in patients receiving eptifibatide or tirofiban prior to randomization if the drugs could be discontinued for at least 4 hours prior to angiography in patients assigned to deferred Gp IIb/IIIa inhibitor use, as called for in the protocol. The study was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

### Randomization and Study Protocol

Telephone randomization was in blocks of 6, stratified by site and by the use or intent to administer a thienopyridine prior to angiography, using a random number generator. Because the ACUITY trial was designed to also study the efficacy of bivalirudin (as reported elsewhere[17]), patients were equally assigned to 1 of 3 antithrombin regimens started prior to angiography in an open-label fashion: heparin (either unfractionated or enoxaparin at site discretion) plus Gp IIb/IIIa inhibitors, bivalirudin plus Gp IIb/IIIa inhibitors, or bivalirudin alone. The antithrombin dosing regimens have been previously described.[15] Unfractionated heparin was dosed to achieve an activated clotting time of 200 to 250 seconds during PCI.

Patients assigned to heparin plus Gp IIb/IIIa inhibitors or to bivalirudin plus Gp IIb/IIIa inhibitors were randomized again in a true $2 \times 2$ factorial design to upstream Gp IIb/IIIa inhibitor initiation in all patients immediately after randomization vs deferred Gp IIb/IIIa inhibitor initiation for selective use in PCI patients starting in the catheterization laboratory. (FIGURE 1) Per current ACC/AHA and ESC guidelines, eptifibatide or tirofiban is recommended for upstream use in ACS, with no comparative studies having been performed to suggest a preference.[10-12] Thus, to reflect current practice, either eptifibatide (a 180-µg/kg bolus plus 2.0 µg/kg per minute of infusion) or tirofiban (0.4 µg/kg per minute of infusion for 30 minutes followed by 0.1 µg/kg per minute of infusion) was permitted for upstream use per investigator choice, with the infusion continued during angioplasty and for 12 to 18 hours thereafter. The infusion was typically discontinued in patients triaged to CABG surgery or medical management, though the infusion could be maintained if clinically indicated.

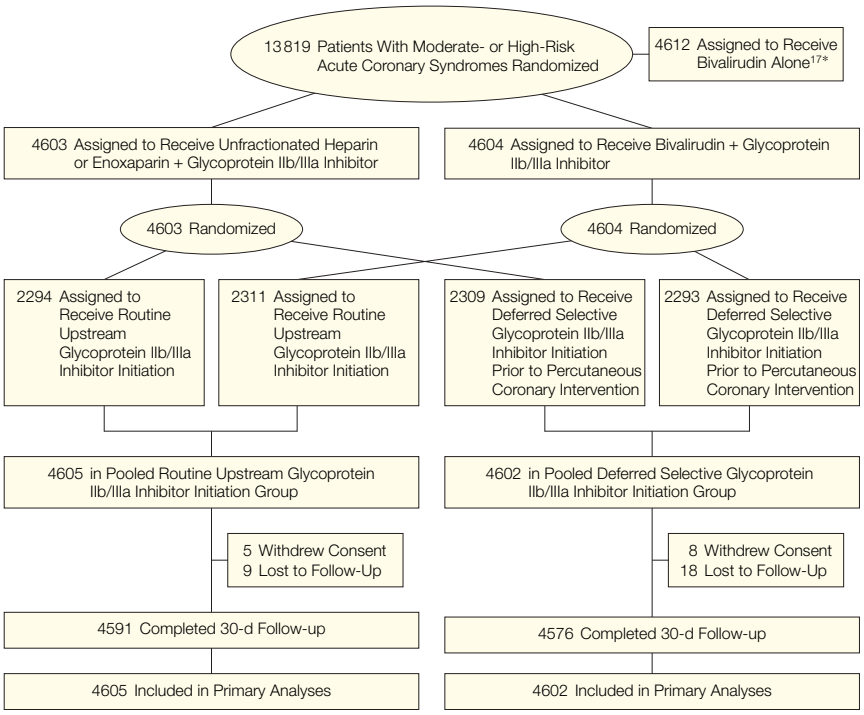
In patients with ACS not treated upstream, eptifibatide or abciximab is recommended for initiation in the catheterization laboratory prior to PCI by the current guidelines, with no comparative studies to suggest a preference.[10-12] Thus, for patients assigned to

deferred selective Gp IIb/IIIa inhibitor use, per investigator choice either eptifibatide (a 180-µg/kg bolus plus 2.0 µg/kg per minute of infusion, with a second bolus given in 10 minutes) or abciximab (a 0.25-mg/kg bolus plus 0.125 µg/kg per minute of infusion, with a maximum of 10 µg/min) was administered only to patients undergoing angioplasty, begun 5 to 10 minutes prior to first balloon inflation, and continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide) thereafter. Glycoprotein IIb/IIIa inhibitor dosing was adjusted for renal impairment as per the US Food and Drug Administration–approved package insert. Provisional Gp IIb/IIIa inhibitor use was permitted prior to angiography in patients randomized to deferred Gp IIb/IIIa inhibitor use for severe breakthrough ischemia.

Angiography was performed in all patients within 72 hours after randomization. Patients then underwent either PCI, CABG, or medical therapy per physician discretion. Aspirin, 300 to 325 mg orally or 250 to 500 mg intravenously, was administered daily during the index hospitalization, and 75 to 325 mg/d was prescribed indefinitely after discharge. The initial dosing and timing of clopidogrel were left to investigator discretion per local standards, although a 300-mg or greater loading dose was required in all cases no later than 2 hours after PCI. Clopidogrel, 75 mg/d, was recommended for 1 year in all patients with coronary artery disease.

**Figure 1.** Flow of Participants in the ACUITY Timing Trial




Clinical end points were assessed at 30 days (permitted follow-up range, 25-35 days). The 40 patients who withdrew consent or were lost to follow-up are included in the primary binary event rate intention-to-treat analysis but were censored at last follow-up in the secondary time-to-event Kaplan-Meier analysis. The number of patients eligible for randomization was not tracked during the course of enrollment.
*4612 patients who are not part of the present analysis were randomized to bivalirudin monotherapy.

## Clinical End Points and Statistical Methods

Clinical end points were assessed at 30 days (permitted follow-up range, 25-35 days). The primary 30-day end point of the ACUITY Timing trial was composite ischemia (death from any cause, MI, or unplanned revascularization for ischemia). Major secondary end points included major bleeding (non–CABG-related) and net clinical outcomes (composite ischemia or major bleeding). The component definitions of the primary end points have been previously detailed.[15] Major bleeding was defined as the occurrence within 30 days of intracranial or intraocular bleeding; access site hemorrhage requiring intervention; 5-cm or larger diameter hematoma; reduction in hemoglobin of 4 g/dL or more without an overt bleeding source or 3 g/dL or more with an overt bleeding source; reoperation for bleeding; or blood product transfusion. Hemorrhagic events occurring prior to CABG surgery were included in the major bleeding end point. A clinical events committee blinded to treatment assignment adjudicated all primary end-point events using original source documents.

The primary hypothesis of the ACUITY Timing trial was that compared with routine upstream Gp IIb/IIIa inhibitor use (the control group), deferred selective Gp IIb/IIIa inhibitor administration would result in noninferior 30-day rates of composite ischemia. Noninferiority would be declared if the upper limit of the 1-sided 97.5% confidence interval (CI) did not exceed a relative margin of 25% from the control event rate, equivalent to a 1-sided test with $\alpha = .025$. With 4600 patients in each group and an anticipated rate of composite ischemia of 5.9% with routine upstream use, the trial had 85% power to demonstrate noninferiority of the deferred selective strategy if the true rates of composite ischemia were equal in the 2 groups. Given the low anticipated control group event rate, the 25% margin was selected to exclude clinically relevant differences between the 2 Gp IIb/IIIa inhibitor use strategies, conforming to generally accepted principles of therapeutic interchangeability.[18]

Categorical variables were compared by $\chi^2$ or Fisher exact test. Continuous variables were compared by the nonparametric Wilcoxon rank sum test. Superiority was tested using a 2-sided $\alpha$ level of .05. All primary categorical bi-

**Table 1.** Baseline Characteristics of the Study Population*

| Characteristics | Routine Upstream Gp IIb/IIIa Inhibitor Use (n = 4605) | Deferred Selective Gp IIb/IIIa Inhibitor Use (n = 4602) |
|---|---|---|
| Age, median (range), y | 63 (21-95) | 63 (21-92) |
| Men | 3249 (70.6) | 3218 (69.9) |
| Diabetes | 1263/4572 (27.6) | 1302/4560 (28.6) |
| Insulin requiring | 373/4572 (8.2) | 412/4560 (9.0) |
| Hypertension | 3071/4585 (67.0) | 3061/4569 (67.0) |
| Hyperlipidemia | 2579/4508 (57.2) | 2589/4511 (57.4) |
| Current smoker | 1284/4507 (28.5) | 1347/4523 (29.8) |
| Prior myocardial infarction | 1371/4503 (30.4) | 1420/4481 (31.7) |
| Prior PTCA | 1751/4558 (38.4) | 1749/4563 (38.3) |
| Prior coronary artery bypass graft surgery | 845/4595 (18.4) | 790/4585 (17.2) |
| Weight, median (IQR), kg | 84 (73-95) | 83 (73-95) |
| Renal insufficiency† | 822/4315 (19.0) | 828/4286 (19.3) |
| Baseline CK-MB or troponin elevation | 2487/4243 (58.6) | 2495/4208 (59.3) |
| Baseline troponin elevation | 2287/3986 (57.4) | 2279/3927 (58.0) |
| Baseline ST-segment deviation ≥1 mm | 1614/4600 (35.1) | 1632/4597 (35.5) |
| Baseline cardiac biomarker elevation or ST-segment deviation | 3142/4367 (71.9) | 3148/4335 (72.6) |
| TIMI risk score[16] | | |
| 0-2 | 628/4081 (15.4) | 656/4079 (16.1) |
| 3-4 | 2263/4081 (55.5) | 2190/4079 (53.7) |
| 5-7 | 1190/4081 (29.2) | 1233/4079 (30.2) |

Abbreviations: CK-MB, creatine kinase–MB fraction; Gp IIb/IIIa, glycoprotein IIb/IIIa; IQR, interquartile range; PTCA, percutaneous transluminal coronary angioplasty.
*Data are expressed as No. (%) unless otherwise indicated. There were no significant differences between groups. Denominators are provided for cells for which data were missing.
†Creatinine clearance calculated as less than 60 mL/min using the Cockcroft-Gault equation.

nary event rate analyses were performed in the intention-to-treat population, with no patient excluded because of loss to follow-up. A secondary analysis was performed using time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), which are displayed using Kaplan-Meier methods and compared using the log-rank test. The impact of treatment assignment on the binary event rates of the composite ischemia, major bleeding, and net clinical outcome end points was tested in multiple subgroups, all of which were prespecified except the US vs non-US patient analysis. Formal interaction testing was performed to determine whether differential effects of treatment assignment were present across the subgroup strata, including the second randomization of heparin vs bivalirudin. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

## RESULTS

### Patients, Procedures, and Medication Use

Between August 23, 2003, and December 5, 2005, 9207 patients with ACS were enrolled at 450 centers in 17 countries and randomized to routine upstream Gp IIb/IIIa inhibitor use (n=4605, including 2294 and 2311 patients randomized to heparin and bivalirudin, respectively) or deferred selective Gp IIb/IIIa inhibitor use (n=4602, including 2309 and 2293 patients randomized to heparin and bivalirudin, respectively) (Figure 1). Follow-up at 30 days (range, 25-35 days) was complete in 9167 patients (99.6%). Baseline characteristics were well balanced between the groups (TABLE 1). Non–ST-segment elevation MI (elevated baseline creatine kinase–MB or troponin levels) was present in 59.0% of patients, whereas 41.0% had unstable angina. Angiography was performed during the index hospitalization in 99.0% of patients a median of 19.6 hours (interquartile range, 6.9-28.8 hours) after admission, after which management included PCI in 56.2%, CABG in 11.4%, and medical therapy in 32.4% of patients (TABLE 2). Stents were used in 92.9% of patients undergoing PCI (4755/5120), 64.9% of whom (3086/4755) received drug-eluting stents.

Glycoprotein IIb/IIIa inhibitors were used in 98.3% of patients in the routine upstream group compared with 55.7% of patients in the deferred selective group, and for a significantly longer duration (median, 18.3 vs 13.1 hours; $P<.001$). Patients assigned to routine upstream Gp IIb/IIIa inhibitor use received either eptifibatide or tirofiban (approximate 1.9:1 ratio), started at a median time of 35 minutes after randomization and infused for a median of 4.0 hours before PCI. In contrast, patients assigned to deferred selective Gp IIb/IIIa inhibitor use received either eptifibatide or abciximab (approximate 1.7:1 ratio), started just prior to PCI, approximately 3.9 hours later than Gp IIb/IIIa inhibitors were begun in the upstream use group (Table 2).

### Clinical Outcomes

As seen in TABLE 3, FIGURE 2, and FIGURE 3, composite ischemia at 30 days occurred in 7.9% of patients assigned to deferred selective Gp IIb/IIIa inhibitor use compared with 7.1% of patients assigned to routine upstream Gp IIb/IIIa inhibitor administration (risk difference, 0.8%; 95% CI, –0.3% to 1.9%; relative risk, 1.12; 95% CI, 0.97-1.29; $P=.044$ for noninferiority; $P=.13$ for superiority). These results are consistent with an increase of up to 29% in the rate of composite ischemic events in the deferred selective treatment group, so that the criterion for noninferiority was not met. Considering the components of composite ischemia, routine upstream compared with deferred selective Gp IIb/IIIa inhibitor use resulted in fewer unplanned revascularization events for ischemia, with no significant differences in the rates of death or MI.

Deferred selective Gp IIb/IIIa inhibitor administration compared with routine upstream use resulted in significantly fewer major and minor bleeding events (Table 3, Figure 2, and Figure 3). The 30-day rates of net clinical outcomes (composite ischemia and major bleeding) were nearly identical between the 2 strategies. Formal interaction testing demonstrated that the treatment effects of the 2 strategies on composite ischemia, major bleeding, and net clinical outcomes did not depend on which antithrombin was used and were consistent across multiple prespecified subgroups, including biomarker-positive patients, patients treated with PCI, and those with the greatest delays to intervention, with the possible exception of patients with baseline ST-segment deviation (FIGURE 4, FIGURE 5, and FIGURE 6). There were no significant differences noted between the 2 randomization groups in the 30-day composite rate of death or MI in any subgroup. Among patients with more than a 24-hour delay from randomization to PCI (median duration, 41.6 hours) assigned to deferred selective compared with routine upstream use of Gp IIb/IIIa inhibitors, there were no significant differences in the 30-day rates of composite ischemia (10.7% vs 10.0%, respectively; relative risk [RR], 1.07; 95% CI, 0.73-1.57), major bleeding (8.1% vs 9.1%; RR, 0.89; 95% CI, 0.58-1.36), or net clinical outcomes (17.1% vs 16.7%; RR, 1.02; 95% CI, 0.77-1.37).

### Relative Impact of Ischemia and Major Bleeding

Among patients developing any ischemic complication (MI or unplanned revascularization) within 30 days, the mortality was 5.4% (32/590) compared with 1.2% (100/8617) in patients who did not develop an ischemic complication (RR, 4.67; 95% CI, 3.17-6.90; $P<.001$ for superiority). Among patients developing an MI within 30 days, the mortality was 6.6% (30/456) compared with 1.2% (102/8751) in patients who did not develop an MI (RR, 5.64; 95% CI, 3.80-8.39; $P<.001$ for superiority). In contrast, among patients developing major non–CABG-related bleeding as defined in the protocol, the mortality was 7.3% (37/505) compared with 1.1% (95/8702) in patients without major bleeding (RR, 6.71; 95% CI, 4.64-9.71; $P<.001$ for superiority). The relative impact of ischemia and major bleeding on 30-day mortality was similar in the 2 treatment groups.

## COMMENT

The principal findings of this multicenter randomized trial examining adjunctive pharmacologic approaches in patients with moderate- and high-risk ACS undergoing an invasive treatment strategy are that (1) although no significant difference in composite ischemia was found between the deferred selective use of Gp IIb/IIIa inhibitors and their

**Table 2.** Procedures and Study Medications*

| | Routine Upstream Gp IIb/IIIa Inhibitor Use (n = 4605) | Deferred Selective Gp IIb/IIIa Inhibitor Use (n = 4602) |
|---|---|---|
| Angiography performed | 4556 (98.9) | 4556 (99.0) |
| Treatment strategy | | |
| Percutaneous coronary intervention | 2613 (56.7) | 2557 (55.6) |
| Coronary artery bypass graft surgery | 535 (11.6) | 513 (11.1) |
| Medical management | 1457 (31.6) | 1532 (33.3) |
| Antithrombin medications | | |
| Antithrombin prerandomization† | 2957 (64.2) | 2960 (64.3) |
| Unfractionated heparin | 1896 (41.2) | 1872 (40.7) |
| Low-molecular-weight heparin | 1168 (25.4) | 1185 (25.7) |
| Study antithrombin (postrandomization, preangiography)‡ | | |
| Unfractionated heparin | 1152 (25.0) | 1136 (24.7) |
| Enoxaparin | 1096 (23.8) | 1103 (24.0) |
| Bivalirudin | 2226 (48.3) | 2200 (47.8) |
| Gp IIb/IIIa inhibitors (all patients) | | |
| Prior to randomization | 373 (8.1) | 351 (7.6) |
| Gp IIb/IIIa inhibitor administration postrandomization, preangiography | 4340 (94.2) | 213 (4.6) |
| Eptifibatide | 2830 (61.5) | 104 (2.3) |
| Tirofiban | 1493 (32.4) | 93 (2.0) |
| Abciximab | 17 (0.4) | 16 (0.4) |
| Gp IIb/IIIa inhibitor use during PCI | 2589/2613 (99.1) | 2407/2557 (94.1) |
| Eptifibatide | 1665/2613 (63.7) | 1449/2557 (56.7) |
| Tirofiban | 900/2613 (34.4) | 105/2557 (4.1) |
| Abciximab | 27/2613 (1.0) | 853/2557 (33.4) |
| Any Gp IIb/IIIa inhibitor during index hospitalization (all patients) | 4525 (98.3) | 2563 (55.7) |
| Time from admission to randomization, median (IQR), h | 6.0 (2.0-15.4) [n = 4575] | 6.1 (2.0-15.5) [n = 4571] |
| Time from randomization to Gp IIb/IIIa inhibitor administration, median (IQR), h§ | 0.6 (0.3-1.0) [n = 4517] | 4.5 (1.7-19.9) [n = 2562]‖ |
| Randomization to PCI, median (IQR), h‖ | 4.7 (2.0-20.0) [n = 2583] | 5.1 (2.0-21.1) [n = 2541] |
| Total duration of Gp IIb/IIIa inhibition, median (IQR), h§ | 18.3 (8.0-28.0) [n = 4444] | 13.1 (12.0-18.0) [n = 2522]‖ |
| Aspirin and thienopyridine medications, No. (%) | | |
| Aspirin use or administration preangiography or PCI | 4429/4524 (97.9) | 4444/4539 (97.9) |
| Thienopyridine use or administration preangiography or PCI | 2894/4513 (64.1) | 2872/4533 (63.4) |

Abbreviations: Gp IIb/IIIa, glycoprotein IIb/IIIa; IQR, interquartile range; PCI, percutaneous coronary intervention.
*Data are expressed as No. (%) unless otherwise indicated. Denominators are provided for cells for which data were missing.
†Some patients received both agents.
‡A study antithrombin was not administered after randomization to all patients if the same antithrombin was administered before randomization and the time to angiography was relatively short.
§In patients receiving study Gp IIb/IIIa inhibitors.
‖In PCI patients only.

routine upstream administration, a relative increase of up to 29% in composite ischemia with the deferred selective strategy cannot be excluded and (2) the deferred selective use of glycoprotein Gp IIb/IIIa inhibitors compared with routine upstream administration significantly reduced major bleeding, minor bleeding, and blood transfusions.

### Upstream Routine vs Deferred Selective Gp IIb/IIIa Inhibition

The addition of platelet Gp IIb/IIIa inhibitors to unfractionated heparin reduces adverse ischemic event rates in patients with ACS undergoing an invasive treatment strategy,[2-9] especially in those in whom PCI is performed.[4,6-9] However, because the coronary anatomy and suitability for PCI are unknown in most patients presenting with ACS and because Gp IIb/IIIa inhibitors decrease adverse events prior to angiography,[5] current class I guidelines recommend their initiation in patients with ACS either upstream to all patients or selectively in the cardiac catheterization laboratory after angiography has identified those appropriate for PCI, with no clear preference.[10-12] Complicating this decision, Gp IIb/IIIa inhibitors are known to increase major and minor bleeding complications in ACS and PCI,[2,3,6-9] the occurrence of which may be exacerbated in the upstream approach because of greater frequency and longer duration of use, as well as obtaining vascular access during profound platelet inhibition. As adverse hemorrhagic events[20-24] and blood transfusions[24,25] have been shown to be independently associated with early and late mortality, the major strategic question that the ACUITY Timing trial sought to answer was as follows: When seeing a patient in the emergency department with moderate- or high-risk ACS in whom an invasive strategy with a Gp IIb/IIIa inhibitor–based regimen is planned, should Gp IIb/IIIa inhibitors be started immediately or should their use be deferred until after coronary arteriography, with selective administration only to those in whom PCI will be performed?

**Table 3.** Clinical Outcomes at 30 Days

| Outcomes | No. (%) Routine Upstream Gp IIb/IIIa Inhibitor Use (n = 4605) | No. (%) Deferred Selective Gp IIb/IIIa Inhibitor Use (n = 4602) | Risk Ratio (95% CI) | *P* Value for Noninferiority* | *P* Value for Superiority† |
|---|---|---|---|---|---|
| Ischemia | | | | | |
| Composite ischemia | 326 (7.1) | 364 (7.9) | 1.12 (0.97-1.29) | .044 | .13 |
| Death from any cause | 62 (1.3) | 70 (1.5) | | | .48 |
| Myocardial infarction | 224 (4.9) | 232 (5.0) | | | .70 |
| Q-wave | 46 (1.0) | 48 (1.0) | | | .83 |
| Non–Q-wave | 178 (3.9) | 186 (4.0) | | | .66 |
| Death or myocardial infarction | 272 (5.9) | 286 (6.2) | | | .54 |
| Unplanned revascularization for ischemia | 98 (2.1) | 130 (2.8) | | | .03 |
| Bleeding | | | | | |
| Major bleeding, non–CABG-related | 281 (6.1) | 224 (4.9) | 0.80 (0.67-0.95) | <.001 | .009 |
| Intracranial | 2 (0.04) | 4 (0.09) | | | .45 |
| Retroperitoneal | 27 (0.6) | 23 (0.5) | | | .57 |
| Access site | 123 (2.7) | 111 (2.4) | | | .43 |
| Requiring intervention or surgery | 21 (0.5) | 31 (0.7) | | | .16 |
| Hematoma ≥5 cm | 110 (2.4) | 93 (2.0) | | | .23 |
| Hemoglobin decrease ≥3 g/dL with overt source | 104 (2.3) | 81 (1.8) | | | .09 |
| Hemoglobin decrease ≥4 g/dL with no overt source | 46 (1.0) | 26 (0.6) | | | .02 |
| Blood transfusion | 137 (3.0) | 107 (2.3) | | | .05 |
| Reoperation for bleeding | 5 (0.1) | 2 (0.0) | | | .45 |
| All major bleeding, including CABG | 573 (12.4) | 482 (10.5) | | | <.001 |
| Minor bleeding, non–CABG-related‡ | 1105 (24.0) | 889 (19.3) | | | <.001 |
| TIMI scale bleeding[19] | 339 (7.4) | 264 (5.7) | | | .001 |
| TIMI major bleeding | 89 (1.9) | 73 (1.6) | | | .20 |
| TIMI minor bleeding | 329 (7.1) | 247 (5.4) | | | <.001 |
| Thrombocytopenia, acquired§ | 519 (11.3) | 489 (10.6) | | | .32 |
| Net clinical outcomes | | | | | |
| Composite ischemia or major bleeding | 541 (11.7) | 538 (11.7) | 1.00 (0.89-1.11) | <.001 | .93 |

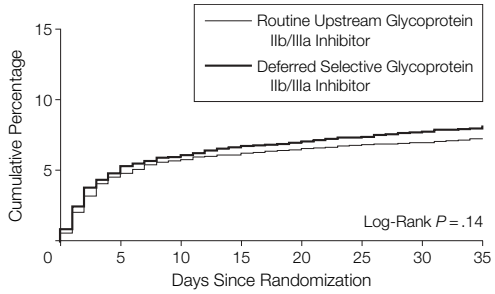
Abbreviations: CABG, coronary artery bypass graft surgery; CI, confidence interval; Gp IIb/IIIa, glycoprotein IIb/IIIa.
*Significance level for noninferiority, $\alpha = .025$.
†Significance level for superiority, $\alpha = .05$.
‡Including ecchymoses, epistaxis, gastrointestinal, genitourinary, puncture site, hemopericardium, pulmonary, or other.
§Platelet count less than 150 000/μL in patients without baseline thrombocytopenia.

In the present trial, the deferred selective use of Gp IIb/IIIa inhibitors compared with routine upstream administration in patients with moderate- and high-risk ACS undergoing an invasive treatment strategy resulted in a numerical increase in the rate of the composite ischemia end point that was not statistically significant, although noninferiority within a relative margin of 25% was not demonstrated. With 95% confidence, the deferred selective Gp IIb/IIIa inhibitor strategy might be associated with a relative risk of composite ischemia ranging from 3% better to 29% worse than routine upstream use (absolute difference in composite ischemia ranging from 0.3% better to 1.9% worse). These results are of interest given the findings of a prior small trial (N=93) in which upstream tirofiban use compared with catheterization laboratory initiation of either tirofiban or abciximab resulted in better baseline and post-PCI myocardial perfusion and reduced periprocedural troponin elevation.[26] Upstream tirofiban use was also shown to reduce thrombus burden and improve myocardial perfusion in the PRISM-PLUS angiographic substudy.[27] However, consistent with the results of an earlier randomized pilot trial (N=311) of early vs deferred eptifibatide use,[28] in the present large-scale trial there were no significant differences in the rates of death or MI between the routine upstream and deferred selective Gp IIb/IIIa inhibitor approaches; rather, any lower rate of composite ischemia with the upstream Gp IIb/IIIa inhibitor strategy was attributable to fewer episodes of recurrent ischemia necessitating repeat revascularization after hospital discharge.

Deferring routine upstream Gp IIb/IIIa inhibitor initiation for selective use in the catheterization laboratory in PCI patients did result in significantly lower rates of major bleeding, minor bleeding, and blood transfusions. These findings may be explained by fewer patients being exposed to Gp IIb/IIIa inhibitors (55.7% vs 98.3%) and for a shorter duration (median, 13.1 vs 18.3 hours), as well as avoidance of femoral access during profound platelet inhibition.

Potentially offsetting these benefits of the deferred selective approach is the concern of increased ischemia; with a baseline rate of ischemia of 7.1% in the control group, the deferred use of Gp IIb/IIIa inhibitors might result in a rate of ischemia as high as 9.0%. However, in an unadjusted analysis, the occurrence of major bleeding as defined in this study was associated with at least as

**Figure 2.** Time-to-Event Curves of Routine Upstream and Deferred Selective Glycoprotein IIb/IIIa Inhibitor Administration for Composite Ischemia

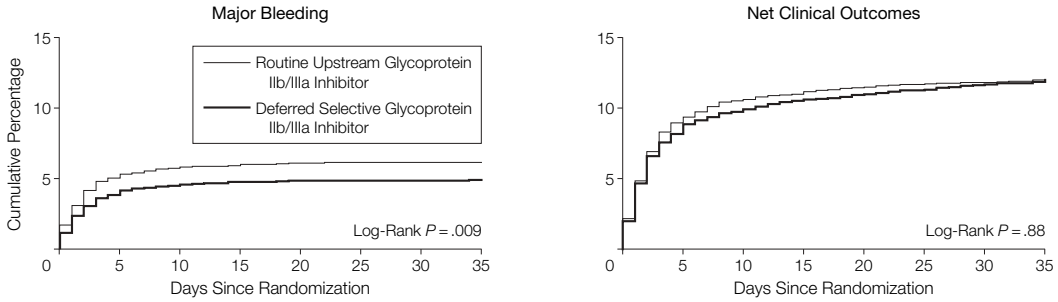



No. at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Routine Upstream Glycoprotein IIb/IIIa Inhibitor | 4605 | 4347 | 4287 | 4261 | 4241 | 4202 | 3694 | 2559 |
| Deferred Selective Glycoprotein IIb/IIIa Inhibitor | 4602 | 4333 | 4274 | 4238 | 4219 | 4178 | 3733 | 2569 |

Kaplan-Meier estimates for routine upstream and deferred selective glycoprotein IIb/IIIa inhibitor use were 7.2% and 8.1%, respectively. Log-rank *P* value is for superiority. Thirty-five-day estimates based on time-to-event data and log-rank *P* value vary slightly from the binary event rate data and $\chi^2$ *P* value in Table 3.

**Figure 3.** Time-to-Event Curves of Routine Upstream and Deferred Selective Glycoprotein IIb/IIIa Inhibitor Administration for Major Bleeding and Net Clinical Outcomes




No. at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Routine Upstream Glycoprotein IIb/IIIa Inhibitor | 4605 | 4304 | 4257 | 4238 | 4225 | 4191 | 3685 | 2563 |
| Deferred Selective Glycoprotein IIb/IIIa Inhibitor | 4602 | 4361 | 4311 | 4286 | 4269 | 4239 | 3805 | 2637 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Routine Upstream Glycoprotein IIb/IIIa Inhibitor | 4605 | 4149 | 4071 | 4043 | 4018 | 3983 | 3500 | 2424 |
| Deferred Selective Glycoprotein IIb/IIIa Inhibitor | 4602 | 4181 | 4104 | 4064 | 4042 | 4005 | 3579 | 2465 |

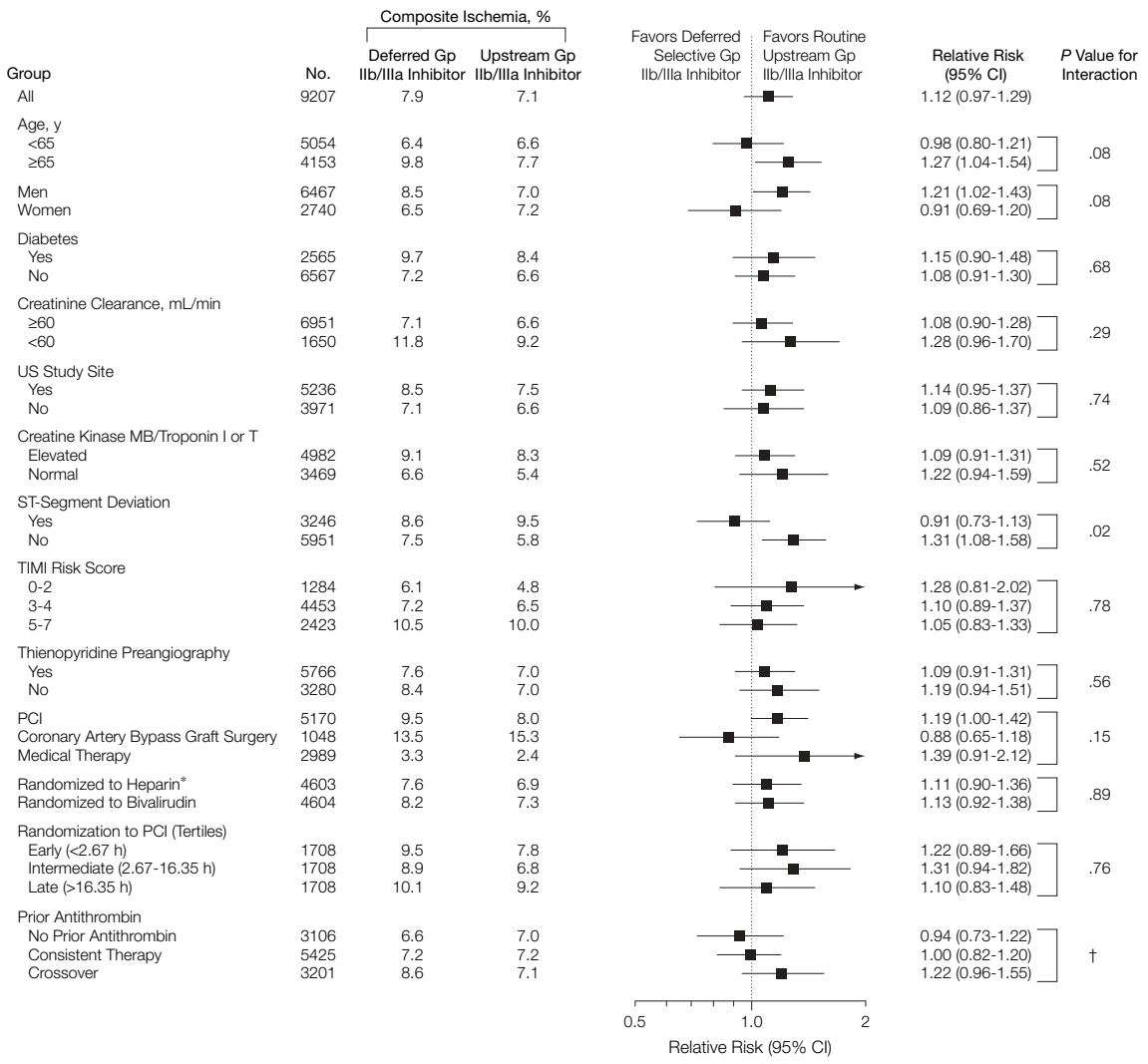
Kaplan-Meier estimates for routine upstream and deferred selective glycoprotein IIb/IIIa inhibitor use were 11.9% and 11.9%, respectively, for net clinical outcomes and 6.1% and 4.9%, respectively, for major bleeding. Log-rank *P* values are for superiority. Thirty-five-day estimates based on time-to-event data and log-rank *P* values vary slightly from the binary event rate data and $\chi^2$ *P* values in Table 3.

great a risk of death within 30 days as occurred with MI or any ischemic complication (RR increase of 6.71-fold vs 5.64-fold vs 4.67-fold, respectively). Similarly, in the REPLACE-2 trial, by multivariate analysis, major bleeding in patients undergoing PCI was a stronger predictor of 1-year mortality than was periprocedural MI.[29] In the present trial, the prespecified combined net clinical benefit outcome end point of composite ischemia or major bleeding occurred with similar frequency in patients treated with the deferred selective compared with the routine upstream administration of Gp IIb/IIIa inhibitors. Finally, the only significant difference in ischemic outcomes between the 2 Gp IIb/IIIa inhibitor use strategies was a small increase in unplanned revascularization, with no significant difference in the "hard" end points of death or MI. Thus, both strategies would appear to be clinically acceptable. The ongoing EARLY-ACS trial will provide important complementary information to the present study.[30]

## Subgroup Analysis

The results of the deferred selective vs routine upstream Gp IIb/IIIa inhibitor approaches in regard to the 3 major endpoint measures were independent of

**Figure 4.** Subgroup Analyses for the 30-Day Rates of Composite Ischemia Comparing Patients Randomized to Routine Upstream Use vs Selective Deferred Use of of Glycoprotein IIb/IIIa (Gp IIb/IIIa) Inhibitors



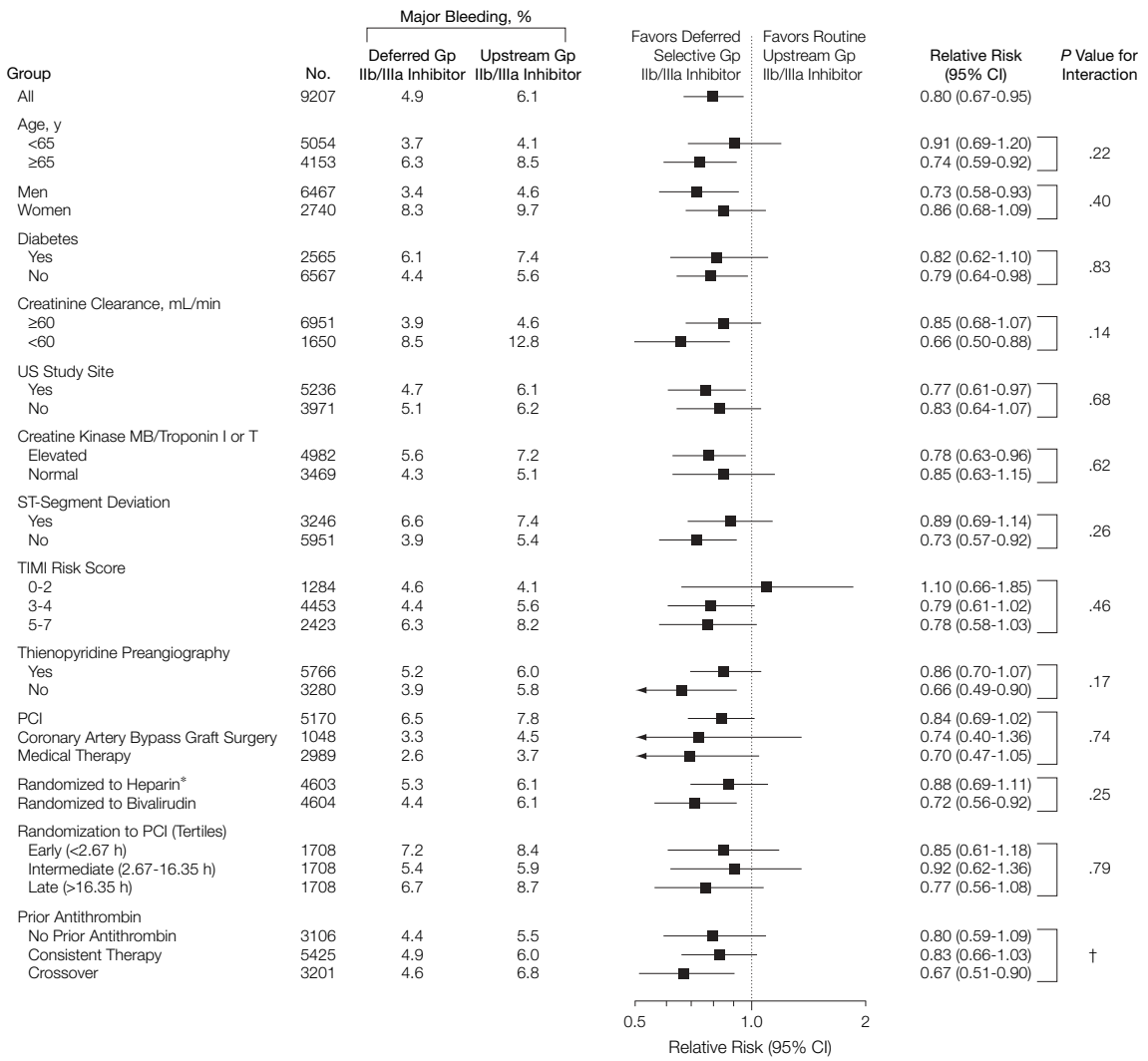

CI indicates confidence interval. Randomization to percutaneous coronary intervention (PCI) refers to the time from primary study drug randomization to the start of PCI, analyzed in 3 approximately equal-sized groups (tertiles) from shortest to longest duration of delay. The prior antithrombin subgroup analysis refers to antithrombin use prior to the time of randomization only. *P* values are for interaction between the variable and the relative treatment effect.
*Heparin indicates unfractionated heparin or enoxaparin.
†Determination of *P* value for interaction not applicable given overlap between the 3 groups.

multiple prespecified subgroups, with the possible exception of patients without baseline ST-segment deviation, in whom routine upstream Gp IIb/IIIa inhibitor use was associated with less composite ischemia at 30 days (with the opposite finding in patients with baseline ST-segment deviation). However, such an interaction was not seen in other high-risk patients, including those with abnormal cardiac biomarkers and high TIMI risk score; given the borderline significance of the interaction and the risk of a spurious finding from examination of multiple subgroups (13 in this case), caution against overinterpretation is warranted. All results of subgroup analysis should thus be considered hypothesis-generating.[31] Further investigation is also required to examine the nonsignificant interactions among age, sex, and Gp IIb/IIIa inhibitor strategy.

## Study Limitations

One aspect of the study that deserves comment is the duration of Gp IIb/IIIa inhibitor administration prior to PCI in the upstream therapy arm. Although the duration of upstream Gp IIb/IIIa inhibition was relatively brief (median, 4.0 hours; mean, 14.7 hours), the median time from hospital admission to angiography was similar to that in other recent large-scale ACS trials,[32,33] and the

**Figure 5.** Subgroup Analyses for the 30-Day Rates of Major Bleeding Comparing Patients Randomized to Routine Upstream Use vs Selective Deferred Use of of Glycoprotein IIb/IIIa (Gp IIb/IIIa) Inhibitors

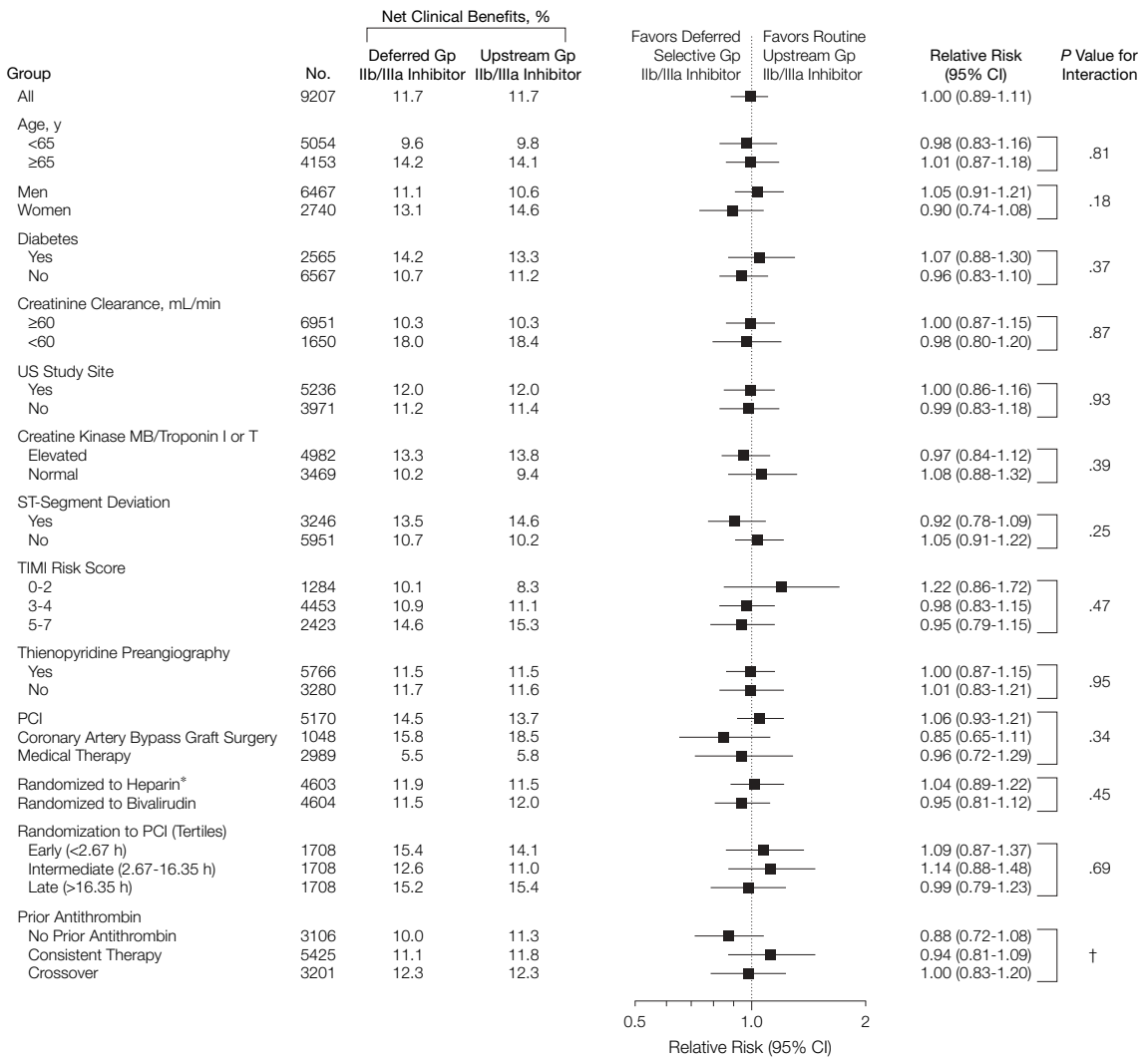



CI indicates confidence interval. Randomization to percutaneous coronary intervention (PCI) refers to the time from primary study drug randomization to the start of PCI, analyzed in 3 approximately equal-sized groups (tertiles) from shortest to longest duration of delay. The prior antithrombin subgroup analysis refers to antithrombin use prior to the time of randomization only. *P* values are for interaction between the variable and the relative treatment effect.
*Heparin indicates unfractionated heparin or enoxaparin.
†Determination of *P* value for interaction not applicable given overlap between the 3 groups.

median time from admission to randomization was actually shorter in the present trial than in SYNERGY (6 vs 10 hours, respectively).[33] Between January 2001 and September 2003, the national median time from hospital presentation to PCI was approximately 27 hours.[14] In this regard, the results of the present study were consistent even in the subgroup of patients with more than 24 hours of delay from randomization to PCI, in whom the median duration of upstream Gp IIb/IIIa inhibition prior to PCI was 41 hours. However, it is unknown whether longer periods of upstream administration of Gp IIb/IIIa inhibitors prior to angiography would result in a different balance between ischemic events and bleeding.

Other potential limitations include the open-label design of the trial, a result of the logistic complexities of the study design, introducing the potential for bias. However, the use of adjunctive medications and revascularization strategies was well balanced between the 2 groups, and all endpoint events were adjudicated by an independent committee blinded to treatment assignment, with original source documentation required to validate each event. There was also high adherence to the study medica-

**Figure 6.** Subgroup Analyses for the 30-Day Rates of Net Clinical Benefits Comparing Patients Randomized to Routine Upstream Use vs Selective Deferred Use of of Glycoprotein IIb/IIIa (Gp IIb/IIIa) Inhibitors




CI indicates confidence interval. Randomization to percutaneous coronary intervention (PCI) refers to the time from primary study drug randomization to the start of PCI, analyzed in 3 approximately equal-sized groups (tertiles) from shortest to longest duration of delay. The prior antithrombin subgroup analysis refers to antithrombin use prior to the time of randomization only. *P* values are for interaction between the variable and the relative treatment effect.
*Heparin indicates unfractionated heparin or enoxaparin.
†Determination of *P* value for interaction not applicable given overlap between the 3 groups.

tions,[17] including Gp IIb/IIIa administration per protocol (Table 2). Because patients with creatinine clearance of less than 30 mL/min were excluded from enrollment, additional study is required to determine the optimal pharmacologic regimen in cases of severe renal insufficiency.

Given the heterogeneity of patients enrolled and treatments received, including the decision whether to administer clopidogrel prior to angiography, choice of Gp IIb/IIIa inhibitor and antithrombin, and selection of destination therapy (medical therapy vs PCI vs CABG), definitive conclusions regarding the relative safety and efficacy of the 2 assigned treatments in all scenarios is problematic. In this regard, subgroup analysis is limited by the likelihood of $\alpha$ or $\beta$ error, and as such, any trends (or lack thereof) in underpowered subgroups should be considered hypothesis-generating only.

Finally, the results of long-term follow-up of all clinical outcomes for 1 year may provide new insights into the relative risks and benefits of the Gp IIb/IIIa inhibitor use strategies evaluated in this trial.

## CONCLUSIONS AND CLINICAL IMPLICATIONS

Optimizing outcomes for patients with moderate- and high-risk ACS requires appreciation of the advantages of early revascularization and the importance of selecting an adjunctive pharmacologic regimen that will suppress ischemia while minimizing iatrogenic hemorrhagic complications. Deferring the routine upstream use of Gp IIb/IIIa inhibitors for selective administration in the cardiac catheterization laboratory only to patients undergoing PCI resulted in a numerical increase in composite ischemia that, while not statistically significant, did not meet the criterion for noninferiority. This was offset by a significant reduction in major bleeding, minor bleeding, and blood transfusions. Given emerging data regarding alternative anticoagulant strategies in ACS[8,17,34] and evolving understanding of the relative importance of bleeding and ischemic events, clinicians should carefully weigh the risks and benefits of adjunctive pharmacologic strategies in individual patients.

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**Author Contributions:** Dr Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Stone, Bertrand, Moses, Ohman, Lincoff, Ware, Pocock, Cox, White.
*Acquisition of data:* Moses, McLaurin, Cox, Jafar, Chandna, Leisch, Strasser, Desaga, Zelman, Lieber, Mehran, White.
*Analysis and interpretation of data:* Stone, Bertrand, Moses, Ohman, Lincoff, Ware, Pocock, Cox, Hartmann, Leisch, Strasser, Stuckey, Cohen, Mehran, White.
*Drafting of the manuscript:* Stone, Pocock, Leisch, White.
*Critical revision of the manuscript for important intellectual content:* Bertrand, Moses, Lincoff, McLaurin, Cox, Jafar, Chandna, Hartmann, Strasser, Desaga, Stuckey, Zelman, Lieber, Cohen, Mehran, White.
*Statistical analysis:* Stone, Ware, Pocock, Stuckey, Cohen.
*Obtained funding:* Cohen.
*Administrative, technical, or material support:* Stone, Ohman, McLaurin, Chandna, Leisch, Lieber.
*Study supervision:* Stone, Bertrand, Moses, Lincoff, Cox, Strasser, Lieber, Mehran.
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