# Platelet Glycoprotein IIb/IIIa Inhibitors in the Treatment of Non-ST-segment Elevation Acute Coronary Syndromes in the Elderly: Part 2 of 2

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## Introduction

The chain of events leading to acute coronary syndromes (ACS), including unstable angina (UA) and non-ST-segment elevation (NSTE) or ST-segment elevation myocardial infarction (STEMI), is triggered by the disruption of an atherosclerotic plaque, which leads to the formation of a platelet-rich thrombus within a coronary artery.[1,2] The inhibition of platelet aggregation is fundamental to the treatment of these patients; however, standard antiplatelet agents such as aspirin do not completely obstruct this activity. Advances in understanding the pathophysiology of ACS have to the recognition of the activation of the glycoprotein IIb / IIIa (Gp IIb / IIIa) receptors on platelets as the final common pathway leading to platelet aggregation. With this target in mind, pharmacological treatment of ACS has been propelled into a new era with agents that completely inhibit platelet aggregation.[3]

In this second of two reviews examining the impact of platelet glycoprotein IIb / IIIa receptor inhibitor (GPI) therapy on patients suffering from ischemic heart disease, the efficacy and safety issues associated with these agents in the medical management of non-ST-segment elevation ACS (NSTE-ACS) will be discussed. Specifically, this appraisal is based on large-scale, phase III, randomized clinical trials and meta-analyses evaluating intravenous (abciximab, eptifibatide, tirofiban and lamifiban) and oral agents (sibrafiban and orbofiban), with particular emphasis on the elderly (as defined in the trials) (Table 1).

## Intravenous GPIs

### Abciximab

Although it was the first GPI to be tested in patients undergoing percutaneous coronary intervention (PCI), abciximab is one of the most recent to be tested in the front-line medical treatment of NSTE-ACS. The investigators of the GUSTO-IV ACS (see Table 1 for full trial names) trial compared the effect of two different lengths of abciximab infusion (24-hour and 48-hour) against a placebo bolus and infusion in NSTE-ACS patients who were not undergoing early PCI (Table 2, page 27).[4] In patients with either a positive troponin T or I test, or transient or persistent ST-segment depression (≥ 0.5mm), there was no benefit from the administration of abciximab, regardless of the length of infusion, at 30 days ((death or MI at 30 days) 8.0% placebo versus 8.2% 24-hour abciximab, odds ratio (OR) 1.0, 95% confidence interval (CI) (0.83-1.24); and 9.1% 48-hour abciximab, OR 1.1, 95% CI(0.94, 1.39)). This lack of effect was also evident in both younger (<65 years) and older ((≥ 65 years) patients (Figure 1). Unlike the investigations of abciximab in patients with refractory angina and in those undergoing PCI, it seems that no additional benefit was derived from the use of abciximab in the medical management of NSTE-ACS.

### Eptifibatide

On the heels of the success of Gp IIb / IIIa

**Table 1**
**Glossary of Intravenous and Oral GPI Trials for the Medical Management of NSTE-ACS Patients**

| | |
|---|---|
| **GUSTO-IV-ACS** | Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes |
| **PURSUIT** | Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression using Integrilin Therapy |
| **PRISM** | Platelet Receptor Inhibition for Ischemic Syndrome Management |
| **PRISM-PLUS** | PRISM-in Patients Limited to very Unstable Signs and symptoms |
| **PARAGON -A and -B** | Platelet GP IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organisation Network-A and -B |
| **OPUS TIMI-16** | Orbofiban in Patients with Unstable Coronary Syndromes |
| **1st & 2nd SYMPHONY** | Sibrafiban versus aspirin to Yield Maximum Protection from Ischemic Heart events post acute coronary syndromes |

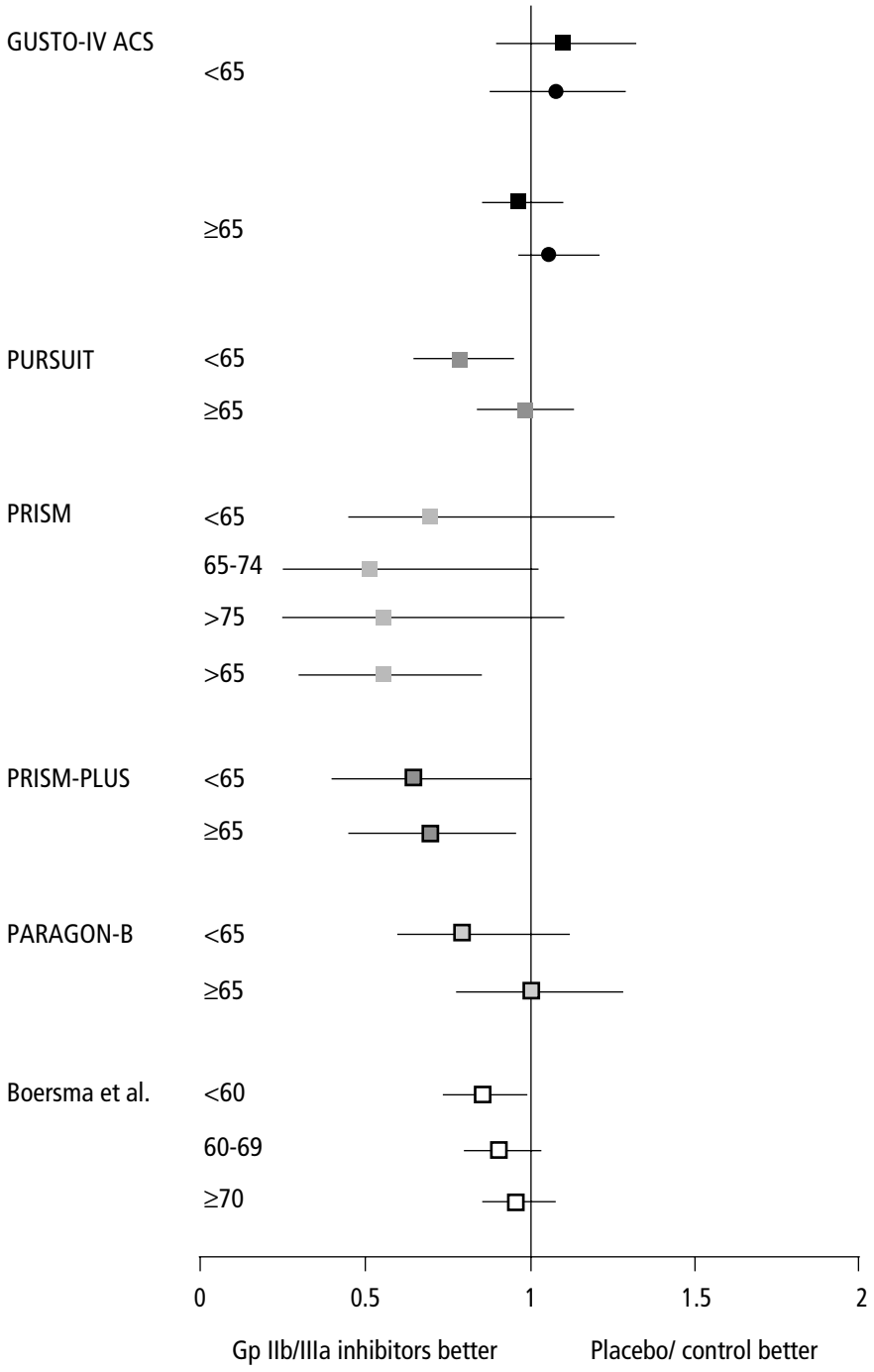


**Figure 1**. Age subgroup analysis of primary composite endpoints of trials evaluating intravenous GPIs in NSTE-ACS patients.
(No age subgroup analysis reported for PARAGON-A.)

GUSTO-IV ACS ■ 24-hour abciximab infusion versus placebo;
● 48-hour abciximab infusion versus placebo;
PURSUIT ■ eptifibatide versus placebo;
PRISM ■ tirofiban versus placebo;
PRISM-PLUS ■ tirofiban versus placebo;
PARAGON B ■ lamifiban versus placebo;
Boersma et al □ GPIs versus placebo/control.

receptor inhibition in patients undergoing PCI, it was suspected that eptifibatide, a small-molecule GPI, could reduce ischemia in UA patients. To follow-up on the promising results of Schulman's dose-finding trial, the PURSUIT trial investigators tested the hypothesis that eptifibatide could significantly reduce death and MI beyond standard therapy, such as aspirin and heparin, in ACS patients without persistent ST-segment elevation (Table 2).[5,6] A unique feature of this trial was its practice-based protocol, which mandated that decisions on treatment strategies, including cardiac catheterization and revascularization, were made at the discretion of the treating physicians.

Overall, the use of eptifibatide in these patients led to a significant reduction in death or non-fatal MI at each time point. On the fourth day after randomization, a 1.5% absolute reduction was achieved and was consistently maintained for 30 days (9.6% relative reduction at 30 days compared to those who received the placebo (15.7% placebo versus 14.2% eptifibatide, p=0.03)). The benefits of eptifibatide therapy were consistent across all age groups (Figure 1).

Interestingly, the incidence of death or nonfatal MI was reduced by 31% (relative) at 30 days in those who received eptifibatide and underwent PCI within 72 hours after randomization (11.6% eptifibatide versus 16.7% placebo, p=0.01), whereas, the relative reduction in patients not undergoing a procedure was substantially attenuated (7% relative risk reduction, 14.5% eptifibatide versus 15.6% placebo, p=0.23).

## Tirofiban

In the late 1990s, another small-molecule GPI, tirofiban, was tested for its efficacy in the medical management of NSTE-ACS (Table 2). In the PRISM trial, UA patients benefited from a 32% relative reduction in the composite endpoint of death, refractory ischemia or MI at 48 hours when treated with tirofiban and aspirin compared to heparin and aspirin (5.6% placebo versus 3.8% tirofiban,

**Table 2 Summary of Trials of Intravenous GPIs in the Medical Management of NSTE-ACS**

| Study (Enrolment period) | No. of Patients | Entry Criteria | Study Medication Endpoints | Primary Efficacy |
|---|---|---|---|---|
| **ABCIXIMAB** | | | | |
| GUSTO-IV ACS (1998–2000) | 7800 | Patients ≥21 years old with NSTE-ACS. | Randomly assigned to:<br>a) abciximab bolus + 24 h infusion (2590)<br>b) abciximab bolus + 48 h infusion (2612)<br>c) Placebo (2598)<br>Abciximab dose: 0.25 mg/kg bolus + 0.125 µg/kg infusion<br>All patients received aspirin, and heparin for non-LMWH-sub-study participants. | Death or MI at 30 days. |
| **EPTIFIBATIDE** | | | | |
| PURSUIT (1995–1997) | 10948 | Patients with NSTE-ACS. | Randomly assigned to:<br>a) eptifibatide 180 µg/kg + eptifibatide 1.3 µg/kg/min infusion (1487) (terminated at the interim analysis as high-dose eptifibatide proved safe)<br>b) eptifibatide 180 µg/kg + eptifibatide 2.0 µg/kg/min infusion (4722)<br>c) placebo bolus + infusion (4739)<br>Infusion of 72 h or until discharge.<br>All patients received aspirin and were allowed to receive heparin. | Death or non-fatal MI at 30 days. |
| **TIROFIBAN** | | | | |
| PRISM (1994–1996) | 3232 | Patients with UA. | Randomly assigned to:<br>a) tirofiban 0.6 µg/kg/min for 30 mins + 0.15 µg/kg for 47.5 h infusion + placebo heparin (1616)<br>b) placebo tirofiban + heparin (1616)<br>All received aspirin. | Death, MI, or refractory ischemia at end of 48 h infusion. |
| PRISM-PLUS (1994–1996) | 1915 | Patients with NSTE-ACS. | Randomly assigned to:<br>a) tirofiban 0.6 µg/kg/min for 30 mins + 0.15 µg/kg for 48 h infusion + placebo heparin (345)<br>b) tirofiban 0.4 µg/kg/min for 30 mins + 0.10 µg/kg for 48 h infusion + dose-adjusted heparin (773)<br>c) dose-adjusted heparin + placebo tirofiban (797)<br>All received aspirin. | Death, new MI, or refractory ischemia, or re-hospitalization for unstable angina within 7 days. |
| **LAMIFIBAN** | | | | |
| PARAGON A (1995–1996) | 2282 | Patients with NSTE-ACS. | Randomly assigned to:<br>a) lamifiban 750 µg bolus + 5.0 µg/min infusion for 3–5 days + heparin (373)<br>b) lamifiban 750 µg bolus + 5.0 µg/min infusion for 3–5 days + heparin placebo (396)<br>c) lamifiban 300 µg bolus + 1.0 µg/min infusion for 3–5 days + heparin (377)<br>d) lamifiban 300 µg bolus + 1.0 µg/min infusion for 3–5 days + heparin placebo (378)<br>e) lamifiban placebo + heparin (758)<br>All patients received heparin. | Death or non-fatal (re)MI at 30 days. |
| PARAGON B (1998–1999) | 5167 | Patients ≥21 years old with NSTE-ACS. | Randomly assigned to:<br>a) 500 µg bolus lamifiban + dose-adjusted lamifiban infusion ≤ 72 h or until discharge (2597)<br>b) placebo (2570)<br>All patients received aspirin and heparin. | Death, MI or severe, recurrent ischemia at 30 days. |

MI, myocardial infarction; NSTE-ACS, non ST-segment elevation acute coronary syndromes; UA, unstable angina.

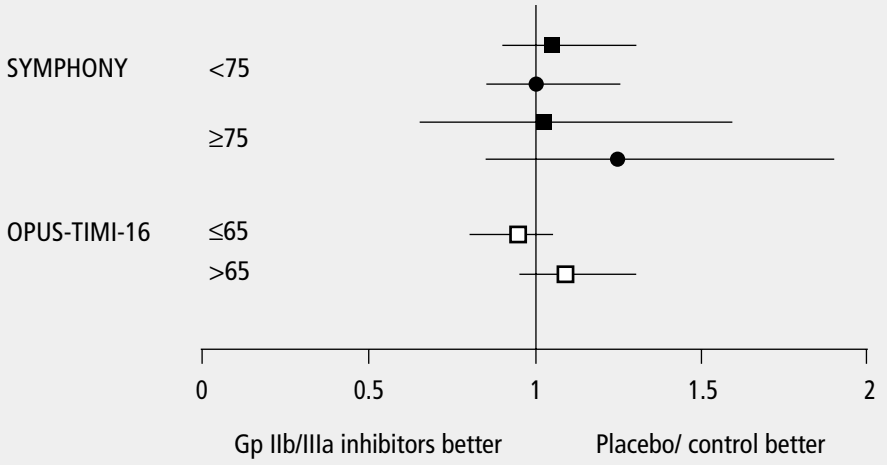


**Figure 2**. Age subgroup analysis of primary composite endpoints of trials evaluating oral GPIs in NSTE-ACS patients. (No age subgroup analysis reported for the Second SYMPHONY trial.)

SYMPHONY (90-day composite endpoint)
■ low-dose sibrafiban versus placebo;
● high-dose sibrafiban versus placebo;

OPUS-TIMI-16 (10-month composite endpoint)
□ orbofiban versus placebo.

p=0.01).[7] This relative benefit was homogenous across all age groups (Figure 1). However, these results were not sustained when evaluated at seven and 30 days.

In the second trial, the PRISM-PLUS investigators compared the efficacy of tirofiban alone, tirofiban and heparin in combination, or heparin alone in patients diagnosed with UA or non-Q-wave MI.[8] After the first interim safety analysis, the tirofiban arm was terminated for safety reasons, as excess mortality at seven days was evident in this group. In the remaining patients, tirofiban administered in combination with aspirin and heparin appeared to reduce the incidence of death, MI, or refractory ischemia at seven days compared to those who had only received aspirin and heparin (17.9% heparin alone versus 12.9% tirofiban, p=0.004, 28% relative risk reduction). Longer-term (i.e., 30 days and six months) benefits were also realized. When the composite was analyzed according to subgroups of age, the investigators found that patients who were 65 years or older and were treated with tirofiban and heparin experienced fewer events (death, MI, refractory ischemia or re-hospitalization for unstable angina) at seven days than did those who were treated with aspirin and heparin (17.8% versus 23.5%, 24% relative risk reduction) (Figure 1). Similar benefits were also realized in those less than 65 years of age (8.5% versus 12.4%, 31% relative risk reduction).

### Lamifiban

Of the four intravenously administered GPIs, only Lamifiban is commercially unavailable. Inconclusive results of the two large-scale efficacy trials, PARAGON-A and -B, may account for the delay in its approval (Table 2).[9,10] PARAGON-A tested the effects of two doses of lamifiban, with or without heparin and aspirin in UA and non-Q-wave MI patients. The use of lamifiban did not significantly reduce ischemic events at 30 days; however, at six months, the low-dose lamifiban performed better than did aspirin and heparin (17.9% control, 13.7% low-dose (versus control p=0.027), 23.5% relative risk reduction, 16.4% high-dose (versus control p=0.450), 8% relative risk reduction). Compared to standard therapy, patients receiving low-dose lamifiban used in combination with heparin experienced the largest reductions in the composite endpoint at 30 days (12%, non-significant) and at 6 months (30%, p=0.025). However, this study was not adequately powered to draw clear conclusions from this data.

Based on retrospective pharmacokinetic analyses of PARAGON-A, it was revealed that a steady-state concentration of 18 to 24 ng / mL lamifiban lead to a significant reduction (40%) in adverse outcomes. A new trial, PARAGON-B, was designed to evaluate the effects of titrated dosing in order to achieve and maintain acceptable plasma levels of lamifiban. Despite these modifications to the dose regime, no significant effect on the 30-day or six-month composite endpoint of death, MI, or severe recurrent ischemia was observed (30-day: 12.8% placebo versus 11.8% lamifiban, p=0.329; six-month: 15% placebo versus 14% lamifiban, p=0.284). A lack of effect was evident in both younger (≤ 65 years) and older (>65 years) patients when the primary composite endpoint was evaluated at six months (Figure 2). Similarly to PARAGON-A, the lack of power in this trial should be taken into account when evaluating these results.

## Overview of Intravenous GPIs in Elderly Patients

In general, the trials of intravenous GPIs in NSTE-ACS patients revealed significant reductions in adverse cardiac events; however, a problem among some of the trials was inadequate power for the detection of a large treatment effect. To provide a global picture of these agents, a meta-analysis of combined trial data was performed.[11] Overall, GPIs significantly reduced (8% relative) the composite endpoint of death or non-fatal MI at 30 days (11.8% control / placebo versus 10.8% GPIs, OR 0.91, 95% CI (0.85,0.98), p=0.015). Similarly, these benefits were observed in the reduction of the composite

endpoint of death or MI in patients of all ages (p (for interaction) = 0.10) (Figure 1). However, reductions in death (3.7% control versus 3.4% GPIs, OR 0.91, 95%CI (0.81, 1.03), p=0.14) and in the composite of death, MI or revascularization (44.3% control versus 42.7% GPIs, OR 0.98 (0.93, 1.02), p=0.33) were not statistically significant with GPI therapy.

## Oral GPIs in Elderly Patients

### Orbofiban & Sibrafiban

The prolonged use of oral GPIs may extend the benefits of intravenous agents and play a role in secondary prevention. However, the results of the trials on the first generation of oral GPIs, OPUS-TIMI-16 (orbofiban) and the first and Second SYMPHONY (sibrafiban) trials did not show significant reductions in clinical events (Figure 2).[12-14] In the older population, those patients receiving the placebo or control experienced fewer events than did those who received the oral GPI. For instance, the administration of orbofiban resulted in an increase in the incidence of the composite endpoint at 10 months in patients over 65 years when compared to those treated with placebo (Figure 2).[12] In addition, in patients over the age of 75 years who were enrolled in the first SYMPHONY trial, those who received high-dose sibrafiban experienced more death, non-fatal (re)-MI or recurrent ischemia at 90 days than did those receiving aspirin (Figure 2).[13]

The next generation of oral agents may find success if the challenges of inter-patient variation in inhibition levels (due to differences in bioavailability or genetics), establishment of titrated doses and development of longer half-lives with higher binding affinities to increase the level of stable inhibition are resolved.[15,16]

## Contraindications and Adverse Effects

Patients with active bleeding or a history of bleeding diathesis, gastrointestinal or genitourinary bleeding (within last six months), major surgery within the past three months, a history of stroke and a history of recent trauma are not recommended recipients of this therapy.[17] Other contraindications include uncontrolled hypertension (≥ 180 mmHg

**Table 3**

**Summary of Oral GPIs for the Secondary Prevention in Acute Coronary Syndrome Patients**

| Study (Enrolment period) | No. of Patients | Indication | Study Treatment Arms Endpoint | Primary Efficacy |
|---|---|---|---|---|
| **ORBOFIBAN** | | | | |
| OPUS-TIMI 16 (1997–1998) | 10288 | Patients ≥18 years old with ACS. | Randomly assigned to:<br>a) 50 mg orbofiban twice daily (3537)<br>b) 50 mg orbofiban twice daily for 30 days +30 mg orbofiban twice daily (3330)<br>c) placebo (3421)<br>All patients received aspirin. | Death, MI, recurrent ischemia at rest leading to rehospitalization or urgent revascularization or stroke at 14 and 30 days, and every 3 months afterwards up until 1 year (6 month minimum). |
| **SIBRAFIBAN** | | | | |
| SYMPHONY (1997–1998) | 9233 | Patients with ACS. | Randomly assigned to:<br>a) low-dose (weight-adjusted) sibrafiban (3105)<br>b) high-dose (weight-adjusted) sibrafiban (3039)<br>c) aspirin (80 mg twice daily) control (3089) | Death, non-fatal (re)MI, or severe recurrent ischemia at 90 days. |
| Second SYMPHONY (1999) | 6671 | Patients with ACS. | Randomly assigned to:<br>a) low-dose (weight-adjusted) sibrafiban + aspirin (80 mg twice daily) (2232)<br>b) high-dose (weight-adjusted) sibrafiban (2174)<br>c) aspirin (80 mg twice daily) control (2231) | Time to death, MI or recurrent ischemia. |

ACS, acute coronary syndromes; MI, myocardial infarction.

systole and / or ≥ 110mmHg diastole), severe anemia and thrombocytopenia.[17]

In general, the use of intravenous GPIs in NSTE-ACS patients was related to an increase in the incidence of major bleeding complications (Table 4).[11] GPI therapy was also a suspected contributor to excess intracranial hemorrhage and stroke; however, the incidence of intracranial hemorrhage (ICH) was rare in the trials of intravenous GPIs in the medical management of NSTE-ACS patients, and its use with or without heparin was not associated with an excess incidence of ICH (Table 4).[11] Similarly, the incidence of stroke was also not associated with this therapy.[11]

Thrombocytopenia is another possible, but infrequent, side effect of this therapy. The incidence of mild thrombocytopenia (< 100 000 platelets / $mm^3$) was 5% in those receiving 24-hour infusion of abciximab ($p<0.05$ versus placebo) and 7% (48-hour infusion; $p<0.05$ versus placebo) compared to 1% (placebo) in the GUSTO-IV-ACS trial.[4] When this safety endpoint was evaluated in the PURSUIT trial, eptifibatide was not associated with excess mild thrombocytopenia (6.8% eptifibatide versus 6.7% placebo). However, those receiving eptifibatide were more likely to suffer from severe thrombocytopenia (< 20 000 platelets / $mm^3$) than were those receiving placebo (0.2% versus <0.1%; relative risk 5.0, 95% CI(1.3, 32.4)).[6] The PRISM and PRISM-PLUS trials also noted that tirofiban was significantly associated with thrombocytopenia (defined as fewer than 90 000 platelets / $mm^3$), but the number of actual patients affected is quite low.[7,8] When compared to the placebo, the use of lamifiban was not associated with the incidence of thrombocytopenia.[10]

Safety concerns with the use of oral

**Table 4**

**Bleeding Complications, Intracranial Hemorrhage and Stroke at 30 days in Patients Enrolled in Trials of Intravenous GPIs in NSTE-ACS Patients**

| Trial | Study Drug (no. of patients) | Major bleeding (%) | Minor bleeding (%) | Intracranial hemorrhage (%) | Stroke (%) |
|---|---|---|---|---|---|
| GUSTO-IV ACS | Placebo (2598) | 0.3 | 2.0 | – | – |
| | Abciximab 24-h infusion (2590) | 0.6 | 3.0* | – | – |
| | Abciximab 48-h infusion (2612) | 1.0* | 4.0* | – | – |
| PURSUIT | Placebo (4696) | 9.1 | 7.4 | 0.1 | 0.8 |
| | Eptifibatide (4679) | 10.6* | 12.9 | 0.1 | 0.7 |
| PRISM | Heparin (1616) | 0.4 | 1.9 | 0.1 | – |
| | Tirofiban (1616) | 0.4 | 2.0 | 0.1 | – |
| PRISM-PLUS | Heparin (797) | 0.8 | – | 0 | – |
| | Tirofiban + heparin (773) | 1.4 | – | 0 | – |
| PARAGON-A | Placebo + heparin (758) | 0.8 | – | – | 0.4 |
| | Low-dose lamifiban + heparin (377) | 0.5 | – | – | 1.1 |
| | Low-dose lamifiban + no heparin (378) | 0.8 | – | – | 1.1 |
| | High-dose lamifiban +heparin (373) | 2.4 | – | – | 0.5 |
| | High-dose lamifiban + no heparin (396) | 1.3 | – | – | 0.8 |
| PARAGON-B | Placebo (2564) | 0.9 | 11.5 | 0.1 | 0.6 |
| | Lamifiban (2594) | 1.3 | 14.0** | 0.1 | 1.1† |
| Boersma et al.[11] | Placebo (13 105) | 1.4 | – | 0.06 | 0.69 |
| | Any GPI (incl. & excl. heparin) (18 297) | 2.4 | – | 0.09 | 0.75 |
| | Placebo (incl. heparin) (11 489) | 1.4 | – | 0.05 | 0.67 |
| | Any GPI (incl. heparin) (15 562) | 2.5 | – | 0.08 | 0.73 |
| | Placebo (incl. heparin) (2735) | 1.8 | – | 0.06 | 0.69 |
| | Any GPI (excl. heparin) (3171) | 1.3 | – | 0.11 | 0.88 |
| | Placebo (incl. heparin) (10 507) | 1.0 | – | 0.07 | 0.71 |
| | Eptifibatide or Tirofiban (incl. and excl. heparin) (13 095) | 1.6 | – | 0.07 | 0.80 |

Bleeding complications defined by Thrombolysis In Myocardial Infarction (TIMI) study group. (21) *$p<0.05$ for comparison with placebo; **$p=0.002$ for comparison with placebo (intermediate bleeding (non-TIMI bleeding classification)). (incl., including; excl., excluding) †$p<0.0006$ for comparison to placebo.

**Table 5**

**Bleeding Complications, Intracranial Hemorrhage and Stroke at 30 days in Patients Enrolled in Trials of Oral GPIs**

| Trial | Study Drug (no. of patients) | Major bleeding (%) | Minor bleeding (%) | Intracranial haemorrhage (%) | Stroke (%) |
|---|---|---|---|---|---|
| OPUS-TIMI 16 | Placebo (3421) | 1.20 | 5.8 | 0.1 | 0.4 |
| | Low-dose orbofiban (3537) | 2.0** | 11.0‡ | 0.1 | 0.5 |
| | High-dose orbofiban (3330) | 2.3† | 11.9‡ | 0.1 | 0.7 |
| SYMPHONY | Aspirin (3075) | 3.9 | 12.6 | – | 0.81 |
| | Low-dose sibrafiban (3083) | 5.2§ | 17.7§ | – | 0.84 |
| | High-dose sibrafiban (3014) | 5.7§ | 24.6§ | – | 0.56 |
| Second SYMPHONY | Aspirin (2229) | 4.0 | 10.5 | – | 0.6 |
| | Low-dose sibrafiban + aspirin (2235) | 5.7§ | 19.9§ | – | 0.7 |
| | High-dose sibrafiban (2173) | 4.6 | 21.0§ | – | 0.7 |

Bleeding complications defined in OPUS-TIMI-16 and the first and Second SYMPHONY trials by Thrombolysis In Myocardial Infarction (TIMI) study group. (21) **p=0.007 for comparison to placebo; †p=0.0006 for comparison to placebo; ‡p<0.0001 for comparison to placebo. 90-day and 7-day safety endpoints evaluated in the first SYMPHONY and Second SYMPHONY trials, respectively. §p<0.05 for comparison to aspirin.

GPIs are minor and are mainly due to gastric bleeding (Table 5). Typically, bleeding was not severe and posed more of an annoyance to patients through bruising and bleeding of the gums, nose, hemorrhoids and menses.

## Conclusion

Although the age- and sex-standardized mortality due to ischemic heart disease has declined over the past two decades, the incidence of acute coronary syndromes is expected to increase as the proportion of the Canadian population above age 65 increases from 13 to 21% over the next twenty years.[18,19] In addition to advanced age, the clinical profile of these patients often includes comorbidities such as diabetes mellitus and hypertension, which add to the overall complexity of medical decision-making. Despite this, older patients do derive similar relative, and hence, greater absolute benefit from GPI therapy in the medical management of NSTE-ACS compared to their younger counterparts.[20]

The majority of the trials only compare the primary composite clinical endpoint in patients younger than 65 years to those over the age of 65 years. Efforts should be made to report more in-depth, age-specific analyses, particularly on safety endpoints. Future investigations should specifically address optimal strategies for this rapidly expanding proportion of the population. ◆

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