Glycoprotein IIb/IIIa receptor blockers in acute coronary syndromes

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Glycoproteine IIb/IIIa receptor blokkers in acute coronaire syndromen

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2. Mahaffey KW, Harrington RA, *Akkerhuis KM*, Kleiman NS, Berdan LG, Crenshaw BS, Tardiff BE, Granger CB, DeJong I, Bhapkar M, Widimsky P, Corbalon R, Lee KL, Deckers JW, Simoons ML, Topol EJ, Califf RM, for the PURSUIT Investigators.
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8. *Akkerhuis KM*, Alexander JH, Tardiff BE, Boersma E, Harrington RA, Lincoff AM, Simoons ML.
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10. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang W-C, Lee KL, *Akkerhuis KM*, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML, for the PURSUIT Investigators.
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11. Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, *Akkerhuis M*, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM, Topol EJ, for the PURSUIT Investigators.
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12. *Akkerhuis KM*, Klootwijk PAJ, Lindeboom W, Umans VAWM, Meij S, Kint PP, Simoons ML.
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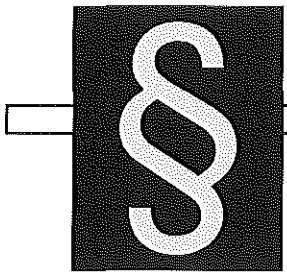

Introduction

1

Acute Coronary Syndromes

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Introduction

Acute coronary syndromes (ACS), which include unstable angina, non-Q-wave myocardial infarction (MI), Q-wave MI, sudden ischemic death and the acute complications resulting from interventional procedures, are the leading causes of morbidity and mortality in the Western world.

In Western European countries, 14% of all deaths (414 000 annually) have been attributed to acute MI and other ischemic heart diseases.[1] In the USA, more than 13 million people suffer from ischemic heart disease, and ACS yearly account for almost 500 000 deaths. Each year, an estimated 1.1 million Americans have a new or recurrent coronary attack, and about one third of them die. At least 250.000 deaths attributed to MI occur within 1 hour of onset of symptoms and before treatment can be started.[2] More than 650 000 Americans are discharged each year with a primary diagnosis of unstable angina. This number approaches that of patients discharged with a primary diagnosis of MI (747.000).[3] Over 10% of patients admitted to the hospital with unstable angina develop an MI within 2 weeks of diagnosis, and 1-year mortality of these patients ranges from 5% to as much as 14%.[4] The ACS therefore have a considerable impact on public health and result in substantial medical expenditure.

Although current interventional and pharmacologic therapies have been effective in reducing the incidence of ischemic events, novel therapeutic targets and strategies are urgently needed to improve further the clinical outcome in patients presenting with ACS.

In the last decade, numerous studies have provided a more detailed understanding of the pathogenesis of ACS. From these insights, new therapeutic targets and pharmacologic approaches to the treatment of ACS have emerged. Additionally, the results of these studies have led to an appreciation of the reasons for the drawbacks and shortcomings, including the relatively limited effectiveness, of the compounds used in the management of patients with ACS.

Pathophysiology of ACS

ACS share the common pathophysiology of myocardial ischemia caused by varying degrees of coronary artery occlusion by platelet-rich thrombi, initiated by the process of disruption or erosion of the covering endothelial layer of an atherosclerotic plaque.[5,6] The two critical events in the pathogenesis of ACS, therefore, are disruption or ulceration (erosion) of an atherosclerotic plaque and the subsequent superimposed formation of a partially or completely occlusive platelet-rich thrombus through the stages of platelet adhesion, activation and aggregation of individually activated platelets.[5,6] The clinical presentation of the ischemia resulting from the platelet-rich coronary thrombus depends on the extent and duration of obstruction of myocardial blood supply.

Disruption or erosion of atherosclerotic plaques

Early plaque development involves the proliferation of smooth muscle cells, the production of collagen and the accumulation of lipid within macrophages, as well as in the extracellular milieu within the lesion.[6] These initial plaques are often asymptomatic owing to the remodelling capacity of the affected coronary artery. An atherosclerotic plaque can become symptomatic, either because additional lipid acquisition leads to plaque growth, causing chronic stenosis which may clinically manifest as stable angina, or because the plaque undergoes erosion or disruption of the covering endothelium, resulting in coronary thrombosis which may present as an acute ischemic coronary syndrome.[5,6] Not all plaque disruptions followed by platelet thrombus formation, however, lead to an acute ischemic coronary event. Plaque ruptures with subclinical thrombosis result in the incorporation of thrombi into the lesion, stimulating plaque growth. In this way, plaque ruptures also contribute to the progression of the atherosclerotic process, which leads to the development of the chronic stenoses that cause stable angina.[5,6] The probability of plaque disruption is determined by several factors, including the shape of the plaque, its composition, some properties of the local circulation and external factors (e.g. blood pressure).

Most patients with coronary artery disease have both concentric plaques, resulting in a fixed degree of obstruction, and eccentric plaques, which may vary in the degree of stenosis owing to changes in coronary artery muscle tone.[5] Concentric plaques are more commonly associated with stable angina, while eccentric plaques carry an increased risk of disruption or erosion, resulting in an ACS.[5-7]

Susceptibility to disruption or fissuring is determined to a great extent by the relative content of the major constituents of the plaque-namely intracellular lipid, extracellular lipid, collagen and proteoglycans. Fibrous plaques are composed primarily of collagen and proteoglycans and are considered 'stable' plaques. In contrast, high lipid content predisposes atherosclerotic plaques to an increased risk of disruption. These plaques contain a lipid-rich core that is separated from the blood by a fibrous cap whose strength is proportional to its thickness. Therefore, the susceptibility of the lipid-rich plaques to rupture may vary depending on the thickness of the fibrous cap and the collagen content, which lends stability to the cap. Lipid-rich atherosclerotic lesions with a thin fibrous cap and a lack of collagen are more susceptible to disruption and are therefore considered 'vulnerable' plaques.[5,8]

High shear forces in the area of stenosis increase the probability of plaque rupture, especially if it concerns a vulnerable plaque that lacks a stable fibrous cap.[8] Changes in coronary tone and pressure can also affect plaque susceptibility to rupture or fissuring by altering the degree of stenosis and the related local shear forces.

Thrombotic response to plaque rupture and platelet thrombus formation

When an atherosclerotic plaque ruptures or ulcerates, platelets in the circulation are exposed to the highly thrombogenic environment within the plaque or the subendothelium. Platelet adhesion is the first step in platelet-mediated thrombosis. Platelet adhesion is mediated primarily by the binding of the platelet glycoprotein (GP) Ib receptor to the subendothelial form of von Willebrand factor (vWF).[9] Adhesion of platelets is followed by platelet activation. Adherent platelets are activated via several potent platelet agonists. The plaque and the subendothelial layer both contain large amounts of collagen while lipid-laden macrophages in the plaque core produce large quantities of tissue factor. Tissue factor stimulates the generation of thrombin (factor IIa) by initiating the coagulation cascade.[10] Thrombin and collagen are two of the major inducers of platelet activation.[11] An other potent platelet agonist is the high shear force of the circulation in the stenotic region.[10,11] These platelet agonists activate several signal transduction pathways within the platelet. The final outcome of platelet activation includes a change in platelet shape and the secretion of additional platelet agonists (adenosine diphosphate [ADP], serotonin and thromboxane A2), adhesive glycoproteins (fibrinogen and vWF), clotting factors and other vasoconstrictors, thus promoting vasospasm and further platelet accumulation and activation.[6,10,11] Activation of platelets by any agonist results in the expression of more than 50 000-80 000 copies of the GP IIb/IIIa receptor on the surface of each and every platelet, and its conversion to a high-affinity binding site for its primary ligands, fibrinogen and vWF. Bivalent molecules of fibrinogen cross-link ligand-competent GP IIb/IIIa receptors on adjacent platelets. Eventually, bridging of platelets by their GP IIb/IIIa receptors on a large scale generates a platelet-rich thrombus at the site of plaque injury.[11] Additionally, the aggregate of activated platelets is the primary source of the negatively-charged phospholipid surface on which the coagulation cascade proceeds, further increasing thrombin generation and the conversion of fibrinogen to fibrin.[9] Local generation of thrombin and fibrin then further enhance both platelet activation and aggregation. Most important, regardless of the proaggregatory stimulus, the final common pathway to platelet aggregation and thus to the formation of the platelet-rich thrombus, a pivotal event in the development of ACS, involves aggregation of activated platelets via their GP IIb/IIIa receptors.

Clinical presentation

The clinical presentation of the myocardial ischemia resulting from the platelet-rich coronary thrombus depends on the extent and acuteness of myocardial blood flow obstruction, as well as on the duration of decreased myocardial perfusion.[6]

The magnitude of the plaque injury determines the strength of the subsequent

thrombotic response and is therefore related to the clinical outcome. Minor plaque fissuring usually results in the formation of small intraintimal platelet thrombi, which are subsequently incorporated into the plaque. These thrombi usually remain asymptomatic but stimulate further plaque growth.[5,6] In lesions that have been disrupted more deeply, increasing platelet activation results in the formation of larger thrombi. These thrombi may grow intraluminally and can be either non-occlusive (mural) or occlusive.[5] The non-occlusive, intraluminal thrombi consist primarily of platelets and fibrin ('white' thrombi).[5,12,13] The outer surface of the white thrombus mass consists of a layer of activated platelets.[5] An occlusive coronary thrombus is composed of a platelet-rich or 'white' part located inside the disrupted atherosclerotic plaque and an intraluminal, occlusive 'red' part. The occlusive part of the thrombus consists mainly of fibrin and red blood cells, while platelets are scarce.[5,12,13] The transitional zone between the intraplaque white thrombus part and the occlusive red thrombus is characterized by a layer of activated platelets, which provide a highly active surface on which the occluding red thrombus layer is generated.[5] Therefore, the aggregation of individual activated platelets by cross-linking of their GP IIb/IIIa receptors to form a white mural thrombus represents an essential step in the generation of the completely occlusive red thrombus.

The presence or absence of a well-developed collateral circulation to the affected vessel is also an important factor determining the clinical outcome of intracoronary thrombosis.[5,14] Disruption of highly stenotic plaques is less likely to interfere significantly with myocardial perfusion since the distal territory is usually supplied by collaterals.[15,16] In contrast, disruption of moderately stenotic plaques carries an increased risk of developing an ACS since the collateral circulation has usually been less well-developed.

The clinical manifestations of ACS depend primarily on the degree and acuteness of coronary blood flow obstruction and the duration of decreased myocardial perfusion.[6] At one end of the spectrum, patients presenting with the ACS of unstable angina usually have non-occlusive, intraluminal thrombi, which are composed primarily of platelets (figures 1 and 2).[12,13]

Additionally, platelet aggregates may embolize distally, causing foci of myocardial necrosis.[5] These patients usually present with ST-segment depression on their electrocardiogram (ECG) and elevated troponin T or troponin I levels. In non-Q-wave infarction, the angiographic form of the responsible lesions is very similar to that seen in unstable angina. In 25% of the non-Q-wave MI patients, however, the infarct-related artery is occluded but the distal myocardium remains perfused by the collateral vasculature. In the remaining 75% of subjects, the mural platelet-rich thrombus is non-occlusive.[6] The principal difference between unstable angina and non-Q-wave MI is the elevated level of cardiac enzymes (creatine

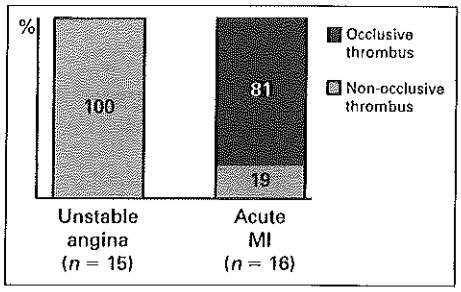


Figure 1
Occlusive and non-occlusive thrombi in acute coronary syndromes. Adapted from White 1997[12] and Mizuno et al 1992.[13]

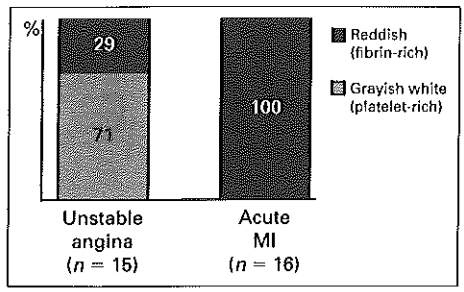


Figure 2
Thrombus composition in acute coronary syndromes. Adapted from White 1997[12] and Mizuno et al 1992.[13]

kinase-MB) in the latter patient population, reflecting myocardial necrosis resulting from a longer duration of coronary blood flow obstruction. In Q-wave infarction, an occlusive thrombus on a deeply injured plaque leads to an abrupt, complete and prolonged cessation of myocardial perfusion.[6] This results in subsequent myocardial ischemia and necrosis of the myocardium supplied by the affected coronary artery. The intraluminal thrombi found in patients with Q-wave MI are occlusive and consist mainly of fibrin and trapped red blood cells (Figures 1 and 2).[12,13] The ECG shows ST-segment elevation and subsequent development of abnormal Q-waves. As in non-Q-wave MI, elevated levels of cardiac enzymes reflect the myocardial necrosis. The pathophysiology of sudden ischemic death involves a rapidly progressing lesion with subsequent occlusive thrombosis.[6] The abrupt and complete obstruction of coronary blood flow results in severe ischemia and fatal ventricular arrhythmias.[6] The probability of sudden ischemic death in patients with acute thrombotic occlusion is increased in absence of a well-developed collateral circulation.

Goals in the management of acute coronary syndromes

In the majority of patients presenting with the ACS of unstable angina and non-Q-wave MI, the platelet-rich thrombus is only partially occlusive. Antithrombotic (anticoagulant in combination with antiplatelet) agents aim to maintain vessel patency by preventing the progression of a non-occlusive thrombus to an occlusive thrombus, and to inhibit the generation of new thrombi by preventing further platelet aggregation. In patients with acute MI, characterized by ST-segment elevation, the affected coronary artery is completely occluded. Therefore, the first goal is to achieve rapid reperfusion by the administration of thrombolytic therapy. Secondly, it is of utmost importance to maintain patency of the infarct-related artery, and to prevent recurrent thrombosis leading to reocclusion and recurrent ischemia. For this reason, thrombolytic therapy is commonly used in combination with antithrombotic drugs.[17]

Angioplasty has been used successfully in patients with all ACS. Although effective in establishing adequate myocardial reperfusion, angioplasty does not affect the underlying pathophysiologic processes, platelet aggregation and thrombus formation. Drawbacks of angioplasty include a significant incidence of both acute (abrupt vessel closure) and long-term (restenosis) ischemic complications, which may result in MI or death.[18,19] These have been managed by intracoronary stent implantation, but stenting is also accompanied by adverse effects, most notably stent thrombosis.[20]

Although current interventional and pharmacological therapies have been effective in the treatment of patients with ACS, none of the current management strategies effectively prevents platelet thrombus formation, and the more thorough understanding of the pathophysiology of ACS has pointed to their drawbacks and limited effectiveness. Additionally, studies have identified the pivotal role of the GP IIb/IIIa receptor in platelet aggregation and coronary thrombosis. This receptor has emerged as a new therapeutic target and several inhibitors of its function have been developed and studied in large clinical trials.[11] Based on the results of these trials, the GP IIb/IIIa receptor inhibitors have shown promising results in improving the outcomes of patients with ACS and those experiencing the ischemic complications of the invasive therapies of these diseases.

Antithrombotic therapy

Antithrombotic therapy consisting of the intravenous infusion of unfractionated heparin plus the oral administration of aspirin is used routinely in the treatment of the various ACS.

Aspirin

In patients with a broad spectrum of cardiovascular diseases, antiplatelet therapy offers protection against recurrent adverse ischemic events.[21] The most widely used antiplatelet drug today is acetylsalicylic acid (aspirin). Aspirin reduces the incidence of death, recurrent MI and stroke in patients presenting with acute MI (Figure 3).[21,22]

Aspirin also reduces mortality and MI when used in the acute management of unstable angina.[23-26] The principal side-effects of aspirin include dose-dependent gastrointestinal symptoms and renal toxicity. Aspirin inhibits the synthesis of the potent platelet activator thromboxane A2 by blocking the cyclo-oxygenase pathway.[27] However, like many other platelet activation antagonists, aspirin inhibits only one of the pathways to platelet activation, leaving the others intact. Most of the platelet agonists can stimulate platelet aggregation by activating the GP IIb/IIIa receptor via numerous alternate platelet activation pathways.[10] Although safe and very cost-effective, aspirin is therefore not a potent platelet antagonist.

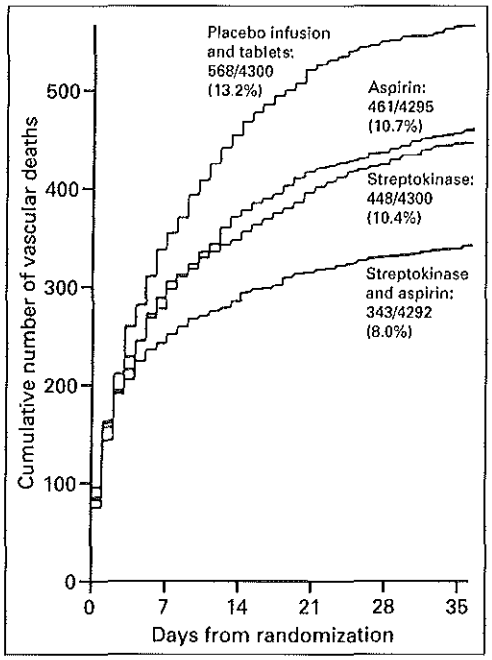


Figure 3
*Cumulative vascular mortality in the ISIS-2 trial in Days 0-35 among patients allocated: (**a**) active streptokinase only; (**b**) active aspirin only; (**c**) both active treatments; and (**d**) neither. Reprinted from ISIS-2 Collaborative Group 1988,[22] with permission from the Lancet.*

Unfractionated heparin

Unfractionated heparin is a heterogeneous mixture of polysaccharides with a molecular weight of 5000-30 000 Da. The mechanism of action of heparin involves binding to antithrombin III (AT-III), thereby greatly increasing its anticoagulant activities.[28] AT-III is a protein capable of inhibiting multiple steps in the intrinsic and common coagulation pathways, and of blocking the actions of free thrombin. Thrombin is thought to play an important role in the pathophysiology of coronary artery thrombosis. It promotes platelet activation and aggregation, cleaves fibrinogen to form fibrin, and catalyses the cross-linkage of the fibrin clot. Additionally, thrombin can self-amplify by means of a positive feedback loop. By binding to AT-III, heparin increases the affinity of AT-III for thrombin 1000-fold. In this way, the heparin-AT-III complex is capable of blocking a higher level of thrombin activity and increasing the time to clot formation.[28] Heparin fragments with a lower molecular weight bound to AT-III are more capable of inhibiting factor Xa activity than blocking the actions of thrombin.[28]

Heparin is the most widely used antithrombin therapy for patients with ACS. In clinical trials, heparin, alone and in combination with aspirin, has been effective in reducing the adverse ischemic outcomes, including death and non-fatal MI among patients with unstable angina and non-Q-wave MI.[25,26,29] A meta-analysis of multiple studies has shown a 33% reduction in MI or death during heparin therapy in patients with unstable angina treated with aspirin plus heparin

compared with those treated with aspirin alone.[4] The usefulness of unfractionated heparin in the management of patients presenting with acute ST-elevation MI is not unequivocal. ACC/AHA guidelines recommend the use of intravenous heparin in patients treated with tPA and in patients who do not receive thrombolytics, while in those who are treated with streptokinase and are not at high risk for systemic emboli the addition of heparin is not recommended.[30,31]

The use of unfractionated heparin is associated with several potential drawbacks. The effectiveness of heparin is limited by several factors, including its inability to inhibit clot-bound thrombin, its dependence on AT-III, its neutralization by protein binding and platelet factor 4, which is secreted by activated platelets and blocks the interaction between heparin and AT-III, and the rebound clinical events that follow the discontinuation of unfractionated heparin. Unfractionated heparin is therefore inconsistent in its effect within and between patients. Furthermore, it leads to thrombocytopenia in about 5% of patients, and requires hospitalization for frequent monitoring of the activated partial thromboplastin time (aPTT) and careful titration to achieve aPTT of 50-70 seconds.[32-35] In the GUSTO-I trial, aPTT values exceeding 70 seconds were related to a progressively increased rate in moderate-to-severe bleeding and were also associated with higher mortality and reinfarction rate.[36] In the GUSTO-IIa trial, a more intensive heparin regimen was accompanied by a 2-fold risk of haemorrhagic stroke in patients receiving thrombolytic therapy.[37] In patients with acute MI, fibrinolytic therapy exposes thrombin, which results not only in the autocatalytic formation of more thrombin but also in enhanced platelet activation. The thrombin activity, but not the increasing formation of more thrombin, may be inhibited by concomitant heparin during thrombolytic therapy. Furthermore, activated platelets create an environment that is potentially resistant to the effects of heparin. When complexed with activated platelets, factor Xa is also relatively resistant to inactivation by the heparin-AT-III complex.[38]

The need for increased efficacy and the limitations of unfractionated heparin have led to the development of alternative and more potent antithrombotic drugs, including low-molecular-weight (LMW) heparins and direct thrombin inhibitors.

Low-molecular-weight heparin

LMW heparins are produced by depolymerization of standard heparin, resulting in shorter polysaccharide fragments with a molecular weight of 4000-8000 Da. LMW heparins have several potential advantages over unfractionated heparin. Owing to a higher resistance to inactivation by platelet factor 4 and a lower affinity for heparin-binding proteins, LMW heparins have a more predictable pharmacokinetic profile, greater bioavailability and longer plasma half-life, all of

which result in more predictable and reliable levels of anticoagulant effect.[34,39] LMW heparins can therefore be administered once or twice daily as subcutaneous injections at fixed or weight-adjusted doses, thus simplifying treatment in the acute phase without the need for laboratory monitoring. The lower-molecular-weight distribution not only decreases the variability of the anticoagulant effect, but also modifies the anticoagulant mechanism. LMW heparins have a higher Xa/IIa inhibition ratio, but a lesser platelet inhibitory effect.[40]

Several clinical trials have evaluated the efficacy and safety of LMW heparins in patients presenting with ACS.

In the FRISC (Fragmin During Instability in Coronary Artery Disease) study, 1506 patients with unstable angina or non-Q-wave infarction were randomised to receive subcutaneous dalteparin (Fragmin; 120 U/kg twice daily for 6 days, followed by 7500 U once daily for the next 35-45 days) or placebo in addition to aspirin.[41] The primary endpoint (death or new MI at 6 days) was significantly lower in the group taking dalteparin (1.8% versus 4.8%). The composite endpoint of death, new MI, revascularization or need for intravenous heparin also showed a significant difference in favour of dalteparin (5.4% versus 10.3%). These differences persisted at 40 days but were no longer significant at 4-5 months after the end of treatment. However, survival analysis showed a risk of reactivation and reinfarction when the dose was decreased. The treatment regimen was safe and compliance was adequate. Of note, this study did not compare dalteparin with unfractionated heparin, but with placebo.

In the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) trial, the effect of the LMW heparin enoxaparin (1 mg/kg every 12 h) was compared with unfractionated heparin (adjusted to achieve an aPTT of 55-85 seconds) in 3171 patients with unstable angina or non-Q-wave MI.[42] All patients received aspirin. The median duration of treatment for both trial therapies was 2.6 days. At 14 days, the risk of death, MI or recurrent angina was significantly lower in patients assigned to enoxaparin than in those randomized to unfractionated heparin (16.6% versus 19.8%). The risk of this composite endpoint remained significantly lower at 30 days (19.8% versus 23.3%). Although the significance of the treatment effect was driven by the differences in the rates of recurrent angina, the risks of both death and MI at 30 days were reduced as well by 20% and 25%, respectively. Treatment with enoxaparin did not increase the incidence of major bleeding complications, although there were slightly more minor bleedings, primarily because of ecchymoses at injection sites.

In the ESSENCE trial, the theoretical advantages of LMW heparin over unfractionated heparin have been translated into a clinical benefit. The more consistent anticoagulant effect together with the higher Xa/IIa inhibition ratio may, in part, account for the better therapeutic index that LMW heparin has over

unfractionated heparin. A major advantage of LMW heparin is, however, that it can be used in fixed doses without the necessity of monitoring, thus simplifying therapy and allowing its continuation beyond hospital discharge. More studies are needed to assess the optimal length of treatment and the long-term outcome. Future clinical trials will investigate the efficacy and safety of LMW heparins in new therapeutic settings and in combination with thrombolytic and other new potent antithrombotic and antiplatelet therapy. A substudy in the GUSTO-IV trial will investigate the simultaneous treatment of unstable angina patients with a GP IIb/IIIa inhibitor (abciximab) and LMW heparin.

Direct thrombin inhibitors

Direct thrombin inhibitors, such as hirudin and hirulog, have potential advantages over heparin. They do not require AT-III as a cofactor, are capable of inhibiting both free-circulating as well as clot-bound thrombin and are not inactivated by plasma proteins or platelet factor 4.[43]

The TIMI 9B trial compared the efficacy and safety of hirudin with intravenous heparin in 3002 patients with acute MI presenting within 12 h from onset and treated with streptokinase or tissue-type plasminogen activator.[44,45] Comparison of the primary endpoint of death, MI, congestive heart failure or shock at 30 days between treatment groups did not show a significant difference (heparin 11.8% versus hirudin 12.8%). The incidence of major bleeding events including intracranial bleeding was also similar between groups.

The HERO (Hirulog Early Reperfusion/Occlusion) trial compared the efficacy of two doses of hirulog with heparin in achieving TIMI grade 3 flow at 90 min among 412 patients with acute ST-elevation MI who were treated with aspirin and streptokinase.[46] TIMI grade 3 flow at 90 minutes was 35% with heparin, 46% with low-dose, and 48% with high-dose hirulog. At 2 - 4 days after treatment, similar rates of TIMI grade 3 flow were present in the three groups. Hirulog was more effective in producing early patency without increasing the risk of major bleeding.

In the large GUSTO-IIB (Global Use of Strategies to Open Occluded Coronary Arteries) trial, 12142 patients with ACS were randomized to receive 72 h of therapy with either intravenous heparin or hirudin.[47] At 24 h, the risk of death or MI was significantly lower in the hirudin group than in the group assigned to heparin (1.3% versus 2.1%). This difference was still significant 48 h after the initiation of treatment (2.3% versus 3.1%). Although hirudin demonstrated an important effect in reducing early events, the extent of the benefit at 30 days was small and of marginal statistical significance (incidence of death or MI at 30 days: 8.9% versus 9.8% in heparin group, representing an 11% risk reduction, $p = 0.058$). The benefit was similar in patients with ST-segment elevation and in those without. Although there was no significant difference in the incidence of

severe bleeding complications, treatment with hirudin was associated with a significantly higher incidence of moderate bleeding (8.8% versus 7.7%, p = 0.03).

Results from trials with direct thrombin inhibitors have questioned the hypothesis that potent direct inhibition of thrombin results in a clinically meaningful long-term benefit in clinical outcome. Although thrombin is one of the most potent platelet activators, inhibition of thrombin only targets a single platelet activation pathway, leaving numerous alternate routes for platelet activation available. Further, it was demonstrated that, while capable of inhibiting thrombin activity, hirudin, like heparin, was incapable of blocking thrombin generation resulting in an accumulation of thrombin exceeding the ability of hirudin to block its activity.[48,49] Therefore, antagonism higher in the coagulation cascade, as achieved using LMW heparin, may appear to be more effective. The lack of long-term benefit may also reflect the lack of passivation of the vessel surface or the rebound hypercoagulability after the discontinuation of treatment.[50] Higher doses of hirudin, however, resulted in excessive bleeding (including intracerebral haemorrhage) in the prematurely discontinued TIMI 9A and GUSTO-IIA trials without indication of improved efficacy.[37,51] Therefore, like heparin, hirudin also requires careful titration to achieve aPTT of 50-70 seconds. The GUSTO-IIB trial showed that patients treated with hirudin required significantly fewer dose adjustments to maintain therapeutic levels of anticoagulation than those treated with heparin.[47] Most important, future trials will have to find ways to improve the durability over time of the therapeutic effect as observed in the early phase, and to assess the additional benefit of a combination of direct thrombin inhibiting agents and platelet GP IIb/IIIa receptor blockers.

Thrombolysis

Thrombolytic therapy has been effective in reducing mortality in patients presenting with acute MI with ST-segment elevation (Figure 3).[22,52] Although primary angioplasty is being used to an increasing extent, thrombolysis is still the most widely used modality of reperfusion therapy. Nevertheless, thrombolytic therapy has significant and relevant efficacy as well as safety limitations.

In patients with acute MI, achievement of rapid, complete and sustained restoration of coronary flow through the infarct-related artery (TIMI-Thrombolysis In Myocardial Infarction-grade 3 flow) results in lower mortality, irrespective of the thrombolytic regimen.[53,54] In the angiographic substudy of the landmark GUSTO-I trial, death occurred in 4.4% of patients with normal coronary flow at 90 min, whereas mortality was as high as 8.9% among patients with no flow.[53,54] The most potent currently available thrombolytic therapy, a combination of accelerated alteplase, aspirin and intravenous heparin, produces complete myocardial reperfusion in only 53% of patients, however.[53]

Treatment with thrombolytics is associated with an increased risk of intracerebral bleeding, particularly in older patients and in those with hypertension.55 In the recently completed GUSTO-III trial, the incidence of haemorrhagic stroke was 0.9%, or approximately 1 in 100 patients.[56]

Furthermore, primary angioplasty for the treatment of acute MI is capable of achieving higher rates of infarct vessel patency (TIMI grade 3 flow approximately 90%) and is associated with a significant reduction in mortality and recurrent MI as compared with pharmacological reperfusion.[57-60]

The primary reason for the lack of efficacy and the relatively high failure rate of thrombolytic therapy is related to the prothrombotic effects of fibrinolytics and the lack of a potent antiplatelet approach in the treatment of acute MI. When fibrinolysis occurs, there is exposure of free thrombin, which not only increases its own production but also leads to platelet activation, thereby strongly promoting further platelet aggregation. The platelet-rich part at the core of the thrombus is, however, fully resistant to fibrinolytic therapy. In addition, activated platelets inhibit fibrinolysis by releasing large amounts of plasminogen activator inhibitor-1, the most potent endogenous inhibitor of fibrinolysis, and by secreting rapid-acting a2-antiplasmin. Release of coagulation factor XIII further increases resistance to thrombolytics by cross-linking fibrin.[61-63]

These interactions in response to fibrinolytic therapy stimulate the formation of platelet-rich thrombi and contribute to the ongoing and recurrent thrombosis observed in the infarct-related coronary artery. Together with the inability of fibrinolytics to interfere with the formation of the platelet-rich (white) thrombi and the lack of a potent antiplatelet approach, they may contribute to the failure of reperfusion and to the reocclusion that are present in many patients treated with thrombolytic therapy.[64]

The prothrombotic state following fibrinolytic therapy may not only account for the lack of benefit of fibrinolysis in patients with unstable angina and non-Q-wave MI, in whom the thrombus is composed primarily of platelets,[65] but also explain the adverse clinical effects of angioplasty after preceding thrombolysis in patients with acute MI.[66-68]

The importance of a potent antiplatelet approach is endorsed by the results of the ISIS-2 trial. Despite the fact that aspirin is a relatively weak antiplatelet agent and its antiaggregatory effect in the acute phase is only modest, this study showed that early administration of aspirin resulted in a 23% risk reduction in mortality in patients with acute MI. This benefit was as large as the mortality reduction achieved with the use of streptokinase alone (figure 3).[22]

A more potent antiplatelet therapy can be achieved with the use of GP IIb/IIIa receptor antagonists. The addition of GP IIb/IIIa receptor blockade to thrombolytic therapy in patients presenting with acute MI has the potential to

counteract the prothrombotic tendencies of fibrinolytic agents, and to result in more rapid, complete and sustained reperfusion, and improved survival.

Platelet glycoprotein IIb/IIIa receptor inhibitors

Based on a more thorough understanding of the pathogenesis of ACS and the identification of the platelet GP IIb/IIIa receptor as the final common pathway to platelet aggregation, a new class of therapeutic agents has emerged, the GP IIb/IIIa receptor antagonists.[11] Several inhibitors of the GP IIb/IIIa receptor have been developed. They act either as irreversible, non-competitive GP IIb/IIIa receptor blockers (monoclonal antibodies) or as reversible, competitive GP IIb/IIIa receptor antagonists (fibrinogen analogs). However, while the common limitation of all antiplatelet agents that target the platelet activation stage of thrombus formation is the existence of numerous alternate platelet activation pathways, all of the GP IIb/IIIa receptor antagonists are potent inhibitors of platelet-platelet interaction and capable of fully blocking platelet aggregation, which represents the final common pathway to coronary thrombosis and ACS.[69] Several of these agents have been evaluated in large-scale, randomized, placebo-controlled clinical trials, and they have shown to be effective in reducing recurrent adverse ischemic events in the treatment of patients undergoing percutaneous intervention and in patients with unstable angina or non-Q-wave infarction.

Abciximab, the Fab fragment of a chimeric human-mouse antibody (c7E3) directed against the GP IIb/IIIa receptor, was the first to undergo clinical evaluation in the EPIC trial, and was approved for use in percutaneous coronary intervention in 1995. In the EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications) trial, 2099 patients scheduled to undergo angioplasty who were at high risk of ischemic complications (severe unstable angina, evolving acute MI, or high-risk coronary morphologic characteristics) were randomised to placebo, a bolus of abciximab just before the procedure, or a bolus and 12-hour infusion of abciximab.[70] The composite endpoint of death, non-fatal MI or urgent revascularisation at 30 days was reduced by 35% (12.8% placebo versus 8.3% bolus/infusion abciximab).[70] This benefit was sustained at 6 months, mainly due to lesser need for repeat revascularisation,[71] and also at 3 years, most notably among patients with unstable angina or evolving acute MI.[72] Abciximab treatment resulted in particular and incremental benefit for patients enrolled with the ACS severe unstable angina or evolving acute MI. In the subset of 64 patients enrolled with acute MI, the composite endpoint was reduced by 83% (26.1% placebo versus 4.5% abciximab bolus/infusion). At 6 months, ischemic events were significantly reduced from 47.8% with placebo to 4.5% with abciximab bolus/infusion, with a significant reduction in reinfarction and a significantly lessened need for repeat revascularisation.[73] Patients with severe unstable angina experienced particularly marked reductions in the risk of death and

MI with abciximab treatment during coronary intervention (62% reduction in the rate of the 30-day endpoint, mainly owing to reduction in the incidences of death and MI); by 6 months, cumulative death and MI were further reduced by abciximab.[74] Among patients who presented with ACS, the incidence of mortality at 3 years with abciximab was less than half that in the placebo group.[72] The long-term results in the EPIC trial extended the benefits of abciximab from reducing the acute-phase ischemic complications from abrupt vessel closure to a diminished need for subsequent revascularization.[71,75] These sustained and, in some respects, incremental long-term benefits might be a result of the phenomenon of culprit vessel wall passivation, whereby the injured vessel wall is transformed from a platelet-reactive surface into one that does not support platelet thrombus formation and deposition.[76]

The particular benefit of a potent antiplatelet therapy in patients with ACS undergoing percutaneous intervention was further endorsed by the CAPTURE (c7E3 Antiplatelet Therapy in Unstable Refractory Angina) trial.[77] In 1265 patients with refractory unstable angina for whom percutaneous coronary intervention was planned, but not immediately performed, there was a significant 30% reduction in the primary endpoint of death, MI or urgent intervention at 30 days in the abciximab group (11.3% versus 15.9% in the placebo group). In contrast to the EPIC trial, CAPTURE involved the administration of placebo or abciximab starting 18-24 h prior to the percutaneous coronary intervention and continuing until one hour after completion of the intervention. A unique observation in the CAPTURE trial was the significant reduction of MI occurring before PTCA in patients receiving abciximab during the 24 h preceding coronary intervention (Figure 4).[77]

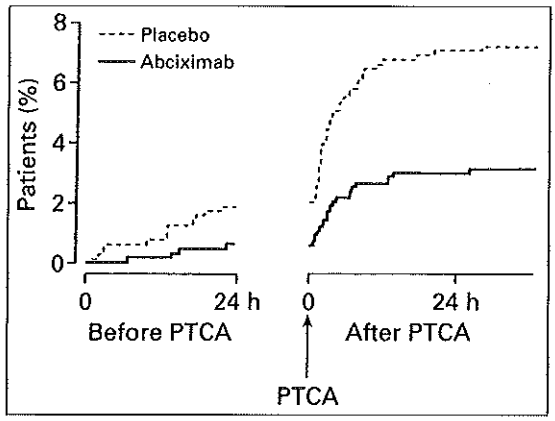


Figure 4
Development of myocardial infarction during treatment with abciximab or placebo, before and in association with PTCA. Results from the CAPTURE study. Reprinted from the CAPTURE Investigators 1997 with permission from The Lancet.

This finding also lends support to the hypothesis that GP IIb/IIIa receptor blockers can stimulate culprit vessel passivation and stabilize patients with ACS, such that subsequent coronary intervention may even be avoided.[77] Treatment with abciximab also showed to significantly reduce procedure-related infarctions. In fact,

most infarcts occurred during or within 24 h following PTCA (Figure 4). This suggests that longer treatment with potent GP IIb/IIIa receptor blockers without subsequent coronary intervention might be an alternative or perhaps even the preferred option for patients with ACS, who are at particular high-risk of procedure-related thrombotic complications such as MI, with early coronary revascularization recommended only for patients with recurrent ischemia despite intensive medical therapy. This new concept of potent antiplatelet therapy with GP IIb/IIIa blockade being effective in achieving culprit vessel wall passivation and stabilizing patients with non-ST-segment elevation ACS on a durable basis, without systematic early coronary revascularization, will be tested in the forthcoming large GUSTO-IV trial.

The effectiveness of platelet GP IIb/IIIa blockade on adverse cardiac events in patients with ACS undergoing coronary angioplasty was further supported by the results of several large clinical trials using several other GP IIb/IIIa receptor inhibitors: Eptifibatide (IntegrilinTM), a cyclic heptapeptide that mimics fibrinogen structure and acts as a reversible, competitive GP IIb/IIIa receptor antagonist, reduced the rates of early ischemic events at 30 days in the IMPACT-II (Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II) trial.[78] Analysis of the treated patient population at 6 months showed a sustained reduction in the composite incidence of death and MI in patients who received eptifibatide.

Tirofiban, another GP IIb/IIIa blocker, was studied in the RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis) trial and provided protection against early cardiac events related to thrombotic closure.[79] At 30 days, the relative reduction was sustained, although to a lesser extent.

The efficacy of platelet GP IIb/IIIa inhibitors as primary therapy in patients with ACS without ST-segment elevation has also been investigated in clinical trials without protocol-mandated revascularization strategies.

In the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial, more than 10 000 patients with unstable angina or non-Q-wave infarction were studied.[80] Treatment with eptifibatide resulted in a significant 1.5% absolute reduction in the primary endpoint (death/non-fatal MI at 30 days) compared with placebo (14.2% versus 15.7%). This reduction was reached by 96 h and maintained for 30 days.[80] Using investigator-determined infarctions, the 30-day incidence of the primary endpoint was 8.1% in the eptifibatide group versus 10% in the placebo group. This almost 2.0% absolute reduction was highly significant . In conformity with the results from the CAPTURE study, eptifibatide reduced the event rate in patients treated medically, with an added benefit if they underwent coronary intervention while receiving study drug.[77,80] As with other antithrombotic therapies, eptifibatide was associated with increased bleeding and need for transfusion but not with an increased risk of haemorrhagic stroke.[80] The PURSUIT trial represented the largest phase III study

of a GP IIb/IIIa receptor inhibitor used as primary ACS therapy in a setting that closely resembled clinical practice. The results from PURSUIT confirm that early treatment using GP IIb/IIIa inhibitors improves outcomes in a broad spectrum of ACS patients presenting without persistent ST-segment elevation.[80]

Three other large studies have evaluated two other small-molecule GP IIb/IIIa inhibitors as primary treatment in patients presenting with unstable angina or non-Q-wave MI. Tirofiban was studied in the PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) and PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) trials.[81,82] In both trials, treatment with tirofiban was associated with a significant reduction in adverse ischemic events including death and non-fatal MI in the acute setting. At 30 days, the benefits had been eroded somewhat but the treatment effect still favoured tirofiban, with a significant reduction in mortality in the PRISM study and a significant reduction in death or MI in the PRISM-PLUS study.

In the PARAGON-A study of 2282 patients with unstable angina or non-Q-wave MI, lamifiban, a nonpeptide platelet GP IIb/IIIa inhibitor, showed no significant benefit for reduced death or MI in the overall study cohort at 30 days (10% relative reduction).[83] At 6 months, however, there was a highly statistically significant 40% reduction in death or MI for the low-dose lamifiban/heparin group as compared with heparin alone. At 1 year, mortality was reduced from 8.7% to 7.0% in the same low-dose lamifiban/heparin group. These findings of incremental late benefit support the arterial passivation hypothesis. In agreement with other trials evaluating the efficacy of GP IIb/IIIa inhibitors in patients with ACS undergoing PTCA, lamifiban reduced the incidence of death and MI at 30 days in the subset of patients undergoing angioplasty (6.8% versus 15.8% with placebo).[84]

Platelet glycoprotein IIb/IIIa receptor inhibition has now been evaluated in nine large randomized clinical trials enrolling more than 30 000 patients. In five trials, GP IIb/IIIa receptor antagonists were compared with standard therapy in patients undergoing coronary revascularization,[70,77-79,85] and in four trials GP IIb/IIIa receptor inhibition was evaluated as primary therapy in patients with unstable angina or non-Q-wave infarction.[60-83] While the magnitude of benefit has varied, the results of these trials have all demonstrated a consistent benefit in the reduction of death and nonfatal MI for different GP IIb/IIIa receptor blockers (figure 5). Four studies have demonstrated that GP IIb/IIIa inhibition therapy, added to heparin and aspirin in the acute-phase treatment of patients with unstable angina or non-Q-wave MI, improves outcomes in these patients beyond the benefit offered by heparin and aspirin.[60-83] A meta-analysis of the nine trials shows a very strong and highly significant 20% reduction in death or MI at 30 days (Figure 5).[63] Although in the first trial with GP IIb/IIIa blockers a doubling of significant bleeding complications

occurred,70 recent trials have only shown a slightly higher bleeding event rate in the GP IIb/IIIa inhibitor group, mainly because of bleeding at the femoral access site in patients undergoing angioplasty. It has been demonstrated that bleeding risk can be reduced by using reduced heparin dosing on a weight-adjusted basis along with more attention to the catheter-access site.[85,86]

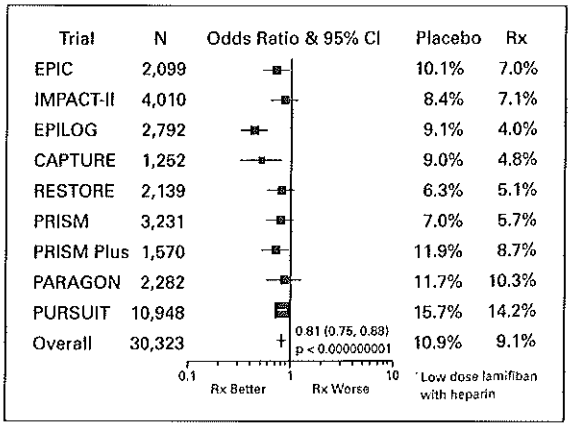


Figure 5
Odds ratio's and 95% confidence intervals for the nine large-scale (over 1000 patients), randomized, placebo-controlled trials of platelet GPIIb/IIIa inhibitors for percutaneous coronary intervention or unstable angina/non-Q-wave MI. Overall, in 30 323 patients, there is a highly statistically significant 20% reduction in death or MI at 30 days. Reprinted from Topol 1998 with permission from Circulation.

Most importantly, GP IIb/IIIa inhibition therapy has not been associated with an excess of intracerebral bleedings in patients enrolled in the large intervention trials.[63] Of note, all trials used aspirin in the placebo group. The effect of the GP IIb/IIIa receptor inhibitors is therefore additional and of a magnitude (25%) that is comparable with that achieved with aspirin more than a decade ago. In addition, at least two trials with different GP IIb/IIIa inhibiting agents have shown evidence for durability or incremental late benefit of the treatment effect achieved in the early phase.[72,83]

GP IIb/IIIa inhibitors in the treatment of acute MI

As discussed, platelet thrombus formation is a major contributor to both the failure of thrombolysis and the pathogenesis of reocclusion in patients with acute MI. Therefore, GP IIb/IIIa receptor blockade therapy added to thrombolytics or used as an adjunct to direct angioplasty may significantly improve treatment outcomes in patients with acute ST-segment elevation MI.

Thrombolytic therapy combined with GP IIb/IIIa receptor blockade

Experimental, preclinical studies have shown that combining GP IIb/IIIa inhibitors with thrombolytic therapy results in more rapid, complete and sustained reperfusion, and that the dosage of fibrinolytics can be decreased with concomitant use of GP IIb/IIIa receptor blockers.[63] In the first clinical study, TAMI 8, 60

patients receiving full-dose alteplase, aspirin and heparin for acute MI received bolus injections of the murine 7E3 monoclonal antibody Fab at varying time points after initiation of the thrombolytic therapy. [87] Ten control patients were treated with alteplase but not with m7E3 Fab. The infarct-related artery was patent (TIMI grade 2 or 3 flow) in 92% of patients receiving m7E3 Fab compared with 56% of patients in the control group. There was no excess of major bleeding complications among patients treated with the combination of alteplase and m7E3 Fab. The IMPACT-AMI (Integrilin to Manage Platelet Aggregation to Combat Thrombus in Acute Myocardial Infarction) trial investigated the preliminary efficacy and safety of a combination of full-dose, accelerated alteplase, aspirin and heparin with variable dosing of the GP IIb/IIIa inhibitor eptifibatide in a pilot study of 180 patients with acute MI.[88] Patients treated with the highest eptifibatide dose had a 69% higher rate of TIMI grade 3 flow than placebo-treated patients (66% versus 39%) at 90 min, and a shorter median time to ST-segment recovery on continuous 12-lead ST-segment monitoring. The combined use of alteplase and eptifibatide was not associated with an excess of significant bleeding complications. In the PARADIGM (Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction) trial, 345 patients with acute MI treated with either alteplase or streptokinase were randomly assigned intravenous lamifiban at 3 different doses or placebo. While there was no trend in reducing clinical endpoints between groups, the continuous 12-lead ECG monitoring showed more rapid and stable resolution of the ST-segment elevation among patients treated with the combination of lamifiban and thrombolytics, suggesting improved early and complete reperfusion.[63,64]

Furthermore, concomitant use of potent antiplatelet therapy facilitating fibrinolysis may allow for lower doses of fibrinolytics needed to achieve reperfusion. Lower doses of fibrinolytic therapy minimize the adverse prothrombotic effects and could reduce the risk of significant bleeding complications including intracerebral haemorrhage.[63] The SPEED (Strategies for Patency Enhancement in the Emergency Department) trial was a dose-finding, phase II study that compared abciximab alone with abciximab plus reduced-dose reteplase in patients with acute ST-elevation MI. The dose of reteplase was escalated to establish the optimal dose of r-PA in combination with full-dose abciximab. Preliminary 60-min angiographic results showed a dose-response with increasing doses reteplase with a higher TIMI 3 flow rate.[89] TIMI 3 flow at 60 minutes was achieved in 52% of patients receiving abciximab plus 10 units r-PA versus 45% in the t-PA meta-analysis.[89] The ongoing TIMI 14A trial evaluates the additional benefit of abciximab when used as adjunct to several fibrinolytic regimens in the management of patients with acute MI. Preliminary data showed that treatment with abciximab alone was capable of achieving TIMI 3 flow rates similar to those seen with a full-dose of streptokinase

in the GUSTO-I trial. When added to streptokinase and t-PA, abciximab increased the rate and extent of reperfusion with reduced doses of the fibrinolytics.[90] The highest TIMI 3 flow rate (79%) was achieved with a 60-minute infusion of 50 mg t-PA in combination with abciximab.[90] Although the angiographic results and/or ST-monitoring data from these studies suggest that the rate and speed of reperfusion can be enhanced by combining GP IIb/IIIa receptor inhibitors with thrombolytic therapy, larger phase III trials are needed to assess further the ability of GP IIb/IIIa inhibitors, alone or in combination with full- or reduced-dose fibrinolytics, to improve clinical outcomes with fewer significant bleeding complications in patients with acute ST-segment elevation MI.

Combining direct angioplasty and GP IIb/IIIa blockade

Initial data pointing to the beneficial effects of adding GP IIb/IIIa receptor blockade to direct angioplasty for acute MI were provided by the subgroup analysis of patients from the EPIC trial enrolled with acute MI and undergoing primary or rescue angioplasty. These have already been discussed in this chapter. In the recent RAPPORT (Reopro and Primary PTCA Organization and Randomized Trial) trial, abciximab was compared with placebo in patients undergoing primary angioplasty for acute MI. Abciximab significantly reduced the incidence of death, reinfarction or urgent target vessel revascularization at 30 days (5.8% versus 11.2%).[91] Furthermore, the need for unplanned, bail-out stenting was reduced by 42% in the abciximab group. Treatment with abciximab was, however, associated with an increased risk of major bleeding (16.6% versus 9.5%). Larger trials will have to confirm the beneficial effects of GP IIb/IIIa inhibition in patients undergoing direct angioplasty for acute ST-segment elevation MI.

In the next few years, it is likely that GP IIb/IIIa inhibitors will come to play an important role in the treatment of patients with acute ST-segment elevation MI. They have the potential to achieve high rates of reperfusion without an increased risk of significant bleeding complications when used combined with low-dose fibrinolytics, and are capable of enhancing the safety of primary or (subsequent) rescue angioplasty.

Oral GP IIb/IIIa receptor antagonists

Where intravenous GP IIb/IIIa receptor inhibitors have shown significant effect in reducing acute ischemic complications in patients undergoing angioplasty and in those with ACS, additional and, potentially, incremental long-term benefit might be obtained by subsequent, continuing longer-term treatment with oral platelet GP IIb/IIIa antagonists. However, whether prolonged administration of oral GP IIb/IIIa blockers is capable of preventing subsequent events in at-risk patients and providing secondary prevention awaits the results of large-scale trials.

This thesis addresses several aspects of the clinical evaluation of GP IIb/IIIa receptor blockers in patients with acute coronary syndromes. A number of manuscripts described in this thesis have been based on data originating from the large Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial. PURSUIT compared the GP IIb/IIIa inhibitor eptifibatide with placebo in addition to standard therapy in 9461 patients with acute coronary syndromes who did not have persistent ST-segment elevation.
In chapters 2 and 3, we reviewed the structure of the Clinical Events Committee and the event-adjudication process as used in the PURSUIT trial.
In chapter 4, we reviewed the geographic variations in patient outcome and treatment effect as observed in PURSUIT.
In chapters 5 and 6, we studied the safety of GP IIb/IIIa receptor blockers with respect to the occurrence of bleeding complications and the risk of stroke, respectively.
Chapters 7 and 8 study the effects of GP IIb/IIIa receptor blockers during pharmacological treatment relative to the effects during percutaneous coronary intervention.
In chapters 9 through 12, we present some methods and decision models for risk stratification in patients admitted with a non-ST-segment elevation acute coronary syndrome.
Finally, chapters 13 and 14 describe the phase II clinical development of an oral GP IIb/IIIa receptor blocker.

References

1 *World Health Statistics Annual 1994*, World Health Organisation, Geneva, Switzerland, 1995.
2 American Heart Association, *Heart and Stroke Facts*, Dallas, Tex: American Heart Association National Center, 1996.
3 Brunelli C, Spallarossa P, Rossettin P, Caponnetto S: Recognition and treatment of unstable angina. *Drugs* 1996;**52**:196-208.
4 Oler A, Whooley MA, Oler J, Grady D: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *J Am Med Assoc* 1996;**276**:811-15.
5 Davies MJ: A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation* 1990;**82(Suppl II)**:II-38-II-46.
6 Fuster V, Badimon L, Badimon JJ, Chesebro JH: The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;**326**:242-50,310-8.
7 Hangartner JRW, Charleston AJ, Davies MJ, Thomas AC: Morphological characteristics of clinically significant coronary artery stenosis in stable angina. *Br Heart J* 1986;**56**:501-8.
8 Richardson PD, Davies MJ, Born GVR: Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989;**2**:941-4.
9 Ware JA, Coller BS: Platelet morphology, biochemistry, and function. In: Beutler E, Lichtman MA, Coller BS (eds), *Williams Hematology*, 5th edn (New York, McGraw-Hill, 1995) 1161-201.
10 Coller BS: Platelets in cardiovascular thrombosis and thrombolysis. In: Fozzard HA, Haber Jennings RB, Katz AM, Morgan HE (eds), *The Heart and Cardiovascular System: Scientific Foundations*, 2nd edn (New York, Raven Press, 1992) Vol.1, 219-73.
11 Lefkovits J, Plow EF, Topol EJ: Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;**332**:1553-9.

12 White HD: Unmet therapeutic needs in the management of acute ischemia. *Am J Cardiol* 1997;**80(4A)**:2B-10B.

13 Mizuno K, Satomura K, Miyamoto A et al: Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med* 1992;**326**:287-91.

14 Davies MJ: The role of plaque pathology in coronary thrombosis. *Clin Cardiol* 1997;**Vol 20(Suppl I)**:I-2-I-7.

15 Cohen M, Sherman W, Rentrop KP, Gorlin R: Determinants of collateral filling observed during sudden controlled coronary artery occlusion in human subjects. *J Am Coll Cardiol* 1989;**13**:297-303.

16 Habib GB, Heibig J, Forman SA et al, and the TIMI Investigators: Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I Thrombolysis in Myocardial Infarction (TIMI) trial. *Circulation* 1991;**83**:739-46.

17 Neuhaus KL: Coronary thrombosis-defining the goals, improving the outcome. *Clin Cardiol* 1997;**Vol 20(Suppl I)**:I-8-I-13.

18 Landau C, Lange RA, Hillis LD: Percutaneous transluminal coronary angioplasty. *N Engl J Med* 1994;**330**:981-93.

19 Ferguson JJ, Wilson JM: Early and late ischemic complications of PTCA. *J Invas Cardiol* 1994;**6(Suppl A)**:3A-12A.

20 Bittl JA: Coronary stent occlusion: Thrombus horribilis. Editorial comment. *J Am Coll Cardiol* 1996;**28**:368-70.

21 Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106.

22 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected myocardial infarction. *Lancet* 1988;**2**:349-60.

23 Lewis HDJ, Davies JW, Archibald DG et al: Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983;**309**:396-403.

24 Cairns JA, Gent M, Singer J et al: Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985;**313**:1369-75.

25 Théroux P, Ouimet H, McCans J et al: Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;**319**:1105-11.

26 The RISC Group: Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;**336**:827-30.

27 Almony GT, Lefkovits J, Topol EJ: Antiplatelet and anticoagulant use after myocardial infarction. *Clin Cardiol* 1996;**19**:357-65.

28 Fiore L, Deykin D: Anticoagulant therapy. In: Beutler E, Lichtman MA, Coller BS (eds), *Williams Hematology*, 5th edn (New York, McGraw-Hill, 1995) 1562-84.

29 Cohen M, Adams PC, Parry G et al, and the Antithrombotic Therapy in Acute Coronary Syndromes Research Group: Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. *Circulation* 1994;**89**:81-8.

30 The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673-82.

31 Ryan TJ, Anderson JL, Antman EM et al: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1996;**94**:2341-50.

32 Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J: Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990;**86**:385-91.

33 Hirsh J: Heparin. *N Engl J Med* 1991;**324**:1565-74.

34 Melandri G, Semprini F, Cervi V et al: Comparison of efficacy of low molecular weight heparin (parnaparin) with that of unfractionated heparin in the presence of activated platelets in healthy subjects. *Am J Cardiol* 1993;**72**:450-4.

35 Théroux P, Waters D, Lam J, Juneau M, McCans J: Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;**327**:141-5.

36 Granger CB, Hirsh J, Califf RM et al: Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction. Results from the GUSTO I trial. *Circulation* 1996;**93**:870-8.

37 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators: Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;**90**:1631-7.

38 Jesty J, Nemerson Y: The pathways of blood coagulation. In: Beutler E, Lichtman MA, Coller BS (eds), *Williams Hematology*, 5th edn (New York, McGraw-Hill, 1995) 1227-38.

39 Hirsh J, Levine MN: Low molecular weight heparin. *Blood* 1992;**79**:1-17.

40 Nurmohamed MT, ten Cate H, ten Cate JW: Low molecular weight heparin(oids)s-Clinical investigations and practical recommendations. *Drugs* 1997;**53**:736-51.

41 Fragmin During Instability in Coronary Artery Disease (FRISC) Study Group: Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996; **347**:561-8.

42 Cohen M, Demers C, Gurfinkel EP et al, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;**337**:447-52.

43 Lefkovits J, Topol EJ: Direct thrombin inhibitors in cardiovascular medicine. *Circulation* 1994;**90**:1522-36.

44 Ferguson JJ: Meeting highlights American Heart Association 68th Scientific Sessions, Anaheim, California, November 3-15, 1995. *Circulation* 1996;**93**:843-6.

45 Ferguson JJ, Lau TK: Newer antithrombotic and antiplatelet agents for acute coronary syndromes. *Acute Coronary Syndromes* 1997;**1**:9-18.

46 White HD, Aylward PE, Frey MJ et al, on behalf of the Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators: Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). *Circulation* 1997;**96**:2155-61.

47 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators: A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775-82.

48 Zoldhelyi P, Janssens S, Lefèvre G, Collen D, Van de Werf F, for the GUSTO IIa Investigators: Effects of heparin and hirudin (CGP 39393) on thrombin generation during thrombolysis for acute myocardial infarction. *Circulation* 1995;**92(Suppl I)**:I-740 [Abstract].

49 Merlini PA, Ardissino D, Bauer KA et al: Persistent thrombin generation during heparin treatment in patients with acute coronary syndromes. *Circulation* 1995;**92(Suppl I)**:I-623 [Abstract].

50 Flather M, Weitz J, Campeau J et al: Evidence for rebound activation of the coagulation system after cessation of intravenous anticoagulant therapy for acute myocardial ischemia. *Circulation* 1995;**92(Suppl I)**:I-485 [Abstract].

51 Antman EM, for the TIMI 9A Investigators: Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation* 1994;**90**:1624-30.

52 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311-22.

53 The GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;**329**:1615-22.

54 Simes RJ, Topol EJ, Holmes DR et al, for the GUSTO-I Investigators: Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial infarction. Importance of early and complete infarct artery reperfusion. *Circulation* 1995; **91**:1923-8.

55 Gore JM, Granger CB, Simoons ML et al: Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation* 1995;**92**:2811-8.

56 The GUSTO-III Investigators: An international, randomized comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;**337**:1118-23.

57 Stone GW, O'Neill WW, Jones D, Grines CL: The central unifying concept of TIMI-3 flow after primary PTCA and thrombolysis therapy in acute myocardial infarction. *Circulation* 1996;**94(Suppl)**:I-515 [abstract].

58 Grines CL, Browne KF, Marco J et al: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;**328**:673-9.

59 Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H: A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680-4.

60 The GUSTO-II Angioplasty Substudy Investigators: A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator and recombinant hirudin with heparin for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621-8.

61 Coller BS: Platelets and thrombolytic therapy. *N Engl J Med* 1990;**322**:33-42.

62 Coller BS: Augmentation of thrombolysis with antiplatelet drugs. *Coron Artery Dis* 1995;**6**:911-4.

63 Topol EJ: Toward a new frontier in myocardial reperfusion therapy. Emerging platelet preeminence. *Circulation* 1998;**97**:211-8.

64 Alexander JH, Ohman EM, Harrington RA: Platelet GP IIb/IIIa inhibitors in acute MI: pathophysiology and clinical effects. *Acute Coronary Syndromes* 1998;**1**:46-51.

65 The TIMI IIIB Investigators: Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB trial. *Circulation* 1994;**89**:1545-56.

66 Topol EJ, Califf RM, George BS, for the Thrombolysis and Angioplasty in Myocardial Infarction Study Group: A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1987;**317**:581-8.

67 Simoons ML, Arnold AER, Betriu A et al: Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous transluminal coronary angioplasty. *Lancet* 1988;**1**:197-203.

68 TIMI Research Group: Immediate versus delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI IIA results. *JAMA* 1988; **260**:2849-58.

69 Topol EJ: Targeted approaches to thrombus inhibition-An end to the shotgun approach, *Clin Cardiol* 1997;**20(Suppl 1)**:I-22-I-26.

70 The EPIC Investigators: Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; **330**:956-61.

71 Topol EJ, Califf RM, Weisman HF et al, on behalf of The EPIC Investigators: Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical stenosis: results at six months. *Lancet* 1994;**343**:881-6.

72 Topol EJ, Ferguson JJ, Weisman HF et al, for the EPIC Investigator Group: Long-term protection from myocardial ischemic events in a randomized trial of brief integrin b_3 blockade with percutaneous coronary intervention. *JAMA* 1997;**278**:479-84.

73 Lefkovits J, Ivanhoe RJ, Califf RM et al, for the EPIC Investigators: Effects of platelet glycoprotein IIb/IIIa receptor blockade by a chimeric monoclonal antibody (abciximab) on acute and six-month outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 1996;**77**:1045-51.

74 Lincoff AM, Califf RM, Anderson KM et al, for the EPIC Investigators: Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. *J Am Coll Cardiol* 1997;**30**:149-56.

75 Ip JH, Fuster V, Israel D, Badimon L, Badimon J, Chesebro JH: The role of platelets, thrombin and hyperplasia in restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991; **17**:77B-88B.

76 Bates ER, Walsh DG, Mu DX, Abams GD, Luchessi BR: Sustained inhibition of the vessel wall-platelet interaction after deep coronary artery injury by temporary inhibition of the platelet glycoprotein IIb/IIIa receptor, *Coron Artery Dis* 1993;**3**:67-76.

77 The CAPTURE Investigators: Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; **349**:1429-35.

78 The IMPACT-II Investigators: Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; **349**:1422-8.

79 The RESTORE Investigators: Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;**96**:1445-53.

80 The PURSUIT Investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;**339**:436-43.

81 The PRISM Study Investigators: A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498-1505.

82 The PRISM-PLUS Study Investigators: Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488-97.

83 The PARAGON Investigators: An international, randomized, controlled trial of lamifiban, a platelet glycoprotein IIb/IIIa inhibitor, heparin or both in unstable angina, *Circulation* 1998;**97**:2386-95.

84 Alexander JH, Newby NK, Moliterno DJ et al, for the PARAGON A Investigators: Relationship of outcomes to treatment with lamifiban in patients undergoing PTCA: analysis of PARAGON A. *J Am Coll Cardiol* 1997;**29(Suppl A)**:409A [Abstract].

85 The EPILOG Investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689-96.

86 Lincoff AM, Tcheng JE, Califf RM et al, for the PROLOG Investigators: Standard versus low-dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. *Am J Cardiol* 1997;**79**:286-91.

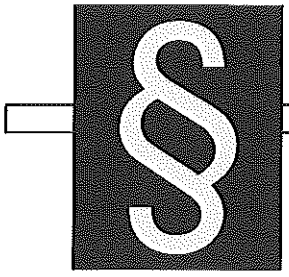
87 Kleiman NS, Ohman EM, Califf RM et al: Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy. Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot study. *J Am Coll Cardiol* 1993;**22**:381-9.

88 Ohman EM, Kleiman NS, Gacioch G et al, for the IMPACT-AMI Investigators: Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. *Circulation* 1997;**95**:846-54.

89 Ohman EM: Dose-escalation evaluation of full dose abciximab in conjunction with low dose r-PA. The SPEED trial. Highlight report from the American College of Cardiology 47th Annual Scientific Session, March 29-April 1, 1998, Atlanta Georgia, USA.

90 Braunwald E: Dose-finding study assessing the value of abciximab as an adjunct to fibrinolytic therapy in acute myocardial infarction. The TIMI 14A study, Highlight report from the American College of Cardiology 47th Annual Scientific Session, March 29-April 1, 1998, Atlanta Georgia, USA.

91 Topol EJ: RAPPORT: outcomes in patients with acute myocardial infarction with abciximab and primary PTCA, Presented at the XIX Congress of the European Society of Cardiology, Stockholm, Sweden, August 24-28, 1997.



Clinical endpoint determination: methodology and impact

2

Systematic Adjudication of Myocardial Infarction Endpoints in an International Clinical Trial

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Abstract

Clinical Events Committees (CEC) are used routinely to adjudicate suspected endpoints in clinical trials, but little information has been published about the various processes used for adjudication. In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial, 10,948 patients with acute coronary syndromes were randomly assigned in blinded fashion to eptifibatide or placebo. A centralized adjudication process was established prospectively to identify all suspected myocardial infarctions and to adjudicate the events based on definitions of infarction in the protocol. Suspected infarctions were identified by systematic reviews of clinical information on case report forms, of cardiac enzyme data, and of electrocardiographic information. All suspected events were independently reviewed by two physicians. If the physicians disagreed about whether an infarction had occurred, the case was adjudicated by a committee of faculty cardiologists. The CEC identified 5005 (46%) suspected infarctions, of which 1415 (28%) were adjudicated as infarctions.

We believe that endpoint adjudication by a Clinical Events Committee is important to provide a standardized, systematic, independent, and unbiased assessment of endpoints, particularly in trials that include patients across geographic regions and clinical-practice settings. Understanding the CEC process is important in interpretation of trial results and event rates.

Introduction

Myocardial infarction is an important endpoint in clinical trials. In fact, the prevention of infarction has been the primary treatment effect assessed in recent trials of antiplatelet and antithrombin therapies.[1-11] Clinical Events Committees (CECs) are now commonly used to adjudicate suspected endpoint events in clinical trials, but only limited information has been published about endpoint adjudication.[12-23] In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial,[6] a centralized, independent CEC systematically identified and adjudicated all suspected infarctions that occurred after enrollment and through 30-day follow-up. The rationale for CEC adjudication was the need for a systematic, unbiased, independent, and standard assessment of this endpoint in a large, international trial. To understand the role of such a committee, and to provide recommendations for future efforts, we reviewed the results of the CEC process used in the PURSUIT trial to identify and adjudicate suspected endpoint infarctions.

Methods

PURSUIT Trial

The PURSUIT trial [6] enrolled 10,948 patients at 726 hospitals in 27 countries from North America, Latin America, and Western and Eastern Europe. Patients with acute coronary syndromes without persistent ST-segment elevation were randomly assigned to placebo or eptifibatide. The inclusion and exclusion criteria, as well as treatment regimens, have been published.[6] The primary endpoint was a composite of death or infarction by 30-day follow-up as adjudicated by a Clinical Events Committee. The composite endpoint also was calculated using the site investigator determination of infarction from case report forms.

Endpoint Definitions

The definition of infarction included clinical, electrocardiographic (ECG), and laboratory criteria (see Appendix).

Data Collection

Data were collected using standard case report forms. Additional information collected from all patients included cardiac enzymes, ECGs (performed at the time of the qualifying episode, at enrollment, at 24 hours, at first hospital discharge, and at 30-day follow-up), revascularization procedure reports, details of ischemic episodes, clinical complications, medications, and readmission records. All enzyme values for each patient were to be reported; study monitors then verified them against source documents. Site investigators were asked to submit supporting

documents for patients with suspected infarction, which included discharge summaries and additional ECGs during the suspected event. Progress notes and procedure notes also were collected if necessary. An independent, blinded ECG core laboratory read the specified ECGs and identified suspected infarctions, defined as new Q-waves ≥0.04 seconds in two contiguous leads.

Process for Event Adjudication

The CEC was a group dedicated to event adjudication within the North American Trial Coordinating Center at the Duke Clinical Research Institute. The group consisted of a managing supervisor, clinical coordinators with a nursing or clinical-research background, administrative assistants, cardiology fellows, and cardiology faculty members. The CEC helped define clinical endpoint events, helped develop computer algorithms to identify patients with suspected endpoint events from case-report-form data, worked with monitoring groups to collect supplemental medical records for event review, and adjudicated suspected clinical endpoint events.

A schematic of the clinical event adjudication process is shown in Figure 1. Computerized algorithms systematically identified key variables from the database that could indicate the occurrence of an infarction. These variables, which were determined from clinical expertise and previous trial experience, included elevated cardiac enzymes, ECG core laboratory identification of suspected infarction, recurrent ischemic events, urgent revascularizations, or site investigator assessment of a post-enrollment infarction. The system was designed for broad identification of all patients with possible infarction.

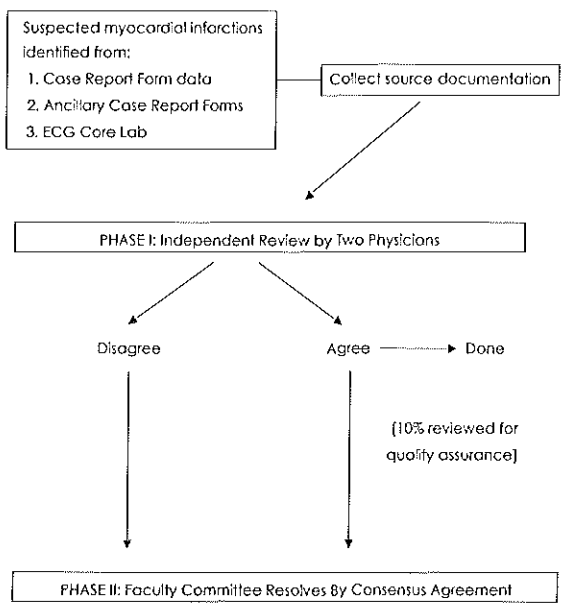

Figure 1:
Process for review of suspected clinical events in the PURSUIT trial.

Each patient with a suspected infarction had a clinical folder prepared by CEC staff at the Duke Clinical Research Institute. Folders included the case report form and ancillary data forms, discharge summaries, cardiac enzyme results, ECGs, and a data worksheet that summarized clinical events, procedures, and cardiac enzyme information. Medical records were translated into English, if necessary; when possible, physicians literate in the other language were used.

Each case was reviewed independently by two physicians blinded to treatment in the Phase I review. If the physicians agreed that an infarction had or had not occurred, the case was classified as resolved. Cases in which there was disagreement between the two CEC physicians were forwarded to a second-level (Phase II) review, for adjudication by consensus by a committee of faculty cardiologists (Figure 1). The committee members also were blinded to treatment, and to the result of the Phase I review. Physicians could request additional medical records, if necessary, to adjudicate a suspected event. If additional records were obtained, the case was rereviewed to ensure that decisions were based on similar documents. For quality assurance, 10% of the cases with agreement by the Phase I physicians were reviewed in a blinded fashion by the Phase II committee to determine if there were any systematic inconsistencies with the Phase I reviews.

Statistical Analysis

Variables were summarized as percentages for dichotomous variables or medians (25th and 75th percentiles) for continuous variables. The chi-square test was used to calculate p values.

Results

In the PURSUIT trial, eptifibatide reduced the incidence of death or infarction by 1.5% (15.7% vs. 14.2%; $p = 0.042$) at 30-days. The benefit was driven primarily by a reduction in nonfatal infarction. Overall, 5005 (46%) cases with a possible or suspected infarction were identified and adjudicated by the CEC. Table 1 shows the number of patients enrolled, the number of patients with suspected infarction, and the number of patients with an endpoint infarction assessed by the CEC by geographic region. The proportion of patients enrolled who had a suspected infarction ranged from 41% in North America to 50% in Western Europe. The proportion of patients with infarction adjudicated by the CEC was similar in North America, Latin America, and Western Europe but tended to be higher in Eastern Europe.

As expected, because of the rigorous effort by the CEC to identify all suspected infarctions for adjudication, the process identified more endpoint events than did the site investigators (Table 2). Smaller absolute and relative treatment effects were

Table 1 Cases Reviewed by the Clinical Events Committee

Region	Patients Enrolled *n (%)*[a]	Patients with Suspected Infarction *n (%)*[b]	Patients with Confirmed Infarction *n (%)*[b]
Eastern Europe	1762 (16)	862 (49)	311 (17.7)
Latin America	585 (5)	253 (43)	68 (11.6)
North America	4358 (40)	1779 (41)	504 (11.6)
Western Europe	4243 (39)	2111 (50)	532 (12.5)
Overall	*10,948*	*5005 (46)*	*1415 (12.9)*

[a]Percentages are based on overall enrollment.

[b]Percentages are based on number enrolled per region.

Table 2 Efficacy Endpoints at 30-day Follow-up

	Eptifibatide[a] (n= 4722) %	Placebo (n= 4739) %	Absolute Reduction %	Relative Reduction %	*p*
Death or Infarction					
Clinical Events Committee	14.2	15.7	1.5	9.6	0.042
Site investigator	8.1	10.0	1.9	19.0	0.0007
Myocardial infarction					
Clinical Events Committee	12.6	13.6	1.0	7.4	0.137
Site investigator	6.2	7.8	1.6	20.5	0.002

[a]High-dose group only.

observed using the CEC-determined infarction rates compared with the site investigator-determined rates.

Disagreements between the site investigator and CEC assessment of infarction occurred in 9% of all patients enrolled in the trial. Disagreement between the site investigator and the CEC assessments was seen in 983 of the 5005 (20%) patients

with suspected infarction that were adjudicated by the CEC (Table 3). Of these 983 patients with disagreements, 816 patients had an infarction assessed by the CEC but not by the site investigator, and 167 patients had an infarction identified by site investigators but not by the CEC.

Table 3 Disagreements Between the Site Investigator and the Clinical Events Committee

	Patients With	Patients With	Disagreements	
	Suspected Infarction	Disagreement	Committee No	Committee Yes
Region	*n (%)*	*n (%)*	Site Yes	Site No
Eastern Europe	862 (49)	206 (24)	24	182
Latin America	253 (43)	52 (21)	8	44
North America	1779 (41)	356 (20)	57	299
Western Europe	2111 (50)	369 (17)	78	291
Overall	5005 (46)	983 (20)	167	816

Discussion

Review of the clinical events classification process in the current study raises some important issues for clinical investigators. First, the rates of infarction were higher than those reported in prior trials of patients with acute coronary syndromes. Second, the Clinical Events Committee identified more events than the site investigators. Third, the site investigator and the CEC assessment of infarction disagreed for 20% of patients reviewed by the Committee.

Clinical Events Committees have become an integral aspect of clinical trials of new therapies for patients with acute coronary syndromes. The primary function of these committees has been to systematically adjudicate nonfatal endpoints such as myocardial infarction. The first large trials in these patient populations used mortality as the primary endpoint; thus, standardized assessment of patient outcome was not required.[24,25] More recent trials, however, have included nonfatal endpoints such as infarction, congestive heart failure, stroke, and safety measures as part of composite clinical endpoints. Myocardial infarction has been considered a "hard" endpoint, but its assessment can be as difficult in clinical trials as in clinical practice, because clinical, laboratory, and ECG data may conflict and physicians therefore often disagree as to whether a patient has suffered an infarction. An example of this difficulty is the evaluation of low-level enzyme

elevations in patients undergoing percutaneous coronary intervention.[27] Although these low-level enzyme elevations are defined as infarctions in many trial protocols, physicians do not consistently consider them to be infarctions in daily clinical practice.

The rates of infarction as adjudicated by the CEC in PURSUIT were higher than reported in previous trials,[1, 7, 8, 28] of patients with acute coronary syndromes, for several reasons. The PURSUIT CEC effort was more liberal in its identification of possible events. Committee physicians reviewed events for almost 50% of the patients in the PURSUIT trial, nearly double the percentage that underwent adjudication by the same CEC group for two other trials: Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II)[1], and the Global Use of Strategies To open Occluded arteries in acute coronary syndromes (GUSTO-IIb).[9] The definition of infarction is evolving and has varied among clinical trials in this patient population. For example, in the GUSTO-IIb trial, criteria for infarction after bypass surgery were more stringent than in the PURSUIT trial and required two of three criteria (creatine kinase or MB fraction at least five times the upper limit of normal, two new Q waves, and/or documentation of new regional wall-motion abnormalities). Finally, more cardiac enzyme samples were collected per patient in PURSUIT than in GUSTO-IIb (median 4.5 [3, 7] vs. 3 [1, 4], unpublished data). These factors, particularly the systematic collection of cardiac enzymes, contributed to a higher ascertainment of infarctions in the PURSUIT trial. Trials relying on investigator-reported infarctions likely underestimate the true event rate.

Before the implementation of the CEC process, the International Steering Committee discussed and agreed upon the definitions for infarction using past experience and clinical expertise. Because of the global nature of the PURSUIT investigation, attempts were made to model definitions after everyday clinical practice. The study protocol provided the endpoint definitions, so that the CEC and site investigators had the same set of criteria to classify infarctions. Nevertheless, myocardial infarctions were underreported by site investigators. Similar findings have been observed in prior trials.[1, 9, 22, 29, 30]

The strategy used to identify suspected infarctions can affect the proportion of events with disagreements. Some trials have confirmed events reported only by the investigators,[5, 7, 8, 11, 28, 31] while others have adjudicated all suspected events identified by systematic screening of patient data.[1-3, 9, 29, 30] In the first strategy, the CEC event rates will be the same as or lower than the site investigator rates. In the second, the CEC event rates may be higher, lower, or the same as the site investigator-reported rates.

The impact of adjudication of cases from other regions of the world by physicians based in North America is unknown. However, in the current study, medical records were translated to English, physicians fluent in foreign languages

were used when needed, and the criteria for reinfarction were based, for the most part, on objective data such as enzyme and ECG data.

There are several key implications of these findings. The strategy used to identify and adjudicate endpoint events is one of many factors to be considered when comparing event rates between clinical studies. During trial planning, the events-classification strategy being considered also may have an important impact on estimation of event rates and the sample-size and power calculations. Education and training of clinical investigators regarding endpoint definitions and ascertainment may help in minimizing differences between the CEC and site investigator assessment of endpoints. Finally, the interpretation of trial results by the clinical and regulatory communities may be influenced by the strategy and rigor of the clinical event adjudication process used. We believe that CEC Committee adjudication of suspected nonfatal infarction endpoint events is important to provide independent, unbiased, standard, systematic assessments, particularly in trials that include broad geographic regions and different clinical-practice settings.

Conclusion

Nonfatal myocardial infarction, inherently undesirable, is an important clinical event and an important component of clinical trial endpoints. Clinical Events Committee adjudication of infarction is necessary and provides standardized, systematic, independent, and unbiased assessments of endpoints in clinical investigation. In PURSUIT, the assessment of infarction by site investigators versus a central CEC disagreed; more infarctions were identified by the CEC than by the site investigators. The impact of these findings affect the comparison of event rates between trials as well as the design of future trials.

Appendix

Definition for Post-enrollment Myocardial Infarction

Myocardial infarction is defined by either enzyme criteria or ECG.

Enzyme Criteria:

1. Myocardial infarction (events without documentation of a prior infarction during the admission): creatine kinase (CK)-MB elevated above the upper limit of normal (ULN) and ≥3% of total CK. If CK-MB is unavailable, then total CK greater than twice the ULN.
2. Myocardial infarction (events with documentation of a prior infarction during the admission, either before or at enrollment)

   Less than 18 hours since previous infarction: Recurrent, severe ischemic discomfort and new or recurrent ST-segment elevation ≥0.1 mV in at least two contiguous leads, either persisting for ≥30 min.

   At least 18 hours since previous infarction: Re-elevation of CK-MB to above the ULN (if prior CK-MB was within normal range) or >50% above the prior level (if prior CK-MB was above the ULN). If CK-MB is unavailable, then total CK at least twice the ULN and increased by ≥25%, or at least 1.5 times the ULN and increased by at least 200 IU above the previous value.
3. Periprocedural (percutaneous coronary intervention) infarction (events occurring during or within 24 hours of an intervention): CK-MB at least three times the ULN and >50% above the prior nadir value. If CK-MB is unavailable, then total CK at least 3 times the ULN.
4. Perioperative myocardial infarction (events occurring during or within 36 hours of bypass surgery): CK-MB at least times the ULN (or CK, in the absence of CK-MB).

ECG Criteria:

New, significant Q waves or Q-wave equivalents ≥0.045 sec in at least two contiguous leads.

If enzyme or ECG data are unavailable, an infarction is considered to have occurred when there is a preponderance of clinical evidence based on patient signs, symptoms, ECG changes, and pathological findings. When enzyme or ECG criteria are available, they take precedence.

References

1. The GUSTO-IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775-782.
2. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;**330**:956-961.
3. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689- 1696.
4. The Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* 1994;**308**:81-106.
5. Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996;**94**:911-922.
6. The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes without persistent ST-segment elevation: a randomized, placebo-controlled, clinical trial. *N Engl J Med* 1998;**339**:436-443.
7. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498-1505.
8. The PRISM PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488-1497.
9. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention. *Lancet* 1997;**349**:1422-1428.
10. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein- IIb/IIIa blockade. *Lancet* 1998;**352**:87-92.
11. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina. *Lancet* 1997;**349**:1429-1435.
12. Mahaffey KW, Granger CB, Woodlief L, et al. Centralized systematic adjudication of clinical endpoints in multicenter trials of acute coronary syndromes identifies patients at high risk for adverse clinical outcomes. *J Am Coll Cardiol* 1996;**27**:250A.
13. Tardiff BE, Mahaffey KW, Sigmon KN, et al. Differences in endpoint identification by investigators versus independent review. *Contr Clin Trials* 1996;**17**:25S.
14. Mahaffey KW, Tardiff BE, Granger CB, et al. Comparison of investigator and central events review of myocardial infarction rates as a means to improve events classification: results from GUSTO-IIa. *Contr Clin Trials* 1996;**17**:136S.
15. Walter SD, Cook DJ, Guyatt GH, et al., for the Canadian Lung Oncology Group. Outcome assessment for clinical trials: how many adjudicators do we need? *Contr Clin Trials* 1997;**18**:27-42.
16. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol* 1995;**5**:278-285.
17. Remington RD. Who should code cause of death in a clinical trial? *Contr Clin Trials* 1984;**5**:241-244.
18. Moussa MA, Shafie MZ, Khogali MM, et al. Reliability of death certificate diagnoses. *J Clin Epidemiol* 1990;**43**:1285-1295.
19. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology* 1991;**98**:786-806.
20. Graafsma YP, Prins MH, Lensing AW, et al. Bleeding classification in clinical trials: observer variability and clinical relevance. *Thromb Haemost* 1997;**78**:1189-1192.

21. Mahaffey KW, Granger CB, Tardiff BE, et al., for the GUSTO-IIb Investigators. Endpoint adjudication by clinical events committee can impact the statistical outcome of a clinical trial: results from GUSTO-IIb. *J Am Coll Cardiol* 1997;**29**:410A.
22. Mahaffey KW, Tardiff BE, Granger CB, et al. Disagreement between site investigators and clinical event committees is common and can affect trial results. *J Am Coll Cardiol* 1998;**31**:184A-185A.
23. Mahaffey KW, Akkerhuis, M, Boersma H, et al. The identification of MI in clinical trials is difficult and there is substantial difference between the assessment by site investigators and a clinical events committee: results from PURSUIT. *Eur Heart J* 1998;**19**:55.
24. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673-682.
25. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 case of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**:349-360.
26. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**1**:397-401.
27. Califf RM, Abdelmeguid AE, Kuntz R, et al. Myonecrosis after revascularization procedures. *J Am Coll Cardiol* 1998;**31**:241-251.
28. Thrombolysis in Myocardial Ischemia (TIMI) Study Group. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;**89**:1545-1556.
29. The CAVEAT Study Group. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med* 1993;**329**:221-227.
30. The RESTORE Study Group. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;**96**:1445-1453.
31. Pfeffer MA, Braunwald E, Moye LA, et al., on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;**327**:669-677.

3

Disagreements Between a Central Clinical Events Committee and Site Investigator Assessments of Myocardial Infarction End Points in an International Clinical Trial: Review of the PURSUIT Study

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Abstract

Background

Limited has been published about the specific processes for event adjudication and the impact on event rates in trials. We reviewed nonfatal myocardial infarctions (MI) reported by site investigators in the PURSUIT trial and those adjudicated by a central Clinical Events Committee (CEC) to determine reasons for the differences in event rates.

Methods and Results

In PURSUIT, 10,948 patients with acute coronary syndromes were randomized in blinded fashion to eptifibatide or placebo. The primary end point was death or MI at 30 days as assessed by the CEC. The primary end point also was constructed using site investigator-reported events. The CEC identified suspected MIs by systematic review of clinical, cardiac enzyme, and electrocardiographic data, and rigorously reviewed all suspected events. The CEC identified 5005 (46%) suspected MIs, of which 1415 (28%) were adjudicated as MI using prespecified criteria. Disagreement between the site investigator and the CEC assessments of whether an MI had occurred was present in 983 (20%) of the 5005 patients with suspected MI. Most disagreements reflected investigator misclassification of post-enrollment MIs (as enrollment MIs instead) or underreported periprocedural MIs.

Conclusions

The adjudication of MI in clinical trials is complex and mirrors the difficulty often seen in clinical practice. We believe that CEC adjudication is important to provide a standard, systematic, independent, and unbiased assessment of end points, particularly in trials that span geographic regions and clinical-practice settings. Understanding the CEC review process and the reasons for disagreement between the CEC and site investigator assessments of MI is important to design future trials and interpret event rates between trials.

Introduction

Myocardial infarction (MI) is a potentially catastrophic event in patients presenting with acute coronary syndromes. In recent trials of antiplatelet and antithrombotic therapies for such patients, prevention of MI was the primary treatment effect assessed.[1-4] Although MI has been considered a "hard" end point, determination of MI end points in clinical trials can be difficult, just as in clinical practice. Because of conflicting clinical, laboratory, and electrocardiographic (ECG) data, physicians often disagree as to whether a patient has suffered an MI. The importance of low-level enzyme elevations also has been controversial, particularly in asymptomatic patients and in those undergoing percutaneous coronary intervention (PCI).[5] Although such enzyme elevations are defined as MIs in many trial protocols, physicians in clinical practice do not consistently consider them as such. In recent cardiovascular trials, the MI rates reported by site investigators have differed from rates adjudicated by a Clinical Events Committee (CEC).[6-9] The reasons for the differences are unclear.

Clinical Events Committees are widely accepted to adjudicate suspected end point events in trials, but only limited information has been published about end point adjudication.[10-15] In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial,[6] a central, independent CEC systematically identified and adjudicated all suspected MIs that occurred through 30 days. The rationale for CEC adjudication was the need for a systematic, unbiased, independent, and standard assessment of MIs in a large international trial. In a previous analysis of the CEC process in PURSUIT, we found that in ~10% of patients the CEC and site investigator assessments of MI disagreed.[16] We retrospectively reviewed these cases, to identify reasons for them and to understand their potential effect on the trial results.

Methods

The PURSUIT trial

The PURSUIT trial examined the role of eptifibatide, a platelet glycoprotein IIb/IIIa antagonist, in patients presenting with acute coronary syndromes without persistent ST-segment elevation. The trial enrolled 10,948 patients in 726 hospitals in 27 countries in North America, Latin America, Western Europe, and Eastern Europe, using previously reported inclusion and exclusion criteria and treatment regimens.[6] The primary end point was a composite of death or MI by 30 days as adjudicated by a CEC. The composite end point also was constructed using the site investigator determination of MI.

Definitions

The protocol defined MI as an end point event based on clinical, ECG, and

laboratory criteria (Appendix); MIs that occurred before enrollment were not to be included in the primary end point. The site investigators and the CEC used the same MI criteria. These criteria were presented in the protocol, at investigator meetings, and in trial materials and newsletters.

Data Collection

Data were captured on standard case-report forms. Information collected for all patients included cardiac enzymes, ECGs (at the time of the qualifying episode, at enrollment, at 24 hours, at initial discharge, and at 30 days), revascularization procedure reports, details of ischemic episodes, clinical complications, medications, and readmission records. All enzyme values for each patient were to be reported, and study monitors verified them against source documents. For patients with suspected MI, site investigators were to submit supporting documents, to include discharge summaries and additional ECGs during the suspected event. An independent, blinded, ECG Core Laboratory read the ECGs and identified suspected MIs, defined as new Q waves ≥0.04 seconds in two contiguous leads.

Clinical Events Classification Process

The structure of the CEC and the event-adjudication process have been reported in detail.[16] Computer algorithms systematically identified key clinical, enzymatic, and ECG data from the database that could indicate the occurrence of an MI. Each case of suspected MI was reviewed independently by two physicians blinded to treatment. If the physicians agreed that an MI had or had not occurred, the case was classified as resolved. A committee of faculty cardiologists reviewed cases about which the CEC physicians disagreed, for adjudication by consensus.

Disagreements Between the Site Investigators and CEC

A faculty cardiologist (K.W.M., R.A.H., B.S.C.) rereviewed cases of disagreement between the site investigator assessment and CEC adjudication of MI, to determine reasons for the disagreement. This review occurred after the main trial results were presented, but the reviewers were blinded to patient treatment assignment. During the rereview, cases were categorized in clinically meaningful groups: MI at enrollment (vs. post-enrollment MI); related to revascularization procedure; related to clinically evident ischemia; asymptomatic cardiac enzyme elevation post-enrollment; clinically significant cardiac event resulting in death (vs. sudden death without evidence of MI).

Despite rigorous criteria to define MI, some cases required a subjective assessment by CEC physicians if cardiac enzyme, ECG, and clinical information conflicted. Thus for MIs identified by the CEC but not by the site investigator (excluding events after PCI or bypass surgery), we assigned a level of clinical certainty. When all clinicians would agree that an MI had occurred, a high clinical

certainty was assigned; a low clinical certainty was assigned when only some clinicians would agree that an MI had occurred.

Statistical Analysis

Data regarding the number of cases with suspected events and cases with disagreements between the site investigators and the CEC were from the entire PURSUIT study population; therefore, the data included patients assigned high-dose eptifibatide, low-dose eptifibatide, or placebo. Comparisons by treatment assignments included only patients assigned to high-dose eptifibatide or placebo, to maintain consistency with the primary efficacy analysis in PURSUIT.[6] P-values were calculated using the χ^2 test.

Results

In all, 5005 (46%) cases of possible or suspected MI were identified and adjudicated by the CEC; the CEC identified more end-point events than did the site investigators (13.6% vs. 7.7% for placebo; 12.6% vs. 6.2% for eptifibatide). The CEC and site investigator assessments of MI disagreed for 9% of all patients enrolled in PURSUIT. Of the 5005 patients with suspected MI, the CEC identified MIs in 1415. The site investigator and the CEC assessments disagreed in 983 (20%) of these 5005 patients. Of these 983 patients with disagreements, 816 patients had an MI identified by the CEC but not the site investigator, and 167 patients had an MI identified by site investigator but not the CEC. The proportion of cases that disagreed was similar among regions.

In most cases where the site investigator identified an MI and the CEC did not, the site investigator had misclassified an MI at enrollment as an end point MI, although by protocol these were not end point events (Table 1). Recurrent ischemic events without elevated cardiac enzymes or ECG evidence of MI also were incorrectly identified by site investigators as MIs (Table 1). Of the cases in which the CEC identified an MI and the site investigators did not, one-third were MIs defined by enzyme elevations without clinical or ECG evidence of ischemia or infarction (Table 2). Enzyme elevations after bypass surgery accounted for 25% of these. Patients with clinically evident ischemia reported by site investigator and associated with cardiac-enzyme elevations were not reported as MIs by investigators in 27% of the cases with disagreements (Table 2). Few infarctions based on new Q waves without clinical evidence of reinfarction were identified by the CEC and not by site investigators.

Table 3 shows the cardiac enzyme elevation for MIs that the CEC identified and the site investigators did not. These data exclude MIs associated with PCI or bypass surgery; by definition, these required enzyme elevations greater than three or five times the upper limit of normal (ULN), respectively. The ratio of creatine

TABLE 1. Myocardial Infarctions Identified by Site Investigators but not Confirmed By the Clinical Events Committee

Clinical Scenario	Eastern Europe (n=24)	Latin America (n=8)	North America (n=57)	Western Europe (n=78)	Overall (n=167)
Enrollment myocardial infarction*	8 (33)	4 (50)	24 (42)	28 (36)	64 (38)
Ischemic event without infarction†	7 (29)	0 (0)	8 (14)	19 (24)	34 (20)
Peri-death infarction‡	6 (25)	2 (25)	13 (23)	8 (10)	29 (17)
Percutaneous coronary intervention-related	0 (0)	1 (12.5)	6 (11)	10 (13)	17 (10)
Coronary artery bypass surgery-related	2 (8)	1 (12.5)	5 (9)	7 (9)	15 (9)
Miscellaneous	1 (4)	0 (0)	1 (2)	6 (8)	8 (5)

*Not an end-point event per protocol. †Clinical evidence of ischemia without ECG or cardiac enzyme evidence of infarction.

‡Infarction suspected at the time of death without supporting clinical, ECG, or cardiac enzyme data. Data are number (%) of patients.

TABLE 2. Myocardial Infarctions Identified by the Clinical Events Committee but Not the Site Investigator

Clinical Scenario	Eastern Europe (n=182)	Latin America (n=44)	North America (n=299)	Western Europe (n=291)	Overall (n=816)
Asymptomatic creatine kinase-MB elevation*	83 (46)	23 (52)	37 (12)	128 (44)	271 (33)
Ischemic event†	89 (49)	12 (27)	48 (16)	68 (23)	217 (27)
Coronary artery bypass graft-related	6 (3)	6 (14)	138 (46)	52 (18)	202 (25)
Percutaneous coronary intervention-related	2 (1)	1 (2)	62 (21)	22 (8)	87 (11)
Early myocardial infarction‡	1 (1)	0 (0.0)	3 (1)	3 (1)	7 (1)
Isolated electrocardiogram (Q waves)§	1 (1)	1 (2)	5 (2)	4 (1)	11 (1)
Peri-death‖	0 (0)	1 (2)	1 (0.3)	4 (1)	6 (1)
Miscellaneous	0 (0)	0 (0)	5 (2)	10 (3)	15 (2)

*No clinical symptoms or ECG evidence of ischemia. †Clinical evidence of ischemia and ECG/cardiac enzyme evidence of infarction. ‡Cardiac enzyme or ECG evidence of infarction <24 hours after enrollment, different from the enrollment event. §Identified by systematic review of ECGs without clinical evidence of reinfarction. ‖MI at the time of death with clinical, ECG, or cardiac enzyme evidence. Data are number (%) of patients.

TABLE 3. Enzyme Elevations in Patients with Myocardial Infarction Identified by the Clinical Events Committee but Not the Site Investigator*

	n	Peak CK/ULN	n	Peak CK-MB/ULN
Eastern Europe	172	0.6 (0.3, 1.2)	167	1.4 (1.2, 1.9)
Latin America	34	0.7 (0.4, 1.2)	34	2.0 (1.3, 2.6)
North America	112	1.6 (1.0, 3.1)	106	2.9 (1.5, 5.5)
Western Europe	202	0.7 (0.4, 2.0)	196	1.7 (1.2, 3.0)
Overall	520	0.9 (0.4, 1.9)	503	1.6 (1.2, 2.9)

*Patients with postprocedural infarction are excluded (see Methods). CK-MB = creatine kinase-MB; ULN, local upper limit of normal. Data are median (25th, 75th percentiles).

TABLE 4. Level of Clinical Certainty* for Myocardial Infarction Identified by the Clinical Events Committee but not the Site Investigator

	High Certainty	Low Certainty	Total
Eastern Europe	133 (76)	42 (24)	175
Latin America	21 (58)	15 (42)	36
North America	111 (98)	2 (2)	113
Western Europe	177 (82)	39 (18)	216
Overall	442 (82)	98 (18)	540

*See Methods. Data presented are number (%) of patients.

kinase-MB (CK-MB) to its ULN was highest in North American cases (median 1.6).[12,29] Enzymes were similarly elevated between patients with MIs defined only by enzyme elevations (without symptoms or ECG changes) and patients with elevations associated with ECG or clinical evidence of ischemia.

Table 4 shows the level of clinical certainty for MIs not associated with PCI or CABG, as identified by the CEC but not the site investigators. Overall, 98 (18%) of these cases of MI were assigned a low level of clinical certainty. The proportion of cases assigned a low level of clinical certainty varied among the regions, with the lowest in North America.

TABLE 5. Event Rates at 30 Days

	All Patients			With Reclassification*		
	Eptifibatide	Placebo	*P*	Eptifibatide	Placebo	*P*
Death or myocardial infarction						
Eastern Europe	21.0	19.7		18.0	17.9	
Latin America	16.1	15.7		14.1	13.2	
North America	11.7	15.0		11.7	15.0	
Western Europe	13.8	14.8		12.9	13.7	
Overall	14.2	15.7	0.042	13.3	14.9	0.021
Myocardial infarction						
Eastern Europe	18.8	17.3		15.8	15.3	
Latin America	11.6	11.7		9.6	9.1	
North America	10.1	12.9		10.1	12.9	
Western Europe	12.6	12.9		11.7	11.8	
Overall	12.6	13.6	0.137	11.6	12.7	0.08

*See Methods: 98 cases with low clinical certainty reclassified as no infarction. Data are percentages.

TABLE 6. 30-Day and 6-Month Mortality for Cases of Disagreement

		Mortality		
	n	30 days	30 days to 6 months	6 months
CEC No / Site No	9366	1.7	2.1	3.8
CEC Yes / Site Yes	599	22.0	5.7	27.7
CEC Yes / Site No	816	7.2	5.4	12.6
CEC No / Site Yes	167	24.0	2.3	26.3

Data are percentages.

The 30-day rates of MI and death or MI overall are shown in Table 5 by geographic region. The event rates also are shown for the analyses in which the 98 cases assigned a low level of certainty were reclassified as no infarction.

The lowest mortality rates were in patients for whom the CEC and site investigators agreed that no MI had occurred by 30 days (Table 6). The highest rates were in patients for whom there was agreement that an MI had occurred. Mortality was high in the group with MI identified by the site investigators but not the CEC, but many of these patients had suspected sudden cardiac death as the event identified as an MI by the investigator (Table 1). The absolute increase in mortality between 30 days and 6 months was greater in patients with CEC-determined MIs not identified by the site investigators than in patients with MI identified by the site investigators but not the CEC.

Discussion

This analyses of the adjudication process of nonfatal MI by a central CEC in PURSUIT has five key findings. First, MI rates were higher than those reported in prior trials of acute coronary syndromes. Second, the site investigator and CEC assessments of MI disagreed for nearly 10% of all patients enrolled. Third, protocol-defined MIs were underreported by the site investigators. Fourth, the observed treatment effect was smaller using the CEC-adjudicated MI rates versus site investigator-identified event rates. Finally, in a retrospective analysis that excluded cases of MI that, despite meeting the prespecified end-point criteria, had conflicting clinical, ECG, and cardiac-enzyme data, the treatment effect was larger than that seen when such cases were included. In aggregate, these findings suggest that the use of a CEC is important for systematic ascertainment of nonfatal end points; however, the definition of MI and its application in CEC event adjudication in PURSUIT may have been too inclusive of MIs defined by low-level

enzyme elevations, which either represented "noise" or clinically unimportant events.

Event Rates

The MI rates adjudicated by the CEC in PURSUIT were higher than those reported in trials of similar patient populations.[6,17-19] The reason for the higher rates have been detailed previously[16] and include: review of nearly 50% of patients by physicians to identify suspected events, more liberal MI criteria, and rigorous measurement of cardiac enzymes in all patients. Studies that have used only investigator-reported events probably underestimate the true MI rate.

Lack of Concordance Between Site Investigator and CEC Event Rates

Myocardial infarctions were underreported by site investigators. A similar lack of concordance between events adjudicated by a CEC and those identified by clinical investigators has been observed in trials in which a similar CEC group adjudicated MIs[1,8] and in other trials.[7,9]

The MI definitions in PURSUIT were formulated by the International Steering Committee based on experience and clinical expertise. Because of the broad geographic enrollment planned for PURSUIT, definitions were designed to be applicable in an array of clinical-practice situations. The definitions were detailed in the study protocol, in study newsletters, and in study materials, so that the CEC and site investigators had the same set of criteria to classify MIs.

The reasons for disagreements in MI assessment between the site investigators and the CEC in PURSUIT (Tables 1 and 2) are similar to those seen in the GUSTO-IIb and the IMPACT-II trials (unpublished data). Many of the disagreements reflect physician reluctance to diagnose MIs in patients they are treating, particularly when the definition of MI includes events with low-level cardiac enzyme elevations (often called "enzyme leaks" in clinical practice). This reluctance by physicians also is apparent for patients undergoing PCI, in which the clinical significance of post-procedure enzyme elevations is controversial, even though such elevations correlate with worse outcomes.[5]

The disagreements also may partly reflect the definitions (Appendix) of MI themselves. These definitions were designed to be applied to a broad set of clinical scenarios, including events after PCI or bypass surgery, and to events occurring early after enrollment, which needed to be differentiated from pre-enrollment MIs. Site investigators may have had difficulty applying these criteria, particularly with conflicting cardiac enzyme, ECG, and clinical information. In addition, the enzyme criteria in PURSUIT required only one cardiac-enzyme value above normal to provide supportive evidence of MI. Substantial clinical uncertainty exists about the need for more than one elevated enzyme value and

whether the CK-MB criteria should specify elevations greater than one or two times the local ULN.

The strategy used by a CEC to adjudicate MIs can dramatically influence event rates and the proportion of events with disagreements between site investigators and a CEC. Some trials have confirmed only events reported by the investigators,[9,17-21] while others have adjudicated all suspected events identified by systematic screening of patient data.[1-3,7,8,22] When only events reported by investigators are reviewed by the CEC, the reported event rates will be identical to or lower than the site investigator rates. When events are identified independently by the CEC, the CEC event rates may be higher, lower, or the same as the site investigator-reported rates.

Difference in Treatment Effect

The absolute difference in the MI rates was 1.6% (6.2% for eptifibatide vs. 7.8% for placebo) as assessed by the site investigators, and 1.0% (12.6% vs. 13.6%) as adjudicated by the CEC. As expected, the higher event rates in both treatment arms using the CEC data, despite the similar absolute difference, reduced the relative treatment effect (7.4% vs. 20.5% reduction). A similar decrease in relative treatment effect has been noted in some prior trials[1,8] but not others.[17-19]

The MIs determined by cardiac-enzyme elevations without clinical symptoms or ECG changes accounted for 33% of the disagreements in which the CEC identified an MI and the site investigators did not. The median CK-MB elevation in these events was 1.6 times the ULN. Thus, about 50% of these events were defined by CK-MB values between 1 and 1.5 times the ULN, with normal median CK values (0.9 times the ULN) (Table 3).

A retrospective but blinded review of MIs identified by the CEC but not the site investigator found that 18% (98/540) of these cases were assigned a low level of clinical certainty because, although the CK or CK-MB elevations met the end-point criteria, the cardiac-enzyme data were considered inconsistent or unreliable or were associated with conflicting clinical and ECG data.

We noted regional differences in the proportion of cases with low clinical certainty. The highest proportions were in Eastern Europe and Latin America, where the observed treatment effect using the CEC definition was negligible. Further, the magnitude of the enzyme elevations (Table 3) parallels discrepancies in the assigned level of certainty. The highest enzyme elevations were observed in North America (median CK-MB elevation 2.9 times the upper limit of normal; median CK elevation 1.6 times the upper limit of normal), where the treatment effect was most pronounced. In other regions, CK-MB elevations were less striking (median 1.4 to 2.0 times the upper limit of normal). However, the regional differences in treatment effect are complex and include differences in patient

demographics; the use of cardiac procedures, medications, and revascularization; and reliability of laboratory data.[23] These findings support the hypothesis that including MI end points defined by low-level cardiac-enzyme elevations or events associated with conflicting clinical and ECG data may dilute the actual treatment effect.

Predictive Value of CEC-Identified Events

The 30-day treatment effect was reduced using CEC-adjudicated end points versus site-investigator assessments, but patients with events adjudicated by the CEC (but not identified by the site investigators) had greater mortality between 30 days and 6 months than did patients with MI reported only by the site investigators (Table 6). In addition, MIs identified by a similar CEC process have been associated with worse long-term outcomes at 3-year follow-up.[24] These data suggest that events identified by the CEC alone are of prognostic importance.

Implications

Clinical Events Committee adjudication of suspected nonfatal MI end point events is important to provide independent, unbiased, standard, systematic assessment. The CEC adjudication does have certain limitations. The criteria used to define MI must be evaluated. In cases in which the clinical history, the cardiac-enzyme data, and ECG information are inconsistent, or cardiac-enzyme data suspect, the determination of MI may require more clinical judgment. We recognize that this may decrease the objectivity that is important for event classification, particularly in trials across geographic regions and clinical-practice settings. At a minimum, events characterized by a low level of clinical certainty should not be classified as MIs.

Although the absolute difference in infarction rates determined by the CEC versus site investigators was small, the relative difference was more substantial. This caused a substantial impact on the statistical outcome of the trial. This phenomenon must be considered in sample-size and power calculations during design of future trials and also may influence how clinical and regulatory bodies interpret trial results. In addition, the CEC process used must be considered, among other factors, when performing comparisons of event rates between trials.

Conclusion

Nonfatal MI is an important clinical outcome; its prevention is a key measure of efficacy in evaluating new therapies for acute coronary syndromes. The determination of MI can be difficult in clinical practice due to conflicting clinical, cardiac enzyme, and ECG data. Clinical Events Committee (CEC) adjudication of MI provides a standard, systematic, independent, and unbiased assessment of this

end point in clinical investigations. In PURSUIT, the assessments of MI by site investigators and a central CEC disagreed; more MIs were identified by the CEC than by site investigators. Most disagreements reflected underreporting of procedure-related events and misclassification of enrollment MIs as post-enrollment (end point) MIs. Understanding the CEC process used in a trial is important in interpreting event rates, particularly when comparing rates between trials. The type of CEC process also has implications in sample-size and power calculations. Our review of the PURSUIT CEC experience has highlighted some of these important issues and the need to further evaluate the strategies used for event adjudication.

Appendix

Definition for Post-enrollment Myocardial Infarction

Enzyme Criteria:

Myocardial infarction (events without documentation of previous infarction during the admission): Creatine kinase (CK)-MB level above upper limit of normal (ULN) and ≥3 % of total CK. If CK-MB was unavailable, then total CK > 2 times the ULN.

Myocardial reinfarction (events with documentation of an infarction before or at enrollment)

If < 18 hours since previous infarction: Recurrent, severe ischemic discomfort and new, recurrent ST-segment elevation ≥0.1 mV in at least two contiguous leads, either persisting ≥30 minutes.

If ≥18 hours since previous infarction: Re-elevation of CK-MB to above the ULN (if prior CK-MB was within normal range) or > 50 % above the prior level (if prior CK-MB was above-normal). If CK-MB was unavailable, then total CK ≥2 times the ULN and increased by ≥25 %, or ≥1.5 times the ULN and increased by ≥200 IU above prior value.

Periprocedural infarction (events occurring during or within 24 hours of percutaneous coronary intervention): CK-MB level ≥3 times the ULN and > 50 % above prior nadir value. If CK-MB was unavailable, total CK ≥3 times the ULN.

Perioperative infarction (events occurring during or within 36 hours of bypass surgery): CK-MB ≥5 times the ULN (or CK, in the absence of CK-MB).

ECG Criteria

New, significant Q waves or equivalents ≥0.045 seconds in at least two contiguous leads.

When enzyme or ECG data were unavailable, an infarction was identified when the bulk of clinical evidence (patient signs, symptoms, ECG changes, and pathological findings) so indicated.

References

1 The GUSTO-IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med.* 1996;335:775-782.

2 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med.* 1994;330:956-961.

3 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med.* 1997;336:1689- 1696.

4 The Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J.* 1994;308:81- 106.

5 Califf RM, Abdelmeguid AE, Kuntz R, Popma JJ, Davidson CJ, Cohen EA, Kleiman NS, Mahaffey KW, Topol EJ, Pepine CJ, Lipicky RJ, Granger CB, Harrington RA, Tardiff BE, Crenshaw BS, Bauman RP, Zuckerman BD, Chaitman BR, Bittl JA, Ohman EM. Myonecrosis after revascularization procedures. *J Am Coll Cardiol.* 1998;31:241-251.

6 The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes without persistent ST-segment elevation: a randomized, placebo-controlled, clinical trial. *N Engl J Med.* 1998;339:436-443.

7 The CAVEAT Study Group. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med.* 1993;329:221-227.

8 The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention - IMPACT-II. *Lancet.* 1997;349:1422-1428.

9 The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med.* 1992;327:669-677.

10 Walter SD, Cook DJ, Guyatt GH, King D, Troyan S, for the Canadian Lung Oncology Group. Outcome assessment for clinical trials: how many adjudicators do we need? *Contr Clin Trials.* 1997;18:27-42.

11 Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol.* 1995;5:278-285.

12 Remington RD. Who should code cause of death in a clinical trial? *Contr Clin Trials.* 1984;5:241-244.

13 Moussa MA, Shafie MZ, Khogali MM, el-Sayed AM, Sugathan TN, Cherian G, Abdel- Khalik AZ, Garada MT, Verma D. Reliability of death certificate diagnoses. *J Clin Epidemiol.* 1990;43:1285-1295.

14 Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology.* 1991;98(Suppl):786-806.

15 Graafsma YP, Prins MH, Lensing AW, de Haan RJ, Huisman MV, Buller HR. Bleeding classification in clinical trials: observer variability and clinical relevance. *Thromb Haemost.* 1997;78:1189-1192.

16 Mahaffey KW, Harrington RA, Akkerhuis M, Kleiman NS, Berdan LG, Tardiff BE, Granger CG, Crenshaw BS, DeJong I, Bhapkar M, Lee KL, Deckers J, Simoons ML, Topol EJ, Califf RM for the PURSUIT Investigators. Systematic adjudication of myocardial infarction endpoints in an international clinical trial. *Contr Clin Trials.* (submitted).

17 Thrombolysis in Myocardial Ischemia (TIMI) Study Group. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. *Circulation.* 1994;89:1545-1556.

18 The PRISM PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med.* 1998;338:1488-1497.

19 The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med.* 1998;338:1498-1505.

20 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina - the CAPTURE study. *Lancet.* 1997;349:1429-1435.

21 Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation.* 1996;94:911-922.

22 The RESTORE Study Group. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;96:1445-1453.

23 Akkerhuis KM, Deckers JW, Boersma E, Harrington RA, Stepinska J, Mahaffey KW, Wilcox RG, Lincoff AM, Keltai M, Topol EJ, Califf RM, Simoons ML for the PURSUIT Investigators. Geographic variability in outcomes within an international trial of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes: Results from PURSUIT. *Eur Heart J.* 2000;21:371-381.

24 The EPIC Investigator Group. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin b_3 blockade with percutaneous coronary intervention. *JAMA.* 1997;278:479-484.

4

Geographic Variability in Outcomes Within an International Trial of Glycoprotein IIb/IIIa Inhibition in Patients With Acute Coronary Syndromes: Results From PURSUIT

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Abstract

Aims

Variations in outcome of patients from different geographic regions have been observed in many large international trials. We analysed the factors that might contribute to the geographic variations in patient outcome and treatment effect as observed in the PURSUIT trial.

Methods

an In PURSUIT, 9461 patients with acute coronary syndromes without persistent ST-elevation were randomized to the platelet inhibitor eptifibatide or placebo for 72 hours in 27 countries in four geographic regions: Western (n = 3697) and Eastern Europe (n = 1541) as well as North (n = 3827) and Latin America (n = 396). The primary end-point was the 30-day composite of death or myocardial infarction. In the initial univariate analysis, the treatment effect appeared greater in N. America than in W. Europe, while no benefit was apparent in L. America and E. Europe. However, the confidence intervals were wide and overlapping.

To study these differences, a subdivision in an early and late patient outcome and treatment effect was made. Accordingly, we analysed the rate of death or infarction at 72 h censored for percutaneous coronary intervention and the rate between 3 and 30 days, respectively. Additional analyses were performed with different definitions of myocardial infarction using progressively higher thresholds of CK(-MB) elevation. Multivariable analysis was used to evaluate the relation between region and outcome and to determine the adjusted odds ratios for the eptifibatide treatment effect.

Results

Major differences in baseline demographics were apparent among the four regions; in particular, more patients from E. Europe had characteristics associated with impaired outcome. Interventional treatment also varied considerably, with more patients from N. America undergoing revascularization. Despite differences in the 72 h event rate, eptifibatide showed a consistent trend towards a reduction in the composite endpoint among all four regions and for all definitions of infarction. Relative reductions ranged from 17-42% in W. Europe, 23-35% in N. America, 0-33% in E. Europe, and 55-82% in L. America. After multivariable adjustment, the pattern of benefit with eptifibatide was consistent among the regions. In patients undergoing percutaneous coronary intervention during study drug infusion in W. Europe (n = 266) and N. America (n = 931), the relative reduction in myocardial infarction during medical therapy ranged from 56-75% in W. Europe and 14-67% in N. America, while the reduction in procedure-related

events ranged from 12-44% and 25-61% for different definitions of infarction. After multivariable adjustment neither benefit nor rebound were apparent after study drug discontinuation, or after 3 days in all regions, except in L. America. In general, the differences in outcome and treatment effect were greatest when the protocol definition of myocardial infarction (CK-MB > 1 upper normal limit) was applied. Under stricter definitions, these differences became smaller and disappeared with the investigator's assessment.

Conclusion

The analysis suggests that the apparent differences in patient outcome and eptifibatide treatment effect can be explained largely by differences in baseline demographics and adjunctive treatment strategies as well as by the methodology of myocardial infarction definition and the adjudication process.

Introduction

The PURSUIT trial (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) compared the glycoprotein IIb/IIIa inhibitor eptifibatide (Integrilin™, COR Therapeutics, Inc.) with placebo in addition to standard therapy in 9461 patients with acute coronary syndromes who did not have persistent ST-segment elevation. PURSUIT is the largest trial to date in this patient population.[1] A total of 726 hospitals from 27 countries in four geographic regions (Western Europe, North America, Eastern Europe, Latin America) participated. Compared with placebo, treatment with eptifibatide resulted in a significant 1.5% absolute reduction in death or myocardial infarction at 30 days. As in other large international trials, there were considerable variations in outcome of patients in different geographic regions.[1-5]

Due to the large number of patients treated in the various regions, this trial afforded a unique opportunity to gain insight into the heterogeneity of the disease and patient population, and to study differences in medical practice patterns and treatment strategies. Therefore, we reviewed these regional differences and analysed the factors that might contribute to the geographic variations in patient outcome and treatment effect.

Methods

The study design and results of the PURSUIT trial have been published in detail.[1,6] Briefly, patients were eligible for enrolment if they had ischaemic chest pain within the previous 24 h and either ECG changes suggestive of ischaemia (ST-segment depression, T-wave inversion, or transient ST-segment elevation) or a creatine kinase-MB fraction above the upper limit of normal for that hospital. Patients with persistent ST-segment elevation were excluded since they should be considered for immediate reperfusion therapy.[7] Patients were randomly assigned in double-blind fashion to an intravenous bolus and infusion of placebo or 180 μg . kg-1 bolus plus infusion of 2.0 μg . kg-1 min-1 eptifibatide. Study drug was to be infused over 72 h, but could be continued for up to 96 h if a percutaneous coronary intervention was performed at the end of the 72 h treatment period. All other treatment decisions, including the use of heparin, other anti-ischaemic medications and coronary angiography as well as the use and timing of percutaneous or surgical coronary revascularization, were left to the discretion of the treating physician. The primary end-point was the 30-day composite of death or non-fatal myocardial (re)infarction as adjudicated by an independent Clinical Events Committee blinded to treatment assignment.

Additional data analysis

Since the treatment effect at the end of the initial study drug infusion period provides the most accurate estimation of the benefit of eptifibatide as well as an

even playing field for comparison of the treatment benefits of eptifibatide across the four geographic regions, treatment effects at 72 h in the study were determined. For each region separately, the incidence of the composite end-point of death or non-fatal myocardial infarction was determined with the Kaplan-Meier method during the scheduled 72 h study drug infusion period among all patients randomized, while patients were censored at the time of intervention. In patients who underwent a percutaneous coronary intervention during the first 72 h, the incidence of myocardial infarction was evaluated in the period before the intervention, while the rate of death or myocardial infarction was assessed within the first 48 h of the intervention as well as in the subsequent time window up to 30 days. In each period, only patients who were event-free at the beginning of that period were considered. Additionally, in patients who did not reach a study end-point and did not undergo a percutaneous coronary intervention during the first 72 h, the rate of the end-point between day 3 and day 30 was determined using the Kaplan-Meier estimate.

Definitions of myocardial infarction

In the assessment by the Clinical Events Committee, myocardial (re)infarction was defined by ECG abnormalities or creatine kinase(-MB) elevation.[1,6] The definitions were specific to clinical scenarios of early or later myocardial infarctions and to infarctions associated with cardiac revascularization procedures.[1,6] A sensitive definition of cardiac enzyme elevation was applied: a single creatine kinase-MB value elevated above the upper limit of normal was sufficient to diagnose a myocardial infarction. Following percutaneous or surgical intervention, the elevation of enzyme levels was required to be at least three or five times the upper limit of normal, respectively.

Additional analyses were performed using the investigator's determination of myocardial infarction, and the assessment by the Clinical Events Committee with application of higher thresholds of creatine kinase-MB (or, in its absence, creatine kinase) of two, three or five times the upper limit of normal. For defining a percutaneous coronary intervention-related myocardial infarction, the creatine kinase-MB was required to be above three times the upper limit of normal during the first 24 h following the intervention, while in the subsequent period up to 48 h post-percutaneous coronary intervention a creatine kinase-MB value was required which exceeded one of the pre-specified thresholds as set for the other time windows.

Statistical methods

Continuous variables are presented as medians with 25th and 75th percentiles, discrete variables as frequencies and percentages. Baseline characteristics and

treatment parameters among the regions were compared univariably using the Kruskal-Wallis test for all continuous variables and Pearson's chi-square test for all incidences. Outcomes between eptifibatide and placebo patients within each region were compared univariably using Fisher's Exact Test. Statistical significance was determined to be $P \leq 0.05$. A multivariable logistic regression model was used to evaluate the relationship between geographic region and outcome for different definitions of myocardial infarction. The model was adjusted for variables found to be significant predictors of the 30-day composite of death or non-fatal myocardial infarction in the overall PURSUIT population.[8] Variables and their independent association with these outcomes are presented as odds ratios with 95% confidence intervals. Multivariable regression was also performed to determine the interaction term between region and eptifibatide treatment. Results of the multivariable regression analysis were then used to calculate the new, multivariable-adjusted odds ratios for the eptifibatide treatment effect.

Results

Baseline demographics and adjunctive therapy

A total of 9461 patients were enrolled in the placebo and the eptifibatide 180/2.0 groups of the PURSUIT study.[1] Of these, 3827 (41%) were enrolled in North America, 3697 (39%) in Western Europe, 1541 (16%) in Eastern Europe and 396 (4%) in Latin America. Major differences in baseline characteristics were apparent among these four geographic regions (Table 1). For example, age was highest in European patients, while in Eastern Europe more female patients were enrolled, as well as more patients with heart failure. Furthermore, patients from Eastern Europe had more severe angina preceding hospitalization, more often exhibited ST-segment depression on the qualifying electrocardiogram, and presented with a higher blood pressure. In contrast, patients from North America had a higher body weight, were more frequent diabetics, and had more frequently undergone revascularization procedures. In more patients from North America the qualifying episode was classified as a myocardial infarction. Medical and interventional treatment also varied among regions, with more patients from North America receiving heparin and undergoing angiography, percutaneous coronary intervention or coronary bypass surgery (Fig. 1). The percentage of percutaneous coronary interventions performed during the 72-h study drug infusion period was substantially higher among patients enrolled in North America than in the other regions. In all regions, over 90% of all patients received aspirin during hospitalization. Beta-blockers were used more frequently in Western Europe, while more Eastern European patients received ACE-inhibitors, reflecting the higher rates of previous infarction and heart failure in this region. The different treatment

Table 1 Baseline characteristics, concomitant therapy and treatment parameters by region

Characteristic	WE (n = 3697)	NA (n = 3827)	EE (n = 1541)	LA (n = 396)
Age (years)	65 (56, 71)	63 (54, 71)	65 (56, 71)	60 (51, 67)
Female sex (%)	31	35	47	37
Weight (kg)	76 (68, 85)	82 (71, 93)	75 (67, 85)	73 (63, 84)
Height (cm)	170 (164, 175)	172 (163, 178)	167 (161, 173)	165 (160, 171)
Systolic BP (mmHg)	130 (120, 145)	128 (113, 142)	135 (120, 150)	121 (110, 140)
Diastolic BP (mmHg)	80 (70, 84)	70 (61, 80)	80 (70, 90)	80 (70, 84)
Hypertension (%)	46	61	62	63
Diabetes (%)	18	27	26	23
CHC in previous 6 weeks (%)				
I or II	36	41	33	45
III or IV	45	36	57	37
Prior MI (%)	28	34	37	37
Prior CHF (%)	8	10	20	8
Prior PCI (%)	10	21	3	5
Prior CABG (%)	9	20	2	6
MI at enrolment (%)	44	48	46	32
Qualifying ECG changes (%)				
ST-depression	54	40	66	44
ST-elevation	13	16	9	16
Concomitant medication (%)				
Aspirin	94	91	95	95
Beta-blockers (oral)	68	66	65	55
ACE inhibitors	23	27	41	33
Heparin infusion (%)	88	97	80	77

For continuous variables, the median values are provided, with the 25th and 75th percentiles given in parentheses. $P = 0.0001$ by Kruskall-Wallis test for differences between the regions for all continuous variables, $P = 0.001$ by Pearson's chi-square test for differences between the regions for all discrete variables; WE = Western Europe; NA = North America; EE = Eastern Europe; LA = Latin America; ACE = angiotensin converting enzyme; BP = blood pressure; CABG = coronary artery bypass grafting; CHC = Canadian Heart Class; CHF = congestive heart failure; ECG = electrocardiographic; MI = myocardial infarction; PCI = percutaneous coronary intervention.

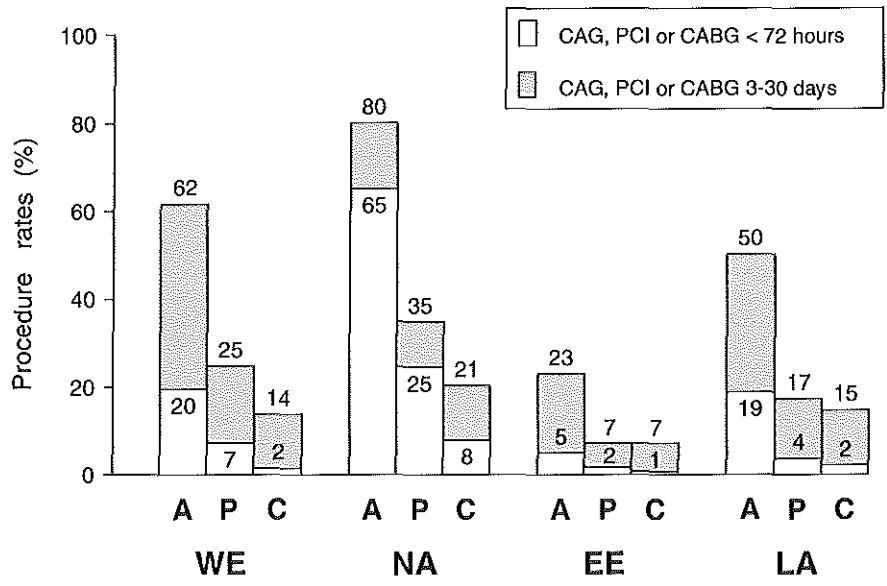

Figure 1:
Angiography and revascularization rates by region.
Percentage of patients undergoing angiography (A), percutaneous coronary intervention (P) or coronary bypass surgery (C) during the 30-day follow-up are shown above the bars, with the percentages with procedures performed within the first 72 h shown separately within the bars.

strategies were also apparent in the duration of hospital stay which was shortest in North America (median 6 days), and twice as long in Eastern Europe (median 13 days) with intermediate figures for Western Europe and Latin America (median 10 days, both).

Early (<72 h) patient outcome and treatment effect

In the PURSUIT study, the effect of eptifibatide on reducing death or myocardial infarction was apparent at 72 h, while this treatment effect remained essentially unchanged during the subsequent 30 days.[1] At 72 h, mortality was highest among patients from Latin America followed by Eastern Europe (Table 2). Applying a variety of definitions of myocardial infarction, patients enrolled in Eastern Europe and Latin America had a higher rate of death or infarction than those enrolled in Western Europe and North America. As expected, the number of end-points decreased in each region when a more stringent definition of myocardial infarction was applied. By multivariable analysis, the rate of death or myocardial infarction at 72 h according to the Clinical Events Committee was related to the geographic region (Table 3). After adjustment for differences in baseline characteristics, patients enrolled in Latin America and Eastern Europe were at a higher risk of adverse cardiac events than those from Western Europe, whereas patients treated in North America were at a lower risk. When progressively

Table 2 Mortality and composite of death or myocardial infarction at 72 h after randomization with censoring for percutaneous coronary intervention

	WE (n = 3697)				NA (n = 3827)				EE (n = 1541)				LA (n = 396)			
	E	P	Δ	RR	E	P	Δ	RR	E	P	Δ	RR	E	P	Δ	RR
Death	0.4	0.9	0.5	0.44	0.4	0.6	0.2	0.67	0.7	1.2	0.5	0.58	1.0	1.5	0.5	0.67
Composite of death or MI according to:CEC	4.6	5.8	1.2	0.79	2.9	4.1	1.2	0.71	10.3	10.2	-0.1	1.01	3.7	8.2	4.5	0.45
CEC > 2	3.7	4.7	1.0	0.79	2.6	3.5	0.9	0.74	6.2	6.5	0.3	0.95	2.6	8.2	5.6	0.32*
CEC > 3	3.3	4.0	0.7	0.83	2.4	3.1	0.7	0.77	5.0	5.6	0.6	0.89	1.6	6.7	5.1	0.24*
CEC > 5	2.2	3.1	0.9	0.71	1.9	2.5	0.6	0.76	3.2	3.8	0.6	0.84	1.6	5.1	3.5	0.31
Investigator	2.1	3.6	1.5	0.58†	2.0	3.1	1.1	0.65*	3.0	4.5	1.5	0.67	1.0	5.6	4.6	0.18*

Values presented as percentages, relative risk as ratio.

CEC = Clinical Events Committee; CEC > 2, CEC > 3, CEC > 5 = composite end-point according to the Clinical Events Committee with application of thresholds of creatine kinase(-MB) of two, three and five times the upper limit of normal in the definition of myocardial infarction, respectively; D = absolute difference between P and E; E = eptifibatide; MI = myocardial infarction; P = placebo; PCI = percutaneous coronary intervention; RR = relative risk. *, † correspond to $P < 0.05$, < 0.005 by Fisher's Exact Test.Other abbreviations, see Table 1.

Table 3 Multivariable-adjusted odds ratios for early (72 h) and late (3-30 days) event rate by region

		Death	CEC	CEC > 2	CEC > 3	CEC > 5	Investigator
Early event rate	LA	3.76 (1.0 - 14)	2.01 (1.1 - 3.6)	2.78 (1.6 - 5.0)	2.75 (1.4 - 5.2)	2.93 (1.4 - 6.0)	2.62 (1.3 - 5.2)
	NA	0.77 (0.3 - 1.7)	0.60 (0.4 - 0.8)	0.69 (0.5 - 1.0)	0.76 (0.5 - 1.1)	0.76 (0.5 - 1.2)	0.82 (0.5 - 1.2)
	EE	1.00 (0.4 - 2.4)	1.65 (1.2 - 2.3)	1.21 (0.8 - 1.8)	1.27 (0.8 - 1.9)	1.09 (0.7 - 1.8)	1.15 (0.7 - 1.8)
	WE	1	1	1	1	1	1
Late event rate	LA	1.37 (0.6 - 2.9)	1.12 (0.6 - 1.9)	1.20 (0.7 - 2.2)	1.02 (0.5 - 1.9)	1.06 (0.5 - 2.0)	1.13 (0.6 - 2.1)
	NA	1.10 (0.8 - 1.6)	1.07 (0.8 - 1.4)	1.16 (0.9 - 1.5)	1.16 (0.9 - 1.5)	1.26 (1.0 - 1.7)	0.98 (0.7 - 1.3)
	EE	0.80 (0.5 - 1.2)	1.00 (0.7 - 1.3)	0.88 (0.6 - 1.2)	0.77 (0.6 - 1.1)	0.75 (0.5 - 1.1)	0.96 (0.7 - 1.3)
	WE	1	1	1	1	1	1

Multivariable-adjusted odds ratios relative to Western Europe are provided with their 95% confidence interval in parentheses. Early event rate represents the 72-h, PCI-censored end-point of death or composite of death or myocardial infarction (figures shown in Table 2), while the late event rate represents the 3-30-day end-point of death or composite of death or myocardial infarction in patients with no end-point or PCI during the first 72 h (figures presented in Table 4). CEC = Clinical Events Committee; CEC > 2, CEC > 3, CEC > 5 = composite end-point according to the Clinical Events Committee with application of thresholds of creatine kinase(-MB) of two, three and five times the upper limit of normal in the definition of myocardial infarction, respectively; PCI = percutaneous coronary intervention. Other abbreviations, see Table 1.

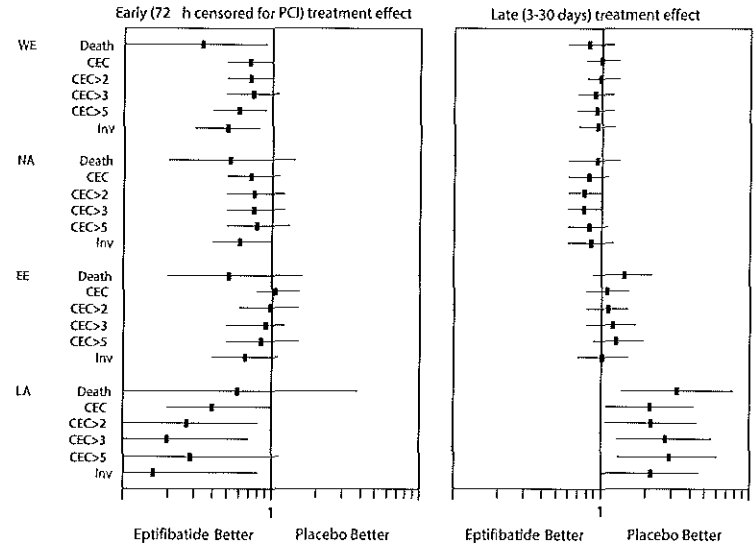

Figure 2:
Multivariable-adjusted odds ratios for the treatment effect on mortality and the composite of death or non-fatal myocardial infarction at 72 h with censoring for percutaneous coronary intervention and between 3 and 30 days.
Odds ratios are presented for each geographic region and for the various definitions of myocardial infarction applied to the composite end-point. The horizontal lines indicate 95% confidence intervals.
CEC = Clinical Events Committee; CEC>2, CEC>3, CEC>5 = composite end-point according to the Clinical Events Committee with application of thresholds of creatine kinase(-MB) of two, three and five times the upper limit of normal in the definition of myocardial infarction, respectively; Inv = site investigator.

higher thresholds of enzyme elevation were used in the definition of myocardial infarction, North America and Eastern Europe were no longer statistically significant predictors of the combined outcome. In contrast, Latin America remained an independent risk factor for the occurrence of death or infarction at 72 h.

The absolute and relative reduction in the composite end-point of death or myocardial infarction after 72 hours in patients receiving eptifibatide when compared with those in the placebo group appeared larger in Latin America than in the other regions for all infarct definitions (Table 2). This difference in treatment effect was, however, not statistically significant. Within each region separately as well as among all four geographic regions there was a remarkable consistency with respect to the directionality of the treatment effect, independent of the definition of myocardial infarction (Fig. 2). Although the magnitude of benefit differed and did not reach statistical significance in all comparisons, a beneficial effect of eptifibatide was apparent for all definitions of myocardial infarction among all four regions. Only one exception was observed: the original assessment by the

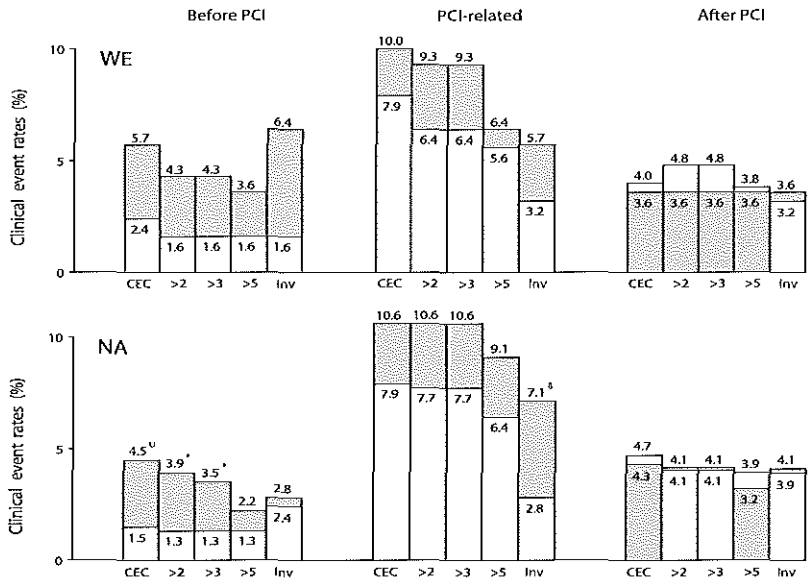

Figure 3:
Adverse cardiac events in patients from Western Europe (upper figure) and North America (lower figure) undergoing percutaneous coronary intervention within the 72 h study drug infusion period.
In both figures, the left bar graphs show the percentage of patients suffering a myocardial infarction in the period prior to the intervention. The middle graphs show the incidence of procedure-related death or infarction during the first 48 h following the intervention. The right graphs indicate the rate of death or non-fatal myocardial infarction from 48 h after the intervention up to one month. The clinical event rates are depicted for the various definitions of myocardial infarction.
CEC = Clinical Events Committee; >2, >3, >5 = end-point according to the Clinical Events Committee with application of thresholds of creatine kinase(-MB) of two, three and five times the upper limit of normal in the definition of myocardial infarction, respectively; Inv = site investigator.
**, †, § correspond to P<0.05, <0.01, <0.005 by Fisher's Exact Test for comparison between eptifibatide (□) and placebo (□+ ▨).*

Clinical Events Committee of myocardial infarction occurring in Eastern Europe (Table 2). After multivariable adjustment, the reduction in death or myocardial infarction at 72 h by eptifibatide did not differ significantly between Western Europe, Eastern Europe and North America when the original Clinical Events Committee adjudication was used or when a definition of myocardial infarction with thresholds of creatine kinase(-MB) of two or three times the upper limit of normal was applied (Fig. 2). In Western Europe, a slightly greater and statistically significant treatment benefit was observed on mortality and the combined end-point with a threshold of creatine kinase(-MB) of five times the upper limit of normal or the investigator's assessment of infarction. Additionally, the odds ratios of the treatment benefit observed in Latin America were significantly lower than in the other regions when a definition of myocardial infarction of creatine kinase(-MB)

Table 4 3 - 30-day mortality and composite of death or myocardial infarction in patients with no end-point or percutaneous coronary intervention in the first 72 h

	WE (n=3251)				NA (n=2759)				EE (n=1356)				LA (n=359)			
	E	P	D	RR	E	P	D	RR	E	P	D	RR	E	P	D	RR
Death	4.1	4.4	0.3	0.93	3.9	4.9	1.0	0.80	6.7	4.8	-1.9	1.40	13.5	5.2	-8.3	2.60*
Composite of death or MI according to CEC	11.7	11.5	-0.2	1.02	9.7	11.4	1.7	0.85	14.3	12.7	-1.6	1.13	18.4	10.3	-8.1	1.79*
CEC>2	9.9	9.7	-0.2	1.02	8.2	10.5	2.3	0.78*	10.9	9.9	-1.0	1.10	17.5	9.2	-8.3	1.90*
CEC>3	9.1	9.5	0.4	0.96	8.0	10.3	2.3	0.78	10.4	8.5	-1.9	1.22	17.5	7.9	-9.6	2.22†
CEC>5	8.1	8.4	0.3	0.96	8.0	9.6	1.6	0.83*	9.4	7.4	-2.0	1.27	16.4	7.2	-9.2	2.28*
Investigator	8.2	8.5	0.3	0.96	6.8	7.9	1.1	0.86	10.0	9.5	-0.5	1.05	14.7	7.3	-7.4	2.01

Values presented as percentages, relative risk as ratio.

CEC = Clinical Events Committee; CEC>2, CEC>3, CEC>5 = composite endpoint according to the Clinical Events Committee with application of thresholds of creatine kinase(-MB) of two, three and five times the upper limit of normal in the definition of myocardial infarction, respectively; D = absolute difference between P and E; E = eptifibatide; MI = myocardial infarction; P = placebo; PCI = percutaneous coronary intervention; RR = relative risk. *, † correspond to $P<0.05$, <0.01 by Fisher's Exact Test. Other abbreviations, see Table 1.

exceeding two or three times the upper limit of normal was applied to the original adjudication by the Clinical Events Committee or when the investigator's assessment was used.

In patients undergoing early (i.e. within 72 h) percutaneous coronary intervention in Western Europe (n = 266) or North America (n = 931), there was a consistent pattern of benefit with eptifibatide during medical therapy, which was augmented by the use of eptifibatide during the intervention. Although only some of the differences reached statistical significance, the directionality of the benefit was again remarkably consistent and apparent for all definitions of myocardial infarction (Fig. 3). During medical therapy preceding percutaneous coronary intervention, the relative reduction in myocardial infarction ranged from 56 to 75% in Western Europe and from 14 to 67% in North America. The rate of myocardial infarction associated with percutaneous coronary intervention was higher than in the preceding clinical treatment period. The absolute and relative treatment benefit of eptifibatide was greater in patients undergoing early percutaneous coronary intervention, both in the medical treatment period preceding the intervention and in association with the intervention, as compared with patients in whom no intervention was performed in the first 72 h. Neither additional treatment effect nor rebound were apparent after discontinuation of eptifibatide or placebo. The numbers of patients undergoing early coronary intervention in Eastern Europe (n = 31) and Latin America (n = 16) were too small for a meaningful analysis.

Late (3-30 days) patient outcome and treatment effect

In patients who did not reach a study end-point or undergo a percutaneous coronary intervention in the first 72 h, the subsequent incidence of the composite of death or myocardial infarction at 30 days was high (Table 4). In contrast to the early patient outcome, geographic region was not a significant predictor of cardiac events in these patients (similar odds ratios, Table 3). Among patients enrolled in Western Europe, neither additional treatment benefit nor rebound effect was apparent following the discontinuation of study drug. In North American patients, a consistent trend towards a treatment benefit with eptifibatide was observed. Additional analysis revealed that this benefit was mostly due to the favourable effect of eptifibatide on patients who were still receiving study drug in the period between 72 and 96 h. In contrast, negative treatment effects were observed in the other two geographic regions, with a small disadvantage for eptifibatide in Eastern Europe and a larger, statistically significant one in Latin America. By multivariable analysis, however, odds ratios of the late treatment effect in Western Europe, Eastern Europe and North America did not differ significantly and showed neither benefit nor rebound, although a trend towards a treatment benefit was apparent

in North America (Fig. 2). The odds ratios reflecting the negative treatment effect between day 3 and 30 in Latin America were significantly different from those observed in the other regions.

Discussion

In the initial univariate PURSUIT analysis, the treatment effect appeared greater in North America than in Western Europe, while no treatment effect was apparent in Latin America and Eastern Europe.[1] However, the confidence intervals for the treatment effects in these regions were wide and overlapping. The present analysis suggests that the apparent differences in patient outcome and treatment effect can be explained largely by differences in patient characteristics and treatment strategies, and by the adjudication process.

Baseline demographics and early (< 72 h) patient outcome and treatment effect

Patients enrolled in Eastern Europe were older, had a history of more severe coronary artery disease including a worse angina pectoris class and heart failure, and more often exhibited ST-segment depression on the qualifying electrocardiogram. These factors are associated with a worse outcome in patients with acute coronary syndromes.[8-13] This is reflected in this analysis by the higher rates of mortality and the combined end-point at 72 h in Eastern European patients. After correction for baseline characteristics in the multivariable analysis, Eastern Europe was no longer a significant predictor of mortality. However, differences in the combined event rate according to the Clinical Events Committee were maintained, with an increased risk in Eastern Europe as compared with Western Europe and North America. Eastern European origin was not an independent risk factor with respect to the combined outcome when more stringent criteria of infarction were applied. Therefore, the original protocol definition of myocardial infarction and the adjudication process should be considered in this context as discussed below. Furthermore, the developed multivariable models concentrated on baseline characteristics and risk factors at the moment of hospital admission. Consequently, differences between countries and regions in applied management styles and treatment strategies are post-randomization events for which it would be impossible to control for adequately. Finally, the role of chance cannot be excluded. The high mortality rate in Latin America remains an unexplained finding.

Despite differences in adverse cardiac event rates among the four geographic regions, eptifibatide showed a consistent trend towards a reduction in mortality and the composite end-point at 72 h in each region and for each definition of myocardial infarction. Although most comparisons failed to reach statistical

significance, most probably due to the small number of patients per subgroup, only one exception was observed: the original assessment by the Clinical Events Committee of myocardial infarction occurring in Eastern Europe. This consistency with respect to the directionality of the treatment benefit was maintained in the multivariable analysis.

Impact of percutaneous coronary intervention

In patients with acute coronary syndromes as well as in patients with stable angina, coronary intervention is associated with a 5% to 10% myocardial infarction rate.[14-19] Some of these infarcts can be avoided by treatment with a glycoprotein IIb/IIIa receptor blocker at the time of coronary intervention.[15-20] The CAPTURE study demonstrated a significant reduction in adverse cardiac events before the percutaneous coronary intervention when patients with refractory unstable angina received a glycoprotein IIb/IIIa inhibitor.[7,21] This prevention of myocardial infarction during medical therapy preceding percutaneous coronary intervention and protection from death or infarction during the procedure were also apparent in PURSUIT patients undergoing intervention during the 72 h study drug infusion period.[22] Despite the relatively small number of patients in Western Europe undergoing percutaneous coronary intervention during this timeframe as compared to North America, the pattern of benefit was remarkably similar in both regions. Recently, this pattern has also been observed in another, large clinical trial of glycoprotein IIb/IIIa inhibition in patients presenting with acute coronary syndromes without ST-elevation.[12] In patients undergoing percutaneous coronary intervention after discontinuation of study drug, no incremental treatment effect is to be expected and none was observed. In fact, coronary intervention in those patients was associated with an increased myocardial infarction rate.

The observed treatment effect at 30 days is thus a combination of the preventive effect during initial medical therapy and the protection by glycoprotein IIb/IIIa inhibition from thrombotic complications associated with percutaneous coronary intervention. The large number of patients in North America undergoing percutaneous coronary intervention while receiving study drug therefore enhanced the apparent treatment effect in this region. In the other regions, coronary intervention was done less frequently and mostly after discontinuation of study drug. Accordingly, in these regions, the treatment effect as observed in the original report merely reflected the effect of medical therapy without an additional effect during percutaneous coronary intervention.

The increased benefit during the medical treatment period in Western European and North American patients subsequently undergoing an early percutaneous coronary intervention, as compared with the 72 h treatment effect in the remaining patients enrolled in these regions, may reflect a patient group

at higher risk of thrombotic complications. It may also reflect investigational sites with staffing and infrastructure capable of performing early coronary intervention, allowing for optimal monitoring of patients and intervening in case of signs or symptoms unfavourably affecting the patient's prognosis (e.g. recurrent ischaemia)[9], thus optimally exploiting the beneficial effects of eptifibatide.

Late (3-30 days) patient outcome and treatment effect

In patients without cardiac complication or percutaneous coronary intervention in the first 72 h, the rate of clinical events reported between day 3 and 30 was high in all regions. This may reflect the great effort expended in this trial to measure and collect data on myocardial enzyme levels in patients with suspected ischaemic events and in those undergoing revascularization. This is supported by the fact that the high event rate was maintained when the more stringent definitions of myocardial infarction of creatine kinase(-MB) above three or five times the upper normal limit were applied. Some of the events were associated with percutaneous coronary interventions performed after discontinuation of study drug. Contrary to its relation to the 72 h outcome, geographic region was not an independent predictor of late outcome. This might suggest that the regional differences in treatment strategies and management styles mainly influence the patient's prognosis during the acute and subacute phase of the acute coronary syndrome. After discontinuation of experimental therapy no incremental treatment benefit is to be expected since platelet function recovers rapidly after the infusion of eptifibatide has been stopped. Indeed, the high event rate associated with late, unprotected coronary interventions may have diluted the actual treatment benefit. The negative treatment effects between day 3 and 30 in Eastern Europe and Latin America contributed to the absence of treatment benefit in these regions at 30 days in the initial univariate analysis. However, in the multivariable analysis there were no significant differences in treatment effect between day 3 and 30, which showed neither benefit nor rebound, among Western Europe, Eastern Europe and North America, although there was a trend towards more beneficial effect in the last region. The negative late treatment effect in Latin America is difficult to explain. However, it should be appreciated that only a very limited number of patients were enrolled in this region. Therefore, the role of chance cannot be excluded.

Impact of myocardial infarction definition and the adjudication process

Since even small, asymptomatic myocardial infarctions detected on the basis of elevated cardiac-enzyme levels in serum portend an unfavourable short- and long-term outcome[23-28], a sensitive definition of myocardial infarction was applied by the Clinical Events Committee: any elevation of creatine kinase-MB above the

upper limit of normal was considered a myocardial infarction. Other recent studies investigating glycoprotein IIb/IIIa blockers have applied a threshold of two or three times the upper limit of normal for creatine kinase-MB or total creatine kinase as part of their definition of myocardial infarction.[12,17,29] The greatest regional variation in treatment effect in PURSUIT and the present analysis was apparent when the original CEC definition of myocardial infarction was applied, while these differences became smaller when more stringent definitions were applied, and disappeared when the clinical definition of myocardial infarction was used as assessed by the local investigator. This might be explained in part by the fact that creatine kinase-MB measurement was introduced for the PURSUIT study in a number of hospitals where this measurement was not part of the routine clinical practice, particularly in Eastern Europe. This may have resulted in a number of erroneous abnormal creatine kinase-MB values. Re-screening of patients with a discrepancy between investigator and CEC assessment of myocardial infarction resulted in identification of patients with spurious creatine kinase-MB elevations, most likely not related to myocardial necrosis.[30] After application of a more strict threshold for myocardial infarction, treatment effects in all regions consistently favoured eptifibatide.

Although accumulating data support the notion that even minor elevations of creatine kinase-MB are prognostically important[23-28], perhaps this level of elevation is too sensitive to allow detection of small treatment effects when employed in a global mega-trial, especially when faced with the realities of collecting enzyme data in regions of the world that do not typically perform these laboratory evaluations. Clearly, the inability to get reasonable creatine kinase-MB data is of concern for future global investigations unless standardization of methods (i.e. a central core laboratory) can be assured. These factors all bear consideration when defining criteria for the diagnosis of myocardial infarction in the context of clinical investigation and, especially, in the conduct of a large international mega-trial. The present data imply that the adjudication process and the creatine kinase methodologic problems may have had a major impact on the inter-region differences that emerged during the PURSUIT trial.[30]

Conclusion

In their attempt to reflect actual clinical practice, the PURSUIT investigators chose the large simple trial model in the real-life clinical setting without mandated additional treatment assignments to study the effects of eptifibatide. In choosing a global approach to the trial, including a broad spectrum of management styles and clinical practices from rural hospitals to major tertiary referral centers in 27 countries, the investigators took the risk of seeing treatment outcomes and effects that would differ in the various regions. The initial PURSUIT analysis observed large differences in patient outcome and treatment effect among the four geographic regions. The present analysis suggests that these apparent differences can largely be explained by differences in baseline patient characteristics and treatment strategies, particularly the use and timing of coronary intervention. The third major factor that contributed to the regional variation was the adjudication process and the methodology of myocardial infarction definition.

The present report should be considered as an explanatory analysis aiming to identify factors contributing to the geographic variations in outcome and treatment effect. In order to explore these differences which result from a complex interplay in each region between baseline characteristics, treatment strategies and results of the adjudication process as well as from the treatment interaction as a function of these factors, the 30-day end-point was subdivided into early and late outcome. The effect of loosing statistical power was outweighed by the insight that was gained into the mechanisms involved in the geographic variations in patient outcome and treatment effect. Clearly, the analyses presented should be viewed with the limitations germane to subgroup analysis of randomized clinical trials.[31] Yet, the differences in baseline demographics, the adjunctive treatment strategies, and methodologic aspects of how events are determined all bear important consideration when analysing data from large international trials. The most important lesson of the present analysis is that global clinical trials should take into account these three important aspects when making observations regarding differences in patient outcome and consistency of the treatment effect across a multi-national network.

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References

1 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339**: 436-43.

2 Van de Werf F, Topol EJ, Lee KL et al. for the GUSTO Investigators. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. Results from the GUSTO trial. JAMA 1995; **273**: 1586-91.

3 Rouleau JL, Moyé LA, Pfeffer MA et al. for the SAVE Investigators. A comparison of management patterns after acute myocardial infarction in Canada and the United States. *N Engl J Med* 1993; **328**: 779-84.

4 Barbash GI, Modan M, Goldbourt U, White HD, Van de Werf F. Comparative case fatality analysis of the International Tissue Plasminogen Activator/Streptokinase mortality trial: variation by country beyond predictive profile. J Am Coll Cardiol 1993; 21: 281-6.

5 LATE Study Group. Late Assessment of Thrombolytic Efficacy (LATE) Study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* 1993; **342**: 759-66.

6 Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. *Am J Cardiol* 1997; **80**: Suppl 4A: 34B-38B.

7 Ryan TJ, Anderson JL, Antman EM et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1996; **94**: 2341-50.

8 Boersma E, Pieper K, Wilcox RG et al. for the PURSUIT Investigators. The risk of adverse outcome in patients with acute coronary syndromes without ST elevation is mainly determined by baseline clinical factors. *J Am Coll Cardiol* 1999; **33** Suppl A: 359A.

9 Armstrong PW, Fu Y, Chang W-C et al. for the GUSTO-IIb Investigators. Acute coronary syndromes in the GUSTO-IIb trial: Prognostic insights and impact of recurrent ischemia. *Circulation* 1998; **98**: 1860-8.

10 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; **335**: 775-82.

11 Lee KL, Woodlief LH, Topol EJ et al. for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. *Circulation* 1995; **91**: 1659-68.

12 The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338**: 1488-97.

13 Van Miltenburg-van Zijl AJM, Simoons ML, Veerhoek RJ, Bossuyt PMM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995; **25**: 1286-92.

14 Serruys PW, de Jaegere P, Kiemeneij F et al. for the BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; **331**: 489-95.

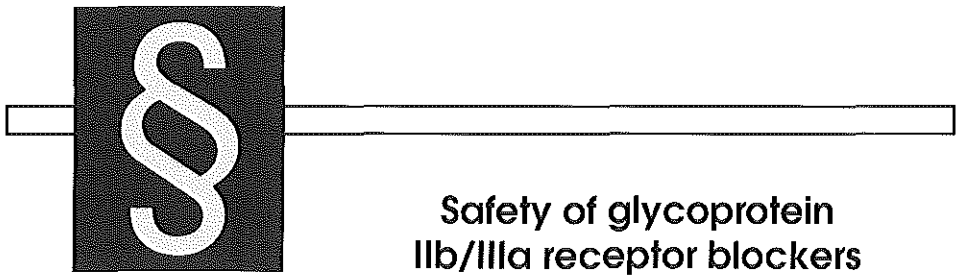
15 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; **330**: 956-61.

16 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997; **336**: 1689-96.

17 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; **349**: 1429-35.

18 The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; **349**: 1422-8.

19 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997; **96**: 1445-53.
20 Alexander JH, Alexander K, Kong DF, Tung CY, Whellan D. Session highlights from the American Heart Association Scientific Sessions: November 9-12, 1997. *Am Heart J* 1998; **135**: 157-80.
21 Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 1998; **98**: 1358-1364.
22 Akkerhuis M, Boersma H, Harrington RA, Deckers JW, Califf RM, Simoons ML. In patients with acute coronary syndromes without ST-segment elevation, eptifibatide particularly reduces complications in those undergoing an early percutaneous intervention: a report of the PURSUIT study. *Eur Heart J* 1998; **19** suppl: 3421.
23 Harrington RA, Lincoff AM, Califf RM et al. for the CAVEAT Investigators. Characteristics and consequences of myocardial infarction after percutaneous coronary intervention: Insights from the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT). *J Am Coll Cardiol* 1995; **25**: 1693-9.
24 Abdelmeguid AE, Topol EJ. The myth of the myocardial infarctlet during percutaneous coronary revascularization procedures. *Circulation* 1996; **94**: 3369-75.
25 Topol EJ, Ferguson JJ, Weisman HF et al. for the EPIC Investigator Group. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin ß3 blockade with percutaneous coronary intervention. JAMA 1997; **278**: 479-84.
26 Simoons ML, Van den Brand M, Lincoff M et al. Minimal myocardial damage during coronary intervention is associated with impaired outcome. *Eur Heart J*. Accepted for publication.
27 Califf RM, Abdelmeguid AE, Kuntz RE et al. Myonecrosis after revascularization procedures. *J Am Coll Cardiol* 1998; **31**: 241-51.
28 Alexander JH, Sparapani RA, Mahaffey KW et al. 30-Day and 6-month mortality is proportional to magnitude of peak creatine kinase elevation in the non-ST-segment elevation acute coronary syndromes. *Circulation* 1998; **98** Suppl 17: I-3306.
29 The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338**: 1498-505.
30 Mahaffey KW, Akkerhuis M, Boersma H et al. The identification of MI in clinical trials is difficult and there is substantial difference between the assessment by site investigators and a Clinical Events Committee: results from PURSUIT. *Eur Heart J* 1998; **19** suppl: 498.
31 Yusuf S, Wittes J, Probsfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. JAMA 1991; **266**: 93-8.



Safety of glycoprotein IIb/IIIa receptor blockers

5

Risk of stroke associated with abciximab among patients undergoing percutaneous coronary intervention: Overview of four large, randomized trials.

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Abstract

Context:
Abciximab, a potent inhibitor of the platelet glycoprotein IIb/IIIa receptor, reduces thrombotic complications in patients undergoing percutaneous coronary intervention. Because of its potent inhibition of platelet aggregation, the effect of abciximab on the risk of stroke has been a concern.

Objective:
To determine whether abciximab is associated with an increased risk of stroke among patients undergoing percutaneous coronary intervention.

Design:
Four double-blind, placebo-controlled, randomized trials (EPIC, CAPTURE, EPILOG, and EPISTENT).

Setting:
A total of 257 academic and community hospitals in the United States and Europe.

Patients:
A total of 8555 patients undergoing percutaneous coronary intervention with or without stent deployment for a variety of indications were randomized.

Interventions:
Bolus and infusion of abciximab or matching placebo. One treatment group in EPIC received a bolus of abciximab only.

Main Outcome Measures:
The incidences of hemorrhagic and non-hemorrhagic stroke were determined.

Results:
Among the 8555 patients randomized, no significant difference in stroke rate was apparent between patients assigned abciximab and those assigned placebo (0.40% versus 0.29%, p = 0.46). With exclusion of the EPIC abciximab bolus-only group, there were 9 strokes among the 3023 patients who received placebo (0.30%) and 15 in 4680 patients treated with abciximab bolus plus infusion (0.32%), a difference of 0.02% (95%CI −0.23% to 0.28%). The incidence of non-hemorrhagic stroke was 0.17% in abciximab-treated patients and 0.20% in placebo-treated patients (difference −0.03%, 95%CI −0.23% to 0.17%). The rates of hemorrhagic stroke were 0.15% and 0.10%, respectively (difference 0.05%, 95%CI −0.11% to 0.21%). Among

patients treated with abciximab, the incidence of hemorrhagic stroke in patients receiving standard-dose heparin in EPIC, CAPTURE, and EPILOG was higher than in those receiving low-dose heparin in the EPILOG and EPISTENT trials (0.27% versus 0.04%, $p = 0.057$).

Conclusions:

Abciximab in addition to aspirin and heparin does not increase the risk of stroke in patients undergoing percutaneous coronary intervention. Patients undergoing percutaneous coronary intervention and treated with abciximab should receive low-dose, weight-adjusted heparin.

Introduction

Intravenous platelet glycoprotein (GP) IIb/IIIa receptor inhibitors effectively reduce ischemic complications in patients undergoing percutaneous coronary intervention and in those with acute coronary syndromes treated medically. [1-8] Randomized studies have shown consistency among agents with respect to the directionality of the benefit, with the most pronounced reductions achieved with abciximab (ReoPro^{TM}, Centocor), a monoclonal antibody Fab fragment directed against the platelet GP IIb/IIIa receptor. [9] In the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina), EPILOG (Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade) and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) studies, treatment with abciximab resulted in an approximate 50% reduction in the composite of death or myocardial infarction at 30 days in the full spectrum of patients undergoing percutaneous coronary intervention.[1-4]

Inhibition of platelet aggregation by abciximab or other GP IIb/IIIa receptor blockers increases the risk of bleeding complications, particularly when combined with conventional doses of heparin.[1-8] Intracerebral hemorrhage is potentially the most catastrophic and dreaded complication of antithrombotic or anticoagulant therapy. The event usually results in fatality or disability.[10] Because of its potent inhibition of platelet aggregation, the effect of abciximab on the risk of stroke has been a concern. Since stroke is infrequent, a combined analysis of 8555 patients from the EPIC, CAPTURE, EPILOG and EPISTENT studies was performed to compare stroke rates between patients treated with abciximab (in addition to aspirin and heparin) and those receiving placebo during coronary intervention, as well as to assess the predictive value of baseline clinical and demographic factors with stroke.

Methods

Data were obtained from the EPIC, CAPTURE, EPILOG and EPISTENT trials, four studies conducted between November 1991 and October 1997. The protocols and results of the four studies have been published in detail.[1-4] In brief, the studies were designed as large, double-blind, placebo-controlled, randomized trials to evaluate the efficacy of the GP IIb/IIIa receptor inhibitor abciximab in reducing ischemic complications in patients undergoing percutaneous coronary intervention for a variety of indications. The EPIC trial enrolled patients scheduled to undergo balloon angioplasty in high-risk clinical situations including unstable angina, evolving myocardial infarction, or high-risk coronary morphology.[1] CAPTURE evaluated the use of abciximab in patients with unstable angina refractory to conventional medical therapy for whom percutaneous coronary

intervention was planned and performed after approximately 24 hours of pre-treatment with abciximab.[2] Patients undergoing elective balloon angioplasty were studied in EPILOG.[3], while EPISTENT evaluated the efficacy of abciximab as an adjunct to coronary stenting. This latter trial enrolled patients scheduled to undergo elective or urgent percutaneous coronary revascularization and tested the hypothesis that stenting or balloon angioplasty plus abciximab would be superior to stenting plus placebo.[4] All trials excluded patients with characteristics associated with an increased risk of bleeding as well as those with a cerebrovascular accident within the preceding two years. Patients were randomized to receive a bolus and an infusion of abciximab (0.25 μg/kg bolus, 10 mg/min infusion in EPIC and CAPTURE and 0.125 μg/kg.min (maximum 10 μg/min) in EPILOG and EPISTENT) or matching placebo. One treatment group in EPIC received a bolus of abciximab only. In EPIC, EPILOG and EPISTENT, study drug was administered from one hour before until 12 hours after the percutaneous coronary intervention, while the CAPTURE trial required administration of placebo or abciximab starting 18 to 24 hours prior to the coronary intervention and continuing until one hour after completion of the intervention. All patients received aspirin as well as intravenous heparin at standard (EPIC) or weight-adjusted (CAPTURE, EPILOG and EPISTENT) dose. In addition to weight-adjustment, one abciximab treatment arm in EPILOG and both abciximab treatment arms in EPISTENT received a low-dose heparin regimen. The primary endpoint in the three studies was the composite of death, myocardial infarction or urgent (re)intervention at 30 days. The study protocols were approved by the institutional review board at each study center and all patients gave written informed consent to participate.

Stroke classification

Patients with suspected strokes were identified from the Case Report Forms. Clinical notes, hospital discharge summaries, neurological consultation reports, (results of) computed tomographic or magnetic resonance imaging studies, and, if applicable, autopsy reports were collected on all patients with suspected stroke for final classification. Any suspected stroke that occurred during the 30-day follow-up period was confirmed and adjudicated by a committee blinded to treatment allocation. Strokes were classified as either hemorrhagic or non-hemorrhagic.

Statistical analysis

The incidence of stroke and intracranial bleeding was determined among all patients as randomized, as well as among all patients as treated, with exclusion of the abciximab bolus-only group in the EPIC trial. This was done to provide an unbiased basis for comparison across the four trials. Continuous variables are

presented as means with standard deviation. Discrete variables are shown as frequencies and percentages. Baseline characteristics among patients with and without stroke were compared univariably using the t-test for all reported continuous variables and Fisher's Exact Test for all reported incidences.

Results

All patients

Among the 8555 patients randomized in the four trials, there were 33 strokes reported in 31 patients (0.36%) within the first 30 days following enrollment. Stroke occurred in 9 (0.29%) of the 3079 patients assigned placebo and in 22 (0.40%) of the 5476 patients assigned abciximab (p = 0.46). Nineteen patients had a non-hemorrhagic stroke: 6 placebo patients (0.20%) versus 13 abciximab patients (0.24%), p = 0.81. Hemorrhagic stroke or intracranial bleeding occurred in 3 (0.10%) patients assigned placebo and in 9 (0.16%) patients assigned abciximab (p = 0.56). In one patient, the type of stroke could not be established. Among the 695 patients in the EPIC abciximab bolus-only group, six strokes occurred in five patients. There were 2 stroke patients in the EPIC trial who were randomized to abciximab bolus plus infusion, but were not treated because the stroke occurred after randomization but before the angioplasty. One patient had a hemorrhagic stroke and the other had a non-hemorrhagic stroke. All patients who experienced strokes or intracranial bleeding events in the CAPTURE, EPILOG and EPISTENT trials received the allocated study drug.

Abciximab bolus and infusion

There were 24 strokes among the 7703 patients who received study drug bolus and infusion: 9 in 3023 placebo-treated patients (0.30%) and 15 in 4680 patients treated with abciximab bolus plus infusion (0.32%, Table 1). The difference in the incidence rate between the groups was 0.02% with an upper limit to the 95% confidence interval (CI) of 0.28%. The incidence of non-hemorrhagic stroke was 0.17% in patients treated with abciximab bolus and infusion, compared with 0.20% in patients receiving placebo (difference -0.03%, 95% CI -0.23% to 0.17%). Among the 3023 patients treated with placebo there were 3 (0.10%) intracranial bleedings/hemorrhagic strokes compared with 7 (0.15%) in the 4680 patients receiving abciximab bolus plus infusion, a difference in incidence of 0.05% with an upper limit to the 95% CI of 0.21%.

Heparin dosing

After grouping the trials by heparin dosing, there was a higher incidence of hemorrhagic stroke in patients receiving abciximab and standard-dose heparin

(patients from EPIC, CAPTURE, and the standard-dose heparin arm of EPILOG) as compared with those receiving abciximab and low-dose heparin (patients from EPISTENT and the low-dose heparin arm of EPILOG). The difference in the incidence rates between these two groups achieved borderline statistical significance (0.27% versus 0.04%, respectively; $p = 0.057$). No differences were observed in the means of the maximum activated clotting time values achieved during the procedure between patients with hemorrhagic stroke and those without. A non-significant higher incidence of non-hemorrhagic stroke was apparent in patients receiving abciximab and low-dose heparin versus abciximab and standard-dose heparin (0.24% versus 0.09%, respectively; $p = 0.30$).

Predictive value of baseline characteristics

Patients with a stroke were older (mean age 67 years versus 60 years in patients without stroke, $p < 0.001$), more often had a history of hypertension (77% versus 54%, $p = 0.012$), but less frequently had a history of diabetes mellitus (7% versus 21%, $p = 0.044$). Non-significant higher incidences of peripheral vascular disease and prior revascularization procedures were apparent among patients who experienced a stroke (Table 2).

Discussion

This combined analysis of more than 8500 patients implies that abciximab in addition to aspirin and heparin does not increase the overall risk of stroke in patients undergoing percutaneous coronary intervention. The risk of stroke in patients receiving abciximab on top of aspirin and heparin in the four trials was similar to that in patients receiving standard therapy and the 95% confidence intervals exclude a clinically meaningful difference in stroke rate. The results are applicable to a diverse population of patients undergoing percutaneous coronary intervention, with or without stent deployment, varying from patients with stable coronary artery disease and a low risk profile to those at increased risk during coronary intervention because of unstable ischemic syndromes or unfavorable lesion morphology on angiography.[1-4]

For comparison, the incidence of stroke in heparin-treated patients undergoing percutaneous coronary intervention for stable coronary artery disease as well as unstable coronary syndromes, including primary angioplasty for acute myocardial infarction, has been reported to be between 0% and 1%.[11-22] In patients with acute myocardial infarction with ST-segment elevation, the incidence of stroke in the era before the routine use of thrombolytic therapy was 1.7-3.2%.[23,24] The majority of these strokes were ischemic as intracranial hemorrhage was exceedingly rare. Intravenous thrombolytic therapy has reduced the incidence of nonhemorrhagic or ischemic stroke (0.1-1.3%), but increased that of intracranial

Table 1. Incidence of stroke and intracranial bleeding

	Abciximab		Placebo		Difference in incidence	95% CI
	n	%	n	%	%	%
Total	15/ 4680	0.32	9/ 3023	0.30	0.02	-0.23, 0.28
EPIC	3/ 678	0.44	4/ 681	0.59	-0.14	-0.91, 0.62
CAPTURE	1/ 622	0.16	4/ 631	0.63	-0.47	-1.17, 0.22
EPILOG	6/ 1811	0.33	0/ 914	0.00	0.33	0.07, 0.60*
Std-dose heparin	4/ 898	0.45	0/ 914	0.00	0.45	0.01, 0.88†
Low-dose heparin	2/ 913	0.22	NA			
EPISTENT	5/ 1569	0.32	1/ 797	0.13	0.19	-0.18, 0.56
Angioplasty	2/ 785	0.25	NA			
Stent	3/ 784	0.38	1/ 797	0.13	0.26	-0.24, 0.75
Intracranial bleeding / hemorrhagic stroke	7/ 4680	0.15	3/ 3023	0.10	0.05	-0.11, 0.21
EPIC	2/ 678	0.29	2/ 681	0.29	0.00	-0.57, 0.58
CAPTURE	0/ 622	0.00	1/ 631	0.16	-0.16	-0.47, 0.15
EPILOG	5/ 1811	0.28	0/ 914	0.00	0.28	0.03, 0.52‡
Std-dose heparin	4/ 898	0.45	0/ 914	0.00	0.45	0.01, 0.88§
Low-dose heparin	1/ 913	0.11	NA			

EPISTENT	0/ 1569	0.00	0/ 797	0.00	0.00	
Angioplasty	0/ 785	0.00	NA			
Stent	0/ 784	0.00	0/ 797	0.00	0.00	
Non-hemorrhagic stroke	8/ 4680	0.17	6/ 3023	0.20	-0.03	-0.23, 0.17
EPIC	1/ 678	0.15	2/ 681	0.29	-0.15	-0.64, 0.35
CAPTURE	0/ 622	0.00	3/ 631	0.48	-0.48	-1.01, 0.06
EPILOG	2/ 1811	0.11	0/ 914	0.00	0.11	-0.04, 0.26
Std-dose heparin	1/ 898	0.11	0/ 914	0.00	0.11	-0.11, 0.33
Low-dose heparin	1/ 913	0.11	NA			
EPISTENT	5/ 1569	0.32	1/ 797	0.13	0.19	-0.18, 0.56
Angioplasty	2/ 785	0.25	NA			
Stent	3/ 784	0.38	1/ 797	0.13	0.26	-0.24, 0.75

Table 1. Incidence of stroke and intracranial bleeding (cont)

Incidence of stroke and intracranial bleeding among patients *treated*, only, and with exclusion of the abciximab bolus-only treatment group from EPIC. Difference in incidence denotes the difference between the incidence in abciximab patients and placebo patients. 95% CI denotes the 95% confidence interval of the difference in incidence between both groups.

*, †, ‡ correspond to p = 0.19, 0.06 and 0.18, respectively, by Fisher's Exact Test for comparison of stroke rates between both treatment groups. The confidence interval of the difference corresponds to testing whether the difference in the incidence rates is equal to zero. The results from both tests do not correspond due to the fact that the event rate in the placebo arm is zero and the test of the difference is therefore testing the event rate in the abciximab arm being equal to zero.

Table 2. Baseline demographics by stroke status

	All stroke (n=31)	No stroke (n=8524)	p-value
Age (yr)	67 (7)	60 (11)	< 0.001
Sex (% male)	65	73	
Weight (kg)	82 (17)	84 (16)	
Height (cm)	171 (9)	172 (10)	
Hypertension (%)	77	54	0.01
Diabetes mellitus (%)	7	21	0.04
Current smoker or quit w/in 1 year (%)	27	35	
Prior CABG (%)	19	11	
Prior PCI (%)	24	20	
Prior CHF (%)	7	6	
History of PVD (%)	17	8	0.08
Prior stroke (%)	3	2	

Continuous variables are shown as means (standard deviation).

CABG denotes coronary artery bypass grafting, CHF, congestive heart failure, PCI, percutaneous coronary intervention, PVD, peripheral vascular disease.

P-values for comparison of continuous variables according to t-test, for discrete variables according to Fisher's Exact Test.

hemorrhage (0.07-1.5%).[25-33] The overall stroke rate remained approximately stable with streptokinase and increased slightly with alteplase.[33] In the current analysis, the rate of nonhemorrhagic stroke as well as the incidence of intracranial hemorrhage in abciximab-treated patients were comparable to those for patients undergoing percutaneous coronary intervention receiving heparin, but were substantially lower than those for patients with a myocardial infarction treated with thrombolytics. Therefore, unlike fibrinolytic therapy which carries an important liability for intracranial hemorrhage, the present data observed in patients undergoing coronary intervention in a variety of clinical settings support

the safety of abciximab with regard to the occurrence of intracranial hemorrhage. This finding is consistent with that of other intravenous GP IIb/IIIa receptor inhibitors in patients undergoing coronary intervention. In the IMPACT-II and RESTORE trials, the incidence of intracranial hemorrhage associated with eptifibatide and tirofiban treatment was 0.1%.[5,6] This observation is especially important in view of the detrimental impact of stroke and, in particular, intracranial hemorrhage on mortality, disability, as well as medical resource use and costs.[10]

In the present study, patients who experienced a stroke were older, more often had a history of hypertension, but less frequently a history of diabetes mellitus. No previous study has determined the risk factors for stroke among patients undergoing percutaneous coronary intervention. However, the present findings are consistent with the established risk factors for both nonhemorrhagic and hemorrhagic stroke among patients with ST-elevation myocardial infarction treated with thrombolytic therapy.[26,28-34]

In patients treated with abciximab, a trend toward a higher incidence of intracranial bleeding was observed among patients receiving standard-dose heparin (patients enrolled in EPIC, CAPTURE, and the standard-dose heparin arm of EPILOG) compared with those receiving the low-dose heparin regimen in the EPISTENT trial and the low-dose heparin treatment arm in the EPILOG trial. As the number of hemorrhagic strokes was small and the difference only reached borderline statistical significance, definitive conclusions cannot be made about the potential risk of heparin dosing on the incidence of hemorrhagic stroke in the patient population studied. However, other major bleeding complications are also reduced by the use of low-dose heparin versus standard-dose heparin in patients receiving abciximab.[1-4] Furthermore, previous studies in patients with acute myocardial infarction treated with thrombolytics have unequivocally shown that inappropriate high dosing of antithrombotic therapy has the potential to substantially increase the incidence of hemorrhagic stroke.[35-37]

The TIMI 9A trial and the GUSTO-IIa trial, which both compared intravenous hirudin with heparin as adjunctive therapy to thrombolysis and aspirin in patients with acute myocardial infarction, were terminated prematurely because of an excess of intracranial hemorrhagic events in both treatment arms.[35,36] These trials achieved a high level of anticoagulation by using a high dose of hirudin and a heparin regimen with titration to a target aPTT of 60 to 90 seconds. In both studies, an elevated aPTT was a significant risk factor for hemorrhagic stroke in both heparin- and hirudin-treated patients. Both trials were re-initiated with lower doses of heparin and hirudin titrated to a lower aPTT target range (50 to 70 seconds). Similarly, a retrospective analysis from the GUSTO-I trial in 29,656 patients with acute myocardial infarction revealed that the aPTT associated with the lowest 30-day mortality, stroke, and bleeding rates was 50 to 70 seconds and

that aPTT values higher than 70 seconds were associated with higher likelihood of mortality, stroke, bleeding, and reinfarction.[37] These observations parallel those in the ASPECT trial, which investigated the efficacy of long-term oral anticoagulant therapy in patients who survived a myocardial infarction.[38] While oral anticoagulant treatment reduced the overall incidence of stroke in these patients, the risk of intracranial hemorrhage was directly related to the intensity of the anticoagulant treatment, measured by the international normalized ratio.[39,40] These data in a variety of patient populations treated with different medications imply that caution should be exercised with respect to dosing of heparin in patients undergoing percutaneous coronary intervention and receiving abciximab. In fact, the EPILOG and EPISTENT trials have shown that the clinical benefit of abciximab can be uncoupled from the risk of hemorrhage by using low-dose, weight-adjusted heparin regimens.[3,4] Adherence to these guidelines should therefore be regarded as a standard treatment strategy in the management of patients undergoing percutaneous coronary intervention and treated with abciximab. On the other hand, surveillance with respect to the efficacy of the low-dose heparin regimen in protecting patients from non-hemorrhagic stroke is also needed.

The safety profile of the GP IIb/IIIa inhibitors has the potential to reduce the risk of intracranial hemorrhage in patients with acute myocardial infarction when combined with reduced-dose fibrinolytic therapy and a low-dose, weight-adjusted heparin regimen.[41-43] However, an adequate number of patients (tens to perhaps hundreds of thousands) need to be treated with this combination to be able to provide more definitive assurance of the lack of risk of intracranial bleeding with such treatment strategy. A large trial to assess the risks and benefits of combined abciximab-thrombolytic therapy is ongoing (GUSTO IV-AMI).

The present analysis of 8555 patients undergoing percutaneous coronary intervention and treated with either abciximab or placebo was limited by the very low incidence of stroke in this patient population. Continued surveillance with respect to the occurrence of stroke in patients treated with abciximab and systemic collection of data in clinical trials are needed. Nonetheless, the present findings provide strong evidence that the efficacy of abciximab in patients undergoing percutaneous coronary intervention is not overshadowed by an increased risk of stroke.

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References

1 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med.* 1994;330:956-961.

2 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet.* 1997;349:1429-1435.

3 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med.* 1997;336:1689-1696.

4 The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet.* 1998;352:87-92.

5 The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet.* 1997;349:1422-1428.

6 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation.* 1997;96:1445-1453.

7 The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med.* 1998;338:1488-1497.

8 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;339:436-443.

9 Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. *Eur Heart J.* 1998;19:1608-1616.

10 Tung CY, Granger CB, Sloan MA, et al. Effects of stroke on medical resource use and costs in acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Study. *Circulation.* 1999;99:370-376.

11 Dorros G, Cowley MJ, Simpson J, et al. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. *Circulation.* 1983;67:723-730.

12 Serruys PW, De Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med.* 1994;331:489-495.

13 Fischman DL, Leon MB, Baim DS, et al, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med.* 1994;331:496-501.

14 Mick MJ, Simpfendorfer C, Arnold AZ, Piedmonte M, Lytle BW. Early and late results of coronary angioplasty and bypass in octogenarians. *Am J Cardiol.* 1991;68:1316-1320.

15 Hearn JA, King SB 3d, Douglas JS Jr, Carlin SF, Lembo NJ, Ghazzal ZM. Clinical and angiographic outcomes after coronary artery stenting for acute or threatened closure after percutaneous transluminal coronary angioplasty. Initial results with a balloon-expandable, stainless steel design. *Circulation.* 1993;88:2086-2096.

16 Schomig A, Neumann F-J, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med.* 1996;334:1084-1089.

17 The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med.* 1996;335:217-225.

18 Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med.* 1993;328:680-684.

19 Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1993;328:673-679.

20 The GUSTO-IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med.* 1997;336:1621-1628.

21 Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA.* 1997;278:2093-2098. Erratum *JAMA.* 1998;279:1876.

22 Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI- 2). *J Am Coll Cardiol.* 1998;31:1240-1245.

23 Thompson PL, Robinson JS. Stroke after acute myocardial infarction: relation to infarct size. *Br Med J.* 1978;2:457-459.

24 Komrad MS, Coffey CE, Coffey KS, McKinnis R, Massey EW, Califf RM. Myocardial infarction and stroke. *Neurology.* 1984;34:1403-1409.

25 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet.* 1994;343:311-322.

26 Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II (GISSI-2), and the International Study Group. *N Engl J Med.* 1992;327:1-6.

27 Gore JM, Sloan M, Price TR, et al. Intracerebral hemorrhage, cerebral infarction, and subdural hematoma after acute myocardial infarction and thrombolytic therapy in the Thrombolysis in Myocardial Infarction Study. Thrombolysis in Myocardial Infarction, Phase II, pilot and clinical trial. *Circulation.* 1991;83:448-459.

28 Gore JM, Granger CB, Simoons ML, et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation.* 1995;92:2811-2818.

29 Maggioni AP, Franzosi MG, Farina ML, et al, on behalf of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Cerebrovascular events after myocardial infarction: analysis of the GISSI trial. *Br Med J.* 1991;302:1428-1431.

30 O'Connor CM, Califf RM, Massey EW, et al. Stroke and acute myocardial infarction in the thrombolytic era: clinical correlates and long-term prognosis. *J Am Coll Cardiol.* 1990;16:533-540.

31 Longstreth Jr WT, Litwin PE, Weaver WD, and the MITI Project Group. Myocardial infarction, thrombolytic therapy, and stroke. A community-based study. *Stroke.* 1993;24:587-590.

32 De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. *J Am Coll Cardiol* 1992;19:289-294.

33 Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet.* 1993;342:1523-1528.

34 Mahaffey KW, Granger CB, Sloan MA, et al. Risk factors for in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis: results from GUSTO-I. *Circulation.* 1998;97:757-764.

35 Antman EM. Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. *Circulation.* 1994;90:1624-1630.

36 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation*. 1994;90:1631-1637.

37 Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation*. 1996;93:870-878.

38 ASPECT Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet*. 1994;343:499-503.
Azar AJ, Koudstaal PJ, Wintzen AR, van Bergen PF, Jonker JJ, Deckers JW. Risk of stroke during long-term anticoagulant therapy in patients after myocardial infarction. *Ann Neurol*. 1996;39:301-307.

39 Azar AJ, Cannegieter SC, Deckers JW, et al. Optimal intensity of oral anticoagulant therapy after myocardial infarction. *J Am Coll Cardiol*. 1996;27:1349-1355.

40 Topol EJ. Toward a new frontier in myocardial reperfusion therapy. Emerging platelet preeminence. *Circulation*. 1998;97:211-218.

41 Antman EM, Giugliano RP, Gibson CM, et al, for the TIMI 14 Investigators. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. *Circulation*. 1999;99:2720-2732.

42 Califf RM. Glycoprotein IIb/IIIa blockade and thrombolytics: early lessons from the SPEED and GUSTO IV trials. *Am Heart J*. 1999;138:12-15.

6

Predictors of Bleeding in Patients With Acute Coronary Syndromes Without Persistent ST-segment Elevation Treated With Glycoprotein IIb/IIIa Receptor Inhibition: Results of an International Trial of 9461 Patients

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Abstract

Objective

To determine the clinical and demographic risk factors for bleeding in the population of patients with acute coronary syndromes without persistent ST-elevation.

Background

An accurate estimation of the risk of bleeding based on clinical evaluation may improve the risk-benefit ratio of GP IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndromes.

Methods

We studied bleeding complications among the 9375 patients with acute coronary syndromes without persistent ST-elevation receiving placebo or the platelet GP IIb/IIIa inhibitor eptifibatide in the PURSUIT trial and determined the multivariable predictors of spontaneous or procedure-unrelated bleeding events as well as bleeding complications associated with percutaneous coronary procedures.

Results

Bleeding was increased with eptifibatide among patients who did not undergo bypass surgery during hospitalization (31% compared with 12% in placebo). In most cases (83%) however, bleeding was mild. Patients undergoing bypass surgery during hospitalization had increased bleeding and accounted for approximately 80% of the patients with major bleeding complications. No increase in bleeding incidence with eptifibatide therapy was observed in patients who underwent bypass surgery. Risk factors for procedure-related bleeding included North American region, allocation to eptifibatide, female gender, the maximal aPTT value and treatment with ticlopidin. Treatment with eptifibatide was the most powerful independent predictor of spontaneous bleeding, followed by older age, female gender, North American region, the maximal aPTT value, smoking status, use of thrombolytics or ticlopidin, and non-caucasian ancestry. These factors were used to develop a scoring nomogram that can predict the patient's baseline risk of spontaneous bleeding and determine to what extent this risk increases during antithrombotic therapy. After combining two risk models, no subgroups of patients could be identified with either a low risk of adverse cardiac events and a high bleeding risk or a low bleeding risk and a high risk of cardiac events.

Conclusion

Bleeding was a common event in patients with non-ST-elevation acute coronary syndromes in the PURSUIT trial. The majority of the bleeding events was mild. In determining indications for GP IIb/IIIa inhibition therapy, the risk of bleeding is of secondary importance.

Introduction

Intravenous platelet glycoprotein (GP) IIb/IIIa receptor inhibitors reduce ischemic complications in patients with acute coronary syndromes without persistent ST-segment elevation undergoing percutaneous coronary intervention (PCI), as well as in those treated medically.[1-6] Inhibition of platelet aggregation by GP IIb/IIIa receptor blockers increases the risk of bleeding complications.[2-5,7,8] An accurate estimation of the risk of bleeding based on clinical evaluation at baseline may improve the risk-benefit ratio of GP IIb/IIIa receptor inhibition therapy in patients with acute coronary syndromes.[9] While the clinical factors associated with bleeding complications in patients with acute myocardial infarction (MI) treated with thrombolytic therapy have been well described,[10-12] the risk factors for bleeding in the population of patients with acute coronary syndromes without persistent ST-segment elevation have not been previously analyzed.

The PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial compared the GP IIb/IIIa inhibitor eptifibatide with placebo in addition to standard therapy in 9461 patients with acute coronary syndromes who did not have persistent ST-segment elevation.[3] We prospectively collected information about patients who experienced hemorrhagic complications in order to determine the incidence and location of bleeding, as well as the independent clinical and demographic predictors of bleeding in this patient population.

Methods

Patients and treatment

The study design and results of the PURSUIT trial have been published in detail.[3,13] In brief, patients were eligible for enrollment if they had ischemic chest pain within the previous 24 hours and either ECG changes suggestive of ischemia (ST-segment depression, T-wave inversion, or transient ST-segment elevation) or a creatine kinase-MB fraction above the upper limit of normal for that hospital. Patients with persistent ST-segment elevation were excluded since they should be considered for immediate reperfusion therapy.[14] Other exclusion criteria included active bleeding, gastrointestinal or genitourinary bleeding within the previous 30 days, a history of bleeding diathesis, major surgery within 6 weeks, systolic blood pressure above 200 mmHg or diastolic blood pressure above 110 mmHg, renal failure, or treatment with thrombolytic therapy within the previous 24 hours.

Patients were randomly assigned in double-blind fashion to an intravenous bolus and infusion of placebo, 180 mg/kg bolus plus infusion of 1.3 mg/kg.min of eptifibatide, or 180 mg/kg bolus plus infusion of 2.0 mg/kg.min of eptifibatide. As prespecified, after 3218 patients had been randomized, an independent Data

Safety Monitoring Board conducted an interim review of safety data and recommended dropping the lower dose, because the high dose had an acceptable safety profile. Study drug was to be infused during 72 hours but could be continued for up to 96 hours if a PCI was performed at the end of the 72-hour treatment period. All patients received aspirin in an initial dose of 160 mg followed by 75-325 mg daily thereafter. Patients who were allergic to or intolerant of aspirin could receive ticlopidin. Heparin was recommended but not mandated. Intravenous heparin was to be given as a 5000 U bolus dose and 1000 U/hour infusion with adjustment to maintain a target activated partial thromboplastin time (aPTT) of 50 to 80 seconds. The heparin regimen in patients undergoing PCI consisted of an initial bolus of 100 U/kg (maximum 10000 U) before the intervention, with additional weight-adjusted boluses administered according to a nomogram intended to achieve and maintain an activated clotting time (ACT) of 300 to 350 seconds. The protocol recommended that vascular sheaths be removed when the aPTT was 45 seconds or less or when the ACT was 150 seconds or less. All other treatment decisions including the use of other anti-ischemic medications, as well as the use and timing of coronary angiography, and percutaneous or surgical revascularization were left at the discretion of the treating physician. The protocol was approved by the institutional review board at each study center and all patients gave informed consent.

Bleeding complications

Following enrollment, patients were continually assessed for the occurrence of bleeding complications. Severity and location of bleeding were determined by the site investigator and filled out in the Case Report Form. Site investigators used the scale from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial for classification of the severity of bleeding events.[12,15] Hemorrhagic complications are scored as mild, moderate, severe, or life-threatening. Severe or life-threatening bleeding was defined as intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention. Moderate bleeding was defined as bleeding that required blood transfusion in the absence of hemodynamic compromise. Blood loss insufficient to meet criteria for moderate bleeding was classified as mild. The Case Report Form specified the following locations: oropharyngeal, pulmonary, brachial, upper or lower gastrointestinal and genitourinary tract hemorrhage, as well as groin, retroperitoneal, coronary artery bypass grafting (CABG)-related, and other bleeding and bleeding with an unidentifiable source requiring transfusion. The Clinical Events Committee used the scale from the Thrombolysis in Myocardial Infarction (TIMI) trial to classify bleeding complications on the basis of laboratory measurements.[3,16] Hemorrhagic events are categorized as insignificant, minor, or

major. For this purpose, hospital discharge summaries, laboratory printouts and transfusion reports were collected on patients with bleeding complications. Intracranial hemorrhages observed in PURSUIT have been reported previously and were not included in the present analysis.[17]

Additional data analysis

In order to determine the predictors of distinct categories of bleeding, spontaneous or procedure-unrelated bleeding events and bleeding complications associated with percutaneous coronary procedures were considered separately. Spontaneous bleeding was defined as oropharyngeal, pulmonary, brachial, upper or lower gastrointestinal and genitourinary tract hemorrhage, as well as other bleeding and bleeding with an unidentifiable source requiring transfusion. Procedure-related hemorrhage was defined as bleeding located at the groin or retroperitoneum. In both categories, bleeding complications associated with CABG were excluded. The incidence of spontaneous bleeding was determined in the 9375 PURSUIT patients receiving placebo or high-dose eptifibatide, whereas procedure-related bleeding was analyzed in the subgroup from this population undergoing coronary intervention within 30 days of randomization, within the first 72 hours, and between day 3 and 30, respectively. In addition, the incidence of spontaneous bleeding was determined in specific patient subsets to explore the relationship to coronary procedures. Patients receiving thrombolysis and experiencing bleeding complications were not excluded but the use of thrombolytics was included as a distinct determinant of bleeding.

Statistical analysis

Continuous variables are shown as means with standard deviations, discrete variables as frequencies and percentages. Logistic regression modeling techniques were used to determine the univariable and multivariable risk factors for spontaneous as well as procedure-related bleeding events. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. The multivariable models were constructed by backward deletion of the least significant characteristics, while applying a threshold of significance of $p = 0.05$. Predictors were tested with the use of the Wald χ^2 test. Results are presented as odds ratios and 95% confidence intervals. The predictive accuracy of the multivariable models is presented as the so-called concordance index (c-index), which describes the discriminant power of the model to reliably predict an outcome. A scoring nomogram for predicting the likelihood of experiencing a spontaneous bleeding was created from the coefficients from the multivariable regression modeling. Each independent predictor was assigned a score according to its predictive value. The sum of the scores indicates the probability of the occurrence of a spontaneous bleeding event.

Results

Baseline results

In PURSUIT, 4679 patients were treated with high-dose eptifibatide, while 4696 patients received placebo. Bleeding was increased with eptifibatide among patients who did not undergo bypass surgery during hospitalization (Figure 1). In total, bleeding occurred in 1258 (31%) of 4032 patients receiving eptifibatide compared with 498 (12%) of 4024 patients in the placebo treatment arm. In most cases (83%) however, bleeding was mild. Patients undergoing bypass surgery during hospitalization had increased bleeding and accounted for approximately 80% of

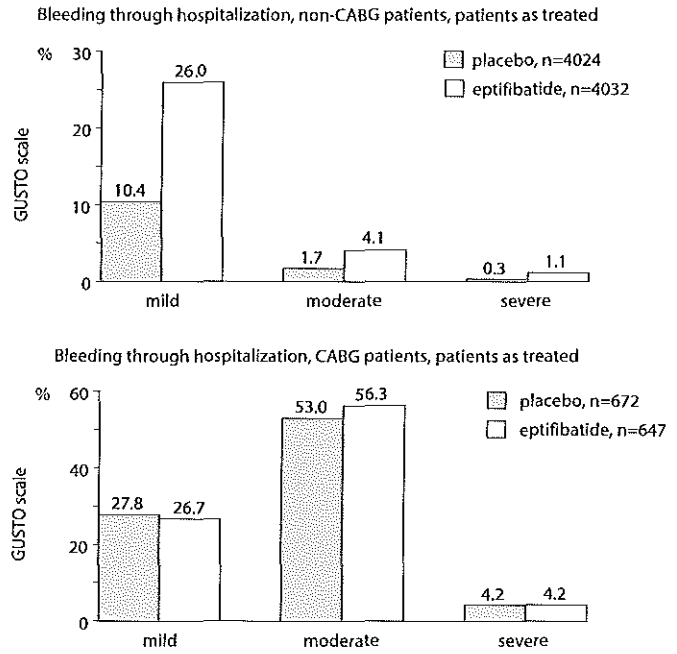


Figure 1
Bleeding through hospitalization classified according to the scale of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial in patients who did not undergo bypass surgery (upper panel) and in patients who underwent bypass surgery (lower panel).

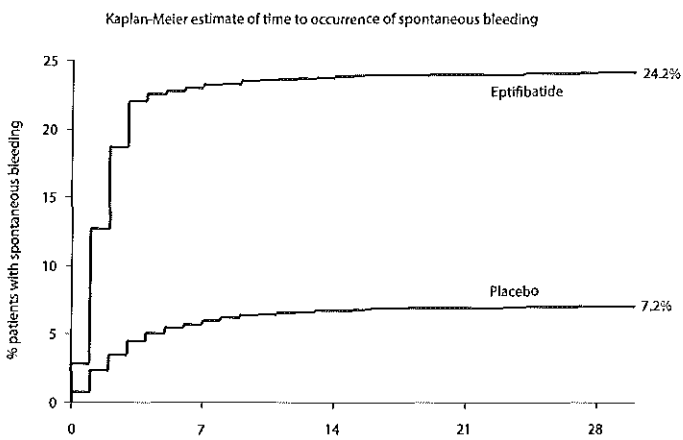


Figure 2
Kaplan-Meier estimate of the time to occurrence of spontaneous bleeding in eptifibatide and placebo patients through 30 days follow-up.

Table 1 **Unadjusted 30-day spontaneous and procedure-related bleeding event rate and odds ratios for baseline characteristics**

Characteristic	Category	Spontaneous bleeding			Procedure-related bleeding		
		Rate (%)	χ^2 (DF)	OR (95% CI)	Rate (%)	χ^2 (DF)	OR (95% CI)
Demographics							
Age (years)[1]	55	10.1	186 (1)#	0.72 (0.68 - 0.75)			
	64	14.8		1			
	71	23.9		1.30 (1.25 - 1.35)			
Gender	Female	19.2	47 (1)#	1.48 (1.33 - 1.66)	29.3	28 (1)#	1.72 (1.41 - 2.10)
	Male	13.8		1	19.4		1
Race	Non-caucasian	18.2	6 (1)†	1.23 (1.04 – 1.45)			
	Caucasian	15.4		1			
Weight (kg)[1]	69	18.1	18 (1)#	1.07 (1.04 - 1.11)			
	78	15.4		1			
	88	13.7		0.92 (0.89 - 0.96)			
Height (cm)[1]	163	18.5	32 (1)#	1.13 (1.08 - 1.18)	27.8	9 (1)§	1.11 (1.04 - 1.20)
	170	15.5		1	20.6		1
	176	13.0		0.90 (0.87 - 0.93)	21.9		0.91 (0.86 - 0.97)
Region	North America	18.1	27 (3)#	1.39 (1.23 - 1.58)	31.7	113 (3)#	3.52 (2.79 - 4.44)
	Latin America	15.2		1.12 (0.84 - 1.50)	2.9	4 (3)†	0.23 (0.06 - 0.94)
	Eastern Europe	14.3		1.05 (0.89 - 1.25)	10.5		0.89 (0.47 - 1.67)
	Western Europe	13.7		1	11.7		1
History							
Hypertension	Yes	16.9	13 (1)¶	1.23 (1.10 - 1.38)	25.2	13 (1)¶	1.43 (1.18 - 1.74)
	No	14.2		1	19.1		1
Diabetes mellitus	Yes	18.2	14 (1)¶	1.27 (1.12 - 1.44)			
	No	14.9		1			
Smoking status	Current	11.2	40 (2)#	0.62 (0.53 - 0.72)	18.8	6 (2)†	0.74 (0.58 - 0.95)
	Former	18.1		1.09 (0.96 - 1.24)	24.5		1.04 (0.83 - 1.30)
	Never	16.9		1	23.8		1
Family history	Yes	14.1	9 (1)§	0.84 (0.74 – 0.94)			
	No	16.4		1			
Myocardial infarction	Yes	17.0	6 (1)†	1.16 (1.03 - 1.30)			
	No	15.0		1			
Worst CCS-class in previous 6 weeks	3 or 4	16.6	4 (1)†	1.12 (1.00 - 1.26)			
	<3	15.0		1			
Congestive heart failure	Yes	19.6	13 (1)¶	1.36 (1.15 - 1.60)			
	No	15.2		1			
Periferal vessel disease	Yes	19.8	11 (1)¶	1.37 (1.14 - 1.65)			
	No	15.3		1			

Medication during hospitalization								
Aspirin	Yes	15.5	3 (1)*	0.83 (0.68 – 1.02)				
	No	18.1		1				
Beta-blocker	Yes	14.9	8 (1)§	0.85 (0.75 - 0.95)				
	No	17.2		1				
Calcium antagonists	Yes	16.9	6 (1)†	1.15 (1.02 - 1.29)				
	No	15.1		1				
Ticlopidin	Yes	18.6	6 (1)†	1.26 (1.05 - 1.50)	32.0	44 (1)#	2.01 (1.63 - 2.46)	
	No	15.4		1	19.0		1	
Maximal aPTT value (secs)(1)	60	14.2	25 (1)#	0.94 (0.91 - 0.96)	19.3	7 (1)‡	0.94 (0.90 - 0.98)	
	86	15.5		1	22.1		1	
	121	18.6		1.09 (1.05 - 1.13)	25.5		1.08 (1.02 - 1.15)	
Dipiridamol	Yes				51.1	19 (1)#	3.75 (2.07 - 6.78)	
	No				21.8		1	
Nitrates	Yes				21.9	3 (1)*	0.75 (0.54 - 1.05)	
	No				27.3		1	
Thrombolytics	Yes	20.7	3 (1)*	1.41 (0.98 – 2.05)	31.1	3 (1)*	1.59 (0.96 - 2.63)	
	No	15.6		1	22.1		1	
Presenting characteristics								
Diastolic blood pressure (mmHg)(1)	67	18.1	13 (1)¶	1.06 (1.03 - 1.10)	27.5	11 (1)§	1.11 (1.04 - 1.17)	
	75	14.8		1	20.0		1	
	83	15.1		0.94 (0.91 - 0.97)	20.0		0.90 (0.85 - 0.96)	
Heart rate (bpm)(1)	62	14.1	13 (1)¶	0.93 (0.90 - 0.97)				
	72	15.4		1				
	80	17.8		1.06 (1.03 - 1.09)				
ST depression (>0.5 mm)	Yes	17.3	18 (1)#	1.27 (1.14 - 1.42)				
	No	14.1		1				
PURSUIT study medication								
Eptifibatide	High dose	24.2	468 (1)#	4.15 (3.65 – 4.72)	27.2	30 (1)#	1.73 (1.42 - 2.09)	
	Placebo	7.2		1	17.8		1	

*, †, ‡, §, ¶, # correspond to p <0.1, <0.05, <0.01, <0.005, <0.001, <0.0001; only variables with p <0.1 are shown.

χ^2 = -2log likelihood; DF = degree(s) of freedom; OR = unadjusted odds ratio; CI = confidence interval; High dose integrelin = 180 µg/kg bolus followed by a 2.0 µg/kg/min continuous infusion

(1) With respect to continuous variables (a) *average* event-rates are presented for the patient cohorts below the 1st quartile, within the interquartile range and above the 3rd quartile, while (b) odds ratios are presented for the 1st and 3rd quartile vs. the median, respectively

the patients with major bleeding complications. No increase in bleeding incidence with eptifibatide therapy was observed in patients who underwent bypass surgery (Figure 1). In these patients, approximately 80% of bleeding was related to the bypass surgery, both in the eptifibatide and placebo treatment arm.

Spontaneous bleeding as defined in the present analysis occurred in 1483 (16%) of 9375 patients treated. Most spontaneous bleeding events occurred during the 72-hour study drug infusion period during the initial hospitalization (Figure 2). Procedure-related bleeding complications were observed in 543 (22%) of 2430 patients undergoing percutaneous coronary intervention during the 30-day follow-up period.

Univariable analysis

Among the patient demographics examined, older age, female gender, lighter body weight, shorter statue and North American origin were closely related to an increased risk of spontaneous bleeding (Table 1, left panel). Patients with a history of hypertension, diabetes mellitus, congestive heart failure, or peripheral vascular disease, as well as those who presented with a lower diastolic blood pressure, higher heart rate, or ST-depression were also at an increased risk of a hemorrhagic event. In contrast, less bleeding was seen among current smokers. Among the medications used during hospitalization, treatment with eptifibatide was the most powerful univariable predictor of spontaneous bleeding. Furthermore, the maximal aPTT value during heparin infusion appeared to be significantly related to the occurrence of spontaneous bleeding.

The number of factors closely associated with hemorrhagic events related to coronary intervention was considerably lower than for non-procedure-related bleeding (Table 1, right panel). Furthermore, there were differences in the ranking order by the degree of risk stratification with North American origin now as most powerful univariable predictor (χ^2 113 versus χ^2 27 for spontaneous bleeding), while the administration of ticlopidin and eptifibatide ranked second and third, respectively. Other factors associated with an increased PCI-related bleeding rate included female gender, a lower diastolic blood pressure, treatment with dipiridamol, and a higher maximal aPTT value. Age had no predictive value for the occurrence of intervention-related bleeding complications.

Multivariable analysis

Many of the univariably significant predictors of spontaneous bleeding remained important in the multivariable model (Table 2). Treatment with eptifibatide was the most powerful independent predictor of spontaneous bleeding, while higher age was the second most important independent predictor. Other variables that added significantly to the model were female gender, the maximal

Table 2 **Independent predictors of spontaneous bleeding**

Variable	Category	Spontaneous bleeding	
		χ^2	OR (95% CI)
Eptifibatide therapy	High dose	476#	4.50 (3.93 - 5.15)
	Placebo		1
Age	10 years	123#	1.36 (1.29 - 1.42)
Gender	Female	28#	1.42 (1.25 - 1.62)
	Male		1
Region	North America	25#	1.39 (1.22 - 1.58)
	Other		1
Maximal aPTT value	Each 10 seconds	17#	1.02 (1.01 - 1.03)
Smoking status	Former	13§	1.31 (1.13 - 1.51)
	Never		1
Use of thrombolytics	Yes	9‡	1.90 (1.26 - 2.87)
	No		1
Use of ticlopidin	Yes	9‡	1.36 (1.11 - 1.65)
	No		1
Race	Non-caucasian	9‡	1.34 (1.10 - 1.61)
	Caucasian		1
ST depression (>0.5 mm)	Yes	8‡	1.20 (1.06 - 1.35)
	No		1
Heart rate	10 bpm	7†	1.06 (1.02 - 1.10)

Variables have been ranked according to their independent contribution to the bleeding model.

†, ‡, §, # correspond to p <0.01, <0.005, <0.001, <0.0001

OR = odds ratio, adjusted for all variables in the model, CI = Confidence interval

Table 3 **Independent predictors of procedure-related bleeding**

Variable	Category	procedure-related bleeding	
		χ^2	OR (95% CI)
Region	North America	111#	3.62 (2.85 - 4.61)
	Other		1
Eptifibatide therapy	High dose	30#	1.77 (1.44 - 2.18)
	Placebo		1
Gender	Female	19#	1.61 (1.30 - 1.99)
	Male		1
Maximal aPTT value	10 seconds	16#	1.04 (1.02 - 1.06)
Use of ticlopidin	Yes	10‡	1.44 (1.15 - 1.80)
	No		1
Smoking status	Former	9‡	1.40 (1.12 - 1.75)
	Never		1
Use of dipiridamol	Yes	4*	2.00 (1.05 – 3.84)
	No		1

Variables have been ranked according to their independent contribution to the bleeding model

*, †, ‡, §, # correspond to p <0.05, <0.01, <0.005, <0.001, <0.0001

OR = odds ratio, adjusted for all variables in the model, CI = Confidence interval

aPTT value during heparin infusion, smoking status, use of thrombolytics or ticlopidin during hospitalization, and non-caucasian ancestry. Adjustment for differences in baseline characteristics and concomitant pharmacological therapy did not eliminate North American origin as a risk factor in the multivariable model. There was no interaction between treatment with eptifibatide and the use of thrombolytics during hospitalization indicating that there was no incremental increase in the incidence of spontaneous bleeding for the combination of these two therapies.

In conformity with the results from the univariable analyses, North American origin was the most powerful independent predictor of procedure-related bleeding (Table 3). Other important risk factors were allocation to eptifibatide, female gender, the maximal aPTT value during heparin infusion, and treatment with ticlopidin. The same variables were also most significantly associated with procedure-related bleeding complications in the patient population undergoing percutaneous coronary intervention within the first 72 hours. In patients who had an intervention between day 3 and 30, treatment with eptifibatide and the maximal aPTT value were no longer independent risk factors.

The c-index corresponding with the spontaneous bleeding model and the procedure-related bleeding model were 0.739 and 0.715, respectively, reflecting good ability to discriminate between patients who had and did not have a bleeding event.

Spontaneous bleeding: relation with geographic region and procedures

The incidence of spontaneous bleeding was determined in specific patient subsets to explore the relationship to geographic region and coronary procedures (Table 4). Although the incidence gradually decreased when patients undergoing CABG, PCI and coronary angiography were successively excluded, spontaneous bleeding persisted to occur more frequently in North American patients than in patients enrolled in one of the other geographic regions (Western and Eastern Europe, Latin America). However, the increase in the incidence of spontaneous bleeding associated with eptifibatide therapy did not differ between the two groups (no statistically significant differences in Breslow-Day test for homogeneity of the odds ratios).

Prediction of bleeding

The predicted value for the probability of experiencing a spontaneous bleeding event in this patient population can be calculated by using the nomogram in Figure 3. The nomogram can be used to assess the patient's baseline risk of spontaneous bleeding and to determine to what extent this risk increases with antithrombotic therapy. The nomogram was created from a separate multivariable analysis

Table 4 Spontaneous bleeding in relation with region and coronary procedures by treatment

Patient subgroup	Region	Incidence of spontaneous bleeding (%) Placebo	Eptifibatide	Odds ratio (95% CI)	Breslow-Day
All patients (n=9461)	NA (n=3827)	8.9	27.5	3.9 (3.2-4.7)	p=0.33
	Other (n=5634)	6.0	22.0	4.4 (3.7-5.3)	
Pts without CABG (n=7998)	NA (n=3042)	8.0	27.1	4.3 (3.5-5.3)	p=0.60
	Other (n=4956)	5.8	22.3	4.7 (3.8-5.6)	
Pts without CABG, PCI (n=5637)	NA (n=1758)	6.1	26.6	5.6 (4.1-7.7)	p=0.55
	Other (n=3879)	5.6	22.8	5.0 (4.0-6.3)	
Pts without CABG,PCI,CAG (n=3364)	NA (n=695)	5.4	31.1	7.9 (4.7-13.2)	p=0.25
	Other (n=2669)	5.4	24.2	5.6 (4.3-7.4)	

CABG = coronary artery bypass grafting, CAG = coronary angiography, CI = confidence interval, NA = North America, Other = one of the other three geographic regions (Western Europe, Eastern Europe, Latin America), PCI = percutaneous coronary intervention. Breslow-Day for homogeneity of odds ratios.

which excluded the region of enrollment to allow applicability beyond the context of the PURSUIT trial. The predictive accuracy of the model was only little affected by this step: the c-index decreased from 0.739 to 0.736. There was a close relationship between the actual bleeding rates observed in each risk category and the expected bleeding rates obtained from the nomogram, calculated by using the average score in each category (Figure 4).

Risk-benefit ratio

The risk of spontaneous bleeding (with and without eptifibatide) and the risk of the composite of death and MI were calculated for each patient using the scoring nomogram presented in Figure 3 and that for predicting the likelihood of death or MI based on an established risk model in the PURSUIT population (18) (Figure 5). No cut-off values could be identified separating subgroups of patients with either a low risk of adverse cardiac events and a high risk of bleeding or a low risk of bleeding and a high risk of cardiac events.

1. Find points for each baseline risk factor

Age		Pulse		Gender		Caucasian		Smoker		ST-depression	
years	Points	bpm	Points		Points		Points		Points		Points
40	0	60	0	Female	4	Yes	0	Former	3	Yes	1
50	4	80	1	Male	0	No	4	Current	-1	No	0
60	8	100	2					Never	0		
70	12	120	3								
80	16	140	4								
80+	20	160	5								
		160+	6								

2. Sum points for all baseline risk factors

_____ + _____ + _____ + _____ + _____ + _____ = _____

Age | Pulse | Gender | Caucasian | Smoker | ST-depression | Point Total of baseline risk

3. Look up baseline risk corresponding to point total

Points	Risk
0 - 11	<5 %
12 - 19	5 - 10 %
20 - 24	10 - 15 %
25 - 27	15 - 20 %
28 - 30	20 - 25 %
31 - 33	25 - 30 %
34+	>30 %

4. To determine to what extent the risk of bleeding increases with antithrombotic therapy, add points for:

Eptifibatide		Thrombolytic		Ticlopidin		Max aPTT	
	Points		Points		Points	seconds	Points
Yes	15	Yes	6	Yes	4	50	0
No	0	No	0	No	0	100	1
						150	2
						200	3
						250	4
						250+	5

5. Add points for treatment parameters to Point Total of baseline risk

_____ + _____ + _____ + _____ + _____ = _____

Point Total of baseline risk | Eptifibatide | Thrombolytic | Ticlopidin | Max aPTT | Overall Point Total

6. To determine total bleeding risk during treatment, look up risk corresponding to overall point total

Points	Risk
0 - 11	<5 %
12 - 19	5 - 10 %
20 - 24	10 - 15 %
25 - 27	15 - 20 %
28 - 30	20 - 25 %
31 - 33	25 - 30 %
34+	>30 %

Figure 3
Nomogram for estimating the risk of spontaneous bleeding at baseline (panels 1 through 3) and after pharmacologic therapy (panels 3 through 6). In panels 1 and 4, find the values most closely matching the patient's risk factors and circle the corresponding point assignment. In panels 2 and 5, sum the points for all predictive factors. In panels 3 and 6, determine the probability of spontaneous bleeding.

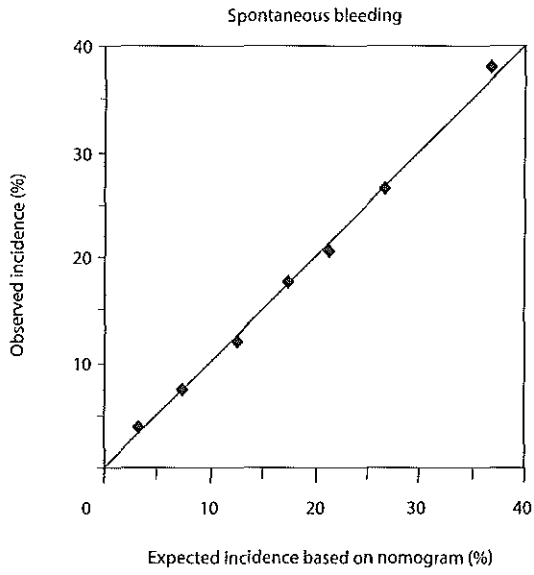


Figure 4
Validation plot of actual incidence versus predicted probability of spontaneous bleeding, respectively observed and expected in each risk category of the scoring nomogram (Figure 3).

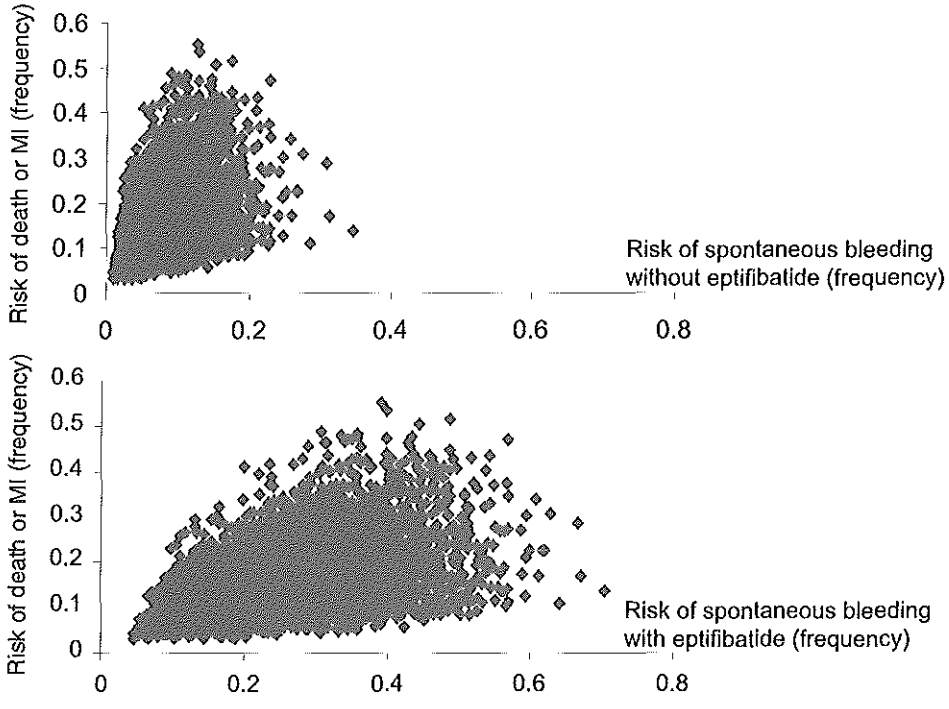


Figure 5
Distribution plot of risk of the composite of death or myocardial infarction (MI) versus risk of spontaneous bleeding without eptifibatide treatment (upper panel) and with eptifibatide treatment (lower panel).

Discussion

In this trial of almost 10,000 patients with non-ST-elevation acute coronary syndromes who were treated according to an array of management strategies, including allocation to GP IIb/IIIa inhibition with eptifibatide, bleeding was a common adverse event. The large sample size and the broad spectrum of management styles and treatment strategies allowed the baseline demographic and clinical risk factors to be determined for distinct categories of bleeding, including procedure-related as well as procedure-unrelated or spontaneous bleeding.

Spontaneous bleeding

Among the patient characteristics at baseline, age and female gender were the most important determinants of spontaneous bleeding in this patient population. This finding is consistent with the established risk factors for bleeding among patients with ST-elevation MI treated with thrombolytic therapy.[10-12] In contrast to the increased risk of bleeding in patients of lighter weight observed in studies of thrombolytic therapy for acute MI, weight was not a predictor of bleeding in the present patient population. This might be explained by the fact that bolus and infusion of both eptifibatide and heparin were administered on a weight-adjusted basis. An additional finding is the higher likelihood of bleeding in patients of non-caucasian ancestry which persisted even after multivariable adjustment. Previous studies of thrombolysis with alteplase for acute MI have found an increased bleeding risk in patients of African ancestry,[12,19] possibly related to an enhanced sensitivity to alteplase resulting in increased thrombolytic efficacy and more pronounced systemic fibrinogenolysis.[19]

As expected, however, most predictive information was captured in the pharmacological therapy administered during the initial hospitalization, including GP IIb/IIIa inhibition with eptifibatide, the use of thrombolytic agents or ticlopidin, as well as the intensity of anticoagulant treatment, measured by the aPTT. Accordingly, the occurrence of spontaneous bleeding coincided with the administration of these agents.

Recent trials have demonstrated an association between high aPTT and bleeding and intracranial hemorrhage in patients with acute coronary syndromes treated with heparin.[20-22] Lower doses of heparin might therefore reduce the risk of bleeding in patients treated with eptifibatide without reducing the clinical efficacy,[23] as supported by the experience in patients undergoing percutaneous revascularization and receiving a GP IIb/IIIa receptor blocker.[24,25] Other possibilities include the use of an automated heparin control system to improve aPTT control of intravenous heparin,[26] or the use of low-molecular-weight heparins which have a more predictable pharmacokinetic profile resulting in a more stable level of anticoagulation.

The finding of increased bleeding in patients enrolled in North America is intriguing. Although the definition of spontaneous bleeding in the present analysis aimed to exclude bleeding complications resulting from coronary procedures, the observation of an increased risk of spontaneous bleeding in North American patients compelled an exploration of the relation between bleeding, geographic region and coronary procedures (Table 4), the hypothesis being that procedure-unrelated bleeding could also have been increased by the enhanced peri-procedural level of anticoagulation. However, even in patients without any invasive procedure during the first 30 days, a higher incidence of spontaneous bleeding was observed in North America .

Procedure-related bleeding

Bleeding occurred at the femoral access site in almost one quarter of all patients undergoing coronary intervention. North American region was the most important predictor, with only two other baseline demographic variables (female gender and smoking status) independently related to this type of bleeding. All remaining multivariable predictors were related to the antithrombotic therapy such as the antiplatelet agents eptifibatide, ticlopidin and dipiridamol. In contrast to their association with procedure-related bleeding events during the first 72 hours, eptifibatide and the maximal aPTT value were no independent predictors of procedure-related bleeding in patients undergoing coronary intervention between day 3 and 30. With respect to eptifibatide, this finding is reassuring and consistent with its short half-life. While the results of the multivariable assessment during the 72-hour study drug infusion period confirm previous observations of a synergistic effect of GP IIb/IIIa receptor blockers and heparin dosing with respect to the occurrence of bleeding complications in patients undergoing PCI,[7,24] the present analysis was limited by the fact that no data on peri-procedural ACT values were collected in the Case Report Forms. This might explain why the intensity of heparin anticoagulation was not a predictor of procedure-related bleeding in patients undergoing coronary intervention at a later stage.

As the recommended heparin regimen in patients undergoing PCI aimed to achieve and maintain an ACT of at least 300 seconds, it is likely that the number of procedure-related bleeding complications can be reduced when eptifibatide is combined with low-dose heparin with a target ACT of 200 seconds.[8,24,27] In fact, the EPILOG and EPISTENT trials have recently shown that the clinical benefit of the GP IIb/IIIa inhibitor abciximab can be uncoupled from the risk of hemorrhage by using low-dose heparin regimens.[24,25] Another possibility to reduce the incidence of access site bleeding complications in patients with acute coronary syndromes undergoing coronary intervention might be to perform the procedure from the radial instead of femoral access site.[28]

Bleeding in CABG patients

Patients undergoing bypass surgery during hospitalization had an increased bleeding risk and accounted for approximately 80% of the patients with major bleeding complications. In these patients, approximately 80% of bleeding was related to the bypass surgery, both in patients assigned eptifibatide and those given placebo. No increase in bleeding incidence with eptifibatide therapy was observed in patients who underwent bypass surgery. This finding is reassuring, consistent with the short half-life of eptifibatide and parallels the observation in a previous study of abciximab.[29]

Prediction models for risk stratification

Patients who present with chest pain or other symptoms suggestive of an acute coronary syndrome and do not have persistent ST-segment elevation, encompass a heterogeneous group that varies considerably with respect to diagnosis as well as future risk for cardiac events. Early risk stratification in these patients is important to tailor pharmacological and invasive treatment to an individual need based on the expected prognosis as well as the benefit-risk ratio of the applied treatment strategy. The admission 12-lead ECG and troponin status have independently proven useful in stratifying patients according to their risk of future adverse cardiac events as well as to the expected benefit of enhanced antiplatelet therapy with GP IIb/IIIa inhibitors.[30-33]

Recently, a risk-model has been developed to determine the prognosis of patients with non-ST-elevation acute coronary syndromes on the basis of an evaluation of demographic and clinical characteristics at hospital admission.[16] In the present analysis, a simple scoring nomogram was developed which can be used by physicians to determine the probability of experiencing a spontaneous bleeding. In the present paper, these two models were integrated by calculating for each patient the risk of death or MI and the corresponding risk of experiencing a spontaneous bleeding, both with and without eptifibatide, by entering the baseline prognostic factors in the respective scoring nomograms. We aimed to identify subgroups of patients with either a low risk of adverse cardiac events accompanied by an increased risk of bleeding or vice versa. These two groups would then represent patients in whom the use of GP IIb/IIIa receptor blockers should be discouraged or rather recommended, respectively. Such patient subsets could, however, not be identified.

As most bleeding events were mild or clinically insignificant and did not require any intervention, and considering the trade-off in terms of reducing death and MI, the baseline assessment of the patient's risk of bleeding will therefore be of secondary importance to the estimation of the risk of adverse cardiac events in the decision whether or not to administer a GP IIb/IIIa receptor blocker.

Furthermore, it is likely that the risk of bleeding can be reduced by additional measures including low-dose heparin regimens,[24,25] meticulous care of vascular access sites.[24,25,27] and reduced-dose thrombolytic therapy in patients experiencing an MI while receiving a GP IIb/IIIa inhibitor.[34] Accordingly, the recommendation to use a GP IIb/IIIa inhibitor like eptifibatide in the management of acute coronary syndrome patients should be made on the basis of the expected prognosis and treatment benefit assessed by the baseline demographic and clinical factors, including 12-lead ECG and troponin status.

References

1 Lincoff AM, Califf RM, Anderson KM, et al. for the EPIC Investigators. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. *J Am Coll Cardiol* 1997;**30**:149-56.

2 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;**349**:1429-35.

3 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;**339**:436-43.

4 The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488-97.

5 The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498-505.

6 Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: Early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;**100**:2045-8.

7 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;**330**:956-61.

8 Aguirre FV, Topol EJ, Ferguson JJ, et al. Bleeding complications with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. *Circulation* 1995;**91**:2882-90.

9 Arnold AE, Simoons ML. Thrombolytic therapy for evolving myocardial infarction needs an approach that integrates benefit and risk. *Eur Heart J* 1995;**16**:1502-9.

10 Califf RM, Topol EJ, George BS, et al. Hemorrhagic complications associated with the use of intravenous tissue plasminogen activator in treatment of acute myocardial infarction. *Am J Med* 1988;**85**:353-9.

11 Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), *Phase II Trial. Ann Intern Me* 1991;**115**:256-65.

12 Berkowitz SD, Granger CB, Pieper KS, et al. for the GUSTO-I Investigators. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997;**95**:2508-16.

13 Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. *Am J Cardiol* 1997;**80**:Suppl 4A:34B-38B.

14 Ryan TJ, Anderson JL, Antman EM et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1996;**94**:2341-50.

15 The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**:673-82.

16 Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation* 1987;**76**:142-54.

17 Mahaffey KW, Harrington RA, Simoons ML, et al. for the PURSUIT Investigators. Stroke in patients with acute coronary syndromes. Incidence and outcomes in the PURSUIT trial. *Circulation* 1999;**99**:2371-7.

18 Boersma H, Pieper K, Steyerberg EW, et al. for the PURSUIT Investigators. Predictors of 30-day outcome in patients with acute coronary syndromes without persistent ST-segment elevation. *Circulation*. In press.

19 Sane DC, Califf RM, Topol EJ, Stump ED, Mark DB, Greenberg CS. Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989;**111**:1010-22.

20 Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;**93**:870-8.

20 Antman EM. Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. *Circulation* 1994;**90**:1624-30.

22 The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;**90**:1631-7.

23 Hochman JS, Wali AU, Gavrila D, et al. A new regimen for heparin use in acute coronary syndromes. *Am Heart J* 1999;**138**:313-8.

24 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689-96.

25 The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;**352**:87-92.

26 Cannon CP, Dingemanse J, Kleinbloesem CH, Jannett T, Curry KM, Valcke CP. Automated heparin-delivery system to control activated partial thromboplastin time: evaluation in normal volunteers. *Circulation* 1999;**99**:751-6.

27 Juran NB. Minimizing bleeding complications of percutaneous coronary intervention and glycoprotein IIb/IIIa antiplatelet therapy. *Am Heart J* 1999;**138**:297-306.

28 Mann T, Cubeddu G, Bowen J, et al. Stenting in acute coronary syndromes: a comparison of radial versus femoral access sites. *J Am Coll Cardiol* 1998;**32**:572-6.

29 Boehrer JD, Kereiakes DJ, Navetta FI, Califf RM, Topol EJ. Effects of profound platelet inhibition with c7E3 before coronary angioplasty on complications of coronary bypass surgery: EPIC Investigators. *Am J Cardiol* 1994;**74**:1166-70.

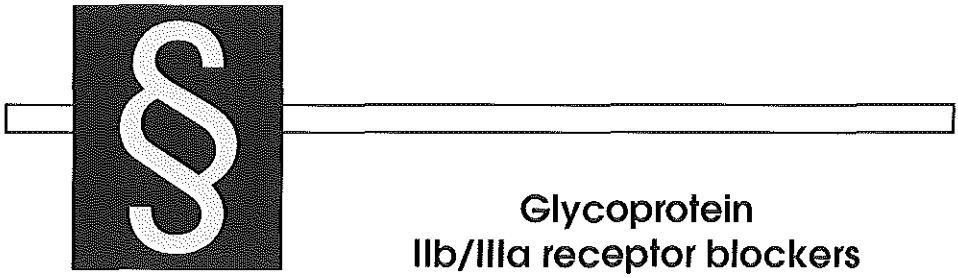
30 Cannon CP, McCabe CH, Stone PH et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q-wave myocardial infarction: results of the TIMI-III Registry ECG Ancillary Study. *J Am Coll Cardiol* 1997;**30**:133-40.

31 Ravkilde J, Nissen H, Horder M, Thygesen K. Independent prognostic value of serum creatine kinase isoenzyme-MB mass, cardiac troponin-T and myosin light-chain levels in suspected acute myocardial infarction. *J Am Coll Cardiol* 1995;**25**:574-81.

32 Hamm CW, Heeschen C, Goldmann B, et al. for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin-T levels. *N Engl J Med* 1999;**340**:1623-9.

33 Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD, for the PRISM Study Investigators. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;**354**:1757-62.

34 Antman EM, Giugliano RP, Gibson CM, et al, for the TIMI 14 Investigators. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. *Circulation* 1999;**99**:2720-32.



Glycoprotein IIb/IIIa receptor blockers and coronary intervention

7

Platelet Glycoprotein IIb/IIIa Receptor Inhibition in Non-ST-elevation Acute Coronary Syndromes Early Benefit During Medical Treatment Only, With Additional Protection During Percutaneous Coronary Intervention

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Abstract

Background

Glycoprotein (GP) IIb/IIIa receptor blockers prevent life-threatening cardiac complications in patients with acute coronary syndromes without ST-segment elevation and protect against thrombotic complications associated with percutaneous coronary interventions (PCIs). The question arises as to whether these 2 beneficial effects are independent and additive.

Methods and Results

We analyzed data from the CAPTURE, PURSUIT, and PRISM-PLUS randomized trials, which studied the effects of the GP IIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban, respectively, in acute coronary syndrome patients without persistent ST-segment elevation, with a period of study drug infusion before a possible PCI. During the period of pharmacological treatment, each trial demonstrated a significant reduction in the rate of death or nonfatal myocardial infarction in patients randomized to the GP IIb/IIIa inhibitor compared with placebo. The 3 trials combined showed a 2.5% event rate in this period in the GP IIb/IIIa inhibitor group (N = 6125) versus 3.8% in placebo (N = 6171), which implies a 34% relative reduction ($P < 0.001$). During study medication, a PCI was performed in 1358 patients assigned GP IIb/IIIa inhibition and 1396 placebo patients. The event rate during the first 48 hours after PCI was also significantly lower in the GP IIb/IIIa inhibitor group (4.9% vs. 8.0%; 41% reduction; $P < 0.001$). No further benefit or rebound effect was observed beyond 48 hours after the PCI.

Conclusions

There is conclusive evidence of an early benefit of GP IIb/IIIa inhibitors during medical treatment in patients with acute coronary syndromes without persistent ST-segment elevation. In addition, in patients subsequently undergoing PCI, GP IIb/IIIa inhibition protects against myocardial damage associated with the intervention.

Coronary thrombosis is a pivotal event in the pathogenesis of acute coronary syndromes and ischemic complications resulting from coronary interventions.[1] Activation of the platelet glycoprotein (GP) IIb/IIIa receptor is the final common pathway in the process leading to platelet aggregation, coronary thrombus formation, and myocardial ischemia. Accordingly, inhibitors of the platelet GP IIb/IIIa receptor are potent agents to prevent progression to myocardial infarction (MI) and death.[2] Indeed, in recent randomized clinical trials, GP IIb/IIIa inhibitors effectively reduced life-threatening complications in patients with acute coronary syndromes without ST-segment elevation.[3,4] Furthermore, these agents protect against life-threatening thrombotic complications associated with percutaneous coronary intervention (PCI).[5] The question arises as to whether these 2 beneficial effects are independent and additive. To date, 3 clinical trials can contribute to answering this question (Table 1).[3,4,6]

CAPTURE studied the effects of abciximab in patients with unstable angina refractory to conventional medical therapy.[6] A reduction was observed in the rate of death or nonfatal MI during the 24-hour period of pharmacological treatment preceding PCI among patients randomized to abciximab versus placebo (Kaplan-Meier estimates 1.3% versus 2.8%; log-rank $P=0.032$; Figure). The event rate during the first 48 hours after PCI was significantly lower in abciximab patients (2.8% versus 5.8% in placebo; $P=0.009$). In the period starting 48 hours after PCI, only a few events occurred, with similar rates in both groups.

Observations in PURSUIT confirmed these findings.[3] Acute coronary syndrome patients randomized to eptifibatide had a 3.2% event rate after the scheduled 72 hours of study drug infusion, versus 4.4% in placebo ($P=0.003$). There were also fewer procedure-related events in eptifibatide patients undergoing a PCI during this period (7.6% versus 10.3% in placebo; $P=0.105$). In the subsequent postprocedural period (all patients were off study medication), event rates were low and similar in both groups.

PRISM-PLUS also confirmed the beneficial effects of GP IIb/IIIa inhibition before and during PCI.[4] Patients assigned tirofiban had fewer events during initial medical management (1.8% versus 3.8% in placebo; $P=0.016$) as well as fewer PCI-related events (2.9% versus 8.0%; $P=0.062$).

There was no evidence of a differential effect of the GP IIb/IIIa blockers between the trials, in any of the 3 stages, because all tests for homogeneity of treatment effect were nonsignificant. Therefore, the separate trial data could be combined (Figure and Table 2). The 3 trials together demonstrated a 34% reduction in the composite of death or nonfatal MI during pharmacological therapy preceding PCI (if any) by GP IIb/IIIa inhibition [2.5% versus 3.8% in placebo; odds ratio (95% CI) 0.66 (0.54 to 0.81)] and an additional 41% reduction in PCI-related events [4.9% versus 8.0%; odds ratio 0.59 (0.44 to 0.81)]. Mortality was low but was still affected

Table 1 *Characteristics and Management of Patients Enrolled in CAPTURE, PURSUIT, and PRISM-PLUS*

	CAPTURE (n = 1265)	PURSUIT (n = 9461)	PRISM-PLUS (n = 1570)
Enrollment criteria	Recurrent ischemia under medical treatment including heparin and nitrates	Ischemic chest pain within previous 24 h, with ECG or enzymatic evidence of myocardial ischemia; no persistent ST-segment elevation	Ischemic chest pain within previous 12 h, with ECG or enzymatic evidence of myocardial ischemia; no persistent ST-segment elevation
Mean (SD) age, y	61 (10)	63 (11)	63 (12)
Male, %	73	65	68
Prior MI, %	40	33	42
Prior CABG, %	3	12	14
Prior PTCA, %	13	13	9
Study medication	Abciximab (0.25 mg/kg bolus plus 10 mg/min infusion) vs placebo	Eptifibatide (180 μg/kg bolus plus2.0 μg • kg-1 • min-1 infusion) vs placebo	Tirofiban (0.4 μg/kg infusion for 30 min followed by 0.1 μg • kg-1 • min-1 infusion) vs placebo
Duration of study drug infusion	1h after percutaneous intervention, which was scheduled at 18-24 h after randomization	72 h after randomization. In case of a PCI, for an additional 24 h	48-96 h post randomization. In case of a PCI, for an additional 12-24 h
Cardiac comedication	Aspirin, heparin, nitrates	Aspirin, heparin	Aspirin, heparin
Further management	Percutaneous intervention at 18-24 h after randomization	At discretion of treating physician	Coronary angiography at 48-96 h after randomization; coronary intervention at discretion of treatingphysician

Table 2. *Mortality and Composite of Death or Nonfatal MI*

	Placebo			GP IIb/IIIa Inhibitor				
	n	Death, %	Death or Nonfatal MI, %	n	Death, %	Death or Nonfatal MI, %	Odds ratio (95% CI)	Breslow-Day
Period: Randomization to randomization + 24 h or until PCI or surgical coronary intervention (if any)								
Patients: All randomized								
CAPTURE	635	1 (0.2)	16 (2.5)	630	0	6 (1.0)	0.37 (0.15-0.96)	
PURSUIT	4739	13 (0.3)	75 (1.6)	4722	6 (0.1)	50 (1.1)	0.67 (0.46-0.95)	0.502
PRISM-PLUS	797	1 (0.1)	7 (0.9)	773	1 (0.1)	5 (0.6)	0.74 (0.23-2.33)	
All	6171	15 (0.2)	98 (1.6)	6125	7 (0.1)	61 (1.0)	0.62 (0.45-0.86)	
Period: Randomization to end of study drug infusion or until PCI or surgical coronary intervention (if any)								
Patients: All randomized								
CAPTURE	635	1 (0.2)	16 (2.5)	630	0	6 (1.0)	0.37 (0.15-0.96)	
PURSUIT	4739	40 (0.8)	190 (4.0)	4722	21 (0.4)	137 (2.9)	0.72 (0.57-0.90)	0.201
PRISM-PLUS	797	5 (0.6)	29 (3.6)	773	2 (0.3)	13 (1.7)	0.45 (0.23-0.88)	
All	6171	46 (0.7)	235 (3.8)	6125	23 (0.4)	156 (2.5)	0.66 (0.54-0.81)	
Period: PCI to PCI + 48 h								
Patients: Undergoing PCI during the scheduled study drug infusion period								
CAPTURE	623	3 (0.5)	36 (5.8)	616	2 (0.3)	17 (2.8)	0.46 (0.26-0.83)	
PURSUIT	622	7 (1.1)	64 (10.3)	606	4 (0.7)	46 (7.6)	0.72 (0.48-1.07)	0.307
PRISM-PLUS	151	1 (0.7)	12 (7.9)	136	1 (0.7)	4 (2.9)	0.35 (0.11-1.12)	
All	1396	11 (0.8)	112 (8.0)	1358	7 (0.5)	67 (4.9)	0.59 (0.44-0.81)	
Period: PCI + 48 h to PCI + 25 days								
Patients: Undergoing PCI during study drug infusion and surviving the first 48 h after PCI								
CAPTURE	620	3 (0.5)	7 (1.1)	614	2 (0.3)	4 (0.7)	0.57 (0.17-1.97)	
PURSUIT	615	4 (0.7)	10 (1.6)	602	9 (1.5)	14 (2.3)	1.44 (0.64-3.27)	0.199
PRISM-PLUS	150	1 (0.7)	1 (0.7)	135	0	4 (3.0)	4.55 (0.50-41.2)	
All	1385	8 (0.6)	18 (1.3)	1351	11 (0.8)	22 (1.6)	1.26 (0.67-2.36)	

Breslow-Day indicates Breslow-Day test for homogeneity of odds ratios (P).

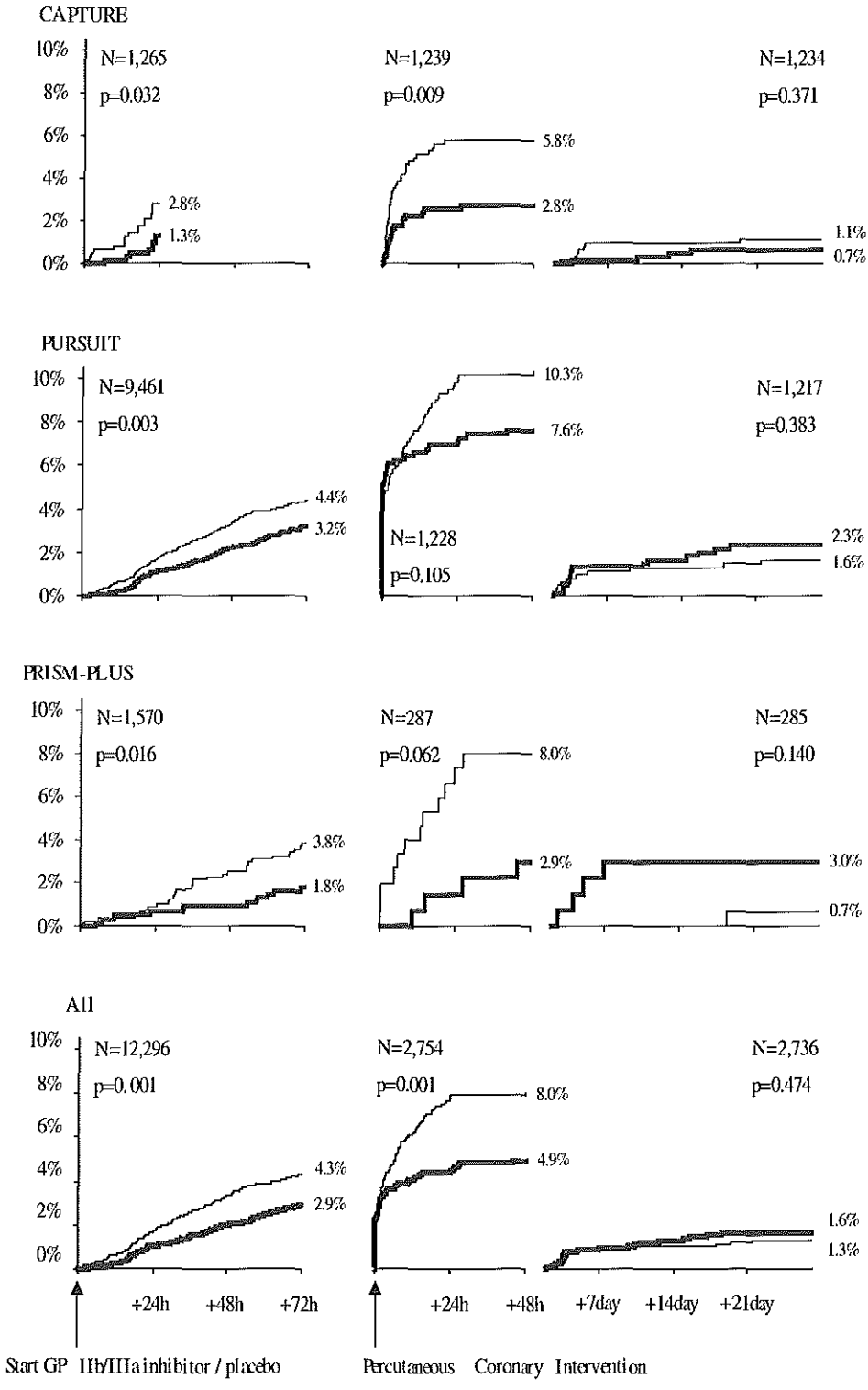
CAPTURE
10%
8%
6%
4%
2%
0%
N=1,265
p=0.032
2.8%
1.3%
N=1,239
p=0.009
5.8%
2.8%
N=1,234
p=0.371
1.1%
0.7%
PURSUIT
N=9,461
p=0.003
4.4%
3.2%
10.3%
7.6%
N=1,228
p=0.105
N=1,217
p=0.383
2.3%
1.6%
PRISM-PLUS
N=1,570
p=0.016
3.8%
1.8%
N=287
p=0.062
8.0%
2.9%
N=285
p=0.140
3.0%
0.7%
All
N=12,296
p=0.001
4.3%
2.9%
N=2,754
p=0.001
8.0%
4.9%
N=2,736
p=0.474
1.6%
1.3%
+24h
+48h
+72h
+24h
+48h
+7day
+14day
+21day
Start GP IIb/IIIa inhibitor / placebo
Percutaneous Coronary Intervention

Figure legend

Kaplan-Meier curves showing cumulative incidence of death or nonfatal myocardial (re)infarction in patients randomly assigned to glycoprotein IIb/IIIa inhibition (bold lines) or placebo.

Data were derived from CAPTURE, PURSUIT, and PRISM-PLUS. Left, Event rates during initial period of pharmacological treatment until moment of a PCI or coronary bypass grafting, if any. Middle, Event rates among PCI patients during 48-hour period after procedure. During and shortly after PCI, all patients were on study medication. Right, Event rates in period starting 48 hours after PCI, during which all patients were off study medication. At beginning of each period, event rates were (re)set at 0%. Any patient still alive contributes to event estimates in each period. In PURSUIT, procedure-unrelated MI was defined as any elevation of creatine kinase (CK)-MB above upper limit of normal (ULN). For consistency with CAPTURE and PRISM-PLUS, in present analyses only CK or CK-MB elevations >2xULN were considered to be infarctions during medical therapy. In all 3 trials, procedure-related infarcts were defined by an elevation of CK or CK-MB >3xULN.

by GP IIb/IIIa inhibition. The incidence of death during medical therapy was 0.4% among patients randomized to GP IIb/IIIa inhibition compared with 0.7% among placebo patients [odds ratio 0.50 (0.30 to 0.83)]. The procedure-related death rates were 0.5% and 0.8%, respectively [odds ratio 0.65 (0.25 to 1.69)].

Intracoronary stents were used in 10.5% of the CAPTURE patients. In PURSUIT and PRISM-PLUS, stenting was done in 50.2% and 20.3% of patients undergoing PCI during study drug infusion, respectively. Irrespective of treatment assignment, the overall procedure-related event rates were higher in stented patients (9.3% versus 5.3% in balloon angioplasty; χ^2 $P < 0.001$). However, the beneficial effect of GP IIb/IIIa inhibition was similar in stented and balloon-only patients, with odds ratios (95% CI) of 0.61 (0.38 to 0.99) and 0.58 (0.38 to 0.88), respectively (homogeneity test: $P = 0.863$). Late event rates were similar in patients with and without stents (1.6% versus 1.4%) and were not influenced by the initial GP IIb/IIIa treatment.

In contrast to CAPTURE, in which all patients were to undergo PCI, in PURSUIT and PRISM-PLUS the decision to perform an intervention was at the discretion of the treating physician. Patients undergoing a PCI in these latter trials were possibly at higher-than-average risk. Indeed, compared with CAPTURE, procedure-related event rates in the placebo arms were higher than expected on the basis of the preprocedural event rates. These higher event rates, however, did not affect the benefit of GP IIb/IIIa blockade, because there was no evidence of a differential effect between the 3 trials. Still, the observed reduction in procedure-related events by GP IIb/IIIa treatment in PURSUIT and PRISM-PLUS might

have been biased because of indistinct selection criteria. However, the incidence of PCI in both treatment arms of these trials was well balanced, as were the baseline characteristics of the patients concerned.[3,4]

The definition of non-PCI-related MI varied among the trials. In particular, the criteria applied in PURSUIT were more sensitive, resulting in a relatively high event rate.[3] In the present analysis, similar infarct definitions were applied to all 3 trials (see Figure caption). Supplementary analyses (not presented) demonstrated that the early beneficial effects were consistent for different definitions of MI.

In contrast to CAPTURE, the PURSUIT and PRISM-PLUS studies showed a slightly higher event rate among patients randomized to GP IIb/IIIa inhibition in the period starting 48 hours after PCI. This might be a result of differences in pharmacodynamics between the agents and between the degree, duration, and specificity of the GP IIb/IIIa inhibition, although there is no statistical evidence of a differential late treatment effect between the trials (and thus between the agents). Additional investigations are needed to clarify this issue.

In all 3 trials, bleeding complications were more common in patients treated with GP IIb/IIIa inhibitors than with placebo.[3,4,6] In most cases, however, bleeding was mild and occurred at the arterial puncture site. The EPILOG trial has shown that the benefit of GP IIb/IIIa inhibition can be uncoupled from the risk of hemorrhage in PCI patients by low-dose, weight-adjusted heparin, adherence to stricter anticoagulation guidelines, and careful vascular access-site management.[7]

We conclude that enhanced platelet inhibition with a GP IIb/IIIa blocker in addition to aspirin and heparin, starting immediately after admission, is beneficial to patients with acute coronary syndromes without persistent ST-segment elevation. In addition, in those undergoing PCI, intensive platelet inhibition protects against myocardial damage associated with the intervention. Thus, to fully explore their beneficial effects, GP IIb/IIIa inhibitors should be initiated early after hospital admission and continued until after the procedure in patients undergoing PCI.

References

1 Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med.* 1992;**326**:242-250,310-318.

2 Coller BS. Blockade of platelet GP IIb/IIIa receptors as an antithrombotic strategy. *Circulation.* 1995;**92**:2373-2380.

3 The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;**339**:436-443.

4 PRISM-PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. *N Engl J Med.* 1998;**338**:1488-1497.

5 Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, Tcheng JE,Lincoff AM, Hasselblad V, Topol EJ. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation.* 1998;**98**:2829- 35.

6 The CAPTURE Investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet.* 1997;**349**:1429-1435.

7 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *New Engl J Med.* 1997;**336**:1689-1696.

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Minor Myocardial Damage and Prognosis: Are Spontaneous and Percutaneous Coronary Intervention-Related Events Different?

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Abstract

Background

The relevance of the adverse prognostic implications of CK-MB elevation following percutaneous coronary intervention (PCI) remains a controversial issue. Therefore, we compared the relationship between the level of post-procedural CK-MB elevation and the risk of death after 6-month follow-up with the relationship between the level of CK-MB elevation and mortality in patients with acute coronary syndromes without persistent ST-elevation treated medically.

Methods and Results

In the PURSUIT trial, 5583 of 9461 patients who presented with a non-ST-elevation acute coronary syndrome did not undergo PCI or coronary artery bypass grafting and had at least 1 CK-MB sample collected during index-hospitalization. In these patients, there was a gradual increase in 6-month mortality with higher CK-MB levels: 4.1%, 8.6%, 9.0%, 14.3%, 15.5% for CK-MB ratios 0-1, >1-3, >3-5, >5-10, and >10 times the upper limit of normal, respectively.

The prognostic significance of cardiac enzyme elevation after PCI was assessed in a combined analysis using data from the CAPTURE, EPIC, EPILOG, IMPACT-II and PURSUIT trials. In all studies, the peak CK-MB value within 48 hours after PCI was considered to represent procedure-related myocardial damage. This combined analysis in 8838 patients revealed a direct, proportional relationship between post-procedural CK-MB levels and 6-month mortality. In patients with CK-MB ratios 0-1, >1-3, >3-5, >5-10 and >10, the risk of death was 1.3%, 2.0%, 2.3%, 4.3% and 7.4%, respectively. The 6-month mortality rates were lower after procedure-related compared with spontaneous infarcts. Yet, the relative increase in 6-month mortality with each increase in the category of peak CK-MB level was of the same magnitude for cardiac enzyme elevations after PCI and those occurring spontaneously in the setting of acute coronary syndromes.

Conclusions

The strong dose-response relationship between the magnitude of post-procedural CK-MB elevation and 6-month mortality, as well as the consistency of this finding among the different studies strongly indicate that peri-procedural myocardial damage is an important marker of subsequent adverse outcome.

Creatine kinase (CK) or CK-MB isoenzyme elevations occur in 5% to 30% of patients undergoing percutaneous coronary intervention (PCI).[1-4] Recent studies have shown a direct, proportional relationship between the level of post-procedural CK-MB elevation and the risk of an adverse clinical outcome during long-term follow-up including death, myocardial infarction (MI) and need for repeat revascularization procedures.[2-5] Post-procedural rises in cardiac enzymes appeared to be an independent predictor of adverse outcome, even in patients with an otherwise apparently uncomplicated and successful coronary intervention and after adjustment for other prognostic factors.[2-5]

Nevertheless, the relevance of these asymptomatic procedure-related rises in cardiac enzymes remains a controversial issue in interventional cardiology. In contrast, the prognostic significance of small MIs occurring spontaneously in the setting of unstable angina or after acute MI has been well established.[6-8]

We investigated whether the adverse prognostic implications of CK-MB elevation following PCI are similar to those of spontaneous, non-procedure-related MI. Accordingly, we compared the relationship between the level of post-procedural CK-MB elevation and the risk of death after 6-month follow-up with the relationship between the level of CK-MB elevation and mortality in patients with acute coronary syndromes treated medically.

Prognostic significance of CK-MB elevation in acute coronary syndromes

The relationship between peak CK-MB level and outcome in patients with acute coronary syndromes was investigated in a retrospective analysis of data from the large PURSUIT trial.[6] PURSUIT compared the glycoprotein IIb/IIIa inhibitor eptifibatide with placebo in addition to standard therapy in 9461 patients with unstable angina or evolving MI without persistent ST-segment elevation.[6]

Mortality at 6 months was assessed in five groups of patients categorized by peak CK-MB level (0-1, >1-3, >3-5, >5-10, or >10 times the upper limit of normal) at the index-hospitalization in the 5583 PURSUIT patients who did not undergo PCI or coronary artery bypass grafting and had at least 1 CK-MB sample collected. Mortality at 6 months was 4.1% in patients with normal peak CK-MB levels, and increased to 8.6% at peak CK-MB levels 1 to 3 times normal, 9.0% at peak CK-MB levels 3 to 5 times normal, 14.3% at peak CK-MB levels 5 to 10 times normal, and 15.5% at peak CK-MB levels greater than 10 times normal (Table). The relation between peak CK-MB level and 6-month mortality remained highly statistically significant (Wald χ^2 74.46; $P < 0.001$) after adjustment for other baseline predictors.[6]

Prognostic significance of CK-MB elevation following PCI

The prognostic significance of cardiac enzyme elevation after PCI was assessed in retrospective analyses using data from the IMPACT-II and PURSUIT

Table. Mortality at 6-month follow-up by category of peak CK-MB level

	CK-MB 0-1 x ULN			CK-MB >1-3 x ULN				
	n	Death	(%)	n	Death	(%)	Odds Ratio (95% CI)	Breslow-Day
Spontaneous	2658	109	(4.1)	1567	135	(8.6)	2.21 (1.70-2.86)	
Post-PCI (Combined)	6548	85	(1.3)	1376	27	(2.0)	1.52 (0.98-2.36)	0.152
Post-PCI (C-E-E)	4034	44	(1.1)	662	14	(2.1)	1.96 (1.07-3.60)	0.726
Post-PCI (IMPACT-II)	1779	27	(1.5)	323	4	(1.2)	0.81 (0.28-2.34)	0.064
Post-PCI (PURSUIT)	735	14	(1.9)	391	9	(2.3)	1.21 (0.52-2.83)	0.182
				CK-MB >3-5 x ULN				
				n	Death	(%)	Odds Ratio (95% CI)	Breslow-Day
Spontaneous				498	45	(9.0)	2.32 (1.62-3.33)	
Post-PCI (Combined)				303	7	(2.3)	1.80 (0.83-3.92)	0.558
Post-PCI (C-E-E)				114	2	(1.8)	1.62 (0.39-6.76)	0.630
Post-PCI (IMPACT-II)				84	2	(2.4)	1.58 (0.37-6.77)	0.614
Post-PCI (PURSUIT)				105	3	(2.9)	1.52 (0.43-5.36)	0.521
				CK-MB >5-10 x ULN				
				n	Death	(%)	Odds Ratio (95% CI)	Breslow-Day
Spontaneous				461	66	(14.3)	3.91 (2.83-5.40)	
Post-PCI (Combined)				301	13	(4.3)	3.43 (1.90-6.23)	0.707
Post-PCI (C-E-E)				110	4	(3.6)	3.42 (1.21-9.70)	0.811
Post-PCI (IMPACT-II)				86	5	(5.8)	4.01 (1.50-10.7)	0.962
Post-PCI (PURSUIT)				105	4	(3.8)	2.04 (0.66-6.32)	0.273
				CK-MB >10 x ULN				
				n	Death	(%)	Odds Ratio (95% CI)	Breslow-Day
Spontaneous				399	62	(15.5)	4.30 (3.09-6.00)	
Post-PCI (Combined)				310	23	(7.4)	6.09 (3.79-9.80)	0.234
Post-PCI (C-E-E)				105	7	(6.7)	6.48 (2.85-14.7)	0.360
Post-PCI (IMPACT-II)				69	6	(8.7)	6.18 (2.46-15.5)	0.464
Post-PCI (PURSUIT)				136	10	(7.4)	4.09 (1.78-9.40)	0.911

Odds ratio for risk of death at 6 months relative to risk in category without CK-MB elevation (CK-MB ratio 0-1). 95% CI denotes 95% confidence interval. Breslow-Day indicates Breslow-Day test for heterogeneity of odds ratios of post-PCI cardiac enzyme elevation versus odds ratio of spontaneous enzyme elevation within each enzyme category (*P*). C-E-E = combined data from CAPTURE, EPIC and EPILOG studies; CK-MB = creatine kinase-MB; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

trials, as well as from a combined analysis of the CAPTURE, EPIC and EPILOG trials.[3,4] These studies were conducted between November 1991 and January 1997. The protocols and results of the studies have been published previously.[3,4,6] In brief, CAPTURE, EPIC and EPILOG were large, double-blind, placebo-controlled, randomized trials evaluating the efficacy of the glycoprotein IIb/IIIa inhibitor abciximab in reducing ischemic complications in patients undergoing PCI for a variety of indications.[4] The IMPACT-II trial evaluated the efficacy of eptifibatide in patients scheduled for elective, urgent, or emergency PCI.[3] A similar analysis was done in the subgroup of PURSUIT patients who underwent PCI in the first 30 days following enrollment and had at least 1 CK-MB sample collected in the first 48 hours following the intervention. In all studies, the peak CK-MB value within 48 hours after PCI was considered to represent procedure-related myocardial damage.

The combined analysis in 5025 patients enrolled in CAPTURE, EPIC and EPILOG demonstrated a gradual increase in 6-month mortality with higher post-procedural CK-MB levels: 1.1%, 2.1%, 1.8%, 3.6%, 6.7% for CK-MB ratios (relative to the upper limit of normal) 0-1, >1-3, >3-5, >5-10 and >10, respectively (Table).[4] The CK-MB ratio remained an independent predictor of outcome after multivariable adjustment for clinical as well as angiographic characteristics.[4]

Similar analyses of data from the IMPACT-II trial and in the subgroup of PURSUIT patients undergoing PCI within 30 days confirmed this observation. In IMPACT-II, the risk of mortality at 6-month follow-up increased from 1.5% in patients without post-procedural CK-MB elevation to 8.7% in patients with a peak CK-MB level exceeding 10 times the upper limit of normal (Table).[3] In PURSUIT patients undergoing PCI, these figures were 1.9% and 7.4%, respectively (Table).

In order to provide an accurate assessment of the 6-month mortality rate in each category of post-procedural peak CK-MB level, the data from all PCI trials were combined. This combined analysis in 8838 patients undergoing PCI for a variety of indications revealed a direct, proportional relationship between post-procedural CK-MB levels and 6-month mortality. In patients with CK-MB ratios 0-1, >1-3, >3-5, >5-10 and >10, the risk of death was 1.3%, 2.0%, 2.3%, 4.3% and 7.4%, respectively.

In each category of peak CK-MB level, mortality at 6-month follow-up was substantially lower in patients after PCI compared with patients presenting with an acute coronary syndrome and treated medically. Acute coronary syndrome patients had a worse cardiovascular baseline risk profile including older age (median 65 years versus 61 years in the PCI patient population; $P < 0.001$), higher heart rate (72 versus 69 years; $P < 0.001$) and a higher percentage of women (40.0% versus 27.5%; $P < 0.001$). In contrast, patients undergoing PCI had a higher

frequency of previous MI (33.5% versus 43.3%; $P < 0.001$). However, the relative increase in 6-month mortality with each increase in the category of peak CK-MB level (as represented by the odds ratios) was of the same magnitude for cardiac enzyme elevations after PCI and those occurring spontaneously in the setting of acute coronary syndromes (Figure), as all tests for heterogeneity of the odds ratios were non-significant (Table).

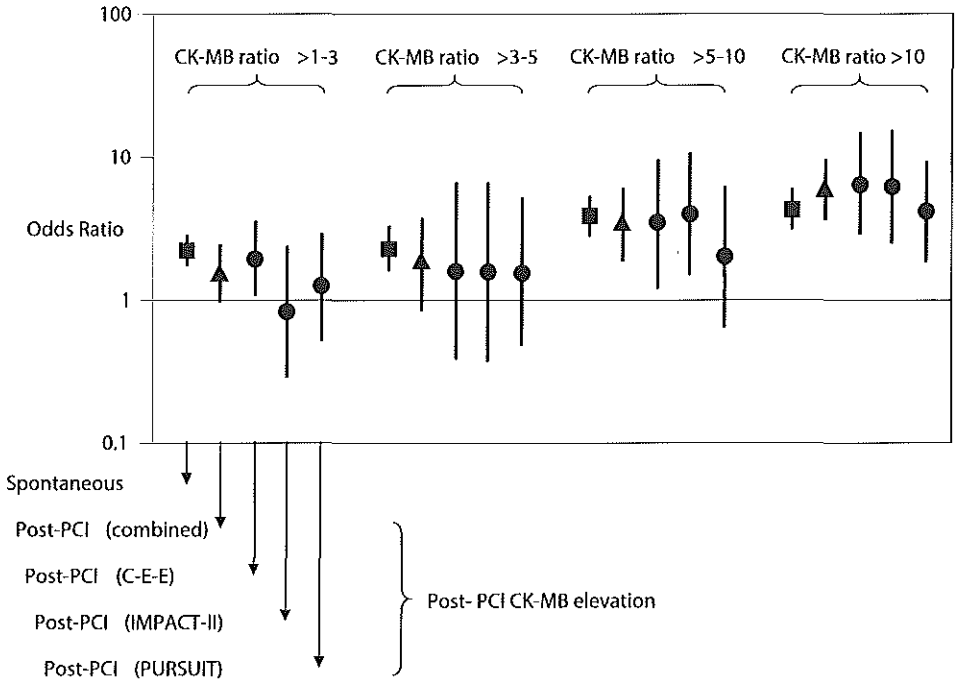


Figure
Odds ratios for mortality at 6-month follow-up presented for four categories of peak CK-MB level for cardiac enzyme elevations following PCI and those occurring spontaneously in patients with acute coronary syndromes treated medically. Odds ratios for risk of death at 6 months relative to risk in category without CK-MB elevation (CK-MB ratio 0-1). Peak CK-MB level shown as ratio relative to upper limit of normal. Vertical lines indicate 95% confidence intervals.
C-E-E = combined data from CAPTURE, EPIC and EPILOG trials; CK-MB = creatine kinase-MB; PCI = percutaneous coronary intervention.

Discussion

This combined analysis in 8838 patients undergoing PCI for a variety of indications clearly demonstrates that the risk of death at 6-month follow-up is directly proportional to the extent of post-procedural CK-MB elevation. Furthermore, although the absolute mortality rates differed, the relative risk for adverse outcome at 6 months after peri-procedural myocardial damage was similar to that observed for MI occurring spontaneously in the setting of acute coronary syndromes. The increased absolute risk of 6-month mortality might be explained by the fact that patients who presented with an acute coronary syndrome represented a population at increased risk of adverse thrombotic complications, while more elective and low-risk patients were included in some of the PCI trials. This was also apparent in the differences in baseline variables known to be important predictors of mortality.

As MI is defined as myocardial cell death which results in the release of specific biomarkers into the circulation, the present findings imply that any abnormal elevation of cardiac markers, whether associated with PCI and regardless of magnitude, should be interpreted as an MI.

Most procedure-related infarcts are small and result from microemboli from the atherosclerotic plaque that has been disrupted during angioplasty, or from thrombus particles.[2] As these small infarcts do not impair myocardial function, pathophysiological mechanisms other than heart failure may explain the impaired long-term prognosis associated with post-procedural cardiac enzyme elevation. It is conceivable that microinfarcts provide a nidus for ventricular arrythmias via a microreentry or a focal mechanism.[1,2,4,5] Indeed, previous studies have demonstrated the association between small procedure-related infarcts and subsequent sudden death.[1,4]

Furthermore, myocardial damage occurring during the procedure may be an expression of vascular instability. Although myocardial cell injury during angioplasty may be a one-time event compared with the often repetitive nature of spontaneously occurring episodes of myocardial ischemia and necrosis, it is likely that patients who develop coronary emboli and small infarcts have atherosclerotic lesions which are apparently unstable and continue to represent a substrate for plaque rupture with subsequent thrombosis resulting in adverse events such as MI, sudden death or death during revascularization procedures.

Post-procedural enzyme elevations, or rather peri-procedural MI, should be interpreted with consideration of lesion morphology and the clinical setting. The present analysis solidly supports the need for systematic assessment of cardiac markers after all PCIs. Measures for secondary prevention, including aspirin, statins, beta-blockers, and ACE inhibitors, should be recommended for patients with post-procedural elevation of cardiac enzymes, similar to the guidelines

for management of other infarcts. Furthermore, patients with peri-procedural myocardial damage should be instructed to seek immediate medical help whenever symptoms reoccur after hospital discharge. Perhaps more important, therapeutic strategies that reduce the incidence and severity of peri-procedural MI are likely to improve the long-term outcome of patients undergoing PCI. Antiplatelet agents, particularly the glycoprotein IIb/IIIa receptor blockers have been shown to reduce the incidence of recurrent acute coronary events.[9] A recent meta-analysis of all studies with abciximab in patients undergoing PCI supports the above concept by showing a 30% relative reduction in mortality at 6-month follow-up in patients treated with this glycoprotein IIb/IIIa inhibitor.[10]

The strong relationship between the magnitude of the post-procedural CK-MB elevation and 6-month mortality as well as the consistency of this finding among the different studies indicate that peri-procedural myocardial damage is an important marker of subsequent adverse outcome. Therefore, measures to avoid or prevent such peri-procedural myocardial damage are warranted.

References

1 Abdelmeguid AE, Topol EJ. The myth of the myocardial infarctlet during percutaneous coronary revascularization procedures. *Circulation*. 1996;**94**:3369-3375.

2 Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ, Cohen EA, Kleiman NS, Mahaffey KW, Topol EJ, Pepine CJ, Lipicky RJ, Granger CB, Harrington RA, Tardiff BE, Crenshaw BS, Bauman RP, Zuckerman BD, Chaitman BR, Bittl JA, Ohman EM. Myonecrosis after revascularization procedures. *J Am Coll Cardiol*. 1998;**31**:241-251.

3 Tardiff BE, Califf RM, Tcheng JE, Lincoff AM, Sigmon KN, Harrington RA, Mahaffey KW, Ohman EM, Teirstein PS, Blankenship JC, Kitt MM, Topol EJ, for the IMPACT-II Investigators. Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. *J Am Coll Cardiol*. 1999;**33**:88-96.

4 Simoons ML, Van den Brand M, Lincoff M, Harrington R, Van der Wieken R, Vahanian A, Rutsch W, Kootstra J, Boersma E, Califf RM, Topol EJ. Minimal myocardial damage during coronary intervention is associated with impaired outcome. *Eur Heart J*. 1999;**20**:1112-1119.

5 Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp SK, Ellis SG. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. *Circulation*. 1996;**94**:1528-1536.

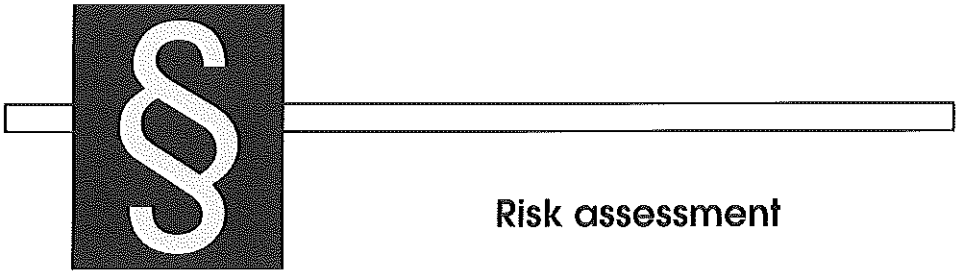
6 Alexander JH, Sparapani RA, Mahaffey KW, Deckers JW, Newby LK, Ohman EM, Corbalan R, Chierchia SL, Boland JB, Simoons ML, Califf RM, Topol EJ, Harrington RA, for the PURSUIT Steering Committee. Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. JAMA. 2000;**283**:347-353.

7 Fioretti P, Sclavo M, Browec RW, Simoons ML, Hugenholtz PG. Prognosis of patients with different peak serum creatine kinase levels after first myocardial infarction. *Eur Heart J*. 1985;**6**:473-478.

8 Savonitto S, Granger CB, Ardissino D, Broccolino M, White HD, Gardner L, Califf RM, Topol EJ. Even minor elevations of creatine kinase predict increased risk of cardiac events in acute coronary syndromes without ST-segment elevations. *J Am Coll Cardiol*. 1999;**33**:346A.

9 Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, Tcheng JE, Lincoff AM, Hasselblad V, Topol EJ. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation*. 1998;**98**:2829-2835.

10 Anderson KM, Califf RM, Ferguson JJ, Miller DP, Neumann FJ, Willerson JT, Weisman HF, Topol EJ. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. Submitted.



Risk assessment

9

Recurrent Ischemia During Continuous 12-Lead ECG-Ischemia Monitoring in Patients With Acute Coronary Syndromes Treated With Eptifibatide: Relation With Death and Myocardial Infarction

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Abstract

Computer-assisted continuous monitoring of the ST-segment allows detection and quantification of recurrent ischemia in patients with acute coronary syndromes. In a substudy of the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial, this technique was used to evaluate the effects of the glycoprotein IIb/IIIa inhibitor eptifibatide on the incidence and severity of recurrent ischemia, and to investigate the relationship between recurrent ischemia and the occurrence of subsequent death or myocardial (re)infarction. A total of 258 patients with unstable angina or evolving myocardial infarction without ST elevation were monitored for 24 hours during infusion with either eptifibatide or placebo with a computer-assisted 12-lead ECG-ischemia monitoring device. Recurrent ischemic episodes were identified by an automated computer algorithm. Two hundred and sixteen patients (84%) had ECG recordings suitable for analysis. Ischemic episodes were detected in 35 (33%) of the 105 eptifibatide patients and in 32 (29%) of the 111 placebo patients (not significant). No difference in ischemic burden was apparent between both treatment groups. Patients who exhibited 2 or more episodes of recurrent ischemia more frequently died or suffered a myocardial infarction, both at 7 and 30 days, as well as through the 6-month follow-up. A greater ischemic burden was significantly related to adverse outcome during the 6-month follow-up period. Real-time computer-assisted continuous multilead ECG-ischemia monitoring may help to identify patients with unstable coronary syndromes at increased risk of adverse outcome and, thus, allow for better prognostic triage and more appropriate selection of therapeutic strategies. Integration of these systems in coronary care units and emergency wards should, therefore, be recommended.

Introduction

In patients with unstable angina pectoris or myocardial infarction without ST-segment elevation, recurrent ischemia may reflect episodes of platelet thrombus formation at the culprit lesion.[1-3] Computer-assisted continuous monitoring of the ST-segment allows detection and quantification of recurrent ischemia and myocardial infarction.[4-8] As such, continuous 12-lead or vectorcardiographic ST monitoring might be suitable to evaluate the efficacy of new pharmacological therapies such as platelet glycoprotein IIb/IIIa receptor inhibitors in patients with acute coronary syndromes. The CAPTURE (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina) ECG-ischemia monitoring substudy showed that treatment with abciximab reduced recurrent ischemia and total ischemic burden in patients with refractory unstable angina.[5] In the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) study, treatment with eptifibatide, a synthetic inhibitor of the platelet glycoprotein IIb/IIIa receptor, resulted in a 1.5% absolute reduction in the 30-day composite endpoint of death or myocardial (re)infarction in patients with unstable angina or evolving myocardial infarction without ST-segment elevation.[9] Twelve-lead computer-assisted ECG-ischemia monitoring was conducted as a substudy within the PURSUIT study to evaluate the effects of eptifibatide compared with placebo on the incidence and severity of recurrent ischemia.

Recurrent ischemia, as detected by continuous ECG monitoring in patients with unstable angina, has been reported to carry an increased risk of unfavorable outcome, including death and myocardial infarction.[5,10-17] A secondary objective of the present PURSUIT substudy was to verify this relationship between recurrent ischemia and ischemic burden as detected during computer-assisted standard 12-lead ECG-ischemia monitoring and the occurrence of subsequent death or myocardial (re)infarction.

Methods

Study Organization

The PURSUIT ECG-ischemia monitoring substudy involved patients from the main PURSUIT study from 10 hospitals in The Netherlands and 16 in the United States. The protocol and the results of the PURSUIT study have been published previously.[9,18] All patients enrolled in the substudy underwent continuous ECG monitoring using a 12-lead ECG-ischemia monitoring device as described later.

Patient Population and Treatment

Patients presenting with unstable angina or myocardial infarction without persistent ST-segment elevation were eligible for inclusion in PURSUIT.[9,18] Inclusion criteria were: symptoms of myocardial ischemia at rest within 24 hours of enrollment, and either transient (< 30 minutes duration) ST-segment elevation 0.5 mm or greater or transient or persistent ST-segment depression 0.5 mm or greater or definite T-wave inversion of 1 mm or greater during or within 12 hours of (an episode of) chest pain, or subsequent creatine kinase-MB above the upper limit of normal. Patients were randomly assigned to receive a bolus and infusion of either eptifibatide (180 μg/kg bolus, 2.0 μg/kg/min infusion) or matching placebo in addition to standard therapy for up to 72 hours or 96 hours if coronary intervention was performed.

All patients selected for enrollment in PURSUIT were eligible for participation in the ECG-ischemia monitoring substudy, except those with ECG abnormalities interfering with ST-segment interpretation such as left bundle branch block, third-degree AV-block, persistent arrhythmias, or pacemakers. All patients gave informed consent before enrollment.

Continuous ST-Segment Monitoring

Continuous ECG monitoring was preferably started at the beginning of study drug infusion and continued for 24 hours. Patients were monitored with the ELI-ST100 (Mortara Instruments, Milwaukee, WI) continuously updated standard 12-lead ECG recording system. This system automatically calculates median ECG complexes of the 12 ECG leads every 20 seconds. The patient's own baseline ECG was used as a template for comparison of subsequent ST-segment levels. The system was programmed to store median ECG complexes every 20 seconds if 100μV or greater ST-segment shift was present in 1 lead relative to the baseline ECG of that patient, or if 50 μV or greater ST-shift was present in any 2 leads of the 12-lead ECG. A baseline median ECG was stored every 20 minutes if ST change was below these levels or absent altogether.

Data Management

All recordings were stored on a hard disk. Once monitoring was completed, the data were downloaded to a floppy disk and sent either to the Cardialysis core laboratory in Rotterdam, The Netherlands (European centers) or to the Duke core laboratory in Durham, NC. (U.S. sites). The final analysis of the recordings was performed at the Cardialysis core laboratory. The timing of the start of study drug infusion and the moment of angiography, as well as the presence of episodes of chest pain during ST monitoring, were obtained from the case report forms. All personnel involved in the ST-segment analysis remained blinded to treatment assignment.

Editing and Analysis of Recorded Data

The procedures of editing of the continuous ECG monitoring data and the analysis with an automated computer-driven ischemic ST episode detection program, as developed and applied by the Cardialysis core laboratory, have been described in detail.[4,5]

In the present study, patients were excluded from the analysis if the recording started more than 12 hours after the start of study drug infusion or contained no analyzable ST monitoring data during the first 12 hours. Recordings with less than 50% analyzable ST monitoring data or with a duration of less than 12 hours were also excluded. The period of study drug infusion was analyzed only, whereas ST episodes occurring during coronary procedures were excluded.

The onset of an ST episode was defined as a change of ST amplitude in 1 or more leads of at least 100 μV from the baseline ST level, developing within a 20-minute period and persisting for at least 1 minute. The end of an episode was defined as a return of the ST level within 100 μV of the baseline ST level, again lasting for at least 1 minute. If 100 μV ST change or greater was present in multiple leads simultaneously, the onset of the ST episode was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest moment of return to baseline ST level. Episodes had to be separated from each other by at least 1 minute.

Ischemic burden was calculated in different ways, such as the total duration of all ST episodes per patient, the sum of the area under the curve of all 12 ECG leads during ST episodes per patient, and the area under the curve of the derived ST vector magnitude (ST-VM) of all episodes per patient, calculated from the 8 independent leads using the inversed Dower transformation formula.[19] The area under the curve was measured from the baseline ST level directly preceding the episode.

Study Endpoints

The endpoints in this substudy were the number of patients with recurrent ischemia, the time from start of study drug to start of the first ischemic episode,

and the time until a second ischemic episode after a first one, as well as the number of ischemic episodes and the ischemic burden in patients with recurrent ischemia. Furthermore, recurrent ischemia was investigated in relation to the occurrence of the composite endpoint of death or myocardial (re)infarction as defined in the PURSUIT trial at 7, 30, and 180 days after randomization. All suspected myocardial infarctions within 30 days were adjudicated by a Clinical Events Committee blinded to treatment assignment.[9,18]

Statistical Analysis

The Wilcoxon Rank Sum test estimated that at least 200 patients were required per treatment group to provide 80% power to detect a relative reduction of 66% in ischemic burden in the total group of patients and a relative reduction of 50% in the subgroup of patients with ischemia.[5] Continuous variables are summarized using the median and interquartile range (25th and 75th percentiles) and were compared using the Mann-Whitney test. Discrete variables are described as percentages and were compared using Fisher's Exact Test. The Kaplan-Meier method was used for the evaluation of the time to the occurrence of the first and second ST episode, with censoring of data. Statistical differences were tested with the log rank test. A 2-sided *P*-value of less than .05 was required for significance. The relationship between recurrent ischemia parameters and adverse outcome was evaluated univariably, as well as after adjustment for baseline variables found to be the strongest independent predictors of the 30-day composite endpoint in the overall PURSUIT population[20], including age, geographic region, enrollment diagnosis (non-ST-segment elevation myocardial infarction versus unstable angina), sex, and worst Canadian Heart Class of angina pectoris in the 6 weeks before enrollment. Variables are presented as odds ratios with 95% confidence intervals.

Results

The PURSUIT trial enrolled 9,461 patients.[9] A subset of 258 patients (2.7%) were included in the ECG-Ischemia Monitoring Substudy. Two hundred and sixteen patients (84%) had continuous ECG recordings suitable for ST analysis. A total of 42 patients (16%) were excluded from analysis because the recording began more than 12 hours after the start of study drug infusion or contained less than 12 hours of analyzable ECG data (n = 19), because of technical failures owing to incorrect user operation of the monitoring system (n = 20), whereas 3 patients had a left bundle branch block that prevented reliable interpretation of the ST-segment.

Of the 216 patients, 105 received eptifibatide and 111 received placebo. The 2 treatment groups were well balanced with regard to baseline characteristics that

were representative of the baseline data of the PURSUIT patients enrolled in Western Europe and North America (Table 1). Total recording time suitable for analysis was similar in patients receiving eptifibatide and those who received placebo (median 24 [25th and 75th percentiles 22,33] hours vs 24 [22,30] hours). Baseline characteristics did not differ significantly between patients with and without ST episodes during ECG monitoring except for age; patients with ST episodes were older than those without recurrent ischemia (median 67 [61,77] years versus 61 [54,68] years, $P < .001$).

Incidence and Severity of Ischemia by Treatment Allocation

Ischemic episodes were detected in 35 (33%) of the 105 eptifibatide patients and in 32 (29%) of the 111 placebo patients (not significant). The Kaplan-Meier estimates of freedom from recurrent ischemia did not show significant differences between both treatment groups, though a trend favoring eptifibatide was apparent

Table 1. Baseline Characteristics by Treatment Allocation

	Eptifibatide (n = 105)	Placebo (n = 111)
Age (y)	62 (56, 69)	64 (55, 71)
Women (%)	24	27
Systolic blood pressure (mmHg)	130 (115, 140)	130 (120, 140)
Diastolic blood pressure (mmHg)	75 (65, 80)	75 (65, 80)
Weight (kg)	81 (74, 87)	82 (73, 91
Body mass index (kg/m2)	27 (25, 29)	27 (25, 30)
Prior MI (%)	31	27
Prior CABG (%)	14	12
Hypertension (%)	45	49
Diabetes (%)	18	21
Hypercholesterolemia (%)	41	39
Current smoker (%)	31	29
Family history of CAD (%)	41	44
Congestive heart failure (%)	5	5
Angina before qualifying episode (%)	87	85

For continuous variables, the median values are provided, with the 25th and 75th percentiles given in parentheses. MI, myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease.

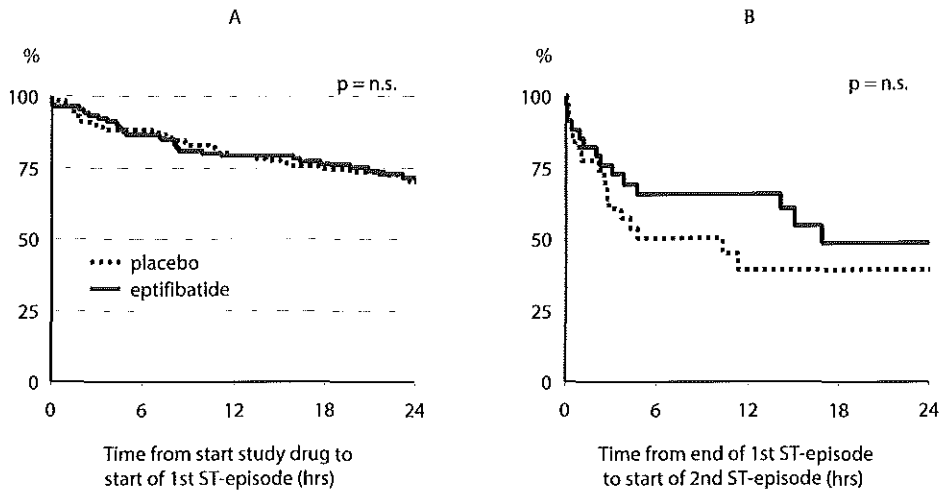

Figure 1.
Kaplan-Meier estimates of the probability to remain free from an ischemic episode during the course of the monitoring period: (A) The probability to remain free from a recurrent ST episode from the start of study drug. (B) The probability to remain free from a second ST episode after the ending of a previous first one. For both comparisons, no statistically significant differences were apparent between the eptifibatide and placebo treatment groups.

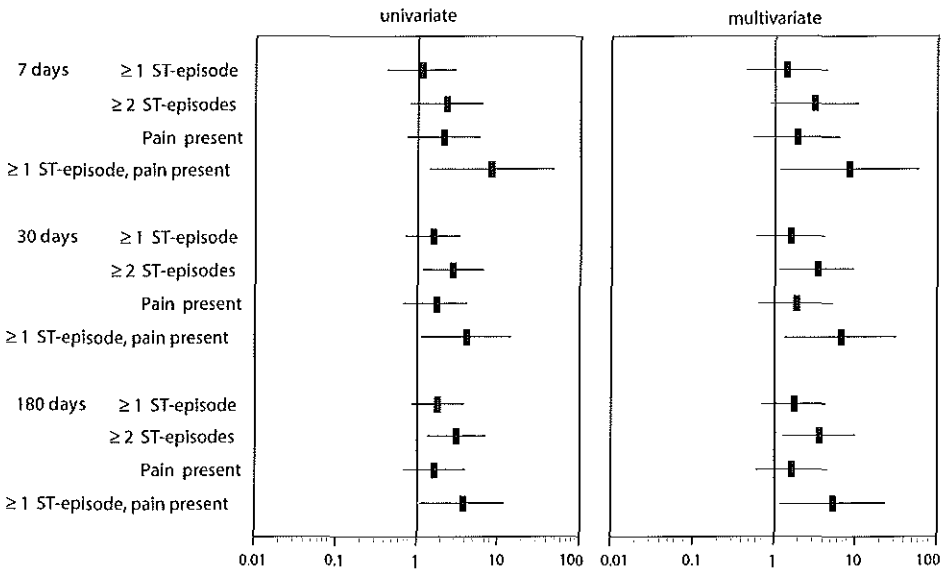

Figure 2.
Univariable and multivariable-adjusted odds ratios for the composite of death or myocardial infarction at 7, 30, and 180 days. Odds ratios are presented for the various parameters of recurrent ischemia detected during ECG monitoring. The horizontal lines indicate 95% confidence intervals.

Table 2. ECG-Ischemia Monitoring Results by Treatment Allocation

	Eptifibatide		Placebo		
	n	%	n	%	P Value
Patients	105		111		
≥ 1 ST episode(s)	35	33	32	29	NS
≥ 2 ST episodes	17	16	18	16	NS
≥ 1 Episode(s) of chest pain	19	18	18	16	NS
≥ 2 Episodes of chest pain	5	5	1	1	NS
Patients with ≥ 1 ST episode(s)					
≥ 1 Episode(s) of chest pain	11	31	8	25	NS
≥ 2 Episodes of chest pain	3	9	0	0	NS
Ischemic burden*					
Total duration / patient (min)	10		23		NS
ST-VM (μV.min)	455		369		NS
12-lead ST-area (μV.min)	7815		9439		NS

* For ischemic burden variables, the median values are provided only for patients with recurrent ischemia (ie, ≥ 1 ST episode). NS, not significant; ST-VM, area under the curve of the ST-vector-magnitude during ST episodes per patient; 12-lead ST-area, sum of the area under the curve of all 12 ECG leads during ST episodes per patient.

Table 3. Relation Between Recurrent Ischemia During ST Monitoring and Clinical Endpoints

		7 Days Death/MI			30 Days Death/MI			180 Days Death/MI		
	n	n	%	*P*	n	%	*P*	n	%	*P*
Patients	216									
No ST episode	149	14	9	.81	20	13	.31	22	15	.12
≥ 1 ST episode	67	7	10		13	19		16	24	
< 2 ST episodes	181	15	8	.12	23	13	.04	26	14	.008
≥ 2 ST episodes	35	6	17		10	29		12	34	
Pain absent	179	15	8	.22	25	14	.31	29	16	.24
Pain present	37	6	16		8	22		9	24	
Patients ≥ 1 ST episode	67									
Pain absent	48	2	4	.02	6	12	.04	8	17	.05
Pain present	19	5	26		7	37		8	42	

P values provided for Fisher's Exact Test. MI, myocardial infarction.

Table 4. Relation Between Ischemic Burden and Clinical Endpoints

	7 Days			30 Days			180 Days		
	No Death/MI (n=60)	**Yes Death/MI** (n=7)	*P*	**No Death/MI** (n=54)	**Yes Death/MI** (n=13)	*P*	**No Death/MI** (n=51)	**Yes Death/MI** (n=16)	*P*
Ischemic burden									
Duration / patient (min)	10	46	.06	9	35	.04	7	30	.03
ST-VM (μV.min)	288	2716	.02	267	2,098	.007	232	1,290	.003
12-lead ST-area (μV.min)	5,943	43,514	.02	4,762	22,078	.02	3,923	17,571	.02

For ischemic burden variables, the median values are provided only for the 67 patients with recurrent ischemia (ie, ≥ 1 ST episode).
MI, myocardial infarction; ST-VM, area under the curve of the ST-vector-magnitude during ST episodes per patient; 12-lead ST-area, sum of the area under the curve of all 12 ECG leads during ST episodes per patient. *P* values provided for Mann-Whitney Test.

in the time until a second ischemic episode after a first episode (Figure 1). No significant differences were apparent between patients treated with eptifibatide and those assigned placebo for a series of indicators of ischemia (Table 2).

Relationship Between Recurrent Ischemia and Outcome

Twenty-one patients enrolled in this substudy (9.7%) developed a myocardial infarction (n = 17) or died (n = 4) within 7 days of follow-up. At 30 days, 33 (15.3%) of the 216 patients had died (n = 8) or developed a myocardial (re)infarction (n = 27), and at six months, death or myocardial infarction had occurred in 38 patients (17.6%). The endpoint rates of the 216 patients participating in this substudy were similar to those of the overall PURSUIT population.[9], and did not differ between the eptifibatide and placebo treatment groups.

In both univariable and multivariable analysis, there was a remarkable consistency with respect to the directionality of the relationship between recurrent ischemic episodes and adverse outcome (Figure 2). For all 3 follow-up periods, patients who exhibited frequent recurrent ischemia, as represented by 2 or more ST episodes during ECG monitoring, more often died or suffered a myocardial infarction (Table 3). Significance was greatest after 6 months of follow-up (P = .008, Table 3). Furthermore, in the subgroup of patients with ST episodes, the presence of at least 1 episode of chest pain during the monitoring period in addition to 1 or more ST episodes appeared an independent predictor of subsequent adverse outcome (Figure 2). Patients with recurrent ischemia with a greater ischemic burden more often died or developed a myocardial infarction compared with those with a lower ischemic burden. This association reached statistical significance in all but 1 comparison (Table 4). At 6 months, death or myocardial infarction most frequently occurred in patients with a total duration of ischemia of 10 minutes or more (incidence of the composite endpoint 40% vs 13% in patients with ischemia duration less than 10 minutes, P = .0003); an ST vector magnitude 450 μV.min or greater (43% vs 13%, P = .0001); or a 12-lead ST area 820 μV.min or greater (41% vs 13%, P = .0001).

Discussion

In the PURSUIT trial, treatment with eptifibatide in addition to aspirin and heparin resulted in a statistically significant, but modest, 1.5% absolute reduction in the 30-day composite endpoint of death or nonfatal myocardial (re)infarction in patients with acute coronary syndromes without persistent ST-segment elevation.[9] Yet, the present substudy failed to show a beneficial effect of eptifibatide on reducing the incidence of recurrent ischemia or the amount of ischemic burden during the first 24 hours of study drug infusion. These data contrast with the results of a pilot study of eptifibatide in patients with unstable angina that did

show a reduction in the frequency and duration of Holter-detected ischemia associated with eptifibatide treatment.[21]

Several possible explanations for the observed results deserve consideration. First, this substudy was powered to detect the predefined (major) reductions in recurrent ischemia and ischemic burden if ST monitoring data of 200 patients per treatment group were suitable for final statistical analysis. Because only 258 patients were enrolled with 216 ECG recordings suitable for analysis, statistical power to detect a difference between both treatment groups was significantly decreased. Using the current sample size, only a relative reduction in ischemic burden of at least 70% would have been identified as statistically significant. Furthermore, patients were monitored only during the first 24 hours of the 72-hour study drug infusion period. At 24 hours, the treatment benefit of eptifibatide was a 0.85% absolute reduction in the composite of death or myocardial infarction censored for percutaneous coronary intervention.[22] This represented a 26% relative reduction. The clinical benefit of eptifibatide in PURSUIT was seen primarily within 24 to 72 hours after enrollment.[9]; the duration of ECG monitoring might have been too short and the relative difference between the eptifibatide and placebo treatment groups at 24 hours in the main PURSUIT trial may have been insufficient to show a reduction in recurrent ischemia during continuous ST-segment monitoring in the small series of patients studied. For comparison, in the CAPTURE ECG-ischemia monitoring substudy, frequent recurrent ischemia and total ischemic burden were significantly reduced by abciximab in 332 patients with refractory unstable angina.[5] This was associated with a 54% relative lower rate of death or myocardial infarction censored for coronary intervention at 24 hours in that trial.[22,23] It should be noticed, however, that CAPTURE had very different design features than PURSUIT.[5,9,23] CAPTURE included patients with unstable angina refractory to standard medical therapy who underwent percutaneous coronary intervention within 24 hours after study enrollment.

Megatrials are conducted to assess reliably the impact of different therapeutic regimens on hard clinical endpoints, such as death, myocardial infarction, or stroke. Substudies in the context of such megatrials may help to verify and understand the pathophysiological mechanisms involved.[24] For example, the angiographic substudy in GUSTO-I helped to link differences in early coronary patency between 4 reperfusion strategies to differences in survival.[25,26] These differences in early coronary patency appeared related to differences in infarct size and residual left ventricular function.[26,27] The ECG-ischemia monitoring substudy in PURSUIT was designed with a similar purpose, to analyze the effect of eptifibatide on recurrent ischemia as a possible explanation for the expected and observed reduction in the primary endpoint of death or myocardial infarction. Regrettably, the start of the ischemia monitoring substudy was delayed considerably until the larger trial

was well underway. An immediate start resulting in an adequately powered substudy would have been the preferred arrangement.

The present study did confirm that patients with frequent recurrent ischemic episodes and a greater ischemic burden in the first 24 hours after admission are at increased risk to die or develop a myocardial infarction during follow-up, when compared with those without recurrent ischemia. In particular, the presence of 2 or more ST episodes or the recurrence of chest pain as reported by the investigator in addition to at least 1 ST episode had a profound impact on outcome. Although the association between recurrent ischemic episodes and adverse outcome did not reach statistical significance in all comparisons, there was a remarkable consistency with respect to the directionality of the relationship, both in univariable and multivariable analysis. This implies that the presence of ischemic episodes during multilead ECG monitoring has predictive value additive to that afforded by baseline characteristics.

It might be suggested that the relation between recurrent ischemic episodes and outcome has been biased by cardiac events occurring during percutaneous coronary intervention performed because of findings during ST monitoring. This is unlikely, however, because monitoring was performed as a black box with the results analyzed afterwards at the core laboratories.

Several other studies have shown that recurrent ischemia, either silent or symptomatic, during the first days after admission for unstable angina portends an unfavorable outcome.[5,10-17,28] This has been shown for ischemia detected during 2- or 3-lead Holter monitoring, as well as for ischemia during computer-assisted vectorcardiographic monitoring.[5,10-17] However, the present study is the first to show the direct relationship between recurrent ischemia and adverse outcome for ischemic episodes detected by computer-assisted continuous standard 12-lead ECG-ischemia monitoring.

In contrast to Holter monitoring which allows for retrospective analysis only, computer-assisted continuous 12-lead and vectorcardiographic ECG-ischemia monitoring offer an accurate continuous real-time measurement of the QRS-complex and ST-segment, and can, therefore, be used for on-line risk prediction of imminent cardiac events. Thus, the present study emphasizes the usefulness of these techniques as a noninvasive tool for further risk assessment and selection of the optimal treatment strategy in patients treated for unstable coronary syndromes.[29]

Patients presenting with unstable angina without elevated troponin T or troponin I levels who stabilize on medical treatment after admission and do not exhibit recurrent ischemia during continuous ECG monitoring have a low risk of death or myocardial infarction, especially when treatment includes a glycoprotein IIb/IIIa receptor inhibitor.[5,17,30-37] In these patients, noninvasive management may

be most beneficial allowing further plaque stabilization.[38] In contrast, patients who present with elevated troponin T or I levels on admission, as well as those who subsequently develop recurrent ischemic episodes during continuous ECG monitoring, are at high risk of adverse cardiac events.[5,17,30-35] Such patients may particularly benefit from a more aggressive therapeutic approach including administration of a glycoprotein IIb/IIIa receptor inhibitor like eptifibatide and an early percutaneous coronary intervention.[22,23,35,39,40]

Among patients treated for acute coronary syndromes, the profound impact of recurrent ischemia on survival and the incidence of myocardial infarction emphasizes the need for continuous ECG-ischemia monitoring. Therefore, integration of continuous multilead ECG-ischemia monitoring systems in coronary care units, emergency wards, and ambulance services may identify patients at increased risk of an unfavorable outcome, and allow for better prognostic triage and more appropriate selection of therapeutic strategies.

Appendix

Investigators and Clinics Participating in the PURSUIT 12-Lead ECG-Ischemia Monitoring Substudy:

The Netherlands

Thoraxcenter, University Hospital Rotterdam-Dijkzigt: *C. van der Zwaan, M.L. Simoons*; Ziekenhuis St. Jansdal, Harderwijk: *R. Dijkgraaf*; Mariaziekenhuis, Tilburg: *H.F. Baars*; Ziekenhuis De Tjongerschans, Heerenveen: *G.M. Jochemsen*; Medisch Centrum Alkmaar, Alkmaar: *V. Umans*; Maasziekenhuis, Boxmeer: *W. Smits*; Medisch Centrum Leeuwarden, Leeuwarden: *R.W. Breedveld*; Spaarneziekenhuis, Heemstede: *E.J. Müller*; Ziekenhuis Hilversum, Hilversum: *P. de Milliano*; Medisch Spectrum Twente, Enschede: *J.C. Poortermans*.

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Coordinating Centers and ECG Core Laboratories

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References

1 Fuster V, Badimon L, Badimon JJ et al: The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 326:**242**, 1992

2 Ambrose JA, Weinrauch M: Thrombosis in ischemic heart disease. *Arch Intern Med* 156:**1382**, 1996

3 Davies MJ, Thomas AC: Plaque fissuring - the cause of acute myocardial infarction, sudden ischemic death, and crescendo angina. *Br Heart J* 53:**363**, 1985

4 Klootwijk P, Meij S, van Es GA et al: Comparison of usefulness of computer assisted continuous 48-h 3-lead with 12-lead ECG ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. *Eur Heart J* 18:**931**, 1997

5 Klootwijk P, Meij S, Melkert R et al: Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 98:**1358**, 1998

6 Dellborg M, Steg PG, Simoons M et al: Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. *Eur Heart J* 16:**21**, 1995

7 Krucoff MW, Croll MA, Pope JE et al: Continuously 12-lead ST segment recovery analysis in the TAMI 7 study. *Circulation* 88:**437**, 1993

8 Klootwijk P, Langer A, Meij S et al: for the GUSTO-I ECG-ischemia monitoring substudy: Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. *Eur Heart J* 17:**689**, 1996

9 The PURSUIT Trial Investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 339:**436**, 1998

10 Gottlieb SO, Weisfeldt ML, Ouyang P et al: Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 314:**1214**, 1986

11 Gottlieb SO, Weisfeldt ML, Ouyang P et al: Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol* 10:**756**, 1987

12 Nademanee K, Intarachot V, Josephson MA et al: Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 10:**1**, 1987

13 Langer A, Freeman MR, Armstrong PW: ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. *J Am Coll Cardiol* 13:**1495**, 1989

14 Romeo F, Rosano GMC, Martuscelli E et al: Unstable angina: role of silent ischemia and total ischemic time (silent plus painful ischemia), a 6-year follow-up. *J Am Coll Cardiol* 19:**1173**, 1992

15 Amanullah AM, Lindvall K: Prevalence and significance of transient - predominantly asymptomatic - myocardial ischemia on holter monitoring in unstable angina pectoris, and correlation with exercise test and thallium-201 myocardial perfusion imaging. *Am J Cardiol* 72:**144**, 1993

16 Holdright D, Patel D, Cunningham D, et al: Comparison of the effect of heparin and aspirin versus aspirin alone on transient myocardial ischemia and in-hospital prognosis in patients with unstable angina. *J Am Coll Cardiol* 24:**39**, 1994

17 Andersen K, Dellborg M, on behalf of the Thrombin Inhibition in Myocardial Ischemia (TRIM) Study Group: Heparin is more effective than inogatran, a low-molecular weight thrombin inhibitor in suppressing ischemia and recurrent angina in unstable coronary disease. *Am J Cardiol* 81:**939**, 1998

18 Harrington RA: Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. *Am J Cardiol* 80:**34B**, 1997

19 Dower GE, Machado HB, Osborne JA: On deriving the electrocardiogram from vectorcardiographic leads. *Clin Cardiol* 3:**87**, 1980

20 Boersma E, Pieper K, Wilcox RG, et al for the PURSUIT Investigators: The risk of adverse outcome in patients with acute coronary syndromes without ST-segment elevation is mainly determined by baseline clinical factors. *Eur Heart J* 20(suppl):**1333**, 1999

21 Schulman SP, Goldschmidt-Clermont PJ, Topol EJ et al: Effects of integrilin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation* **94**:2083, 1996

22 Boersma E, Akkerhuis KM, Theroux P et al: Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: Early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 100:**2045**, 1999

23 The CAPTURE Investigators: Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 349:**1429**, 1997

24 Topol EJ, Califf RM: Answers to complex questions cannot be derived from simple trials. *Br Heart J* 68:**348**, 1992

25 Simes RJ, Topol EJ, Holmes Jr DR, et al for the GUSTO-I Investigators: Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. *Circulation* 91:**1923**, 1995

26 Ross AM, for the GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 329:**1615**, 1993

27 Baardman T, Hermens WT, Lenderink T et al: Differential effects of tissue plasminogen activator and streptokinase on infarct size and on rate of enzyme release: Influence of early infarct related artery patency. The GUSTO enzyme substudy. *Eur Heart J* 17:**237**, 1996

28 Armstrong PW, Fu Y, Chang W-C, et al for the GUSTO-IIb Investigators: Acute coronary syndromes in the GUSTO-IIb trial: Prognostic insights and impact of recurrent ischemia. *Circulation* 98:**1860**, 1998

29 Klootwijk APJ: Dynamic computer-assisted ST segment monitoring in patients with acute coronary syndromes. Thesis, Erasmus University, Rotterdam, The Netherlands, 1998.

30 Van Miltenburg-van Zijl AJM: Management policies and prognosis in unstable angina pectoris. Thesis, Erasmus University, Rotterdam, The Netherlands, 1992.

31 Lindahl B, Venge P, Wallentin L: Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 93(9):**1651**, 1996

32 Ohman EM, Armstrong PW, Christenson RH, et al for the GUSTO-IIa Investigators: Cardiac Troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 335:**1333**, 1996

33 Antman EM, Tanasijevic MJ, Thompson B et al: Cardiac-specific Troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 335:**1342**, 1996

34 Hamm CW, Meinertz T, Berger J et al: Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 337:**1648**, 1997

35 Hamm CW, Heeschen C, Goldmann B, et al for the CAPTURE Investigators: Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 340:**1623**, 1999

36 The PRISM Study Investigators: A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 338:**1498**, 1998

37 The PRISM-PLUS Study Investigators: Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl Med* 338:**1488**, 1998

38 Boden WE, O'Rourke RA, Crawford MH, et al for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators: Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 338:**1785**, 1998

39 Akkerhuis M, Boersma H, Harrington RA et al: In patients with acute coronary syndromes without ST-segment elevation, eptifibatide particularly reduces complications in those undergoing an early percutaneous intervention: A report of the PURSUIT study. *Eur Heart J* 19 (suppl):**3421**, 1998

40 Akkerhuis M, Boersma H, Harrington RA et al: Eptifibatide protects against adverse cardiac complications both before and during percutaneous intervention in patients with acute coronary syndromes without ST-elevation. *J Am Coll Cardiol* 33 (suppl A):**40A**, 1999

10

Predictors of Outcome in Patients With Acute Coronary Syndromes Without Persistent ST-Segment Elevation

Results From an International Trial of 9461 Patients

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Abstract

Background

Appropriate treatment policies should include an accurate estimate of a patient's baseline risk. Risk modeling to date has been underutilized in patients with acute coronary syndromes without persistent ST-segment elevation.

Methods and Results

We analyzed the relation between baseline characteristics and the 30-day incidence of death and the composite of death or myocardial (re)infarction in 9461 patients with acute coronary syndromes without persistent ST-segment elevation enrolled in the PURSUIT trial [Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy]. Variables examined included demographics, history, hemodynamic condition, and symptom duration. Risk models were created with multivariable logistic regression and validated by bootstrapping techniques. There was a 3.6% mortality rate and 11.4% infarction rate by 30 days. More than 20 significant predictors for mortality and for the composite end point were identified. The most important baseline determinants of death were age (adjusted $\chi^2 = 95$), heart rate ($\chi^2 = 32$), systolic blood pressure ($\chi^2 = 20$), ST-segment depression ($\chi^2 = 20$), signs of heart failure ($\chi^2 = 18$), and cardiac enzymes ($\chi^2 = 15$). Determinants of mortality were generally also predictive of death or myocardial (re)infarction. Differences were observed, however, in the relative prognostic importance of predictive variables for mortality alone or the composite end point; for example, sex was a more important determinant of the composite end point ($\chi^2 = 21$) than of death alone ($\chi^2 = 10$). The accuracy of the prediction of the composite end point was less than of mortality (C-index 0.67 versus 0.81).

Conclusion

The occurrence of adverse events after presentation with acute coronary syndromes is affected by multiple factors. These factors should be considered in the clinical decision-making process.

Patients with acute coronary syndromes have a range of therapeutic alternatives. The decision of which therapy to use for individual patients depends on the clinical presentation and the estimated treatment benefits. Such benefits usually are proportional to the risk of adverse outcome in the absence of a specific therapy.[1,2] An appropriate treatment policy should include an estimate of this baseline risk, which can be achieved by application of a risk model that integrates important prognostic features. A number of such models have been developed for acute myocardial infarction (MI) with ST-segment elevation,[2-5] but few such tools exist for patients with unstable angina pectoris (UAP) or suspected MI without persistent ST-segment elevation.[6,7]

The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial studied the effects of eptifibatide versus placebo in 9461 patients with acute coronary syndromes without persistent ST-segment elevation.[8] This population covers a variety of patients, hospital settings, and treatment policies and therefore is suitable for development of a clinical risk model. We assessed the relation between the baseline characteristics and the occurrence of death and of death or nonfatal (re)MI at 30 days.

Methods

Patient Population

The design and methods of the PURSUIT trial have been described in detail.[8] In summary, patients were eligible if they presented within 24 hours of an episode of ischemic chest pain (>10 minutes) and had either transient ST-segment elevation (>0.5 mm), transient or persistent ST-segment depression (>0.5 mm), T-wave inversion (>1.0 mm), or elevation of the creatine kinase-MB fraction (CK-MB) above the upper limit of normal (ULN). Patients with persistent (>30 minutes) ST-segment elevation were excluded. There were no restrictions regarding age. Eligible patients were randomly assigned to treatment with eptifibatide or placebo. PURSUIT enrolled 9461 patients in 726 hospitals in 28 countries in Western and Eastern Europe and North and South America. There were 4308 patients (45.5%) with elevated CK-MB at admission; these were classified as having MI. The other 5129 patients (54.2%) were classified as having UAP. In 24 cases (0.3%), the qualifying ischemic episode was undefined.

Definition of MI

The primary efficacy end point of PURSUIT was a composite of death or nonfatal (re)MI at 30 days. Within 18 hours of enrollment, MI was diagnosed on the basis of ischemic chest pain and new ST-segment elevation. After 18 hours,

MI was diagnosed on the basis of new Q waves or new or repeated CK-MB elevations above the ULN. For patients undergoing percutaneous intervention or coronary bypass surgery, CK-MB elevation above 3 or 5 times the ULN was required. End points were adjudicated by a central Clinical Events Committee (CEC). A computerized algorithm was used to review the raw data. If a possible event was identified, additional documentation was collected and the case reviewed in detail. Local investigators also reported whether the patient had had an acute MI. Discrepancies that appeared between the CEC opinion and that of the investigator have been investigated and discussed in detail.[9] This analysis presents data based on the CEC judgment. Differences with analyses based on the investigators' opinions are discussed, but data will not be shown.

Statistical Analysis

Univariable and multivariable logistic regression analyses were applied to evaluate the relations between baseline characteristics and the 30-day occurrence of death alone and the composite of death or nonfatal (re)MI. All variables entered the multivariable stage, irrespective of the results of univariable analyses. The final multivariable model was constructed by backward deletion of the least significant characteristics, while the Akaike information criterion was applied (that is, the applied threshold of significance depended on the degrees of freedom [*df*] associated with the variable at hand; if $df = 1$, then $P \approx 0.157$).[10]

The shape of the relation between continuous variables and outcome was examined by a model-fitting technique involving cubic spline functions.[11] A disadvantage of this approach is the complexity of the resulting regression function. Therefore, when the relation appeared to be nonlinear, the cubic polynomial was approximated by a limited number of high-order terms.

Furthermore, we evaluated whether the prognostic relation of any predictive characteristic differed for patients enrolling with UAP or MI: we tested for interactions between prognostic factors and the enrollment diagnosis. To prevent false-positive findings, we did not test for other interactions among prognostic variables. An unexpected finding in PURSUIT was the interaction between sex and study medication with respect to the composite end point.[8] We evaluated the extent to which the model performance would have changed had this interaction been incorporated.

Clinical variables were missing for 8% of the patients. This subset had a higher 30-day mortality rate than patients with complete data (4.7% versus 3.5%; $P = 0.08$). The exclusion of patients with missing data, therefore, could lead to biased risk estimates.[12] To partly correct for this, all multivariable analyses were performed on a data set that included imputed predictive variables. The applied iterative imputation technique estimated the missing value of a given predictor on the basis

of multivariable regression on all other predictors.[12,13] End point data were not used in this process. Computations were performed with S-PLUS statistical software (version 3.3).[14]

The predictive accuracy of multivariable models was evaluated by the C-index.[15] The models developed in the full study population were further evaluated by bootstrapping techniques: 100 bootstrap samples were drawn, with replacement, to estimate the extent to which the predictive accuracy of the models based on the entire population was overoptimistic.[16]

Results

Baseline characteristics of the population are described in Table 1. Data for the 30-day occurrence of death or nonfatal (re)MI were complete. A total of 342 patients (3.6%) died, and another 1075 (11.4%) had a nonfatal (re)MI.

Univariable Analyses

Table 2 presents the univariable relations between dichotomous baseline characteristics and 30-day outcome. The relations between continuous variables and outcome are described in Figures 1 and 2. Age was strongly related with death, as were measures of left ventricular function (rales and history of heart failure), ST-segment depression on the presenting ECG, and admission heart rate. Other important risk factors were diabetes mellitus, prior MI, previous anginal symptoms, and CK-MB level at enrollment (enrollment MI versus UAP). The region of enrollment appeared to be prognostic, with higher mortality rates in Latin America and Eastern Europe relative to Western Europe and North America. Systolic and diastolic blood pressures were only weak predictors. There was a significant nonlinear relation between weight and mortality. Patients taking cardiac medications had a worse prognosis than patients not taking such medication before enrollment.

Clinical characteristics that predicted 30-day mortality generally also predicted the occurrence of either death or nonfatal (re)MI. The ranking order according to prognostic importance, however, was somewhat different, with enrollment diagnosis among the most important risk factors for the composite end point, whereas heart rate was of only modest predictive value. Unlike death alone, the composite event rate in Latin America was rather close to that of Western Europe and North America.

With respect to 30-day mortality, there were interactions between enrollment diagnosis and the variables age, heart rate, rales, and PURSUIT study medication. As far as the composite end point was concerned, interactions were observed between enrollment diagnosis and the variables diabetes, history of heart failure, rales, and T-wave inversion.

Table 1. Baseline Characteristics

Demographics	
Age, y	64 (55,71)
Male sex, %	65
White, %	89
Weight, kg	78 (69,88)
Height, cm	170 (163,176)
Region of enrollment, %	
Latin America	4
North America	40
Eastern Europe	16
Western Europe	39
History	
Hypertension, %	55
Diabetes mellitus, %	23
Smoking status, %	
Current	28
Former	33
Never	39
Hypercholesterolemia, %	42
Family history of CAD, %	36
MI, %	32
Worst CCS class past 6 weeks, %	
No angina	19
I	12
II	26
III	18
IV	25
CHF, %	11
Stroke, %	4
PVD, %	8
Bypass surgery, %	12
Angioplasty, %	13
Prior medication	
Aspirin, %	64
β-Blockers, %	43
Calcium antagonists, %	33
Nitrates, %	69
ACE inhibitors, %	24
Presenting characteristics	
Enrollment diagnosis, %	
MI	46
UAP	54
SBP, mmHg	130 (116,145)
DBP, mmHg	75 (67,83)
Heart rate, bpm	72 (63,80)
Rales, %	
$<1/3$	8
$\geq 1/3$	1
ST depression, %	50
ST elevation, %	14
T-wave inversion, %	51
Time course	
Symptom onset to randomization, h	11.1 (5.7,18.8)
PURSUIT study medication	
Eptifibatide, %	50

Data presented are median (25th, 75th percentiles) or percentages. CAD indicates coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; PVD, peripheral vascular disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Table 2. Univariable Relation Between Dichotomous Baseline Characteristics and 30-Day Outcome

	Death			Death or Nonfatal (Re)MI		
	Rate, %	χ^2 (*df*)	OR (95% CI)*	Rate, %	χ^2 (*df*)	OR (95% CI)*
Demographics						
Sex						
Female	3.8	<1 (1)	1.06 (0.85-1.33)	14.3	2 (1)	0.92 (0.81-1.03)
Male	3.5		1	15.4		1
Race						
Nonwhite	3.9	<1 (1)	1.09 (0.78-1.52)	12.8	5 (1)§	0.82 (0.67-0.99)
White	3.6		1	15.3		1
Region of enrollment						
Latin America	7.6	20 (3)¶	2.42 (1.60-3.67)	15.9	42 (3)‡	1.14 (0.85-1.51)
North America	3.2		0.97 (0.75-1.26)	13.4		0.93 (0.81-1.06)
Eastern Europe	4.5		1.39 (1.02-1.87)	20.4		1.54 (1.32-1.79)
Western Europe	3.3		1	14.3		1
History						
Hypertension						
Yes	4.3	16 (1)‡	1.59 (1.26-1.99)	16.2	13 (1)¶	1.24 (1.10-1.39)
No	2.8		1	13.5		1
Diabetes mellitus						
Yes	5.6	30 (1)‡	1.92 (1.53-2.41)	18.5	25 (1)‡	UAP: 1.16 (0.96-1.42) MI: 1.60 (1.35-1.90)
No	3.0		1	14.0		1
Smoking status						
Current	2.2	23 (2)‡	0.55 (0.41-0.75)	12.3	25 (2)‡	0.77 (0.66-0.87)
Former	4.4		1.10 (0.86-1.39)	16.8		1.11 (0.97-1.26)
Never	4.0		1	15.4		1
Hypercholesterolemia						
Yes	3.2	4 (1)§	0.80 (0.64-1.00)	15.0	<1 (1)	1.00 (0.89-1.12)
No	3.9		1	15.0		1
Family history of CAD						
Yes	3.1	4 (1)§	0.79 (0.63-1.00)	14.2	3 (1)	0.90 (0.80-1.02)
No	3.9		1	15.5		1
MI						
Yes	5.1	28 (1)‡	1.82 (1.46-2.26)	17.8	27 (1)‡	1.37 (1.22-1.54)
No	2.9		1	13.6		1
Worst CCS class past 6 weeks						
III or IV	4.8	27 (1)‡	1.78 (1.43-2.22)	17.9	48 (1)‡	1.50 (1.33-1.68)
Other	2.7		1	12.7		1
CHF						
Yes	9.0	73 (1)‡	3.25 (2.54-4.15)	21.6	37 (1)‡	UAP: 1.22 (0.94-1.58) MI: 2.04 (1.66-2.52)
No	2.9		1	14.1		1
Stroke						
Yes	5.8	4 (1)§	1.69 (1.06-2.69)	20.1	7 (1)#	1.45 (1.11-1.90)
No	3.5		1	14.8		1
PVD						
Yes	6.1	13 (1)¶	1.86 (1.36-2.55)	21.7	28 (1)‡	1.66 (1.38-1.98)
No	3.4		1	14.4		1
Bypass surgery						
Yes	5.2	8 (1)‖	1.56 (1.17-2.08)	15.9	<1 (1)	1.08 (0.91-1.28)
No	3.4		1	14.9		1

Table 2. Cont Univariable Relation Between Dichotomous Baseline Characteristics and 30-Day Outcome

	Death			Death or Nonfatal (Re)MI		
	Rate, %	χ^2 (*df*)	OR (95% CI)*	Rate, %	χ^2 (*df*)	OR (95% CI)*
Angioplasty						
Yes	2.0	12 (1)¶	0.50 (0.33-0.77)	13.4	3 (1)	0.86 (0.72-1.03)
No	3.9		1	15.2		1
Prior medication						
Aspirin						
Yes	4.0	9 (1)‖	1.43 (1.13-1.81)	16.1	17 (1)‡	1.29 (1.14-1.45)
No	2.9		1	13.0		1
β-Blocker						
Yes	4.1	5 (1)§	1.27 (1.02-1.58)	16.8	18 (1)‡	1.28 (1.14-1.43)
No	3.3		1	13.7		1
Calcium antagonists						
Yes	5.1	26 (1)‡	1.78 (1.43-2.21)	17.8	28 (1)‡	1.37 (1.22-1.54)
No	2.9		1	13.6		1
Nitrates						
Yes	4.2	25 (1)‡	1.92 (1.46-2.51)	16.4	32 (1)‡	1.44 (1.27-1.64)
No	2.3		1	12.0		1
ACE inhibitors						
Yes	4.6	8 (1)‖	1.42 (1.12-1.79)	17.0	9 (1)‖	1.22 (1.08-1.39)
No	3.3		1	14.3		1
Presenting characteristics						
Enrollment diagnosis						
MI	4.7	26 (1)‡	1.77 (1.42-2.21)	18.4	73 (1)‡	1.64 (1.46-1.84)
UAP	2.7		1	12.1		1
Rales						
≥1/3	10.5	109 (2)‡	5.85 (3.32-10.3)	23.2	63 (2)‡	2.77 (1.81-4.26)
<1/3	15.1		UAP: 2.34 (1.40-3.89)	31.1		UAP: 1.21 (0.88-1.68)
			MI: 4.93 (3.58-6.78)			MI: 2.19 (1.76-2.73)
None	2.8		1	13.9		1
ST depression						
Yes	5.1	65 (1)‡	2.54 (2.00-3.21)	17.9	63 (1)‡	1.59 (1.42-1.78)
No	2.1		1	12.1		1
ST elevation						
Yes	2.9	2 (1)	0.78 (0.55-1.09)	13.0	5 (1)§	0.83 (0.70-0.99)
No	3.7		1	15.3		1
T-wave inversion						
Yes	2.9	16 (1)‡	0.65 (0.52-0.80)	14.1	5 (1)§	UAP: 0.83 (0.70-0.98)
						MI: 1.07 (0.92-1.25)
No	4.4		1	15.8		1
PURSUIT study medication						
Eptifibatide	3.5	<1 (1)	UAP: 1.25 (0.9-1.8)	14.2	4 (1)§	0.89 (0.79-1.00)
			MI: 0.74 (0.4-1.6)			
Placebo	3.7		1	15.7		1

χ^2 indicates -2 log likelihood of the univariable model without interaction terms.

*If a significant interaction was observed between the variable and enrollment diagnosis (MI or UAP), 2 separate ORs are presented.

‡$P<0.0001$; §$P<0.05$; ‖$P<0.005$; ¶$P<0.001$; #$P<0.01$.

Abbreviations as in Table 1.

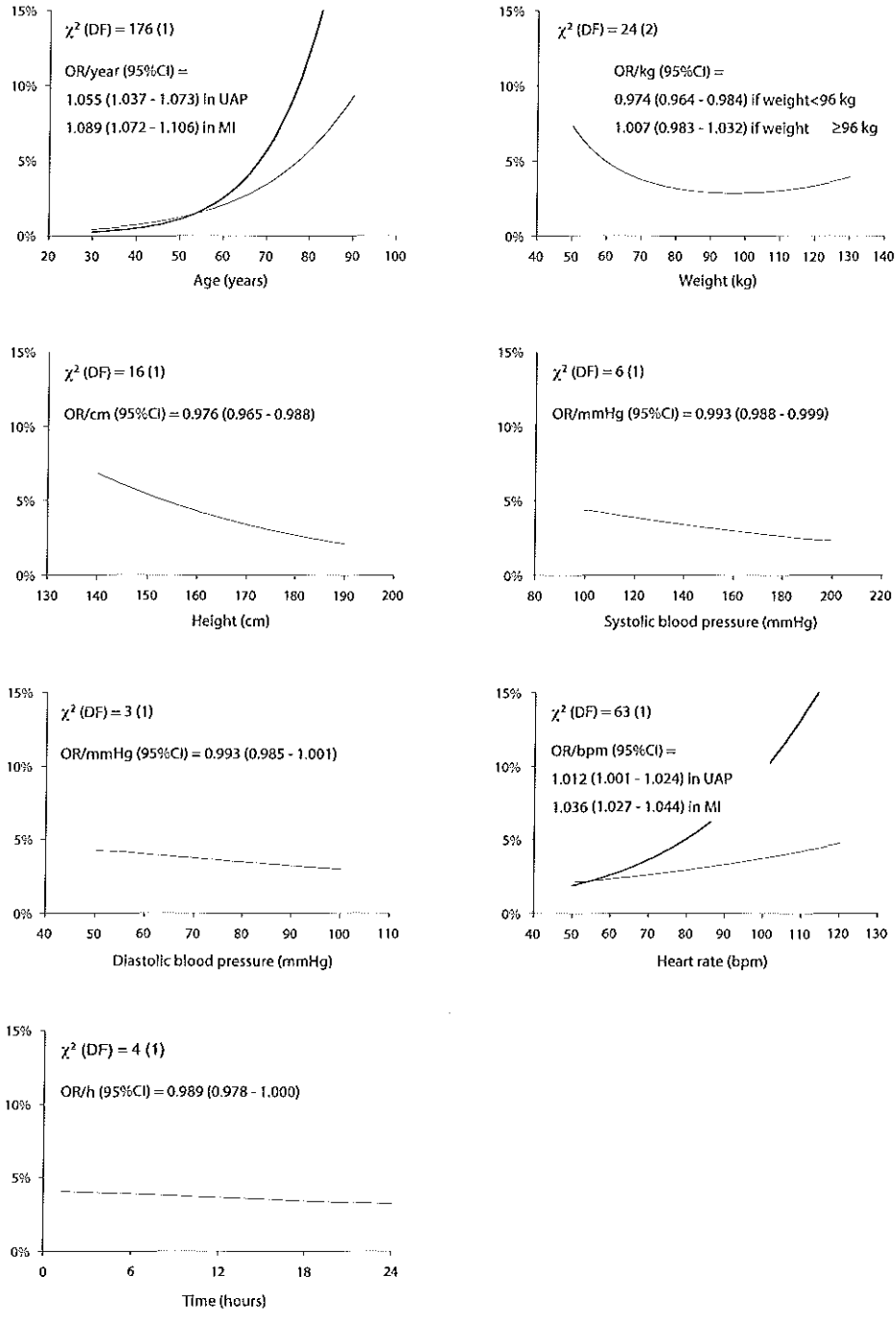
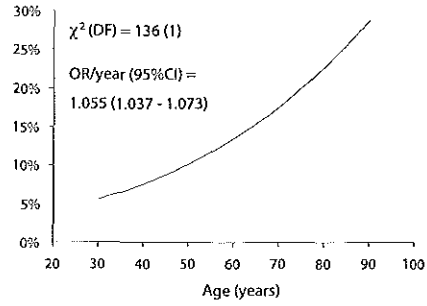
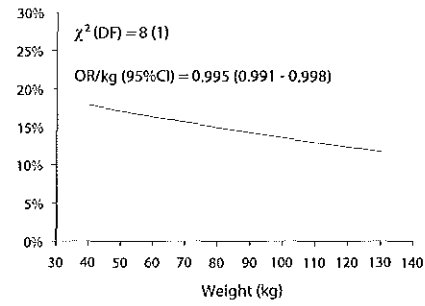
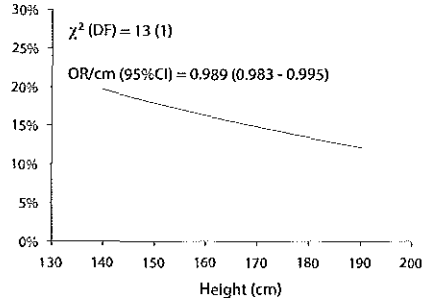
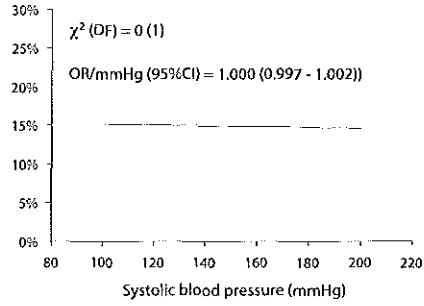


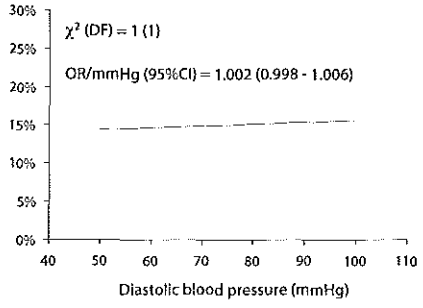
Figure 1.
Univariable relations between continuous baseline characteristics and 30-day mortality. If 2 curves are presented, bold curve indicates MI patients and light curve indicates UAP patients. χ2 indicates -2log-likelihood of the univariable model without interaction terms; OR, unadjusted odds ratio; CI, confidence interval; bpm, beats per minute.

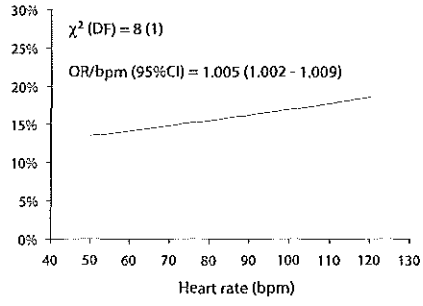












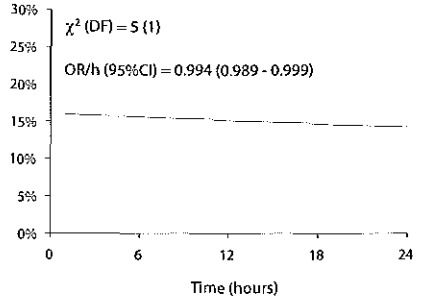


Figure 2.
Univariable relation between continuous baseline characteristics and 30-day rate of death or nonfatal MI. Abbreviations as in Figure 1.

TABLE 3. Multivariably Adjusted Effects of Baseline Characteristics on 30-Day Outcome

	Death		Death or Nonfatal (Re)MI	
	χ^2 (df)	OR (95% CI)*	χ^2 (df)	OR (95% CI)*
Demographics				
Age, y†				
55	95 (1)‡	UAP: 0.63 (0.53-0.74) MI: 0.47 (0.40-0.55)	75 (1)‡	0.77 (0.73-0.82)
64		1		1
71		UAP: 1.44 (1.26-1.65) MI: 1.81 (1.59-2.05)		1.23 (1.17-1.28)
Sex				
Female	9 (1)§	0.61 (0.44-0.84)	21 (1)‡	0.56 (0.45-0.69)
Male		1		1
Weight, kg†				
69	14 (2)‖	1.04 (0.95-1.15)	7 (2)¶	1.02 (0.97-1.07)
78		1		1
88		1.05 (0.96-1.14)		1.01 (0.97-1.06)
Height, cm†				
163	6 (1)¶	1.18 (1.04-1.33)	12 (1)‖	1.12 (1.05-1.20)
170		1		1
176		0.87 (0.78-0.97)		0.91 (0.86-0.96)
Region of enrollment				
Latin America	23 (3)‡	3.04 (1.93-4.78)	22 (3)‡	1.31 (0.98-1.77)
North America		0.90 (0.68-1.21)		0.95 (0.82-1.10)
Eastern Europe		1.03 (0.74-1.43)		1.40 (1.19-1.65)
Western Europe		1		1
History				
Hypertension				
Yes	3 (1)	1.25 (0.97-1.62)	-	
No		1		
Diabetes mellitus				
Yes	6 (1)¶	1.38 (1.07-1.76)	6 (1)¶	1.18 (1.03-1.36)
No		1		1
Smoking status				
Current	3 (1)	1.29 (0.91-1.83)	3 (1)	1.09 (0.92-1.29)
Former		1.27 (0.97-1.66)		1.14 (0.99-1.32)
Never		1		1
Worst CCS class past 6 weeks				
III or IV	14 (1)‡	1.56 (1.23-1.97)	26 (1)‡	1.36 (1.20-1.53)
Other		1		1
CHF				
Yes	5 (1)¶	1.73 (1.31-2.28)	-	
No		1		
PVD				
Yes	-		7 (1)#	1.29 (1.06-1.56)
No				1
Bypass surgery				
Yes	5 (1)¶	1.44 (1.04-2.00)	-	
No		1		
Angioplasty				
Yes	9 (1)§	0.51 (0.33-0.80)	-	
No		1		

TABLE 3. Cont Multivariably Adjusted Effects of Baseline Characteristics on 30-Day Outcome

	Death		Death or Nonfatal (Re)MI	
	χ^2 (df)	OR (95% CI)*	χ^2 (df)	OR (95% CI)*
Prior medication				
β-Blockers				
Yes	8 (1)§	1.40 (1.10-1.79)	14 (1)‡	1.26 (1.11-1.43)
No		1		1
Calcium antagonists				
Yes	6 (1)¶	1.35 (1.06-1.70)	8 (1)§	1.20 (1.06-1.36)
No		1		1
Nitrates				
Yes	3 (1)	1.34 (0.99-1.81)	4 (1)¶	1.16 (1.01-1.34)
No		1		1
Presenting characteristics				
Diagnosis				
MI	15 (1)‡	**	68 (1)‡	**
UAP				
SBP, mmHg†				
116	20 (1)‡	1.21 (1.12-1.31)	7 (1)#	1.08 (1.02-1.13)
130		1		1
145		0.82 (0.75-0.89)		0.92 (0.87-0.97)
DBP, mmHg†				
67	-		4 (1)¶	0.95 (0.91-1.00)
75				1
83				1.05 (1.00-1.10)
Heart rate, bpm†				
62	32 (1)‡	UAP: 0.90 (0.80-1.01) MI: 0.73 (0.67-0.80)	-	
72		1		
80		UAP: 1.09 (0.99-1.19) MI: 1.28 (1.19-1.37)		
Rales				
≥1/3	18 (2)‡	1.85 (1.36-2.51)	17 (2)‡	2.00 (1.27-3.13)
<1/3		2.05 (1.08-3.88)		UAP: 0.96 (0.69-1.34) MI: 1.59 (1.26-2.01)
None		1		1
ST depression				
Yes	20 (1)‡	1.80 (1.40-2.33)	14 (1)‡	1.27 (1.12-1.44)
No		1		1
Time course				
Symptom onset to randomization, h†				
5.7	3 (1)	1.05 (0.99-1.12)	2 (1)	1.02 (0.99-1.06)
11.2		1		1
18.8		0.93 (0.85-1.02)		0.97 (0.93-1.01)
PURSUIT study medication				
Eptifibatide	<1 (1)	UAP: 1.28 (0.91-1.81) MI: 0.79 (0.58-1.07)	3 (1)	0.90 (0.80-1.01)
Placebo		1		1

Results are based on the imputed data set (see Methods). χ^2 indicates difference between -2 log likelihood of the full model and the model with the variable at hand removed, both without interaction terms.
*If a significant interaction was seen between the variable and enrollment diagnosis (MI or UAP), 2 separate ORs are presented. †For continuous variables, ORs are presented for the first and third quartiles vs the median. ‡P < 0.0001; §P < 0.005; ||P < 0.001; ¶P < 0.05; #P < 0.01. **The contribution of enrollment diagnosis should be interpreted in combination with all interaction terms. Therefore, the OR for diagnosis separately is not presented. Abbreviations as in Table 1.

Multivariable Models

Many of the univariably significant mortality predictors remained important in the multivariable models (Table 3; the mortality model is described in detail in the Appendix). After correction for other determinants, age showed the strongest relationship with 30-day mortality; baseline heart rate was the next-strongest predictor. The interactions between enrollment diagnosis and both age and heart rate were maintained. The adjusted 30-day mortality rate for Eastern Europe was similar to Western Europe and North America, but patients treated in Latin America still had a higher risk of death. Other important risk factors were (lower) systolic blood pressure, ST-segment depression, and signs of heart failure (rales). Sex also appeared to be an important determinant of 30-day mortality in the multivariate analysis: women were at lower risk than men. This observation was not made in the univariable analysis: the crude 30-day mortality rates of men and women were similar (Table 2). The prognostic importance of systolic blood pressure was more pronounced in multivariable than in univariable analyses.

In combination with other baseline information, age was again the strongest predictor of the composite of 30-day death or nonfatal (re)MI, but the relative contribution of age in the composite end point model was smaller than in the mortality model. In contrast, the relative contribution of enrollment diagnosis was greater in the composite end point model. Again, there was a difference between univariable and multivariable analyses with respect to the sex-outcome relation: after correction for differences in baseline characteristics, women appeared to be at lower risk for the composite end point than men.

Predictive Accuracy

The C-index for the mortality model was 0.814, reflecting good ability to discriminate between patients who did and did not have a fatal outcome. The correction factor determined by bootstrapping was 0.01 (reducing the C-index to 0.804), implying that there was little overoptimism in the estimated predictive accuracy of the model. The composite end point model had a weaker discriminative power, with a C-index of 0.669 (correction factor also 0.01). The performance of the latter model showed only minimal improvement after incorporation of the interaction between sex and eptifibatide (C-index 0.670). If events were ignored that occurred within 48 hours of an invasive procedure, the C-indices of both the mortality and the composite end point model increased to 0.844 and 0.736, respectively.

Discussion

The prognosis of patients with acute coronary syndromes generally depends on the occurrence and extent of myocardial damage. Patients presenting without persistent ST-segment elevation or a typical enzyme rise have the lowest incidence of mortality and morbidity.[7] Intermediate complication rates are seen in those presenting without ST-segment elevation but with a rise in cardiac enzymes,[7] whereas prognosis is worst in patients with ST-segment elevation and substantial myocardial damage.[1,3] Apart from this simple classification, analyses of the GUSTO-1 (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) population have demonstrated that age, heart rate, blood pressure, and signs of heart failure (Killip class) are the key factors in predicting outcome in patients with ST-segment-elevation MI.[3] The present analysis in non-ST-segment-elevation acute coronary syndromes showed a remarkable homology with ST-segment-elevation patients, as basically the same prognostic factors were determined.

Demographics

Age was the most important determinant of outcome in this non-ST-segment-elevation population, as was the case in a population with ST-segment elevation.[3] The contribution of age to mortality was more pronounced in patients with MI rather than in those with UAP. This suggests that the relation between age and outcome depends on the presence and extent of myocardial necrosis at admission.

The results with respect to sex (and blood pressure) emphasize that possible prognostic factors should be considered in association with other outcome predictors. In univariable analysis, no relation was observed between sex and mortality, whereas multivariable analysis revealed women to be at lower risk than men.

The difference in outcome between regions of enrollment could not be explained fully on the basis of other baseline differences. Univariable analysis showed an increased risk for adverse events in Eastern Europe compared with Western Europe and North America. After correction for differences in baseline characteristics, mortality rates in these regions were similar, but the difference in the combined end point remained. The definition of MI should be considered in this respect. Particularly in Eastern Europe, the number of MIs differed according to the definition of the CEC versus the local investigator.[9] Eastern European origin was not a risk factor for the combined outcome of death or nonfatal (re)MI when MI was classified by local investigators. Furthermore, there were interregional differences in applied treatment strategies.[17] Percutaneous interventions were much more common in North America than in Eastern Europe. These variations in treatment may have caused differences in outcome. The high mortality rate in Latin America is still an unexplained finding.

Presenting Features

The contribution of heart rate to the mortality model was of similar importance as in patients with persistent ST-segment elevation.[3] In contrast to observations in ST-segment elevation,[3] however, no U-shaped relation between heart rate and mortality was observed, although the numbers of patients with very low or very high values were too small to draw strong conclusions.

The enrollment diagnosis was the second most important predictor of the composite end point. Patients presenting with MI had an almost 50% increase in the 30-day (re)infarction rate compared with UAP. According to local investigator reports, the prognostic importance of enrollment diagnosis was less pronounced. Patients classified as having MI by the CEC who were not labeled as such by the investigators represent a subgroup with minor CK-MB elevations. These patients are probably similar to patients with elevated cardiac troponin levels, who are at increased risk for repeat thrombotic events.[18]

History

Among the history variables, the prognostic contribution of prior revascularization was most interesting. Patients who had undergone angioplasty generally had a better survival rate than those who had not, but previous bypass surgery was associated with worse prognosis. Most likely, the type of prior revascularization procedure is a marker of coronary disease severity, which is less severe in the angioplasty group (single-vessel disease) and more severe in the bypass group (multivessel disease and impaired left ventricular function).

Treatment, In-Hospital Course, and Modeling Aspects

The treatment of acute coronary syndrome patients is an interactive process that is guided by the physician's perceptions of patient risk and risk reduction by available therapies and by the response to such therapy. Because we concentrated on risk estimation at hospital admission, response to treatment was not part of the model, nor were markers of changes during hospitalization, such as recurrent ischemia. An exception was assignment to eptifibatide, which occurred at random in PURSUIT.

The predictive power of the mortality model was substantial and was similar to an established model for patients with ST-segment elevation.[3] Prediction of (re)MI was less accurate, which reflects the fact that disruption of atherosclerotic plaque, which ultimately leads to MI, often occurs at multiple locations in the coronary system, independently of prior ischemic events.[19] MIs caused by percutaneous interventions are even more difficult to predict from information known at hospital admission. Indeed, if these events are ignored, the predictive power of both the mortality and the composite end point models improved significantly.

		Score	
		Mortality only	Mortality or infarction
Age (year)	50	0	8 (11)
	60	2 (3)	9 (12)
	70	4 (6)	11 (13)
	80	6 (9)	12 (14)
Gender	Female	0	0
	Male	1	1
Worst CCS-class in previous 6 weeks	No angina; I or II	0	0
	III or IV	2	2
Heart rate (bpm)	80	0	0
	100	1 (2)	0
	120	2 (5)	0
Systolic blood pressure (mmHg)	120	0	0
	100	1	0
	80	2	0
Signs of heart failure (rales)	No	0	0
	Yes	3	2
ST-depression on presenting ECG	No	0	0
	Yes	3	1

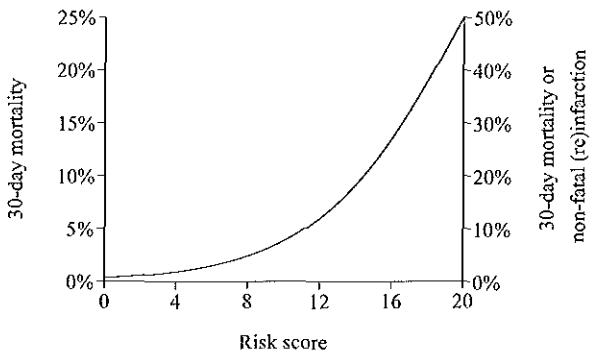


Figure 3. Simple scheme to estimate risk of 30-day complications in individual patients. Points are given for each predictive factor. With respect to age and heart rate, there are separate points for enrollment diagnosis of UAP and MI (between parentheses). Summed points will provide a risk score, which can be converted into a probability with help of the graph. CCS indicates Canadian Cardiovascular Society.

Clinical Implications

Although the developed risk models can be helpful for evaluating a patient's prognosis at hospital admission, these may be too complex to be integrated in clinical practice. We therefore present in Figure 3 a simple risk-evaluation scheme based on the most important prognostic factors. The observed 30-day mortality rates in the first quartile of predicted mortality according to this scheme (≤1%), the interquartile range (>1% and ≤4%), and the highest quartile (>4%) were 0.6%, 2.2%, and 8.9%, respectively. The observed event rates in the first quartile of the predicted composite end point (≤10%), the interquartile range (>10% and ≤19%), and the highest quartile (>19%) were 8.2%, 16.5%, and 24.1%.

It is beyond the scope of the data presented in this article to make firm statements about the appropriate treatment of patients in the several risk categories. Still, we may indicate how knowledge of the risk profile may affect the clinical decision-making process. For patients at low risk for recurrent events, early discharge seems warranted. The intermediate-risk group may benefit from a strategy of "watchful waiting": close observation in intensive or medium-care units with ischemia monitoring and serial determination of markers of myocardial damage. Some of these patients will be candidates for additional, invasive therapy; others may be treated medically. Antiplatelet therapy should be considered for high-risk patients, especially in case of elevated levels of cardiac troponins. Platelet glycoprotein IIb/IIIa inhibitors can reduce the probability of MI beyond that achieved by aspirin and heparin.[8,20,21] Percutaneous revascularization may be of particular benefit in this group.[22] Again, platelet glycoprotein IIb/IIIa receptor blockers should be given to reduce the risk of procedure-related thrombotic complications.[23] Bypass surgery should be considered in patients with impaired left ventricular function and multivessel disease.

Conclusions

By systematic analysis of the PURSUIT database, several pivotal factors were identified that have a profound impact on clinical outcome. Knowledge of these factors may facilitate the clinical decision-making process.

Appendix

The probability of 30-day mortality is $[1 + \exp(+8.9294 - S)]^{-1}$, where S is the sum of:

0.0483x[age (years)] + 0.0317x[age (years)]x[enrollment MI]

-0.4787x[female sex]

0.1608x[weight (kg)]-2.8481x ÷ [weight (kg)]

-0.0216x[height (cm)]

-0.1048x[North America] + 1.0978x[Latin America] + 0.0336x[Eastern Europe]

0.2247x[history of hypertension]

0.3197x[diabetes mellitus]

0.2508x[current smoker] + 0.2185x[former smoker]

0.4418x[worst Canadian Cardiovascular Society class in previous 6 weeks = III or IV]

0.3517x[history of heart failure]

0.3771x[history of angioplasty]

-0.6552x[history of bypass surgery]

0.3510x[b-blocker use]

0.2977x[calcium antagonist use]

0.2744x[nitrate use]

-3.0787x[enrollment infarction]

-0.0127x[systolic blood pressure (mm Hg)]

0.0088x[heart rate (bpm)] + 0.0204x[heart rate (bpm)]x[enrollment MI]

0.6150x[rales $< 1/3$] + 0.7174x[rales $\geq 1/3$]

0.5906x[ST-segment depression]

-0.0098x[time from onset of symptoms]

0.2635x[eptifibatide]-0.4760x[eptifibatide]x[enrollment MI]

Age, weight, height, systolic blood pressure, heart rate, and time from onset are continuous variables; all other determinants are 0/1 variables, with 0 = no and 1 = yes.

Acknowledgments

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References

1 The Reperfusion Therapy Consensus Group. Selection of reperfusion therapy for individual patients with evolving myocardial infarction. *Eur Heart J.* 1997;**18**:1371-1381.

2 Boersma E, Steyerberg EW, Van der Vlugt MJ, et al. Reperfusion therapy for acute myocardial infarction: which strategy for which patient? *Drugs.* 1998;**56**:31-48.

3 Lee KL, Woodlief LH, Topol EJ, et al, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation.* 1995;**91**:1659-1668.

4 Simoons ML, Arnold AER. Tailored thrombolytic therapy: a perspective. *Circulation.* 1993;**88**:2556-2564.

5 Boersma E, Vlugt van der M, Arnold AER, et al. Estimated gain in life expectancy: a simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction. *Eur Heart J.* 1996;**17**:64-75.

6 Maseri A, Rebuzzi AG, Cianflone D. Need for a composite risk stratification of patients with unstable coronary syndromes tailored to clinical practice. *Circulation.* 1997;**96**:4141-4142.

7 Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. *Circulation.* 1998;**98**:1860-1868.

8 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;**339**:436-443.

9 Harrington RA. Clinical trials in acute coronary syndromes: lessons from PURSUIT. *Eur Heart J* 1999;**1**(suppl. R):R28-R34.

10 Akaike H. Information theory as an extension of the maximum likelihood principle. In: Petrov BN, Csaki F, eds. *Second International Symposium on Information Theory.* Budapest, Hungary: Akademia Kiado; **1973**:267-281.

11 Smith PL. Splines as a useful and convenient statistical tool. Am Statistician. 1979;33:57-62.

12 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996;**15**:361-387.

13 Little RJ. Regression with missing X's: a review. *J Am Stat Assoc.* 1992;**87**:1227-1237.

14 *S-Plus Guide to Statistical and Mathematical Analysis,* Version 3.3. Seattle, Wash: Statistical Sciences; 1996.

15 Kendal DG. Rank Correlation Methods. 3rd ed. London, UK: Charles Griffin; 1962.

16 Gong G. Cross-validation, the jackknife, and the bootstrap: excess error estimation in forward logistic regression. *J Am Stat Assoc.* 1986;**81**:108-113.

17 Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. *Circulation.* 2000;**101**:751-757.

18 Lindahl B, Venge P, Wallentin L, for the FRISC Study Group. Relation between troponin-T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation.* 1996; **93**:1651-1657.

19 Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation.* 1995;**92**:657-671.

20 Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation.* 1998;**98**:2829-2835.

21 Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med.* 1999;**340**:1623-1629.

22 Madsen JK, Grande P, Saunamaki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI): DANish trial in Acute Myocardial Infarction. *Circulation.* 1997;**96**:748-755.

23 Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation*. 1999;**100**:2045-2048.

11

Clinical and Therapeutic Profile of Patients Presenting with Acute Coronary Syndromes Who Do Not Have Significant Coronary Artery Disease

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Abstract

Background

A proportion of patients who present with suspected acute coronary syndromes (ACS) are found to have insignificant coronary artery disease (CAD) during coronary angiography, but these patients have not been well characterized.

Methods and Results

Of the 5767 patients with non-ST-segment elevation ACS enrolled in the PURSUIT trial who underwent in-hospital angiography, 88% had significant CAD (any stenosis >50%), 6% had mild CAD (any stenosis >0% to ≤50%), and 6% had no CAD (no stenosis identified). The frequency of death or nonfatal myocardial infarction at 30 days was reduced with eptifibatide treatment in patients with significant CAD (18.3% vs. 15.6% for placebo, $P=0.006$), but not in those with mild CAD (6.6% vs. 5.4%, $P=0.62$) and no CAD (3.0% vs. 1.2%, $P=0.28$). We identified independent, baseline predictors of insignificant CAD (mild or no CAD) and used them to develop a simple, predictive nomogram of the probability of insignificant CAD for use at hospital presentation. This nomogram was validated in a separate population of patients with non-ST-segment elevation ACS.

Conclusions

Patients with suspected ACS found to have insignificant CAD have a low risk of adverse outcomes, do not appear to benefit from treatment with eptifibatide, and can be predicted with a simple nomogram using baseline characteristics. Since patients with significant CAD appear to have an enhanced benefit from eptifibatide treatment, the predictive nomogram developed can be used to determine indications for glycoprotein IIb/IIIa blockade.

Introduction

Acute coronary syndromes (ACS) most commonly begin with atherosclerotic plaque rupture and intracoronary thrombus formation.[1] Whereas occlusive intracoronary thrombi are present in most cases of ST-segment-elevation myocardial infarction (MI), the degree of coronary blood-flow disruption and the morphology of intracoronary thrombi are more diverse in patients who present with non-ST-segment elevation ACS (unstable angina or non-Q-wave MI).[2] Thus, angiographic findings in non-ST-elevation ACS range from complex, ulcerated lesions to no significant coronary disease, which occurs in up to 15% to 20% of patients who undergo angiography.[3,4]

Complex lesion morphology is a powerful predictor of adverse outcomes in unstable angina, but the impact of insignificant coronary-artery disease (CAD) in unstable angina is not clearly understood.[5-8] In the Thrombolysis In Myocardial Ischemia (TIMI)-IIIA trial, 53 of 391 patients with unstable angina (14%) had no critical coronary lesions during angiography and had a low incidence of in-hospital adverse outcomes.[9] However, longer-term outcomes and the efficacy of anti-ischemic therapies have not been well characterized in patients with ACS found to have insignificant CAD .

The recent Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial is the largest trial to date of non-ST-elevation ACS with almost 11,000 patients enrolled.[10] In this trial, eptifibatide significantly reduced the composite incidence of death or nonfatal MI at 30 days. We evaluated patients from the PURSUIT trial who underwent angiography and compared the clinical profiles, treatment responses, and outcomes of those with insignificant versus significant CAD.

Methods

Patient Enrollment

The enrollment criteria for the PURSUIT trial have been reported.[10,11] Patients were enrolled among 28 countries if they presented < 24 hours after ischemic chest-pain onset with either ECG signs of ischemia or an elevated creatine kinase (CK)-MB level. Patients with persistent ST-segment elevation, active bleeding, or recent major surgery were excluded from enrollment. The study protocol was approved by the institutional review committee of each participating institution, and all patients gave informed consent before enrollment.

Randomization and Treatment

Patients were randomized in a double-blind fashion to placebo or one of two doses of eptifibatide.[10] In a protocol-specified analysis of the first 3218 patients

enrolled, a safety-monitoring committee determined that the higher eptifibatide dose had an acceptable safety profile; thereafter, the low-dose arm was discontinued. The study drug was to be infused until discharge or for 72 hours, whichever occurred first. Aspirin and intravenous heparin were encouraged, and other medications were not restricted.

Coronary Angiography

Decisions about the use of coronary angiography and revascularization were not restricted and were made by the treating physician. The maximum percent stenosis of all major epicardial coronary arteries and bypass grafts were recorded on the case-report form. Angiographic characteristics of coronary plaques (including intracoronary thrombus) were not recorded.

Patient Selection

The study group consisted of patients who underwent coronary angiography during the initial admission. We excluded patients who did not undergo angiography during the initial hospitalization, those who did not receive study drug after randomization, and those randomized to low-dose eptifibatide treatment.

Patients were separated into three groups, based on the severity of CAD identified on the baseline diagnostic angiogram. Patients in the significant-CAD group had at least one stenosis >50% in a major epicardial vessel. Patients in the mild-CAD group had at least one stenosis >0% to ≤50%. Patients in the no-CAD group had no coronary stenosis recorded.

After angiography, nine patients in the mild-CAD group underwent revascularization (eight underwent angioplasty, one underwent bypass surgery), as did three patients in the no-CAD group (two underwent angioplasty, one underwent bypass surgery). These 12 patients were excluded from further analyses due to concerns that the angiographic findings were not recorded accurately. After exclusion of these 12 patients, the final cohort for this analysis comprised 5767 patients, 62% of the 9375 patients randomized to and receiving placebo or high-dose eptifibatide.

Endpoints

The primary endpoint of the PURSUIT trial (and of this analysis) was a composite of all-cause mortality or nonfatal MI at 30 days. The criteria for MI have been reported.[10] In brief, all suspected infarctions that occurred within 30 days of randomization were independently reviewed and adjudicated by a clinical-events committee blinded to treatment assignment. Investigators at enrolling sites also determined whether an MI had occurred through 6-month follow-up.

We also analyzed the following endpoints: 6-month mortality, nonfatal MI at

30 days as adjudicated by the clinical-events committee, nonfatal MI at 6 months as determined by investigators, and a composite of death or nonfatal, investigator-determined MI at 6 months. Bleeding complications were classified by the Thrombolysis in Myocardial Infarction (TIMI) scale,[12] and significant thrombocytopenia was classified as described.[13]

Statistical Analysis

Baseline characteristics were summarized as frequencies and percentages for categorical factors and as medians (25th, 75th percentiles) for the continuous factors. We calculated Kaplan-Meier event rates for patients with significant, mild, or no CAD for the endpoints evaluated, overall and by treatment assignment. Log-rank tests were used to compare event rates among the three disease groups and the treatment effect of eptifibatide within each group.

We used stepwise logistic-regression techniques to identify baseline variables that were independent predictors of insignificant CAD, defined as mild or no coronary disease. Data from patients in these two groups were pooled for this analysis. Candidate variables included demographic, clinical, and ECG factors; initial cardiac enzyme results; and medications used before randomization. The variable "Enrollment MI" was adjudicated by the clinical events committee and was defined as any elevation of creatine kinase (CK) greater than twice the upper limit of normal (ULN) or CK-MB above the ULN within 16 hours of randomization. Multivariable predictors were tested with the Wald χ^2 test and retained when $P < 0.05$. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). We used the coefficients from the full model (as shown in Table 5) to create a simple predictive nomogram.[14] The sum of the scores for each independent predictor represents the probability that a given patient has insignificant CAD.

A C-index value (area under the receiver-operator characteristic [ROC] curve) was generated for the regression model, to measure the concordance of predictions of insignificant CAD with actual angiographic findings. The regression model created from the PURSUIT population in this study was validated against patients with non-ST-elevation ACS enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial.[15] The C-index was recalculated to determine how well this model could discriminate between patients with and without significant CAD in the separate population of patients from GUSTO-IIb who underwent angiography. Finally, another regression model was generated in the GUSTO-IIb population to evaluate all 16 factors in the original PURSUIT model and to determine whether any factors had a different multivariable relationship with the outcome of insignificant CAD than was found in the PURSUIT population.

Results

Patient Characteristics

As seen in Table 1, of the 5767 patients who underwent angiography during the initial hospitalization, 5071 (88%) had significant CAD, 366 (6%) had mild CAD, and 330 (6%) had no CAD. Patients with significant CAD were older, more often

TABLE 1. Baseline Characteristics by Degree of Coronary Artery Disease (CAD)

	Significant CAD (n = 5071)	Mild CAD (n = 366)	No CAD (n = 330)	*P**
Male sex	70.1	52.2	48.2	<0.001
Caucasian	88.4	84.1	74.8	<0.001
Age, y	63 (55, 70)	58 (50, 67)	54 (47, 63)	<0.001
Diabetes	23.9	13.1	10.3	<0.001
Hypertension	55.6	55.2	50.3	0.17
Current smoking	30.1	31.1	30.3	0.92
Hypercholesterolemia	46.5	39.9	30.9	<0.001
Family history of CAD	38.7	39.6	36.3	0.64
Congestive heart failure	8.2	7.4	5.5	0.18
Prior myocardial infarction	33.8	20.5	5.5	<0.001
Prior angina	83.3	72.7	69.5	<0.001
Prior angioplasty	18.2	15.6	1.2	<0.001
Prior bypass surgery	15.9	0.3	0.3	<0.001
Enrollment infarction	48.1	23.6	19.7	<0.001
ECG changes†				
ST-segment depression	47.1	32.2	28.5	<0.001
ST-segment elevation	15.5	14.8	13.0	0.45
T-wave inversion	50.4	60.9	67.0	<0.001

Data are presented as percentages or median (25th, 75th percentiles). *Across the three groups. †Not mutually exclusive.

male, and more often had diabetes mellitus, hypercholesterolemia, prior MI, prior angina, prior revascularization procedures, enrollment MI, and ST-segment depression compared with patients with mild or no CAD.

In the group with mild CAD, one patient had prior bypass surgery, yet all recorded native coronary stenoses were ≤50%. In the group with no CAD, four patients had prior angioplasty and one had prior bypass surgery, yet there were no recorded stenoses (0%). No adverse clinical events (death or nonfatal MI) occurred in these patients by 6 months.

Medical Treatment

Study drug was infused for a median 72 (52, 72) hours in patients with significant CAD, 72 (30, 72) hours in patients with mild CAD, and 70 (24, 72) hours in patients with no CAD. Aspirin was used during the first admission in about 95% of patients in all three groups. b-blockers were used in 79% of patients with significant CAD, 69% of patients with mild CAD, and 63% of patients with no CAD. Intravenous heparin was used in 96%, 93%, and 92% of patients, respectively.

Outcomes

As seen in Table 2, adverse ischemic events occurred more often in the

TABLE 2. Outcomes by Severity of Coronary Artery Disease (CAD)*

	Significant CAD (n = 5071)	Mild CAD (n = 366)	No CAD (n = 330)
30 Days			
Death	3.3	0.5	0.6
Nonfatal MI (by CEC)	15.3	5.7	1.5
Nonfatal MI (by investigators)	8.0	0.8	0.6
Death or nonfatal MI (by CEC)	17.0	6.0	2.1
Death or nonfatal MI (by investigators)	10.0	1.4	0.9
6 Months			
Death	5.5	0.6	1.2
Nonfatal MI (by investigators)	9.9	1.7	1.2
Death or nonfatal MI (by investigators)	13.4	2.2	2.2

Data presented are percentages. MI, myocardial infarction; CEC, clinical events committee.

*All $P<0.001$ across the three groups for each outcome analyzed.

group with significant CAD. Patients with mild CAD had a lower adjusted risk of the composite of death or nonfatal MI at 30 days than patients with significant CAD (hazard ratio [HR], 0.45; 95% CI, 0.25 to 0.80; $P=0.007$). The group with no CAD also had a lower adjusted risk of this composite endpoint (HR, 0.20; 95% CI, 0.08 to 0.49; $P<0.001$). At 6 months, patients with mild or no CAD continued to have a lower risk of adverse events than did those with significant CAD.

Treatment Efficacy

As seen in Table 3, the frequency of the composite endpoint of death or nonfatal MI at 30 days was reduced from 18.3% to 15.6% in patients with significant CAD treated with eptifibatide (absolute risk reduction [RR], 2.7%; relative RR, 15%; $P=0.006$). The Kaplan-Meier event curves for the frequency of the composite endpoint separated early during the study drug infusion in the group with significant CAD and thereafter, fewer events were seen in eptifibatide-treated patients through 30 days (Figure 1). By contrast, no apparent treatment benefit was seen in patients who did not have significant CAD. The frequency of the composite endpoint was similar among patients treated with placebo and those treated with eptifibatide in the group with mild CAD (6.6% vs. 5.4%; $P=0.63$) and the group with no CAD (3.0% vs. 1.2%; $P=0.28$).

Safety

In all patients treated with eptifibatide, the incidence of major or minor bleeding was highest in the group with significant CAD compared with the groups with mild CAD and no CAD (34.5% vs. 9.7% vs. 8.1%, respectively; $P<0.001$). Most bleeding events in patients with significant CAD treated with eptifibatide, however, were related to revascularization procedures. The incidence of major or minor bleeding with eptifibatide treatment in patients with significant CAD was 25.8%

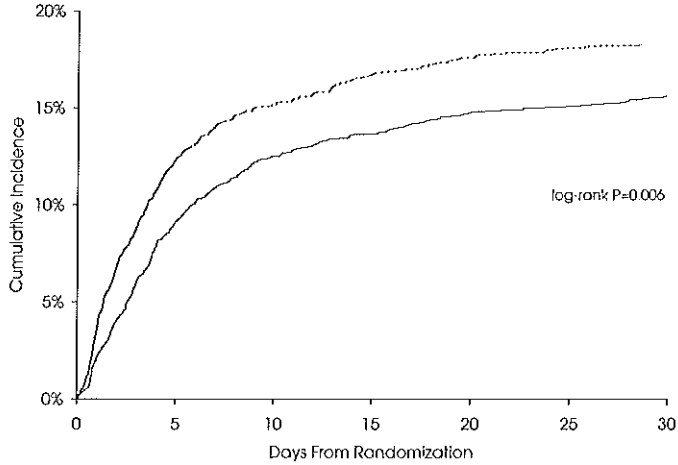

Figure 1.
Kaplan Meier plot of death or nonfatal myocardial infarction through 30 days in patients with significant coronary artery disease receiving eptifibatide (solid line) or placebo (dashed line).

TABLE 3. Outcomes at 30 Days* by Severity of Coronary Artery Disease (CAD) and Treatment Assignment

	Significant CAD			Mild CAD			No CAD		
	Placebo (n=2548)	Eptifibatide (n=2523)	*P*	Placebo (n=181)	Eptifibatide (n=185)	*P*	Placebo (n=169)	Eptifibatide (n=161)	*P*
Death, %	3.7	2.9	0.11	0.6	0.5	0.99	1.2	0.0	0.16
Nonfatal MI %	16.6	14.1	0.01	6.1	5.4	0.77	1.8	1.2	0.68
Death or nonfatal MI, %	18.3	15.6	0.01	6.6	5.4	0.62	3.0	1.2	0.28

*As adjudicated by the clinical events committee. MI, myocardial infarction.

TABLE 4. Independent Baseline Predictors of Insignificant Coronary Artery Disease

	Wald χ^2	*P*	Odds Ratio (95% CI)
No enrollment MI	178.2	<0.001	4.24 (3.43–5.24)
Age (per 10-year decrease)	143.6	<0.001	1.72 (1.57–1.88)
Female sex	94.7	<0.001	2.51 (2.09–3.03)
No angina <6 weeks before entry	63.5	<0.001	2.39 (1.93–2.96)
No diabetes	39.6	<0.001	2.36 (1.81–3.08)
No ST-segment depression	37.7	<0.001	1.82 (1.51–2.21)
No current smoking	29.2	<0.001	1.77 (1.44–2.17)
No previous MI	25.6	<0.001	1.97 (1.51–2.55)
No previous bypass surgery	25.2	<0.001	35.86 (8.86–145.1)
No hyperlipidemia	12.9	<0.001	1.40 (1.17–1.69)
Non-Caucasian race	11.4	<0.001	1.50 (1.19–1.90)
No peripheral vascular disease	7.4	0.007	2.16 (1.24–3.76)
No β-blocker treatment before entry	6.9	0.009	1.28 (1.07–1.54)
No previous angioplasty	6.3	0.012	1.49 (1.09–2.03)
No ST-segment elevation	4.6	0.032	1.32 (1.03–1.71)
Congestive heart failure	4.3	0.039	1.48 (1.02–2.14)

Model χ^2, 947.025; C-index, 0.827. Of the 5767 patients included in the model, 696 had insignificant CAD. CI, confidence interval; MI, myocardial infarction.

for patients who underwent angioplasty, 81.7% for those who had bypass surgery, and 13.0% for patients who did not undergo revascularization. Additionally, thrombocytopenia was more common in the group with significant CAD compared with the other groups (10.4% vs. 1.2% vs. 0.7%, respectively; $P < 0.001$).

Predictors of Insignificant CAD

As seen in Table 4, several baseline characteristics were found to predict insignificant CAD (mild or no disease) versus significant CAD. The strongest

independent predictors of insignificant CAD included younger age; female sex; and the absence of enrollment MI, prior angina, diabetes, or ST-segment depression. The overall model χ^2 was 947 ($P < 0.001$) and the C-index value was 0.827, indicating that the model can reliably predict the presence of insignificant CAD. An estimate of the probability of insignificant CAD can be calculated for individual patients by using the nomogram created from this model (Figure 2).

When the predictive model was applied to the GUSTO-IIb population, the C-index value was 0.796. The validation plot of actual incidence versus predicted probability of insignificant CAD in the GUSTO-IIb population illustrates the excellent discrimination of this model when applied to a different population

1. Find Points for Each Predictive Factor

Age	Points
20	100
30	86
40	71
50	57
60	43
70	29
80	14
90	0

Other Baseline Clinical Factors	Points
No enrolling MI	38
Female sex	24
Non-Caucasian	11
Congestive heart failure	10
Absence of:	
Hyperlipidemia	9
Previous MI	18
Previous bypass surgery	94
Diabetes	23
Current smoking	15
Peripheral vascular disease	20
Previous angina (within 6 weeks)	23
Previous angioplasty	10
Beta-blocker use before hospitalization	7

ECG Factors	Points
No ST Elevation	7
No ST Depression	16

2. Sum Points for All Predictive Factors

_____ (Age) + _____ (Other Baseline Clinical Factors) + _____ (ECG Factors) = _____ (Point Total)

3. Look Up Probability of Insignificant Coronary Disease Corresponding to Point Total

Total Points	Probability	Total Points	Probability
223	2%	286	18%
242	4%	289	20%
253	6%	303	30%
261	8%	315	40%
268	10%	326	50%
273	12%	336	60%
278	14%	348	70%
282	16%	362	80%

Figure 2.
Nomogram to predict the probability of insignificant coronary artery disease (CAD) from baseline clinical characteristics. In panel 1, find the values that most closely match the patient's baseline characteristics and determine the corresponding point assignment. In panel 2, add the points for all predictive factors. In panel 3, determine the likelihood of insignificant CAD based on the total points.

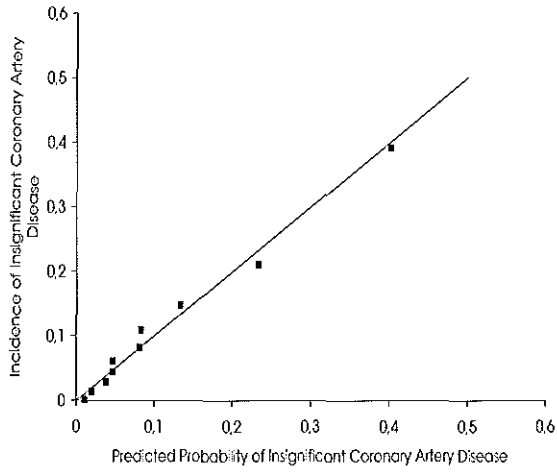

Figure 3.
Validation plot for the actual incidence versus predicted probability of insignificant CAD in the GUSTO-IIb population, by deciles of probability. This plot shows the excellent concordance of the PURSUIT model for insignificant CAD in a separate patient population.

(Figure 3). Most of the 16 factors in the model derived from the PURSUIT population remained significant when the model was applied to the GUSTO-IIb population. No previous angioplasty and congestive heart failure were not predictors of insignificant CAD in the GUSTO-IIb population, but these two factors were among the least powerful predictors of insignificant CAD in the PURSUIT population.

Discussion

Even in this clinical trial that used objective evidence of ischemia as enrollment criteria (chest pain, ECG changes, and cardiac enzyme elevations), a sizable proportion of patients with non-ST-elevation ACS were found to have insignificant CAD during coronary angiography. Patients with insignificant CAD had a low incidence of adverse outcomes and did not benefit from treatment with the glycoprotein (GP) IIb/IIIa inhibitor eptifibatide. By contrast, an enhanced treatment effect was demonstrated in patients with significant CAD treated with eptifibatide. Baseline clinical characteristics were used to create a simple model that accurately predicted the probability of insignificant CAD in a separate population of patients.

Although patients with ACS and insignificant CAD have been shown to have better in-hospital outcomes than ACS patients with significant CAD, longer-term outcomes have not been closely examined.[9] Our results show a low incidence of death or nonfatal MI through 6 months in patients with insignificant CAD. In previous angiographic studies, however, progression of coronary lesions in unstable angina has been common and associated with an increased incidence of ischemic events.[16,17] In this analysis, we could not evaluate angiographic progression of disease, but patients with insignificant CAD had a low risk of adverse clinical events through 6 months. Further evaluation is needed to determine whether patients with

insignificant CAD have a similar prognosis through longer-term follow-up.

The underlying mechanisms that contribute to the clinical presentation of ACS in patients with insignificant CAD are not well understood. Since almost 25% of the patients with insignificant CAD in this analysis presented with myocardial infarction at enrollment, intracoronary thrombus may have first formed at the site of a minimal coronary lesion, as described by Pecora et al.[18] Embolization of platelet-fibrin thrombi to the microvascular circulation, endothelial dysfunction caused by abnormalities in distal coronary flow, or both also may be present in patients with ACS who have no significant coronary epicardial lesions.[9,19,20] Elevated troponin levels are a possible marker of lesion complexity, thrombus burden, and microvascular obstruction in patients with non-ST-segment elevation ACS.[10, 21] However, troponin levels were not routinely measured in the PURSUIT trial, so we could not assess their predictive and prognostic abilities in patients with insignificant CAD. Finally, given the limited prognostic significance of T-wave changes in patients with unstable angina, the high prevalence of T-wave inversion in patients with insignificant CAD suggests these ECG findings may have contributed to the incorrect diagnosis of ACS in a certain proportion of patients.[22]

Since we have demonstrated that patients with insignificant CAD do not benefit from treatment with GP IIb/IIIa blockade, early identification of patients with suspected ACS who have insignificant CAD may help to guide therapeutic decisions in this low-risk cohort. The probability of insignificant CAD can be reliably predicted before angiography using baseline characteristics, so the nomogram we created can potentially be used to identify patients who are not likely to benefit from treatment with a GP IIb/IIIa inhibitor upon hospital presentation.[23,24] The clinical significance of this predictive nomogram was demonstrated by our finding that patients with significant CAD treated with eptifibatide had an enhanced reduction in the frequency of the primary composite endpoint compared with the overall PURSUIT trial (2.7% vs. 1.5%).[10] Elevated troponin levels also appear to identify patients with ACS who have enhanced benefit from treatment with GP IIb/IIIa blockade.[23,24] However, further studies are needed to determine which combination of high-risk features (CK-MB, troponins, ischemic ST-segment changes) should be used together with our predictive nomogram to select patients with suspected ACS for treatment with a GP IIb/IIIa inhibitor.

Limitations

Only patients who underwent angiography were evaluated, so a selection bias relating to the decision to perform angiography may have influenced the results. The angiographic information recorded was limited and did not include assessments of lesion characteristics, intracoronary thrombus, or coronary flow. Additionally, there was no verification of the severity of coronary lesions in an angiographic

core laboratory. The PURSUIT trial, however, was designed as a large, "simple" trial that enrolled almost 11,000 patients with non-ST-elevation ACS.[25] Detailed angiographic analysis and verification of the findings in a core laboratory would have been impractical in a trial of this size. Finally, the enrollment criteria of PURSUIT were designed to select a moderate- to high-risk group of patients with non-ST-elevation ACS, so the patient population studied in this analysis may have been "enriched" compared with that seen in typical clinical practice.

Conclusions

Patients with ACS found to have insignificant CAD during coronary angiography have a low risk of adverse outcomes. While patients with insignificant CAD did not appear to benefit from treatment with eptifibatide, those with significant CAD were shown to have an enhanced treatment benefit. Baseline clinical characteristics were used to accurately predict the probability of insignificant CAD using a simplified nomogram. Therefore, early identification of patients with suspected ACS who have insignificant CAD may help refine triage algorithms for acute ischemic chest pain and determine indications for GP IIb/IIIa inhibitors.

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References

1 Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med.* 1992;326:**242**-250.

2 Mizuno K, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, Kurita A, Nakamura H, Ambrose JA. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med.* 1992;**326**:287-291.

3 Freeman MR, Williams AE, Chisholm RJ, Armstrong PW. Intracoronary thrombus and complex morphology in unstable angina. *Circulation.* 1989;**80**:17-23.

4 Williams AE, Freeman MR, Chisholm RJ, Patt NL, Armstrong PW. Angiographic morphology in unstable angina. *Am J Cardiol.* 1988;**62**:1024-1027.

5 Bugiardini R, Pozzati A, Borghi A, Morgagni GL, Ottani F, Muzi A, Puddu P. Angiographic morphology in unstable angina and its relation to transient myocardial ischemia and hospital outcome. *Am J Cardiol.* 1991;**67**:460-464.

6 Dangas G, Mehran R, Wallenstein S, Courcoutsakis NA, Kakarala V, Hollywood J, Ambrose JA. Correlation of angiographic morphology and clinical presentation in unstable angina. *J Am Coll Cardiol.* 1997;**29**:519-525.

7 Ahmed WH, Bittl JA, Braunwald E. Relation between clinical presentation and angiographic findings in unstable angina pectoris, and comparison with that in stable angina. *Am J Cardiol.* 1993;**72**:544-550.

8 Rupprecht HJ, Sohn HY, Kearney P, Bickel C, Nafe B, Meyer J. Clinical predictors of unstable coronary lesion morphology. *Eur Heart J.* 1995;**16**:1526-534.

9 Diver D, Bier J, Ferreira P, Sharaf B, McCabe C, Thompson B, Chaitman B, Williams D, Braunwald E. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA trial). *Am J Cardiol.* 1994;**74**:531-537.

10 The PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;**339**:436-443.

11 Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. *Am J Cardiol.* 1997;**80**:34B-8B.

12 Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial - phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988;**11**:1-11.

13 McClure MW, Berkowitz SD, Sparapani R, Tuttle R, Kleiman NS, Berdan LG, Lincoff AM, Deckers J, Diaz R, Karsch KR, Gretler D, Kitt M, Simoons M, Topol EJ, Califf RM, Harrington RA. Clinical significance of thrombocytopenia during a non-ST-elevation acute coronary syndrome. *Circulation.* 1999;**99**:2892-2900.

14 Harrell FE. Design: S plus functions for biostatistical/epidemiologic modeling, testing, estimation, validation, graphics, prediction, and type-setting by storing enhanced model design attributes for the fit. UNIX version available from statlib@lib.stat.cmu.edu; 1996.

15 The GUSTO-IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med.* 1996;**335**;775-782.

16 Chen L, Chester MR, Redwood S, Huang J, Leatham E, Kaski JC. Angiographic stenosis progression and coronary events in patients with 'stabilized' unstable angina. *Circulation.* 1995;91:2319-2324.

17 Ambrose J, Winters S, Arora R, Eng A, Riccio A, Gorlin R, Fuster V. Angiographic evolution of coronary artery morphology in unstable angina. *J Am Coll Cardiol.* 1986;**7**:472-478.

18 Pecora MJ, Roubin GS, Cobbs BW Jr, Ellis SG, Weintraub WS, King SB III. Presentation and late outcome of myocardial infarction in the absence of angiographically significant coronary artery disease. *Am J Cardiol.* 1988;**62**:363-367.

19 Hasdai D, Holmes DR, Higano S, Burnett J, Lerman A. Prevalence of coronary blood flow reserve abnormalities among patients with nonobstructive coronary artery disease and chest pain. *Mayo Clin Proc.* 1998;**73**:1133-1140.

20 Egashira K, Inou T, Hirooka Y, Yamada A, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. *N Engl J Med.* 1993;**328**:1659-1664.

21 Heeschen C, van den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. *Circulation* 1999;**104**:1509-14.

22 Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q-wave myocardial infarction: results of the TIMI III Registry Ancillary Study. *J Am Coll Cardiol.* 1997;**30**:133-140.

23 Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med.* 1999;**340**:1623-1629.

24 Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;**354**:1757-1762.

25 Topol EJ, Califf RM. Answers to complex questions cannot be derived from "simple" trials. *Br Heart J.* 1992;**68**:348-351.

12

Recurrent Ischemia During Continuous Multilead ST-segment Monitoring Identifies Patients With Unstable Angina at High Risk of Subsequent Cardiac Events: Meta-analysis of Three Studies Involving 995 Patients

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Abstract

Background

Recurrent ischemia detected by continuous ECG monitoring in patients with unstable angina carries an increased risk of unfavorable outcome. Studies that evaluated this relationship have been limited by small series of patients. By combining data of three studies, the present analysis aims to provide an accurate assessment of the impact of recurrent ischemia detected by multilead ECG-ischemia monitoring on the occurrence of death and myocardial infarction in patients with acute coronary syndromes.

Methods and Results

Data were obtained from CAPTURE, PURSUIT and FROST, three trials evaluating glycoprotein IIb/IIIa blockers in patients with non-ST-elevation acute coronary syndromes. Patients were monitored for 24 hours after enrolment with a computer-assisted 12-lead or vectorcardiographic ECG-ischemia monitoring device. In a retrospective blinded analysis, recurrent ischemic episodes were identified by a computer algorithm. The number of ischemic episodes was normalized to 24 hours. Ischemic episodes were detected in 271 (27%) of 995 patients. There was a direct proportional relationship between the number of ischemic episodes per 24 hours and the probability of cardiac events at 5 and 30 days. The 30-day composite of death and myocardial infarction occurred in 5.7% of patients without episodes and increased to 19.7% in patients with ≥ 5 episodes. After adjustment for baseline predictors of adverse outcome, the relative risk of death or myocardial infarction at 5 and 30 days increased by 25% for each additional ischemic episode per 24 hours.

Conclusions

This analysis emphasizes the need for integration of multilead ECG-ischemia monitoring systems in coronary care units and emergency wards to improve early risk-stratification in patients with acute coronary syndromes.

Introduction

Recurrent ischemia detected by Holter monitoring or computer-assisted ECG analysis in patients with unstable angina carries an increased risk for an unfavorable outcome, including death and myocardial infarction.[1-9] Computer-assisted multilead ECG monitoring offers an accurate continuous real-time measurement of the QRS-complex and the ST-segment [10,11] and can be used as a non-invasive tool for on-line risk stratification in patients with acute coronary syndromes [4-9] In contrast, Holter monitoring is limited by a restricted number of two or three ECG leads and allows for retrospective analysis only.[10,11]

Studies that evaluated the relationship between recurrent ischemia detected during continuous multilead ECG-ischemia monitoring (or Holter monitoring) and adverse outcome have been limited by small series of patients.[1-9] By combining data of 3 studies, the present analysis aims to provide an accurate assessment of the impact of recurrent ischemia detected by multilead ECG-ischemia monitoring on the occurrence of death and myocardial infarction in patients admitted with an acute coronary syndrome.

Methods

Patients and Treatment

Data were obtained from the ECG-ischemia monitoring substudies of the CAPTURE (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina) and PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trials ,[5,9] as well as from the FROST (Fibrinogen Receptor Occupancy STudy) trial.[12] The protocols and results of the 3 studies have been published.[5,9,12] All patients were monitored using a multilead ECG-ischemia monitoring device as described below.

In brief, the studies were designed as double-blind, placebo-controlled, randomized trials to evaluate glycoprotein IIb/IIIa inhibitors in patients presenting with an acute coronary syndrome without persistent ST-elevation. CAPTURE evaluated abciximab in patients with unstable angina refractory to conventional medical therapy for whom percutaneous coronary intervention was planned and performed after approximately 24 hours of pretreatment with abciximab.[13] PURSUIT tested the hypothesis that inhibition of platelet aggregation with eptifibatide would have an incremental benefit beyond that of heparin and aspirin in reducing the incidence of adverse outcomes in patients with unstable angina or non-ST-segment elevation myocardial infarction.[14] A similar patient population was studied in FROST which assessed the safety and preliminary efficacy of one-month treatment with the oral glycoprotein IIb/IIIa blocker lefradafiban.[12]

All ECG-ischemia monitoring studies excluded patients who presented with

ECG abnormalities interfering with ST-segment interpretation such as left bundle branch block, third-degree AV-block, persistent arrhythmias, or pacemakers. The protocols were approved by the institutional review board at each center and all patients gave informed consent.

Continuous ECG-ischemia Monitoring

ECG monitoring was started at the beginning of study drug administration and continued for 24 hours in all studies, and at least until 6 hours after completion of the percutaneous coronary intervention in CAPTURE.[5,9,12] In the latter study, ECG monitoring was performed using the MIDA-1000 vectorcardiographic ECG monitoring device (Ortivus Medical, Täby, Sweden).[5,11] This system calculates and stores averaged QRS-T complexes from the Frank orthogonal X-Y-Z leads at 1-minute intervals.[15] In PURSUIT and FROST, patients were monitored with the ELI-ST100 continuously updated 12-lead ECG recording system (Mortara Instruments, Milwaukee, U.S.A.).[9,10] This system automatically calculates median ECG complexes of the 12 ECG leads every 20 seconds. The system was programmed to store median ECG complexes and ST-trend data every 20 seconds if $\geq$ 100μV ST-segment shift was present in one lead relative to the preceding ECG of that patient, or if $\geq$ 50μV ST-shift was present in any two leads of the 12-lead ECG. A baseline median ECG was stored every 5 minutes if ST-change was below these levels or absent altogether.

Data Management

Recordings were stored on a hard disk, subsequently downloaded to floppy disk and sent to the Cardialysis ECG core laboratory for editing and analysis. The timing of the start of study drug administration and the moment of coronary procedures, as well as the presence of episodes of chest pain during ECG monitoring were obtained from the Case Report Forms. All personnel involved in the analysis remained blinded to study treatment and patient outcome.

Editing and Analysis of Recorded Data

The procedures of editing of the continuous ECG monitoring data and the analysis with an automated computer-driven ischemic ST-episode detection program have been described in detail.[5,9,10] After editing, trends of the ST-segment level measured at J-point +60 mseconds were generated for each single lead of the 12-lead ECG (except aVR) in PURSUIT and FROST, and for each single lead of the derived 12-lead ECG (except aVR) in CAPTURE, which was calculated from the X-Y-Z leads using the transformation formulas of Dower.[16]

The onset of an ST-episode was defined as a change of ST-amplitude $\geq$ 100μV from the baseline ST-level in one or more of the 12 leads, developing within a 10-

minute period in CAPTURE and a 20-minute period in PURSUIT and FROST, and persisting for at least 1 minute. The end of an episode was defined as a return of the ST-level within 100μV of the baseline ST-level, again lasting for at least one minute. If ≥ 100μV ST-change was present in multiple leads simultaneously, the onset of the ST-episode was defined by the lead exhibiting the first significant ST-change. Similarly, the end of an episode was defined by the lead exhibiting the latest moment of return to baseline ST-level. Episodes had to be separated from each other by at least one minute. A computer algorithm programmed according to these criteria for ischemia was used for detection of ST-episodes, with visual confirmation afterwards. Examples of the ST-trend analysis have been published previously.[5,10]

Patients were excluded from the present analysis if the recording started >12 hours after the start of study drug administration in PURSUIT and FROST and >1 hour in CAPTURE. Recordings with <50% analyzable data or with a duration of <12 hours were also excluded. ST-episodes occurring during coronary procedures were excluded.

Ischemic burden was calculated in different ways: the total duration of all ST-episodes per patient, the sum of the area under the curve of all 12 ECG leads during ST-episodes per patient, and the area under the curve of the ST-vector magnitude (ST-VM) of all episodes per patient, calculated from the X-Y-Z leads (CAPTURE) or the 8 independent leads with subsequent use of the inversed Dower transformation formula (PURSUIT and FROST).[16] The area under the curve was measured from the baseline ST-level directly preceding the episode.

Endpoints

The relationship between recurrent ischemia and mortality, as well as the composite of death and myocardial infarction was investigated at 5 and 30 days following randomization. In all studies, a blinded Clinical Events Committee adjudicated suspected myocardial infarctions within 30 days according to previously-published criteria.[12-14]

Statistical Analysis

Continuous variables are summarized using the median and interquartile range (25th and 75th percentiles) and were compared using Wilcoxon Two-sample Test. Discrete variables are described as percentages and were compared using Fisher's Exact Test. A two-sided p-value of less than 0.05 was required for significance. The number of ST-episodes was normalized to a period of 24 hours. Patients were subsequently classified by the number of ST-episodes per 24 hours into one of the following categories: 0, 0-1, 1-2, 2-3, 3-4, 4-5 and ≥ 5. The relationship between recurrent ischemia and adverse outcome was evaluated univariably and after

adjustment for baseline variables known to be independent predictors of death and myocardial infarction in patients with non-ST-elevation acute coronary syndromes, based on an established risk model for this patient population.[17] These included age, gender, pulse, ST-depression at enrolment, smoking status, history of diabetes mellitus or congestive heart failure, as well as previous myocardial infarction, percutaneous coronary intervention or bypass surgery.[17] Variables are presented as odds ratios with 95% confidence intervals.

Results

A total of 1181 patients were enrolled in the three trials together. One hundred and eighty-six (16%) patients were excluded from the present analysis for the

Table 1. Baseline Characteristics

	Patients without ischemic episodes (n=724)	Patients with any ischemic episode (n=271)	P-value
Age, yr	62 (54,69)	66 (58,71)	<0.001
Male sex, %	69	75	0.07
Current smoker, %	35	37	0.55
Diabetes, %	14	16	0.69
Previous MI, %	32	38	0.10
Previous PCI, %	14	19	0.07
Previous CABG, %	8	11	0.18
Congestive heart failure, %	3	5	0.19
Heart rate, bpm	70 (64,79)	72 (64,83)	0.06

For continuous variables, median values are provided, with 25th and 75th percentiles in parentheses; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention. P-value by Fisher's Exact Test for discrete variables and by Wilcoxon Two-sample Test for continuous variables.

following reasons: 1) the recording began too late or contained < 12 hours or < 50% of analyzable ECG data (n = 58), 2) technical failures due to incorrect user operation of the monitoring system (n = 124), and 3) left bundle branch block that prevented interpretation of the ST-segment (n = 4). Thus, ECG recordings suitable for ST-analysis were available in 995 (84%) patients. The median total recording time suitable for ST-analysis was 25 hours (25th and 75th percentiles, 24 and 28 hours).

Ischemic episodes during continuous ECG monitoring were detected in 271 (27%) of the 995 patients. Almost half (49%) of the patients who exhibited recurrent ischemia had two or more ischemic episodes per 24 hours. Patients with recurrent ischemia had a worse cardiovascular baseline risk profile including older age, higher heart rate and a higher frequency of previous myocardial infarction and coronary revascularization when compared with patients without ischemia (Table 1). Episodes of recurrent chest pain during monitoring were reported by the investigator in 216 (22%) of the 995 patients.

Relationship Between Recurrent Ischemia and Outcome

Eight patients (0.8%) died within 5 days of follow-up. The incidence of the composite of death and myocardial infarction was 4.7%. At 30 days, the incidence of death was 2.2%, while the composite of death and myocardial infarction occurred in 76 patients (7.6%).

Patients who exhibited recurrent ischemia during ECG monitoring more frequently died or suffered from an myocardial infarction (Table 2). The differences in cardiac event rates between patients with recurrent ischemia and those without were substantial, and all comparisons were statistically significant. The results were consistent for death alone and for the composite of death and myocardial infarction, as well as for events occurring during short-term (5 days) and long-term (30 days) follow-up. The association between recurrent ischemia and adverse outcome was even more apparent in patients with frequent recurrent ischemia, as represented by two or more and three or more ST-episodes during ECG monitoring (Table 2). In fact, there was a direct relationship between the number of recurrent ischemic episodes per 24 hours and the probability of adverse cardiac events (Figure 1). At 5 days, the incidence of the composite of death and myocardial infarction was 3.3% among patients without ST-episodes which increased up to 15.5% in patients with more than 5 ST-episodes. At 30 days, these figures were 5.7% and 19.7%, respectively.

Both in univariable and multivariable analysis, the relationship between recurrent ischemia and unfavorable outcome was remarkably consistent (Figure 2). All ischemia parameters univariably associated with impaired outcome remained independent predictors in the multivariable analysis, with comparable odds ratios. After multivariable adjustment, the relative risk of death or myocardial

Table 2. Relation Between Recurrent Ischemia During ECG-Ischemia Monitoring and Clinical Outcome

		5 days					30 days					
		Death		Death / MI			Death			Death / MI		
	n	n	%	*P*	n	%	*P*	n	%	*P*	n	%	*P*
Patients	995											
No ST-episode	724	1	0.1	<0.001	24	3.3	0.001	10	1.4	0.006	41	5.7	<0.001
Any ST-episode	271	7	2.6		23	8.5		12	4.4		35	12.9	
<2 ST-episodes	861	3	0.3	0.002	31	3.6	<0.001	14	1.6	0.005	54	6.3	<0.001
≥2 ST-episodes	134	5	3.7		16	11.9		8	6.0		22	16.4	
<3 ST-episodes	885	3	0.3	<0.001	33	3.7	<0.001	14	1.6	0.001	57	6.4	<0.001
≥3 ST-episodes	110	5	4.5		14	12.7		8	7.3		19	17.3	
No pain episode	779	6	0.8	0.69	30	3.9	0.02	18	2.3	0.80	53	6.8	0.08
Any pain episode	216	2	0.9		17	7.9		4	1.9		23	10.6	
<2 pain episodes	963	6	0.6	0.03	43	4.5	0.06	20	2.1	0.16	72	7.5	0.30
≥2 pain episodes	32	2	6.3		4	12.5		2	6.3		4	12.5	

Data have been normalized to 24 hours. MI = myocardial infarction. P-values provided for Fisher`s Exact Test.

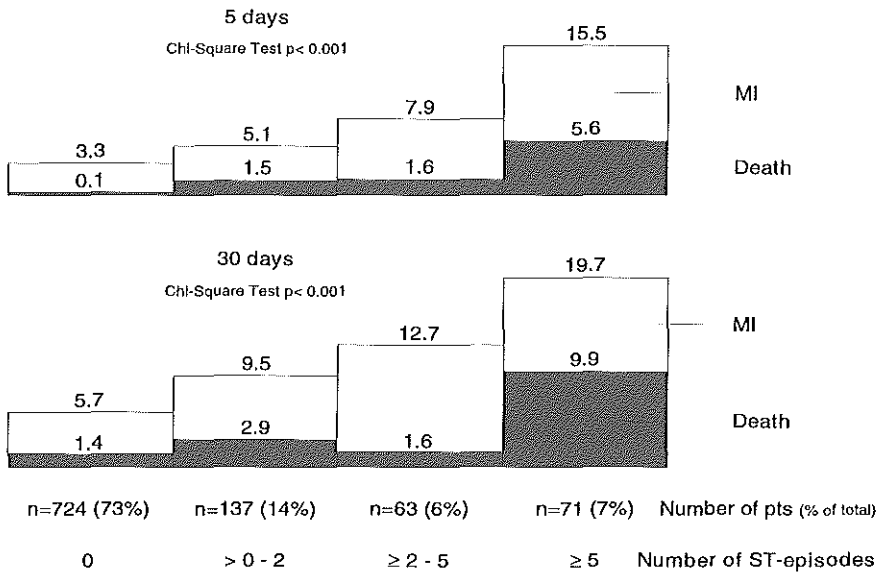


Figure 1
Incidence (%) of death and composite of death and myocardial infarction at day 5 and 30 in patients with a non-ST-elevation acute coronary syndrome classified according to the number of ischemic episodes per 24 hours as detected by continuous multilead ECG-ischemia monitoring. MI = myocardial infarction.

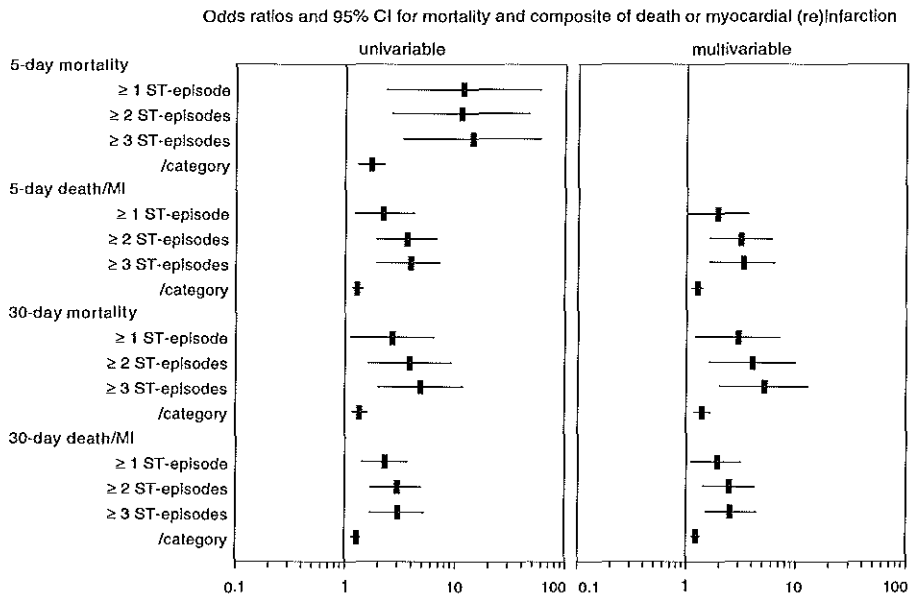


Figure 2
Univariable and multivariable-adjusted odds ratios for mortality and composite of death and myocardial infarction at 5 and 30 days. Odds ratios presented for various parameters of recurrent ischemia. Horizontal lines indicate 95% confidence intervals (CI). /category = for each increase in category of the number of ischemic episodes per 24 hours (0, 0-1, 1-2, 2-3, 3-4, 4-5, ≥5). Number of deaths in first 5 days was too low for a meaningful multivariable assessment. MI = myocardial infarction.

Table 3. Relation Between Ischemic Burden and Clinical Outcome in Patients With Recurrent Ischemia

	5 days						30 days					
	No death (n=264)	Yes death (n=7)	*P*	No death/MI (n=248)	Yes death/MI (n=23)	*P*	No death (n=259)	Yes death (n=12)	*P*	No death/MI (n=236)	Yes death/MI (n=35)	*P*
Frequency of ischemia												
Number of ST-episodes	2 (1,5)	6 (2,11)	0.09	2 (1,5)	5 (1,9)	0.14	2 (1,5)	7 (1,11)	0.06	2 (1,5)	3 (1,7)	0.14
Ischemic burden												
Duration (min)	6	32	0.47	6	4	0.62	5	44	0.03	6	10	0.24
ST-VM (μV.min)	2052	7722	0.03	1745	15573	<0.001	1957	6867	0.004	1632	7505	<0.001
12-lead ST-area (μV.min)	8550	46259	0.02	8048	112217	<0.001	8261	37500	0.002	7617	46259	<0.001

Data provided only for patients with any ischemic episode per 24 hours. Number of ST-episodes presented as median value with 25th and 75th percentiles in parentheses. Median values provided for ischemic burden variables. MI = myocardial infarction; ST-VM = area under curve of ST-vector-magnitude during ST-episodes per patient; 12-lead ST-area = sum of area under curve of all 12 ECG leads during ST-episodes per patient. P-values provided for Wilcoxon Two-sample Test.

infarction both at 5 and 30 days increased by 25% for each increase in the category of ischemic episodes per 24 hours (Figure 2). The risk of death at 30 days increased by almost 40%. The number of deaths in the first 5 days was too low for a meaningful multivariable assessment.

Patients with recurrent episodes of chest pain exhibited a trend towards an increased risk of death and myocardial infarction (Table 2). Although the association between chest pain and adverse cardiac outcome did not reach statistical significance in most comparisons, the directionality of the effect on outcome parallels that of recurrent ischemia detected by ECG-ischemia monitoring.

In patients with ischemia, those who had a greater ischemic burden more often died or developed a myocardial infarction as compared with those with a lower ischemic burden (Table 3).

Discussion

The present analysis in almost 1000 patients with acute coronary syndromes without persistent ST-elevation currently represents the largest assessment of the prognostic implications of recurrent ischemia as detected by computer-assisted continuous multilead ECG-ischemia monitoring in this patient population. The results confirm that recurrent ischemia is an independent and important predictor of death and myocardial infarction. In addition, the present analysis demonstrates that almost 75% of all patients admitted with a non-ST-elevation acute coronary syndrome do not exhibit any episode of recurrent ischemia. Despite the fact that these patients met the electrocardiographic or enzymatic criteria for enrollment in the respective studies, they had a relatively low risk of death and myocardial infarction (3.3% at day 5 and 5.7% at day 30). The results also confirm previous observations that recurrent ischemia detected by multilead ECG monitoring is a more sensitive and better prognostic marker than recurrence of chest pain.[1,8]

Several previous studies have shown that recurrent ischemia, either silent or symptomatic and detected by either Holter or computer-assisted multilead ECG monitoring, during the first few days after admission for an acute coronary syndrome portends an unfavorable outcome.[1-9] In some of these studies, the prognostic information of recurrent ischemia appeared to be independent from and additive to that of the baseline characteristics as well as to the presence of ST-depression on the enrolment ECG and to the biochemical markers of myocardial necrosis at admission, including the creatine kinase-MB and troponin levels.[7,8] However, the small sample sizes of the individual studies with relatively few cardiac events during follow-up limited the assessment of the magnitude of the risk associated with recurrent ischemia after multivariable adjustment. Consequently, the odds ratios varied considerably across the studies and the 95% confidence intervals were wide. Accordingly, all previous studies evaluating multilead ECG-

ischemia monitoring in acute coronary syndrome patients failed to demonstrate a direct relation between the number of ischemic episodes and the risk of adverse outcome. By combining three studies on multilead ECG-ischemia monitoring in almost 1000 patients, the present analysis was able to provide an accurate assessment of the impact of recurrent ischemia on outcome and to establish a direct proportional relationship between the number of recurrent ischemic episodes and the risk of death or myocardial infarction. After multivariable adjustment, the relative risk of death or myocardial infarction both at 5 and 30 days increased by 25% for each additional ischemic episode per 24 hours. The large sample size also allowed a risk assessment for death alone: the risk of death at 30 days was particularly high in patients with ≥ 5 episodes of recurrent ischemia (5.6% at day 5 and 9.9% at day 30). The results were obtained in a diverse population of patients presenting with non-persistent ST-elevation acute coronary syndromes, varying from patients with unstable angina accompanied by T-wave inversion and a low risk profile to those at increased risk of adverse outcome because of refractory unstable angina or non-Q-wave myocardial infarction.

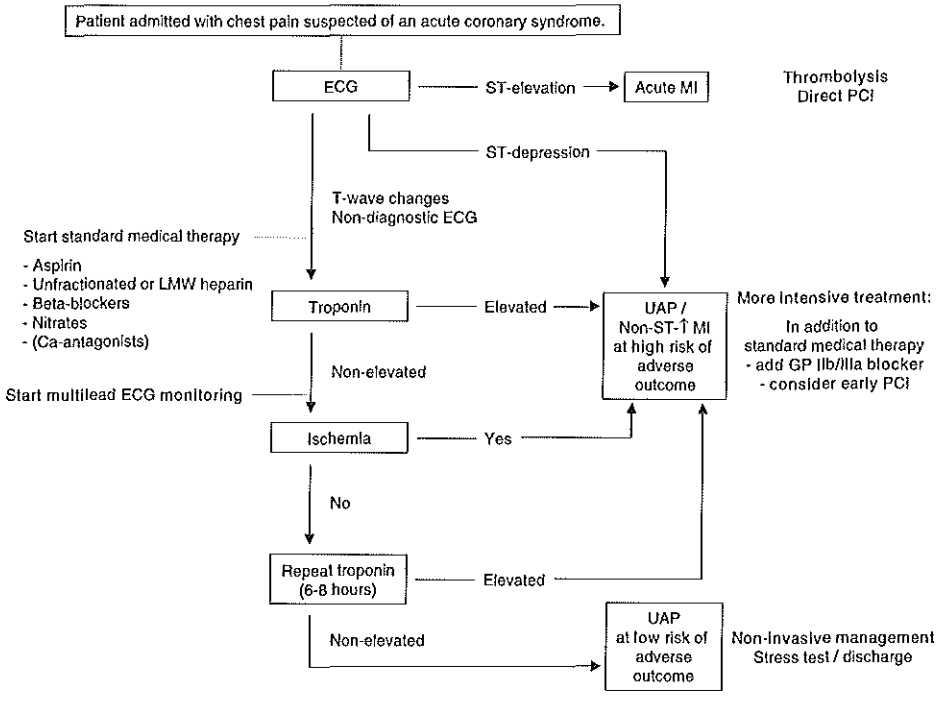


Figure 3
Protocol for triage of patients admitted with chest pain suspected of an acute coronary syndrome.

Incorporation of Continuous Multilead ECG-Ischemia Monitoring in Patient Triage

Patients who present with chest pain or other symptoms suggestive of an acute coronary syndrome and do not have persistent ST-segment elevation on the electrocardiogram, encompass a heterogeneous group that varies considerably with respect to diagnosis as well as future risk for cardiac events. Early risk stratification in these patients is important to tailor pharmacological and invasive treatment to an individual need based on the expected prognosis. Baseline characteristics, the admission 12-lead electrocardiogram, biochemical markers of myocardial necrosis as well as continuous multilead ECG-ischemia monitoring have all independently proven useful in risk stratification and could be combined in an emergency department protocol for patient triage as suggested in Figure 3.[4-9,17-23]

Recent clinical trials suggest that patients identified as having a high risk of subsequent cardiac events based on ST-depression on the admission ECG or an elevated troponin T or I level, may particularly benefit from a more aggressive therapeutic approach including administration of a glycoprotein IIb/IIIa receptor inhibitor and an early percutaneous coronary intervention.[22-26] In patients with an elevated troponin level, glycoprotein IIb/IIIa receptor blockers have been shown to reduce the high risk of cardiac events to that of patients without elevated troponin levels.[22,23] This applies to thrombotic complications arising from spontaneous plaque disruption as well as those associated with intervention-induced plaque ruptures.[22,23]

If it is impossible to perform immediate percutaneous coronary intervention, high-risk patients may still receive a glycoprotein IIb/IIIa blocker as there appears to be a benefit of these agents during pharmacological treatment only.[22-24] A recent meta-analysis showed a 34% relative reduction (from 3.8% to 2.5% at 72 hours) in the composite endpoint of death or myocardial infarction during pharmacological treatment among the full spectrum of patients with non-ST-elevation acute coronary syndromes.[24] In retrospective studies, the benefit appears even greater in patients with an elevated troponin level at admission.[22,23] However, this observation is investigated in a prospective way in the forthcoming GUSTO-IV-ACS study.

Patients admitted with a low-risk profile and a non-elevated troponin level should undergo continuous multilead ECG-ischemia monitoring while receiving standard medical therapy (Figure 3).[21,27] Measurement of troponin level should be repeated after approximately 8 hours. Patients who stabilize and do not exhibit recurrent ischemic episodes have a low risk of death and myocardial infarction. In these patients, a non-invasive management strategy might be preferred.[7,21-23,26] Early transfer to a low level of care and early hospital discharge may result in economic gains without jeopardizing the safety. By contrast, in patients with an

initial low-risk profile who do exhibit recurrent ischemia, the risk of adverse outcome increases with the number of ischemic episodes. These patients should be considered high-risk even when the serum troponin level is not elevated.[7,8,27] Glycoprotein IIb/IIIa inhibition therapy and an early revascularization should be considered. This would apply even more to patients who exhibit frequent recurrent ischemia as the present analysis shows that the 30-day event rate of almost 20% in this group surpasses the risk associated with an early intervention protected by a glycoprotein IIb/IIIa blocker. Clearly, the above protocol for patient triage needs to be evaluated for its safety and efficacy in prospective studies.

The present analysis was limited by the fact that the troponin level at admission could not be included in the multivariable analysis as this information was not systematically available in the three studies. However, two recent studies have demonstrated that the presence of ischemic episodes during multilead ECG monitoring has predictive value additive to that afforded by the troponin level.[7,8] A potential limitation of the ECG monitoring studies is that the ST-trend data could not be blinded during the recording. However, clinicians were only instructed on how to operate the monitoring function of the ECG system and no information was provided on how the ST-trend data could be retrieved. Furthermore, the monitoring devices were specifically introduced in most investigational centers for these studies and were not used for routine monitoring of patients. Finally, decisions based on ST-trend data or the on-line observation of ischemic episodes would more likely have resulted in an underestimation rather than an overestimation of the prognostic value of ischemic episodes detected by multilead ECG-ischemia monitoring.

In conclusion, the profound impact of recurrent ischemia on survival and the incidence of myocardial infarction among patients treated for acute coronary syndromes emphasizes the need for continuous on-line ECG-ischemia monitoring. Therefore, integration of continuous multilead ECG-ischemia monitoring systems in coronary care units and emergency wards will identify patients at increased risk of an unfavorable outcome, and allow for better prognostic triage and more appropriate selection of therapeutic strategies.

References

1 Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986; **314**: 1214-9.

2 Nademanee K, Intarachot V, Josephson MA, Rieders D, Vaghaiwalla Mody F, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 1987; **10**: 1-9.

3 Arnim TV, Krawietz GW, Hofling B. Prognostic implications of transient-predominantly silent-ischemia in patients with unstable angina pectoris. *Eur Heart J* 1988; **8**: 435-40.

4 Patel DJ, Knight CJ, Holdright DR et al. Long-term prognosis in unstable angina. The importance of early risk stratification using continuous ST segment monitoring. *Eur Hear J* 1998; **19**: 240-9.

5 Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 1998; **98**: 1358-64.

6 Holmvang L, Andersen K, Dellborg M et al. Relative contributions of a single-admission 12-lead electrocardiogram and early 24-hour continuous electrocardiographic monitoring for early risk stratification in patients with unstable coronary artery disease. *Am J Cardiol* 1999; **83**: 667-74.

7 Norgaard BL, Andersen K, Dellborg M, Abrahamsson P, Ravkilde J, Thygesen K, for the TRIM study group. Admission risk assessment by cardiac troponin-T in unstable coronary artery disease: additional prognostic information from continuous ST-segment monitoring. *J Am Coll Cardiol* 1999; **33**: 1519-27.

8 Jernberg T, Lindahl B, Wallentin L. ST-segment monitoring with continuous 12-lead ECG improves early risk stratification in patients with chest pain and ECG nondiagnostic of acu myocardial infarction. *J Am Coll Cardiol* 1999; **34**: 1413-9.

9 Akkerhuis KM, Maas ACP, Klootwijk PAJ et al. Recurrent ischemia during continuous 12-lead ECG-ischemia monitoring in patients with acute coronary syndromes treated with eptifibatide: relation with death and myocardial infarction. *J Electrocardiol* 2000; **33**: 127-36.

10 Klootwijk P, Meij S, van Es GA et al. Comparison of usefulness of computer-assisted continuous 48-h 3-lead with 12-lead ECG-ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. *Eur Heart J* 1997; **18**: 931-40.

11 Dellborg M, Malmberg K, Ryden L, Svensson A, Swedberg K. Dynamic on-line vectorcardiography improves and simplifies in-hospital ischemia monitoring of patients w unstable angina. *J Am Coll Cardiol* 1995; **26**: 1501-7.

12 Akkerhuis KM, Neuhaus KL, Wilcox RG et al. Safety and preliminary efficacy of one-month glycoprotein IIb/IIIa inhibition with lefradafiban in patients with acute coronary syndromes without persistent ST-elevation. *Eur Heart J*. In press.

13 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; **349**: 1429-35.

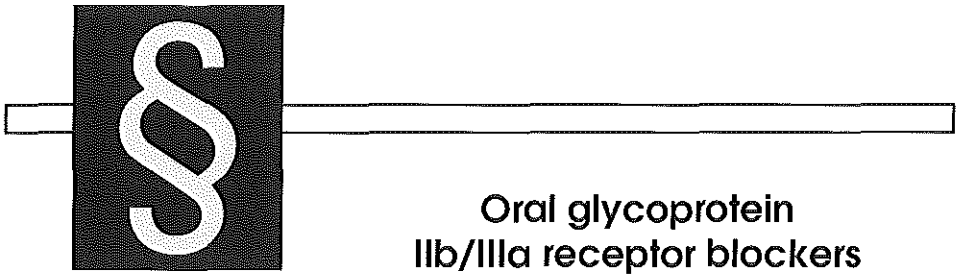
14 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339**: 436-43.

15 Frank E. Accurate, clinically practical system for spatial vectorcardiography. *Circulation* 1956; **13**: 737-44.

16 Dower GE, Machado HB, Osborne JA. On deriving the electrocardiogram from vectorcardiographic leads. *Clin Cardiol* 1980; **3**: 87-95.

17 Boersma E, Pieper KS, Steyerberg EW et al, for the PURSUIT Investigators. Predictors of outcome in patients with acute coronary syndromes without persistent ST-elevation: results from an international trial of 9,461 patients. *Circulation*. In press.

18 Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999; **281**: 707-13.
19 Ravkilde J, Nissen H, Horder M, Thygesen K. Independent prognostic value of serum creatine kinase isoenzyme-MB mass, cardiac troponin-T and myosin light-chain levels in suspected acute myocardial infarction. *J Am Coll Cardiol* 1995; **25**: 574-81.
20 Lindahl B, Venge P, Wallentin L. Relation between troponin-T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996; **93**: 1651-7.
21 Klootwijk P, Hamm CW. Acute coronary syndromes: diagnosis. *Lancet* 1999; 353(suppl-II): 10-5.
22 Hamm CW, Heeschen C, Goldmann B et al, for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin-T levels. *N Engl J Med* 1999; **340**: 1623-9.
23 Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD, for the PRISM Study Investigators. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; **354**: 1757-62.
24 Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: Early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999; **100**: 2045-8.
25 Ronner E, Boersma E, Harrington RA, Lincoff AM, Deckers JW, Simoons ML. Optimal timing of percutaneous intervention (PCI) in unstable angina. *Circulation* 1999; **100**: I-455.
26 FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC-II prospective randomised multicentre study. *Lancet* 1999; **354**: 708-15.
27 Pitt B. Risk stratification in patients with unstable angina. 'Deja vue all over again?'. *Circulation* 1996; **93**: 1618-20.



Oral glycoprotein IIb/IIIa receptor blockers

13

Pharmacodynamics and Safety of an Oral Platelet Glycoprotein IIb/IIIa Receptor Antagonist, Lefradafiban, in Patients With Stable Coronary Artery Disease Undergoing Elective Percutaneous Transluminal Angioplasty

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Heart. In press.

Abstract

Background
Oral platelet glycoprotein IIb/IIIa receptor blockers might enhance the early benefit of an intravenous agent. Lefradafiban is the orally active prodrug of fradafiban, a glycoprotein IIb/IIIa blocker.

Objective
To determine the dose of lefradafiban that provides 80% blockade of the glycoprotein IIb/IIIa receptors (FRO = Fibrinogen Receptor Occupancy) by fradafiban and to study the pharmacodynamics and safety of different doses in patients with stable angina undergoing angioplasty.

Design
A double-blind, placebo-controlled, dose-finding study.

Setting
Four academic and community hospitals in The Netherlands.

Patients
A total of 64 patients with stable coronary artery disease undergoing elective percutaneous transluminal coronary angioplasty.

Interventions
30 mg, 45 mg and 60 mg lefradafiban tid or placebo was administered for 48 hours.

Main Outcome Measures
The primary safety endpoint was the occurrence of bleeding classified as major, minor or insignificant according to the TIMI criteria. Efficacy parameters included the % FRO, ex-vivo platelet aggregation and plasma concentrations of fradafiban.

Results
Levels of FRO increased in a dose-dependent manner: administration of lefradafiban 30, 45 and 60 mg tid resulted in median FRO levels of 71%, 85% and 88%, respectively. Inhibition of platelet aggregation was closely related to FRO. There were no major bleeding events. Lefradafiban 60 mg tid resulted in a high (71%) incidence of minor and insignificant bleeding. The incidence of bleeding was 44% in the lefradafiban 30 and 45 mg tid groups, compared with 9% in placebo patients. Puncture site bleedings were most common. The odds of bleeding increased by 3% for every increase in FRO by 1%.

Conclusions

Lefradafiban is an effective oral glycoprotein IIb/IIIa receptor blocker. The clinical effectiveness of dosages up to 45 mg tid should be investigated.

Introduction

Platelet adhesion, activation and aggregation are pivotal events in the process leading to coronary thrombosis in patients with unstable coronary artery disease.[1] This process is also activated during percutaneous transluminal coronary angioplasty (PTCA) by local vascular injury which exposes circulating platelets to various prothrombotic stimuli within the subendothelium.[2,3] The final common pathway to coronary thrombus formation involves aggregation of platelets via cross-linking of their glycoprotein (GP) IIb/IIIa receptors by the primary binding ligand fibrinogen.[4]

Several inhibitors of the GP IIb/IIIa receptor have been developed. The monoclonal antibody c7E3 (abciximab) has been shown to reduce the incidence of death and myocardial infarction in patients undergoing PTCA, with or without stent deployment.[5,6,7,8] Small molecules (eptifibatide, tirofiban) given intravenously also reduce complications associated with PTCA, although their effects were of borderline significance.[9,10] Furthermore, these intravenous GP IIb/IIIa receptor blockers have recently been shown to reduce the incidence of death, recurrent myocardial infarction and recurrent ischemia in patients with unstable angina or non-ST-segment elevation myocardial infarction.[11,12,13]

The clinical use of monoclonal antibodies and small molecules as GP IIb/IIIa receptor blockers is limited to the treatment of acute episodes of unstable angina, or treatment during coronary procedures, since oral administration is not feasible. Lefradafiban (Boehringer Ingelheim, Germany) is an orally active prodrug which is metabolised in two steps to fradafiban, an intravenously-active, non-peptide GP IIb/IIIa receptor inhibitor.[14] In studies with healthy volunteers, fradafiban as well as lefradafiban lead to a reversible and dose-dependent inhibition of platelet aggregation.[14]

The aim of the present, first phase II study was to determine the dose regimen of lefradafiban that provides 80% blockade of the platelet GP IIb/IIIa receptors (FRO = Fibrinogen Receptor Occupancy) by fradafiban as well as to study the pharmacodynamics and safety of different doses in patients with stable coronary artery disease undergoing elective PTCA to select the appropriate range of dose regimens for subsequent larger studies.

Methods

Study population

Patients aged between 18 and 80 years with stable coronary artery disease were eligible for enrolment if they were scheduled for elective PTCA. Patients were excluded if they suffered from unstable angina or if there was a total occlusion of the vessel to be treated. Other criteria for exclusion included myocardial infarction within the preceding 14 days, planned stent implantation, major surgery or trauma within the preceding 6 weeks, any history of cerebrovascular haemorrhage or haemorrhagic diathesis, cardiopulmonary resuscitation or complicated puncture of a major vein or artery within the preceding 6 weeks, retinopathy grade 3 or greater, gastrointestinal or genitourinary bleeding within the preceding 6 weeks, peptic ulcer disease, platelet count $< 100 \times 10^9/l$, uncontrolled hypertension (systolic blood pressure > 200 mmHg and/or diastolic blood pressure > 100 mmHg), current therapy with oral anticoagulants or any antiplatelet agent other than acetylsalicylic acid, including any non-steroidal anti-inflammatory agent, pregnant or nursing women or women not using medically approved means of contraception, known hepatic or renal insufficiency or any other concomitant serious illness which would limit life expectancy or interfere with the study endpoints. The study protocol was reviewed and approved by each hospital's Institutional Review Board, and informed consent was obtained from each patient prior to participation in the trial.

Study design and dose selection

The initial protocol envisaged a dose-escalation, starting with lefradafiban 60 mg tid or placebo and subsequent series of 75 mg tid and 90 mg tid. Based on phase I data in healthy volunteers, the latter dose was expected to achieve FRO levels of more than 80%.[14] However, after completion of the first group of 21 patients treated with lefradafiban 60 mg tid, it became apparent that this dose was associated with a high incidence of bleeding and FRO levels of more than 80% (see results). Therefore, the dose for the next group was reduced to 30 mg tid. After the safety of this regimen had been established, a third group was investigated receiving lefradafiban 45 mg tid or placebo.

Within each dose level, patients were randomised in a 4:1 ratio to receive lefradafiban or placebo in a double-blind manner. Study medication was administered as an oral solution 3 times a day for two days. It was not to be taken within 2 hours after or 1 hour prior to a meal. The first dose was given 2 hours before the start of the PTCA. An additional loading dose was administered 3.5 hours following the first dose while subsequent doses were given at 8-hour intervals.

Concomitant therapy

Before the start of the PTCA, all patients received an intravenous bolus of heparin of 5000 IU as well as an intravenous bolus of 250 mg acetylsalicylic acid. During the procedure, heparin was repeated in boluses of 5000 IU after 30, 60 and, if necessary, 120 minutes. Aspirin was continued in a dose of 100 mg daily. The use of ticlopidin together with lefradafiban was excluded by the protocol because no interaction data were available at that time. Therefore, if stenting was performed, study drug was discontinued and ticlopidin (250 mg once a day or bid) was initiated. Other medications were continued as before randomisation and adjusted as required by the clinical status of the patient.

Clinical and laboratory monitoring

A coronary angiogram was performed immediately before and after PTCA. Coronary flow was classified according to the Thrombolysis In Myocardial Infarction (TIMI) Study classification by a central angiographic core laboratory (Cardialysis BV).[15] Sheaths were removed 4-6 hours after discontinuation of the heparin infusion and as close as possible before the next intake of study medication, assuming that the platelet inhibitory activity of fradafiban would be at its nadir. Patients underwent daily clinical assessment for the occurrence of bleeding complications and other adverse events as well as extensive laboratory evaluation for haematology, coagulation and biochemistry. Patients returned for a follow-up visit two weeks after hospital discharge, which was not to take place within 48 hours from first study drug administration.

Samples for determination of FRO and fradafiban plasma concentration were drawn at baseline and 2, 4, 12, 24, 36 and 48 hours after study drug initiation. Blood for determination of FRO was stored in a Monovette prefilled with ACD (trisodium citrate, citric acid, dextrose). Platelet-rich plasma was prepared by centrifugation and mixed with labelled fradafiban. After incubation and centrifugation, the supernatant as well as the platelet pellet were counted for free ligand in 4 ml scintillation cocktail. Unspecific binding was determined in the presence of unlabelled fradafiban. The specific binding was calculated using corrections for spill-over, extracellular space and unspecific binding. The percentage of FRO was then calculated from the specific binding data using corrections for receptor affinity and dilution of ACD.

Blood for determination of fradafiban plasma levels was drawn into tubes with EDTA. Plasma was prepared immediately through centrifugation and stored at -20 °C until analysis. Plasma concentrations of fradafiban were measured using a validated high-performance liquid chromatographic method with fluorescence detection.[14] The lower limit of quantification was 1 ng/ml.

Ex-vivo platelet aggregation was assessed in a subgroup of 32 patients at

baseline and 2, 4, 24 and 48 hours after study drug initiation. Platelet aggregation was measured in citrated platelet-rich plasma and recorded by a Chrono-log aggregometer during a 6-8 minute interval after induction by two agonists: 1 mmol/l ADP and 2 mg/ml collagen, respectively. Results are expressed as maximum percent aggregation achieved in platelet-rich plasma, using platelet-poor plasma as reference of 100%.

Ivy bleeding times determined with standard techniques were obtained at baseline and at the end of the 48-hour treatment period. Measurement of bleeding times was discontinued at 15 minutes.

Safety and efficacy parameters

The primary safety endpoint in this trial was the occurrence of bleeding complications classified as major, minor or insignificant according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) Study Group.[16] Major bleeding was defined as intracranial or bleeding associated with a decrease in haemoglobin of more than 3.1 mmol/l (5 g/dl) or a drop in hematocrit of more than 15%. Minor bleeding was defined as observed blood loss with a decrease in haemoglobin of 1.9-3.1 mmol/l (3.1-5.0 g/dl) or a drop in hematocrit of 10-15%. Spontaneous gross haematuria or haematemesis as well as a decrease in haemoglobin of 2.5-3.1 mmol/l or a drop in hematocrit of 12-15% without an identifiable bleeding site were also considered to indicate minor bleeding. Blood loss insufficient to meet criteria for minor bleeding was classified as insignificant. Haemoglobin values were adjusted if patients received packet red blood cells or whole blood within 48 hours prior to the measurement.[17]

The primary efficacy parameter was the FRO level in percentages expressed as area under the curve normalised per hour. Secondary efficacy variables included the ex-vivo platelet aggregation and plasma concentrations of fradafiban.

Statistical analysis

Descriptive analyses of angiographic, aggregation and safety data are presented. The association of % FRO, expressed as Area Under the Curve (AUC), with the first bleeding event was assessed using logistic regression analysis, the null hypothesis being that the risk of bleeding was not affected by FRO levels. The AUC was calculated until the first bleeding, as well as over the whole treatment interval. The relationship between bleeding and heparin administration as well as aPTT AUC was investigated with logistic regression analysis in a similar way.

Results

A total of 64 patients were enrolled: 16 patients received lefradafiban 30 mg tid, 16 lefradafiban 45 mg tid, 21 lefradafiban 60 mg tid and 11 placebo. The majority (73%) of the patients were male (Table 1). The mean age was 61 years (range 39-79 years). A previous myocardial infarction was present in 15 patients (23%), while 3 patients (5%) had undergone coronary artery bypass surgery and 7 (11%) PTCA. All patients received study drug and underwent PTCA, as scheduled. The treated segments were in the right coronary artery in 14 (22%), the circumflex coronary artery in 19 (30%), and the left anterior descending coronary artery in 31 (48%) patients. Coronary flow was normal (TIMI grade III) in 54 patients (84%). Following PTCA, TIMI grade III flow was achieved in all patients, except 2 in the placebo group (TIMI 0), both caused by dissection. A stent was placed in 9 patients. In these patients, study medication was discontinued and ticlopidin (250 mg once a day or bid) was initiated.

Pharmacodynamics and inhibition of platelet aggregation

Plasma concentrations of fradafiban increased in a dose-dependent manner in patients treated with lefradafiban. Geometric means of the maximum plasma concentration of fradafiban at steady state were 158, 314 and 394 ng/ml during treatment with lefradafiban 30, 45 and 60 mg tid, respectively (Table 2). The pharmacokinetic profile of lefradafiban was predictable and no significant deviations from dose-proportionality were observed.

There was a close correlation between the plasma concentrations of fradafiban and the FRO levels (Figure 1). Levels of FRO increased in a dose-dependent manner in patients treated with lefradafiban. Median levels of FRO were 0% in the placebo group, 71% in patients treated with lefradafiban 30 mg tid, 85% in patients treated with lefradafiban 45 mg tid and 88% in patients on Lefradafiban 60 mg tid (Table 2). Minimum, mean and maximum values of FRO were also dose-dependent. Fradafiban plasma levels of 170 ng/ml were required to achieve 80% FRO (Figure 1). There was little variation in FRO level within each patient (Figure 2), while the interpatient variability was greater among patients receiving the lower dose than among those treated with the higher dosages (Figure 2 and Table 2), reflecting the plasma concentration–FRO relationship (Figure 1).

Ex-vivo platelet aggregation was measured in 32 patients and decreased with higher FRO levels (Figure 3). In placebo patients, platelet aggregation was approximately 60% of normal. Inhibition of platelet aggregation to values below 20%, or greater than 80% inhibition, was observed in all patients with FRO levels higher than 80%.

Bleeding times measured at 48 hours were in the normal range for all patients with FRO values below 70%, while prolonged bleeding times were observed in the

majority of patients with higher FRO levels (Figure 4).

Adverse events

Adverse events resulting in discontinuation of study medication occurred in 4 patients: angina with cardiogenic shock in one (30 mg), leucopenia in one (30 mg) and bleeding in two other patients, both receiving 45 mg. No major bleeding events were reported. Minor and insignificant bleeding complications were frequent in the highest dose group (60 mg tid) in which 15 out of 21 patients (71%) experienced such events (Table 2). There was one haematoma in the placebo group, while bleeding was reported in 7 (44%) of 16 patients receiving lefradafiban 30 mg tid as well as in 7 (44%) of 16 patients receiving lefradafiban 45 mg tid (Table 2). Arterial and venous puncture site bleedings were most common. All bleeding events occurred later than 2 hours following administration of the first dose.

By logistic regression analysis, higher levels of FRO were found to be significantly related to an increased incidence of bleeding. The odds of bleeding increased with a factor of 1.03 for every increase in FRO level with 1% point ($p < 0.01$). The relationship between bleeding and heparin administration as well as the aPTT AUC was explored in a similar way. When heparin administration and aPTT AUC were restricted to observations prior to the bleeding event, the relation with bleeding was statistically significant for heparin ($p = 0.04$) but failed to reach conventional statistical significance for aPTT ($p = 0.08$).

A clinically relevant drop in leukocytes ($< 3.0 \times 10^9/l$) was observed in 3 patients, 2 of whom were treated with lefradafiban 60 mg tid, and one with lefradafiban 30 mg tid. The lowest values were $0.9 \times 10^9/l$ (from $5.9 \times 10^9/l$ at baseline), $1.9 \times 10^9/l$ (from $4.7 \times 10^9/l$) and $2.3 \times 10^9/l$ (from $7.4 \times 10^9/l$), observed at 4, 24 and 48 hours after first study drug administration, respectively. After discontinuation of study drug, the leukocyte count in these patients returned to normal levels without additional measures within 2-5 days.

Median values of haematology parameters at baseline were within normal limits in all treatment groups. There was a small decrease in the levels of haemoglobin and thrombocytes during the trial, which was comparable among all treatment groups. Median levels of leukocytes did not change. Serum levels of thromboplastine, thrombin and fibrinogen were not affected. Median concentrations of biochemistry parameters at baseline were within the normal range in all treatment groups and remained within these limits at 24 and 48 hours.

Table 1. Clinical and angiographic characteristics at baseline

		Lefradafiban		
	Placebo	**30 mg tid**	**45 mg tid**	**60 mg tid**
	n = 11	n = 16	n = 16	n = 21
Patient demographics				
Age (years)	58 (7)	65 (8)	62 (13)	60 (12)
Male gender (n)	8	14	11	14
Diabetes (n)	-	3	1	2
Hypertension (n)	2	2	6	5
Previous MI (n)	1	5	5	4
Previous PTCA or CABG (n)	1	3	3	3
Angiographic parameters				
Segments to be treated (n)				
RCA	3	2	3	6
LAD	6	9	8	8
LCX	2	5	5	7
Perfusion grade, TIMI flow (n)				
Grade 0	1	-	1	-
Grade 1	1	-	-	1
Grade 2	1	2	1	2
Grade 3	8	14	14	18
Lesion type by AHA/ACC (n)				
A	1	-	2	1
B1	5	3	5	4
B2	5	10	6	9
C	-	3	3	5
missing	-	-	-	2

For age, the mean values are provided with the standard deviation in parentheses.

AHA/ACC = American Heart Association/American College of Cardiology, CABG = coronary artery bypass grafting, LAD = left anterior descending artery, LCX = left circumflex artery, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery, TIMI = Thrombolysis in Myocardial Infarction.

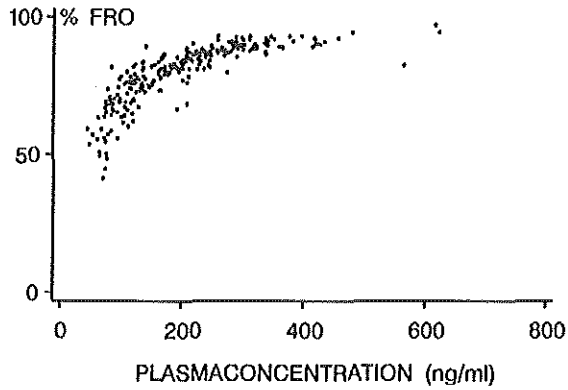

Figure 1
Relationship between the plasma concentration of the active drug fradafiban and the degree of fibrinogen receptor occupancy (FRO).

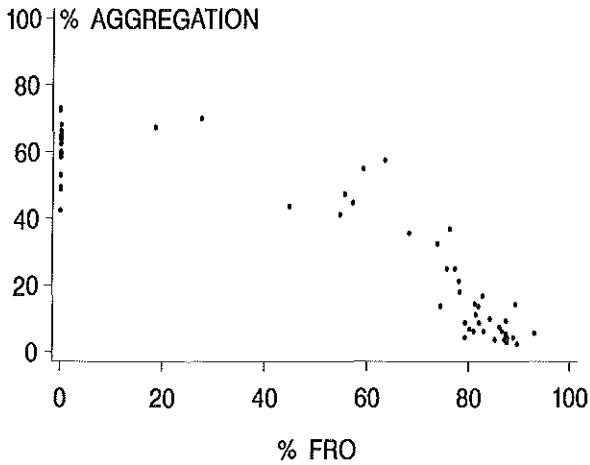

Figure 3
Relation between the degree of fibrinogen receptor occupancy (FRO) and inhibition of ex-vivo platelet aggregation induced by 1 mmol/l ADP in platelet-rich plasma. Each point represents data from a subject at a single time point during the 48 hours of oral treatment with lefradafiban 30, 45 or 60 mg tid.

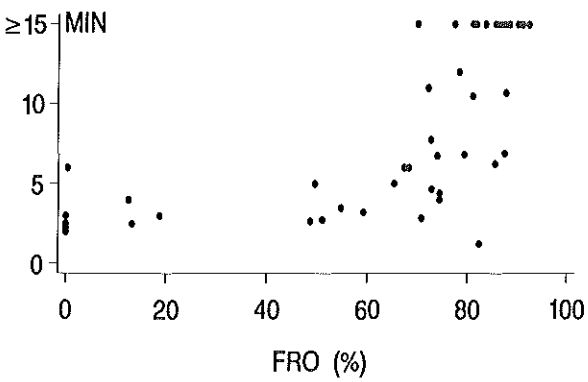

Figure 4
Relation between the degree of fibrinogen receptor occupancy (FRO) and ivy bleeding times at 48 hours after first study drug administration. Each point represents data from a subject in the lefradafiban 30, 45 or 60 mg tid group. Min denotes minutes.

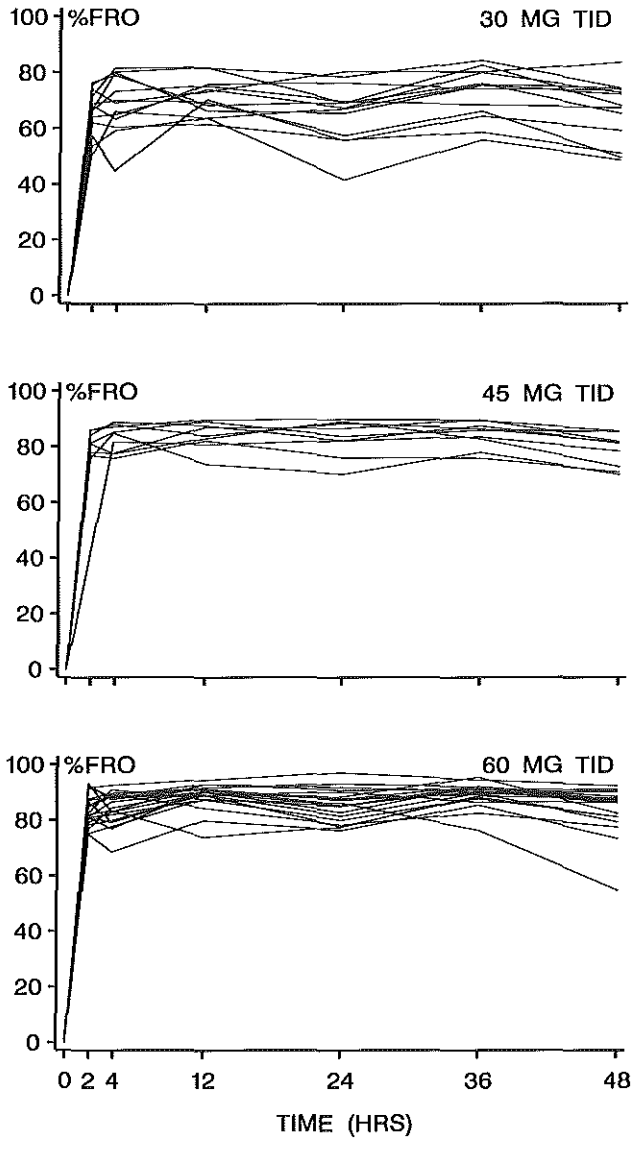

Figure 2
Degree of fibrinogen receptor occupancy (FRO) during oral administration of lefradafiban 30, 45 and 60 mg tid. Each line represents data from an individual patient in one of the three lefradafiban groups during the 48 hours of oral treatment. Each line is based on FRO data obtained at one of the prespecified sample time points (baseline and 2, 4, 12, 24, 36, and 48 hours after study drug initiation).

Table 2. Efficacy and safety endpoints

		Lefradafiban		
	Placebo	**30 mg tid**	**45 mg tid**	**60 mg tid**
	n = 11	n = 16	n = 16	n = 21
Efficacy parameters				
Plasma concentration fradafiban, $C_{max,ss}$ in ng/ml	0	158 (27)	314 (24)	394 (22)
FRO (%) – minimum	0	54	74	78
FRO (%) – median	0	71	85	88
FRO (%) – maximum	0	80	89	95
FRO (%) – mean	0	69 (12)	83 (6)	87 (5)
Bleeding time				
At baseline (min)	3.3	4.0	4.1	5.3
After 48 hours (min)	4.4	7.8	19.2	25.0
Bleeding complications				
Patients with bleeding, n (%)	1 (9)	7 (44)	7 (44)	15 (71)
Number of bleeding events (n)	1	8	9	29
Location of bleeding (n)				
Vascular puncture site	1	6	6	15
Gingival	-	1	2	10
Skin	-	1	1	2
Haematuria	-	-	-	2
Severity of bleeding by TIMI (n)				
Major	-	-	-	-
Minor	-	-	1	2
Insignificant	1	8	8	27

For fradafiban plasma concentration, the means of the maximum fradafiban plasma concentration at steady state ($C_{max,ss}$) are provided with the relative coefficient of variation (%) in parentheses.
For FRO, the minimum, median and maximum values are provided, as well as the means with the relative coefficient of variation (%) in parentheses. All FRO values are expressed as area under the curve normalised per hour. Relative coefficient of variation = 100 x (standard deviation/mean).
FRO = Fibrinogen Receptor Occupancy, TIMI = Thrombolysis in Myocardial Infarction.

Discussion

Administration of lefradafiban, an oral prodrug of the GP IIb/IIIa receptor blocker fradafiban, resulted in rapid and effective inhibition of platelet aggregation in patients with stable coronary artery disease undergoing elective PTCA. Dosages of lefradafiban 30, 45 and 60 mg tid caused a dose-dependent increase in fradafiban plasma levels, increase in FRO and inhibition of platelet aggregation. With the tid dosing, a stable FRO was achieved within each patient (Figure 2). The level of inhibition achieved in patients, who also received aspirin and heparin, was greater than observed in volunteers receiving lefradafiban without additional medication. In the placebo group, platelet aggregation was already decreased to 60%. In the phase I studies, inhibition of platelet aggregation of more than 80% was achieved with lefradafiban doses of 90 mg tid.[14] In the present study, this was achieved with 45 mg tid. This suggests an interaction between the GP IIb/IIIa receptor blocker and aspirin.

As in other studies with GP IIb/IIIa receptor blockers, bleeding occurred frequently at these levels of platelet inhibition and was dose-dependent. The incidences of bleeding complications in the lefradafiban 30 and 45 mg groups were similar to the rates observed in studies with other oral GP IIb/IIIa blockers at similar levels of platelet inhibition,[18,19] while even more bleeding occurred in the highest dose group (71%). In studies with sibrafiban and xemilofiban, a gradual increase in bleeding was observed for higher dose levels with a higher degree of platelet inhibition.[18,19] The results of the logistic regression analysis in the present study support these observations with an increase in the risk of bleeding by 3% for every increase in FRO with 1% point. It should be appreciated that the majority of the bleedings were insignificant, with a low incidence of minor bleeding complications following TIMI classification, and no major bleedings (Table 2). Furthermore, all patients received aspirin and heparin and underwent invasive coronary procedures. Interactions between the GP IIb/IIIa receptor blocker abciximab and heparin have been reported in previous studies.[5,6] As demonstrated in the EPILOG and EPISTENT studies, it is likely that further reduction of the heparin dose in a weight-adjusted manner might reduce bleeding complications in patients receiving lefradafiban without decreasing the clinical efficacy.[7,8] Special care should be given to the access site of vascular sheaths. Sheaths should be removed early (4-6 hours) following the procedure, after the heparin has been stopped and the activated clotting time is 175 seconds or less.[7] Given the interpatient variability in the degree of platelet inhibition observed with oral GP IIb/IIIa receptor antagonists, another potential strategy for reducing bleeding complications during longer-term therapy could be to monitor the degree of platelet inhibition achieved in individual patients by using a platelet-function bedside assay and to titrate the dose to a target level of inhibition.[20,21]

While a gradual dose-dependent increase in bleeding was observed, as in studies with sibrafiban and xemilofiban,[18][19] the relation between bleeding time and % FRO in the present study suggests a threshold effect. The bleeding time was not increased at FRO levels less than 70%, while a marked increase was observed at higher levels. It should be appreciated, however, that measurement of bleeding time does not reflect a tendency to spontaneous bleeding in clinical practice.

In three patients receiving lefradafiban, a clinically significant drop in leukocyte count was observed, although the mean leukocyte count did not change in the overall population. Leukopenia due to bone marrow depression has been reported for other antiplatelet agents (ticlopidin).[22] These, however, occur mostly after 2 to 4 weeks of treatment. In the present study, leukopenia occurred immediately after the first dose or within 2 days. In all three patients, leukocytes returned rapidly in the peripheral blood after discontinuation of study medication. Leukopenia had not been observed in previous studies with lefradafiban in healthy volunteers and, therefore, was an unexpected finding in the present study. Following the observation of the leukopenia in the three patients, an amendment was made which increased the frequency of the haematology evaluations to monitor the safety of the patients and investigate the potential underlying pathophysiological mechanisms. However, no additional patients experienced this adverse event. A recently-presented second phase II study with lefradafiban in patients with acute coronary syndromes has confirmed the increased incidence of leukopenia, or rather neutropenia, associated with lefradafiban and provided some insight in the pathophysiological mechanisms involved.[23] In accordance with the present study, the decrease in neutrophils was characterised by an early onset (immediately after first study drug administration or within the next two days) and a fast recovery after discontinuation of lefradafiban. Based on analysis of blood and bone marrow samples obtained in patients with neutropenia in that study, it was concluded that the observed neutropenia did not result from bone marrow depression but rather from a reversible redistribution of neutrophils by margination or clustering. Yet, more investigations are needed to further identify the exact mechanisms involved, as well as to determine the optimal duration of surveillance and the possible clinical associations.

The clinical benefit of treatment with GP IIb/IIIa receptor blockers in patients undergoing percutaneous intervention has been established by several studies using different inhibitors.[5,6,7,8,9,10] In the present limited series, all patients receiving lefradafiban had a successful PTCA without apparent thrombotic complications, while acute closure was observed during PTCA in one patient in the placebo group. Oral compounds such as lefradafiban offer an opportunity for long-term treatment with an effective platelet aggregation inhibitor, which may

enhance the early benefit of an intravenous agent and prevent subsequent thrombotic events in patients at risk.

Three recently-presented large clinical trials have evaluated this concept of long-term oral GP IIb/IIIa inhibition with xemilofiban in patients after percutaneous coronary intervention (EXCITE) and with orbofiban and sibrafiban in patients after acute coronary syndromes (OPUS-TIMI-16 and SYMPHONY).[24,25,26] None of the trials showed a clear treatment benefit of long-term GP IIb/IIIa inhibition therapy, while all three trials showed a trend towards an increased mortality in the GP IIb/IIIa inhibitor group.[24,25,26] In this respect, several points deserve consideration. First, the patient populations included in these trials were at a relative low risk of recurrent thrombotic events.[24,25,26] Furthermore, the pharmacokinetic and pharmacodynamic profile of these agents is characterised by a steep dose-response relationship and by a short half-life relative to the dosing interval.[18,19,25] This may have caused widely fluctuating inhibition of platelet aggregation and allowed complete recovery in platelet function between doses in some patients, with exposure of activated GP IIb/IIIa receptors on the platelet's surface.[27] Additionally, recent studies have raised the possibility that platelet receptor antagonists may, at low concentrations, alter the steric conformation of the GP IIb/IIIa receptor sites and, paradoxically, enhance the thrombogenicity of these sites.[27,28] Compared with the other oral agents, the lefradafiban tid dosing regimen may result in higher average fradafiban levels with less peak-trough fluctuation and more stable levels of inhibition of platelet aggregation.

It is a challenge to exploit the potential beneficial antithrombotic effect of oral GP IIb/IIIa inhibitors in balance with the associated risk of haemorrhage. Dose-titration to a target degree of platelet inhibition, measured with a rapid platelet-function assay, may improve the overall safety and efficacy profile.[20,29] To increase the treatment benefit of (oral) GP IIb/IIIa blockers, one may choose to treat only patients who are at high risk of recurrent thrombotic complications, such as those who present with elevated troponin levels and continue on medical therapy. These patients may particularly benefit from a more aggressive long-term therapeutic approach.[29,30]

Lefradafiban in doses up to 45 mg tid achieved stable FRO levels to more than 80% in patients with stable coronary artery disease undergoing elective PTCA, with an acceptable safety during short-term treatment. Thus, these doses may be tested in further studies to assess whether long-term treatment is indeed beneficial in patients with acute coronary syndromes at high risk of thrombotic complications, without an excess of bleeding complications.

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References

1 Fuster V, Badimon L, Badimon JJ, *et al.* The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;**326**:242-50,310-8.

2 Haerker LA. Role of platelets and thrombosis in mechanisms of acute occlusion and restenosis after angioplasty. *Am J Cardiol* 1987;**60**:20-8B.

3 Tcnaglia AN, Fortin DF, Califf RM, *et al.* Predicting the risk of abrupt vessel closure after angioplasty in an individual patient. *J Am Coll Cardiol* 1994;**24**:1004-11.

4 Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;**332**:1553-9.

5 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;**330**:956-61.

6 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;**349**:1429-35.

7 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;**336**:1689-96.

8 The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;**352**:87-92.

9 The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997;**349**:1422-8.

10 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;**96**:1445-53.

11 The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498-505.

12 The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488-97.

13 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;**339**:436-43.

14 Müller TH, Weisenberger H, Brickl R, *et al.* Profound and sustained inhibition of platelet aggregation by fradafiban, a nonpeptide platelet glycoprotein IIb/IIIa antagonist, and its orally active prodrug lefradafiban in men. *Circulation* 1997;**96**:1130-8.

15 Chesebro J, Knatterud G, Roberts R, *et al.* Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I: a comparison between intravenous plasminogen activator and intravenous streptokinase. *Circulation* 1987;**76**:142-54.

16 Rao AK, Pratt C, Berke A, *et al.* Thrombolysis in Myocardial Infarction (TIMI) Trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokin ase. *J Am Coll Cardiol* 1988;**11**:1-11.

17 Landefeld CS, McGuire E, Rosenblatt MW. A bleeding risk index for estimating the probability of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med* 1990;**89**:569-78.

18 Kereiakes DJ, Kleiman NS, Ferguson JJ, *et al.* for the ORBIT Trial Investigators. Pharmacodynamic efficacy, clinical safety, and outcomes after prolonged platelet glycoprotein IIb/IIIa receptor blockade with oral xemilofiban: results of a multicenter, placebo-controlled, randomized trial. *Circulation* 1998;**98**:1268-78.

19 Cannon CP, McCabe CH, Borzak S, *et al.* for the TIMI 12 Investigators. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. *Circulation* 1998;**97**:340-9.

20 Coller BS. Monitoring platelet GP IIb/IIIa antagonist therapy. *Circulation* 1998;**97**:5-9.
21 Smith JW, Steinhubl SR, Lincoff AM, *et al.* Rapid platelet-function assay: an automated and quantitative cartridge-based method. *Circulation* 1999;**99**:620-5.
22 Yeh SP, Hsueh EJ, Wu H, *et al.* Ticlopidine-associated aplastic anemia. A case report and review of literature. *Ann Hematol* 1998;**76**:87-90.
23 Wilcox RG for the FROST Investigators. Preliminary results of the Fibrinogen Receptor Occupancy STudy (FROST). Congress of the American College of Cardiology, March 7-10, 1999.
24 O'Neill WW for the EXCITE Investigators. Results of the Evaluation of oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial. Congress of the American College of Cardiology, March 7-10, 1999.
25 Cannon CP for the OPUS-TIMI-16 Investigators. Preliminary results of the TIMI-16 Orbofiban in Patients with Unstable coronary Syndromes (OPUS) trial. Congress of the American College of Cardiology, March 7-10, 1999.
26 The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomized trial. *Lancet* 2000;**355**:337-45.
27 Peter K, Straub A, Kohler B, *et al.* Platelet activation as a potential mechanism of GP IIb/IIIa inhibitor-induced thrombocytopenia. *Am J Cardiol* 1999;**84**:519-24.
28 Peter K, Schwarz M, Ylanne J, *et al.* Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa ($a_{IIB}b_3$) inhibitors. *Blood* 1998;**92**:3240-9.
29 Hamm CW, Heeschen C, Goldmann B, *et al.* for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;**340**:1623-9.
30 Heeschen C, Hamm CW, Goldmann B, *et al.* for the PRISM Study Investigators. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;**354**:1757-62.

14

Safety and Preliminary Efficacy of One Month Glycoprotein IIb/IIIa Inhibition With Lefradafiban in Patients With Acute Coronary Syndromes Without ST-elevation: a Phase II Study

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* *Investigators and study organisation of the Fibrinogen Receptor Occupancy STudy are listed in the Appendix.*

Eur Heart J. In press.

Abstract

Aims

Oral glycoprotein IIb/IIIa inhibitors might enhance the early benefit of an intravenous agent and prevent subsequent cardiac events in patients with acute coronary syndromes. We assessed the safety and preliminary efficacy of one month treatment with three dose levels of the oral GP IIb/IIIa blocker lefradafiban in patients with unstable angina or myocardial infarction without persistent ST-elevation.

Methods

The Fibrinogen Receptor Occupancy STudy (FROST) was designed as a dose-escalation trial with 20, 30 and 45 mg lefradafiban tid or placebo. Five hundred and thirty-one patients were randomised in a 3:1 ratio to lefradafiban or placebo in a double-blind manner. Efficacy was assessed by the incidence of death, myocardial infarction, coronary revascularisation and recurrent angina. Safety was evaluated by the occurrence of bleeding classified according to the TIMI criteria and by measuring clinical laboratory parameters.

Results

There was a trend towards a reduction in cardiac events with lefradafiban 30 mg when compared with placebo and lefradafiban 20 mg. The benefit was particularly apparent in patients with a positive (≥0.1 ng/ml) troponin I test at baseline and less so in those with a negative test result. In patients receiving lefradafiban, the cardiac event rate decreased with increasing minimal levels of fibrinogen receptor occupancy. There was a dose-dependent increase in the incidence of bleeding: the composite of major or minor bleeding occurred in 1% of placebo patients, 5% of patients receiving lefradafiban 20 mg and in 7% of patients receiving 30 mg, with an excessive risk (15%) in the 45 mg group which resulted in early discontinuation of this dose level. Gingival and arterial or venous puncture site bleedings were most common and accounted for more than 60% of all haemorrhagic events. There was an increased incidence of neutropenia (neutrophils $<1.5x10^9/l$) in the lefradafiban groups (5.2% versus 1.5% in the placebo group), which did not result from bone marrow depression but rather from a reversible redistribution of neutrophils by margination or clustering.

Conclusion

One month treatment with the oral glycoprotein IIb/IIIa inhibitor lefradafiban in patients with unstable angina and myocardial infarction without persistent ST-elevation resulted in a decrease in cardiac events with lefradafiban 30 mg and a

dose-dependent increase in haemorrhagic events. The observed favourable trend towards a reduction in cardiac events in patients with elevated troponin levels requires confirmation in a large clinical trial.

Introduction

Coronary thrombosis is a pivotal event in the pathogenesis of acute coronary syndromes and ischemic complications resulting from coronary interventions.[1-3] The final common pathway to coronary thrombus formation involves aggregation of platelets via their glycoprotein (GP) IIb/IIIa receptors.[4] Intravenous inhibitors of GP IIb/IIIa receptors have demonstrated efficacy in reducing ischemic complications in patients undergoing percutaneous coronary intervention and in those with unstable angina or myocardial infarction without persistent ST-elevation.[5-13] Studies with these IIb/IIIa inhibitors have shown early clinical benefit during the short-term period of intravenous administration with no additional benefit after the infusions were stopped.[12-15] Despite intensive medical therapy including short-acting GP IIb/IIIa inhibitors during the acute phase, outcomes among patients hospitalised with acute coronary syndromes remain unsatisfactory with a continuous increase in ischemic events after discontinuation of initial therapy, such that the risk of death or myocardial infarction within the first month after development of the acute coronary syndrome is as high as 10-15%.[12,13,16,17] This may reflect incomplete healing of the vessel wall or the continuance of an activated haemostatic system for several weeks or months after the acute event.[18,19] These data suggest a need for prolonged and profound inhibition of platelet aggregation, which might be afforded by oral GP IIb/IIIa receptor blockers, in order to enhance the early benefit achieved by intravenous agents and prevent subsequent events.

Lefradafiban is an orally active prodrug which is metabolised in two steps to fradafiban, a non-peptide GP IIb/IIIa receptor inhibitor.[20] A recently conducted first phase II study confirmed that lefradafiban causes a dose-dependent inhibition of platelet aggregation which was safe when administered for 48 hours in dosages up to 45 mg tid in patients with stable coronary artery disease undergoing percutaneous coronary intervention.[21] The present FROST study (Fibrinogen Receptor Occupancy STudy) was designed to assess the safety and preliminary efficacy of one month treatment with different dose levels of lefradafiban in patients admitted with unstable angina or myocardial infarction without persistent ST-elevation.

Methods

Study population

In 41 European centres, patients aged between 18 and 80 years with either unstable angina or non-ST-segment elevation myocardial infarction were eligible for enrolment if they presented within 24 hours of the onset of chest pain and had ECG evidence of myocardial ischemia (ST-segment depression, transient ST-

segment elevation or T-wave changes). Criteria for exclusion included concomitant serious illness (active cancer or significant liver or renal disease), history of cerebrovascular accident or epilepsy, history of cranial or intraspinal surgery, active bleeding, peptic ulcer disease, past or present haemorrhagic diathesis or gastrointestinal bleeding within the preceding 3 months, recent major surgery or organ biopsy, puncture of a non-compressible vessel within the preceding 3 weeks, uncontrolled hypertension (systolic blood pressure above 200 mmHg or diastolic blood pressure above 100 mmHg), history of thrombocytopenia or platelet count < 100,000 per ml within the preceding 24 hours, concurrent use of or anticipated need for oral anticoagulation, recent myocardial infarction or receipt of thrombolytic therapy, ECG abnormalities interfering with a reliable interpretation of the ST-segment (e.g. left ventricular hypertrophy with major repolarisation changes or left bundle branch block), planned percutaneous coronary intervention or coronary bypass surgery within 24 hours following enrolment, child-bearing potential, unwillingness to accept blood products, planned administration of a glycoprotein IIb/IIIa inhibitor or receipt of such agent within the preceding 30 days, or use of an investigational device or drug in the preceding 30 days. The protocol was approved by the institutional review board at each study centre and all patients gave written informed consent to participate.

Concomitant therapy

All patients were treated with aspirin and either unfractionated or low-molecular-weight heparin, according to local preference. Aspirin was administered orally in a dose of 150-250 mg immediately following the first intake of study drug and subsequently in a dose of 100 mg daily. Intravenous heparin was to be given as a bolus of 70 U/kg (maximum 5000 U), followed by an infusion at a rate of 15 U/kg per hour (maximum 1000 U per hour) for 2-5 days to achieve and maintain an activated partial-thromboplastin time between 1.5 and 2.0 times the local control value. No recommendations were made with respect to the dosing of low-molecular-weight heparin which was given for 2-5 days. Other medications were given at the discretion of the treating physician.

Study design

The study was designed as a dose-escalation trial with 20, 30 and 45 mg lefradafiban tid or placebo. Within each dose level, patients were randomised in a 3:1 ratio to receive lefradafiban or placebo in a double-blind manner. These dose levels were selected based on results from previous studies with lefradafiban, to achieve and maintain mean values of platelet glycoprotein IIb/IIIa receptor inhibition (FRO = fibrinogen receptor occupancy) of 56%, 67% and 75%, respectively. Study medication was administered as an oral solution 3 times a day

and was to be continued for 30 days. It was not to be taken within 2 hours after or 1 hour prior to a meal. The first dose was given immediately after enrolment in the study while subsequent doses were given at 8-hour intervals. An additional loading dose was administered 3.5 hours following the first dose.

A Data and Safety Monitoring Board was established to continuously monitor the data on safety and efficacy and to provide continued surveillance as necessary in case of untoward bleeding complications or other adverse events. The decision to proceed to a higher dose level was made after this Board had reviewed the safety profile of the preceding dose level. The protocol did not prespecify statistical rules for stopping the study. If the Data and Safety Monitoring Board recommended adjustment in the study design or early cessation of the trial or a certain dose level, the Steering Committee reviewed the recommendation and made the final decision.

Clinical and laboratory monitoring

Patients underwent physical examination and extensive laboratory evaluation for haematology, coagulation and biochemistry at baseline and at regular intervals during hospitalisation and subsequent 30-day follow-up. Qualitative determination of cardiac troponin-I status was performed at baseline. The assessment was performed by the local hospital staff using the Cardiac STATus™ rapid format troponin-I bedside assay (Spectral Diagnostics Inc, threshold 0.1 ng/ml). ECGs were obtained before enrolment and both during as well as 30 minutes after episodes of chest pain. Additional ECGs were recorded 2, 3 and 30 days after enrolment. Patients were continually assessed for the occurrence of bleeding complications and other adverse events. After hospital discharge, patients returned for a follow-up visit every 7 days during the first 5 weeks and then at 2 and 6 months after enrolment.

During enrolment and follow-up in the 20 mg dose level, it was observed that patients receiving lefradafiban more frequently exhibited a clinically relevant drop in leukocyte count as compared with placebo. To obtain a more complete overview on the occurrence, time course and severity of the leukopenia and to provide an increased surveillance on the safety of study patients, a protocol amendment was made which increased the frequency of the haematology evaluations and added blood samples to be taken for central analysis to further investigate the potential underlying pathophysiological mechanisms. In patients in whom a drop in leukocyte count was observed (i.e. value below the lower limit of normal and/or decrease in leukocytes of at least 30% relative to the baseline value), measurements were to be continued until leukocyte count had normalised or returned to otherwise medically acceptable values. From these samples, the incidence of neutropenia was re-estimated using absolute cell count cut-off values similar to

the ranges defined for ticlopidin. This method accommodates for the relative decline in leukocyte count which occurs in patients with acute myocardial infarction and unstable angina after hospital treatment. In two patients puncture of bone marrow was performed. Intake of trial medication was discontinued if leukocyte count dropped below 50% of the lower limit of normal.

Pharmacokinetics and pharmacodynamics

In all lefradafiban dose groups, blood samples were drawn at baseline and day 2, as well as during the weekly follow-up visits for determination of the fradafiban plasma concentration and associated pharmacokinetic parameters. Levels of FRO were calculated from the fradafiban plasma concentration using a pharmacokinetic model whose parameters were established from preceding studies.[20,21]

ECG core laboratory

Computer-assisted continuous 12-lead ECG-ischemia monitoring (ELI ST-100, Mortara Instruments, Milwaukee, U.S.A.) was performed, starting immediately after the intake of the first study medication and continuing for 24 hours to detect and quantify recurrent ischemia. All continuous ECG recordings were analysed at the ECG core laboratory (Cardialysis BV) by independent reviewers unaware of treatment assignment. The procedures of editing and analysis of the continuous ECG recording data as developed and applied by the core laboratory have been described in detail elsewhere.[22,23] The onset of an ischemic episode was defined as either ST-depression or ST-elevation of at least 100mV in one or more of the 12 ECG leads developing within a 10-minute period and persisting for at least 1 minute. The number of patients with recurrent ischemia, the number of ischemic episodes and the ischemic burden in patients with recurrent ischemia were determined.

Study endpoints

The primary safety endpoint in this trial was the occurrence of bleeding complications classified as major, minor, or insignificant according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) Study Group.[24] Major bleeding was defined as intracranial haemorrhage or bleeding associated with a drop of 3.1 mmol/l (5 g/dl) or more in the haemoglobin concentration or of 15 percentage points or more in the hematocrit. Bleeding was defined as minor if it was spontaneous and observed as gross haematuria or haematemesis, or if blood loss was observed with a drop of 1.9 mmol/l (3 g/dl) or more in haemoglobin or of 10 percentage points or more in the hematocrit. If no bleeding site was identifiable, a drop of 2.5 mmol/l (4 g/dl) or more in haemoglobin or of 12 percentage points or more in the hematocrit was considered to indicate minor bleeding. Blood loss

insufficient to meet criteria for minor bleeding was classified as insignificant. To account for transfusion, haemoglobin and hematocrit values were adjusted if patients received packed red blood cells or whole blood within 48 hours prior to the measurement by using the method of Landefeld et al.[25]

The efficacy endpoint was the composite of any of the following events during the one-month treatment period: death from any cause, non-fatal myocardial infarction, any percutaneous coronary intervention or coronary artery bypass grafting. Myocardial infarction was considered to have occurred if there was an elevation of creatine kinase (CK)-MB or CK above the upper limit of normal in at least 2 samples with one value above 2 times the upper limit of normal. Following percutaneous and surgical revascularisation, the elevation of cardiac enzyme levels had to be at least 3 and 5 times above the upper limit of normal, respectively. Suspected infarctions were assessed by a Clinical Events Committee blinded to treatment assignment. Secondary endpoints included the recurrence of unstable angina during study treatment (defined as chest pain with concomitant ischemic ECG changes) as well as the number of patients exhibiting recurrent ischemia and the ischemic burden in patients with ischemia as detected and quantified by continuous 12-lead ECG-ischemia monitoring within 24 hours after the start of study medication.

Statistical analysis

Based on an expected rate of study drug discontinuation of 25%, the number of patients to be enrolled in each lefradafiban group to evaluate the primary safety outcomes was approximately 100. Therefore, approximately 132 patients were to be enrolled in each dose level (99 lefradafiban and 33 placebo). Continuous variables are presented as means with standard deviation, and dichotomous variables as percentages. Data from the three placebo groups were combined to provide more stable outcome estimates. Bleeding incidences were determined at 72 hours after the last intake of study medication in order to provide the most conservative estimate of the safety of lefradafiban. The times from start of study treatment to the first bleeding event are displayed as Kaplan-Meier curves censored at 72 hours after the last intake. A multiple logistic regression analysis for predictors of bleeding was performed, which also included the FRO, duration of heparin use and median on-treatment aPTT level. Frequencies of the clinical efficacy endpoints were determined on an intention-to-treat basis at 30 days after randomisation, as well as from randomisation until 72 hours after the last intake of study medication to account for the high number of patients discontinuing study treatment. The efficacy parameters were evaluated among all patients as well as among patients with elevated troponin-I levels at baseline versus those with normal levels.

FRO-efficacy outcome analysis

The relation between the level of FRO and the composite of death, myocardial infarction and recurrent unstable angina was investigated in patients who received lefradafiban and had at least one sample for determination of fradafiban plasma concentration within 8 hours of last study drug administration. The FRO was calculated from up to 4 plasma concentrations. Per patient, the minimum of the FRO values was investigated in relation to cardiac outcome. As this was a mechanistic type of analysis, the frequency of the composite endpoint was determined while patients were still receiving treatment.

Results

A total of 531 patients were enrolled between April 1997 and October 1998: 218 patients received lefradafiban 20 mg tid, 136 lefradafiban 30 mg tid, 47 lefradafiban 45 mg tid and 130 placebo. In the initial study design, approximately 132 patients were to be enrolled in each dose level (99 Lefradafiban and 33 placebo). During enrolment in the first (20 mg) dose level, however, it became apparent that more patients than anticipated discontinued trial medication due to revascularisation procedures (PCI with subsequent ticlopidin and CABG). The use of ticlopidin together with lefradafiban was excluded by the protocol because no interaction data were available at that time. To obtain more safety data on this dose level, the Data and Safety Monitoring Board advised to increase the group size of this dose level to 300 patients before proceeding to the next (30 mg) dose level. The FROST trial was discontinued in October 1998 after 61 patients had been enrolled in the 45 mg dose level (47 assigned lefradafiban and 14 placebo). At that time, the Data and Safety Monitoring Board recommended cessation of recruitment and discontinuation of treatment in this dose group since 5 (11%) of 47 patients receiving lefradafiban 45 mg had had a major bleeding complication.

There were no substantial differences in baseline characteristics among the treatment groups (Table 1): 69% were male, 33% had had a previous myocardial infarction, 14% had undergone a percutaneous coronary intervention and 11%

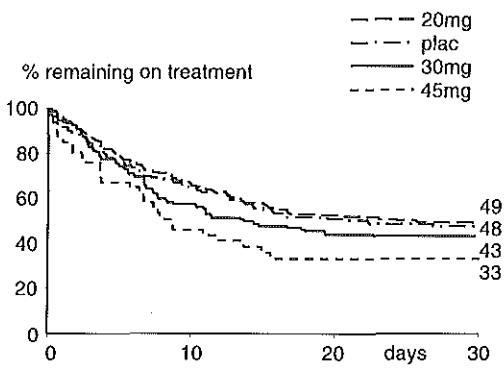

Figure 1
Kaplan-Meier estimates of the probability to continue study drug during the 30-day treatment period.

Table 1. Baseline characteristics

		Lefradafiban		
	Placebo	**20 mg tid**	**30 mg tid**	**45 mg tid**
	n = 130	n = 218	n = 136	n = 47
Age (years)	63 (10)	62 (10)	63 (10)	63 (12)
Gender (% male)	74	67	68	72
Weight (kg)	80 (15)	78 (13)	78 (15)	80 (15)
Height (cm)	171 (9)	170 (9)	171 (9)	171 (10)
SBP (mmHg)	128 (19)	131 (21)	131 (22)	121 (19)
DBP (mmHg)	74 (12)	76 (12)	75 (14)	70 (11)
Heart rate (bpm)	72 (11)	71 (13)	72 (13)	69 (14)
Diabetes (%)	15	15	21	17
Current smoker (%)	28	30	26	30
Previous MI (%)	32	31	38	34
Previous PCI (%)	12	15	15	11
Previous CABG (%)	13	11	12	4
CHF (%)	6	3	4	6

For continuous variables, the mean values are provided with the standard deviation in parentheses. CABG = coronary artery bypass grafting, CHF = congestive heart failure, DBP = diastolic blood pressure, MI = myocardial infarction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure.

Table 2. Reasons for early discontinuation from study drug (%)

		Lefradafiban		
	Placebo	**20 mg tid**	**30 mg tid**	**45 mg tid**
	n = 130	n = 218	n = 136	n = 47
Total of patients	55 %	51 %	58 %	77 %
Reasons				
Early stop 45 mg group	2			17
Adverse event	12	15	23	21
PCI (ticlopidin/abciximab)	15	12	12	19
CABG	12	11	10	6
Consent withdrawn	0	2	4	2
Normal angiography	4	2	4	0
Other	10	10	6	11

Abbreviations, see legend to Table 1.

coronary artery bypass surgery. In all treatment groups, study drug was discontinued prematurely in more than 50% of patients (Figure 1 and Table 2). Early discontinuation was highest among patients treated with lefradafiban 45 mg (60%, excluding those discontinued prematurely due to the early cessation of the trial), followed by patients in the 30 mg group (58%), with slightly lower rates in the placebo and 20 mg treatment arms (55% and 51%, respectively). Discontinuation occurred mainly within the first two weeks of study drug administration. The majority of the patients who did not withdraw from study drug during this period completed the intended 30-day treatment period. Among all treatment groups, major reasons for study drug discontinuation were the occurrence of an adverse event (mostly bleeding), planned coronary artery bypass surgery and the use of other antiplatelet agents (abciximab, ticlopidin) during or following percutaneous coronary intervention (Table 2).

Efficacy results

Cardiovascular events

Event rates determined from start of treatment up to 72 hours of study drug discontinuation showed a trend towards a beneficial effect of lefradafiban 30 mg when compared with placebo and lefradafiban 20 mg on the incidence of death or myocardial (re)infarction according to the Clinical Events Committee. When compared with placebo, there was a 30% relative reduction in the composite endpoint of death, myocardial (re)infarction, PCI or CABG in the lefradafiban 30 mg group (Table 3). Also, the composite outcome of death, myocardial (re)infarction or recurrent angina leading to rehospitalisation determined at 72 hours after study drug discontinuation was reduced in patients receiving lefradafiban 30 mg (Table 3). A similar pattern was apparent when the incidence of death, myocardial (re)infarction or any recurrent unstable angina was evaluated among the four treatment groups. At 30 days, the incidence of death or myocardial (re)infarction was low and comparable among all treatment groups, while the reduction in the 30-day composite of death, myocardial (re)infarction, PCI or CABG was less pronounced (relative reduction 24% when compared with placebo, Table 3).

Efficacy by troponin-I status

Of the 531 patients entered, 455 (86%) had troponin-I assay results available. The test result at baseline was positive (≥0.1 ng/ml) in 118 (26%) of these patients and was negative in 337 (74%) patients. The proportion of patients with positive versus negative troponin-I assay results were comparable among the four treatment arms. In each treatment group, the incidence of the 30-day composite endpoint of death, myocardial (re)infarction, PCI or CABG was higher among patients with a positive troponin-I test result at baseline when compared with those with

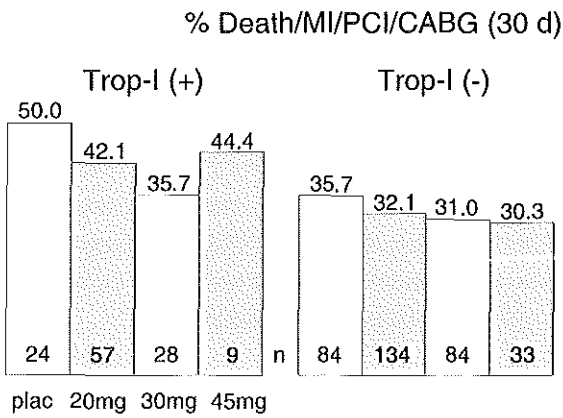

Figure 2
Incidence of the composite endpoint of death, MI, PCI or CABG at 30-day follow-up among patients with a positive troponin-I test result at baseline (left panel) versus those with a negative test result (right panel). CABG = coronary artery bypass grafting; MI = myocardial infarction as adjudicated by the Clinical Events Committee; PCI = percutaneous coronary intervention.

Table 3. Efficacy outcomes (%)

		Lefradafiban		
	Placebo	**20 mg tid**	**30 mg tid**	**45 mg tid**
	n = 130	n = 218	n = 136	n = 47
At 72 hours following last study drug administration				
Death/MI	3.1 %	3.2 %	2.2 %	4.3 %
Death/MI/PCI/CABG	31.5	30.7	22.1	25.5
Death/MI/AP-rehosp	7.7	6.9	2.9	6.4
Death/MI/AP-any	17.7	17.0	4.4	12.8
At 30-day follow-up				
Death/MI	3.1	4.1	4.4	4.3
Death/MI/PCI/CABG	43.1	35.9	32.6	40.4

Percentages refer to total number of patients in each treatment group. P-value (2-sided) provided according to Fisher's Exact Test for comparison between placebo and lefradafiban 30 mg. AP-any = any recurrent unstable angina pectoris; AP-rehosp = recurrent angina pectoris leading to rehospitalization; CABG = coronary artery bypass grafting; MI = myocardial infarction as adjudicated by the Clinical Events Committee; PCI = percutaneous coronary intervention.

a negative test result (Figure 2). In patients with a positive troponin-I as well as in those with a negative test result, the composite endpoint occurred most frequently in patients receiving placebo, while the event rate decreased with increasing doses of lefradafiban, with exception of the 45 mg dose (very small number of patients). The dose-dependent reduction in event rate associated with lefradafiban 20 mg and 30 mg appeared greater in patients with a positive troponin-I at baseline (ca. 15% and 30%, respectively) than in those with a negative test result (10% and 13%).

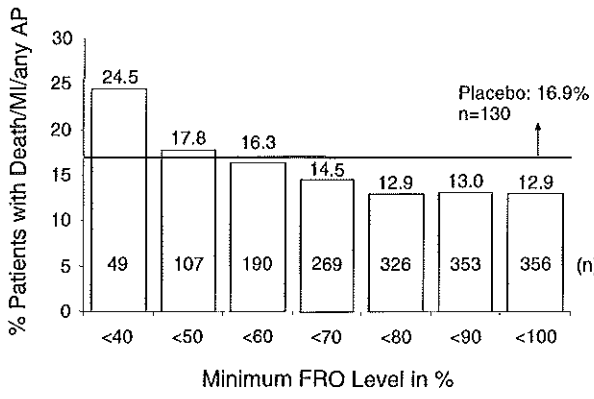

Figure 3
Incidence of the composite endpoint of death, myocardial infarction or any recurrent angina in relation to the minimum FRO level. Event rates are determined while patients were still receiving study treatment. AP = any recurrent angina; FRO = fibrinogen receptor occupancy; MI = myocardial infarction as adjudicated by the Clinical Events Committee.

Efficacy by FRO level

There were 356 patients who received lefradafiban and had at least one evaluable fradafiban plasma concentration value for determination of the FRO level. There was a clear relation between the minimum FRO level and the observed incidence of the composite of death, myocardial infarction and any recurrent unstable angina (Figure 3). The event rate decreased with increasing minimal FRO levels. The lowest event rate was found in patients with a minimal FRO level of at least 70%. In contrast, in patients with a minimal FRO level below 50%, the cardiac event rate appeared higher than in those receiving placebo (Figure 3).

ECG-ischemia monitoring results

Four hundred and thirteen patients (78%) had continuous ECG recordings suitable for analysis. During the 24-hour monitoring period, ischemic episodes were detected in 33 (33%) of the 99 placebo patients, 56 (31%) of the 178 lefradafiban 20 mg patients, 25 (25%) of the 101 lefradafiban 30 mg patients and 16 (46%) of the 35 lefradafiban 45 mg patients. There were no differences between groups in the number of recurrent ischemic episodes or the amount of ischemic burden.

Haemorrhagic events

A dose-dependent increase in bleeding incidence was observed with the majority of the bleedings occurring during the first two weeks of study drug administration (Figure 4). The incidence of major or minor bleeding complications was low in patients receiving placebo (1%) while it gradually increased with higher doses of lefradafiban up to 15% in patients treated with 45 mg tid (Table 4). Intracranial haemorrhage occurred in a single patient who was treated with thrombolysis for acute myocardial infarction while receiving lefradafiban 20 mg (Table 5). The percentage of patients who required a blood transfusion ranged from 1% in the placebo group to 9% in the 45 mg group with intermediate figures for

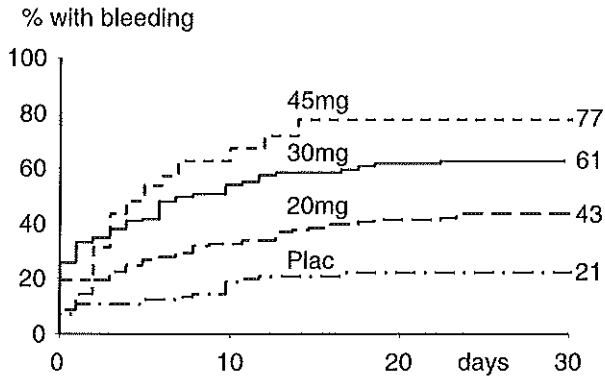

Figure 4
Kaplan-Meier estimates of the occurrence of any bleeding complication. Bleeding episodes are included up to 72 hours following last study drug administration.

the 20 mg and 30 mg groups. A dose-related increase for bleeding complications leading to discontinuation from study drug was observed. A similar dose-related increase was apparent for insignificant bleeding events; the percentage of patients in the placebo group experiencing any bleeding was 19% as compared with 39% in the 20 mg group, 57% in the 30 mg group and 67% in the 45 mg group (Table 4). Among all treatment groups, gingival and arterial or venous puncture site bleedings were most common and accounted for more than 60% of all haemorrhagic events (Table 5).

By multiple logistic regression analysis (model terms: FRO, age, weight and estimated creatinine clearance as continuous measurements, as well as gender), higher levels of FRO and a higher age were found to be significantly related to an increased bleeding incidence. The odds for bleeding increased with a factor of 1.023 for every increase in FRO level by 1% point (95% confidence interval (CI), 1.016-1.030) and 1.022 for one year increase in age (95%CI, 1.003-1.044). In addition, gender proved to be a significant predictor of bleeding (female versus male, odds ratio 1.54 with 95%CI, 1.03-2.46). In separate analyses, no statistically significant association was found between the occurrence of bleeding and the duration of heparin therapy or the median on-treatment aPTT level.

Haematological changes

Treatment with lefradafiban was associated with an increased incidence of leukopenia, or, more precisely, neutropenia. The incidence of leukopenia, defined as leukocyte count below 4×10^9/l, was estimated at 5.7% in the lefradafiban groups compared with 2.3% in the placebo group. Neutropenia (neutrophils below 1.5×10^9/l) occurred in 5.2% of the lefradafiban groups and 1.5% of the placebo group. In the patients with observed neutropenia, the decrease in neutrophils was characterised by an early onset (immediately after first study drug administration or within the next 2 days) and a fast recovery after discontinuation of lefradafiban (Figure 5).

Table 4. Incidence and severity of bleeding events until 72 hours after study drug discontinuation (%)

		Lefradafiban		
	Placebo	**20 mg tid**	**30 mg tid**	**45 mg tid**
	n = 130	n = 218	n = 136	n = 47
Bleeding event				
TIMI – major	1 %	3 %	3 %	11 %
TIMI – minor	0	1	4	6
TIMI – major or minor	1	5	7	15
Requiring transfusion	1	2	4	9
Leading to discontinuation	2	5	10	15
Any	19	39	57	67

Percentages refer to total number of patients in each treatment group.

TIMI = Thrombolysis in Myocardial Infarction

Table 5. Location of bleeding (%)

		Lefradafiban		
	Placebo	**20 mg tid**	**30 mg tid**	**45 mg tid**
	n = 130	n = 218	n = 136	n = 47
Bleeding event				
Intracranial	0 %	1 %	0 %	0 %
Retroperitoneal	0	1	0	0
Gastrointestinal	0	7	10	11
Genitourinary	3	5	10	4
Hematoma	5	9	9	11
Oral / gingival / epistaxis	3	15	31	28
Puncture site	12	19	29	34

Percentages refer to total number of bleedings located at each site.

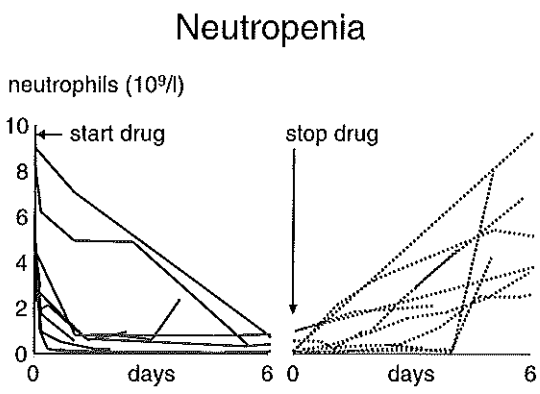

Figure 5
Neutrophil counts in individual patients experiencing neutropenia, in relation to study drug start and discontinuation.

Although the clinical symptoms of chills and fever occurred in patients with neutropenia, none developed a serious infection or permanent neutrophil deficiency. Based on central analysis of blood and bone marrow samples obtained in patients with severe neutropenia by independent expert haematologists, it was concluded that the observed neutropenia most likely resulted from a reversible redistribution of neutrophils by margination or clustering rather than from bone marrow depression. All bone marrow samples showed continued cellularity with a deficiency of later-stage cells of the granulocyte series. There was no evidence of aplastic anaemia or changes associated with agranulocytosis. In addition, patients with neutropenia responded to treatment with G-CSF or steroids with prompt normalisation of their neutrophil counts. In patients with simultaneous decrease in other blood cell populations the pattern was consistent with a generalised redistribution but not with impaired production by or release of cells from the bone marrow.

Thrombocytopenia (platelets below 90×10^9/l) occurred in only 2 (0.5%) of 401 patients treated with lefradafiban. No placebo recipient had thrombocytopenia.

Discussion

In this double-blind, randomised, dose-escalation trial of one-month GP IIb/IIIa inhibition with lefradafiban in patients with acute coronary syndromes, we observed a decrease in cardiovascular events with lefradafiban 30 mg and a dose-dependent increase in haemorrhagic events.

Safety

Close relations between the dose of lefradafiban administered, the plasma concentration of fradafiban, the fibrinogen receptor occupancy (FRO), and the degree of platelet inhibition have been established in previous studies with lefradafiban and fradafiban, both in healthy volunteers and in patients with coronary artery disease.[20,21]

Bleeding

As in other studies with long-term treatment with oral GP IIb/IIIa receptor blockers, bleeding occurred frequently and was dose-dependent. However, the majority of the bleedings were mild or clinically insignificant. The incidences of bleeding complications in the lefradafiban 20 mg and 30 mg groups were similar to the rates observed with other oral GP IIb/IIIa receptor blockers at similar levels of platelet inhibition.[26-30], while the very high risk of major or minor bleeding in the 45 mg group resulted in cessation of recruitment and discontinuation of treatment in this dose group. The results of the multivariable logistic regression analysis in the present study support earlier observations with an increase in the risk of bleeding of 2.3% for every increase in FRO level by 1% point.[26,27] The magnitude of this association is similar to that found in a previous study of lefradafiban in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention.[21]

The clinical pattern of bleeding was largely mucocutaneous: epistaxis, gingival bleeding, gastro-intestinal and genito-urinary bleeding, or bruising. No excess strokes were observed with lefradafiban. This pattern has also been observed with other GP IIb/IIIa receptor blockers.[6,13,26-30], and is similar to that seen with thrombocytopenia and in Glanzmann's thrombasthenia.[31] Arterial and venous puncture sites were the second most common location of bleeding. Other studies have demonstrated that bleeding at vascular puncture sites can be reduced by the use of low-dose, weight-adjusted heparin regimens, early femoral arterial sheath removal and careful access site management.[7,10,32] Although the protocol recommended a low-dose, weight-adjusted heparin regimen during the early phase of medical treatment, no specific heparin dosing regimen during percutaneous coronary intervention was provided.

Given the interpatient variability in drug level and degree of platelet inhibition

observed with oral GP IIb/IIIa receptor antagonists, another potential strategy for reducing bleeding complications could be to monitor the degree of platelet inhibition achieved in individual patients and to adjust the dose to a target level, as is done with anticoagulant therapy.[33,34]

Neutropenia and thrombocytopenia

Treatment with lefradafiban was associated with an increased incidence of neutropenia.[21] Whereas leukopenia due to bone marrow depression has been reported for other antiplatelet agents (ticlopidin).[35], expert analysis of blood and bone marrow samples obtained in FROST patients revealed that the observed neutropenia most likely did not result from bone marrow depression but rather from a reversible redistribution of neutrophils by margination or clustering. It was reassuring that all patients showed a fast recovery of neutrophil count after discontinuation of lefradafiban, and that none developed infection or permanent neutrophil deficiency. Yet, more investigations are needed to further elucidate the exact mechanisms involved, as well as to determine the optimal duration of surveillance and the possible clinical associations.

The incidence of thrombocytopenia associated with lefradafiban (0.5%) was low and similar to that reported for other oral GP IIb/IIIa receptor blockers.[26-30]

Efficacy

The 30-day incidence of death or non-fatal myocardial infarction was low in this study. The study was not designed to detect differences in clinical outcomes between the treatment groups, yet there was a trend towards a reduction in cardiovascular events in the lefradafiban 30 mg group compared with placebo and lefradafiban 20 mg. The sample size for the 45 mg cohort of patients was too small to detect a meaningful trend. The reduction in the composite of death, myocardial infarction, PCI or CABG was greater in the on-treatment analysis than when the endpoint was determined at 30 days. This suggests that the treatment benefit may be enhanced in patients who continue on medical therapy.[36] In patients undergoing PCI or CABG, the post-procedural event rates are very low and no benefit is to be expected.[28,37]

Patients with a positive troponin-I bedside assay at baseline were at increased risk of unfavourable outcome. This observation is concordant with the results of previous studies which have shown that among patients with unstable angina, elevated serum troponin-T and troponin-I levels are independent predictors of short- and long-term risk of adverse cardiac events.[38-41] Troponin-T and troponin-I reflect minimal or larger myocardial injury due to occlusion of the culprit vessel or distal embolisation of platelet thrombi originating from the culprit lesion.[42,43] As glycoprotein IIb/IIIa receptor blockers inhibit thrombus formation

at the culprit lesion and facilitate the resolution of thrombi.[44], they are expected to be particularly effective in patients with elevated troponin levels.[45,46] Indeed, treatment benefit among FROST patients appeared greatest in those with positive troponin-I at baseline. This observation parallels those of the FRISC and FRISC II trials, and the recently reported troponin substudies of the CAPTURE and PRISM trials.[36,38,45,46] The data from the present study therefore support the therapeutic concept that elevated troponin-T or troponin-I levels identify the group of patients with acute coronary syndromes and active thrombosis who are at high risk for cardiac events and who will benefit most from a more intensive treatment strategy including the administration of GP IIb/IIIa receptor blockers and low-molecular-weight heparin.

The trend towards a reduction in clinical events with lefradafiban 30 mg in this study contrasts with the results of recent, large-scale clinical trials of long-term oral GP IIb/IIIa inhibition with xemilofiban, orbofiban and sibrafiban in patients after PCI.[28] and acute coronary syndromes.[29,30] In this respect, several points deserve consideration. First, the risk of recurrent ischemic events in the patient populations included in these trials may have been too low to detect benefit of long-term GP IIb/IIIa receptor blockade. In the EXCITE trial, xemilofiban or placebo was administered prior to and for six months after PCI.[28] In accordance with the results of previous trials of intravenous glycoprotein IIb/IIIa receptor blockers, xemilofiban protected against procedure-related complications. However, the risk of subsequent events following PCI was very low, and no further benefit was observed. In OPUS-TIMI-16, patients were included for up to 72 hours following an episode of chest pain, while ischemic ECG changes or positive cardiac enzymes were not mandatory for enrolment.[29] Long-term treatment with orbofiban in this trial resulted in a modest 11% relative reduction in cardiac events at 30 days, primarily due to a reduction in urgent coronary intervention. In the SYMPHONY trial, patients could be included for up to 7 days after the onset of the acute coronary syndrome, and had to be stabilised for more than 12 hours from the initial presentation.[30] Almost 25% of all patients underwent a percutaneous coronary intervention between the qualifying episode and randomisation. No benefit was observed with sibrafiban after 90 days of treatment. All trials showed a trend towards an increased mortality in the GP IIb/IIIa inhibitor treatment groups.

The pharmacokinetic and pharmacodynamic profile of these agents is characterised by a steep dose-response relationship and by a short half-life relative to the dosing interval.[26,27,29] Thus, the twice-daily dosing regimen in the orbofiban and sibrafiban trials may have caused widely fluctuating inhibition of platelet aggregation..[29,30] This may have allowed complete recovery in platelet function between doses in some patients, with exposure of activated GP IIb/IIIa receptors on the platelet's surface.[47] Whereas it has been reported that high peak blood levels

of oral GP IIb/IIIa receptor blockers increase the risk of bleeding.[26,27], recent studies of platelet activation have also raised the possibility that platelet receptor antagonists may, at low concentrations, alter the steric conformation of the GP IIb/IIIa receptor sites, and paradoxically, enhance the thrombogenicity of these sites.[47,48]

In this study, the cardiac event rate decreased with increasing minimal FRO levels, with the lowest event rate found in patients with a minimal FRO level of at least 70%. In contrast, patients with a minimal FRO level below 50% appeared to have a higher cardiac event rate than patients receiving placebo. These findings suggest that an effective treatment with the GP IIb/IIIa receptor antagonist lefradafiban can be anticipated with marked levels of inhibition of platelet aggregation (i.e. FRO levels of at least 70%).

It should be emphasised that the present study was not designed and powered to definitively evaluate differences in clinical outcomes between treatment groups. The observed favourable trend in the lefradafiban 20 mg and 30 mg groups with a reduction in clinical events requires confirmation in an adequately-powered clinical trial.

Conclusion

It is a challenge to exploit the potential beneficial antithrombotic effect of oral GP IIb/IIIa inhibitors in relation to the associated risk of haemorrhage.[26,49] Dose-adjustment on the basis of patient characteristics that influence drug levels, such as renal function and body weight.[26,29,30], as well as dose-titration to a target level of platelet inhibition, measured with a rapid platelet-function assay.[33,34], may improve the overall safety and efficacy profile. To increase the treatment benefit of (oral) GP IIb/IIIa receptor blockers, one may choose to treat only patients who are at high risk of adverse cardiac events, such as those who present with elevated troponin levels or who exhibit recurrent ischemia and continue on medical therapy.[23,38,45,46] These patients may particularly benefit from a more aggressive therapeutic approach.[38,45,46]

Although data from this study may suggest that an effective treatment with the GP IIb/IIIa receptor antagonist lefradafiban can only be anticipated with marked levels of inhibition of platelet aggregation (i.e. FRO levels of at least 70%), the level of platelet inhibition needed to prevent recurrent ischemic cardiac events, as well as the optimal duration of treatment after an acute coronary syndrome require further investigation. A potential treatment strategy for patients admitted with acute coronary syndromes would include the administration of a rapid-acting intravenous GP IIb/IIIa receptor blocker during the acute phase, followed by conversion to an orally active preparation of the same compound for prolonged outpatient secondary prevention.[49] If a patient undergoes percutaneous

coronary intervention, it may be advised to continue the oral drug, or to convert to the intravenous preparation during and for 12-24 hours following the intervention.[5-10] As the risk of subsequent events following PCI is low, no further treatment with oral GP IIb/IIIa receptor blockers seems required.[28,37] The need for concomitant anticoagulant therapy should be evaluated.

The intravenous GP IIb/IIIa receptor blocker fradafiban and its orally active prodrug lefradafiban, as two complementary preparations of the same compound,[20] are suited to be used in such strategy, and might be evaluated for their efficacy in reducing ischemic cardiac events among patients with acute coronary syndromes in a large clinical trial.

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Appendix

FROST study organization

Steering Committee

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References

1 Davies MJ, Thomas AC. Plaque fissuring – the cause of acute myocardial infarction, sudden ischemic death, and crescendo angina. *Br Heart J* 1985; **53**: 363-73.

2 Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992; **326**: 242-50, 310-8.

3 Ambrose JA, Weinrauch M. Thrombosis in ischemic heart disease. *Arch Intern Med* 1996; **156**: 1382-94.

4 Lefkovits J, Plow EF, Topol EJ, Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine, *N Engl J Med* 1995; **332**: 1553-9.

5 The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; **330**: 956-61.

6 The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; **349**: 1429-35.

7 The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997; **336**: 1689-96.

8 The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997; **349**: 1422-8.

9 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997; **96**: 1445-53.

10 The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998; **352**: 87-92.

11 The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338**: 1498-505.

12 The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338**: 1488-97.

13 The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; **339**: 436-43.

14 Tanguay J-F. Do differences in pharmacology of platelet glycoprotein IIb/IIIa inhibitors affect clinical outcomes. Eur Heart J Supplements 1999; 1 (Suppl E): E27-35.

15 Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. *Eur Heart J* 1998; **19**: 1608-16.

16 Fragmin During Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996; **347**: 561-8.

17 The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB trial. *Circulation* 1994; **89**: 1545-56.

18 Merlini PA, Bauer KA, Oltrona L et al. Persistent activation of the coagulation system in unstable angina and myocardial infarction. *Circulation* 1994; **90**: 61-8.

19 Ault KA, Cannon CP, Mitchell J et al. Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction. *J Am Co Cardiol* 1999; **33**: 634-9.

20 Müller TH, Weisenberger H, Brickl R, Narjes H, Himmelsbach F, Krause J. Profound and sustained inhibition of platelet aggregation by fradafiban, a nonpeptide platelet glycoprotein IIb/IIIa antagonist, and its orally active prodrug, lefradafiban, in men. *Circulation* 1997; **96**: 1130-8.

21 Van den Brand MJBM, Baardman T, Suryapranata H et al. Initial experience with BIBU 104XX; a new, oral glycoprotein IIb/IIIa receptor blocker. *Eur Heart J* 1997; 18 (Abstr. Suppl.): **244**.

22 Klootwijk P, Meij S, van Es GA et al. Comparison of usefulness of computer assisted continuous 48-h 3-lead with 12-lead ECG ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. *Eur Heart J* 1997; **18**: 931-40.

23 Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 1998; **98**: 1358-64.

24 Rao AK, Pratt C, Berke A et al. Thrombolysis in Myocardial Infarction (TIMI) Trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokina *J Am Coll Cardiol* 1988; **11**: 1-11.

24 Landefeld CS, McGuire E, Rosenblatt MW. A bleeding risk index for estimating the probability of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med* 1990; **89**: 569-78.

25 Cannon CP, McCabe CH, Borzak S et al. for the TIMI 12 Investigators. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. *Circulation* 1998; **97**: 340-9.

26 Kereiakes DJ, Kleiman NS, Ferguson JJ et al. for the ORBIT Trial Investigators. Pharmacodynamic efficacy, clinical safety, and outcomes after prolonged platelet glycoprotein IIb/IIIa receptor blockade with oral xemilofiban: results of a multicenter, placebo-controlled, randomized trial. *Circulation* 1998; **98**: 1268-78.

27 O'Neill WW for the EXCITE Investigators. Results of the Evaluation of oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial. Congress of the American College of Cardiology, March 7-10, 1999.

28 Cannon CP for the OPUS-TIMI-16 Investigators. Preliminary results of the TIMI-16 Orbofiban in Patients with Unstable coronary Syndromes (OPUS) trial. Congress of the American College of Cardiology, March 7-10, 1999.

29 The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomized trial. *Lancet* 2000;**355**:337-45.

30 George JN, Caen JP, Nurden AT. Glansmann's thrombasthenia: the spectrum of clinical disease. *Blood* 1990; **75**: 1383-95.

31 Lincoff AM, Tcheng JE, Califf RM et al. for the PROLOG Investigators. Standard versus low dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. *Am J Cardiol* 1997; **79**: 286-91.

32 Coller BS. Monitoring platelet GP IIb/IIIa antagonist therapy. *Circulation* 1998; **97**: 5-9.

33 Smith JW, Steinhubl SR, Lincoff AM et al. Rapid platelet-function assay: an automated and quantitative cartridge-based method. *Circulation* 1999; **99**: 620-5.

34 Yeh SP, Hsueh EJ, Wu H, Wang YC. Ticlopidine-associated aplastic anemia. A case report and review of literature. *Ann Hematol* 1998; **76**: 87-90.

35 The FRISC II Investigators. Long-term low-molecular-mass heparin in unstable coronary artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999; **354**: 701-7.

36 FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999; **354**: 708-15.

37 Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. FRISC study group. *J Am Coll Cardiol* 1997; **29**: 43-8.

38 Ohman EM, Armstrong PW, Christenson RH et al. for the GUSTO-IIa Investigators. Cardiac Troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996; **335**: 1333-41.

39 Antman EM, Tanasijevic MJ, Thompson B et al. Cardiac-specific Troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; **335**: 1342-9.

40 Hamm CW, Meinertz T, Berger J, Kreymann G, Heeschen C, Goldmann BU. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponi T or troponin I. *N Engl J Med* 1997; **337**(23): 1648-53.

41 Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985; **71**: 699-708.

42 Davies MJ, Thomas AC, Knapman PA, Hangartner JR. Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac death. *Circulation* 1986; **73**: 418-27.

43 Heeschen C, Van den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. *Circulation* 1999; **100**:1509-14.

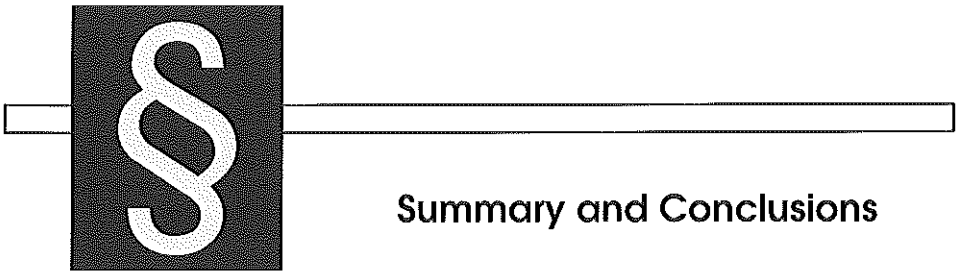
44 Hamm CW, Heeschen C, Goldmann B, et al. for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999; **340**: 1623-9.

45 Hamm CW, Heeschen C, Goldmann BU, White HD. Benefit of tirofiban in high-risk patients with unstable angina identified by troponins in the PRISM trial. *Circulation* 1999; **18** I-775: 4092.

46 Peter K, Straub A, Kohler B et al. Platelet activation as a potential mechanism of GP IIb/IIIa inhibitor-induced thrombocytopenia. *Am J Cardiol* 1999; **84**: 519-24.

47 Peter K, Schwarz M, Ylanne J et al. Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa (aIIBb3) inhibitors. *Blood* 1998; **92**: 3240-9.

48 Vorchheimer DA, Fuster V. Oral platelet glycoprotein IIb/IIIa receptor antagonists: the present challenge is safety. *Circulation* 1998; **97**: 312-4.



Summary and Conclusions

Samenvatting

Summary and conclusions

Acute coronary syndromes, which include unstable angina, acute myocardial infarction, and the acute complications of percutaneous coronary intervention, are important global public health problems and the leading causes of morbidity and mortality in the Western World.[1] Patients presenting with these syndromes are at increased short-term and long-term risk of death, myocardial (re-)infarction, recurrent angina, congestive heart failure, arrhythmias, and the need for coronary revascularization procedures. As described in **chapter 1**, the development of an acute coronary ischemic event is believed to involve a disruption (rupture, fissuring or erosion) in atherosclerotic vascular plaque, resulting in activation of platelets and the coagulation cascade. Formation of a local thrombus as a response to vascular injury can then lead to several consequences: varying degrees of vessel occlusion with resultant diminished coronary blood flow, distal embolism of thrombotic material causing capillary plugging and myocardial necrosis, and incorporation of the local thrombus into the growing plaque leading to a progression of atherosclerosis.[2-4] As summarized in **chapter 1**, recognition of the pivotal role of thrombosis in the pathophysiologic process of the acute coronary syndromes has led to a focus on antithrombotic therapies, specifically antiplatelets and antithrombins. Aggregation of activated platelets plays a central role in the process of coronary thrombosis.[5] Irrespective of the pro-aggregatory stimulus, the final common pathway to platelet aggregation involves bridging of platelets via their activated glycoprotein (GP) IIb/IIIa receptors by fibrinogen and other adhesive ligands.[5] A new class of agents, known as GP IIb/IIIa receptor blockers, has been designed to block this terminal step and thereby inhibit coronary thrombosis. The efficacy of GP IIb/IIIa blockers in reducing ischemic complications was clearly shown in a large number of patients undergoing percutaneous coronary revascularization procedures with and without stent deployment.[6-11] In these trials of percutaneous coronary interventions, patients receiving GP IIb/IIIa inhibitors had an approximately 30% lower occurrence of the composite of death, myocardial infarction, or need for urgent repeat revascularization within 30 days. Based on these favorable results, the use of GP IIb/IIIa blockers was extended to the empiric treatment of acute coronary syndrome patients. As reviewed in **chapter 1**, two major treatment strategies, using a variety of agents, have been studied. One approach focuses on the use of medical therapy and the other combines GP IIb/IIIa blockers with percutaneous coronary intervention.

This thesis addresses several aspects of the clinical evaluation of GP IIb/IIIa receptor blockers in patients with acute coronary syndromes. A number of manuscripts described in this thesis have been based on data originating from the large Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial.[12,13]

PURSUIT compared the GP IIb/IIIa inhibitor eptifibatide with placebo in addition to standard therapy in 9461 patients with acute coronary syndromes who did not have persistent ST-segment elevation. A total of 726 hospitals from 27 countries in four geographic regions (Western Europe, North America, Eastern Europe, Latin America) participated. Patients were eligible for enrollment if they had ischemic chest pain within the previous 24 hours and either ECG changes suggestive of ischemia (ST-segment depression, T-wave inversion, or transient ST-segment elevation) or a creatine kinase-MB fraction above the upper limit of normal for that hospital. Patients were randomly assigned in double-blind fashion to an intravenous bolus and infusion of placebo or 180 μg . kg^{-1} bolus plus infusion of 2.0 μg . kg^{-1} min-1 eptifibatide. Study drug was to be infused over 72 hours, but could be continued for up to 96 hours if a percutaneous coronary intervention was performed at the end of the 72-hour treatment period. All other treatment decisions, including the use of heparin, other anti-ischemic medications and coronary angiography, as well as the use and timing of percutaneous or surgical coronary revascularization, were left to the discretion of the treating physician. Compared with placebo, treatment with eptifibatide resulted in a statistically significant 1.5% absolute reduction in the 30-day composite endpoint of death and non-fatal (re)myocardial infarction as adjudicated by an independent Clinical Events Committee blinded to treatment assignment. The composite endpoint was also calculated using the site investigator determination of myocardial infarction.

Clinical endpoint determination: methodology and impact

Myocardial infarction is a potentially catastrophic event in patients presenting with acute coronary syndromes and an important efficacy endpoint in clinical trials. Although myocardial infarction has been considered a "hard" end point, determination of myocardial infarction endpoints in clinical trials can be difficult, just as in clinical practice, because of conflicting clinical, laboratory, and electrocardiographic data. As prevention of myocardial infarction has been the primary treatment effect assessed in recent trials of antiplatelet and antithrombotic therapies,[6-12, 14-18] Clinical Events Committees have become an integral aspect of clinical trials of new therapies for patients with acute coronary syndromes to provide a systematic, unbiased, independent, and standard assessment of this endpoint.[19-23] Accordingly, in the PURSUIT trial, a centralized, independent Clinical Events Committee systematically identified and adjudicated all suspected infarctions that occurred after enrollment and through 30-day follow-up.

In **chapters 2 and 3**, we reviewed the structure of the Clinical Events Committee and the event-adjudication process as used in the PURSUIT trial. The Clinical Events Committee identified 5005 suspected infarctions, of which 1415 (28%) were adjudicated as infarctions. Review of the clinical events classification

process raised important issues. First, the rates of infarction were higher than those reported in prior trials of patients with acute coronary syndromes.[12,17,18,24] Second, protocol-defined myocardial infarctions were underreported by the site investigators. Third, the site investigator and the Clinical Events Committee assessment of infarction disagreed for 983 (20%) of the 5005 patients reviewed by the Committee. Most of the disagreements reflected investigator misclassification of post-enrollment myocardial infarctions (as enrollment myocardial infarctions instead) or underreporting of peri-procedural myocardial infarctions as well as myocardial infarctions defined by cardiac enzyme elevations without clinical or ECG evidence of ischemia or infarction. Fourth, the observed treatment effect was smaller using the Clinical Events Committee adjudicated myocardial infarction rates versus site investigator-identified event rates. Finally, in a retrospective analysis that excluded cases of myocardial infarction that, despite meeting the prespecified endpoint criteria, had conflicting clinical, ECG, and cardiac-enzyme data, the treatment effect was larger than that seen when such cases were included.

Several explanations for these five observations are provided. In aggregate, the findings suggest that Clinical Events Committee adjudication of suspected nonfatal myocardial infarction endpoint events is important to provide independent, unbiased, standard, systematic assessment. However, the definition of myocardial infarction and its application in Clinical Events Committee event adjudication in PURSUIT may have been too inclusive of myocardial infarctions defined by low-level enzyme elevations (creatine kinase-MB above once the upper limit of normal), which either represented "noise" or clinically unimportant events. Therefore, Clinical Events Committee adjudication does have certain limitations; in cases in which the clinical history, the cardiac-enzyme data, and ECG information are inconsistent, or cardiac-enzyme data suspect, the determination of myocardial infarction may require more clinical judgment although this may decrease the objectivity that is important for event classification, particularly in trials across geographic regions and clinical-practice settings. Although the absolute difference in infarction rates determined by the Clinical Events Committee versus site investigators was small, the relative difference was more substantial. This caused a substantial impact on the statistical outcome of the trial. This phenomenon has also been observed in other large clinical trials and must be considered in sample-size and power calculations during design of future trials. Furthermore it also influences how clinical and regulatory bodies interpret trial results. Therefore, the Clinical Events Committee process used must be considered, among other factors, when performing comparisons of event rates between trials.

In PURSUIT, as in other large international trials, there were considerable variations in outcome of patients in different geographic regions.[12, 25-28] In the

initial univariate PURSUIT analysis, the treatment effect appeared greater in North America than in Western Europe, while no treatment effect was apparent in Latin America and Eastern Europe. However, the confidence intervals for the treatment effects in these regions were wide and overlapping. Due to the large number of patients treated in the various regions, this trial afforded a unique opportunity to gain insight into the heterogeneity of the disease and patient population, and to study differences in medical practice patterns and treatment strategies. Therefore, in **chapter 4**, we reviewed these regional differences and analyzed the factors that might contribute to the geographic variations in patient outcome and treatment effect.

Major differences in baseline demographics were apparent among the four regions. Interventional treatment also varied considerably. After multivariable adjustment, the pattern of benefit with eptifibatide was consistent among the regions. In general, the differences in outcome and treatment effect were greatest when the protocol definition of myocardial infarction (CK-MB > 1 upper normal limit) was applied. Under stricter definitions, these differences became smaller and disappeared with the investigatoris assessment.

The analysis suggests that the apparent differences in patient outcome and eptifibatide treatment effect can be explained largely by differences in baseline demographics and adjunctive treatment strategies, particularly the use and timing of coronary intervention, as well as by the methodology of myocardial infarction definition and the adjudication process. Therefore, global clinical trials should take into account these three important aspects when making observations regarding differences in patient outcome and consistency of the treatment effect across a multi-national network.

Safety of glycoprotein IIb/IIIa receptor blockers

In the early trials, GP IIb/IIIa receptor blockade was associated with a significantly higher rate of bleeding complications,[6,7] but this proved to be largely attributable to excessive and prolonged concurrent heparin administration.[6,7] All of the later trials, incorporating low-dose, weight-adjusted heparin regimens and careful vascular access site management, have shown no excess in major bleeding.[8,11,29]

An accurate estimation of the risk of bleeding based on clinical evaluation at baseline may improve the risk-benefit ratio of GP IIb/IIIa inhibition therapy in patients with non-ST-elevation acute coronary syndromes. In **chapter 6**, we therefore studied bleeding complications among the 9375 patients with acute coronary syndromes without persistent ST-elevation receiving placebo or the platelet GP IIb/IIIa inhibitor eptifibatide in the PURSUIT trial and determined the multivariable baseline predictors of spontaneous or procedure-unrelated bleeding

events as well as bleeding complications associated with percutaneous coronary procedures.

Bleeding was a common event in patients with non-ST-elevation acute coronary syndromes and was increased with eptifibatide among patients who did not undergo bypass surgery during hospitalization (31% compared with 12% in placebo). In most cases (83%) however, bleeding was mild. Patients undergoing bypass surgery during hospitalization had increased bleeding and accounted for approximately 80% of the patients with major bleeding complications. No increase in bleeding incidence with eptifibatide therapy was observed in patients who underwent bypass surgery. Risk factors for procedure-related bleeding included North American region, allocation to eptifibatide, female gender, the maximal aPTT value and treatment with ticlopidin. Treatment with eptifibatide was the most powerful independent predictor of spontaneous bleeding, followed by older age, female gender, North American region, the maximal aPTT value, smoking status, use of thrombolytics or ticlopidin, and non-caucasian ancestry. These factors were used to develop a scoring nomogram that can predict the patientís baseline risk of spontaneous bleeding and determine to what extent this risk increases during antithrombotic therapy. After combining the bleeding risk model and the risk model for prediction of adverse cardiac outcome, which is described in **chapter 10**, no subgroups of patients could be identified with either a low risk of adverse cardiac events and a high bleeding risk or a low bleeding risk and a high risk of cardiac events. Therefore, in determining indications for GP IIb/IIIa inhibition therapy, the risk of bleeding is of secondary importance.

Because of their potent inhibition of platelet aggregation, the effect of the GP IIb/IIIa receptor blockers on the risk of stroke has been a concern. Since stroke is infrequent, a combined analysis of 8555 patients from the EPIC, CAPTURE, EPILOG and EPISTENT studies was performed to compare stroke rates between patients treated with the GP IIb/IIIa receptor blocker abciximab (in addition to aspirin and heparin) and those receiving placebo during percutaneous coronary intervention. The analysis is presented in **chapter 5** and implies that abciximab in addition to aspirin and heparin does not increase the overall risk of stroke in a diverse population of patients undergoing percutaneous coronary intervention.

The safety of the GP IIb/IIIa receptor blockers is further supported by the cumulative frequency of intracerebral hemorrhage in the 10 large, placebo-controlled randomized trials of 0.1% in both the placebo and the GP IIb/IIIa blocker arms.[30] Furthermore, emergency bypass surgery was not complicated by excess bleeding in these trials.[31]

Glycoprotein IIb/IIIa receptor blockers and coronary intervention

Therapy with the intravenous GP IIb/IIIa receptor blockers for non-ST-

elevation acute coronary syndromes has been demonstrated to reduce the composite of death and myocardial infarction by 10-50%.[32-34] However, given the established benefit of these agents in the setting of percutaneous coronary intervention, there was uncertainty about whether the effect in acute coronary syndromes was confined to patients who underwent percutaneous coronary intervention while receiving study drug. There were 3 clinical trials that could contribute to addressing this issue.

Accordingly, in **chapter 7**, we analyzed data from the CAPTURE, PURSUIT, and PRISM-PLUS randomized trials, which studied the effects of the GP IIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban, respectively, in acute coronary syndrome patients without persistent ST-segment elevation, with a period of study drug infusion before a possible percutaneous coronary intervention. During the period of pharmacological treatment, each trial demonstrated a significant reduction in the rate of death or nonfatal myocardial infarction in patients randomized to the GP IIb/IIIa inhibitor compared with placebo. The 3 trials combined showed a 2.5% event rate in this period in the GP IIb/IIIa inhibitor group (N = 6125) versus 3.8% in placebo (N = 6171), which implies a 34% relative reduction ($P < 0.001$). During study medication, a percutaneous coronary intervention was performed in 1358 patients assigned GP IIb/IIIa inhibition and 1396 placebo patients. The event rate during the first 48 hours after percutaneous coronary intervention was also significantly lower in the GP IIb/IIIa inhibitor group (4.9% vs. 8.0%; 41% reduction; $P < 0.001$). No further benefit or rebound effect was observed beyond 48 hours after the percutaneous coronary intervention.

Thus, these data suggest that enhanced platelet inhibition with a GP IIb/IIIa blocker in addition to aspirin and heparin, starting immediately after admission, is beneficial to patients with acute coronary syndromes without persistent ST-segment elevation. This hypothesis is further investigated in the forthcoming GUSTO-IV-ACS study. In addition, in those undergoing percutaneous coronary intervention, intensive platelet inhibition protects against myocardial damage associated with the intervention.[6-11] Thus, to fully explore their beneficial effects, GP IIb/IIIa inhibitors should be initiated early after hospital admission in patients at risk and continued until after the procedure in those undergoing percutaneous coronary intervention.

Studies in patients undergoing percutaneous coronary intervention and receiving GP IIb/IIIa receptor blockers consistently show a reduction in procedure-related myocardial infarction.[6-11] Most infarcts occurred at the time of angioplasty and were characterized by elevated creatine kinase-MB levels without apparent clinical symptoms.[6-11] Although studies have shown a direct, proportional relationship between the level of post-procedural CK-MB elevation and the risk of an adverse clinical outcome during long-term follow-up including death,

myocardial infarction, and need for repeat revascularization procedures,[35-39] the relevance of the adverse prognostic implications of CK-MB elevation following percutaneous coronary intervention remains however a controversial issue in interventional cardiology. In contrast, the prognostic significance of small myocardial infarctions occurring spontaneously in the setting of unstable angina or after acute myocardial infarction has been well established.[40-42]

In **chapter 8**, we therefore compared the relationship between the level of post-procedural (within 48 hours following percutaneous coronary intervention) CK-MB elevation and the risk of death after 6-month follow-up in 8838 patients undergoing percutaneous coronary intervention with the relationship between the level of CK-MB elevation and mortality in the 5583 PURSUIT patients with non-ST-elevation acute coronary syndromes who were treated medically. In both patient groups, there was a gradual increase in 6-month mortality with higher CK-MB levels. The 6-month mortality rates were lower after procedure-related compared with spontaneous infarcts. Yet, the relative increase in 6-month mortality with each increase in the category of peak CK-MB level was of the same magnitude for cardiac enzyme elevations after percutaneous coronary intervention and those occurring spontaneously in the setting of acute coronary syndromes.

The strong dose-response relationship between the magnitude of post-procedural CK-MB elevation and 6-month mortality indicates that peri-procedural myocardial damage is an important marker of subsequent adverse outcome. Therefore, prevention of myocardial damage by GP IIb/IIIa receptor blockers is likely to be of clinical importance and improve the long-term outcome of patients undergoing percutaneous coronary intervention.[43-45] A recent meta-analysis of all studies with abciximab in patients undergoing percutaneous coronary intervention supports this concept by showing a 30% relative reduction in mortality at 6-month follow-up in patients treated with this GP IIb/IIIa inhibitor.[43] The most impressive effect for mortality reduction is that reported in EPISTENT: 1-year mortality amongst stented patients was reduced by 58% (from 2.4% for the placebo group to 1.0% for the abciximab patients [P = 0.03]).[45]

Risk assessment

Patients who present with chest pain or other symptoms suggestive of an acute coronary syndrome and do not have persistent ST-segment elevation on the electrocardiogram, encompass a heterogeneous group that varies considerably with respect to diagnosis as well as future risk for cardiac events. Early risk stratification in these patients is important to tailor pharmacological and invasive treatment to an individual need based on the estimated treatment benefit which is usually proportional to the risk of adverse outcome in the absence of a specific therapy. Accordingly, an appropriate treatment policy should include an estimate of the

risk of adverse outcome at baseline, which can be achieved by application of a risk stratification protocol that integrates important prognostic features. A number of risk models using baseline characteristics have been developed for acute myocardial infarction with ST-segment elevation but risk modelling has been underutilized in patients with acute coronary syndromes without persistent ST-segment elevation.[46-50]

Therefore, in **chapter 10**, we analyzed the relation between baseline characteristics and the 30-day incidence of death and the composite of death or myocardial (re)infarction in the 9461 PURSUIT patients with acute coronary syndromes without persistent ST-segment elevation. Variables examined included demographics, history, hemodynamic condition, and symptom duration. More than 20 significant predictors for mortality and for the composite endpoint were identified. The most important baseline determinants of death were age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure, and cardiac enzymes. Determinants of mortality were generally also predictive of death or myocardial (re)infarction. Differences were observed, however, in the relative prognostic importance of predictive variables for mortality alone or the composite endpoint. The accuracy of the prediction of the composite endpoint was less than of mortality. The most important prognostic factors from this risk model were used to develop a simple scoring nomogram to estimate the risk of adverse outcome at 30 days.

Complementary, a proportion (15-20%) of patients who present with suspected acute coronary syndromes are found to have insignificant coronary artery disease when they undergo coronary angiography.[51,52] Whereas complex lesion morphology is a powerful predictor of adverse outcome in acute coronary syndromes,[53-56] long-term outcome and the efficacy of anti-platelet therapy has not been well characterized in patients with acute coronary syndromes found to have insignificant coronary artery disease.

Accordingly, in **chapter 11**, we evaluated patients from the PURSUIT trial who underwent angiography and compared the clinical profiles, treatment responses, and outcomes of those with insignificant versus significant coronary artery disease. Of the 5767 patients with non-ST-segment elevation acute coronary syndromes who underwent in-hospital angiography, 88% had significant coronary artery disease (any stenosis >50%), 6% had mild coronary artery disease (any stenosis >0% to 50%), and 6% had no coronary artery disease (no stenosis identified). Patients with suspected acute coronary syndromes found to have insignificant coronary artery disease during coronary angiography had a low risk of adverse outcomes. While patients with insignificant coronary artery disease did not appear to benefit from treatment with the GP IIb/IIIa receptor blocker eptifibatide, those with significant coronary artery disease were shown to have an

enhanced treatment benefit. Baseline clinical characteristics were used to develop a simple scoring nomogram that accurately predicted the probability of insignificant coronary artery disease for use at hospital presentation. This nomogram was validated in a separate population of patients with non-ST-segment elevation acute coronary syndromes.

In conclusion, early identification of patients with suspected acute coronary syndromes at high and low risk of adverse outcome by incorporating the predictive risk models presented in **chapters 10 and 11** into the clinical decision-making process may help refine triage algorithms for acute ischemic chest pain and determine indications for GP IIb/IIIa inhibition therapy.

Following hospital admission, the presence of transient ischemia during subsequent continuous ECG-ischemia monitoring may provide important additional information for risk stratification. It had been established that recurrent ischemia detected by Holter monitoring or computer-assisted ECG analysis in patients with acute coronary syndromes carries an increased risk for an unfavorable outcome, including death and myocardial infarction.[57-64] This relationship between recurrent ischemia and adverse outcome was verified in the PURSUIT ECG-ischemia Monitoring Substudy which used a computer-assisted standard 12-lead ECG-ischemia monitoring device, in contrast to previous studies that used 2- or 3-lead Holter and vectorcardiographic monitoring. The results of this study are reported in **chapter 9**.

As computer-assisted multilead ECG monitoring offers an accurate continuous real-time measurement of the QRS-complex and the ST-segment,[65,66] it can be used as a non-invasive tool for on-line risk stratification in patients with acute coronary syndromes,[60-64] in contrast to Holter monitoring which is limited by a restricted number of two or three ECG leads and allows for retrospective analysis only.[65,66] However, studies that evaluated the relationship between recurrent ischemia detected during continuous multilead ECG-ischemia monitoring (or Holter monitoring) and adverse outcome have been limited by small series of patients.[57-64] By combining data of 3 studies, the analysis presented in **chapter 12** aimed to provide an accurate assessment of the impact of recurrent ischemia detected by multilead ECG-ischemia monitoring on the occurrence of death and myocardial infarction in patients admitted with an acute coronary syndrome.

With almost 1000 patients, this analysis currently represents the largest assessment of the prognostic implications of recurrent ischemia as detected by computer-assisted continuous multilead ECG-ischemia monitoring in the non-persistent ST-segment elevation acute coronary syndrome patient population. The main finding was a direct proportional relationship between the number of ischemic episodes normalized per 24 hours and the probability of cardiac events at 5 and 30 day follow-up. The 30-day composite of death and myocardial infarction

occurred in 5.7% of patients without episodes and increased to 19.7% in patients with ≥ 5 episodes. After adjustment for baseline predictors of adverse outcome, the relative risk of death or myocardial infarction at 5 and 30 days increased by 25% for each additional ischemic episode per 24 hours.

Other recent studies have shown that the prognostic information of recurrent ischemia during continuous computer-assisted multilead ECG monitoring appears to be independent from and additive to not only baseline characteristics and admission ECG but also the biochemical markers of myocardial necrosis, including creatine kinase-MB and troponin levels.[63,64] It can therefore be concluded that further integration of multilead ECG-ischemia monitoring systems in coronary care units and emergency wards should be recommended to improve early risk stratification in patients admitted with an acute coronary syndrome.

Over the past decade, the therapeutic endeavour to rapidly identify the patients at the highest risk for adverse events to individualize therapy and promote improved outcome has identified the cardiac-specific troponins to be powerful and independent predictors of future cardiac events in patients with acute coronary syndromes.[67-75]

The troponin complex is formed by three distinct structural proteins (troponin I, C, and T) and is located on the thin filament of the contractile apparatus in both skeletal and cardiac muscle tissue regulating the calcium-dependent interaction of myosin and actin.[73] Cardiac isoforms for all three troponins, however, are encoded each by different genes and can be distinguished by monoclonal antibodies recognising the aminoacid sequence characteristic of the cardiac isoforms.[73,76,77] The cardiac isoforms of troponin T and I are exclusively expressed in cardiac myocytes. Accordingly, the detection of cardiac troponin T and troponin I is completely specific for myocardial damage, attributing to these markers a new gold standard.[73] The superiority of cardiac-specific troponins over the ECG as prognostic markers is confirmed by both prospective and retrospective analyses.[72,78] The risk for myocardial infarction and death increases with increasing serum troponin concentrations and may be as high as 20% at 30 days and 25% within 6 months in patients with the highest troponin levels.[71,72,74,75,78]

The association between minor myocardial damage represented by troponin elevation and unfavorable outcome might be explained by the link between the diseased epicardial artery and events occurring in the microcirculation following plaque fissure or rupture.[79,80] The ruptured atherosclerotic plaque disturbs epicardial flow and acts as a nidus for platelet deposition and activation.[30,79,80] Distal embolization of the plaque-platelet aggregate results in microvascular obstruction and myocardial necrosis manifested by troponin elevation.[79] The severity of the plaque disruption appears to be directly correlated with the extent of local platelet activation and epicardial occlusion. Because of the central role platelets play in

this cascade of events, considerable effort has been devoted to interrupting this vicious cycle with platelet GP IIb/IIIa receptor inhibition, thus limiting the frequency, extent and consequences of microvascular embolization.[79]

Indeed, recent evidence from the CAPTURE study and the PRISM study suggests that GP IIb/IIIa receptor blockers are particularly effective in patients with acute coronary syndromes and an elevated troponin T or troponin I level.[74,75] In patients with an elevated troponin level, GP IIb/IIIa receptor blockers have been shown to reduce the high risk of cardiac events to that of patients without elevated troponin levels.[74,75] This applies to thrombotic complications arising from spontaneous plaque disruption as well as those associated with intervention-induced plaque ruptures.[74,75]

An emergency-department algorithm for triage of patients who present with suspected acute coronary syndromes based on the admission 12-lead ECG, serum troponin level and continuous multilead ECG-ischemia monitoring is suggested in Figure 3 from **chapter 12**.

Recent clinical trials suggest that patients identified as having a high risk of subsequent cardiac events based on ST-depression on the admission ECG or an elevated troponin T or I level, may particularly benefit from a more aggressive therapeutic approach including administration of a glycoprotein IIb/IIIa receptor blocker, a low-molecular-weight heparin and an early percutaneous coronary intervention.[74,75,81-83] If it is impossible to perform immediate percutaneous coronary intervention, high-risk patients may still receive a glycoprotein IIb/IIIa blocker as there appears to be a benefit of these agents during pharmacological treatment. The meta-analysis presented in **chapter 7** showed a 34% relative reduction (from 3.8% to 2.5% at 72 hours) in the composite endpoint of death or myocardial infarction during pharmacological treatment among the full spectrum of patients with non-ST-elevation acute coronary syndromes. The benefit appears even greater in patients with an elevated troponin level at admission.[74,75] Patients admitted with a low-risk profile and a non-elevated troponin level should undergo continuous multilead ECG-ischemia monitoring while receiving standard medical therapy.[73] Measurement of troponin level should be repeated after approximately 8 hours. Patients who stabilize and do not exhibit recurrent ischemic episodes have a low risk of death and myocardial infarction. In these patients, a non-invasive management strategy might be preferred.[63,73-75] Early transfer to a low level of care and early hospital discharge may result in economic gains without jeopardizing the safety. By contrast, in patients with an initial low-risk profile who do exhibit recurrent ischemia, the risk of adverse outcome increases with the number of ischemic episodes. These patients should be considered high-risk even when the serum troponin level is not elevated.[63,64] Glycoprotein IIb/IIIa inhibition therapy and revascularization should be considered. This would apply even more to

patients who exhibit frequent recurrent ischemia as the analysis presented in **chapter 12** shows that the 30-day event rate of almost 20% in this group surpasses the risk associated with an early intervention protected by a glycoprotein IIb/IIIa blocker. Clearly, the suggested protocol for patient triage needs to be evaluated for its safety and efficacy in prospective studies.

Oral glycoprotein IIb/IIIa receptor blockers

Although intravenous GP IIb/IIIa inhibitors reduce thrombotic complications in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention, platelets remain activated for several weeks or months after the acute event.[84,85] This suggests that prolonged inhibition of platelet aggregation by oral GP IIb/IIIa receptor blockers might provide an additional reduction in recurrent events in patients with acute coronary syndromes. In **chapters 13 and 14**, we describe the phase II clinical development of lefradafiban, an orally active prodrug which is metabolised in two steps to fradafiban, a non-peptide GP IIb/IIIa receptor blocker.[86]

Chapter 13 describes the first phase II study which determined the dose of lefradafiban that provides 80% blockade of the GP IIb/IIIa receptors (FRO = Fibrinogen Receptor Occupancy) by fradafiban and studied the pharmacodynamics and safety of different doses of lefradafiban when administered for 48 hours in 64 patients with stable coronary artery disease undergoing percutaneous transluminal coronary angioplasty. Plasma concentrations of fradafiban increased in a dose-dependent manner in patients treated with lefradafiban. There was a close correlation between the plasma concentrations of fradafiban and the FRO levels. Levels of FRO increased in a dose-dependent manner in patients treated with lefradafiban. Median levels of FRO were 0% in the placebo group, 71% in patients treated with lefradafiban 30 mg tid, 85% in patients treated with lefradafiban 45 mg tid and 88% in patients on Lefradafiban 60 mg tid. Fradafiban plasma levels of 170 ng/ml were required to achieve 80% FRO. There was little variation in FRO level within each patient, while the interpatient variability was greater among patients receiving the lower dose than among those treated with the higher dosages, which reflected the plasma concentrationñFRO relationship. Inhibition of platelet aggregation was closely related to FRO. There were no major bleeding events. Lefradafiban 60 mg tid resulted in a high (71%) incidence of minor and insignificant bleeding. The incidence of bleeding was 44% in the lefradafiban 30 and 45 mg tid groups, compared with 9% in placebo patients. Puncture site bleedings were most common. The odds of bleeding increased by 3% for every increase in FRO by 1%.

Based on the results from this first phase II study we conducted a second study which assessed, in a double-blind, randomized manner, the safety and preliminary

efficacy of one month treatment with three dose levels of lefradafiban (20, 30 and 45 mg tid versus placebo) in 531 patients with acute coronary syndromes without persistent ST-segment elevation. This study is reported in **chapter 14**. Although this study was not powered to definitively evaluate differences in clinical outcomes among treatment groups, there was a trend towards a reduction in cardiac events with lefradafiban 30 mg when compared with placebo and lefradafiban 20 mg. The benefit was particularly apparent in patients with a positive (≥0.1 ng/ml) troponin I test at baseline and less so in those with a negative test result. In patients receiving lefradafiban, the cardiac event rate decreased with increasing minimal levels of fibrinogen receptor occupancy. There was a dose-dependent increase in the incidence of bleeding: the composite of major or minor bleeding occurred in 1% of placebo patients, 5% of patients receiving lefradafiban 20 mg and in 7% of patients receiving 30 mg, with an excessive risk (15%) in the 45 mg group which resulted in early discontinuation of this dose level. Gingival and arterial or venous puncture site bleedings were most common and accounted for more than 60% of all haemorrhagic events. There was an increased incidence of neutropenia (neutrophils $< 1.5 \times 10^9/l$) in the lefradafiban groups (5.2% versus 1.5% in the placebo group), which did not result from bone marrow depression but rather from a reversible redistribution of neutrophils by margination or clustering.

Along with this study, four large-scale clinical trials evaluated the efficacy of long-term oral GP IIb/IIIa inhibition with xemilofiban, orbofiban and sibrafiban in patients after percutaneous coronary intervention and acute coronary syndromes.[87-89] None of the trials showed benefit of long-term GP IIb/IIIa inhibition therapy. On the contrary, there was a higher incidence of the composite endpoint of death or myocardial infarction at the end of the follow-up periods in patients treated with an oral GP IIb/IIIa receptor blocker than in those receiving placebo (Table). The impact on mortality alone was even worse with an approximate 25% relative increase associated with oral GP IIb/IIIa inhibition therapy when the data of all trials were combined (Table).

Several hypotheses can be considered for the lack of benefit of the first generation of oral GP IIb/IIIa receptor blockers in the light of the benefit of the intravenous compounds.[87] The pharmacokinetic and pharmacodynamic profiles of these agents are characterized by low bioavailability (5-20%) and the existence of peaks and troughs in plasma drug level corresponding to the drugís short half-life relative to the dosing interval.[87,90,91] Accordingly, substantial variability between and within patients in the level of platelet inhibition has been observed with the oral agents.[87,90,91] As such, with a fixed dose, some patients may have as high as 100% inhibition at peak and others as low as 0% to 20% inhibition at trough.[87] This may result in average levels of platelet inhibition that are too low to provide optimal protection against new thrombotic events. In comparison, the benefit of the

Table. Characteristics and outcomes of the four large phase III trials on long-term treatment with oral glycoprotein IIb/IIIa receptor blockers

Study acronym	Agent	Background with aspirin	Patient category	Number of patients	Follow-up (months)	Mortality (%)			Composite of death and MI (%)		
						Placebo	Low-dose	High-dose	Placebo	Low-dose	High-dose
EXCITE	Xemilofiban	Yes	PCI	7232	6	1.0	1.7	1.1	8.9	9.2	8.2
OPUS-TIMI-16	Orbofiban	Yes	ACS	10288	10	3.7	5.1	4.5	8.1	9.7	9.5
SYMPHONY-1	Sibrafiban	No	ACS	9169	3	1.8	2.0	2.0	7.0	7.4	7.9
SYMPHONY-2	Sibrafiban	Yes	ACS	6637	3	1.3	1.7	2.4	6.1	6.8	8.6
Total phase III				33326		2.0	2.7		7.3	8.3	
OR (95% CI)							1.35 (1.16-1.60)			1.14 (1.05-1.24)	

ACS = acute coronary syndromes, CI = confidence interval, MI = myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention

intravenous GP IIb/IIIa receptor blockers has been observed with high levels (>80%) of inhibition of platelet aggregation. However, these levels of inhibition during long-term treatment are currently associated with a high incidence of bleeding complications.[87-89]

Additionally, it has been shown that (oral) GP IIb/IIIa inhibitors are both antagonists and partial agonists of the GP IIb/IIIa receptor,[92] and that at low concentrations these agents can demonstrate an intrinsic activating property, which can result in fibrinogen binding to the GP IIb/IIIa receptor and consequently in platelet aggregation.[92-95] Thus, it is possible that at trough periods, low blood concentrations of the oral GP IIb/IIIa inhibitor induces a prothrombotic state, thereby increasing the propensity to new thrombotic events.[87] Indeed, several subanalyses have shown that the excess mortality mainly resulted from increased rates of new thrombotic events.[87,95] Accordingly, these events may occur early after discontinuation of GP IIb/IIIa inhibition therapy.[87,95]

Another possibility is that the risk of recurrent ischemic events in the patient populations included in these trials may have been too low to detect benefit of long-term GP IIb/IIIa receptor blockade.[88,89] Particularly following percutaneous coronary intervention, the event rates are low.

Further possibilities include the inability of GP IIb/IIIa receptor blockers to affect plaque growth, inflammation and rupture, as well as the fact that concomitant antithrombin therapy may be required for benefit as observed with the intravenous agents.[18]

Finally, decreasing the propensity of platelets to become activated may be more effective for long-term prevention of new thrombotic events than direct inhibition of platelet aggregation, which may be most important in the acute phase.[87]

Perspective for oral glycoprotein IIb/IIIa receptor blockers

Newer drugs with higher bioavailability and longer half-lives will be associated with fewer peaks and troughs in the level of platelet inhibition, thereby providing a more stable antiplatelet action.[96] The development of drugs with a tight binding affinity for the GP IIb/IIIa receptor might also avoid low levels of platelet inhibition and the prothrombotic effect seen with the present agents that rapidly move on and off the receptor. Studies evaluating these newer agents with tight receptor binding are underway.[97]

Second, dose-adjustment on the basis of patient characteristics that influence drug levels such as renal function and body weight, as well as individual dose-titration to a target level of platelet inhibition measured with a bedside rapid platelet-function assay,[98,99] as is done routinely for warfarin, may improve the safety profile, as well as improve clinical outcomes. Furthermore, as the risk of thrombotic events declines after an acute episode while the bleeding risk continues, an

additional potential strategy may be to select only patients at high risk of recurrent thrombotic events.

Finally, in parallel with the therapeutic exploitation of the GP IIb/IIIa receptor pathway there has been improvement in antagonists to the ADP receptor.[32] Therefore, if oral GP IIb/IIIa antagonism with the second generation drugs proves to be safe and clinically effective, will this therapy remain more effective than a combination of other platelet antagonists (i.e. aspirin plus clopidogrel) and will the margin of improved efficacy justify the increased cost.?[32]

Glycoprotein IIb/IIIa receptor blockers combined with thrombolytic therapy in acute ST-elevation myocardial infarction

Although primary angioplasty is being used to an increasing extent, thrombolysis is still the most widely used modality of reperfusion therapy in patients with acute ST-segment elevation myocardial infarction. Although thrombolytic therapy produces an important survival benefit,[100,101] it has well-established efficacy as well as safety limitations. As described in **chapter 1**, the limitations relate to the prothrombotic effects of fibrinolytic agents coincident with a lack of a sound antiplatelet approach.[30] Accordingly, GP IIb/IIIa receptor inhibition added to (reduced-dose) fibrinolytic therapy may improve treatment outcomes in patients with acute ST-elevation myocardial infarction. Indeed, preclinical and early phase II studies have shown that GP IIb/IIIa inhibition accelerates thrombolysis and prevents reocclusion.[102,103]

Recently, three large, phase II angiographic studies demonstrated that GP IIb/IIIa inhibition with abciximab and eptifibatide enhances the rate and extent of thrombolysis, producing early, marked increases in complete reperfusion (TIMI 3 flow) when combined with reduced-dose fibrinolytic therapy.[104-106] The TIMI-14 trial demonstrated that 60- and 90-minute TIMI 3 flow could be achieved in 75% to 80% of patients treated with a combination of abciximab and a protracted infusion of half-dose alteplase, compared with 57% of patients treated with full-dose accelerated alteplase alone.[105] This improvement in reperfusion with alteplase occurred without an increase in the risk of major bleeding. Modest improvements in TIMI 3 flow were seen when abciximab was combined with streptokinase, but there was an increased risk of bleeding. This pattern was also apparent when streptokinase was administered with eptifibatide in another study.[107] A possible explanation for this observation may be the more profound systemic disturbances of the hemostatic system that occur with a less fibrin-specific fibrinolytic agent such as streptokinase. The SPEED (abciximab in combination with low-dose reteplase) and INTRO-AMI (eptifibatide added to alteplase) trials endorsed the TIMI-14 trial observations.[104,106] Although achievement of rapid, complete and sustained restoration of coronary flow through the infarct-related artery (TIMI grade 3

flow) is associated with lower mortality,[108,109] the GUSTO-IV-Acute Myocardial Infarction trial, which will randomize more than 16,000 patients to reteplase with or without abciximab, is underway to evaluate whether the earlier more complete reperfusion observed in the phase II studies translates into improved survival. Furthermore, the large sample size of this trial will allow for a more statistically robust estimate of the risk of intracerebral bleeding with the new reperfusion regimen.

Finally, the use of low-dose fibrinolytic and GP IIb/IIIa inhibition as an initial pharmacological strategy has the potential not only to achieve reperfusion in a high proportion of patients but also to support acute-phase intervention.[30] Without the hazard of promoting coronary thrombosis or inducing serious bleeding complications, combined low-dose fibrinolytic and GP IIb/IIIa inhibition has considerable potential to bridge the long-term gap between mechanical and pharmacological reperfusion therapies.[30]

Further perspectives

Despite the impressive progress in our understanding of the platelet GP IIb/IIIa receptor and its role in platelet function and the improved patient outcome with GP IIb/IIIa receptor blockers in clinical trials, there are several unresolved issues.[5,30,32]

More clinical trials are required to determine the optimal management strategy in different risk categories of patients with non-ST-elevation acute coronary syndromes. Although data from subanalyses suggest that the intravenous GP IIb/IIIa receptor blockers are beneficial in these patients during pharmacological treatment only, especially in those presenting with an elevated troponin T or I level,[74,75] this observation is investigated in a prospective way in the forthcoming GUSTO-IV-ACS study. In addition, the optimal timing of percutaneous coronary intervention needs to be determined.[82,83]

Further, there has not yet been a direct comparison, head-to-head trial of one of the intravenous GP IIb/IIIa receptor blockers versus another. The perspectives for the oral GP IIb/IIIa receptor blockers, as well as for the combined use of GP IIb/IIIa inhibitors and reduced-dose fibrinolytics in the treatment of patients presenting with an acute ST-segment elevation myocardial infarction have been described in previous paragraphs.

Refinement of dosing of antiplatelet agents to optimize patient care will require definition of the extent of platelet inhibition necessary to reduce ischemic events and prevent bleeding complications in a variety of clinical settings including acute coronary syndromes, percutaneous coronary interventions, and long-term prevention.[110] After definition of the optimal extent of platelet inhibition, treatment can be improved by titration of dosage according to the needs of individual

patients.[110] Therefore, correlation between platelet reactivity or aggregation, measured by a platelet function assay, and subsequent outcome should be an important aspect in ongoing clinical research and clinical trials.[110]

A better understanding of the structure and function of the platelet GP IIb/IIIa receptor has the potential for design of new and better GP IIb/IIIa receptor antagonists that might selectively target the activated receptor and allow for a more safe and effective use of these agents.[32] Another question is whether the interaction of GP IIb/IIIa blockers with other integrins, notably the $\alpha_V\beta_3$, is advantageous.[32]

Finally, will treatment with GP IIb/IIIa receptor blockers remain more effective than other antiplatelet antagonists and regimens and will the margin of improved efficacy justify the increased cost? [32]

The potency of effects with these agents in clinical trials support the view that the GP IIb/IIIa receptor blockers have taken the clinician and patient out of the era of aspirin monotherapy when platelet inhibition is required.[32] Continued clinical research coupled with the completion of more clinical trials should allow clinicians to offer patients enhanced antiplatelet protection with proven benefits and understood risks.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349: 1269-1276.
2. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992; 326: 242-50, 310-8.
3. Ambrose JA, Weinrauch M. Thrombosis in ischemic heart disease. Arch Intern Med 1996; 156: 1382-94.
4. Davies MJ. The role of plaque pathology in coronary thrombosis. Clin Cardiol 1997; 20 (Suppl I): I-2-I-7.
5. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Engl J Med 1995; 332: 1553-1559.
6. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
7. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-1435.
8. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336: 1689-1896.
9. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349: 1422-1428.
10. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997; 96: 1445-1453.
11. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
12. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.
13. Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. Am J Cardiol 1997; 80: Suppl 4A: 34B-38B.
14. The GUSTO-IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996; 335: 775(782.
15. The Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994; 308: 81(106.
16. Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996; 94: 911(922.
17. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498(1505.
18. The PRISM PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488(1497.
19. Mahaffey KW, Granger CB, Woodlief L, et al. Centralized systematic adjudication of clinical endpoints in multicenter trials of acute coronary syndromes identifies patients at high risk for adverse clinical outcomes. J Am Coll Cardiol 1996; 27: 250A.
20. Tardiff BE, Mahaffey KW, Sigmon KN, et al. Differences in endpoint identification by investigators versus independent review. Contr Clin Trials 1996; 17: 25S.

21. Mahaffey KW, Tardiff BE, Granger CB, et al. Comparison of investigator and central events review of myocardial infarction rates as a means to improve events classification: results from GUSTO-IIa. Contr Clin Trials 1996; 17: 136S.
22. Mahaffey KW, Granger CB, Tardiff BE, et al. for the GUSTO-IIb Investigators. Endpoint adjudication by clinical events committee can impact the statistical outcome of a clinical trial: results from GUSTO-IIb. J Am Coll Cardiol 1997; 29: 410A.
23. Mahaffey KW, Tardiff BE, Granger CB, et al. Disagreement between site investigators and clinical event committees is common and can affect trial results. J Am Coll Cardiol 1998; 31: 184A(185A.
24. Thrombolysis in Myocardial Ischemia (TIMI) Study Group. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Circulation. 1994; 89: 1545(1556.
25. Van de Werf F, Topol EJ, Lee KL, et al. for the GUSTO Investigators. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. Results from the GUSTO trial. JAMA 1995; 273: 1586-1591.
26. Rouleau JL, MoyÈ LA, Pfeffer MA, et al. for the SAVE Investigators. A comparison of management patterns after acute myocardial infarction in Canada and the United States. N Engl J Med 1993; 328: 779-784.
27. Barbash GI, Modan M, Goldbourt U, White HD, Van de Werf F. Comparative case fatality analysis of the International Tissue Plasminogen Activator/Streptokinase mortality trial: variation by country beyond predictive profile. J Am Coll Cardiol 1993; 21: 281-286.
28. LATE Study Group. Late Assessment of Thrombolytic Efficacy (LATE) Study with alteplase 6-24 hours after onset of acute myocardial infarction. Lancet 1993; 342: 759-766.
29. Lincoff AM, Tcheng JE, Califf RM, et al. for the PROLOG Investigators. Standard versus low-dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. Am J Cardiol 1997; 79: 286-291.
30. Topol EJ. Toward a new frontier in myocardial reperfusion therapy. Emerging platelet preeminence. Circulation 1998; 97: 211-218.
31. Topol EJ, Lincoff AM, Sapp S. Coronary stenting and use of abciximab. Lancet 1998; 352: 1311-1312.
32. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999; 353: 227-231.
33. Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. Eur Heart J 1998; 19: 1608-1616.
34. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998; 98: 2829-2835.
35. Abdelmeguid AE, Topol EJ. The myth of the myocardial infarctlet during percutaneous coronary revascularization procedures. Circulation 1996; 94: 3369-3375.
36. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998; 31: 241-251.
37. Tardiff BE, Califf RM, Tcheng JE, et al. for the IMPACT-II Investigators. Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. J Am Coll Cardiol 1999; 33: 88-96.
38. Simoons ML, Van den Brand M, Lincoff M, et al. Minimal myocardial damage during coronary intervention is associated with impaired outcome. Eur Heart J 1999; 20: 1112-1119.
39. Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp SK, Ellis SG. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. Circulation 1996; 94: 1528-1536.

40. Alexander JH, Sparapani RA, Mahaffey KW, et al. for the PURSUIT Steering Committee. Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. JAMA 2000; 283: 347-353.
41. Fioretti P, Sclavo M, Browec RW, Simoons ML, Hugenholtz PG. Prognosis of patients with different peak serum creatine kinase levels after first myocardial infarction. Eur Heart J 1985; 6: 473-478.
42. Savonitto S, Granger CB, Ardissino D, et al. Even minor elevations of creatine kinase predict increased risk of cardiac events in acute coronary syndromes without ST-segment elevations. J Am Coll Cardiol 1999; 33: 346A.
43. Anderson KM, Califf RM, Ferguson JJ, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. Submitted.
44. Lincoff AM, Califf RM, Moliterno DJ, et al. for the EPISTENT Investigators. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. N Engl J Med 1999; 341: 319-327.
45. Topol EJ, Mark DB, Lincoff AM, et al. for the EPISTENT Investigators. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. Lancet 1999; 354: 2019-2024.
46. Lee KL, Woodlief LH, Topol EJ, et al. for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. Circulation 1995; 91: 1659-1668.
47. Simoons ML, Arnold AER. Tailored thrombolytic therapy: a perspective. Circulation 1993; 88: 2556-2564.
48. Boersma E, Vlugt van der M, Arnold AER, et al. Estimated gain in life expectancy: a simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction. Eur Heart J 1996; 17: 64-75.
49. Maseri A, Rebuzzi AG, Cianflone D. Need for a composite risk stratification of patients with unstable coronary syndromes tailored to clinical practice. Circulation 1997; 96: 4141-4142.
50. Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. Circulation 1998; 98: 1860-1868.
51. Freeman MR, Williams AE, Chisholm RJ, Armstrong PW. Intracoronary thrombus and complex morphology in unstable angina. Circulation 1989; 80: 17(23.
52. Williams AE, Freeman MR, Chisholm RJ, Patt NL, Armstrong PW. Angiographic morphology in unstable angina. Am J Cardiol 1988; 62: 1024(1027.
53. Bugiardini R, Pozzati A, Borghi A, Morgagni GL, Ottani F, Muzi A, Puddu P. Angiographic morphology in unstable angina and its relation to transient myocardial ischemia and hospital outcome. Am J Cardiol 1991; 67: 460(464.
54. Dangas G, Mehran R, Wallenstein S, Courcoutsakis NA, Kakarala V, Hollywood J, Ambrose JA. Correlation of angiographic morphology and clinical presentation in unstable angina. J Am Coll Cardiol 1997; 29: 519(525.
55. Ahmed WH, Bittl JA, Braunwald E. Relation between clinical presentation and angiographic findings in unstable angina pectoris, and comparison with that in stable angina. Am J Cardiol 1993; 72: 544(550.
56. Rupprecht HJ, Sohn HY, Kearney P, Bickel C, Nafe B, Meyer J. Clinical predictors of unstable coronary lesion morphology. Eur Heart J 1995; 16: 1526(1534.
57. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214-1219.
58. Nademanee K, Intarachot V, Josephson MA, Rieders D, Vaghaiwalla Mody F, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987; 10: 1-9.
59. Arnim TV, Krawietz GW, Hofling B. Prognostic implications of transient-predominantly silent-ischemia in patients with unstable angina pectoris. Eur Heart J 1988; 8: 435-440.

60. Patel DJ, Knight CJ, Holdright DR, et al. Long-term prognosis in unstable angina. The importance of early risk stratification using continuous ST segment monitoring. Eur Heart J 1998; 19: 240-249.
61. Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). Circulation 1998; 98: 1358-1364.
62. Holmvang L, Andersen K, Dellborg M, et al. Relative contributions of a single-admission 12-lead electrocardiogram and early 24-hour continuous electrocardiographic monitoring for early risk stratification in patients with unstable coronary artery disease. Am J Cardiol 1999; 83: 667-674.
63. Norgaard BL, Andersen K, Dellborg M, Abrahamsson P, Ravkilde J, Thygesen K, for the TRIM study group. Admission risk assessment by cardiac troponin-T in unstable coronary artery disease: additional prognostic information from continuous ST-segment monitoring. J Am Coll Cardiol 1999; 33: 1519-1527.
64. Jernberg T, Lindahl B, Wallentin L. ST-segment monitoring with continuous 12-lead ECG improves early risk stratification in patients with chest pain and ECG nondiagnostic of acute myocardial infarction. J Am Coll Cardiol 1999; 34: 1413-1419.
65. Klootwijk P, Meij S, van Es GA, et al. Comparison of usefulness of computer-assisted continuous 48-h 3-lead with 12-lead ECG-ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. Eur Heart J 1997; 18: 931-940.
66. Dellborg M, Malmberg K, Ryden L, Svensson A, Swedberg K. Dynamic on-line vectorcardiography improves and simplifies in-hospital ischemia monitoring of patients with unstable angina. J Am Coll Cardiol 1995; 26: 1501-1507.
67. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992; 327: 146-150.
68. Ravkilde J, Nissen H, Horder M, Thygesen K. Independent prognostic value of serum creatine kinase isoenzyme-MB mass, cardiac troponin-T and myosin light-chain levels in suspected acute myocardial infarction. J Am Coll Cardiol 1995; 25: 574-581.
69. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335:1342-1349.
70. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996; 335: 1333-1341.
71. Lindahl B, Venge P, Wallentin L. Relation between troponin-T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. Circulation 1996; 93: 1651-1657.
72. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997; 337:1648-1653.
73. Klootwijk P, Hamm CW. Acute coronary syndromes: diagnosis. Lancet 1999; 353 (suppl-II): 10-15.
74. Hamm CW, Heeschen C, Goldmann B, et al. for the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin-T levels. N Engl J Med 1999; 340: 1623-1629.
75. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD, for the PRISM Study Investigators. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. Lancet 1999; 354: 1757-1762.
76. Katus HA, Looser S, Hallermayer K, et al. Development and in vitro characterisation of a new immunoassay of cardiac troponin T. Clin Chem 1992; 38: 386-393.

77. Davies E, Gawad Y, Takahashi M, et al. Analytical performance and clinical utility of a sensitive immunoassay for determination of human cardiac troponin I. Clin Biochem 1997; 30: 479-490.
78. Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation 2000; 102: 118-122.
79. Brener SJ, Topol EJ. Troponin, embolization and restoration of microvascular integrity. Eur Heart J 2000; 21: 1117-1119.
80. Heeschen C, Van den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. Circulation 1999; 100:1509-1514.
81. The FRISC II Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999; 354: 701-707.
82. Ronner E, Boersma E, Harrington RA, Lincoff AM, Deckers JW, Simoons ML. Optimal timing of percutaneous intervention (PCI) in unstable angina. Circulation 1999; 100: I-455.
83. FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC-II prospective randomised multicentre study. Lancet 1999; 354: 708-715.
84. Merlini PA, Bauer KA, Oltrona L, et al. Persistent activation of the coagulation system in unstable angina and myocardial infarction. Circulation 1994; 90: 61-68.
85. Ault KA, Cannon CP, Mitchell J, et al. Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1999; 33: 634-639.
86. M¸ller TH, Weisenberger H, Brickl R, Narjes H, Himmelsbach F, Krause J. Profound and sustained inhibition of platelet aggregation by fradafiban, a nonpeptide platelet glycoprotein IIb/IIIa antagonist, and its orally active prodrug, lefradafiban, in men. Circulation 1997; 96: 1130-1138.
87. Cannon CP, McCabe CH, Wilcox RG, et al. for the OPUS-TIMI 16 Investigators. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation 2000; 102: 149-156.
88. OíNeill WW, Serruys P, Knudtson M, et al. Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. N Engl J Med 2000; 342: 1316-1324.
89. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomized trial. Lancet 2000; 355: 337-345.
90. Cannon CP, McCabe CH, Borzak S, et al. for the TIMI 12 Investigators. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. Circulation 1998; 97: 340-349.
91. Kereiakes DJ, Kleiman NS, Ferguson JJ, et al. for the ORBIT Trial Investigators. Pharmacodynamic efficacy, clinical safety, and outcomes after prolonged platelet glycoprotein IIb/IIIa receptor blockade with oral xemilofiban: results of a multicenter, placebo-controlled, randomized trial. Circulation 1998; 98: 1268-1278.
92. Cox D, Smith R, Quinn M, et al. Evidence of platelet activation during treatment with a GP IIb/IIIa antagonist in patients presenting with acute coronary syndromes. J Am Coll Cardiol. In press.
93. Holmes MB, Sobel BE, Cannon CP, et al. Increased platelet reactivity in patients given orbofiban after an acute coronary syndrome: an OPUS-TIMI 16 substudy. Am J Cardiol 2000; 85: 491-493.
94. Peter K, Schwarz M, Ylanne J, et al. Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa ((IIb(3) inhibitors. Blood 1998; 92: 3240-3249.

95. Roth U, Hoffmann J, Nehmiz G, Akkerhuis KM, Brickl R, Baardman T, Simoons ML. Level of inhibition of platelet aggregation predicts outcome of patients treated with the oral glycoprotein IIb/IIIa receptor antagonist lefradafiban: results from the FROST study. Eur Heart J 2000; 21: P-3457.
96. Mousa SA, Bozarth JM, Lorelli W, et al. Antiplatelet efficacy of XV459, a novel nonpeptide platelet GP IIb/IIIa antagonist: comparative platelet binding profiles with c7E3. J Pharmacol Exp Ther 1998; 286: 1277-1284.
97. Mousa SA, Khurana S, Forsythe MS. Comparative in vitro efficacy of different platelet glycoprotein IIb/IIIa antagonists on platelet-mediated clot strength induced by tissue factor with use of thromboelastography: differentiation among glycoprotein IIb/IIIa antagonists. Arterioscler Thromb Vasc Biol 2000; 20: 1162-1167.
98. Coller BS. Monitoring platelet GP IIb/IIIa antagonist therapy. Circulation 1998; 97: 5-9.
99. Smith JW, Steinhubl SR, Lincoff AM, et al. Rapid platelet-function assay: an automated and quantitative cartridge-based method. Circulation 1999; 99: 620-625.
100. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected myocardial infarction. Lancet 1988; 2: 349-360.
101. Fibrinolytic Therapy Trialistsí (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343: 311-322.
102. Kleiman NS, Ohman EM, Califf RM, et al. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy. Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot study. J Am Coll Cardiol 1993; 22: 381-389.
103. Ohman EM, Kleiman NS, Gacioch G, et al. for the IMPACT-AMI Investigators. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. Circulation 1997; 95: 846-854.
104. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group.Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000; 101: 2788-2794.
105. Antman EM, Giugliano RP, Gibson CM, et al. for the TIMI 14 Investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial. Circulation 1999; 99: 2720-2732.
106. Verheugt FWA. Hotline sessions of the 21st European Congress of Cardiology. Eur Heart J 2000; 20: 1603-1606.
107. Ronner E, van Kesteren HAM, Zijnen P, et al. Combined therapy with streptokinase and Integrilin. J Am Coll Cardiol 1998; 31(suppl A): 191A.
108. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-1622.
109. Simes RJ, Topol EJ, Holmes DR, et al. for the GUSTO-I Investigators. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial infarction. Importance of early and complete infarct artery reperfusion. Circulation 1995; 91: 1923-1928.
110. Holmes MB, Schneider DJ. Optimizing antiplatelet therapy in patients with acute coronary syndromes: A role for monitoring platelet reactivity. J Invas Cardiol 1999; 11: 21C-25C.

Samenvatting

Acute coronaire syndromen, een verzamelnaam voor onstabiele angina pectoris, acuut myocardinfarct en de acute complicaties van een percutane coronaire interventie, vormen mondiaal gezien een belangrijk probleem voor de gezondheidszorg en zijn de belangrijkste veroorzakers van morbiditeit en mortaliteit in de westerse wereld. Patienten met deze syndromen hebben zowel op korte termijn alsook op lange termijn een verhoogd risico op overlijden, een (recidief) myocardinfarct, recidief angina pectoris, hartfalen, aritmieën en een noodzakelijke coronaire revascularisatieprocedure. Zoals beschreven in **hoofdstuk 1** wordt de ontwikkeling van een acuut coronair ischaemisch syndroom verondersteld te beginnen met disruptie (ruptuur, fissuur of erosie) van een atherosclerotische plaque, hetgeen resulteert in activatie van thrombocyten en van de stollingscascade. Het ontstaan van een locale thrombus als reactie op de vaatwandbeschadiging kan vervolgens aanleiding geven tot een wisselende mate van vaatocclusie met als gevolg verminderde coronaire bloeddoorstroming, embolisatie van thrombotisch materiaal naar distaal resulterend in obstructie van de capillaire bloeddoorstroming en necrose van hartspierweefsel, en incorporatie van de locale thrombus in de groter wordende plaque resulterend in progressie van de atherosclerose. Zoals samengevat in **hoofdstuk 1** heeft onderkenning van de cruciale rol van thrombose in de pathofysiologie van acute coronaire syndromen geleid tot concentratie op antithrombotische therapie, met name thrombocytenremmers en anticoagulantia. Aggregatie van geactiveerde thrombocyten speelt een centrale rol in dit proces van coronaire thrombose. Ongeacht de aggregatie-inducerende stimulus wordt de laatste gemeenschappelijke stap tot aggregatie van thrombocyten gevormd door binding van fibrinogeen en andere plasma-eiwitten aan geactiveerde glycoproteine IIb/IIIa receptoren op meerdere thrombocyten. Een nieuwe groep geneesmiddelen, bekend als de glycoproteine (GP) IIb/IIIa receptor blokkers, is ontwikkeld om deze laatste, gemeenschappelijke stap te blokkeren en daarmee coronaire thrombose te voorkomen. De effectiviteit van GP IIb/IIIa blokkers in het verminderen van ischaemische complicaties is onomstotelijk vastgesteld bij een groot aantal patienten die een percutane coronaire revascularisatieprocedure, al dan niet met stentimplantatie, ondergingen. In deze studies werd bij patienten behandeld met GP IIb/IIIa blokkers een reductie van ongeveer 30% bereikt in het samengestelde eindpunt van overlijden, myocardinfarct of noodzaak tot een spoedinterventie binnen 30 dagen. Gebaseerd op deze gunstige resultaten werd de experimentele behandeling met GP IIb/IIIa blokkers uitgebreid naar patienten met acute coronaire syndromen. Zoals beschreven in **hoofdstuk 1** werden met diverse middelen twee belangrijke behandelingsstrategieën onderzocht. Eén behandelingsstrategie richt zich op medicamenteuze behandeling en de andere richt zich op GP IIb/IIIa blokkers in combinatie met percutane coronaire interventie.

Dit proefschrift behandelt diverse aspecten van de klinische evaluatie van GP IIb/IIIa blokkers bij patienten met acute coronaire syndromen. Een aantal artikelen uit dit proefschrift zijn gebaseerd op gegevens voortvloeiend uit de omvangrijke 'Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin (eptifibatide) Therapy (PURSUIT)' studie. PURSUIT vergeleek eptifibatide met placebo toegevoegd aan de standaardmedicatie bij 9461 patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie. In totaal namen 726 ziekenhuizen uit 27 verschillende landen in 4 geografische regio's deel (West-Europa, Noord-Amerika, Oost-Europa en Zuid-Amerika). Patienten kwamen in aanmerking voor deelname aan de studie indien zij binnen de voorafgaande 24 uur pijn op de borst hadden met daarnaast hetzij ECG-veranderingen suggestief voor ischaemie (ST-segment depressie, T-top inversie, voorbijgaande ST-segment elevatie), hetzij een creatine kinase-MB fractie hoger dan de bovengrens gehanteerd door het desbetreffende ziekenhuis. Patienten werden op dubbel-blinde wijze gerandomizeerd naar hetzij behandeling met placebo als intraveneuze bolus plus infuus hetzij behandeling met eptifibatide als 180 $\mu g.kg.^{-1}$ bolusinjectie plus 2.0 $\mu g.kg.^{-1}min.^{-1}$ infuus. De toediening van de studiemedicatie diende minstens 72 uur te duren. Echter, wanneer aan het einde van deze periode van 72 uur een percutane coronaire interventie plaatsvond, bestond de mogelijkheid de infusie te verlengen tot maximaal 96 uur. De beslissing tot andere vormen van behandeling zoals bijvoorbeeld het toedienen van heparine en andere anti-ischaemische medicatie en het verrichten van coronair-angiografie, maar ook het gebruik en tijdstip van percutane of chirurgische revascularisatie werd geheel overgelaten aan de behandelend cardioloog. In vergelijking met placebo resulteerde behandeling met eptifibatide in een statistisch significante absolute reductie van 1.5% in het samengestelde 30-dagen eindpunt van mortaliteit en niet-fataal (recidief)-myocardinfarct, welke werd vastgesteld door een onafhankelijke Eindpunt Validatie Commissie die geen informatie had over de werkelijke behandelingsvorm.

De methodologie en impact van het beoordelen van eindpunten in een klinische studie

Een myocardinfarct is een potentieel dodelijke complicatie welke kan optreden bij patienten met een acuut coronair syndroom en is tevens een belangrijk eindpunt voor het beoordelen van de effectiviteit van een experimentele behandeling in klinische studies. Hoewel een myocardinfarct gezien werd als een duidelijk omschreven eindpunt kan het vaststellen van een myocardinfarct zowel in klinische studies als in de klinische praktijk lastig zijn vanwege elkaar tegensprekende klinische, laboratorium, en electrocardiografische gegevens. Daar in recente studies naar thrombocytenremmende en antithrombotische

therapieën de preventie van myocardinfarct de meest belangrijke maat voor effect van de behandeling was, zijn Eindpunt Validatie Commissies een essentieel onderdeel geworden van klinische studies naar nieuwe therapieën voor de behandeling van acute coronaire syndromen. Dit om het systematisch, onbevooroordeeld, onafhankelijk en gestandaardiseerd vaststellen van dit eindpunt te kunnen waarborgen. Dientengevolge beoordeelde in PURSUIT een onafhankelijke Eindpunt Validatie Commissie alle vermoedelijke myocardinfarcten die optraden tussen het moment van inclusie en 30 dagen later.

In de **hoofdstukken 2 en 3** wordt de structuur van de Eindpunt Validatie Commissie en het beoordelingsproces van eindpunten zoals gehanteerd in PURSUIT nader bestudeerd. De Eindpunt Validatie Commissie identificeerde 5005 vermoedelijke infarcten, waarvan 1415 (28%) uiteindelijk werden beoordeeld als zijnde een myocardinfarct. Terugkijkend op het beoordelingsproces vallen een aantal punten op. Ten eerste, het percentage vastgestelde infarcten was hoger dan in voorgaande studies met een vergelijkbare patientenpopulatie. Ten tweede, myocardinfarcten volgens de definities van het protocol werden ondergerapporteerd door de behandelende cardiologen. Ten derde verschilde de beoordeling van infarcten door behandelend cardioloog of Eindpunt Validatie Commissie bij 983 (20%) van de 5005 patienten die door de Eindpunt Validatie Commissie werden beoordeeld. Het grootste deel van dit verschil in beoordeling was te wijten zowel aan misclassificatie door de behandelende cardiologen van infarcten reeds bestaand tijdens inclusie als zijnde infarcten die optraden ná inclusie, als ook aan de onderrapportage van myocardinfarcten rondom coronaire revascularisatie-procedures en myocardinfarcten vastgesteld op basis van enzymstijgingen zonder klinisch of electrocardiografisch bewijs voor ischaemie of infarct. Ten vierde was het effect van behandeling met eptifibatide kleiner wanneer het infarctpercentage volgens de Eindpunt Validatie Commissie werd gehanteerd, dan wanneer dit percentage volgens de behandelende cardiologen werd gebruikt. Ten slotte, in een retrospectieve analyse was het behandeleffect groter wanneer dié infarcten werden uitgesloten die, hoewel werd voldaan aan de vastgestelde criteria, gebaseerd waren op tegenstrijdige klinische, electrocardiografische en enzymatische informatie.

Diverse verklaringen voor deze vijf constateringen kunnen worden aangedragen. Samenvattend kan worden gesteld dat bovenstaande bevindingen bevestigen dat beoordeling van myocardinfarcering als eindpunt door een Eindpunt Validatie Commissie van belang is om te zorgen voor een onafhankelijke, onbevooroordeelde, gestandaardiseerde en systematische vaststelling van dit eindpunt. Echter, met de definitie van myocardinfarct (creatine kinase-MB hoger dan éénmaal de bovengrens) zoals gehanteerd en toegepast binnen PURSUIT zijn mogelijk teveel myocardinfarcten geïncludeerd welke werden gekenmerkt door

geringe enzymstijgingen, welke òf vals-positieve uitslagen waren òf klinisch onbelangrijke infarcten representeerden. Hierdoor heeft vaststelling van eindpunten door een Eindpunt Validatie Commissie tevens zekere beperkingen; in gevallen waarin klinische, enzymatische en electrocardiografische informatie inconsistent is, of indien onzekerheid bestaat over de juistheid van laboratoriumuitslagen van verhoogde cardiale enzymen, zou het vaststellen van een myocardinfarct een meer klinische subjectieve beoordeling vereisen, hoewel dit de objectiviteit noodzakelijk voor eindpunt-classificatie zou kunnen verminderen, met name in internationale studies. Hoewel het absolute verschil in infarctpercentages bepaald door de Eindpunt Validatie Commissie versus de behandelend cardiologen klein was, was het relatieve verschil daarentegen duidelijk groter. Dit oefende een aanzienlijke invloed uit op de statistische uitkomst van de studie. Dit fenomeen moet daarom in aanmerking worden genomen bij het berekenen van de grootte van de te onderzoeken populatie tijdens het opzetten van toekomstige studies. Tevens beinvloedt het de manier waarop de medische wereld en overheidsinstanties de onderzoeksresultaten beoordelen. Voorts moet het gehanteerde Eindpunt Validatie Commissie - beoordelingsproces in aanmerking worden genomen wanneer infarctpercentages tussen verschillende studies worden vergeleken.

In PURSUIT bestonden, net als in andere grote internationale studies, aanzienlijke verschillen in uitkomsten tussen patienten uit de diverse geografische regio's. In de eerste univariate PURSUIT analyse leek het effect van behandeling in Noord-Amerika groter dan in West-Europa, terwijl geen effect duidelijk was in Zuid-Amerika en Oost-Europa. Echter, de betrouwbaarheidsintervallen voor het behandeleffect in deze regio's waren groot en overlappend. Dankzij het grote aantal patienten in de diverse regio's bood deze studie de unieke mogelijkheid om inzicht te verwerven in de heterogeniteit van de ziekte en patientenpopulatie alsmede om de verschillen in medische praktijkvoering en behandelstrategieën te onderzoeken.

Dientengevolge bestudeerden we in **hoofdstuk 4** deze regionale verschillen en analyseerden we de factoren die mogelijk bijgedragen hebben aan de geografische variaties. Er waren belangrijke verschillen in de uitgangssituatie van patienten uit de verschillende regio's. Behandeling met coronaire interventie verschilde ook aanzienlijk. Na multivariate analyse was het patroon van behandelvoordeel met eptifibatide consistent over de diverse regio's. In het algemeen waren de verschillen in uitkomst van patienten en behandeleffect het grootst, wanneer de definitie van myocardinfarct volgens het protocol (CK-MB > 1 bovengrens van normaal) gehanteerd werd. Deze verschillen werden kleiner wanneer strengere definities werden toegepast en verdwenen met de beoordeling van myocardinfarct door de behandelend cardioloog. Deze analyse laat zien dat

de verschillen in de uitkomst van patienten en het effect van behandeling met eptifibatide grootendeels verklaard kunnen worden door de verschillen in de kenmerken van patientenpopulaties bij inclusie en door verschillen in aanvullende behandeling, met name het gebruik en tijdstip van coronaire interventie, als ook door de definitie van myocardinfarct en de toepassing ervan in het beoordelingsproces. Deze drie belangrijke aspecten moeten daarom in aanmerking worden genomen wanneer binnen internationale klinische studies analyses worden gedaan naar verschillen in uitkomsten en behandeleffect.

Veiligheid van glycoproteine IIb/IIIa receptor blokkers

In de eerste studies ging behandeling met GP IIb/IIIa receptor blokkers gepaard met significant meer bloedingscomplicaties, echter dit bleek grootendeels te wijten aan overmatige en langdurige gelijktijdige toediening van heparine. Alle latere studies waarbij lage-dosis, aan gewicht aangepaste heparineschema's toegepast werden en waarbij intravasculaire toegangswegen met voorzichtigheid werden behandeld, lieten geen overschot aan ernstige bloedingscomplicaties zien.

Een schatting van het bloedingsrisico gebaseerd op klinische evaluatie bij aankomst van de patient kan de verhouding tussen risico en voordeel van behandeling met GP IIb/IIIa receptor blokkers bij patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie gunstig beinvloeden. In **hoofdstuk 6** bestudeerden we daarom de bloedingscomplicaties welke optraden bij de 9375 PURSUIT patienten met acute coronaire syndromen, die òf placebo òf de GP IIb/IIIa receptor blokker eptifibatide kregen, en bepaalden we de multivariate voorspellende factoren voor spontane of niet-interventie gerelateerde bloedingen alsmede voor bloedingscomplicaties geassocieerd met percutane coronaire interventies.

Bloedingen traden regelmatig op bij deze groep patienten. Het percentage bloedings-complicaties was hoger in de eptifibatide groep bij patienten die geen bypassoperatie tijdens ziekenhuisopname ondergingen (31% versus 12 % in de placebogroep). Echter, in de meeste gevallen (83%) waren deze bloedingscomplicaties niet ernstig. Patienten die een bypassoperatie tijdens ziekenhuisopname ondergingen, hadden een verhoogd risico op bloedingscomplicaties en namen bij benadering 80% van de ernstige bloedingen voor hun rekening. Het gebruik van eptifibatide bij deze patienten deed het aantal bloedingscomplicaties niet toenemen. Risicofactoren voor interventie-gerelateerde bloedingscomplicaties waren behandeling in Noord-Amerika, eptifibatide, vrouwelijk geslacht, de maximale aPTT-waarde en behandeling met ticlopidine. Behandeling met eptifibatide was de sterkste onafhankelijke voorspeller van spontane bloedingen, gevolgd door hogere leeftijd, vrouwelijk geslacht,

behandeling in Noord-Amerika, de maximale aPTT-waarde, rookgewoontes en behandeling met thrombolytica of ticlopidine. Deze factoren werden gebruikt om een nomogram te ontwikkelen waarmee het basisrisico van een patient op spontane bloedingen voorspeld kan worden en waarmee bepaald kan worden in welke mate dit risico toeneemt wanneer gestart wordt met antithrombotische therapie. Na het combineren van twee risicomodellen konden geen patienten-subgroepen geidentificeerd worden met hetzij een laag risico op cardiale complicaties en een hoog bloedingsrisico, hetzij een hoog risico op cardiale complicaties en een laag bloedingsrisico. Daarom is het basisrisico op bloedingscomplicaties van secundair belang bij de indicatiestelling tot behandeling met GP IIb/IIIa receptor blokkers.

Vanwege het krachtig remmende effect van GP IIb/IIIa receptor blokkers op de aggregatie van thrombocyten, was het risico op cerebrovasculair accident (CVA) een punt van zorg. Omdat de incidentie van CVA laag is, werd een gecombineerde analyse gedaan bij 8555 patienten uit de EPIC, CAPTURE, EPILOG en EPISTENT studies om het risico op CVA te bepalen bij patienten behandeld met de GP IIb/IIIa receptor blokker abciximab (toegevoegd aan aspirine en heparine) versus patienten behandeld met placebo, allen tijdens percutane coronaire interventie. Deze analyse wordt beschreven in **hoofdstuk 5** en laat zien dat het totale risico op een CVA niet verhoogd wordt wanneer abciximab wordt toegevoegd aan aspirine en heparine bij patienten die een percutane coronaire interventie ondergaan.

De veiligheid van GP IIb/IIIa receptor blokkers wordt verder ondersteund door de cumulatieve incidentie van intracerebrale bloedingen van 0,1% in 10 grote, placebo-gecontroleerde, gerandomizeerde studies in zowel de placebogroep als de GP IIb/IIIa behandelgroep. Voorts werd acute bypasschirurgie in deze studies niet gecompliceerd door een verhoogd bloedingsrisico bij gebruik van GP IIb/IIIa receptor blokkers.

Glycoproteine IIb/IIIa receptor blokkers en coronaire interventie

Behandeling met intraveneuze GP IIb/IIIa receptor blokkers bij patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie heeft geresulteerd in een reductie in het samengestelde eindpunt van mortaliteit en myocardinfarct van 10-50%. Echter, gezien het gunstige effect van deze middelen bij percutane coronaire interventie bestond er onduidelijkheid of het effect bij acute coronaire syndromen voorbehouden was aan patienten die een percutane coronaire interventie onder studie-medicatie ondergingen. Er waren 3 klinische studies die konden helpen dit vraagstuk op te lossen.

Dientengevolge hebben we in **hoofdstuk 7** data uit de CAPTURE, PURSUIT en PRISM-PLUS studies geanalyseerd, welke respectievelijk het effect van de GP

IIb/IIIa receptor blokkers abciximab, eptifibatide en tirofiban bestudeerden bij de behandeling van patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie, allen met een periode van infusie van studie medicatie voor een eventuele percutane coronaire interventie. Gedurende deze periode van enkel medicamenteuze behandeling liet elk van deze studies een significante reductie zien in het gecombineerde eindpunt van mortaliteit en niet-fataal myocardinfarct in de patientengroep gerandomiseerd naar de GP IIb/IIIa receptor blokker ten opzichte van de placebogroep. Gecombineerd lieten deze 3 studies een eindpunt percentage zien van 2.5% in de GP IIb/IIIa receptor blokker groep (n = 6125) in deze periode versus 3.8% in de placebogroep (n = 6171), hetgeen een relatieve reductie van 34% impliceert ($p < 0.001$). Tijdens behandeling met studie medicatie werd een percutane coronaire interventie verricht bij 1358 patienten in de GP IIb/IIIa receptor blokker groep versus 1396 patienten in de placebogroep. Het eindpunt percentage binnen de eerste 48 uur na percutane coronaire interventie was wederom significant lager in de GP IIb/IIIa receptor blokker groep (4.9% versus 8.0%; 41% reductie; $p < 0.001$). Noch een additioneel gunstig effect noch een negatief effect werd gezien in de periode aanvangend 48 uur na de percutane coronaire interventie.

Deze data suggereren dat additionele thrombocytenremming met GP IIb/IIIa receptor blokkers naast behandeling met aspirine en heparine, gestart direkt na opname, een gunstig effect heeft bij patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie. Deze hypothese wordt nader onderzocht in de GUSTO-IV-ACS studie die binnenkort zal worden gerapporteerd. Verder kan worden gesteld dat bij patienten die vervolgens een percutane coronaire interventie ondergaan intensieve thrombocytenremming beschermend werkt tegen myocardschade ten gevolge van de interventie. Dus, om maximaal effect te bewerkstelligen, dient de behandeling met GP IIb/IIIa receptor blokkers vroeg na ziekenhuisopname te worden gestart en te worden gecontinueerd tot na de interventie bij patienten die vervolgens een percutane coronaire interventie ondergaan.

Studies bij patienten die een percutane coronaire interventie ondergaan en behandeld worden met GP IIb/IIIa receptor blokkers laten allen een consistente reductie in interventie- gerelateerde myocardinfarcten zien. Het meerendeel van deze infarcten traden op tijdens de interventie en werden gekenmerkt door verhoogde creatine kinase-MB waarden in het bloed zonder duidelijke klinische symptomen. Ondanks het feit dat studies een proportionele relatie hebben laten zien tussen de mate van creatine kinase-MB elevatie na de interventie enerzijds en het risico op een nadelige klinische prognose bij langdurige follow-up (mortaliteit, myocardinfarct en noodzaak tot het verrichten van coronaire revascularisatie) anderzijds, blijft de betekenis van deze implicatie van creatine

kinase-MB elevatie na percutane coronaire interventie een discussiepunt binnen de interventiecardiologie. De prognostische betekenis van kleine myocardinfarcten die spontaan optreden tijdens onstabiele angina pectoris of na een acuut myocardinfarct staat daarentegen wèl duidelijk vast.

In **hoofdstuk 8** hebben we daarom bij 8838 patienten die een percutane coronaire interventie ondergingen de relatie tussen de hoogte van de CK-MB stijging binnen 48 uur na de interventie en mortaliteit na 6 maanden follow-up duur vergeleken met de relatie tussen de hoogte van de CK-MB stijging en mortaliteit bij 5583 PURSUIT patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie die medicamenteus werden behandeld. In beide patientengroepen was stijging van de CK-MB waarden geassocieerd met een geleidelijke toename van de mortaliteit op 6 maanden. De mortaliteitspercentages na 6 maanden waren lager na interventie-gerelateerde infarcten dan na spontane infarcten. Echter, de relatieve toename in mortaliteit na 6 maanden geassocieerd met elke stijging in maximale CK-MB waarde was voor enzymstijgingen na percutane coronaire interventie even groot als voor spontane enzymstijgingen bij acute coronaire syndromen.

De sterke relatie tussen de mate van enzymstijging na interventie en mortaliteit na 6 maanden suggereert dat myocardschade ontstaan gedurende de interventie een belangrijke prognostische factor is, geassocieerd met een nadelige klinische uitkomst. Dientengevolge lijkt preventie van myocardschade door behandeling met GP IIb/IIIa receptor blokkers van klinisch belang om de langetermijn uitkomst te verbeteren van patienten die een percutane coronaire interventie ondergaan. Een recente meta-analyse van alle studies met abciximab bij patienten die een percutane coronaire interventie ondergaan, onderschrijft dit concept door te laten zien dat behandeling met deze GP IIb/IIIa receptor blokker tijdens de interventie resulteert in een 30% relatieve reductie in het risico op overlijden na 6 maanden follow-up. De meest indrukwekkende reductie in mortaliteit werd gerapporteerd in de EPISTENT-studie: de 1-jaars mortaliteit bij patienten behandeld met een stent was gereduceerd met 58% (van 2.4% in de placebogroep tot 1.0% in de abciximab-groep; p=0.03).

Risicostratificatie

Patienten met pijn op de borst of met andere klachten suggestief voor een acuut coronair syndroom en die electrocardiografisch geen persisterende ST-segment elevatie hebben, vormen een heterogene groep met aanzienlijke variaties wat betreft diagnose en toekomstig risico voor cardiale complicaties. Vroege risico-stratificatie is bij deze patienten van belang om een op maat gesneden medicamenteuze en invasieve behandeling aan te kunnen bieden, gebaseerd op het geschatte voordeel van behandeling welke meestal proportioneel verloopt met

het risico op een nadelige uitkomst zonder die specifieke therapie. Overeenkomstig dient een gepast behandelplan tevens een schatting te geven van het basisrisico op een nadelige uitkomst, hetgeen kan worden bereikt door het toepassen van een risicostratificatie-protocol waarin belangrijke prognostische factoren geintegreerd zijn. Diverse risicomodellen zijn ontwikkeld voor patienten die zich presenteren met een myocardinfarct met persisterende ST-segment elevatie, echter voor patienten met een acuut coronair syndroom zonder persisterende ST-segment elevatie zijn er tot op heden slechts weinig modellen ontwikkeld.

Daarom hebben we in **hoofdstuk 10** de relatie onderzocht tussen enerzijds kenmerken van de patient bij presentatie en anderzijds mortaliteit na 30 dagen alsmede het samengestelde eindpunt van mortaliteit en myocardinfarct bij de 9461 patienten geincludeerd in PURSUIT. Uiteindelijk werden meer dan 20 statistisch significante voorspellers van mortaliteit en het samengestelde eindpunt geidentificeerd. De belangrijkste voorspellers van mortaliteit waren leeftijd, hartfrequentie, systolische bloeddruk, ST-segment depressie, tekenen van hartfalen en stijging van de cardiale enzymen. Voorspellers van mortaliteit waren in het algemeen ook voorspellend voor het samengestelde eindpunt van mortaliteit of myocardinfarct. De belangrijkste prognostische factoren uit dit risicomodel werden gebruikt om een eenvoudig nomogram te ontwikkelen waarmee het risico op een cardiale complicatie binnen 30 dagen geschat kan worden.

Een deel (15-20%) van de patienten die zich presenteren met een vermoedelijk acuut coronair syndroom blijken bij coronair-angiografie geen significante atherosclerotische laesie te hebben. Terwijl coronair-anatomie met complexe laesies geldt als een sterke voorspeller van een slechte prognose bij acute coronaire syndromen, is de lange-termijn uitkomst en de effectiviteit van thrombocytenremmende therapie bij patienten met acute coronaire syndromen die geen significante coronaire laesies blijken te hebben nog niet goed vastgesteld.

Daarom evalueerden we in **hoofdstuk 11** de gegevens van patienten die binnen PURSUIT een coronair-angiografie ondergingen en vergeleken we de klinische kenmerken, de reaktie op behandeling en de uitkomst van patienten met niet-significante coronairsclerose met die van patienten met significante coronaire atherosclerotische laesies. Van de 5767 patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie die coronair-angiografie ondergingen, had 88% significante coronaire laesies (1 of meerdere stenosen >50%), 6% matige-ernstige laesies (stenose >0% ≤ 50%) en 6% geen laesies (geen stenose). Patienten verdacht van een acuut coronair syndroom die geen significante coronaire laesie bij angiografie bleken te hebben, hadden een laag risico op cardiale complicaties. Daar waar patienten met niet-significante coronairsclerose geen baat hadden van behandeling met de GP IIb/IIIa blokker eptifibatide, bleek het effect van behandeling bij patienten met significante laesies juist toegenomen.

Klinische kenmerken werden gebruikt om een eenvoudig nomogram te ontwikkelen dat nauwkeurig de waarschijnlijkheid van niet-significant coronairlijden voorspelde. Dit nomogram kan gebruikt worden wanneer een patient zich in het ziekenhuis presenteert. Het nomogram werd gevalideerd binnen een aparte groep patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie.

Concluderend, een vroege indeling van patienten verdacht van een acuut coronair syndroom naar een hoog- of laag-risicogroep door in het klinische beslissingsproces gebruik te maken van de voorspellende risico-modellen zoals weergegeven in **hoofdstuk 10 en 11**, kan van nut zijn bij het verfijnen van de risicostratificatie van acute ischaemische coronaire syndromen en bij het bepalen van indicaties voor behandeling met een GP IIb/IIIa blokker.

Na opname in het ziekenhuis kan de aanwezigheid van voorbijgaande episodes van ischaemie tijdens continue ECG-bewaking belangrijke additionele informatie verschaffen voor het proces van risicostratificatie. Het is gebleken dat terugkerende episodes van ischaemie geregistreerd met Holter-bewaking of gecomputeriseerde ECG-analyse bij patienten met een acuut coronair syndroom geassocieerd is met een verhoogd risico op overlijden en myocardinfarct. Deze relatie tussen terugkerende episodes van ischaemie en een nadelige uitkomst werd geverifieerd in een substudie van PURSUIT, waarbij een computer-ondersteund, 12-afleidingen ECG-bewakingssysteem gebruikt werd, dit in tegenstelling tot eerdere studies waarbij gebruik werd gemaakt van Holter-bewaking met 2- of 3-afleidingen of vectorcardiografische bewaking. De resultaten van deze studie zijn weergegeven in **hoofdstuk 9**.

Daar computer-ondersteunde, multilead ECG-registratie de mogelijkheid biedt tot accurate continue on-line meting van QRS-complex en ST-segment, kan het gebruikt worden als een niet-invasief instrument voor on-line risicostratificatie bij patienten met acute coronaire syndromen, dit in tegenstelling tot Holter-registratie welke gelimiteerd wordt door een beperkt aantal ECG-afleidingen en alléén kan worden gebruikt voor retrospectieve analyse. Echter, eerdere studies naar de relatie tussen terugkerende episodes van ischaemie geregistreerd met continue multilead ECG-bewaking en prognose werden beperkt door kleine patienten-aantallen. Door gegevens van 3 verschillende studies te combineren, tracht de analyse beschreven in **hoofdstuk 12** een accurate bepaling te geven van de invloed van terugkerende episodes van ischaemie zoals geregistreerd met multilead ECG-bewaking op het risico op overlijden en myocardinfarct bij patienten opgenomen met een acuut coronair syndroom.

Deze studie is met bijna 1000 patienten het grootste onderzoek naar de prognostische betekenis van terugkerende episodes van ischaemie geregistreerd met computer-ondersteunde multilead ECG-bewaking bij patienten met acute

coronaire syndromen zonder persisterende ST-segment elevatie. De belangrijkste bevinding was een proportionele relatie tussen het aantal episodes van ischaemie gedurende 24 uur en de kans op het optreden van cardiale complicaties na 5 en 30 dagen follow-up. Het samengestelde eindpunt van mortaliteit en myocardinfarct na 30 dagen trad op bij 5.7% van de patienten zonder episodes van ischaemie en dit percentage steeg naar 19.7% voor patienten met ≥5 episodes van ischaemie. Na correctie voor patientkarakteristieken geassocieerd met een slechte prognose nam het relatieve risico op mortaliteit en myocardinfarct na 5 en 30 dagen met telkens 25% toe voor elke episode van ischaemie per 24 uur.

Andere recente studies hebben laten zien dat de prognostische betekenis van terugkerende episodes van ischaemie geregistreerd met continue, computer-ondersteunde, multilead ECG-bewaking onafhankelijk is van en van toegevoegde waarde is aan niet alleen de patientkarakteristieken en het opname-ECG, maar ook de waarden van biochemische stoffen die necrose van myocardweefsel aanduiden, inclusief creatine kinase-MB en troponine. Hieruit kan worden geconcludeerd dat verdergaande integratie van continue, multilead ECG-bewakingssystemen op hartbewakingsafdelingen en spoedeisende hulp-afdelingen moet worden aanbevolen om de risicostratificatie van patienten opgenomen met een acuut coronair syndroom te verbeteren.

Orale glycoproteine IIb/IIIa receptor blokkers

Hoewel behandeling met intraveneuze GP IIb/IIIa receptor blokkers het aantal thrombotische complicaties vermindert bij patienten met acute coronaire syndromen en bij patienten die een percutane coronaire interventie ondergaan, blijven thrombocyten gedurende enkele weken tot maanden na het acute coronaire syndroom in een geactiveerde staat. Dit suggereert dat langdurige remming van thrombocytenaggregatie middels orale GP IIb/IIIa receptor blokkers een additionele reductie in cardiale complicaties zou kunnen bewerkstelligen bij patienten met acute coronaire syndromen. In de **hoofdstukken 13 en 14** beschrijven we de fase II klinische ontwikkeling van lefradafiban, een pro-drug dat oraal wordt toegediend en in het lichaam in twee stappen wordt gemetaboliseerd tot fradafiban, een synthetische GP IIb/IIIa receptor blokker.

Hoofdstuk 13 beschrijft de eerste fase II studie waarin vastgesteld werd welke dosis van lefradafiban resulteert in 80% blokkade van de GP IIb/IIIa receptoren door fradafiban (FRO = fibrinogen receptor occupancy), en bestudeert de farmacodynamiek en veiligheid van verschillende lefradafiban doseringen wanneer dit gedurende 48 uur wordt toegediend aan 64 patienten met stabiel coronairlijden die een percutane coronaire angioplastiek ondergaan. De toename in plasmaconcentratie van fradafiban was dosis-afhankelijk van de toediening van lefradafiban. Er bestond een sterke correlatie tussen de plasmaconcentratie van

fradafiban en de FRO-waarden. Toename in FRO-waarden was dosis-afhankelijk van de toediening van lefradafiban. Mediane FRO-waarden waren 0% in de placebogroep, 71% in de patientengroep behandeld met drie maal daags 30 mg lefradafiban, 85% in de patientengroep behandeld met drie maal daags 45 mg en 88% in de groep behandeld met drie maal daags 60 mg. Fradafiban plasmaspiegels van 170 ng/ml waren nodig om een FRO-waarde van 80% te bereiken. De variatie in FRO-waarde binnen elke patient was gering, terwijl de variatie tussen verschillende patienten in de lage doseringsgroep groter was dan in de hoge doseringsgroep, hetgeen de relatie tussen de plasmaconcentratie en FRO-waarde weerspiegelde. Remming van thrombocytenaggregatie was sterk gecorreleerd met de FRO-waarde. Ernstige bloedingscomplicaties traden niet op. Behandeling met drie maal daags lefradafiban 60 mg was geassocieerd met een hoge incidentie (71%) van geringe en niet-significante bloedingen. De incidentie van bloedingscomplicaties was 44% in de lefradafiban 30 mg en 45 mg behandelgroepen, vergeleken met 9% in de placebogroep. Bloedingen ter plaatse van vasculaire punctieplaatsen waren het meest frequent. Het bloedingsrisico nam met 3% toe voor elke 1% toename in FRO-waarde.

Gebaseerd op de resultaten van deze eerste fase II studie hebben we een tweede studie uitgevoerd welke op dubbelblinde en gerandomizeerde manier bij 531 patienten met acute coronaire syndromen zonder persisterende ST-segment elevatie de veiligheid en effectiviteit onderzocht van een 1-maand durende behandeling met 3 verschillende lefradafiban doseringen (20 mg, 30 mg en 45 mg drie maal daags versus placebo). Deze studie wordt gepresenteerd in **hoofdstuk 14**. Hoewel deze studie niet ontworpen was om verschillen in effectiviteit tussen de behandelgroepen aan te tonen, bestond er een trend tot een reductie in cardiale eindpunten in de patientengroep behandeld met 30 mg lefradafiban ten opzichte van de patientengroepen behandeld met placebo en 20 mg lefradafiban. Het gunstige effect was met name duidelijk bij patienten met een verhoogde (≥0.1 ng/ml) troponine-I waarde bij aanvang van behandeling en minder bij patienten zonder verhoogde troponine-I waarde. Bij patienten behandeld met lefradafiban daalde het percentage cardiale eindpunten met toenemende FRO-waarden. Er bestond een dosis-afhankelijke toename in het risico op bloedingscomplicaties. Het samengestelde eindpunt van ernstige en geringe bloedingen trad op bij 1% van de patienten in de placebogroep, bij 5% van de patienten behandeld met 20 mg lefradafiban en bij 7% van de patienten behandeld met 30 mg, met een overmatig bloedingsrisico van 15% in de 45 mg groep waardoor behandeling met deze dosering voortijdig werd beëindigd. Slijmvliesbloedingen en bloedingen vanuit arteriële of veneuze punctieplaatsen waren het meest frequent en namen meer dan 60% van alle bloedingscomplicaties voor hun rekening. Een verhoogde incidentie van neutropenie (neutrofielen $<1.5x10^9$/ ltr) werd geconstateerd in de

gecombineerde lefradafiban groep (5.2% versus 1.5% in de placebogroep), hetgeen niet het gevolg was van beenmergdepressie, maar eerder van een reversibele redistributie van neutrofiele granulocyten door marginatie of clustering.

Het slothoofdstuk **Summary and conclusions** bevat uitgebreide samenvattingen van de in dit proefschrift beschreven hoofdstukken. Tevens worden recente ontwikkelingen op het gebied van de orale GP IIb/IIIa receptor blokkers beschreven alsmede op het gebied van de gecombineerde toediening van GP IIb/IIIa receptor blokkers en thrombolytica bij de behandeling van patienten met een acuut myocardinfarct met ST-elevatie. Tevens worden kort enkele mogelijke toekomstige ontwikkelingen besproken op het gebied van de GP IIb/IIIa receptor blokkers en de behandeling van patienten met acute coronaire syndromen.

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Curriculum Vitae

The author of this thesis was born on 21 July 1972 in Vlaardingen, The Netherlands where he attended grammar school at the Openbare Scholengemeenschap Professor Casimir. He started his medical training at the Erasmus University Rotterdam in 1990. During his studies, he performed a research project on the management of diabetes in the general practitioner's population (Dr. R.F.A. Weber and Dr. M.L. Jacobs, Department of Internal Medicine, University Hospital Rotterdam – Dijkzigt). He obtained his medical degree in 1996. He subsequently started working as a clinical trial manager and research fellow to Prof. dr. M.L. Simoons and Dr. J.W. Deckers at Cardialysis, Clinical Research Management and Core Laboratories, Rotterdam, The Netherlands. He was involved in the design, conduct and analysis of several large, international, clinical studies on new antithrombotic treatment modalities in acute coronary syndrome patients. In March 2000, he became a resident at the Department of Cardiology, Thoraxcenter, University Hospital Rotterdam – Dijkzigt.

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