

Myocardial infarction and angina

Glycoprotein IIb/IIIa receptor antagonists

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The third part of the special feature on myocardial infarction and angina discusses recent clinical trials of glycoprotein IIb/IIIa receptor antagonists and their role in both ACS and coronary revascularisation

Acute coronary syndromes (ACS) encompass the clinical spectrum of acutely and rapidly evolving symptoms of myocardial ischaemia, ranging from unstable angina to non-Q-wave myocardial infarction (MI) to Q-wave MI.

The adhesion of platelets to other platelets and to the blood vessel wall is a critical step in thrombus development. While therapeutic strategies, such as aspirin and heparin, provide important benefits, the glycoprotein (GP) IIb/IIIa receptor antagonists offer a significant addition to the management of ACS and coronary revascularisation.

This paper includes the recommendations from the Task Force of the European Society

of Cardiology (ESC) as well as the National Institute for Clinical Excellence (NICE).

Risk stratification Patients presenting with ischaemic chest pain at rest are divided on the basis of initial electrocardiograph (ECG) into those with or without ST-segment elevation. Most patients with ST-segment elevation will go on to develop full Q-wave myocardial infarction. These patients require immediate reperfusion therapy with fibrinolytic agents (streptokinase or tPA) with or without direct coronary revascularisation, ie, percutaneous coronary intervention (PCI). Many patients without ST-segment elevation will have subsequently either unstable angina or non-ST-segment elevation myocardial infarction. These high-risk patients require urgent treatment with antiplatelet agents (GP IIb/IIIa antagonists) to stabilise their condition and prevent a full MI.

ECG changes An ECG should be recorded during an episode of chest pain. A normal ECG during this period will be suggestive of a non-cardiac pain. However, shifts in the ST-segments or T-wave inversion are strongly supportive of unstable angina or non-Q-wave MI.

Troponin measurements A number of studies have demonstrated that troponin measurements have a major role to play in risk stratification and in identifying suitable candidates for GP IIb/IIIa antagonist therapy.¹⁻³ Troponin measurements are complementary to ECG records. However, a patient with a normal ECG but raised troponin levels is at a higher risk than a patient with normal troponin levels. Elevated levels give an indication for increased risk over both the short and long term.⁴ There is, however, a lag time of two to four hours after the onset of chest pain before troponin

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becomes detectable, and peak concentrations are seen at 12 to 24 hours. Therefore, the accuracy of the test will depend on a series of measurements.⁵ Measurement of troponin T or I (using an assay licensed for risk stratification) together with electrocardiography should be a routine part of the diagnostic approach.

GP IIb/IIIa receptor antagonists All the mediators that stimulate platelet activation share a final common pathway. Regardless of the pathway, the platelet-rich thrombus is ultimately formed by the activation of GP IIb/IIIa receptors. Platelet activation changes the conformation of GP to a form that is able to bind to fibrinogen. Inhibition of the GP IIb/IIIa receptors leads to inability of the platelets to bind with fibrinogen.

There are three parenteral GP IIb/IIIa receptor antagonists available and several in various stages of development. Properties of the three licensed GP IIb/IIIa receptor antagonists are listed in the Table.

Abciximab (Reo-Pro) is a chimeric monoclonal antibody to GP IIb/IIIa. It has a relatively long pharmacological half-life of eight to 16 hours. The receptor occupancy and the inhibition of platelet aggregation are dose-dependent. Abciximab exhibits a high affinity for the GP IIb/IIIa receptor.⁷ It cross-reacts with other receptors on the platelet, such as vitronectin. The clinical significance of this has not been identified yet.

Eptifibatid (Integrelin) is a synthetic peptide molecule with a high affinity and specificity for GP IIb/IIIa receptor.

Tirofiban (Aggrastat) is a non-peptide tyrosine derivative with a low binding affinity and high selectivity for GP IIb/IIIa

receptors. For both drugs, plasma concentration, receptor occupancy and platelet aggregation are proportional to the dose. Both have short half lives.^{8,9}

PUBLISHED TRIALS

A brief summary of the major clinical trials with the three GP IIb/IIIa receptor antagonists follows. It should be noted that the designs of the trials are not comparable.

EPIC This trial involved over 2,000 patients, not all of whom had ACS. They were undergoing percutaneous transluminal coronary angioplasty (PTCA) and were at high risk of acute ischaemic complications.¹⁰

All patients received aspirin and unfractionated heparin and were randomised to one of the three arms: abciximab 0.25mg per kg intravenous bolus plus a 10µg per minute infusion for 12 hours (bolus and infusion), or a bolus dose of abciximab and placebo infusion (bolus only), or a placebo bolus and placebo infusion (placebo). The primary endpoint of the trial (death, MI or urgent revascularisation) was significantly reduced (35 per cent) in group one compared with the placebo group. The benefit was significant at six months and three years. However, the benefit was accompanied by a higher risk of bleeding complications (intracranial haemorrhage and a decrease in haemoglobin and haematocrit). Fairly liberal use of unfractionated heparin was given as a possible explanation for the increased rate of major bleeding.

EPILOG The objectives of this trial were to determine whether the benefits of abcix-

imab seen in EPIC would extend to a low-risk population undergoing PCI and whether the use of a lower dose of unfractionated heparin in conjunction with abciximab would enhance the safety while preserving efficacy. EPILOG, originally scheduled to recruit 4,800 patients, was stopped after recruitment of 2,792 patients when an interim analysis showed a 6.4 per cent absolute difference in the 30-day endpoint of death, MI or need for urgent revascularisation (56 per cent relative risk reduction, $P < 0.001$) in the abciximab group compared with placebo.¹¹ Data after six months and one year showed that the results were durable.

CAPTURE This trial was going to recruit 1,400 patients with refractory unstable angina scheduled for PTCA. Data for 1,265 patients were presented showing a significantly lower occurrence of endpoint of death, MI, or urgent revascularisation. By 30 days, the primary endpoint had occurred in 11.3 per cent of patients who received abciximab compared with 15.9 per cent of patients on placebo. The rate of MI was lower in the abciximab compared with the placebo group before and during PTCA. However, at six months, rate of death and MI did not differ significantly between the two groups. Patients recruited for CAPTURE had more severe refractory unstable angina compared to EPIC. CAPTURE proved that treatment 24 hours before PTCA can reduce preprocedural or periprocedural events.¹²

EPISTENT This is the largest published study of GP IIb/IIIa antagonists in elective

Table: Properties of GP IIb/IIIa receptor antagonists

Property	Abciximab	Eptifibatid	Tirofiban
Specificity for GP receptor	No	Yes	Yes
Evidence for antigenicity	Yes	No	No
Restoration of platelet function to baseline (less than 50 per cent inhibition) within four hours of stopping infusion	No	Yes	Yes
Half life	8–16 hours	2 hours	2 hours
Management of bleeding complications	Platelet transfusion	Stop infusion and compression. Platelet transfusion if reduced platelets.	Stop infusion and compression. Platelet transfusion if reduced platelets.
Requirement for refrigeration	Yes	Yes	No
Cost per course (NICE report)	£840	£455	£440
NNT for PCI trials (NICE report)	17	69	41
NNT for troponin positive across trials (NICE report)	Not reported	Not reported	11
Absolute risk reduction figures in ACS trials ⁶ (NB: Trial designs were not comparable)	EPIC, 4.5 per cent, EPILOG, 6.5 per cent, CAPTURE, 4.6 per cent	IMPACT II, 2.2 per cent, PURSUIT (sub-group undergoing PTCA), 2.2 per cent	RESTORE, 1.9 per cent PRISM (sub-group undergoing PTCA), 5.7 per cent PRISM PLUS (subgroup undergoing PTCA), 6.5 per cent

or urgent PCI. It recruited 2,399 patients, not all of whom had ACS.¹³ Patients were randomly assigned to stenting plus placebo, or stenting plus abciximab or balloon PCI plus abciximab. The 30-day primary endpoint analysis showed a 51 per cent decrease in the risk of death, MI, or urgent revascularisation, which confirmed the efficacy of abciximab. By six months, the benefits of stenting had become apparent, as had the complementary nature of the two strategies (stenting plus abciximab). Additionally, in the diabetic group of patients where the rates of acute ischaemic endpoints were higher in either the stenting plus placebo or angioplasty plus abciximab groups, event rates were virtually the same in the diabetics and non-diabetics with the combination of stenting and abciximab. More recently, one-year follow-up results of the trial have shown a significant 60 per cent reduction in mortality by the combination of stenting and abciximab compared with either therapy alone. This reduction was over 70 per cent in the diabetic group who received abciximab plus stenting.

IMPACT II This was a randomised trial of over 4,000 patients in all risk strata undergoing PTCA. The groups were given eptifibatide 135µg per kg bolus plus 0.5µg per kg per min or 0.75µg per kg per min infusion or placebo for 20 to 24 hours. Major ischaemic complications and emergency revascularisation was lower in the active groups (6.8 per cent in group 1, 7 per cent in group 2, and 9.3 per cent in group 3 placebo).¹⁴ However, the 30 days and six months follow-up showed no difference between the groups. The dosage of eptifibatide was questioned as being suboptimal. The dosage was changed again for recruitment into the PURSUIT trial.

PURSUIT In the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial, 10,948 patients were assigned to receive eptifibatide 180µg per kg bolus plus either a 1.3µg per kg per minute or 2µg per kg per minute infusion or placebo for 72 to 96 hours. The low dose arm was dropped once the safety of the high dose was confirmed. At 30 days, the rate of death or MI was 14.2 per cent in the active group and 15.7 per cent in the placebo group. The effect was the same regardless of whether PTCA was performed or not.¹⁵ On the basis of this trial, eptifibatide was approved for management of unstable angina and non-Q-wave MI in patients treated medically or undergoing PTCA.

ESPRIT This was a placebo-controlled trial of eptifibatide in patients undergoing elective stent placement.²⁰ All patients received heparin (at 60 units per kg with a target activated clotting time of over 200 seconds), clopidogrel and aspirin. Patients were ran-

domised to either placebo or eptifibatide (two 180mg boluses 10 minutes apart followed by an infusion of 2µg per kg per min for 18 to 24 hours). The primary endpoint of the study was the composite endpoint of death, MI and urgent revascularisation. The results, after inclusion of over 2,000 patients, showed that treatment reduced the primary end-point from 10.5 per cent to 6.6 per cent ($P=0.0015$). The key 30-day secondary endpoint was also reduced from 10.5 per cent with placebo to 6.8 per cent with treatment ($P=0.0034$). Major bleeding was infrequent but occurred more often with eptifibatide than placebo. The benefits were observed at six months follow up.

ESPRIT included a broader group of patients including lower risk patients who would not normally qualify for GP IIb/IIIa antagonists. Additionally, the heparin dose administered in the placebo group was 60 units per kg. There has been some discussion as to whether the heparin dose of 60 units per kg was sufficient in the placebo group. If it was too low, this could have contributed towards the lower composite endpoint in the eptifibatide group. Normally, higher doses of heparin are administered before coronary stenting. However, ESPRIT has shown that even lower risk patients will benefit from IIb/IIIa receptor antagonists.

RESTORE This trial of tirofiban enrolled 2,139 high-risk patients undergoing PTCA within 72 hours of ACS. Patients received tirofiban 10µg per kg bolus plus 0.15 µg per kg per minute infusion for 12 hours, then 0.1µg per kg per minute for 24 hours or a placebo infusion. At 48 hours, the composite endpoints (death, MI, urgent coronary artery bypass graft and repeat PTCA) were reduced by 38 per cent in the tirofiban treated group. However, the 30-day results did not reach significance. The rate of major bleeding and thrombocytopenia did not differ in tirofiban and placebo groups.¹⁶

PRISM This trial included patients with unstable angina and non-Q-wave MI who had had chest pain during the previous 24 hours.

Patients received aspirin and either tirofiban (0.6µg per kg per min over 30 minutes plus 0.15µg per kg per minute infusion) or unfractionated heparin (5,000 units intravenous plus 1,000 units per hour) for 48 hours. During the infusion period, PTCA was not performed. Mortality, new MI or refractory angina was significantly lower in the tirofiban group compared with the heparin group (3.8 per cent versus 5.6 per cent) at 48 hours. The survival benefit due to tirofiban was maintained at 30 days, although the reduction in acute MI was no longer significant. At 30 days, the mortality rate was significantly lower with tirofiban than with heparin (2.3 per cent versus 3.6 per cent, $P=0.02$). The frequency of major bleeding

was 0.4 per cent in both groups. The PRISM study was the first to demonstrate that GP IIb/IIIa receptor antagonists can reduce mortality in patients already receiving aspirin.¹⁷ The trial suggested that the greatest benefit was obtained in high-risk patients, particularly in those with high troponin levels, where the average number needed to treat (NNT), to prevent one death or MI, might be as low as 11 at 30 days.¹⁷

PRISM-PLUS Patients with unstable angina and non-Q-wave MI were assigned to tirofiban plus unfractionated heparin or heparin alone in the same dosage as in the PRISM trial. This trial demonstrated that tirofiban, in combination with standard medical therapy, improves outcomes in patients with unstable angina and non-Q-wave MI, including those who require PTCA. There was a 32 per cent reduction ($P=0.004$) in the composite endpoint (death, MI, refractory ischaemia or readmission to hospital for unstable angina and non-Q-wave MI) at seven days in patients receiving tirofiban when compared with patients receiving placebo. The event rates for MI alone were significantly reduced for patients receiving tirofiban at seven days (relative risk reduction [RRR] 47 per cent, $P=0.006$) and 30 days (RRR 30 per cent, $P=0.05$). Benefits could be seen as early as 48 hours (before invasive procedures) and were maintained for up to six months.

Benefits of treatment were consistently observed across demographic sub-populations within PRISM-PLUS, including both younger and older patients, men and women, patients receiving or not receiving aspirin at entry, and patients receiving or not receiving heparin at entry.¹⁸

Overall the findings of PURSUIT, PRISM and PRISM-PLUS demonstrated the value of this class of drugs outside the coronary intervention setting.

ACUTE This trial recruited 55 non-Q-wave MI patients to receive either tirofiban combined with enoxaparin or tirofiban combined with intravenous unfractionated heparin. The results showed no major or minor bleeding problems in either group. The combination of tirofiban and enoxaparin (1mg per kg 12-hourly) was well tolerated. There was a more consistent inhibition of platelet aggregation and lower adjusted bleeding time with the tirofiban-enoxaparin combination versus tirofiban-unfractionated heparin.¹⁹

UNPUBLISHED TRIALS

The following trials have not been published but have been presented at international meetings.

TARGET This trial was the only trial comparing abciximab and tirofiban in 4,300

patients undergoing coronary intervention, primarily stenting. All patients were given clopidogrel and 70 units per kg of heparin plus either tirofiban 10µg per kg bolus over 10 minutes followed by an infusion of 0.15µg per kg per minute over 18 to 24 hours, or abciximab (licensed dose). This trial was carried out to show non-inferiority with a primary composite endpoint of death, MI and urgent revascularisation at 30 days. The study was presented at the American Heart Association meeting in November, 2000. It suggested that abciximab was superior to tirofiban in reducing the incidence of adverse cardiac ischaemic events during the first 30 days after intracoronary stent placement. There has been a suggestion that the dose of tirofiban used in the study had not been optimised. A double bolus dose initially may have given different results. This hypothesis remains to be tested. There were no differences in rates of major bleeding, but significant differences in minor bleeding and thrombocytopenia were observed favoring tirofiban. The study concluded that, for PCI patients in whom GP IIb/IIIa treatment is initiated in the catheter laboratories, abciximab remains the reference standard.

GUSTO IV The entry criteria for this trial was either a positive troponin level or ECG changes, with early revascularisation strongly discouraged. Unexpectedly, this trial of 7,800 patients did not show a benefit of abciximab therapy compared with placebo. This appears to be related to the lower risk population involved in the trial who were not taken for early revascularisation. Additionally, increased troponin levels without ECG changes or angiography data do not identify high-risk patients suitable for GP IIb/IIIa antagonist therapy. These results were presented at the European Society of Cardiology meeting in August, 2000. However, the results of GUSTO IV do not seem to change the evidence for using abciximab in ACS in conjunction with early revascularisation.

The evidence for using tirofiban or eptifibatide for the management of high-risk unstable angina and non-Q-wave MI with ST-segment depression and positive troponins remains unchanged.

TACTICS This trial recruited over 2,000 patients with unstable angina/non-ST elevation MI, randomised to receive either invasive therapy (routine early revascularisation) or conservative management (revascularisation if positive stress test). All patients were treated with aspirin, heparin and tirofiban. The study, presented at the American Heart Association meeting in November, 2000, showed that early invasive strategy resulted in a significant reduction in major cardiac events such as death, MI and readmission to hospital for ACS (19.4 per

cent in the conservative group, 15.9 per cent in the invasive group, $P=0.025$). Troponin measurements confirmed that troponin positive patients benefited significantly from early revascularisation. Invasive therapy was preferred in intermediate and high risk patients. In lower risk groups, both strategies seemed to be equal.

ESC RECOMMENDATIONS

A task force recommendation²¹ was commissioned by the ESC and was developed without any involvement from pharmaceutical companies. A summary of the recommendations for diagnosis of ACS, based on a consensus of expert opinions, is shown below.

In patients with suspected acute ischaemic heart disease:

- an ECG should be obtained at rest and multi-lead continuous ST-segment monitoring initiated (or frequent ECGs recorded where monitoring is unavailable)
- troponin T or I should be measured at admission and at six to 12 hours later
- myoglobin and/or myocardial creatine kinase (CK-MB) mass should be measured in patients with recent (less than six hours) symptoms as an early marker of myocardial infarction and in patients with recurrent ischaemia after recent (less than two weeks) infarction to detect further infarction

The recommendations for risk stratification is based on data derived from multiple randomised clinical trials or meta analyses.

1. Markers of acute thrombotic risk:

- recurrence of chest pain
- ST-segment depression
- dynamic ST-segment depression
- elevated level of cardiac troponins
- thrombus on angiography

2. Markers of underlying disease, that is, long-term risk:

- clinical markers (age, history of prior MI, history of severe angina, diabetes)
- biological markers (level of C-reactive protein)

3. Angiographic markers:

- LV dysfunction
- extent of coronary artery disease

Patients at high risk for progression to MI or death include the following groups:²¹

- those with recurrent ischaemia (either recurrent chest pain or dynamic ST-segment changes, in particular

ST-segment depression, or transient ST-segment elevation)

- those with elevated troponin levels
- those who develop haemodynamic instability within the observational period
- those with major arrhythmias (repetitive ventricular fibrillation)
- those with early post-infarction unstable angina

Coronary angiography (and angioplasty or stenting as appropriate) should be performed in this group of patients as soon as possible. GP IIb/IIIa antagonist plus heparin is recommended in the above high-risk group. Abciximab can be continued for 12 hours or tirofiban or eptifibatide for 24 hours after the angioplasty. If revascularisation is not judged to be feasible, then low molecular weight heparin is recommended as per FRISC II protocol.²¹

Patients at low risk for progression to MI or death include the following groups:²²

- those who have no recurrence of chest pain during the observational period
- those without elevated troponin levels or other biochemical markers of myocardial necrosis
- those without ST-segment depression or elevation but rather negative T-waves, flat T-waves or normal ECG

In the above group GP IIb/IIIa antagonists were not recommended by the task force. Low molecular weight heparins can be discontinued if no ECG changes are apparent and a second troponin measurement is negative.

NICE RECOMMENDATIONS

The NICE report was published in September, 2000,²³ and a summary of the guidelines in the report (which applied to patients with unstable angina or non-Q-wave MI, and those patients undergoing acute or elective PCI) are as follows:

- for high-risk patients with unstable angina or non-Q-wave MI, the intravenous use of GP IIb/IIIa antagonist (consistent with current UK licence) in addition to aspirin and low (adjusted) dose unfractionated heparin was recommended
- a raised blood level of troponin was recommended to be used to identify high-risk patients
- GP IIb/IIIa (consistent with current UK licence) was recommended in patients undergoing PCI

Unstable angina and non-Q-wave MI

The NICE report highlights the significant benefits of GP IIb/IIIa receptor antagonists

in terms of the reduction of the number of deaths and MIs with different studies, specifying that the average NNT for different GP IIb/IIIa receptor antagonists varied between 27 and 100. The report describes the PRISM trial with tirofiban, which suggested greatest benefit would be obtained in high-risk patients, particularly in those with high troponin levels, where the NNT (to prevent one death or MI) might be as low as 11 at 30 days.²³ These results highlight the cost-effectiveness of using agents such as tirofiban in the high-risk patient groups.

The report describes the UK-based economic studies suggesting a range of cost (per death or acute MI at 30 days) of intravenous GP IIb/IIIa receptor antagonists for all patients, of up to £30,000. For high-risk patients with raised troponin levels, the cost-effectiveness improves to £5,000 per outcome.²³

Adjunctive treatment in PCI The report included a pooling of published randomised trials highlighting the NNT values of 17 for abciximab, 41 for tirofiban, and 69 for eptifibatide, in order to decrease composite endpoints of death and MI at 30 days.

Abciximab trials have shown consistent long-term benefits. The report also described the consistency of benefit of abciximab in both stented patients and those without stent as observed in the EPISTENT trial. The subgroup containing diabetic patients gained particular benefit from the drug therapy.

The NICE report also described UK-based economic studies suggesting a range of cost from £7,000 to £11,500 per life year gained.

Implications for the NHS A third of 115,000 patients admitted with unstable angina were deemed to need an intravenous GP IIb/IIIa antagonist (tirofiban at £440 per case or eptifibatide at £455 per case). At an average cost of £450 per case, the cost to the NHS for treating high-risk patients was estimated to be £17m per annum.

Based on the cost of abciximab at £840 per case, the cost to the NHS for 20,000 PCIs will be about £17m per annum.

Licensed indications The report from the NICE puts an emphasis on the choice of GP IIb/IIIa receptor antagonists based on their licensed indication in the UK. It should therefore be noted that both eptifibatide and tirofiban are licensed for medical management and PCI where intervention is part of the patient's continuing programme of care, and abciximab is licensed for use in the cardiac catheterisation laboratories.

CONCLUSION

Significant evidence from large clinical trials on GP IIb/IIIa receptor antago-

nists, supported by recommendations from the ESC and the NICE have paved the way for using this class of intravenous drugs according to their licensed indication. However, their use is associated with the need for a significant increase in the drugs budget. Specialist cardiac pharmacists are now in an ideal position to work with the cardiologists and managers, to develop business plans and protocols for using these drugs, including participation in audit to ensure appropriate use and selection of these agents according to clinical evidence.

Evidence from the NICE will be an extremely useful tool for obtaining financial support towards practising evidence-based medicine and providing a better quality of life for our patients.

REFERENCES

- Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease (FRISC) study group. *J Am Coll Cardiol* 1997;29:43-8.
- Heescheen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White H. Troponin concentration for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. For the PRISM study investigators. *Lancet* 1999;354:1757-62.
- Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. *BMJ* 1996;313:262-4.
- Sayre MR, Kaufmann KH, Chen IW, Sperling M, Sidman RD, Dierks DB, et al. Measurement of cardiac troponin T is an effective method for predicting complications among emergency department patients with chest pain. *Ann Emerg Med* 1998;31:539-49.
- Selker HP, Zalenski RJ, Antman EM, Aufderhelde TP, Bernard SA, Bonow RO, et al. An evaluation of technologies for identifying acute cardiac ischaemia in the emergency department: a report from the National Heart Attack Alert Programme working group. *Ann Emerg Med* 1997;29:13-87.
- Redwood S, Marber M, Jackson G. Glycoprotein IIb/IIIa antagonists: do they have a role in the management of unstable angina? *Int J Clin Pharmacol* 1999;53:618-22.
- ABPI compendium of data sheets and summaries of product characteristics. Abciximab (Reo-Pro), Eli Lilly, 2000.
- ABPI compendium of data sheets and summaries of product characteristics. Eptifibatide (Integrelin), Schering Plough, 2000.
- ABPI compendium of data sheets and summaries of product characteristics. Tirofiban (Aggrastat), MSD, 2000.
- The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. *New Engl J Med* 1994;330:956-61.
- The EPILOG investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low dose heparin during percutaneous heparin revascularisation. *New Engl J Med* 1997;336:1689-96.
- 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.
- 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.
- The IMPACT-II investigators. Randomised placebo controlled trial of the effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997;349:1422-8.
- The PURSUIT investigators. Inhibition of glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndrome. *New Engl J Med* 1998;339:436-43.
- 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.
- The PRISM study investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *New Engl J Med* 1998;338:1498-505.
- The PRISM-PLUS study investigators. Inhibition of platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *New Engl J Med* 1998;338:1488-97.
- Cohen M, Theroux P, Weber S, Laramie P, Huynh T, Borzak S, et al. Combination therapy with tirofiban and enoxaparin in acute coronary syndromes. *Int J Cardiol* 1999;71:273-281.
- The ESPRIT investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356:2037-44.
- The FRISCII investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISCII prospective randomised multicentre study. Fragmin and fast revascularisation during instability in coronary artery disease. *Lancet* 1999;354:708-15.
- Recommendations of the task force of the European Society of Cardiology. Management of acute coronary syndrome: acute coronary syndrome without persistent ST segment elevation. *Eur Heart J* 2000;21:1406-32.
- National Institute for Clinical Excellence. Technology Appraisal Guidance number 12. Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. London: NICE; 2000.