EuroIntervention

Adjunctive Antiplatelet / Antithrombotic therapy in percutaneous coronary intervention

Jonas Eichhöfer, PhD, MRCP; Douglas Fraser, MRCP; Farzin Fath-Ordoubadi*, MD, FRCP

Manchester Heart Centre, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom

All authors declare no conflict of interest.

KEYWORDS

Antiplatelet therapy, antithrombotic therapy, clopidogrel, bivalirudin, glycoprotein IIb/IIIa inhibitors, percutaneous coronary intervention.

Abstract

Antiplatelet and antithrombotic treatment is successful in minimising acute and subacute stent thrombosis as well as reducing recurrent cardiac events and mortality in PCI. In this review we explore the evidence for different treatment strategies.

Aspirin and clopidogrel together with heparin at the time of the procedure are now well established. Glycoprotein (GP) IIb/IIIa blockers have been shown to reduce events in high risk patients. However, their routine use has been questioned in recent studies.

Clopidogrel 600 mg given at least 2 hours preprocedure negates the need for additional routine GP IIb/IIIa blockade in elective, even diabetic patients. Bivalirudin is equivalent to the routine use of GP IIb/IIIa blockade in both elective and ACS patients. Replacing routine GP IIb/IIIa blockade in these patients would be significantly cost saving, reduce bleeding complications and facilitate rapid discharge policies. However, these studies do not have the patient selection to advocate the wholesale replacement of GP IIb/IIIa blockade since high risk patients were excluded. Furthermore, with the advent of drug eluting stents, progressively more complex lesions are being treated that are underrepresented in these trials. Therefore, there still remains a rational for continuing to use GP IIb/IIIa blockade in high risk subsets of both elective and ACS patients. These subsets are yet to be defined. In the setting of primary PCI clear benefits have been shown for the use of adjunctive abciximab, with the greatest benefits seen for upfront treatment. Future studies will test combinations of GP IIb/IIIa blockade and thrombolytic treatment in these patients.

** Corresponding author: Manchester Heart Centre, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom*
E-mail: farzin.fath-ordoubadi@cmmc.nhs.uk

Early studies - Aspirin and clopidogrel

The efficacy of aspirin in percutaneous coronary intervention has mainly been shown in the pre-stent era[1,2]. With the introduction of stents early studies described acute and subacute thrombosis in up to 18% of procedures when aspirin was used alone[3]. Anticoagulation with warfarin in addition to aspirin was found to significantly reduce major adverse events in patients undergoing PCI with or without stent at the cost of increased bleeding rates and access site complications[4,5]. Subsequently, dual antiplatelet therapy with aspirin and post procedural ticlopidine was shown to be superior to aspirin and warfarin[6-10]. Clopidogrel has now replaced ticlopidine following studies demonstrating equivalent efficacy with fewer side-effects[11,12]. With the widespread adoption of stenting in all lesion subsets, aspirin and clopidogrel have remained the mainstay of adjunctive medical therapy in percutaneous coronary intervention.

Glycoprotein IIb/IIIa blockade

Periprocedural intravenous glycoprotein IIb/IIIa blockade has been investigated in several randomized studies. These studies have included patients with acute coronary syndromes (CAPTURE[13], RESTORE[14]); and both stable and acute patients (EPILOG[15], EPISTENT[16], IMPACT II[17], ESPRIT[18], EPIC[19]). The results have conclusively shown reductions in death and MI associated with these agents leading to their widespread use. However, subsequent analyses have suggested that the most pronounced effects are seen in the highest risk patients. Bhatt *et al.*[20] examined the effect of diabetes in the EPIC, EPILOG and EPISTENT trials and found a significant reduction in death in the 1,462 diabetics (4.5% to 2.5%, p=0.003) but a nonsignificant reduction in death in the 5,072 non-diabetics (2.6% to 1.9%, p=0.099). The mortality benefit of glycoprotein IIb/IIIa blockade in diabetic patients with multivessel disease was also especially marked (7.7% to 0.9%, p=0.018). Similarly Cura *et al.*[21] reported that abciximab reduced death or MI by 50% in patients with complex lesions in the EPISTENT and EPILOG trials (15% to 7.7%) with a lesser 36% reduction in simple lesions (9.7% to 6.1%). Thus relative as well as absolute benefits of these agents appear to be greater in higher risk subgroups.

A head to head comparison of abciximab with tirofiban in the TARGET[22] study in 4809 patients (62% with acute coronary syndromes) showed higher event rates (composite of death, MI, urgent TVR) in those treated with tirofiban compared to abciximab (7.6% versus 6.0%, p=0.038).

Glycoprotein IIb/IIIa blockade has also been tested as upfront treatment in patients with acute coronary syndromes (PRISM[23], PRISM-PLUS[24], PARAGON-A[25], PURSUIT[26], PARAGON-B[27], GUSTO-IV ACS[28]). A meta-analysis[29] of these trials that included 31,402 patients showed an overall 9% reduction in death/MI at 30 days from 11.8% to 10.8%, p=0.015. However the benefit was restricted to patients who underwent PCI. Death/MI in the 4,378 patients undergoing PCI within 5 days was significantly reduced from 14.5% to 11.8%, whereas death/MI in the 27,024 patients not undergoing PCI within 5 days was not significantly different at 11.4% in placebo and 10.7% in treated patients. The benefits in these studies also appeared to be restricted to patients with elevated troponin levels. Death/MI at 30 days in 4,964 patients with raised troponin fell significantly from 12.0% to 10.3%; whereas in 6,095 patients without raised troponin, death/MI rates were similar. It is also of note that upfront tirofiban and eptifibitide were found to be beneficial in the PRISM-PLUS and PURSUIT trials, whereas upfront abciximab was not found to be beneficial in the GUSTO IV ACS trial; However only a minority of patients in the GUSTO IV ACS study underwent PCI.

The conclusions from these studies are that periprocedural glycoprotein IIb/IIIa blockade significantly reduces event rates with the benefits concentrated in higher risk patients such as those with diabetes, complex lesions and patients with troponin positive acute coronary syndromes. Upfront glycoprotein IIb/IIIa blockade in ACS patients appears to be of little benefit if PCI is not performed. Periprocedural abciximab is superior to tirofiban, however upfront abciximab without intervention is ineffective. Glycoprotein IIb/IIIa blockade in these studies doubled major bleeding rates that predominantly occurred at the access site.

Recent studies evaluating preprocedural clopidogrel

The CURE[30] trial examined the use of clopidogrel in 12,562 patients with non-ST elevation acute coronary syndromes associated with cardiac enzyme elevation or ECG changes. In this study a conservative rather than invasive interventional strategy was adopted with 2,658 patients undergoing PCI. This subset was examined in the PCI-CURE[31] study that reported a reduction from 4.4% to 2.9% in 30 day death/MI rate (p=0.04). Concomitant glycoprotein IIb/IIIa blockade was used in only 21% of these patients and intervention was performed after a median of 6 days. This study therefore differed in terms of patient selection, timing of PCI and adjunctive treatment from current practice that endorses an invasive interventional strategy, routine use of glycoprotein IIb/IIIa blockade in troponin positive patients and early PCI performed within 72 hours of admission. However, it did suggest a clear benefit from preprocedural clopidogrel in acute coronary syndrome (ACS) patients.

The benefits of preprocedural clopidogrel were specifically analysed in the CREDO[32] trial that included 694 patients with stable angina and 1407 ACS patients. Clopidogrel 300mg at least 3 hours preprocedure led to a nonsignificant reduction of 28 day death, MI or urgent revascularization from 8.3% to 6.8%, p=0.23. Subsequent analysis showed that the 893 patients receiving preloading 3-6 hours preprocedure had no benefit from preloading whereas a strong trend towards benefit was found in the 851 patients who received clopidogrel 6-24 hours preprocedure (relative risk reduction 38.6%, p= 0.051). Subsequent investigations with higher doses of clopidogrel have shown that 600mg may achieve effective platelet inhibition more quickly than 300mg with maximal inhibition of aggregation reached within 2 hours[33].

These studies have led to the adoption of clopidogrel preloading with 300mg in elective patients at least 6 hours preprocedure or preloading with 600mg if PCI is performed within 6 hours. In ACS patients, clopidogrel is also commonly started on admission as in the CURE trial.

The need for adjunctive abciximab on top of clopidogrel preloading has subsequently been tested in elective patients in the ISAR

REACT[34] and ISAR SWEET[35] trials. The ISAR REACT trial examined the benefit of abciximab in 2,159 elective PCI patients pretreated at least 2 hours preprocedure with 600mg of clopidogrel. No benefit of abciximab was found with 30 day death, MI or urgent TVR in 4.2% of the abciximab and 4.1% of the untreated group. The case mix included 20% non-insulin dependent diabetics (insulin dependent diabetics were excluded), 75% had multivessel disease and 65% had type B2 or type C lesions. Transfusion requirements were greater in the abciximab group. The ISAR SWEET study examined the benefit of abciximab in 200 insulin dependent and 501 non-insulin dependent diabetics undergoing elective PCI and similarly detected no benefit in patients treated with abciximab. Death, MI or urgent TVR at 30 days was 5.7% in the abciximab patients and 4.3% in the placebo group with 1 year composite event rates of 29.9% and 32.0% respectively. Restenosis rates were reduced with the use of abciximab, however this effect was negated in patients treated with drug eluting stents. In this study 69% of patients had type B2 or type C lesions and 85% had multivessel disease.

These studies do not therefore support the role of routine glycoprotein IIb/IIIa blockade in patients undergoing elective PCI who have been preloaded with 600mg clopidogrel at least 2 hours preprocedure. This lack of benefit appears to be present even in patients with multivessel disease, complex lesions and diabetes. The replacement of glycoprotein IIb/IIIa blockade with clopidogrel preloading in these patients would have significant cost savings, reduce access site complications and facilitate early discharge and day case angioplasty[36]. However, it should be noted that in particular the ISAR SWEET trial is relatively underpowered. It had for instance only a 69% power to detect a 50% reduction in death and MI. These studies have also specifically excluded ACS patients. In addition, although the majority of patients had multivessel disease, it is unclear how many patients underwent multivessel stenting. Therefore, whilst these trials suggest that routine glycoprotein IIb/IIIa blockade has no additional benefit on top of clopidogrel preloading, significant benefits in higher risk subgroups can not be excluded.

Direct thrombin inhibition

The direct thrombin inhibitor bivalirudin blocks thrombin induced platelet activation in addition to its anticoagulant effect, by inhibiting both circulating and clot bound thrombin. Bivalirudin was compared to routine glycoprotein IIb/IIIa blockade (abciximab or eptifibatide) in 1,492 stable patients and 4,510 ACS patients in the REPLACE II[37] study. Diabetes was present in 27% of patients and multivessel intervention was attempted in 16%. Clopidogrel 300mg had been given at least 2 hours preprocedure. Death, MI or urgent TVR at 30 days was 7.6% in patients treated with bivalirudin and 7.1% in patients treated with glycoprotein IIb/IIIa blockade (p=0.41). This difference was due to a nonsignificant excess in myocardial infarction (Q wave and non Q wave MI) in the bivalirudin arm (p=043). Major bleeding was reduced from 4.1% to 2.4% in patients treated with bivalirudin (p<0.001). Post hoc analysis showed equivalence of eptifibatide and bivalirudin (death/MI/urgent revascularisation 7.0% and 7.1% respectively, p=0.40), and a trend towards benefit for patients treated with abciximab compared to bivalirudin (death/MI/urgent revascularisation 7.0% and 8.5% respectively).

This trial therefore showed equivalence of bivalirudin to the routine glycoprotein IIb/IIIa blockade in a cohort of predominantly ACS patients. The nonsignificant excess in non Q MI was balanced by a significant reduction in major bleeds. The one year mortality results presented at the AHA have subsequently shown that equivalence is maintained with a 1.9% mortality in the bivalirudin arm and a 2.5% mortality in the glycoprotein IIb/IIIa inhibitor arm (p=0.16). These results therefore show an alternative strategy to routine glycoprotein IIb/IIIa blockade in ACS patients. Bivalirudin is cheaper than either eptifibatide or abciximab and does not involve a postprocedural infusion. This would facilitate rapid discharge protocols including same-day transfer of ACS patients back to community hospital beds[38]. However, in view of the nonsignificant excess in myocardial infarction (p=0.43), the use of abciximab in a proportion of higher risk ACS patients may still be advocated.

Primary PCI

Primary PCI involves coronary intervention in the setting of significant thrombus load. Consequently the risks of distal embolisation, no reflow and stent thrombosis are higher than PCI in other settings. Five trials have examined the role of adjunctive abciximab (RAPPORT[39], ISAR-2[40], ADMIRAL[41], CADILLAC[42] and ACE[43]). A meta-analysis of these trials has shown a significant reduction in death/MI at 30 days from 4.8% to 3.2% with the use of abciximab[44]. This treatment benefit was sustained up to 6 months in ADMIRAL and ACE, but not CADILLAC. The weaker treatment effect in CADILLAC has been related to the lower event rate in this trial[44]. However, it is intriguing to note that this was the only trial in which ticlopidine or clopidogrel was given preprocedure.

The ADMIRAL trial suggested a benefit for upfront treatment with significantly improved preprocedural flow and more pronounced clinical benefits in patients in whom abciximab was started at the point of first medical contact. This finding has been supported by several additional trials that have compared early and late administration of IIb/IIIa blockade in patients undergoing primary PCI. A meta-analysis of six trials by Montalescot *et al.* has shown increased TIMI flow rates (p=0.01) and a meta-analysis of 11 trials by De Luca *et al.* showed a significant reduction in 30 day (p=0.047) and long-term mortality (p=0.01) with early treatment[45,46]. These trials have therefore established a clear role for adjunctive abciximab in patients undergoing primary PCI with greatest benefits seen with upfront use.

Future directions

The need for glycoprotein IIb/IIIa blockade in ACS patients preloaded with clopidogrel will be tested in the ISAR-REACT II study. Clopidogrel reloading in elective patients taking 75mg daily has been investigated by Kastrati *et al.* who found that platelet aggregation was reduced by an additional loading dose[47]. This suggests not only that an additional loading dose may be beneficial in elective patients but also that higher maintenance doses may be appropriate. Studies using new ADP receptor blockers are also underway. Prasugrel has a faster onset of action and has potentially more antiplatelet effects than clopidogrel. This agent has shown promise in the JUMBO-TIMI 26 trial. A head to head comparison of prasugrel and clopido-

grel is now been tested in 13,000 ACS patients in the TRITON-TIMI 38 trial. A reversible ADP receptor blocker called AZD6140 is also currently tested being tested in phase II studies. The role of glycoprotein IIb/IIIa blockade is being further investigated in the TITAN-TIMI 34 trial including patients with ACS randomised to either early eptifibatide given in the emergency department or eptifibatide given in the cardiac catheterization laboratory.

The upfront use of reduced dose thrombolytic combined with glycoprotein IIb/IIIa blockade in patients undergoing primary PCI (so-called facilitated PCI) is being tested in several large studies. ADVANCE-MI is comparing eptifibatide with tenecteplase plus eptifibatide. FINESSE is comparing no pre-treatment, abciximab and abciximab plus reteplase. TIGER is comparing full dose tenecteplase to eptifibatide plus half dose tenecteplase.

Conclusion

The ISAR REACT and ISAR SWEET studies have shown that 600mg of clopidogrel given at least 2 hours preprocedure negates the need for additional routine glycoprotein IIb/IIIa blockade in elective patients, even in the presence of diabetes. Similarly, the REPLACE II trial suggests that bivalirudin is equivalent to the routine use of glycoprotein IIb/IIIa blockade in both elective and ACS patients. Replacing routine glycoprotein IIb/IIIa blockade in these patients would be significantly cost saving, reduce bleeding complications and facilitate rapid discharge policies such as daycase elective angioplasty and daycase transfer of ACS patients to community hospital beds. However, these studies do not have the patient selection to advocate the wholesale replacement of glycoprotein IIb/IIIa blockade since high risk patients were not included. Furthermore, with the advent of drug eluting stents, progressively more complex lesions are being treated that are unlikely to have been well represented in these trials. Therefore, considering the substantial benefits of glycoprotein IIb/IIIa blockade previously shown in high risk patients, there remains a rational for continuing to use these agents in the higher risk subsets of both elective and ACS patients. These subsets are yet to be defined. In the setting of primary PCI clear benefits have been shown for the use of adjunctive abciximab, with the greatest benefits seen for upfront treatment. Future studies will test combinations of glycoprotein IIb/IIIa blockade and thrombolytic treatment in these patients.

References

1. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, Henderson M, Bonan R, David PR. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988;318(26):1714-9.

2. Lembo NJ, Black AJ, Roubin GS, Wilentz JR, Mufson LH, Douglas JS, Jr., King SB, 3rd. Effect of pretreatment with aspirin versus aspirin plus dipyridamole on frequency and type of acute complications of percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1990;65(7):422-6.

3. Tan K, Sulke N, Taub N, Sowton E. Clinical and lesion morphologic determinants of coronary angioplasty success and complications: current experience. *J Am Coll Cardiol* 1995;25(4):855-65.

4. Ten Berg JM, Kelder JC, Suttorp MJ, Mast EG, Bal E, Ernst SM, Verheugt FW, Plokker HW. Effect of coumarins started before coronary angioplasty on acute complications and long-term follow-up: a randomized trial. *Circulation* 2000;102(4):386-91.

5. Ten Berg JM, Hutten BA, Kelder JC, Verheugt FW, Plokker HW. Oral anticoagulant therapy during and after coronary angioplasty the intensity and duration of anticoagulation are essential to reduce thrombotic complications. *Circulation* 2001;103(16):2042-7.

6. Kastrati A, Schuhlen H, Hausleiter J, Walter H, Zitzmann-Roth E, Hadamitzky M, Elezi S, Ulm K, Dirschinger J, Neumann FJ and others. Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) Trial. *Circulation* 1997;96(2):462-7.

7. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO and others. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998;339(23):1665-71.

8. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M and others. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. *Circulation* 1998;98(16):1597-603.

9. Urban P, Macaya C, Rupprecht HJ, Kiemeneij F, Emanuelsson H, Fontanelli A, Pieper M, Wesseling T, Sagnard L. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). *Circulation* 1998;98(20):2126-32.

10. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E and others. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;334(17):1084-9.

11. Berger PB, Bell MR, Rihal CS, Ting H, Barsness G, Garratt K, Bellot V, Mathew V, Melby S, Hammes L and others. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999;34(7):1891-4.

12. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;101(6):590-3.

13. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;349(9063):1429-35.

14. 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. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;96(5):1445-53.

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

16. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;352(9122):87-92.

17. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;349(9063):1422-8.

18. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000;356(9247):2037-44.

19. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994;330(14):956-61.

20. Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000;35(4):922-8.

21. Cura FA, Bhatt DL, Lincoff AM, Kapadia SR, L'Allier PL, Ziada KM, Wolski KE, Moliterno DJ, Brener SJ, Ellis SG and others. Pronounced benefit of coronary stenting and adjunctive platelet glycoprotein IIb/IIIa inhibition in complex atherosclerotic lesions. *Circulation* 2000;102(1):28-34.

22. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW and others. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344(25):1888-94.

23. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;338(21): 1498-505.

24. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;338(21):1488-97.

25. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998;97(24):2386-95.

26. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;339(7):436-43.

27. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation* 2002;105(3):316-21.

28. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001;357(9272):1915-24.

29. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG and others. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359(9302):189-98.

30. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345(7): 494-502.

31. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S and others. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358(9281):527-33.

32. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *Jama* 2002;288(19):2411-20.

33. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, Bestehorn HP, Buttner HJ, Neumann FJ. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005;111(20):2560-4.

34. Kastrati A, Mehilli J, Schuhlen H, Dirschinger J, Dotzer F, ten Berg JM, Neumann FJ, Bollwein H, Volmer C, Gawaz M and others. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004;350(3):232-8.

35. Mehilli J, Kastrati A, Schuhlen H, Dibra A, Dotzer F, von Beckerath N, Bollwein H, Pache J, Dirschinger J, Berger PP and others. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004;110(24):3627-35.

36. Banning AP, Ormerod OJ, Channon K, McKenna CJ, Orr W, Boulton B, Bashir Y, Forfar JC. Same day discharge following elective percutaneous coronary intervention in patients with stable angina. *Heart* 2003;89(6):665.

37. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R and others. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *Jama* 2003;289(7):853-63.

38. Blackman DJ, Clarke NR, Orr WP, Wilkinson E, Beswick A, Coppock D, Sprigings DC, Banning AP. Day-case transfer for percutaneous coronary intervention with adjunctive abciximab in acute coronary syndromes. *Heart* 2002;87(4):375-6.

39. Brener SJ, Barr LA, Burchenal JE, Katz S, George BS, Jones AA, Cohen ED, Gainey PC, White HJ, Cheek HB and others. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation* 1998;98(8):734-41.

40. Neumann FJ, Kastrati A, Schmitt C, Blasini R, Hadamitzky M, Mehilli J, Gawaz M, Schleef M, Seyfarth M, Dirschinger J and others. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 2000;35(4):915-21.

41. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansieri M and others. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344(25):1895-903.

42. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Carroll JD and others. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346(13):957-66.

43. Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, Parodi G, Fernandez-Pereira C, Moschi G, Bartorelli A and others. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;42(11):1879-85.

44. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol* 2003;42(11):1886-9.

45. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *Jama* 2004;292(3):362-6.

46. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, Van de Werf F, Antman EM, Topol EJ. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Jama* 2005;293(14):1759-65.

47. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schomig A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation* 2004;110(14):1916-9.