

## **Differential effect of aspirin on platelet aggregation in patients with coronary artery disease in relation with associated risk factors.**

**Ersoz G, Tikiz H, Yakaryilmaz A, Tezcan K, Genc Y, Korkmaz S.**

**P**latelets play a key role in the pathogenesis of atherosclerosis and acute coronary syndromes and antiplatelet therapy offers a clinical benefit. Although aspirin is the most widely used agent, there are several conditions in which aspirin may fail to provide a full antithrombotic benefit. Furthermore, data concerning the relationship between platelet function, aspirin, and the associated risk factors are limited. In the present study. ADP and collagen-induced platelet aggregation of 200 consecutive patients with suspected coronary artery disease (CAD) who underwent coronary angiography were evaluated. The patients were classified into three groups according to the number of stenotic vessels. One hundred and eight patients were using 300 mg/day of aspirin. The associated cardiovascular risk factors were also considered. The collagen-induced platelet aggregation of smokers was significantly higher than non-smokers ( $P < 0.05$ ). Although platelet aggregation was higher in diabetic and hypertensive patients, the difference was not statistically significant. No significant correlation was found between platelet aggregation and other risk factors. The collagen-induced platelet aggregation of the subjects with non-stenotic vessels was reduced by aspirin ( $P < 0.05$ ). Aspirin did not sufficiently inhibit ADP and collagen-induced aggregation in patients with CAD. This finding supports the idea that the nonplatelet-mediated effects of aspirin could be more important than its antiplatelet effect in clinical use and the use of new potent antiplatelet drugs may complete its antiplatelet effect.

**"Routine invasive" versus "selective invasive" approaches to non-ST-segment elevation acute coronary syndromes management in the post-stent/platelet inhibition era.**

**Boden WE.**

Is a "routine invasive" or "selective invasive" strategy the best approach for patients with non-ST-segment elevation acute coronary syndrome (ACS)? A "selective invasive" strategy incorporates ischemia-guided use of aggressive medical therapy followed by angiography and revascularization for angina or stress-induced myocardial ischemia. The "routine invasive" strategy (cardiac catheterization followed by percutaneous coronary intervention within 24 to 48 h of symptom-onset) is frequently employed, but no randomized, controlled trials have demonstrated improved clinical outcomes. Recently, the second Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC-II) and the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS TIMI-18) trials found significant reductions in death, recurrent myocardial infarction, or hospitalization for biomarker-positive ACS. Also, the third Randomized Intervention Trial of unstable Angina (RITA-3) recently reported a halving of refractory angina and reduction in the use of antianginal medication with early intervention. Early trials failed to demonstrate the superiority of the "routine invasive" approach, presumably because of fewer revascularizations, unavailability of stents, and more recent use of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparins. The FRISC-II, TACTICS TIMI-18, and RITA-3 studies indicate that higher-risk patients benefit from early revascularization, but that aggressive antiplatelet, antithrombin, and anti-ischemic therapy are also important. While all three trials support an "early invasive" approach in intermediate- and high-risk patients, other trials support a more "conservative" approach in those without electrocardiographic changes or enzyme elevations. Optimal management should incorporate both strategies.

## **Oral anticoagulants in patients with coronary artery disease.**

**Anand SS, Yusuf S.**

Oral anticoagulants have been used in patients with vascular disease for over 40 years, yet their role in the secondary prevention of recurrent cardiovascular (CV) events remains controversial. The objectives of this systematic review are to more reliably determine the role of oral anticoagulants with and without antiplatelet therapy in patients with established coronary artery disease (CAD). Randomized trials in which oral anticoagulants were tested in CAD patients who were treated for at least three months were identified, and each trial was classified by the targeted level of intensity of anticoagulation. Data from the trials were combined using the modified Mantel-Haenszel method, and odds ratios were computed. Data from over 20,000 patients indicated that high-intensity oral anticoagulation (international normalized ratio [INR] >2.8) significantly reduced CV complications and increased bleeding compared with controls. Moderate-intensity oral anticoagulation (INR 2 to 3) also reduced CV complications compared with controls. The combination of moderate-intensity oral anticoagulation and aspirin is more effective and equally as safe as aspirin alone. Low-intensity oral anticoagulation (INR <2) in the presence of aspirin does not reduce CV complications and increases bleeding compared with aspirin alone.

## **The role of platelet receptors and adhesion molecules in coronary artery disease.**

**Samara WM, Gurbel PA.**

**P**latelets play a significant role in coronary artery disease through interactions with each other and with other cell types. These interactions are mediated by certain receptors on the surface of platelets and other cells which can lead to intra-coronary thrombus formation and occlusion that may result in acute coronary syndromes. The important roles of the currently available anti-platelet therapies have been well established in many clinical outcome trials in cardiovascular patients. An understanding of these different interactions provides the clinician with a background that supports the clinical importance of currently available anti-platelet therapies. Moreover, knowledge of the mechanisms of cellular crosstalk will lead to important advances in the development of better antithrombotic therapies.

## **Clopidogrel but not aspirin reduces P-selectin expression and formation of platelet-leukocyte aggregates in patients with atherosclerotic vascular disease.**

**Klinkhardt U, Bauersachs R, Adams J, Graff J, Lindhoff-Last E, Harder S.**

**F**ormation of platelet-leukocyte aggregates via the CD62 ligand represents an important mechanism by which leukocytes contribute to thrombotic events. In a cross-sectional study, we investigated platelet-leukocyte aggregate formation and markers indicative for platelet, leukocyte, and endothelial activation (CD62, activated fibrinogen receptor glycoprotein IIb/IIIa [PAC-1], CD11b/CD18 [MAC-1], and soluble intercellular adhesion molecule 1) in 44 patients with atherosclerotic vascular disease and peripheral occlusions receiving clopidogrel (n = 12), aspirin (n = 17), their combination (n = 8), or no treatment (n = 7), as well as in a group of healthy subjects (n = 9). Whole-blood flow cytometry was performed before (baseline) and after stimulation with thrombin receptor-activating peptide or adenosine diphosphate. Both at baseline and after stimulation, untreated patients and those receiving aspirin monotherapy exhibited significantly higher levels of platelet CD62 expression (baseline CD62: untreated, 22% [median]; with aspirin, 16%) and had higher rates of platelet-leukocyte aggregate formation (monocyte-platelet-leukocyte aggregates at baseline: untreated, 27%; with aspirin, 16%) when compared with patients receiving clopidogrel alone (baseline CD62: 10% [P <.05]; monocyte-platelet-leukocyte aggregates: 13% [P <.05]) or combined with aspirin (baseline CD62: 5% [P <.05]; monocyte-platelet-leukocyte aggregates: 7% [P <.05]). Up-regulation of MAC-1 on monocytes after stimulation with thrombin receptor-activating peptide and adenosine diphosphate was significantly lower in patients treated with clopidogrel and aspirin. Plasma levels of soluble intercellular adhesion molecule 1 were significantly lower in the group of healthy subjects (median, 186 ng/mL) when compared with those in untreated patients (median, 352 ng/mL) (P <.05), whereas intercellular adhesion molecule 1 levels in treated patients were similar for any antiplatelet regimen (aspirin, 262 ng/mL; clopidogrel, 274 ng/mL; combination therapy, 273 ng/mL) but significantly lower than those in untreated patients. This is the first report showing that platelet-leukocyte aggregate formation is enhanced in atherosclerotic vascular disease but was found to be reduced in patients receiving clopidogrel.

**Cost effectiveness of extended treatment with low molecular weight heparin (dalteparin) in unstable coronary artery disease: results from the FRISC II trial.**

**Janzon M, Levin LA, Swahn E; Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease II Investigators.**

**B**ACKGROUND: In unstable coronary artery disease short term treatment with low molecular weight heparin in addition to aspirin has been shown to be effective. OBJECTIVE: To assess the cost effectiveness of extended treatment with dalteparin in patients managed with a non-invasive treatment strategy. DESIGN: Prospective, randomised, multicentre study. SETTING: 58 centres in Sweden, Denmark, and Norway, of which 16 were interventional. PATIENTS: After at least five days' treatment with open label dalteparin, 2267 patients were randomised to continue double blind treatment with either subcutaneous dalteparin twice daily or placebo for three months. The patients' use of health service resources was recorded prospectively. MAIN OUTCOME MEASURE: Death/myocardial infarction. RESULTS: After one month into the double blind period there was a 47% relative reduction in death or myocardial infarction in the dalteparin group compared with the placebo group ( $p = 0.002$ ). There was a non-significant mean cost difference, favouring the placebo group, of 849 Swedish crowns (SEK) per patient (equivalent to 58 pounds sterling). The incremental cost effectiveness ratio for giving dalteparin treatment for one month was SEK 30 300 (range -78 000 to 139 000) (2060 pounds sterling, range -5300 pounds sterling to pound 9400 pounds sterling) per avoided death or myocardial infarct. At three months, the decrease in death or myocardial infarction was not significant, precluding cost effectiveness analyses. CONCLUSIONS: There is a marginal and non-significant increase in costs for one month of extended dalteparin treatment compared with placebo. Extended dalteparin treatment lowers the risk of death or myocardial infarction in patients with unstable coronary artery disease. While in many countries the resources for early intervention are limited, extended dalteparin treatment up to one month is a cost effective bridge to invasive intervention.

## **Effect of a single dose aspirin on platelets in humans with multiple risk factors for coronary artery disease.**

**Malinin AI, Atar D, Callahan KP, McKenzie ME, Serebruany VL.**

**W**e sought to assess how one tablet of non-enteric coated aspirin (325 mg) affects human platelets in subjects with risk factors for coronary artery disease. Data from 63 individuals with multiple cardiac risk factors were analyzed. Platelets were assessed twice at baseline (pre-aspirin), and after 3-4 h (post-aspirin). We employed 5 microM epinephrine-induced conventional aggregometry, closure time with epinephrine/collagen cartridge by PFA-100(R) (Dade-Behring), and aspirin response units (ARU) stimulated by propyl gallat with Ultegra (Accumetrics, San Diego, CA, USA) for measuring platelet function. In addition, the expression of platelet receptors was determined by using the following monoclonal antibodies: anti-CD31, CD41, CD42b, CD51/CD61, CD62p, CD63, CD107a, and CD151. Platelet-leukocyte formation was detected utilizing dual antibodies for a pan-platelet marker CD151, and CD14, a monocyte/macrophage marker. PAC-1 was used to measure fibrinogen-platelet binding. One pill of aspirin significantly decreased platelet-rich plasma (PRP) aggregation (74.18+/-16.75% vs. 24.92+/-8.64%;  $p<0.0001$ ) and resulted in reduction of the aspirin response units (ARU) (662.24+/-65.65 vs. 451.05+/-69.31;  $p<0.0001$ ). There was also prolongation of the closure time (194.4+/-25.3 vs. 258.63+/-55.61 s;  $p<0.0001$ ). High correlation ( $r(2)=0.73-0.86$ ) between platelet analyzer readings and aggregation was observed. One tablet of aspirin moderately inhibited expression of most surface platelet receptors measured, and such inhibition reached significance ( $p<0.05$ ) for PAC-1, CD31, CD41, CD42, CD62p, and CD151. We conclude that a single dose of aspirin affects major platelet receptors, presumably directly or indirectly through the inhibition of prostanoids via platelet cyclooxygenase-1 blockade. The Ultegra Analyzer with a novel cartridge seems to be reliable in reflecting aspirins' effects on platelets and could be used in the future in clinical practice for monitoring aspirin therapy.

**Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial.**

Tolleson TR, O'Shea JC, Bittl JA, Hillegass WB, Williams KA, Levine G, Harrington RA, Tchong JE.

**OBJECTIVES:** We evaluated the relationship between the degree of heparin anticoagulation and clinical efficacy and bleeding in patients undergoing contemporary percutaneous coronary intervention (PCI) with stent implantation. **BACKGROUND:** Despite universal acceptance of heparin anticoagulation as a standard of care in PCI, considerable controversy still exists regarding the appropriate dosing of heparin. **METHODS:** The study population (n = 2,064) comprised all patients enrolled in the Enhanced Suppression of the Platelet Iib/IIIa Receptor with Integrilin Therapy (ESPRIT) trial. The index activated clotting time (ACT) was defined as the ACT measured after the last heparin dose and before first device activation and was correlated with outcome and bleeding events. **RESULTS:** No association was observed between decreasing ACT levels and the rate of ischemic events in the treatment or placebo arms. The incidence of the primary composite end point (death, myocardial infarction, urgent target vessel revascularization, and thrombotic bailout glycoprotein Iib/IIIa inhibitor therapy at 48 h) was actually lowest in the lowest ACT tertile for both the placebo (10.0%) and treatment groups (6.1%). When analyzed by tertile, major bleeding rates did not increase in the lowest ACT tertile in patients given placebo (0.6%) versus those receiving eptifibatide (0.7%). Major bleeding rates increased as the ACT increased in the eptifibatide-treated patients. **CONCLUSIONS:** Ischemic end points in patients undergoing contemporary PCI with stent placement do not increase by decreasing ACT levels, at least to a level of 200 s. Bleeding events do increase with increasing ACT levels and are enhanced with eptifibatide treatment. An ACT of 200 to 250 s is reasonable in terms of efficacy and safety with the use of contemporary technology and pharmacotherapy.

## **Secondary and primary prevention of coronary heart disease: platelet aggregation inhibitors and anticoagulants]**

**Kubler W.**

**T**his review presents the results of primary and secondary prevention of coronary heart disease (CHD) with antiplatelet drugs and anticoagulants; therapeutic recommendations are derived. According to the results of the trials and due to its low price aspirin (ASS) can be still considered as the drug of choice. Its protective action has been documented for secondary prevention in patients with previous myocardial infarction, coronary angioplasty (PCI), unstable and stable angina, but not in patients with coronary artery bypass surgery, heart failure as well as in primary prevention. The doses recommended are 75-325 mg/d. If ASS is not tolerated clopidogrel is an alternative, but an expensive one. Anticoagulation for primary prevention of CHD may be considered in high risk patients, who do not tolerate ASS (alternative: clopidogrel). In secondary prevention anticoagulation is only recommended for special conditions, such as ASS intolerance (alternative: clopidogrel), ventricular aneurysm, ventricular thrombus, severe heart failure and/or atrial fibrillation.

## **Platelet aggregation in different antithrombotic regimens. Possible proaggregant effect of low level oral anticoagulation.**

**Perez Gomez F, Lourenzo PI, Companion J, Escriba A, Perez Saldana D, Guillen M, Vargas E, S-Harguindey L.**

Few trials have studied platelet activity during oral anticoagulation and all show a tendency for platelet aggregation to increase. This adverse effect has also been shown in some patients treated with unfractionated heparin, the so-called white clot syndrome. We studied platelet aggregation in patients with atrial fibrillation enrolled in the NASPEAF study and receiving antiaggregant, anticoagulant and both treatments. **METHODS:** 15 healthy control subjects (group C) and 99 patients were enrolled, the latter receiving 4 different antithrombotic regimens for platelet aggregation: group 1, 600 mg of the antiplatelet drug triflusal; group 2, anticoagulation for an INR of 2-3; and both treatments with 2 different levels of anticoagulation, mean INR of 1.85 (group 3) and of 2.15 (group 4). The same amounts of the agonists ADP, arachidonic acid and collagen were used in all tests. For statistical analysis we used the interval in min, from the addition of the agonist to the beginning of aggregation and the % of aggregation at 5 and 8 min. **RESULTS:** After arachidonic acid was given, the interval to the beginning of aggregation was shorter in group 2 than in group C:  $0.6 \pm 0.21$  and  $1.1 \pm 1.2$ , and in both was significantly shorter than in the other three receiving antiplatelet drugs alone: group 1 =  $1.58 \pm 1.4$  or combined with anticoagulants: group 3 =  $1.7 \pm 1.7$  and group 4 =  $2.4 \pm 2.1$ . The % of aggregation at 5 min, in groups C, 2, 1, 3 and 4 was respectively  $48 \pm 24$ ,  $43.2 \pm 19$ ,  $29.6 \pm 17$ ,  $34.8 \pm 22$  and  $23.2 \pm 22.5$ . The data showed significantly increased platelet activity in groups C and 2 compared to groups 1, 3 and 4. Group 3 with a low anticoagulation level (mean INR = 1.85) showed a tendency to greater platelet activity than group 1 and 4 with p value = 0.08. **CONCLUSIONS:** The antiplatelet drug triflusal alone or combined with a therapeutic level of anticoagulation effectively reduces platelet aggregation and is not influenced by anticoagulant treatment. A low level of anticoagulation (INR < 2) shows a tendency to increase platelet activity.

## **Current agents for the treatment of patients with heparin-induced thrombocytopenia.**

### **Warkentin TE.**

Several counterintuitive treatment paradoxes complicate the management of immune heparin-induced thrombocytopenia (HIT). For example, simple discontinuation of heparin often fails to prevent subsequent HIT-associated thrombosis. Thus, current treatment guidelines recommend substituting heparin with a rapidly acting alternative anticoagulant (eg, danaparoid, lepirudin, or argatroban) even when HIT is suspected on the basis of thrombocytopenia alone ("isolated HIT"). Another paradox—coumarin (warfarin) anticoagulation—can lead to venous limb gangrene in a patient with HIT-associated deep-vein thrombosis. Thus, warfarin is not recommended during acute thrombocytopenia secondary to HIT. However, warfarin can be given as overlapping therapy with an alternative anticoagulant, provided that (1) initiation of warfarin is delayed until substantial platelet count recovery has occurred (to at least above  $100 \times 10^9/L$ ); (2) low initial doses of warfarin are used; (3) at least 5 days of overlapping therapy are given; and (4) the alternative agent is maintained until the platelet count has normalized. It has recently been recognized that HIT antibodies are transient and usually do not recur upon subsequent re-exposure to heparin. This leads to a further paradox—patients with previous HIT can be considered for a brief re-exposure to heparin under exceptional circumstances; for example, heart surgery requiring cardiopulmonary bypass, if HIT antibodies are no longer detectable using sensitive assays. For patients with acute or recent HIT who require urgent heart surgery, other approaches include use of alternative anticoagulants (eg, lepirudin or danaparoid) for cardiopulmonary bypass or antiplatelet agents (eg, tirofiban or eptoprostenol) to permit intraoperative use of heparin.

**Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial.**

van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group.

**B**ACKGROUND: Antiplatelet treatment with aspirin and oral anticoagulants reduces recurrence of ischaemic events after myocardial infarction. We aimed to investigate which of these drugs is more effective in the long term after acute coronary events, and whether the combination of aspirin and oral anticoagulants offers greater benefit than either of these agents alone, without excessive risk of bleeding. **METHODS:** In a randomised open-label trial in 53 sites, we randomly assigned 999 patients to low-dose aspirin, high-intensity oral anticoagulation, or combined low-dose aspirin and moderate intensity oral anticoagulation. Patients were followed up for a maximum of 26 months. The primary composite endpoint was first occurrence of myocardial infarction, stroke, or death. **FINDINGS:** The primary endpoint was reached in 31 (9%) of 336 patients on aspirin, in 17 (5%) of 325 on anticoagulants (hazard ratio 0.55 [95% CI 0.30-1.00],  $p=0.0479$ ), and in 16 (5%) of 332 on combination therapy (0.50 [0.27-0.92],  $p=0.03$ ). Major bleeding was recorded in three (1%) patients on aspirin, three (1%) on anticoagulants (1.03 [0.21-5.08],  $p=1.0$ ), and seven (2%) on combination therapy (2.35 [0.61-9.10],  $p=0.2$ ). Frequency of minor bleeding was 5%, 8% (1.68 [0.92-3.07],  $p=0.20$ ), and 15% (3.13 [1.82-5.37],  $p<0.0001$ ), in the three groups, respectively. 164 patients permanently discontinued the study drug. Analyses were done by intention to treat. **INTERPRETATION:** In patients recently admitted with acute coronary events, treatment with high-intensity oral anticoagulants or aspirin with medium-intensity oral anticoagulants was more effective than aspirin on its own in reduction of subsequent cardiovascular events and death.

## Vascular closure devices in patients treated with anticoagulation and I Ib/IIIa receptor inhibitors during percutaneous revascularization.

Applegate RJ, Grabarczyk MA, Little WC, Craven T, Walkup M, Kahl FR, Braden GA, Rankin KM, Kutcher MA.

**OBJECTIVES:** The study assessed clinical outcomes of closure device use following percutaneous coronary revascularization using current standards of anticoagulation and antiplatelet therapy. **BACKGROUND:** Evaluation of the outcomes of patients by use of vascular closure devices during coronary interventions employing current standards of anticoagulation and glycoprotein (GP) I Ib/IIIa inhibitor therapy is limited. **METHODS:** We evaluated outcomes of 4,525 consecutive patients who underwent percutaneous coronary intervention between July 1997 and April 2000. All patients received anticoagulation with heparin and GP I Ib/IIIa inhibitor therapy with abciximab. The closure method was manual in 1,824 patients, Angioseal in 524 patients and Perclose in 2,177 patients. Procedural and hospital vascular outcomes were evaluated. **RESULTS:** Closure device success was 97.1% Angioseal and 94.1% Perclose ( $p < 0.05$ ). Minor vascular complications occurred in 1.8% of manual patients, 1.1% of Angioseal patients and 1.2% of Perclose patients ( $p = \text{NS}$ ); major complications occurred in 1.3% of manual patients, 1.1% of Angioseal patients and 1.0% of Perclose patients ( $p = \text{NS}$ ). Multivariate logistic regression identified only closure device failure as an independent predictor of a vascular complication. In patients with successful closure with a device, minor complications (0.8% vs. 1.8%,  $p < 0.05$ ) and any complication (1.5% vs. 2.5%,  $p < 0.05$ ) were reduced compared to manual compression. **CONCLUSIONS:** Arterial closure following coronary interventions using anticoagulation and GP I Ib/IIIa inhibitor therapy can be safely and effectively performed, with vascular complication rates similar to or lower than with manual pressure. Additionally, vascular complication rates using GP I Ib/IIIa inhibitor therapy regardless of the method of arterial closure are equivalent to or lower than previously published rates of vascular complications.

## **Pharmacodynamic and clinical trials of glycoprotein IIb/IIIa inhibitors and potential relationship of results to dosing.**

**Hobbach HP, Schuster P.**

**G**lycoprotein IIb/IIIa inhibitors have become the standard of care for patients undergoing percutaneous coronary intervention (PCI) and for those presenting with non-ST-segment elevation myocardial infarction (NSTEMI-ACS). Clinical effects of GP IIb/IIIa inhibitors in PCI and NSTEMI-ACS strongly correlate with potency, consistency, and durability of platelet aggregation inhibition. Under standardized conditions [light transmission aggregometry (LTA), 20 μmol adenosine diphosphate (ADP) as an agonist, and D-phenylalanyl-L-propyl-L-arginine chloromethyl ketone (PPACK) as an anticoagulant], we demand consistent platelet aggregation inhibition >80% during the time of PCI (initial balloon inflation), and during the entire duration of therapy in NSTEMI-ACS. The benefit of abciximab (bolus 0.25 mg/kg plus infusion 10 μg/kg/min) correlates with >80% inhibition of platelet aggregation during the intervention (PCI) and immediately thereafter (<6 hours). The absence of a benefit with abciximab in NSTEMI-ACS is most likely due to <80% inhibition during the major part of the infusion period (>6 hours). Tirofiban does not achieve >80% inhibition at the time of PCI at a dose of 10 μg/kg bolus plus 0.15 μg/kg/min infusion, and at a dose of 0.4 μg/kg/min loading infusion for 30 minutes plus 0.1 μg/kg/min maintenance infusion, the target value is only reached after 18 h. Eptifibatid (double-bolus 180 μg/kg 10 min apart, followed immediately by a 2.0 μg/kg/min infusion) provided an instant, consistent, and durable antiplatelet effect for the entire duration of infusion, and a significant clinical benefit in both PCI (non-ACS patients) and medically managed NSTEMI-ACS patients.

*Catheter Cardiovasc Interv* 2003 Apr;58(4):481-4

## Acute stent thrombosis after early withdrawal of platelet glycoprotein IIb/IIIa antagonists: Potential rebound prothrombotic effect?

Angiolillo DJ, Sabate M, Fernandez-Ortiz A, Macaya C.

We report on two cases of acute coronary stent thrombosis after early withdrawal of different competitive inhibitors of the platelet glycoprotein IIb/IIIa receptor, eptifibatide and tirofiban. Differences in pharmacokinetics between different types of glycoprotein IIb/IIIa receptor blockers and a potential rebound prothrombotic effect with the use of these antiplatelet drugs are reviewed.

## Coronary stenting in stable patients: Identification of a low-risk subgroup that may not require adjunctive antiplatelet therapy.

Mann T, Cubeddu RJ, Raynor L, Bowen J, Schneider JE, Rose G, Cubeddu G, Ali Raza J, Jobe RL, Newman W, Zellinger M.

The present study prospectively evaluated adjunctive antiplatelet therapy in patients without insulin-requiring diabetes during elective coronary stenting. Three hundred patients were randomized to one of three treatment groups: clopidogrel pretreatment, adjunctive abciximab, or control. Stenting was successful in 98% and no deaths occurred. Thirty-day and 1-year major adverse coronary events (MACEs) was similar in all groups. A subgroup of 109 patients undergoing single-vessel stenting of type A/B1 lesions with short guidewire times had no postprocedure myocardial infarction or 30-day MACE. We conclude that patients with these characteristics may safely undergo elective coronary stenting without adjunctive antiplatelet therapy.

## **Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention.**

**Mehta SR, Yusuf S.**

Platelets play a central role in both the short- and long-term manifestations of atherothrombosis. In acute coronary syndrome (ACS), there is a steep rise in cardiovascular events early, followed by an incremental rise in cardiovascular events over the long term. This long-term event rate is related to persistent platelet activation and thrombin generation. There is therefore a need to optimize both short- and long-term oral antiplatelet and antithrombotic strategies. The benefits of aspirin therapy, when administered early and continued over the long term, were demonstrated in several early randomized trials. The Antithrombotic Trialists' Collaboration found a 46% reduction in vascular events with antiplatelet therapy (mostly aspirin). However, despite treatment with aspirin and proven therapies, recurrent events remain high. The adenosine diphosphate receptor antagonists, ticlopidine and clopidogrel, inhibit the early steps of platelet activation, degranulation, and release of prothrombotic and inflammatory mediators, while also preventing activation of the glycoprotein IIb/IIIa receptor. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated the benefits of aspirin plus clopidogrel in reducing major cardiovascular events (cardiovascular death, myocardial infarction [MI], and stroke reduced by 20%,  $p = 0.00009$ ) in a broad range of patients with ACS when administered early and continued over the long term. The benefits emerge very rapidly after a 300 mg loading dose. For the large number of patients undergoing percutaneous coronary intervention in the CURE trial, there was a substantial risk reduction with clopidogrel pretreatment followed by long-term therapy ( $p < 0.002$ ). This benefit was present, regardless of whether intervention was performed early or late. The significant benefits of aspirin and clopidogrel persist for the combined efficacy-safety end point of cardiovascular death, MI, stroke, or life-threatening bleeding when clopidogrel is started early, combined with aspirin and other standard therapies, and continued for up to one year.

## **Pharmacologic plaque passivation for the reduction of recurrent cardiac events in acute coronary syndromes.**

**Monroe VS, Kerensky RA, Rivera E, Smith KM, Pepine CJ**

**A**cute coronary syndrome (ACS) is often associated with the rupture of vulnerable atherosclerotic plaque, coronary thrombus formation, and abrupt limitation of blood flow, leading to adverse outcomes. Passivation of vulnerable plaque represents a therapeutic concept that has the potential to prevent or limit the magnitude of a new rupture in order to reduce the recurrence or severity of events. Plaque passivation can be defined as a process by which the structure or content of the atherosclerotic plaque is changed to reduce the risk of subsequent rupture and thrombosis. This may be achieved by using strategies that address different components of the plaque or the endothelium. The following factors can affect the susceptibility of plaque to rupture: macrophage infiltration; accumulation of inflammatory cells; paracrine secretion of enzymes that may cause degradation of the fibrous cap of coronary plaque; shear stress; circadian rhythm variation in stress hormone release; and infectious agents. The use of pharmacologic agents to reduce plaque vulnerability by passivation has been explored. Clinical studies demonstrate that lipid-modifying agents (e.g., statins), antiplatelet agents (acetylsalicylic acid, thienopyridines, thianopyridines, glycoprotein IIb/IIIa inhibitors), and antithrombotic agents (unfractionated heparin and low-molecular-weight heparin) can reduce the occurrence of acute coronary events in ACS patients. In addition, angiographic studies suggest that statins may also promote regression of atherosclerosis. Angiotensin-converting enzyme inhibitors, niacin, and calcium antagonists may also contribute to plaque passivation. This article reviews atherosclerotic plaque development and vulnerability and discusses some clinical studies highlighting the role of plaque passivation in the management of ACS patients.

## **Ticlopidine-induced cholestatic hepatitis.**

**Skurnik YD, Tcherniak A, Edlan K, Sthoeger Z.**

**OBJECTIVE:** To report 2 cases of ticlopidine-induced cholestatic hepatitis, investigate its mechanism, and compare the observed main characteristics with those of the published cases. **CASE SUMMARIES:** Two patients developed prolonged cholestatic hepatitis after receiving ticlopidine following percutaneous coronary angioplasty, with complete remission during the follow-up period. T-cell stimulation by therapeutic concentration of ticlopidine was demonstrated in vitro in the patients, but not in healthy controls. **DISCUSSION:** Cholestatic hepatitis is a rare complication of the antiplatelet agent ticlopidine; several cases have been reported but few in the English literature. Our patients developed jaundice following treatment with ticlopidine and showed the clinical and laboratory characteristics of cholestatic hepatitis, which resolved after discontinuation of the drug. Hepatitis may develop weeks after discontinuation of the drug and may run a prolonged course, but complete remission was observed in all reported cases. An objective causality assessment revealed that the adverse drug event was probably related to the use of ticlopidine. The mechanisms of this ticlopidine-induced cholestasis are unclear. Immune mechanisms may be involved in the drug's hepatotoxicity, as suggested by the T-cell stimulation study reported here. **CONCLUSIONS:** Cholestatic hepatitis is a rare adverse effect of ticlopidine that may be immune mediated. Patients receiving the drug should be monitored with liver function tests along with complete blood cell counts. This complication will be observed even less often in the future as ticlopidine is being replaced by the newer antiplatelet agent clopidogrel.

## **A novel S-nitrosothiol causes prolonged and selective inhibition of platelet adhesion at sites of vascular injury.**

Miller MR, Hanspal IS, Hadoke PW, Newby DE, Rossi AG, Webb DJ, Megson IL.

**O**BJECTIVE: Platelet adhesion to areas of endothelial denudation following angioplasty is an important factor contributing to the limitations of this technique. Lipophilic S-nitrosothiols like S-nitroso-N-valerylpenicillamine (SNVP) are novel nitric oxide (NO) donor drugs with anti-platelet and vasodilator properties that are selective for areas of endothelial denudation. Here we assess the inhibitory effect of SNVP on platelet adhesion to angioplastied rabbit carotid arteries. **METHODS:** A rabbit model was used to measure adhesion of radiolabelled platelets to carotid arteries following balloon angioplasty. The effects of SNVP were compared to the conventional NO donor, nitroglycerin (NTG). Electron microscopy was used to visualize adhering platelets. **RESULTS:** Angioplasty resulted in endothelial denudation with only a modest reduction in vessel contractility. In vivo administration of NTG and SNVP (both 200 nmol) prevented the hyper-aggregability (approximately 20%) of circulating platelets caused by angioplasty. However, bolus NTG failed to inhibit adhesion of radiolabelled platelets 30 min after angioplasty, despite inducing a transient 30% reduction in systemic blood pressure. In contrast, equimolar SNVP had little effect on blood pressure but markedly inhibited platelet adhesion (62% compared to control;  $P=0.003$ ). Platelet adhesion was confirmed with electron microscopy. **CONCLUSION:** The prolonged effects of SNVP at sites of endothelial damage suggest that novel S-nitrosothiols might offer a means of targeted delivery of an antiplatelet agent to areas of vascular injury.

## **Antiplatelet effects of angiotensin-converting enzyme inhibitors compared with aspirin and clopidogrel: a pilot study with whole-blood aggregometry.**

**Bauriedel G, Skowasch D, Schneider M, Andrie R, Jabs A, Luderitz B.**

**B**ACKGROUND: Although specific antiplatelet drugs are well-established and effective in atherosclerosis prevention, recent clinical trials have also shown that use of angiotensin-converting enzyme (ACE) inhibitors results in a decrease in cardiovascular events. Therefore, in this study, we sought to assess the coagulative activity of patients with cardiovascular disease grouped for treatment with either ACE inhibitors, aspirin, clopidogrel/aspirin, or none of these medications. METHODS: Blood samples from 303 patients with cardiovascular disease were analyzed with whole-blood aggregometry. Platelet aggregation was determined by the increase in impedance across paired electrodes in response to the aggregatory agents adenosine diphosphate (ADP) or collagen. RESULTS: As the central finding, platelet aggregation was attenuated by ACE inhibitors and by aspirin or clopidogrel/aspirin, which was indicated by a lower impedance increase compared with no medication. With ACE inhibition, platelet aggregation decreased by 33% ( $P = .042$ ) after ADP induction. No significant antithrombotic effect was seen with aspirin alone (17%,  $P = 1.0$ ), whereas a decrease in ADP-induced platelet aggregation was extensive with clopidogrel/aspirin (85%,  $P = .001$ ). After collagen induction, platelet aggregation was reduced by 16% ( $P = .028$ ) in the presence of ACE inhibitor therapy, whereas inhibition with aspirin and clopidogrel/aspirin was 23% ( $P = .004$ ) and 35% ( $P = .026$ ), respectively, compared with participants who were not treated. CONCLUSIONS: These *ex vivo* data on whole-blood aggregometry provide direct evidence that ACE inhibitors decrease platelet aggregation, whereas aspirin and clopidogrel are confirmed as established antithrombotics. Pleiotropic effects of ACE inhibition on platelet function may contribute to the clinical benefit observed with this drug class on major cardiovascular end points.

**Antiinflammatory, gastrosparing, and antiplatelet properties of new NO-donor esters of aspirin.**

Cena C, Lolli ML, Lazzarato L, Guaita E, Morini G, Coruzzi G, McElroy SP, Megson IL, Fruttero R, Gasco A.

**A** new series of NSAIDs in which aspirin is joined by an ester linkage to furoxan moieties, with different ability to release NO, were synthesized and tested for NO-releasing, antiinflammatory, antiaggregatory, and ulcerogenic properties. Related furazan derivatives, aspirin, its propyl ester, and its gamma-nitrooxypropyl ester were taken as references. All the products described present an antiinflammatory trend, maximized in derivatives 12, 16, and 17, they are devoid of acute gastrotoxicity, principally due to their ester nature, and show an antiplatelet activity primarily determined by their ability to release NO. They do not behave as aspirin prodrugs in human serum.

## **Resistance to aspirin in vitro at rest and during exercise in patients with angiographically proven coronary artery disease.**

**Christiaens L, Macchi L, Herpin D, Coisne D, Duplantier C, Allal J, Mauco G, Brizard A.**

**B**ACKGROUND: Acetylsalicylic acid, or aspirin, is widely used in secondary prevention of coronary artery diseases, but the inhibition of platelet aggregation is not uniform in all individuals. OBJECTIVE: To investigate the prevalence of aspirin resistance at rest and during exercise in coronary artery disease patients. MATERIALS AND METHODS: Fifty patients with stable coronary artery disease were prospectively studied. All patients received aspirin (75–300 mg/day for >1 month) and no other antiplatelet therapy. Aspirin resistance was studied, at rest and immediately after a stress test, using the standardized platelet function analyzer (PFA-100(R), Dade-Behring). Aspirin resistance was defined as a normal collagen/epinephrine closure time (<186 s). RESULTS: Ten patients (20%) were aspirin-resistant at rest. Out of the 40 patients who were aspirin-sensitive at rest, 9 (22%) were aspirin-resistant immediately after the exercise stress test. There were no differences in aspirin sensitivity regarding gender, age, diabetes, hypertension, dyslipidemia, platelet count, medical treatment or number of the coronary arteries involved. CONCLUSIONS: Aspirin resistance is detected, at rest, in 20% of our patients with stable coronary artery disease. Aspirin treatment does not seem to protect against exercise-induced platelet activation in 22% of such patients, despite aspirin sensitivity at rest.

## **Nonplatelet-mediated effects of aspirin.**

**Aude YW, Mehta JL.**

**A**spirin has nonplatelet-mediated effects that contribute to its efficacy in the primary and secondary prevention of coronary events. These include antiarrhythmic effects, as shown in animal studies, and antiatherosclerotic effects related to increase in nitric oxide synthesis/activity and reduction in inflammatory mediators. Epidemiological studies have also shown primary antiinflammatory properties. Aspirin is known to inhibit vascular smooth muscle cell proliferation and to produce an endothelial stabilizing effect. Other observed outcomes from the administration of this compound include a modest anticoagulant activity, angiogenesis reduction and a decrease in oxidant stress. We believe that these results complement the antiplatelet effect and make this agent unique in the management of ischemic heart disease.

## **Acetylsalicylic acid inhibits cell proliferation by involving transforming growth factor-beta.**

Redondo S, Santos-Gallego CG, Ganado P, Garcia M, Rico L, Del Rio M, Tejerina T.

**B**ACKGROUND: Acetylsalicylic acid (ASA) inhibits cell proliferation. This may be mediated by transforming growth factor-beta (TGF-beta). TGF-beta directly stops cell proliferation, restrains cells in G(0), and inhibits the uptake of platelet-derived growth factor and insulin-like growth factor. These effects are identical to those observed with ASA treatment. **METHODS AND RESULTS:** We cultured rat thoracic aorta vascular smooth muscle cells and measured cytotoxicity, cell proliferation, cell cycle, transcription of TGF-beta1, and concentration of TGF-beta1 in supernatant medium. ASA dose-dependently restrained cells in G(0) phase with no cytotoxic effect and inhibited cell proliferation by 30.86%. Anti-TGF-beta1 reversed this inhibition by 30.21%. However, ASA treatment decreased TGF-beta1 transcription and had no significant effect on TGF-beta1 concentration. **CONCLUSIONS:** TGF-beta seems to play an important role in ASA-mediated inhibition of cell proliferation. Therefore, treatment with ASA prevents coronary disease not only by means of its antiplatelet properties but also by an important inhibition of plaque growth. This relationship between ASA and TGF-beta explains many other effects, such as cancer chemoprevention, immunomodulation, and wound healing. The aim of this study was to demonstrate this link.

## **The role of platelets in peripheral vascular disease.**

**Cassar K, Bachoo P, Brittenden J.**

**P**latelets play a major role in acute ischaemic syndromes and peripheral vascular disease. They are involved in the development and progression of atherosclerosis, native vessel and graft thrombosis. They have a central role in the development of restenosis and reocclusion after peripheral percutaneous transluminal angioplasty. Antiplatelet therapy has been shown to be beneficial in patients undergoing peripheral vascular surgery or radiological intervention. Yet current routine therapy, namely aspirin and dipyridamole are limited in their mode of action and efficacy. Recent developments in the understanding of platelet function has led to the development of new more potent drugs such as clopidogrel. Combination of drugs and more specific investigation of individual platelet function may well result in improved bypass and angioplasty patency rates. The results of proposed large randomised controlled trials on the role and safety of aspirin and clopidogrel are awaited with interest. Given the importance of platelets in peripheral vascular disease highlighted in this review, achieving an optimal safe anti-platelet effect for each patient with peripheral vascular disease should be the target of future research.

**Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction.**

Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DG, Guyer KE, Bates ER.

**B**ACKGROUND: We observed that the prodrug clopidogrel was less effective in inhibiting platelet aggregation with coadministration of atorvastatin during point-of-care platelet function testing. Because atorvastatin is metabolized by cytochrome P450 (CYP) 3A4, we hypothesized that clopidogrel might be activated by CYP3A4. METHODS AND RESULTS: Platelet aggregation was measured in 44 patients undergoing coronary artery stent implantation treated with clopidogrel or clopidogrel plus pravastatin or atorvastatin, and in 27 volunteers treated with clopidogrel and either erythromycin or troleandomycin, CYP3A4 inhibitors, or rifampin, a CYP3A4 inducer. Atorvastatin, but not pravastatin, attenuated the antiplatelet activity of clopidogrel in a dose-dependent manner. Percent platelet aggregation was 34+/-23, 58+/-15 (P=0.027), 74+/-10 (P=0.002), and 89+/-7 (P=0.001) in the presence of clopidogrel and 0, 10, 20, and 40 mg of atorvastatin, respectively. Erythromycin attenuated platelet aggregation inhibition (55+/-12 versus 42+/-12% platelet aggregation; P=0.002), as did troleandomycin (78+/-18 versus 45+/-18% platelet aggregation; P<0.0003), whereas rifampin enhanced platelet aggregation inhibition (33+/-18 versus 56+/-20% platelet aggregation, P=0.001). CONCLUSIONS: CYP3A4 activates clopidogrel. Atorvastatin, another CYP3A4 substrate, competitively inhibits this activation. Use of a statin not metabolized by CYP3A4 and point-of-care platelet function testing may be warranted in patients treated with clopidogrel.

## **Oral antithrombotic use among myocardial infarction patients.**

Van Der Elst ME, Cisneros-Gonzalez N, De Blaey CJ, Buurma H, De Boer A.

**O**BJECTIVE: To examine the use of oral antithrombotics (i.e., antiplatelet agents, oral anticoagulants) after myocardial infarction (MI) in the Netherlands from 1988 to 1998. **METHODS:** Retrospective follow-up of 3800 patients with MI, using data from the PHARMO Record Linkage System. **RESULTS:** From 1988 to 1998, oral antithrombotic treatment increased significantly from 54.0% to 88.9%. In 1998, only 75.8% of patients who experienced a MI in the late 1980s received oral antithrombotic treatment compared with 94.4% of those who experienced a recent MI. **CONCLUSIONS:** Oral antithrombotics were considerably underused in patients with a past history of MI. Therefore, these patients should be reviewed for antithrombotic therapy to assess whether their failure to use oral antithrombotics was right or wrong, and whether treatment should be initiated if possible.

## **Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease.**

**Storey RF, Wilcox RG, Heptinstall S.**

**W**e compared the antiplatelet effects of clopidogrel and the intravenous platelet P2Y(12) receptor antagonist AR-C69931MX, which acts on the same receptor as clopidogrel by a different and reversible mechanism and, unlike clopidogrel, is active in vitro. Thirteen patients with acute coronary syndromes entered into a phase II study of intravenous AR-C69931MX (Group 1) and eight patients undergoing intracoronary stent implantation and treated with clopidogrel (Group 2) were studied using a whole blood single-platelet counting aggregation assay. Group 2 patients were also studied using turbidimetry with ADP and TRAP as agonists and whole blood [(14)C]5HT release to study dense granule secretion in response to ADP, collagen and TRAP. In Group 2 studies, a therapeutic concentration of AR-C69931MX was added in vitro before and after clopidogrel administration. AR-C69931MX in Group 1 achieved greater inhibition of ADP-induced platelet aggregation than clopidogrel in Group 2 and AR-C69931MX in vitro added to the effects of clopidogrel on ADP-induced aggregation. AR-C69931MX but not clopidogrel inhibited TRAP-induced aggregation and granule secretion and AR-C69931MX had a more consistent inhibitory effect on collagen-induced responses. In conclusion, therapeutic administration of clopidogrel moderately inhibits platelet P2Y(12) receptor activation and substantially greater P2Y(12) receptor blockade can be achieved with AR-C69931MX.

## **Monitoring of antiplatelet therapy with the PFA-100(R) in peripheral angioplasty patients.**

**Ziegler S, Maca T, Alt E, Speiser W, Schneider B, Minar E.**

**B**ACKGROUND: In patients suffering from peripheral arterial occlusive disease (PAOD) the risk of restenosis after percutaneous transluminal angioplasty (PTA) might be influenced by platelet mediated factors. OBJECTIVE: To look for a correlation between the effect of antiplatelet therapy and recurrence of disease after PTA by monitoring platelet function in 3-month intervals by the platelet function analyzer system, PFA-100(R), over a period of 1 year. PATIENTS AND METHODS: A group of 98 patients (43 females, 55 males) with PAOD, treated with aspirin (n = 52), thienopyridine (n = 34) or combination therapy of both (n = 12) were followed over a period of 12 months after elective PTA of the lower extremities with regard to occurrence of restenosis or reocclusion at the site of angioplasty, to demonstrate inhibitory effects on platelets, induced by antiplatelet therapy. RESULTS: PFA-100 proved suitable to identify 'non-responders' to antiplatelet therapy, in a 12-month follow-up period. In 'non-responders' to clopidogrel therapy, a higher incidence of restenosis or reocclusion after PTA of the lower limbs was detected compared with 'responders'. CONCLUSION: PFA-100, upon stimulation with ADP, might predict patients under clopidogrel therapy with elevated risk for the development of complications following PTA of the lower limbs. This could offer the chance to switch to an alternative therapy or adapt the dose.

**Influence of heparin coating of coronary stents and ex vivo efficacy of different doses of acetylsalicylic acid and ticlopidine in a pulsed floating model of recirculating human plasma.**

Brockmann MA, Gutensohn K, Bau J, Kuehnl P, Meinertz T, Nienaber C, Beythien C.

**A**cute occlusion of stented coronary vessels still occurs in up to 3%. Activated platelets have been found to play a major role in the pathogenesis of these complications. We therefore analyzed the efficacy of a heparin coating of coronary stents and investigated the ex vivo efficacy of different antiplatelet drugs. Each of seven healthy volunteers was treated with each of the following medications for 7 days: ASA 100 mg/day, ASA 300 mg/day, ticlopidine 250 mg/day, and ticlopidine 500 mg/day. Three standardized in vitro silicon tubing models, one of them containing an uncoated stent, one a heparin-coated stent, and one without a stent (control) were filled with PRP and circulation was started. TOS in systems with heparin-coated stents was 2.4-times longer compared to systems with uncoated stents ( $P < 0.001$ ), and 1.5-times longer compared to the control ( $P < 0.01$ ). The increase of CD62p expression within the first 5 min was 2.5-times higher in systems with uncoated stents and 1.7-times higher in the control than in systems with heparin-coated stents ( $P < 0.05$ ). Aggregometry revealed significant medication- and dose-dependent inhibition of platelet aggregability for all medications. Heparin-coating of coronary stents reduces their thrombogenicity significantly. ASA and ticlopidine effectively reduce platelet activation ex vivo. The used in vitro system facilitates a reproducible method to estimate the thrombogenicity of coronary stents prior to in vivo trials.

## **Reversal of slow flow phenomenon during primary stenting by bail-out administration of abciximab.**

**Kaul U, Sapra R, Singh B, Sudan D, Ghose T, Dixit NS, Wasir HS.**

**B**ACKGROUND: Slow flow or no reflow phenomenon is increasingly being recognized as a serious problem during coronary angioplasty and stenting. This phenomenon is seen more often during angioplasty in highly thrombogenic milieu, especially in a setting of acute myocardial infarction. The treatment of this complication is often not satisfactory. In this study the authors assessed the efficacy of abciximab, a potent antiplatelet drug, in treating slow flow or no reflow phenomenon during primary percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI). METHODS: Twenty-one instances of persistent slow flow phenomenon were encountered in 131 consecutive patients subjected to primary PTCA for AMI (16%). It was more common in patients presenting with AMI complicated by cardiogenic shock (nine of 21, 43%). Of these 21 cases of slow flow, 10 patients were given injection abciximab during the procedure of primary PTCA as a bail-out measure after encountering the complication of slow flow or no reflow. A pre-discharge coronary angiography was carried out in all patients who survived. RESULTS: In seven of 10 patients in the abciximab group flow had improved to TIMI-3. In contrast, in the non-abciximab group TIMI flow improved in only four of 11 patients. Patients with persistent slow flow had significantly higher mortality at the first 30-day follow-up than patients with TIMI-3 flow (33% versus 1.8%,  $p < 0.001$ ). CONCLUSION: In this small nonrandomized study significant improvement in coronary flow was achieved by using intravenous abciximab after observing slow flow or no reflow phenomenon during primary PTCA. More frequent use of this drug in this milieu might help in preventing the development of this complication. Larger studies are warranted to confirm this life-saving beneficial effect of bail-out administration of abciximab during primary angioplasty.

## **Preventing thrombosis: update of first-line therapy in the management of non-ST segment elevation acute coronary syndromes.**

**Fitchett D, Goodman SG, Gupta M, Langer A.**

**N**on-ST segment elevation acute coronary syndrome (NSTE ACS) has a high rate of recurrence. Both antithrombotic and antiplatelet agents in association with coronary revascularization play an important role in the prevention of an adverse outcome. Acetylsalicylic acid, heparin and low molecular weight heparin (especially enoxaparin), and the intravenous small-molecule glycoprotein IIb/IIIa inhibitors, are of proven value. Recently, clopidogrel has been shown to reduce recurrent ischemic events, both early and during the first year after the index ACS. Furthermore, two recent trials have shown that an early invasive strategy is preferable to a conservative approach in the higher risk patient. As yet, no study has shown either the efficacy or the safety of combining all these treatment modalities in the management of the NSTE ACS patient. The initial choice of antithrombotic and antiplatelet agents and a strategy for early revascularization is made after considering the risk of recurrent acute ischemic events. For patients destined to have an early invasive strategy, it is desirable to choose an anti-thrombotic/antiplatelet combination that will reduce events before revascularization, enhance the revascularization procedure and not be associated with excessive bleeding. A risk-determined algorithm is presented, which applies observations made at the time of presentation to decide the optimal management for the individual patient.

**Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial.**

Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators.

**C**ONTEXT: The direct thrombin inhibitor bivalirudin has been associated with better efficacy and less bleeding than heparin during coronary balloon angioplasty but has not been widely tested during contemporary percutaneous coronary intervention (PCI). **OBJECTIVE:** To determine the efficacy of bivalirudin, with glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibition on a provisional basis for complications during PCI, compared with heparin plus planned Gp IIb/IIIa blockade with regard to protection from periprocedural ischemic and hemorrhagic complications. **DESIGN, SETTING, AND PARTICIPANTS:** The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, a randomized, double-blind, active-controlled trial conducted among 6010 patients undergoing urgent or elective PCI at 233 community or referral hospitals in 9 countries from October 2001 through August 2002. **INTERVENTIONS:** Patients were randomly assigned to receive intravenous bivalirudin (0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI), with provisional Gp IIb/IIIa inhibition (n = 2999), or heparin (65-U/kg bolus) with planned Gp IIb/IIIa inhibition (abciximab or eptifibatide) (n = 3011). Both groups received daily aspirin and a thienopyridine for at least 30 days after PCI. **MAIN OUTCOME MEASURES:** The primary composite end point was 30-day incidence of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding; the secondary composite end point was 30-day incidence of death, myocardial infarction, or urgent repeat revascularization. **RESULTS:** Provisional Gp IIb/IIIa blockade was administered to 7.2% of patients in the bivalirudin group. By 30 days, the primary composite end point had occurred among 9.2% of patients in the bivalirudin group vs 10.0% of patients in the heparin-plus-Gp IIb/IIIa group (odds ratio, 0.92; 95% confidence interval, 0.77-1.09; P =.32). The secondary composite end point occurred in 7.6% of patients in the bivalirudin vs 7.1% of patients in the heparin-plus-Gp IIb/IIIa groups (odds ratio, 1.09; 95% confidence interval 0.90-1.32; P =.40). Prespecified statistical criteria for noninferiority to heparin plus Gp IIb/IIIa were satisfied for both end points. In-hospital major bleeding rates were significantly reduced by bivalirudin (2.4% vs 4.1%; P<.001). **CONCLUSIONS:** Bivalirudin with provisional Gp IIb/IIIa blockade is statistically not inferior to heparin plus planned Gp IIb/IIIa

blockade during contemporary PCI with regard to suppression of acute ischemic end points and is associated with less bleeding.

**Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial.**

Tolleson TR, O'Shea JC, Bittl JA, Hillegass WB, Williams KA, Levine G, Harrington RA, Tchong JE.

**OBJECTIVES:** We evaluated the relationship between the degree of heparin anticoagulation and clinical efficacy and bleeding in patients undergoing contemporary percutaneous coronary intervention (PCI) with stent implantation. **BACKGROUND:** Despite universal acceptance of heparin anticoagulation as a standard of care in PCI, considerable controversy still exists regarding the appropriate dosing of heparin. **METHODS:** The study population (n = 2,064) comprised all patients enrolled in the Enhanced Suppression of the Platelet Iib/IIIa Receptor with Integrilin Therapy (ESPRIT) trial. The index activated clotting time (ACT) was defined as the ACT measured after the last heparin dose and before first device activation and was correlated with outcome and bleeding events. **RESULTS:** No association was observed between decreasing ACT levels and the rate of ischemic events in the treatment or placebo arms. The incidence of the primary composite end point (death, myocardial infarction, urgent target vessel revascularization, and thrombotic bailout glycoprotein Iib/IIIa inhibitor therapy at 48 h) was actually lowest in the lowest ACT tertile for both the placebo (10.0%) and treatment groups (6.1%). When analyzed by tertile, major bleeding rates did not increase in the lowest ACT tertile in patients given placebo (0.6%) versus those receiving eptifibatide (0.7%). Major bleeding rates increased as the ACT increased in the eptifibatide-treated patients. **CONCLUSIONS:** Ischemic end points in patients undergoing contemporary PCI with stent placement do not increase by decreasing ACT levels, at least to a level of 200 s. Bleeding events do increase with increasing ACT levels and are enhanced with eptifibatide treatment. An ACT of 200 to 250 s is reasonable in terms of efficacy and safety with the use of contemporary technology and pharmacotherapy.

## **Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions.**

**Karvouni E, Katritsis DG, Ioannidis JP.**

**OBJECTIVES:** We sought to evaluate the impact of intravenous antagonists of the platelet IIb/IIIa receptor on the survival of patients undergoing percutaneous coronary interventions (PCIs). **BACKGROUND:** Several trials have shown that intravenous antagonists of the platelet glycoprotein (GP) IIb/IIIa receptor reduce the incidence of myocardial infarction (MI) and composite cardiac outcomes (death, MI, or revascularization) in patients undergoing PCI. However, individual studies have not had adequate power to examine differences in mortality. **METHODS:** We performed a meta-analysis of 19 randomized, placebo-controlled trials (20 comparisons, n = 20,137). Death was the primary outcome. Secondary outcomes included MI, composite cardiac outcomes, and major bleeding. **RESULTS:** Mortality was significantly reduced at 30 days (risk ratio [RR] 0.69 [95% confidence interval [CI] 0.53 to 0.90]), at six months (RR 0.79 [95% CI 0.64 to 0.97]), and including longer follow-up (RR 0.79 [95% CI 0.66 to 0.94]), with no significant between-study heterogeneity. The relative risk reduction was largely similar in trials of patients with or without acute myocardial infarction (AMI), in trials continuing or discontinuing heparin after the procedure, and in trials using stents or another PCI as the intended primary procedure. Myocardial infarction and composite outcomes were significantly reduced ( $p < 0.001$  for all) at 30 days and six months. Major bleeding was significantly increased only in trials where heparin infusion was continued after the procedure (RR 1.70 [95% CI 1.36 to 2.14]), although there was no excess bleeding when heparin was discontinued (RR 1.02 [95% CI 0.85 to 1.24]). **CONCLUSIONS:** In patients undergoing PCI, GP IIb/IIIa receptor antagonists confer a significant and sustained decrease (20% to 30%) in the risk of death.

**Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.**

Bhatt DL, Lee BI, Casterella PJ, Pulsipher M, Rogers M, Cohen M, Corrigan VE, Ryan TJ Jr, Breall JA, Moses JW, Eaton GM, Sklar MA, Lincoff AM; Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.

**OBJECTIVES:** This study was designed to assess whether use of enoxaparin during percutaneous coronary intervention (PCI) increased bleeding compared with unfractionated heparin, in addition to background therapy with eptifibatide. **BACKGROUND:** Data supporting the benefits of enoxaparin and the glycoprotein IIb/IIIa inhibitor eptifibatide evolved in parallel. Information on combining these two classes of medications is limited. **METHODS:** A total of 261 patients undergoing elective or urgent PCI were randomized to either eptifibatide plus enoxaparin or eptifibatide plus unfractionated heparin. **RESULTS:** The primary end point of the study, the bleeding index (change in hemoglobin corrected for blood transfusions), was 0.8 in the patients randomized to enoxaparin and 1.1 in patients randomized to unfractionated heparin ( $p = 0.15$ ). The rate of vascular access site complications was 9.3% in the enoxaparin arm versus 9.8% in the unfractionated heparin arm ( $p = \text{NS}$ ). The rate of bleeding complications was not significantly different between the two arms of the study, including in those patients who received vascular closure devices. The rate of angiographic complications was 6.3% in the enoxaparin group and 6.2% in the unfractionated heparin group ( $p = \text{NS}$ ). Similarly, there were no significant differences in the composite of death, myocardial infarction, or urgent target vessel revascularization at 48 h or 30 days. **CONCLUSIONS:** Compared with unfractionated heparin plus eptifibatide, the combination of enoxaparin plus eptifibatide is not associated with an excess of bleeding or vascular complications, including in those receiving closure devices. Despite no monitoring of anticoagulation activity with enoxaparin, there was no apparent increase in angiographic or clinical complications.

**Platelet glycoprotein IIb/IIIa receptor inhibition in primary angioplasty for acute myocardial infarction: The new paradigm of direct revascularization.**

**Albirini A, Brener SJ.**

**A**cute myocardial infarction results from thrombotic occlusion superimposed on a ruptured atherosclerotic plaque. Immediate restoration of normal flow in the infarct-related artery can be achieved either with fibrinolytic or with direct mechanical revascularization. Primary PTCA has been shown to be superior to fibrinolytic therapy with respect to mortality, reinfarction, non-fatal stroke and length of hospitalization. Its results can be further improved by the addition of potent platelet inhibitors directed against the final common component of all stimuli for platelet aggregation, the glycoprotein (GP) IIb/IIIa receptor. In randomized clinical trials, primary angioplasty with adjunctive abciximab – a monoclonal antibody against the GP IIb/IIIa – was better than conventional primary angioplasty with heparin only. Abciximab use was associated with a significant reduction in reinfarction, need for urgent target vessel revascularization, microcirculatory dysfunction and regional left ventricular dysfunction as well as with a strong trend towards a reduction in mortality, even in patients receiving coronary stents.

## **Argatroban anticoagulation during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia.**

Lewis BE, Matthai WH Jr, Cohen M, Moses JW, Hursting MJ, Leya F; ARG-216/310/311 Study Investigators.

**H**eparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome associated with thrombosis. Alternative anticoagulation to heparin is needed for HIT patients during percutaneous coronary intervention (PCI). We evaluated argatroban, a direct thrombin inhibitor, for anticoagulation in this setting. Ninety-one HIT patients underwent 112 PCIs while on intravenous argatroban (25 microg/kg/min [350 microg/kg initial bolus], adjusted to achieve an activated clotting time of 300-450 sec). Primary efficacy endpoints were subjective assessments of the satisfactory outcome of the procedure and adequate anticoagulation during PCI. Among patients undergoing initial PCIs with argatroban (n = 91), 94.5% had a satisfactory outcome of the procedure and 97.8% achieved adequate anticoagulation. Death (zero patients), myocardial infarction (four patients), or revascularization (four patients) at 24 hr after PCI occurred in seven (7.7%) patients overall. One patient (1.1%) experienced periprocedural major bleeding. For patients who had subsequent hospitalizations (mean separation of 150 days) for repeat PCI using argatroban anticoagulation (n = 21), there were no unsatisfactory outcomes. Overall, outcomes were comparable with those historically reported for heparin. Argatroban therefore is a reasonable anticoagulant option in this setting, where current options are limited.

**Is glycoprotein IIb/IIIa antagonism as effective in women as in men following percutaneous coronary intervention?. Lessons from the ESPRIT study.**

Fernandes LS, Tcheng JE, O'Shea JC, Weiner B, Lorenz TJ, Pacchiana C, Berdan LG, Maresh KJ, Joseph D, Madan M, Mann T, Kilaru R, Hochman JS, Kleiman NS; ESPRIT investigators.

**OBJECTIVE:** The study was done to determine whether eptifibatide, a platelet glycoprotein (GP) IIb/IIIa antagonist, prevents ischemic complications following percutaneous coronary interventions (PCIs) in women as well as in men. **BACKGROUND:** Eptifibatide reduces ischemic complications after nonurgent coronary stent interventions. **METHODS:** We compared outcomes in women (n = 562) and men (n = 1,502) enrolled in the Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial of double-bolus eptifibatide during PCI. **RESULTS:** Women in the ESPRIT trial were older, and more frequently had hypertension, diabetes mellitus, or acute coronary syndromes, but were less likely to have prior PCI or coronary artery bypass graft surgery. The primary end point, a composite at 48 h of death, myocardial infarction (MI), urgent target vessel revascularization (TVR), and unplanned GP IIb/IIIa use, occurred in 10.5% of women and 7.9% of men (p = 0.082). The composite of death, MI, or TVR after one year occurred in 24.5% of women compared with 18% of men (p = 0.0008). At 48 h, eptifibatide reduced the composite of death, MI, and TVR from 14.5% to 6.0% in women versus 9.0% to 6.8% in men. At one year, these differences persisted: 28.9% versus 20.0% for women and 19.5% versus 16.6% for men. No statistical interaction existed between treatment and gender at either 48 h (p = 0.063) or one year (p = 0.2). Bleeding occurred more commonly in women (5.5% vs. 2.6%, p = 0.002), and was more common in eptifibatide-treated women. After adjustment for age, weight, and hypertension, no interaction between treatment and gender was present. **CONCLUSION:** Eptifibatide is effective to prevent ischemic complications of PCI in women and may eliminate gender-related differences in PCI outcomes.

**Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial).**

Bonz AW, Lengenfelder B, Strotmann J, Held S, Turschner O, Harre K, Wacker C, Waller C, Kochsiek N, Meesmann M, Neyses L, Schanzenbacher P, Ertl G, Voelker W.

**OBJECTIVES:** The Troponin in Planned PTCA/Stent Implantation With or Without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban (TOPSTAR) trial investigated: 1) the amount of troponin T (TnT) release after nonacute, elective percutaneous coronary intervention (PCI) in patients pretreated with aspirin and clopidogrel; and 2) the effect of additional glycoprotein (GP) IIb/IIIa receptor inhibition on postinterventional TnT release. **BACKGROUND:** No data are available yet as to whether additional administration of a GP IIb/IIIa receptor antagonist might be beneficial in patients undergoing elective PCI already pretreated with aspirin and clopidogrel. **METHODS:** After bolus application of the study medication (tirofiban [T] or placebo [P]), PCI was performed followed by an 18-h continuous infusion of T/P. Primary end point of the study was incidence and amount of TnT release after elective PCI after 24 h. **RESULTS:** A total of 12 h after PCI troponin release was detected in 63% of the patients receiving P and in 40% of the patients receiving T ( $p < 0.05$ ), after 24 h in 69% (P) and 48% (T) ( $p < 0.05$ ) and after 48 h in 74% (P) versus 58% (T) ( $p < 0.08$ ) of the patients. No differences were observed regarding major bleeding, intracranial bleeding or nonhemorrhagic strokes. After nine months a reduction of combined death/myocardial infarction/target vessel revascularization could be observed in the tirofiban group ([T] 2.3% vs. [P] 13.04%,  $p < 0.05$ ). **CONCLUSIONS:** Troponin T release occurs after successful intervention in 74% of the patients undergoing elective PCI after 48 h even after pretreatment with aspirin and clopidogrel. The GP IIb/IIIa receptor antagonist tirofiban is able to decrease the incidence of troponin release significantly in this patient population.

**Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation.**

Antoniucci D, Valenti R, Migliorini A, Moschi G, Trapani M, Dovellini EV, Bolognese L, Santoro GM.

The impact of abciximab therapy on mortality in patients with acute myocardial infarction (AMI) who are undergoing infarct-related artery (IRA) stent implantation, which is complicated by cardiogenic shock (CS) due to predominant ventricular failure has not been established, whereas concluded randomized trials comparing IRA stenting plus abciximab with IRA stenting alone in patients with AMI have produced conflicting results. Moreover, these trials have excluded patients with CS from randomization. This study sought to determine whether IRA stenting plus abciximab treatment has an impact on 1-month mortality compared with IRA stenting alone in consecutive patients with AMI complicated by CS due to predominant ventricular failure. Of 77 patients with CS and IRA stenting, 44 had abciximab therapy, whereas 33 underwent primary IRA stenting alone. There were no differences between groups in major baseline characteristics except for a higher incidence of women in the stent alone group compared with the abciximab group (36% vs 14%,  $p = 0.020$ ). The 1-month overall mortality rate was 18% in the abciximab group and 42% in the stent alone group ( $p < 0.020$ ). There were no differences between groups in reinfarction and target vessel revascularization rates. Multivariate analysis showed that abciximab therapy was the only variable that was independently related to 1-month mortality (odds ratio 0.36; 95% confidence intervals 0.15 to 0.86,  $p = 0.021$ ). The results of this study support the use of abciximab in patients with AMI complicated by CS who are undergoing IRA stent implantation. The mechanism of the clinical benefit of abciximab at 1 month was not related to the patency of the IRA.

## ANTIPLATELET and ANTICOAGULATION

1. Differential effect of aspirin on platelet aggregation in patients with coronary artery disease in relation with associated risk factors.

Ersoz G, Tikiz H, Yakaryilmaz A, Tezcan K, Genc Y, Korkmaz S.  
Jpn Heart J 2003 Jan;44(1):21-9

2. Oral anticoagulants in patients with coronary artery disease.

Anand SS, Yusuf S.  
J Am Coll Cardiol 2003 Feb 19;41(4 Suppl S):S62-9

3. Oral anticoagulants in patients with coronary artery disease.

Anand SS, Yusuf S.  
J Am Coll Cardiol 2003 Feb 19;41(4 Suppl S):S62-9

4. The role of platelet receptors and adhesion molecules in coronary artery disease.

Samara WM, Gurbel PA.  
Coron Artery Dis 2003 Feb;14(1):65-79

5. Clopidogrel but not aspirin reduces P-selectin expression and formation of platelet-leukocyte aggregates in patients with atherosclerotic vascular disease.

Klinkhardt U, Bauersachs R, Adams J, Graff J, Lindhoff-Last E, Harder S.  
Clin Pharmacol Ther 2003 Mar;73(3):232-41

6. Cost effectiveness of extended treatment with low molecular weight heparin (dalteparin) in unstable coronary artery disease: results from the FRISC II trial.

Janzon M, Levin LA, Swahn E; Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease II Investigators.  
Heart 2003 Mar;89(3):287-92

7. Effect of a single dose aspirin on platelets in humans with multiple risk factors for coronary artery disease.

Malinin AI, Atar D, Callahan KP, McKenzie ME, Serebruany VL.  
Eur J Pharmacol 2003 Feb 21;462(1-3):139-43

8. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial.

Tolleson TR, O'Shea JC, Bittl JA, Hillegass WB, Williams KA, Levine G, Harrington RA, Tcheng JE.  
J Am Coll Cardiol 2003 Feb 5;41(3):386-93

9. Secondary and primary prevention of coronary heart disease: [platelet aggregation inhibitors and anticoagulants]

Kubler W.

Z Kardiol 2002;91 Suppl 2:40-8

10. Platelet aggregation in different antithrombotic regimens. Possible proaggregant effect of low level oral anticoagulation.

Perez Gomez F, Lourenzo PI, Companion J, Escriba A, Perez Saldana D, Guillen M, Vargas E, S-Harguindey L.

Rev Port Cardiol 2002 May;21(5):541-51

11. Current agents for the treatment of patients with heparin-induced thrombocytopenia.

Warkentin TE.

Curr Opin Pulm Med 2002 Sep;8(5):405-12

12. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial.

van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group.

Lancet 2002 Jul 13;360(9327):109-13

13. Vascular closure devices in patients treated with anticoagulation and IIB/IIIa receptor inhibitors during percutaneous revascularization.

Applegate RJ, Grabarczyk MA, Little WC, Craven T, Walkup M, Kahl FR, Braden GA, Rankin KM, Kutcher MA.

J Am Coll Cardiol 2002 Jul 3;40(1):78-83

14. Pharmacodynamic and clinical trials of glycoprotein IIB/IIIa inhibitors and potential relationship of results to dosing.

Hobbs HP, Schuster P.

Z Kardiol 2003 Mar;92(3):213-218

15. Acute stent thrombosis after early withdrawal of platelet glycoprotein IIB/IIIa antagonists: Potential rebound prothrombotic effect?

Angiolillo DJ, Sabate M, Fernandez-Ortiz A, Macaya C.

Catheter Cardiovasc Interv 2003 Apr;58(4):481-4

16. Coronary stenting in stable patients: Identification of a low-risk subgroup that may not require adjunctive antiplatelet therapy.

Mann T, Cubeddu RJ, Raynor L, Bowen J, Schneider JE, Rose G, Cubeddu G, Ali Raza J, Jobe RL, Newman W, Zellinger M.

Catheter Cardiovasc Interv 2003 Apr;58(4):459-66

17. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention.

Mehta SR, Yusuf S.

J Am Coll Cardiol 2003 Feb 19;41(4 Suppl S):S79-88

18. Pharmacologic plaque passivation for the reduction of recurrent cardiac events in acute coronary syndromes.

Monroe VS, Kerensky RA, Rivera E, Smith KM, Pepine CJ

J Am Coll Cardiol 2003 Feb 19;41(4 Suppl S):S23-30

19. Ticlopidine-induced cholestatic hepatitis.

Skurnik YD, Tcherniak A, Edlan K, Sthoeger Z.

Ann Pharmacother 2003 Mar;37(3):371-5

20. A novel S-nitrosothiol causes prolonged and selective inhibition of platelet adhesion at sites of vascular injury.

Miller MR, Hanspal IS, Hadoke PW, Newby DE, Rossi AG, Webb DJ, Megson IL.

Cardiovasc Res 2003 Mar;57(3):853-60

21. Antiplatelet effects of angiotensin-converting enzyme inhibitors compared with aspirin and clopidogrel: a pilot study with whole-blood aggregometry.

Bauriedel G, Skowasch D, Schneider M, Andrie R, Jabs A, Luderitz B.

Am Heart J 2003 Feb;145(2):343-8

22. Antiinflammatory, gastrosparring, and antiplatelet properties of new NO-donor esters of aspirin.

Cena C, Lolli ML, Lazzarato L, Guaita E, Morini G, Coruzzi G, McElroy SP, Megson IL, Fruttero R, Gasco A.

J Med Chem 2003 Feb 27;46(5):747-54

23. Resistance to aspirin in vitro at rest and during exercise in patients with angiographically proven coronary artery disease.

Christiaens L, Macchi L, Herpin D, Coisne D, Duplantier C, Allal J, Mauco G, Brizard A.

Thromb Res 2002 Nov 1;108(2-3):115-9

24. Nonplatelet-mediated effects of aspirin.

Aude YW, Mehta JL.

Drugs Today (Barc) 2002 Jul;38(7):501-7

25. Acetylsalicylic acid inhibits cell proliferation by involving transforming growth factor-beta.

Redondo S, Santos-Gallego CG, Ganado P, Garcia M, Rico L, Del Rio M, Tejerina T.

Circulation 2003 Feb 4;107(4):626-9

26. The role of platelets in peripheral vascular disease.

Cassar K, Bachoo P, Brittenden J.

Eur J Vasc Endovasc Surg 2003 Jan;25(1):6-15

27. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction.

Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DG, Guyer KE, Bates ER.

Circulation 2003 Jan 7;107(1):32-7

28. Oral antithrombotic use among myocardial infarction patients.

Van Der Elst ME, Cisneros-Gonzalez N, De Blaey CJ, Buurma H, De Boer A.

Ann Pharmacother 2003 Jan;37(1):143-6

29. Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease.

Storey RF, Wilcox RG, Heptinstall S.

Platelets 2002 Nov;13(7):407-13

30. Monitoring of antiplatelet therapy with the PFA-100(R) in peripheral angioplasty patients.

Ziegler S, Maca T, Alt E, Speiser W, Schneider B, Minar E.

Platelets 2002 Dec;13(8):493-7

31. Influence of heparin coating of coronary stents and ex vivo efficacy of different doses of acetylsalicylic acid and ticlopidine in a pulsed floating model of recirculating human plasma.

Brockmann MA, Gutensohn K, Bau J, Kuehnl P, Meinertz T, Nienaber C, Beythien C.

Platelets 2002 Dec;13(8):443-9

32. Reversal of slow flow phenomenon during primary stenting by bail-out administration of abciximab.

Kaul U, Sapra R, Singh B, Sudan D, Ghose T, Dixit NS, Wasir HS.

Int J Cardiovasc Intervent 2000 Mar;3(1):35-39

33. Preventing thrombosis: update of first-line therapy in the management of non-ST segment elevation acute coronary syndromes.

Fitchett D, Goodman SG, Gupta M, Langer A.

Can J Cardiol 2002 Nov;18(11):1179-90

34. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial.

Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators.

JAMA 2003 Feb 19;289(7):853-63

35. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial.

Tolleson TR, O'Shea JC, Bittl JA, Hillegass WB, Williams KA, Levine G, Harrington RA, Tcheng JE.

J Am Coll Cardiol 2003 Feb 5;41(3):386-93

36. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions.

Karvouni E, Katritsis DG, Ioannidis JP.

J Am Coll Cardiol 2003 Jan 1;41(1):26-32

37. Safety of concomitant therapy with eptifibatid and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.

Bhatt DL, Lee BI, Casterella PJ, Pulsipher M, Rogers M, Cohen M, Corrigan VE, Ryan TJ Jr, Breall JA, Moses JW, Eaton GM, Sklar MA, Lincoff AM; Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.

J Am Coll Cardiol 2003 Jan 1;41(1):20-5

38. Safety of concomitant therapy with eptifibatid and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.

Bhatt DL, Lee BI, Casterella PJ, Pulsipher M, Rogers M, Cohen M, Corrigan VE, Ryan TJ Jr, Breall JA, Moses JW, Eaton GM, Sklar MA, Lincoff AM; Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study.

J Am Coll Cardiol 2003 Jan 1;41(1):20-5

39. Platelet glycoprotein IIb/IIIa receptor inhibition in primary angioplasty for acute myocardial infarction: The new paradigm of direct revascularization.

Albirini A, Brener SJ.

Int J Cardiovasc Intervent 2001 Mar;4(1):7-14

40. Argatroban anticoagulation during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia.

Lewis BE, Matthai WH Jr, Cohen M, Moses JW, Hursting MJ, Leya F; ARG-216/310/311 Study Investigators.

Catheter Cardiovasc Interv 2002 Oct;57(2):177-84

41. Is glycoprotein IIb/IIIa antagonism as effective in women as in men following percutaneous coronary intervention?. Lessons from the ESPRIT study.

Fernandes LS, Tchong JE, O'Shea JC, Weiner B, Lorenz TJ, Pacchiana C, Berdan LG, Maresh KJ, Joseph D, Madan M, Mann T, Kilaru R, Hochman JS, Kleiman NS; ESPRIT J Am Coll Cardiol 2002 Sep 18;40(6):1085-91

42. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial).

Bonz AW, Lengenfelder B, Strotmann J, Held S, Turschner O, Harre K, Wacker C, Waller C, Kochsiek

N, Meesmann M, Neyses L, Schanzenbacher P, Ertl G, Voelker W.

J Am Coll Cardiol 2002 Aug 21;40(4):662-8

43. Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation.

Antoniucci D, Valenti R, Migliorini A, Moschi G, Trapani M, Dovellini EV, Bolognese L, Santoro GM.

Am J Cardiol 2002 Aug 15;90(4):353-7

**Circulation 2001 Apr 10;103(14):1838-43**

**Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia.**

Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, Bartholomew J, Sham R, Lerner RG, Zeigler ZR, Rustagi PK, Jang IK, Rifkin SD, Moran J, Hursting MJ, Kelton JG; ARG-911 Study Investigators.

**BACKGROUND:** Heparin-induced thrombocytopenia (HIT) is an immune-mediated syndrome caused by heparin. Complications range from thrombocytopenia to thrombocytopenia with thrombosis. We report a prospective, historical- controlled study evaluating the efficacy and safety of argatroban, a direct thrombin inhibitor, as anticoagulant therapy in patients with HIT or HIT with thrombosis syndrome (HITTS). **METHODS AND RESULTS:** Patients with HIT (isolated thrombocytopenia, n=160) or HITTS (n=144) received 2 microgram. kg(-1). min(-1) IV argatroban, adjusted to maintain the activated partial thromboplastin time 1.5 to 3.0 times baseline value. Treatment was maintained for 6 days, on average. Clinical outcomes over 37 days were compared with those of 193 historical control subjects with HIT (n=147) or HITTS (n=46). The incidence of the primary efficacy end point, a composite of all-cause death, all-cause amputation, or new thrombosis, was reduced significantly in argatroban-treated patients versus control subjects with HIT (25.6% versus 38.8%, P=0.014). In HITTS, the composite incidence in argatroban-treated patients was 43.8% versus 56.5% in control subjects (P=0.13). Significant between-group differences by time-to-event analysis of the composite end point favored argatroban treatment in HIT (P=0.010) and HITTS (P=0.014). Argatroban therapy, relative to control subjects, also significantly reduced new thrombosis and death caused by thrombosis (P<0.05). Argatroban-treated patients achieved therapeutic activated partial thromboplastin times generally within 4 to 5 hours of starting therapy and, compared with control subjects, had a significantly more rapid rise in platelet counts (P=0.0001). Bleeding events were similar between groups. **CONCLUSIONS:** Argatroban anticoagulation, compared with historical control subjects, improves clinical outcomes in patients who have heparin-induced thrombocytopenia, without increasing bleeding risk.

Circulation 2001 Apr 24;103(16):2042-2047

Oral Anticoagulant Therapy During and After Coronary Angioplasty : The Intensity and Duration of Anticoagulation Are Essential to Reduce Thrombotic Complications.

Berg JM, Hutten BA, Kelder JC, Verheugt FW, Plokker HW.

**Background**-In the randomized Balloon Angioplasty and Anticoagulation Study (BAAS), the addition of oral anticoagulants to aspirin significantly reduced early and late events after coronary angioplasty. However, bleeding episodes were increased. The present report studied the intensity and the duration of anticoagulation as predictors of thrombotic and bleeding events. **Methods and Results**-A total of 530 patients, 34% of whom received a stent, were treated with aspirin plus coumarins. Half of the patients were randomized to angiographic follow-up. The target international normalized ratio (INR) was 2.1 to 4.8 during angioplasty and 6-month follow-up. Thrombotic events were death, myocardial infarction, target lesion revascularization, and thrombotic stroke. Bleeding complications were hemorrhagic stroke, major extracranial bleeding, and false aneurysm. "Optimal" anticoagulation was defined as an INR in the target range for at least 70% of the follow-up time. There were 17 early thrombotic events (3.2%), 7 early bleeding episodes (1.3%), and 10 false aneurysms (1.9%). The incidence rate for both early thrombotic and bleeding events was lowest in patients in the target range. A total of 61 late thrombotic events occurred (11.6%). Optimal anticoagulation was an independent predictor of late thrombotic events (relative risk, 0.33; 95% CI, 0.19 to 0.57) and was associated with a 0.21 mm (95% CI, 0.17 to 0.42) larger vessel lumen at 6 months. Late bleeding episodes (1.4%) were lowest in patients in the target range. **Conclusions**-Coumarins started before coronary angioplasty with a target INR of 2.1 to 4.8 led to the lowest procedural event rate, without an increase in bleeding episodes. During follow-up, optimal anticoagulation was associated with a decrease in the incidence of late events by 67% and a significant improvement in 6-month angiographic outcome.

J Am Coll Cardiol 2001 Apr;37(5):1323-8

Antiplatelet effects of abciximab, tirofiban and eptifibatide in patients undergoing coronary stenting.

Neumann FJ, Hochholzer W, Pogatsa-Murray G, Schomig A, Gawaz M.

**OBJECTIVES:** We sought to investigate whether abciximab, tirofiban and eptifibatide achieve comparable antiplatelet effects with coronary stenting. **BACKGROUND:** The glycoprotein (GP) IIb/IIIa antagonists abciximab, tirofiban and eptifibatide differ in chemical structure, binding site and pharmacokinetics. **METHODS:** Sixty patients undergoing coronary stenting were randomly assigned to abciximab (bolus 0.25 mg/kg body weight, infusion 10 microg per min for 12 h), tirofiban (bolus 10 microg/kg, infusion 0.15 microg/kg per min for 72 h) or eptifibatide (bolus 180 microg/kg, infusion 2 microg/kg per min for 72 h). We took serial blood samples to analyze platelet function by using flow cytometry, turbidimetric aggregometry and the rapid platelet-function assay (RPFA). **RESULTS:** As assessed by RPFA, platelet aggregation after 2 h of infusion was reduced to 5.9 +/- 7.8% (mean +/- SD) of baseline by abciximab, to 5.0 +/- 5.4% by tirofiban and to 7.8 +/- 7.1% by eptifibatide (p = 0.42). Turbidimetric aggregometry with adenosine diphosphate stimulation yielded similar results, whereas percent inhibition of platelet aggregation after thrombin receptor stimulation was 45.8 +/- 16.8% with abciximab, 51.3 +/- 17.6% with tirofiban and 52.9 +/- 14.8% with eptifibatide (p = 0.37). Tirofiban and eptifibatide maintained their level of platelet inhibition during infusion. Flow cytometry revealed that the reduction in the monocyte-platelet interaction by abciximab, tirofiban and eptifibatide was not significantly different (20.0 +/- 21.9%, 23.8 +/- 18.2% and 21.0 +/- 19.8%, respectively; p = 0.87). **CONCLUSIONS:** Abciximab, tirofiban and eptifibatide, at currently recommended doses, achieved similar levels of inhibition of platelet aggregation and a similar reduction in the platelet-monocyte interaction.

Circulation 2001 May 22;103(20):2453-60

Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis.

Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP; Investigators of the "Duree Optimale du Traitement AntiVitamines K" (DOTAVK) Study.

**BACKGROUND:** The optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism remains controversial. **METHODS AND RESULTS:** We performed an open-label, randomized trial comparing a short oral anticoagulant course (3 months for proximal deep vein thrombosis [P-DVT] and/or pulmonary embolism [PE]; 6 weeks for isolated calf DVT [C-DVT]) with a long course of therapy (6 months for P-DVT/PE; 12 weeks for C-DVT). The outcome events were recurrences and major, minor, or fatal bleeding complications. A total of 736 patients were enrolled. There were 23 recurrences of venous thromboembolism in the short treatment group (6.4%) and 26 in the long treatment group (7.4%); the 2 treatment regimens had an equivalent effect. For the hemorrhage end point, the difference between the short and the long treatment groups was not significant: 15.5% versus 18.4% for all events ( $P=0.302$ ), 1.7% versus 2.8% ( $P=0.291$ ) for major events, and 13.9% versus 15.3% for minor bleeding. Subgroup analysis demonstrated that the rate of recurrence was lower for C-DVT than for P-DVT or PE. **CONCLUSIONS:** After isolated C-DVT, 6 weeks of oral anticoagulation is sufficient. For P-DVT or PE, we demonstrated an equivalence between 3 and 6 months of anticoagulant therapy. For patients with temporary risk factors who have a low risk of recurrence, 3 months of treatment seems to be sufficient. For patients with idiopathic venous thromboembolism or permanent risk factors who have a high risk of recurrence, other trials are necessary to assess prolonged therapy beyond 6 months.

Circulation 2001 May 15;103(19):2332-5

Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS).

Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, Taaffe M, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KK, Lindsay J.

**BACKGROUND:**Intracoronary gamma-radiation reduces recurrent in-stent restenosis. Late thrombosis (>30 days after radiation therapy) is identified as a serious complication. The Washington Radiation for In-Stent Restenosis Trial (WRIST) PLUS, which involved 6 months of treatment with clopidogrel and aspirin, was designed to examine the efficacy and safety of prolonged antiplatelet therapy for the prevention of late thrombosis. **Methods and RESULTS:**A total of 120 consecutive patients with diffuse in-stent restenosis in native coronary arteries and vein grafts with lesions <80 mm underwent percutaneous coronary transluminal

angioplasty, laser ablation, and/or rotational atherectomy. Additional stents were placed in 34 patients (28.3%). After the intervention, a closed-end lumen catheter was introduced into the artery, a ribbon with different trains of radioactive ( $^{192}\text{Ir}$ ) seeds was positioned to cover the treated site, and a dose of 14 Gy to 2 mm was prescribed. Patients were discharged with clopidogrel and aspirin for 6 months and followed angiographically and clinically. All patients but one tolerated the clopidogrel. The late occlusion and thrombosis rates were compared with the gamma-radiation-treated (n=125) and the placebo patients (n=126) from the WRIST and LONG WRIST studies (which involved only 1 month of antiplatelet therapy). At 6 months, the group receiving prolonged antiplatelet therapy had total occlusion and late thrombosis rates of 5.8% and 2.5%, respectively; these rates were lower than those in the active gamma-radiation group and similar to those in the placebo historical control group. **CONCLUSIONS:** Six months of clopidogrel and aspirin and a reduction in re-stenting for patients with in-stent restenosis treated with gamma-radiation is well tolerated and associated with a reduction in the late thrombosis rate compared with a similar cohort treated with only 1 month of clopidogrel and aspirin.

Circulation 2001 May 29;103(21):2572-8

Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study.

Steinhubl SR, Talley JD, Braden GA, Tchong JE, Casterella PJ, Moliterno DJ, Navetta FI, Berger PB, Popma JJ, Dangas G, Gallo R, Sane DC, Saucedo JF, Jia G, Lincoff AM, Theroux P, Holmes DR, Teirstein PS, Kereiakes DJ.

**BACKGROUND:** The optimal level of platelet inhibition with a glycoprotein (GP) IIb/IIIa antagonist necessary to minimize thrombotic complications in patients undergoing a percutaneous coronary intervention (PCI) is currently unknown. **METHODS AND RESULTS:** Five hundred patients undergoing a PCI with the planned use of a GP IIb/IIIa inhibitor had platelet inhibition measured at 10 minutes, 1 hour, 8 hours, and 24 hours after the initiation of therapy with the Ultegra Rapid Platelet Function Assay (Accumetrics). Major adverse cardiac events (MACEs: composite of death, myocardial infarction, and urgent target vessel revascularization) were prospectively monitored, and the incidence correlated with the measured level of platelet function inhibition at all time points. One quarter of all patients did not achieve  $\geq 95\%$  inhibition 10 minutes after the bolus and experienced a significantly higher incidence of MACEs (14.4% versus 6.4%,  $P=0.006$ ). Patients whose platelet function was  $<70\%$  inhibited at 8 hours after the start of therapy had a MACE rate of 25% versus 8.1% for those

$\geq 70\%$  inhibited ( $P=0.009$ ). By multivariate analysis, platelet function inhibition  $\geq 95\%$  at 10 minutes after the start of therapy was associated with a significant decrease in the incidence of a MACE (odds ratio 0.46, 95% CI 0.22 to 0.96,  $P=0.04$ ). CONCLUSIONS: Substantial variability in the level of platelet function inhibition is achieved with GP IIb/IIIa antagonist therapy among patients undergoing PCI. The level of platelet function inhibition as measured by a point-of-care assay is an independent predictor for the risk of MACEs after PCI.

JAMA 2001 May 16;285(19):2468-73

Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial.

O'Shea JC, Hafley GE, Greenberg S, Hasselblad V, Lorenz TJ, Kitt MM, Strony J, Tcheng JE; ESPRIT Investigators (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial).

CONTEXT: The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial showed the efficacy of adjunctive, double-bolus eptifibatide therapy in reducing ischemic complications of nonurgent coronary stent implantation at 48 hours and at 30 days. OBJECTIVE: To determine whether the beneficial effects of eptifibatide persist at 6 months after treatment. DESIGN: Follow-up study of a randomized, double-blind, placebo-controlled, crossover-permitted trial conducted from June 1999 through February 2000. SETTING: Ninety-two tertiary care centers in the United States and Canada. PARTICIPANTS: A total of 2064 patients scheduled to undergo nonurgent percutaneous coronary intervention with stent implantation. INTERVENTION: Patients were randomly assigned to receive placebo or eptifibatide (two 180-microg/kg boluses 10 minutes apart and continuous infusion of 2.0 microg/kg per minute), started immediately before stent implantation and continued for 18 to 24 hours. Complete follow-up data were available for 988 (95.0%) of 1040 patients given eptifibatide and 977 (95.4%) of 1024 patients given placebo. MAIN OUTCOME MEASURES: Composite rates of death or myocardial infarction (MI); death, MI, or target vessel revascularization; and their individual components 6 months after enrollment, compared between the 2 groups. RESULTS: By 6 months, the composite end point of death or MI had occurred in 7.5% of eptifibatide-treated patients and in 11.5% of placebo-treated patients (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.47-0.84;  $P = .002$ ). The composite of death, MI, or target vessel revascularization was 14.2% in eptifibatide-treated patients vs 18.3% in placebo-treated patients (HR, 0.75; 95% CI, 0.60-0.93;  $P = .008$ ). Most of this benefit accrued early ( $<48$  hours after initiation of therapy) and was maintained through 6 months. Six-month mortality in the eptifibatide group was 0.8% vs 1.4% in the placebo group (HR, 0.56; 95% CI, 0.24-1.34;  $P = .19$ ) and target vessel

revascularization occurred in 8.6% of the eptifibatide group vs 9.4% of the placebo group (HR, 0.91; 95% CI, 0.68-1.22; P =.51). CONCLUSION: Adjunctive eptifibatide therapy during coronary stent implantation provides benefit through 6-month follow-up.

N Engl J Med 2001 Jun 21;344(25):1888-94

Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization.

Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L; TARGET Investigators. Do Tirofiban and ReoPro Give Similar Efficacy Trial.

**BACKGROUND:** In the setting of percutaneous coronary revascularization, agents in the class known as platelet glycoprotein IIb/IIIa inhibitors have significantly reduced the incidence of death or nonfatal myocardial infarction at 30 days. We assessed whether there are differences in safety or efficacy between two such inhibitors, tirofiban and abciximab. **METHODS:** Using a double-blind, double-dummy design at 149 hospitals in 18 countries, we randomly assigned patients to receive either tirofiban or abciximab before undergoing percutaneous coronary revascularization with the intent to perform stenting. The primary end point was a composite of death, nonfatal myocardial infarction, or urgent target-vessel revascularization at 30 days. The trial was designed and statistically powered to demonstrate the noninferiority of tirofiban as compared with abciximab. **RESULTS:** The primary end point occurred more frequently among the 2398 patients in the tirofiban group than among the 2411 patients in the abciximab group (7.6 percent vs. 6.0 percent; hazard ratio, 1.26; one-sided 95 percent confidence interval of 1.51, demonstrating lack of equivalence, and two-sided 95 percent confidence interval of 1.01 to 1.57, demonstrating the superiority of abciximab over tirofiban; P=0.038). The magnitude and the direction of the effect were similar for each component of the composite end point (hazard ratio for death, 1.21; hazard ratio for myocardial infarction, 1.27; and hazard ratio for urgent target-vessel revascularization, 1.26), and the difference in the incidence of myocardial infarction between the tirofiban group and the abciximab group was significant (6.9 percent and 5.4 percent, respectively; P=0.04). The relative benefit of abciximab was consistent regardless of age, sex, the presence or absence of diabetes, or the presence or absence of pretreatment with clopidogrel. There were no significant differences in the rates of major bleeding complications or transfusions, but tirofiban was associated with a lower rate of minor bleeding

episodes and thrombocytopenia. CONCLUSIONS: Although the trial was intended to assess the noninferiority of tirofiban as compared with abciximab, the findings demonstrated that tirofiban offered less protection from major ischemic events than did abciximab.

Circulation 2001 Jun 26;103(25):3069-74

Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery.

Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S.

BACKGROUND: Patients with a non-ST-elevation acute coronary syndrome and prior CABG are at high risk of a recurrent ischemic event despite aspirin therapy. This trial investigated the potential benefit of secondary prevention with warfarin. METHODS AND RESULTS: In a double-blind randomized trial, 135 patients with unstable angina or non-ST-segment elevation myocardial infarction, with prior CABG, and who were poor candidates for a revascularization procedure received therapy with aspirin and placebo+warfarin, warfarin and placebo+aspirin, or aspirin and warfarin for 12 months. Warfarin was titrated to an international normalized ratio of 2.0 to 2.5. The primary end point (death or myocardial infarction or unstable angina requiring hospitalization 1 year after randomization) occurred in 14.6% of the patients in the warfarin-alone group, in 11.5% of patients in the aspirin-alone group, and in 11.3% of patients randomized to the combination therapy (P=0.76). Subgroup analyses by risk features provided no indications that warfarin alone or in combination with aspirin could be of benefit over aspirin alone. Bleeding was more frequent in the 2 groups of patients administered warfarin. CONCLUSIONS: Moderate-intensity oral anticoagulation alone or combined with low-dose aspirin does not appear to be superior to low-dose aspirin in the prevention of recurrent ischemic events in patients with non-ST-elevation acute coronary syndromes and previous CABG.

Circulation 2001 Jul 31;104(5):539-43

Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population.

Taniuchi M, Kurz HI, Lasala JM.

**BACKGROUND:** Although clopidogrel is used to prevent subacute stent thrombosis, its safety and efficacy have not been compared with ticlopidine in a randomized manner in the United States. **METHODS AND RESULTS:** Patients with successful intracoronary stent implantation were randomly assigned to therapy with ticlopidine or clopidogrel. Loading doses were administered immediately after the procedure, and the drugs were prescribed for 2 weeks. One thousand sixteen patients were enrolled: 522 patients were randomly assigned to ticlopidine therapy and 494 to clopidogrel. High-risk characteristics included recent myocardial infarction in 41.4% of the cases, angiographically evident thrombus in 20.9%, and abrupt or threatened closure in 3.64%. An intravenous glycoprotein IIb/IIIa inhibitor was used in 48.2% of the cases, and thrombocytopenia occurred in 1.43% of these patients. Failure to complete 2 weeks of therapy occurred in 3.64% of the patients treated with ticlopidine and in 1.62% of the patients treated with clopidogrel ( $P=0.043$ ). Within 30 days, thrombosis of the stent occurred in 1.92% of the patients in the ticlopidine group and in 2.02% of the clopidogrel group ( $P=0.901$ ). A major adverse cardiac event occurred in 4.60% of patients receiving ticlopidine and in 3.85% of patients receiving clopidogrel ( $P=0.551$ ). **CONCLUSIONS:** Clopidogrel is better tolerated than ticlopidine during a 2-week regimen after intracoronary stent implantation. Combining either thienopyridine with an intravenous platelet IIb/IIIa inhibitor appears to be safe. When applied to a broad spectrum of patients receiving stent implantation, clopidogrel confers similar protection as ticlopidine against subacute stent thrombosis and major adverse cardiac events.

Circulation , 2001;104(2):163-7

Abciximab suppresses the rise in levels of circulating inflammatory markers after percutaneous coronary revascularization.

Lincoff AM, Kereiakes DJ, Mascelli MA, Deckelbaum LI, Barnathan ES, Patel KK, Frederick B, Nakada MT, Topol EJ.

**BACKGROUND:** Previous investigators have shown that systemic markers of inflammation may be increased

in patients with acute ischemic syndromes or after percutaneous coronary revascularization and that persistent elevation in these markers is predictive of excess risk of subsequent adverse cardiac events. By virtue of its cross-reactivity with the glycoprotein IIb/IIIa,  $\alpha$ v $\beta$ 3, and  $\alpha$ IIb $\beta$ 2 receptors, abciximab may reduce inflammatory processes. **Methods and Results--** Assays for the inflammatory markers C-reactive protein, interleukin-6, and tumor necrosis factor- $\alpha$  were performed on serum samples obtained from 160 patients in a placebo-controlled, randomized trial of abciximab during angioplasty. Eighty patients each had received a placebo or abciximab bolus plus a 12-hour infusion. Serum samples were drawn at baseline (before revascularization), 24 to 48 hours after study drug administration, and 4 weeks after study drug administration. Between baseline and 24 to 48 hours, the increase in C-reactive protein was 32% less in patients receiving abciximab than placebo ( $P=0.025$ ); the rise in interleukin-6 levels was 76% less in the abciximab group ( $P<0.001$ ); and the rise in tumor necrosis factor- $\alpha$  levels was 100% less with abciximab therapy ( $P=0.112$ ). By 4 weeks, most marker levels had returned to baseline, with no significant differences between placebo and abciximab groups. **CONCLUSIONS:** Systemic markers of inflammation increase in the first 24 to 48 hours after angioplasty, but the magnitude of that rise is diminished by periprocedural abciximab. Some of the long-term clinical benefit derived from this agent may be related to an anti-inflammatory effect.

Circulation, 2001;104(4):406-11

Pharmacodynamics and pharmacokinetics of higher-dose, double-bolus eptifibatide in percutaneous coronary intervention.

Gilchrist IC, O'Shea JC, Kosoglou T, Jennings LK, Lorenz TJ, Kitt MM, Kleiman NS, Talley D, Aguirre F, Davidson C, Runyon J, Tchong JE.

**BACKGROUND:** Pharmacodynamics of eptifibatide, a cyclic heptapeptide antagonist of platelet glycoprotein IIb/IIIa, are substantially altered by anticoagulants that chelate calcium, resulting in overestimation *ex vivo* of the *in vivo* effects of this agent. We conducted a dose-ranging study to characterize the pharmacodynamics and pharmacokinetics of eptifibatide under physiological conditions. **METHODS AND RESULTS:** Patients ( $n=39$ ) undergoing elective percutaneous coronary intervention were randomly assigned to an eptifibatide bolus followed by an infusion (180-microgram/kg bolus followed by 2 microgram/kg per minute or 250-microgram/kg bolus followed by 3 microgram/kg per minute) for 18 to 24 hours. In a 2:1 ratio, these patients received either a second bolus of eptifibatide (90 microgram/kg or 125 microgram/kg for the initial 180-

microgram/kg or 250-microgram/kg groups, respectively) or placebo 30 minutes after the initial bolus. Bleeding times, ex vivo platelet aggregation, receptor occupancy, and plasma eptifibatide levels at baseline and at 1, 2, 3, 4, 6, and 8 hours were evaluated. Platelet inhibition was dose dependent and >80% in all groups by steady state. The single-bolus regimens had a transient loss of inhibition at 1 hour, consistent with rapid distribution and drug elimination. Pharmacokinetic modeling suggested that optimal dosing of eptifibatide would be obtained with a 180-microgram/kg bolus and a 2-microgram/kg per minute infusion followed by a second 180-microgram/kg bolus 10 minutes later. CONCLUSIONS: A novel higher-dose, double-bolus regimen of eptifibatide in coronary intervention attains and maintains >90% inhibition of platelet aggregation in >90% of patients, providing the pharmacodynamic construct for the design of the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial of adjunctive eptifibatide in coronary stent implantation

N Engl J Med , 2001;345(7):494-502

Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators.

BACKGROUND: Despite current treatments, patients who have acute coronary syndromes without ST-segment elevation have high rates of major vascular events. We evaluated the efficacy and safety of the antiplatelet agent clopidogrel when given with aspirin in such patients. METHODS: We randomly assigned 12,562 patients who had presented within 24 hours after the onset of symptoms to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) (6259 patients) or placebo (6303 patients) in addition to aspirin for 3 to 12 months. RESULTS: The first primary outcome--a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke--occurred in 9.3 percent of the patients in the clopidogrel group and 11.4 percent of the patients in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95 percent confidence interval, 0.72 to 0.90;  $P<0.001$ ). The second primary outcome--the first primary outcome or refractory ischemia--occurred in 16.5 percent of the patients in the clopidogrel group and 18.8 percent of the patients in the placebo group (relative risk, 0.86; 95 percent confidence interval, 0.79 to 0.94;  $P<0.001$ ). The percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7 percent vs. 2.7 percent; relative risk, 1.38;

P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.2 percent [corrected] vs. 1.8 percent; P=0.13) or hemorrhagic strokes (0.1 percent vs. 0.1 percent). CONCLUSIONS: The antiplatelet agent clopidogrel has beneficial effects in patients with acute coronary syndromes without ST-segment elevation. However, the risk of major bleeding is increased among patients treated with clopidogrel.

Lancet , 2001;358(9281):527-33

Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study.

Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators.

**BACKGROUND:** Despite the use of aspirin, there is still a risk of ischaemic events after percutaneous coronary intervention (PCI). We aimed to find out whether, in addition to aspirin, pretreatment with clopidogrel followed by long-term therapy after PCI is superior to a strategy of no pretreatment and short-term therapy for only 4 weeks after PCI. **METHODS:** 2658 patients with non-ST-elevation acute coronary syndrome undergoing PCI in the CURE study had been randomly assigned double-blind treatment with clopidogrel (n=1313) or placebo (n=1345). Patients were pretreated with aspirin and study drug for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label thienopyridine for about 4 weeks, after which study drug was restarted for a mean of 8 months. The primary endpoint was a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI. The main analysis was by intention to treat. **FINDINGS:** There were no drop-outs. 59 (4.5%) patients in the clopidogrel group had the primary endpoint, compared with 86 (6.4%) in the placebo group (relative risk 0.70 [95% CI 0.50-0.97], p=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, myocardial infarction, or any revascularisation (p=0.03), and of cardiovascular death or myocardial infarction (p=0.047). Overall (including events before and after PCI) there was a 31% reduction cardiovascular death or myocardial infarction (p=0.002). There was less use of glycoprotein IIb/IIIa inhibitor in the clopidogrel group (p=0.001). At follow-up, there was no significant difference in major bleeding between the groups (p=0.64). **INTERPRETATION:** In patients with acute coronary syndrome receiving aspirin, a strategy of clopidogrel

pretreatment followed by long-term therapy is beneficial in reducing major cardiovascular events, compared with placebo.

Circulation, 2001;104(8):870-5

Abciximab readministration: results of the ReoPro Readministration Registry.

Tcheng JE, Kereiakes DJ, Lincoff AM, George BS, Kleiman NS, Sane DC, Cines DB, Jordan RE, Mascelli MA, Langrall MA, Damaraju L, Schantz A, Effron MB, Braden GA.

**BACKGROUND:** Platelet glycoprotein IIb/IIIa blockade with abciximab (ReoPro) improves the clinical outcomes of percutaneous coronary intervention. This registry was conducted to characterize the effects of repeated administration of abciximab during intervention. **METHODS AND RESULTS:** We recruited 500 consecutive patients at 22 centers in the United States who were receiving abciximab for at least a second time during percutaneous coronary intervention. Safety was measured as the incidence of hypersensitivity reactions, major bleeding, and thrombocytopenia. Efficacy was assessed as event-free clinical success. Human antichimeric antibody (HACA) responses were also characterized. There were no cases of hypersensitivity (95% upper confidence bound, 0.3%), major bleeding, or death. Clinical success was 94.4%. Thrombocytopenia occurred in 23 patients (4.6%; 95% CI, 2.8% to 6.4%), including 12 (2.4%; 95% CI, 1.1% to 3.7%) who developed profound thrombocytopenia ( $<20 \times 10^9$  cells/L). In 2 patients (0.4%), profound thrombocytopenia did not develop until after hospital discharge; in 4 (0.8%), profound thrombocytopenia recurred despite platelet transfusion. Before a first readministration, a positive HACA titer was present in 22 of 454 patients (4.8%); after a first readministration, an additional 82 of 432 (19.0%) became HACA-positive. HACA did not neutralize the *in vitro* inhibition of platelet aggregation by abciximab or correlate with clinical events. **CONCLUSIONS:** The results, including overall rates of thrombocytopenia, were consistent with randomized clinical trials of first abciximab treatment. However, there was a shift from mild to profound thrombocytopenia, and cases of delayed presentation and of recurrent thrombocytopenia were seen. These findings suggest that indications and guidelines for first-time use apply to retreatment, particularly the systematic monitoring for thrombocytopenia.

JAMA , 2001;286(10):1187-94

Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: A propensity analysis.

Gum PA, Thamarasan M, Watanabe J, Blackstone EH, Lauer MS.

**CONTEXT:** Although aspirin has been shown to reduce cardiovascular morbidity and short-term mortality following acute myocardial infarction, the association between its use and long-term all-cause mortality has not been well defined. **OBJECTIVES:** To determine whether aspirin is associated with a mortality benefit in stable patients with known or suspected coronary disease and to identify patient characteristics that predict the maximum absolute mortality benefit from aspirin. **DESIGN AND SETTING:** Prospective, nonrandomized, observational cohort study conducted between 1990 and 1998 at an academic medical institution, with a median follow-up of 3.1 years. **PATIENTS:** Of 6174 consecutive adults undergoing stress echocardiography for evaluation of known or suspected coronary disease, 2310 (37%) were taking aspirin. Patients with significant valvular disease or documented contraindication to aspirin use, including peptic ulcer disease, renal insufficiency, and use of nonsteroidal anti-inflammatory drugs, were excluded. **MAIN OUTCOME MEASURE:** All-cause mortality according to aspirin use. **RESULTS:** During 3.1 years of follow-up, 276 patients (4.5%) died. In a simple univariable analysis, there was no association between aspirin use and mortality (4.5% vs 4.5%). However, after adjustment for age, sex, standard cardiovascular risk factors, use of other medications, coronary disease history, ejection fraction, exercise capacity, heart rate recovery, and echocardiographic ischemia, aspirin use was associated with reduced mortality (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.51-0.87;  $P = .002$ ). In further analysis using matching by propensity score, 1351 patients who were taking aspirin were at lower risk for death than 1351 patients not using aspirin (4% vs 8%, respectively; HR, 0.53; 95% CI, 0.38-0.74;  $P = .002$ ). After adjusting for the propensity for using aspirin, as well as other possible confounders and interactions, aspirin use remained associated with a lower risk for death (adjusted HR, 0.56; 95% CI, 0.40-0.78;  $P < .001$ ). The patient characteristics associated with the most aspirin-related reductions in mortality were older age, known coronary artery disease, and impaired exercise capacity. **CONCLUSION:** Aspirin use among patients undergoing stress echocardiography was independently associated with reduced long-term all-cause mortality, particularly among older patients, those with known coronary artery disease, and those with impaired exercise capacity.

Does ticlopidine reduce reocclusion and other adverse events after successful balloon angioplasty of occluded coronary arteries? Results from the Total Occlusion Study of Canada (TOSCA).

Berger PB, Dzavik V, Penn IM, Catellier D, Buller CE.

**OBJECTIVES:** Ticlopidine reduces stent thrombosis and other adverse events among patients receiving coronary stents. Whether ticlopidine is beneficial after balloon angioplasty is unknown. Our purpose was to compare the clinical outcome of patients undergoing balloon angioplasty treated with both aspirin and ticlopidine versus aspirin alone. **METHODS AND RESULTS:** We performed a databank analysis of the Total Occlusion Study of Canada (TOSCA), a randomized trial with angiographic follow-up comparing the frequency of reocclusion after angioplasty of a subtotal or total coronary occlusion in patients receiving  $\geq 1$  heparin-coated Palmaz-Schatz stent versus balloon angioplasty alone. In TOSCA, 102 patients undergoing balloon angioplasty were treated with both aspirin and ticlopidine (generally for 15-30 days) and 94 were treated with aspirin alone, by physician preference. After 6 months, failure to sustain patency (less than Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow on follow-up angiography) occurred in 23% of patients on ticlopidine and aspirin versus 16% of patients on aspirin alone ( $P = .21$ ); the frequency of target vessel revascularization was also similar in the 2 groups (32% vs 25%,  $P = .27$ ). Myocardial infarction was infrequent in both groups (2.0% vs 1.1%, respectively,  $P$  not significant). Patients treated with aspirin and ticlopidine had more adverse angiographic and procedural characteristics, including longer lesions and treatment lengths. Multivariate analysis to adjust for these and other differences failed to reveal a benefit of ticlopidine in maintaining patency and reducing adverse clinical events. **CONCLUSIONS:** After balloon angioplasty of a subtotal or total coronary occlusion, no reduction in adverse events was observed among patients in whom ticlopidine was added to aspirin, even after adjustment for clinical and lesion characteristics

Circulation, 2001;104(19):2311-7

Oral anticoagulation thresholds.

Brummel KE, Paradis SG, Branda RF, Mann KG.

**BACKGROUND:** Monitoring patients on oral anticoagulation is essential to prevent hemorrhage and recurrent thrombosis. We studied tissue factor-induced whole-blood coagulation in patients on warfarin therapy with similar international normalized ratios (INRs). **METHODS AND RESULTS:** Contact pathway-suppressed whole-blood coagulation initiated with tissue factor was studied in 8 male subjects (group W) and in 1 individual multiple times (subject A). Coagulation profiles for group W showed that subjects with similar INRs had widely varying clot times (6.2 to 23 minutes) and thrombin-antithrombin III (TAT) profiles with rates of 25 to 40 nmol. L(-1). min(-1) and maximum levels varying from 192 to 349 nmol/L. The normal control group exhibited clot times of 5.7+/-0.3 minutes and TAT rates of 57+/-13 nmol. L(-1). min(-1), reaching maximum levels of 742+/-91 nmol/L. Subject A, who was stably anticoagulated at an INR of 2.1+/-0.4 for 6 months, had widely ranging profiles with clot times of 9.0 to 22.7 minutes, TAT maximums varying from 141 to 345 nmol/L, and TAT formation rates of 10 to 57 nmol. L(-1). min(-1). INR did not correlate with TAT formation. Platelet activation was decreased by anticoagulants but also displayed variability. Fibrinopeptide A generation showed threshold variability independent of the INR. Factor VIII levels were increased (P=0.03) in group W (204+/-34.4%) compared with normal control subjects (149.4+/-37.4%). A significant correlation was identified between increasing factor VIII levels and years on warfarin therapy (r=0.78, P=0.01), suggesting a possible factor VIII compensatory mechanism. **CONCLUSIONS:** These results suggest that control of anticoagulation in patients to a set INR therapeutic range may be less secure than anticipated. Patients with similar INRs show significant individual variability in their tissue factor coagulation response, suggesting different risks to anticoagulation when confronted with underlying vascular anomalies.

J Am Coll Cardiol, 2001;38(6):1608-13

A randomized, placebo-controlled trial of enoxaparin after high-risk coronary stenting: the ATLAST trial.

Batchelor WB, Mahaffey KW, Berger PB, Deutsch E, Meier S, Hasselblad V, Fry ET, Teirstein PS, Ross AM, Binanay CA, Zidar JP; The ATLAST Trial Investigators.

**OBJECTIVES:** We performed a multicenter, double-blind placebo-controlled trial to examine the efficacy and safety of enoxaparin in patients at high risk for stent thrombosis (ST). **BACKGROUND:** The optimal antithrombotic regimen for such patients is unknown. **METHODS:** We randomized 1,102 patients with clinical, angiographic or ultrasonographic features associated with an increased risk of ST to receive either twice-daily

injections of weight-adjusted enoxaparin or placebo for 14 days after stenting. All patients received aspirin and ticlopidine. The primary end point was a 30-day composite end point of death, myocardial infarction (MI) or urgent revascularization. RESULTS: The target enrollment for the study was 2,000 patients. However, the trial was terminated prematurely at 1,102 patients after interim analysis revealed an unexpectedly low event rate. The primary outcome occurred in 1.8% enoxaparin-treated patients versus 2.7% treated with placebo (odds ratio [OR] 0.66; 95% confidence interval [CI] 0.29 to 1.5,  $p = 0.30$ ); for death or MI the rates were 0.9% vs. 2.2%, respectively (OR 0.41, 95% CI 0.14 to 1.2,  $p = 0.13$ ); and for MI, 0.4% vs. 1.6%, respectively (OR 0.22, 95% CI 0.05 to 0.99,  $p = 0.04$ ). The groups had comparable rates of major bleeding (3.3% for enoxaparin, 1.6% for placebo,  $p = 0.08$ ), but minor nuisance bleeding was increased with enoxaparin (25% vs. 5.1%,  $p < 0.001$ ). CONCLUSIONS: The clinical outcomes of patients at increased risk of ST are more favorable than previously reported, rendering routine oral antiplatelet therapy adequate for most. However, given its relative safety and potential to reduce the risk of subsequent infarction, a 14-day course of enoxaparin may be considered for carefully selected patients.

Lancet, 2001;358(9296):1855-63

Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial.

White H; The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators.

BACKGROUND: The combination of fibrinolytic therapy and heparin for acute myocardial infarction fails to achieve reperfusion in 40-70% of patients, and early reocclusion occurs in a substantial number. We did a randomised, open-label trial to compare the thrombin-specific anticoagulant, bivalirudin, with heparin in patients undergoing fibrinolysis with streptokinase for acute myocardial infarction. METHODS: 17073 patients with acute ST-elevation myocardial infarction were randomly assigned an intravenous bolus and 48-h infusion of either bivalirudin ( $n=8516$ ) or heparin ( $n=8557$ ), together with a standard 1.5 million unit dose of streptokinase given directly after the antithrombotic bolus. The primary endpoint was 30-day mortality. Secondary endpoints included reinfarction within 96 h and bleeding. Strokes and reinfarctions were adjudicated by independent committees who were unaware of treatment allocation. Analysis was by intention to treat. FINDINGS: By 30 days, 919 patients (10.8%) in the bivalirudin group and 931 (10.9%) in the heparin group had died (odds ratio 0.99 [95% CI 0.90-1.09],  $p=0.85$ ). The mortality rates adjusted for baseline risk factors

were 10.5% for bivalirudin and 10.9% for heparin (0.96 [0.86-1.07],  $p=0.46$ ). There were significantly fewer reinfarctions within 96 h in the bivalirudin group than in the heparin group (0.70 [0.56-0.87],  $p=0.001$ ). Severe bleeding occurred in 58 patients (0.7%) in the bivalirudin group versus 40 patients (0.5%) in the heparin group ( $p=0.07$ ), and intracerebral bleeding occurred in 47 (0.6%) versus 32 (0.4%), respectively ( $p=0.09$ ). The rates of moderate and mild bleeding were significantly higher in the bivalirudin group than the heparin group (1.32 [1.00-1.74],  $p=0.05$ ; and 1.47 [1.34-1.62],  $p<0.0001$ ; respectively). Transfusions were given to 118 patients (1.4%) in the bivalirudin group versus 95 patients (1.1%) in the heparin group (1.25 [0.95-1.64],  $p=0.11$ ). INTERPRETATION: Bivalirudin did not reduce mortality compared with unfractionated heparin, but did reduce the rate of adjudicated reinfarction within 96 h by 30%. Small absolute increases were seen in mild and moderate bleeding in patients given bivalirudin. Bivalirudin is a new anticoagulant treatment option in patients with acute myocardial infarction treated with streptokinase.

BMJ 2002

Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.

OBJECTIVE: To determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events. DESIGN: Collaborative meta-analyses (systematic overviews). INCLUSION CRITERIA: Randomised trials of an antiplatelet regimen versus control or of one antiplatelet regimen versus another in high risk patients (with acute or previous vascular disease or some other predisposing condition) from which results were available before September 1997. Trials had to use a method of randomisation that precluded prior knowledge of the next treatment to be allocated and comparisons had to be unconfounded—that is, have study groups that differed only in terms of antiplatelet regimen. STUDIES REVIEWED: 287 studies involving 135 000 patients in comparisons of antiplatelet therapy versus control and 77 000 in comparisons of different antiplatelet regimens. MAIN OUTCOME MEASURE: “Serious vascular event”: non-fatal myocardial infarction, non-fatal stroke, or vascular death. RESULTS: Overall, among these high risk patients, allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal myocardial infarction was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth (with no apparent adverse effect on other deaths). Absolute reductions in the risk of having a serious vascular event were 36 (SE 5) per 1000 treated for two years among patients with previous myocardial infarction; 38 (5) per 1000 patients treated for one month among patients with acute myocardial infarction; 36

(6) per 1000 treated for two years among those with previous stroke or transient ischaemic attack; 9 (3) per 1000 treated for three weeks among those with acute stroke; and 22 (3) per 1000 treated for two years among other high risk patients (with separately significant results for those with stable angina (P=0.0005), peripheral arterial disease (P=0.004), and atrial fibrillation (P=0.01)). In each of these high risk categories, the absolute benefits substantially outweighed the absolute risks of major extracranial bleeding. Aspirin was the most widely studied antiplatelet drug, with doses of 75-150 mg daily at least as effective as higher daily doses. The effects of doses lower than 75 mg daily were less certain. Clopidogrel reduced serious vascular events by 10% (4%) compared with aspirin, which was similar to the 12% (7%) reduction observed with its analogue ticlopidine. Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Among patients at high risk of immediate coronary occlusion, short term addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin prevented a further 20 (4) vascular events per 1000 (P<0.0001) but caused 23 major (but rarely fatal) extracranial bleeds per 1000. CONCLUSIONS: Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischaemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation. Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed. Am J Cardiol , 2002;89(2):132-6

Long-term mortality benefit with the combination of stents and abciximab for cardiogenic shock complicating acute myocardial infarction.

Chan AW, Chew DP, Bhatt DL, Moliterno DJ, Topol EJ, Ellis SG.

Cardiogenic shock secondary to ischemic heart disease is associated with a high mortality rate, and recent trials have established the benefit of an early invasive approach. However, the role of adjunctive and stenting for cardiogenic shock has not been established. We prospectively examined collected data from 96 consecutive patients who underwent emergent percutaneous coronary intervention for cardiogenic shock over the past 7 years. Patients were classified as receiving stent plus abciximab, stent alone, percutaneous transluminal coronary angioplasty (PTCA) plus abciximab, or PTCA alone. Baseline characteristics of the 4 groups were similar. During 2.5 years of follow-up, the mortality rates for stent plus abciximab, stent only, PTCA plus abciximab, and PTCA alone were 33%, 43%, 61%, and 68%, respectively (log-rank p = 0.028). Achievement of postprocedural Thrombolysis In Myocardial Infarction 3 flow was higher with stent plus abciximab than with

the other interventions (85% vs 65%,  $p = 0.048$ ). By multivariate analysis, absence of stent use (hazard ratio 2.58, 95% confidence interval 1.36 to 4.90,  $p = 0.004$ ) and left ventricular ejection function  $\leq 30\%$  (hazard ratio 3.89, 95% confidence interval 1.53 to 9.87,  $p = 0.004$ ) were independent predictors for mortality during 2.5 years of follow-up. In conclusion, treatment with the combination of stent and abciximab resulted in higher procedural Thrombolysis In Myocardial Infarction 3 flow rates and a long-term mortality benefit in patients with cardiogenic shock complicating acute myocardial infarction.

J Am Coll Cardiol , 2002 ;39(1):9-14

Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting.

Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, Dangas G, Taniuchi M, Lasala JM, Holmes DR, Ellis SG, Topol EJ.

**OBJECTIVES:** We sought to determine whether clopidogrel is at least as efficacious as ticlopidine. **BACKGROUND:** Several trials have supported the enhanced safety and tolerability of clopidogrel compared with ticlopidine after coronary stent deployment. However, none of these individual trials were powered to detect possible differences in the efficacy for reducing ischemic end points. **METHODS:** Published data from trials and registries that compared clopidogrel with ticlopidine in patients receiving coronary stents were pooled, and a formal meta-analysis was performed. The rate of 30-day major adverse cardiac events (MACE), as defined in each trial, was used as the primary end point. **RESULTS:** There were a total of 13,955 patients. The pooled rate of major adverse cardiac events was 2.10% in the clopidogrel group and 4.04% in the ticlopidine group. After adjustment for heterogeneity in the trials, the odds ratio (OR) of having an ischemic event with clopidogrel, as compared with ticlopidine, was 0.72 (95% confidence interval [CI] 0.59 to 0.89,  $p = 0.002$ ). Mortality was also lower in the clopidogrel group compared with the ticlopidine group-0.48% versus 1.09% (OR 0.55, 95% CI 0.37 to 0.82;  $p = 0.003$ ). **CONCLUSIONS:** Based on all available evidence from randomized clinical trials or registries, clopidogrel, in addition to better tolerability and fewer side effects, is at least as efficacious as ticlopidine in reducing MACE. This finding may be due to the more rapid onset of an antiplatelet effect seen with the loading dose of clopidogrel, which was used in most of these studies, or to better patient compliance with clopidogrel therapy. Therefore, clopidogrel plus aspirin should replace ticlopidine plus aspirin as the standard antiplatelet regimen after stent deployment.

Lancet , 2002 Jan ;359(9302):189-98

Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials.

Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML.

**BACKGROUND:** Platelet glycoprotein IIb/IIIa inhibitors have been shown to reduce cardiac complications in patients undergoing percutaneous coronary intervention. The clinical efficacy of these drugs in acute coronary syndromes, however, is still unclear. We did a meta-analysis of all large randomised trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularisation. **METHODS:** Inclusion criteria were: randomisation of patients with acute coronary syndromes but without persistent ST elevation; comparison of a glycoprotein IIb/IIIa inhibitor with placebo or control therapy; non-recommendation of early coronary revascularisation during study-drug infusion; and enrollment of at least 1000 patients. Data on individual patients were obtained from all participants in these trials. **FINDINGS:** Six trials, enrolling 31402 patients, fulfilled the inclusion criteria. 30 days after randomisation, 3530 (11.2%) patients died or developed a myocardial infarction. At 30 days, a 9% reduction in the odds of death or myocardial infarction was seen with glycoprotein IIb/IIIa inhibitors compared with placebo or control (10.8% [1980/18297] vs 11.8% [1550/13105] events; odds ratio 0.91 [95% CI 0.84-0.98];  $p=0.015$ ). The relative treatment benefit was similar in subgroups of patients according to important clinical baseline characteristics; hence, the absolute treatment benefit was largest in high-risk patients. An unexpected and significant interaction was seen between sex and allocated treatment, with a treatment benefit in men (0.81 [0.75-0.89] but not in women (1.15 [1.01-1.30])). However, once patients were stratified according to troponin concentration, there was no evidence of a sex difference in treatment response, and a risk reduction was seen in men and women with raised troponin concentrations. Major bleeding complications were increased by glycoprotein IIb/IIIa inhibitors (2.4% [445/18297] vs 1.4% [180/13105];  $p<0.0001$ ), but intracranial bleeding was not (16 [0.09%] vs 8 [0.06%];  $p=0.40$ ). **INTERPRETATION:** Glycoprotein IIb/IIIa inhibitors reduce the occurrence of death or myocardial infarction in patients with acute coronary syndromes not routinely scheduled for early revascularisation. The event reduction is greatest in patients at high risk of thrombotic complications. Treatment with a glycoprotein IIb/IIIa inhibitor might therefore be considered especially in such patients early after admission, and continued until a decision about

early coronary revascularisation has been made.

Am Heart J , 2002;143(2):229-34

Bivalirudin as a replacement for unfractionated heparin in unstable angina/non-ST-elevation myocardial infarction: observations from the TIMI 8 trial. *The Thrombolysis in Myocardial Infarction*.

Antman EM, McCabe CH, Braunwald E.

**BACKGROUND:** The Thrombolysis in Myocardial Infarction (TIMI) 8 trial was undertaken to compare the efficacy and safety of bivalirudin versus unfractionated heparin in a double-blind phase III trial of patients with unstable angina/non-ST-elevation myocardial infarction (MI). **METHODS:** All patients received aspirin and were randomized either to unfractionated heparin (bolus of 70 U/kg followed by an infusion of 15 U/kg/h) or bivalirudin (bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/h) for a minimum of 72 hours. The primary efficacy end point was a composite of all cause mortality or nonfatal recurrent MI. **RESULTS:** A total of 133 of the planned 5320 patients were enrolled, at which point the study was terminated by the sponsor because of a decision at the time to suspend further development of bivalirudin. Through 14 days, the incidence of death or nonfatal MI was 9.2% in the 65 patients in the unfractionated heparin group and was 2.9% in the 68 patients in the bivalirudin group, odds ratio (95% CI) 0.30 (0.06-1.53). Major hemorrhage occurred in 3 patients in the unfractionated heparin group (4.6%) but in none of the patients in the bivalirudin group (P =.11). **CONCLUSIONS:** The trend toward a lower rate of death or nonfatal MI in the bivalirudin group is consistent with a therapeutic effect of the drug and is consistent with other trials of bivalirudin in patients with acute coronary syndromes. The potential for clinically meaningful antithrombotic activity without an increased risk of bleeding and availability of an alternative anticoagulation strategy in patients who cannot tolerate unfractionated heparin are particularly attractive and underscore the need for further evaluation of bivalirudin.

Am Heart J , 2002 ;143(2):334-41

Abciximab improves 6-month clinical outcome after rescue coronary angioplasty.

Petronio AS, Musumeci G, Limbruno U, De Carlo M, Baglini R, Paterni G, Grazia Delle Donne M, Caravelli P, Nardi C, Mariani M.

**BACKGROUND:** Few data are available concerning the effects on clinical outcome and left ventricular function of abciximab administration in patients undergoing rescue percutaneous transluminal coronary angioplasty (PTCA) after failed thrombolysis for acute myocardial infarction. The aim of the study was to investigate such effects. **METHODS:** Eighty-nine consecutive patients referred to our laboratory from other hospitals for rescue PTCA within 24 hours from the onset of chest pain were prospectively randomized before the procedure to abciximab treatment (44 patients) or placebo (45 patients). No significant differences in baseline characteristics were observed between the 2 groups. Study end points were the occurrence of major adverse cardiac events (MACE) such as death, reinfarction, congestive heart failure, target lesion revascularization, or recurrent ischemia at 30-day and 6-month follow-up and the occurrence of periprocedural bleeding. **RESULTS:** Mean time from symptom onset to reperfusion was 8.5 +/-5.4 hours; rescue PTCA was successful in 96% of patients. The incidence of major, moderate, and minor bleeding was similar in the 2 groups. At 30-day follow-up, the echocardiographic left ventricular wall motion score index showed a significantly higher improvement in the abciximab group versus the placebo group ( $P < .001$ ). At 6-month follow-up, the incidence of MACE was 11% in the abciximab group versus 38% in the placebo group ( $P = .004$ ). Abciximab administration ( $P = .003$ ) and cardiogenic shock ( $P = .005$ ) were the only independent predictors of the occurrence of MACE at multivariable analysis. **CONCLUSION:** Treatment with abciximab during rescue PTCA positively affects clinical outcome at 6-month follow-up without increasing periprocedural bleeding.

Catheter Cardiovasc Interv, 2002 ;55(3):315-20

Heparin and coumadin versus acetylsalicylic acid for prevention of restenosis after coronary angioplasty.

Garachemani AR, Fleisch M, Windecker S, Pfiffner D, Meier B.

The purpose of the present study was to determine whether postprocedural antithrombotic therapy with prolonged heparin infusion followed by 6 months of oral anticoagulation in addition to acetylsalicylic acid (ASA) reduces the incidence of angiographic restenosis after successful PTCA. One hundred ninety-one patients with

uncomplicated PTCA were randomized into two groups: one group was discharged with ASA 100 mg only (G1) and the other group was additionally treated with 12--24 hr of heparin infusion and overlapping oral anticoagulation with coumadin for 6 months (G2). The two groups were comparable with respect to age, gender, coronary risk profile, clinical presentation, and angiographic lesion characteristics. Stents were implanted in 33% and 36% of the G1 and G2 patients, respectively. In-hospital myocardial infarction occurred in 4% of the G1 and 3% of the G2 patients. One patient in G1 died of subacute stent thrombosis (day 3). Six-month angiographic follow-up was obtained in 90% of G1 patients and 94% of G2 patients. Restenosis occurred in 30% and 33% of the patients and mean diameter stenoses at follow-up were 40% plus minus 28% and 39% plus minus 24%, respectively. Thrombin inhibition with heparin infusion followed by 6 months of oral anticoagulation did not reduce angiographic restenosis among patients undergoing PTCA with or without stent implantation. The occurrence of acute ischemic complications was also comparable in the two groups. *Cathet Cardiovasc Intervent* 2002;55:315--320.

*N Engl J Med*, 1994;330:956-61

Use of a Monoclonal Antibody Directed against the Platelet Glycoprotein IIb/IIIa Receptor in High-Risk Coronary Angioplasty

The EPIC Investigators

**Background.** Platelets are believed to play a part in the ischemic complications of coronary angioplasty, such as abrupt closure of the coronary vessel during or soon after the procedure. Accordingly, we evaluated the effect of a chimeric monoclonal-antibody Fab fragment (c7E3 Fab) directed against the platelet glycoprotein IIb/IIIa receptor, in patients undergoing angioplasty who were at high risk for ischemic complications. This receptor is the final common pathway for platelet aggregation.

**Methods.** In a prospective, randomized, double-blind trial, 2099 patients treated at 56 centers received a bolus and an infusion of placebo, a bolus of c7E3 Fab and an infusion of placebo, or a bolus and an infusion of c7E3 Fab. They were scheduled to undergo coronary angioplasty or atherectomy in high-risk clinical situations involving severe unstable angina, evolving acute myocardial infarction, or high-risk coronary morphologic characteristics. The primary study end point consisted of any of the following: death, nonfatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, unplanned implantation of a coronary stent, or insertion of an intraaortic balloon pump for refractory ischemia. The

numbers of end-point events were tabulated for 30 days after randomization.

**Results.** As compared with placebo, the c7E3 Fab bolus and infusion resulted in a 35 percent reduction in the rate of the primary end point (12.8 vs. 8.3 percent,  $P = 0.008$ ), whereas a 10 percent reduction was observed with the c7E3 Fab bolus alone (12.8 vs. 11.5 percent,  $P = 0.43$ ). The reduction in the number of events with the c7E3 Fab bolus and infusion was consistent across the end points of unplanned revascularization procedures and nonfatal myocardial infarction. Bleeding episodes and transfusions were more frequent in the group given the c7E3 Fab bolus and infusion than in the other two groups.

**Conclusions.** Ischemic complications of coronary angioplasty and atherectomy were reduced with a monoclonal antibody directed against the platelet IIb/IIIa glycoprotein receptor, although the risk of bleeding was increased.

N Engl J Med , 1997;337:1124-30

## A Comparison of Continuous Infusion of Alteplase with Double-Bolus Administration for Acute Myocardial Infarction

The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators

**Background.** Accelerated infusion of alteplase (tissue plasminogen activator) over a period of 90 minutes induces more rapid lysis of coronary-artery thrombi than a 3-hour infusion. With two bolus doses of alteplase, further shortening the duration of administration, complete reperfusion was achieved in more than 85 percent of the patients in initial angiographic studies. We tested the hypothesis that double-bolus alteplase is at least as effective as accelerated infusion.

**Methods.** In 398 hospitals, 7169 patients with acute myocardial infarction were randomly assigned to weight-adjusted, accelerated infusion of 100 mg of alteplase or to a bolus of 50 mg of alteplase over a period of 1 to 3 minutes followed 30 minutes later by a second bolus of 50 mg (or 40 mg for patients who weighed less than 60 kg). The primary end point was death from any cause at 30 days. The trial was stopped prematurely because of concern about the safety of the double-bolus injection.

**Results.** Thirty-day mortality was higher in the double-bolus group than in the accelerated-infusion group: 7.98 percent as compared with 7.53 percent. The absolute difference was 0.44 percent, with a one-sided 95 percent upper boundary of 1.49 percent, which exceeded the prespecified upper limit of 0.40 percent to indicate equivalence in 30-day mortality between the two regimens. The respective rates of any stroke and of

hemorrhagic stroke were 1.92 and 1.12 percent after double-bolus alteplase, as compared with 1.53 and 0.81 percent after an accelerated infusion of alteplase ( $P = 0.24$  and  $P = 0.23$ , respectively).

**Conclusions.** Double-bolus alteplase was not shown to be equivalent, according to the prespecified criteria, to accelerated infusion with regard to 30-day mortality. There was also a slightly higher rate of intracranial hemorrhage with the double-bolus method. Therefore, accelerated infusion of alteplase over a period of 90 minutes remains the preferred regimen.

Journal of the American College of Cardiology, 30:1729-1734

“Rescue” Utilization of Abciximab for the Dissolution of Coronary Thrombus Developing as a Complication of Coronary Angioplasty

Joseph B. Muhlestein, MD, FACC, Labros A. Karagounis, MD, FACC, Sanjeev Treehan, MD, Jeffrey L. Anderson, MD, FACC

**Objectives.** This study sought to test the effect on thrombus score of the “rescue” utilization of the glycoprotein IIb/IIIa antagonist abciximab given to patients in whom intracoronary thrombus has developed as a complication after percutaneous transluminal coronary angioplasty (PTCA) and to determine its clinical utility.

**Background.** Abciximab is effective in the prevention of acute ischemic complications when given prophylactically to patients during high risk PTCA. However, its ability to therapeutically dissolve newly formed intracoronary thrombus occurring as a complication after PTCA is not known.

**Methods.** We performed an observational study in 29 consecutive patients who received abciximab (0.25 mg/kg body weight intravenous bolus, followed by a 12-h infusion at 10 g/min) after attempted PTCA caused either the new development or further progression of thrombus. Angiograms were analyzed to determine thrombus score and Thrombolysis in Myocardial Infarction (TIMI) flow grade before and after abciximab. Procedural and clinical success and long-term outcome were also determined.

**Results.** Thrombus score decreased from  $3.0 \pm 0.9$  (mean  $\pm$  SD) to  $0.86 \pm 0.92$  ( $p < 0.001$ ), and TIMI flow grade increased from  $2.5 \pm 0.7$  to  $2.9 \pm 0.3$  ( $p = 0.008$ ). No instances of distal embolization or no-reflow were noted. The procedural success ( $\geq 50\%$  residual stenosis) rate was 97%. The clinical success (procedural success with no in-hospital myocardial infarction, bypass surgery or death) rate was 93%.

**Conclusions.** Dissolution of thrombus and restoration of TIMI grade 3 flow were readily achieved after administration of abciximab when delivered in a “rescue” manner after the development of thrombosis after

PTCA. This novel use of abciximab will need to be validated in randomized trials.

Circulation, 1997 ;96: 1445-1453

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

**Background.** Adverse cardiovascular events associated with thrombotic occlusion occur in 4% to 12.8% of patients after coronary angioplasty. Recently, potent antiplatelet agents have been used to reduce those thrombotic complications. Tirofiban is a highly selective, short-acting inhibitor of fibrinogen binding to platelet glycoprotein (GP) IIb/IIIa that inhibits ex vivo platelet aggregation in response to a variety of agonists. **Methods and Results.** The RESTORE trial (Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis) was a randomized, double-blind, placebo-controlled trial of tirofiban in patients undergoing coronary interventions (balloon angioplasty or directional atherectomy) within 72 hours of presentation with an acute coronary syndrome (unstable angina pectoris or acute myocardial infarction). The end points of the study were death from any cause, myocardial infarction, coronary bypass surgery due to angioplasty failure or recurrent ischemia, repeat target-vessel angioplasty for recurrent ischemia, and insertion of a stent due to actual or threatened abrupt closure of the dilated artery, and the primary end point was a composite representing the occurrence of any of these events. The prespecified primary hypothesis of the study was that tirofiban, administered as a bolus of 10  $\mu\text{g}/\text{kg}$  over a 3-minute period and followed by a 36-hour infusion of 0.15  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , would result in a reduction in the 30-day composite end point compared with placebo. Patients (n=2139) who were already receiving treatment with aspirin and heparin were randomized to receive tirofiban or placebo. The primary composite end point at 30 days was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group, a 16% relative reduction (P=.160). However, 2 days after angioplasty, the tirofiban group had a 38% relative reduction in the composite end point (P $\leq$ 0.05), and at 7 days there was a 27% relative reduction (P=.022), largely because of a reduction in nonfatal myocardial infarction and the need for repeat angioplasty. When repeat angioplasty or coronary artery bypass surgery procedures were included in the composite only if performed on an urgent or emergency basis, the composite 30-day event rates were 10.5% for the placebo group and 8.0% for the tirofiban group, a relative reduction of 24% (P=.052). Major bleeding, including transfusion, was not significantly different between the two groups (3.7% in the placebo group and

5.3% in the tirofiban group;  $P=.096$ ). When the Thrombolysis In Myocardial Infarction (TIMI) criteria for major bleeding were used, the incidence was 2.1% in the placebo group compared with 2.4% in the tirofiban group ( $P=.662$ ). Thrombocytopenia was similar in the placebo and tirofiban groups (0.9% for the placebo group versus 1.1% for the tirofiban group;  $P=.709$ ).

**Conclusions.** In patients undergoing coronary angioplasty for acute coronary syndromes, tirofiban protects against early adverse cardiac events related to thrombotic closure. At 30 days, however, the reduction in adverse cardiac events was no longer statistically significant. The bleeding observed with tirofiban was not statistically different from that observed with placebo.

Journal of the American College of Cardiology, 1997;30:5:1264-1269

#### Bivalirudin Compared With Heparin During Coronary Angioplasty for Thrombus-Containing Lesions

Pinak B. Shah, MD, Waqar H. Ahmed, MD, FACC, Peter Ganz, MD, FACC, John A. Bittl, MD, FACC

**Objectives.** We investigated whether bivalirudin is more effective than heparin in preventing ischemic complications in high risk patients undergoing coronary angioplasty for thrombus-containing lesions detected by angiography.

**Background.** Heparin is administered during coronary angioplasty to prevent closure of the dilated vessel. Bivalirudin (Hirulog) is a direct thrombin inhibitor that can be safely substituted for heparin during angioplasty. Bivalirudin has several theoretic advantages over heparin as an anticoagulant agent.

**Methods.** We performed an observational analysis of the Hirulog Angioplasty Study in which 4,098 patients with unstable or postinfarction angina were randomized to receive either bivalirudin or heparin during coronary angioplasty. The study group for this analysis consisted of 567 patients who had thrombus-containing lesions on angiography. The primary end point was death, myocardial infarction, emergency coronary artery bypass graft surgery or abrupt vessel closure before hospital discharge.

**Results.** Patients with thrombus-containing lesions had a higher incidence of myocardial infarction (5.1% vs. 3.2%,  $p = 0.03$ ) and abrupt vessel closure (13.6% vs. 8.3%,  $p < 0.001$ ) than those without thrombus. In patients with thrombus-containing lesions, however, the incidence of the primary end point was not different between the bivalirudin and heparin treatment groups. Furthermore, no difference in the incidence of ischemic events at 6 months was seen between the treatment groups.

**Conclusions.** Bivalirudin is not more effective than heparin in preventing ischemic complications in patients

undergoing coronary angioplasty for thrombus-containing lesions detected by angiography. Other approaches, perhaps involving potent antiplatelet agents, should be considered for patients with thrombus-containing lesions.

N Engl J Med , 1997;337:1118-23

### A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators

**Background.** Reteplase (recombinant plasminogen activator), a mutant of alteplase tissue plasminogen activator, has a longer half-life than its parent molecule and produced superior angiographic results in pilot studies of acute myocardial infarction. In this large clinical trial, we compared the efficacy and safety of these two thrombolytic agents.

**Methods.** A total of 15,059 patients from 807 hospitals in 20 countries who presented within 6 hours after the onset of symptoms with ST-segment elevation or bundle-branch block were randomly assigned in a 2:1 ratio to receive reteplase, in two bolus doses of 10 MU each given 30 minutes apart, or an accelerated infusion of alteplase, up to 100 mg infused over a period of 90 minutes. The primary hypothesis was that mortality at 30 days would be significantly lower with reteplase.

**Results.** The mortality rate at 30 days was 7.47 percent for reteplase and 7.24 percent for alteplase (adjusted  $P = 0.54$ ; odds ratio, 1.03; 95 percent confidence interval, 0.91 to 1.18). The 95 percent confidence interval for the absolute difference in mortality rates was -1.1 to 0.66 percent. Stroke occurred in 1.64 percent of patients treated with reteplase and in 1.79 percent of those treated with alteplase ( $P = 0.50$ ). The respective rates of the combined end point of death or nonfatal, disabling stroke were 7.89 percent and 7.91 percent ( $P = 0.97$ ; odds ratio, 1.0; 95 percent confidence interval, 0.88 to 1.13). **Conclusions.** As compared with an accelerated infusion of alteplase, reteplase, although easier to administer, did not provide any additional survival benefit in the treatment of acute myocardial infarction. Other results, particularly for the combined end point of death or nonfatal, disabling stroke, were remarkably similar for the two plasminogen activators.

N Engl J Med, 1997;336:1689-96

Platelet Glycoprotein IIb/IIIa Receptor Blockade and Low-Dose Heparin during Percutaneous Coronary Revascularization

## The EPILOG Investigators

**Background.** Blockade of the platelet glycoprotein IIb/IIIa receptor with abciximab (a monoclonal-antibody Fab fragment directed against the receptor) has been shown to diminish ischemic complications among patients undergoing high-risk coronary angioplasty or atherectomy but increases bleeding complications. The widespread applicability of this treatment is unknown, particularly in view of the observed risk of hemorrhage. **Methods.** In a prospective, double-blind trial, we randomly assigned patients undergoing urgent or elective percutaneous coronary revascularization at 69 centers to receive abciximab with standard-dose, weight-adjusted heparin (initial bolus of 100 U per kilogram of body weight); abciximab with low-dose, weight-adjusted heparin (initial bolus of 70 U per kilogram); or placebo with standard-dose, weight-adjusted heparin. The primary efficacy end point was death from any cause, myocardial infarction, or urgent revascularization within 30 days of randomization.

**Results.** The trial was terminated at the first interim analysis, with 2792 of the planned 4800 patients enrolled. At 30 days, the composite event rate was 11.7 percent in the group assigned to placebo with standard-dose heparin; 5.2 percent in the group assigned to abciximab with low-dose heparin (hazard ratio, 0.43; 95 percent confidence interval, 0.30 to 0.60;  $P<0.001$ ); and 5.4 percent in the group assigned to abciximab with standard-dose heparin (hazard ratio, 0.45; 95 percent confidence interval, 0.32 to 0.63;  $P<0.001$ ). There were no significant differences among the groups in the risk of major bleeding, although minor bleeding was more frequent among patients receiving abciximab with standard-dose heparin.

**Conclusions.** Inhibition of the platelet glycoprotein IIb/IIIa receptor with abciximab, together with low-dose, weight-adjusted heparin, markedly reduces the risk of acute ischemic complications in patients undergoing percutaneous coronary revascularization, without increasing the risk of hemorrhage

Journal of the American College of Cardiology, 30:149-156

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

A. Michael Lincoff, MD, FACC, Robert M. Califf, MD, FACC, Keaven M. Anderson, PhD, Harlan F. Weisman, MD, FACC, Frank V. Aguirre, MD, FACC, Neal S. Kleiman, MD, FACC, Robert A. Harrington, MD, FACC, Eric

J. Topol, MD, FACC for the EPIC Investigators

#### Objectives.

We sought to evaluate whether patients with unstable angina undergoing coronary intervention derive particular clinical benefit from potent platelet inhibition.

**Background.** Plaque rupture and platelet aggregation are pathogenetic processes common to unstable angina and ischemic complications of percutaneous coronary intervention.

#### Methods.

Of the 2,099 patients undergoing a coronary intervention in the Evaluation of 7E3 in Preventing Ischemic Complications (EPIC) trial, 489 were enrolled with the diagnosis of unstable angina and randomized to receive placebo, an abciximab (c7E3) bolus immediately before the intervention or an abciximab bolus followed by a 12-h infusion. The primary end point was a composite of death, myocardial infarction (MI) or urgent repeat revascularization within 30 days of randomization. The occurrence of death, MI or any revascularization within 6 months was also assessed.

#### Results.

Compared with placebo, the bolus and infusion of abciximab resulted in a 62% reduction in the rate of the primary end point (12.8% vs. 4.8%,  $p = 0.012$ ) among patients with unstable angina, due primarily to a reduction in the incidences of death (3.2% vs. 1.2%,  $p = 0.164$ ) and MI (9% vs. 1.8%,  $p = 0.004$ ). By 6 months, cumulative death and MI were further reduced by abciximab (6.6% vs. 1.8%,  $p = 0.018$  and 11.1% vs. 2.4%,  $p = 0.002$ , respectively). The magnitude of the risk reduction with abciximab was greater among the patients with unstable angina than among other patients in the EPIC trial without unstable angina for the end points of death (interaction:  $p = 0.008$  at 30 days,  $p = 0.002$  at 6 months) and MI (interaction:  $p = 0.004$  at 30 days,  $p = 0.003$  at 6 months).

#### Conclusions.

The syndrome of unstable angina identifies patients who will experience particularly marked reductions in the risk of death and MI with abciximab during coronary intervention.

Circulation ,1997 ;96: 3396-3402

Effect of Nadroparin, a Low-Molecular-Weight Heparin, on Clinical and Angiographic Restenosis After Coronary Balloon Angioplasty : The FACT Study

Jean-Marc Lablanche, Eugene P. McFadden, Nicolas Meneveau, Jean Rene Lusson, Bernard Bertrand, Jean-Philippe Metzger, Victor Legrand, Gilles Grollier, Carlos Macaya, Bernard de Bruyne, Alec Vahanian, Alain Grentzinger, Christiane Masquet, Jean-Eric Wolf, Gerard Tobelem, Sylvie Fontecave, Andre Vacheron, Pascal d'Azemar, and Michel E. Bertrand

**Background** Experimental studies suggest that the antiproliferative effect of heparin after arterial injury is maximized by pretreatment. No previous studies of restenosis have used a pretreatment strategy. We designed this study to determine whether treatment with nadroparin, a low-molecular-weight heparin, started 3 days before the procedure and continued for 3 months, affected angiographic restenosis or clinical outcome after coronary angioplasty.

**Methods and Results** In a prospective multicenter, double-blind, randomized trial, elective coronary angioplasty was performed on 354 patients who were treated with daily subcutaneous nadroparin (0.6 mL of 10 250 anti-Xa IU/mL) or placebo injections started 3 days before angioplasty and continued for 3 months. Angiography was performed just before and immediately after angioplasty and at follow-up. The primary study end point was angiographic restenosis, assessed by quantitative coronary angiography 3 months after balloon angioplasty. Clinical follow-up was continued up to 6 months. Clinical and procedural variables and the occurrence of periprocedural complications did not differ between groups. At angiographic follow-up, the mean minimal lumen diameter and the mean residual stenosis in the nadroparin group ( $1.37 \pm 0.66$  mm,  $51.9 \pm 21.0\%$ ) did not differ from the corresponding values in the control group ( $1.48 \pm 0.59$  mm,  $48.8 \pm 18.9\%$ ). Combined major cardiac-related clinical events (death, myocardial infarction, target lesion revascularization) did not differ between groups (30.3% versus 29.6%).

**Conclusions** Pretreatment with the low-molecular-weight heparin nadroparin continued for 3 months after balloon angioplasty had no beneficial effect on angiographic restenosis or on adverse clinical outcomes.

Circulation ,1997 ;96: 76-81

**First Chronic Platelet Glycoprotein IIb/IIIa Integrin Blockade : A Randomized, Placebo-Controlled Pilot Study of Xemilofiban in Unstable Angina With Percutaneous Coronary Interventions**

Conrad Simpfordorfer, Kandice Kottke-Marchant, Marsha Lowrie, Robert J. Anders, Daniel M. Burns, Dave P. Miller, Christopher S. Cove, Anthony C. DeFranco, Stephen G. Ellis, David J. Moliterno, Russell E. Raymond, Joseph M. Sutton, and Eric J. Topol

Background Clinical studies have demonstrated the efficacy of intravenous administration of agents that block platelet glycoprotein IIb/IIIa receptors in the setting of percutaneous coronary revascularization. Although the optimal duration of treatment has not been determined, more prolonged receptor blockade has been associated with increased efficacy. Orally active glycoprotein IIb/IIIa receptor antagonists may be advantageous and required for chronic therapy.

Methods and Results Thirty patients with unstable angina who were undergoing percutaneous coronary interventions were randomized to placebo or Xemilofiban 35 mg orally before and 20 to 25 mg TID for 30 days after angioplasty. Bleeding events, platelet aggregation, and pharmacokinetic and hematologic parameters were assessed during hospitalization and at 2 and 4 weeks after drug initiation. Xemilofiban produced a rapid, sustained, marked inhibition of platelet aggregation. ADP-induced platelet aggregation at 2 hours after the initial dose at 2 and 4 weeks was 15%, 8%, and 11% in the Xemilofiban group compared with 80%, 68%, and 69% in the placebo group. Among 20 patients randomized to Xemilofiban there was 1 death after emergency coronary bypass surgery complicated by severe bleeding diathesis, and 3 patients had major bleeding events. Patients on Xemilofiban for 30 days reported episodes of mild mucocutaneous bleeding.

Conclusions Xemilofiban, an orally active glycoprotein IIb/IIIa receptor inhibitor, produced rapid, sustained, extensive inhibition of platelet aggregation for a period of up to 30 days. At the dose initially tested, however, acute major bleeding and mucocutaneous bleeding during chronic administration were encountered.

The American Journal of Cardiology, 1997;80:985-988

Effect of Platelet Glycoprotein IIb/IIIa Receptor Inhibition on Distal Embolization During Percutaneous Revascularization of Aortocoronary Saphenous Vein Grafts

Koon-Hou Mak, MBBS, Ram Challapalli, MD, Mark J. Eisenberg, MD, MPH, Keaven M. Anderson, PhD, Robert M. Califf, MD, Eric J. Topol, MD for the EPIC Investigators

Percutaneous treatment of narrowed aortocoronary saphenous vein graft disease represents a viable option for patients with recurrent angina following coronary artery bypass grafting. Present strategies are limited by high rates of distal embolization, non-Q-wave acute myocardial infarction (AMI), and restenosis. Because these

complications may be mediated by platelets, inhibition of platelet glycoprotein IIb/IIIa receptor, the final common pathway for aggregation, may improve clinical outcomes. In the Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial, 2,099 patients undergoing high-risk percutaneous coronary revascularization were randomized to receive abciximab bolus and infusion, abciximab bolus followed by placebo infusion or placebo. A total of 101 patients were treated for narrowing of saphenous vein grafts, 38 in the bolus and infusion group, 34 in the bolus group and 29 in the placebo group. Clinical end points included all-cause mortality, nonfatal AMI and need for repeat revascularization at 30 days. Compared with placebo, bolus and infusion therapy resulted in a significant reduction in distal embolization (2% vs 18%,  $p = 0.017$ ) and a trend towards reduction in early large non-Q-wave AMI (2% vs 12%,  $p = 0.165$ ). The occurrence of a 30-day composite end point was similar among the 3 treatment groups. At 6 months, there was also no difference in the composite end point. These results suggest that adjunctive therapy with abciximab during percutaneous treatment of narrowed saphenous vein grafts reduces the occurrence of distal embolization, and possibly non-Q-wave AMI.

Circulation , 1997 ;96: 1117-1121

#### Sustained Platelet Glycoprotein IIb/IIIa Blockade With Oral Xemilofiban in 170 Patients After Coronary Stent Deployment

Dean J. Kereiakes, Neal Kleiman, James J. Ferguson, John Paul Runyon, Thomas M. Broderick, Nancy A. Higby, Linda H. Martin, Gary Hantsbarger, Shawn McDonald, and Robert J. Anders

Background Inhibition of platelet aggregation with parenteral glycoprotein (GP) IIb/IIIa receptor blockers can reduce the ischemic complications of angioplasty. Sustained efficacy and safety of protracted GP IIb/IIIa blockade with an orally administered agent have not previously been determined. This study is the first randomized, dose-ranging, single-blind, placebo-controlled trial of xemilofiban, an oral platelet GP IIb/IIIa receptor antagonist, administered to patients after intracoronary stent deployment. The pharmacodynamic efficacy of xemilofiban-induced platelet inhibition and clinical safety of this agent was evaluated during chronic therapy.

Methods and Results After elective intracoronary stent deployment, patients were randomized to receive placebo (250 mg ticlopidine PO BID) or xemilofiban in doses of 5, 10, 15, or 20 mg PO BID. All patients received 325 mg aspirin PO QD. Inhibition of ex vivo platelet aggregation in response to 20  $\mu\text{mol/L}$  ADP and 4  $\mu\text{g/mL}$

collagen was measured over time after the initial dose of study drug and at 1 and 2 weeks of chronic therapy. Study drug was discontinued after 2 weeks, and all patients were followed clinically for  $\geq 30$  days. Oral xemilofiban resulted in a dose-dependent inhibition of platelet aggregation in response to both agonists that was sustained through 2 weeks of chronic therapy. Doses of xemilofiban required to achieve  $\geq 50\%$  inhibition of platelet aggregation were 10 mg, and the duration of inhibition was 8 to 10 hours. No significant hemorrhagic episodes or blood transfusions were observed in this trial.

**Conclusions** Oral xemilofiban in doses of  $\geq 10$  mg produced  $\geq 50\%$  inhibition of platelet aggregation in response to ADP and collagen for 8 to 10 hours after dosing. Platelet inhibition was sustained through 2 weeks of chronic therapy. The optimal duration of oral GP IIb/IIIa blockade to effectively suppress recurrent ischemic events after coronary intervention remains to be determined.

J Am Coll Cardiol, 1997;29:13-20

#### Ticlopidine and Aspirin Pretreatment Reduces Coagulation and Platelet Activation During Coronary Dilation Procedures

Luisa Gregorini, MD, Jean Marco, MD, Jean Fajadet, MD, Monique Bernies, MD, Bernard Cassagneau, MD, Philippe Brunel, MD, Irene M. Bossi, MD, Pier Mannuccio Mannucci, MD

**Objectives.** It is unknown whether a therapeutic combination of aspirin (ASA) and ticlopidine might effectively decrease activation of hemostasis.

**Background.** Percutaneous transluminal coronary angioplasty (PTCA), rotational atherectomy and stent implantation are procedures that fracture or ablate endothelium and plaque, a situation that activates hemostasis.

**Methods.** In 85 patients undergoing PTCA for a  $77.8 \pm 1\%$  stenosis, we measured markers of coagulation and platelet activation (thrombin-antithrombin complexes [TAT], prothrombin fragment 1+2 [F1+2] serotonin and the presence of circulating activated platelets reacting with monoclonal antibodies against glycoproteins exposed on platelet membranes). Blood samples were drawn from a peripheral vein and from the coronary ostium before the procedures. Both immediately and 10 min after angioplasty, and 10 min afterward, samples were collected from a probing catheter (0.018 in. [0.46 cm] positioned beyond the stenosis. All patients were being treated with antianginal drugs and ASA, 250 mg/day. Seventy of them had taken ticlopidine, 250 mg, twice daily for  $\leq 1$  day ( $\geq 24$  h) (n=28) or for  $\geq 3$  days ( $\geq 72$  h) (n=42). Heparin (150 U/kg) was administered

before angioplasty. Thirty patients underwent PTCA; 15 of them were not treated with ticlopidine and 15 were given ticlopidine ( $\geq 72$  h). Thirty-five patients had stent implantation, 20 rotational atherectomy.

Results. Before and during the procedures, there was greater thrombin generation (expressed by higher TAT and F1+2 plasma levels) in patients not taking it for  $\leq 24$  h ( $p < 0.05$ ). Platelet activation and plasma serotonin levels were also significantly higher in the no ticlopidine or  $\leq 24$ -h ticlopidine groups.

Conclusions. The combined use of ticlopidine, ASA and heparin effectively controls activation of coagulation in patients with stable angina undergoing coronary dilation.

Figure. Intraprocedure thrombin generation.

Circulation 1998 98: 1597-1603

Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting : The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study

Michel E. Bertrand, Victor Legrand, Jean Boland, Eckart Fleck, Johannes Bonnier, Hakan Emmanuelson, Matty Vrolix, Luc Missault, Sergio Chierchia, Michele Casaccia, Luigi Niccoli, Ali Oto, Christopher White, Michael Webb-Peploe, Eric Van Belle, and Eugene P. McFadden

Background-Dual therapy with ticlopidine and aspirin has been shown to be as effective as or more effective than conventional anticoagulation in patients with an optimal result after implantation of intracoronary metallic stents. However, the safety and efficacy of antiplatelet therapy alone in an unselected population has not been evaluated.

Methods-Patients were randomized to conventional anticoagulation or to treatment with antiplatelet therapy alone. Indications for stenting were classified as elective (decided before the procedure) or unplanned (to salvage failed angioplasty or to optimize the results of balloon angioplasty). After stenting, patients received aspirin and either ticlopidine or conventional anticoagulation (heparin or oral anticoagulant). The primary end point was the occurrence of bleeding or peripheral vascular complications; secondary end points were cardiac events (death, infarction, or stent occlusion) and duration of hospitalization.

Results-In 13 centers, 236 patients were randomized to anticoagulation and 249 to antiplatelet therapy. Stenting was elective in 58% of patients and unplanned in 42%. Stent implantation was successfully achieved in 99% of patients. A primary end point occurred in 33 patients (13.5%) in the antiplatelet group and 48 patients (21%) in

the anticoagulation group (odds ratio=0.6 [95% CI 0.36 to 0.98], P=0.03). Major cardiac-related events in electively stented patients were less common (odds ratio=0.23 [95% CI 0.05 to 0.91], P=0.01) in the antiplatelet group (3 of 123, 2.4%) than the anticoagulation group (11 of 111, 9.9%). Hospital stay was significantly shorter in the antiplatelet group ( $4.3\pm 3.6$  versus  $6.4\pm 3.7$  days, P=0.0001).

Conclusions-Antiplatelet therapy after coronary stenting significantly reduced rates of bleeding and subacute stent occlusion compared with conventional anticoagulation.

Journal of the American College of Cardiology, 32:7:2003-2010

Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) Trial

The Paradigm Investigators

**Objectives.** The trial was designed to assess the safety, pharmacodynamics and effects on reperfusion of the platelet glycoprotein (GP) IIb/IIIa inhibitor lamifiban when given with thrombolysis to patients with ST segment elevation acute myocardial infarction.

**Background.** Studies of fibrinolytic agents in acute myocardial infarction have demonstrated a direct relationship between early complete reperfusion and survival. Blockade of the platelet GP IIb/IIIa receptor complex inhibits platelet aggregation and may speed reperfusion when given in conjunction with thrombolysis to patients with acute myocardial infarction.

**Methods.** Patients with ST segment elevation presenting within 12 h of symptom onset who were treated with either tissue-plasminogen activator or streptokinase were enrolled in this three-part Phase II dose exploration study. In Part A, all patients received the GP IIb/IIIa inhibitor lamifiban in an open-label, dose escalation scheme. Parts B and C were a randomized, double-blind comparison of a bolus plus 24-h infusion of lamifiban versus placebo with patients randomized in a 2:1 ratio. The goal was to identify a dose(s) of lamifiban that provided >85% adenosine diphosphate (ADP)-induced platelet aggregation inhibition. A composite of angiographic, continuous electrocardiographic and clinical markers of reperfusion was the primary efficacy end point, and bleeding was the primary safety end point.

**Results.** Platelet aggregation was inhibited by lamifiban in a dose-dependent manner with the highest doses exceeding 85% ADP-induced platelet aggregation inhibition. There was more bleeding associated with

lamifiban (transfusions in 16.1% lamifiban-treated vs. 10.3% placebo-treated patients). Lamifiban induced more rapid reperfusion as measured by all continuous electrocardiographic (ECG) parameters.

Conclusions. Lamifiban given with thrombolytic therapy appears to be associated with more rapid and complete reperfusion than placebo. As expected in this small sample, there were no obvious clinical benefits to lamifiban over placebo. Reconciliation of ECG monitoring with clinical outcomes will require a larger, adequately powered clinical trial.

N Engl J Med ,1998;339:436-43

### Inhibition of Platelet Glycoprotein IIb/IIIa with Eptifibatide in Patients with Acute Coronary Syndromes

The PURSUIT Trial Investigators

**Background.** Aggregation of platelets is the pathophysiologic basis of the acute coronary syndromes. Eptifibatide, a synthetic cyclic heptapeptide, is a selective high-affinity inhibitor of the platelet glycoprotein IIb/IIIa receptor, which is involved in platelet aggregation. We tested the hypothesis that inhibition of platelet aggregation with eptifibatide would have an incremental benefit beyond that of heparin and aspirin in reducing the frequency of adverse outcomes in patients with acute coronary syndromes who did not have persistent ST-segment elevation.

**Methods.** Patients who had presented with ischemic chest pain within the previous 24 hours and who had either electrocardiographic changes indicative of ischemia (but not persistent ST-segment elevation) or high serum concentrations of creatine kinase MB isoenzymes were enrolled in the study. They were randomly assigned, in a double-blind manner, to receive a bolus and infusion of either eptifibatide or placebo, in addition to standard therapy, for up to 72 hours (or up to 96 hours, if coronary intervention was performed near the end of the 72-hour period). The primary end point was a composite of death and nonfatal myocardial infarction occurring up to 30 days after the index event.

**Results.** A total of 10,948 patients were enrolled between November 1995 and January 1997. As compared with the placebo group, the eptifibatide group had a 1.5 percent absolute reduction in the incidence of the primary end point (14.2 percent, vs. 15.7 percent in the placebo group;  $P=0.04$ ). The benefit was apparent by 96 hours and persisted through 30 days. The effect was consistent in most major subgroups except for women (odds ratios for death or nonfatal myocardial infarction, 0.8 [95 percent confidence interval, 0.7 to 0.9] in men, and 1.1 [0.9 to 1.3] in women). Bleeding was more common in the eptifibatide group, although there was no increase in

the incidence of hemorrhagic stroke.

Conclusions. Inhibition of platelet aggregation with eptifibatid reduced the incidence of the composite end point of death or nonfatal myocardial infarction in patients with acute coronary syndromes who did not have persistent ST-segment elevation

Circulation 1998 ;98: 2126-2132

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)

Philip Urban, Carlos Macaya, Hans-Jurgen Rupprecht, Ferdinand Kiemeneij, Hakan Emanuelsson, Alessandro Fontanelli, Michael Pieper, Thea Wesseling, and Luc Sagnard

Background-Although the association of ticlopidine and aspirin has been shown to be superior to anti-vitamin K agents and aspirin after coronary stent implantation in low-risk patients, the latter combination has remained an unproven reference regimen for high-risk patients until recently.

Methods and Results-We randomized 350 high-risk patients within 6 hours after stent implantation to receive during 30 days either aspirin 250 mg and ticlopidine 500 mg/d (A+T group) or aspirin 250 mg/d and oral anticoagulation (A+OAC group) targeted at an international normalized ratio of 2.5 to 3. The primary composite end point was defined as the occurrence of cardiovascular death, myocardial infarction, or repeated revascularization at 30 days. Patients were eligible if (1) the stent(s) were implanted to treat abrupt closure after PTCA; (2) the angiographic result after implantation was suboptimal; (3) a long segment was stented (>45 mm and/or  $\geq 3$  stents); or (4) the largest balloon inflated in the stent had a nominal diameter of  $\leq 2.5$  mm. The primary cardiac end point was reached for 10 patients (5.6%) in the A+T group and 19 (11%) in the A+OAC group (relative risk [RR], 1.9; 95% CI, 0.9 to 4.1; P=0.07). Major vascular and bleeding complications were less frequent in the A+T group (3 patients, 1.7%) than in the A+OAC group (12 patients, 6.9%) (RR, 4.1; 95% CI, 1.2 to 14.3; P=0.02).

Conclusions-High-risk patients should be treated with A+T rather than A+OAC after coronary stenting because the bleeding and vascular complications are significantly reduced and there is a marked trend suggesting a decrease in cardiac events.

Cathet. Cardiovasc. Diagn. 44:405-406, 1998

Vasoseal hemostasis following coronary interventions with Abciximab

Leo Lunney, Khalid Karim, Thomas Little

Femoral arteriotomy management using a collagen vascular hemostasis device (VasoSeal) was studied in 50 consecutive patients following interventional coronary procedures performed with Abciximab (ReoPro). Low dose weight adjusted or no heparin was employed. The first 25 patients were permitted to sit up after 6 hours with ambulation the following day. The second 25 patients were allowed to sit up after 1 hour and ambulate after 6 hours. Despite early activity and ambulation, there were no hemorrhagic complications including hematoma, pseudoaneurysm, blood transfusion, or surgical repair. Hemoglobin and platelet counts remained stable overnight prior to discharge.

This pilot study demonstrates the potential efficacy of VasoSeal in achieving early sheath removal and ambulation in patients undergoing interventional procedures using ReoPro.

N Engl J Med 1998;338:1498-505

A Comparison of Aspirin plus Tirofiban with Aspirin plus Heparin for Unstable Angina

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators

**Background.** Activation of platelets is central to the pathophysiology of unstable angina. We studied whether inhibition of the final common pathway for platelet aggregation with tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist, would improve clinical outcome in this condition.

**Methods.** In a double-blind study, we randomly assigned 3232 patients who were already receiving aspirin to additional treatment with intravenous tirofiban or heparin for 48 hours. The primary end point was a composite of death, myocardial infarction, or refractory ischemia at 48 hours.

**Results.** The incidence of the composite end point was 32 percent lower at 48 hours in the group that received tirofiban (3.8 percent, vs. 5.6 percent with heparin; risk ratio, 0.67; 95 percent confidence interval, 0.48 to 0.92;

P=0.01). Percutaneous revascularization was performed in 1.9 percent of the patients during the first 48 hours. At 30 days, the frequency of the composite end point (with the addition of readmission for unstable angina) was similar in the two groups (15.9 percent in the tirofiban group vs. 17.1 percent in the heparin group, P=0.34). There was a trend toward a reduction in the rate of death or myocardial infarction with tirofiban (a rate of 5.8 percent, as compared with 7.1 percent in the heparin group; risk ratio, 0.80; 95 percent confidence interval, 0.61 to 1.05; P=0.11), and mortality was 2.3 percent, as compared with 3.6 percent in the heparin group (P=0.02). Major bleeding occurred in 0.4 percent of the patients in both groups. Reversible thrombocytopenia occurred more frequently with tirofiban than with heparin (1.1 percent vs. 0.4 percent, P=0.04).

**Conclusions.** Tirofiban was generally well tolerated and, as compared with heparin, reduced ischemic events during the 48-hour infusion period, during which revascularization procedures were not performed. The incidence of refractory ischemia and myocardial infarction was not reduced at 30 days, but mortality was lower among the patients given tirofiban. Platelet inhibition with aspirin plus tirofiban may have a role in the management of unstable angina.

N Engl J Med 1998;338:1488-97

## Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-Wave Myocardial Infarction

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators

**Background.** Antithrombotic therapy improves the prognosis of patients with acute coronary syndromes, yet the syndromes remain a therapeutic challenge. We evaluated tirofiban, a specific inhibitor of the platelet glycoprotein IIb/IIIa receptor, in the treatment of unstable angina and non-Q-wave myocardial infarction.

**Methods.** A total of 1915 patients were randomly assigned in a double-blind manner to receive tirofiban, heparin, or tirofiban plus heparin. Patients received aspirin if its use was not contraindicated. The study drugs were infused for a mean ( $\pm$ SD) of  $71.3 \pm 20$  hours, during which time coronary angiography and angioplasty were performed when indicated after 48 hours. The composite primary end point consisted of death, myocardial infarction, or refractory ischemia within seven days after randomization.

**Results.** The study was stopped prematurely for the group receiving tirofiban alone because of excess mortality at seven days (4.6 percent, as compared with 1.1 percent for the patients treated with heparin alone). The

frequency of the composite primary end point at seven days was lower among the patients who received tirofiban plus heparin than among those who received heparin alone (12.9 percent vs. 17.9 percent; risk ratio, 0.68; 95 percent confidence interval, 0.53 to 0.88;  $P=0.004$ ). The rates of the composite end point in the tirofiban-plus-heparin group were also lower than those in the heparin-only group at 30 days (18.5 percent vs. 22.3 percent,  $P=0.03$ ) and at 6 months (27.7 percent vs. 32.1 percent,  $P=0.02$ ). At seven days, the frequency of death or myocardial infarction was 4.9 percent in the tirofiban-plus-heparin group, as compared with 8.3 percent in the heparin-only group ( $P=0.006$ ). The comparable figures at 30 days were 8.7 percent and 11.9 percent ( $P=0.03$ ), respectively, and those at 6 months were 12.3 percent and 15.3 percent ( $P=0.06$ ). The benefit was consistent in the various subgroups of patients and in those treated medically as well as those treated with angioplasty. Major bleeding occurred in 3.0 percent of the patients receiving heparin alone and 4.0 percent of the patients receiving combination therapy ( $P=0.34$ ).

**Conclusions.** When administered with heparin and aspirin, the platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban was associated with a lower incidence of ischemic events in patients with acute coronary syndromes than in patients who received only heparin and aspirin.

Journal of the American College of Cardiology, 32:2:311-319

Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization

Scott D. Berkowitz, David C. Sane, Kristina N. Sigmon, Jane H. Shavender, Robert A. Harrington, James E. Tchong, Eric J. Topol, Robert M. Califf for the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) Study Group

**Objectives.** This study sought to determine the frequency of thrombocytopenia and its relation with clinical outcomes in high risk patients undergoing percutaneous coronary revascularization who received either the platelet glycoprotein (GP) IIb/IIIa receptor antagonist abciximab (ReoPro, c7E3 Fab) or conventional therapy.

**Background.** The development of thrombocytopenia on exposure to GPIIb/IIIa antagonists threatens the utility and economic viability of this drug class for patients with vascular disease.

**Methods.** We analyzed data from the Evaluation of c7E3 for the Prevention of Ischemic Complications trial (EPIC), a 2,099-patient, randomized trial of placebo, abciximab bolus or abciximab bolus plus a 12-h infusion during high-risk coronary revascularization.

**Results.** Thrombocytopenia (nadir platelet count  $<100 \times 10^9/\text{liter}$ ) developed in 81 patients (3.9%) during their hospital stay, with 19 (0.9%) developing severe ( $<50 \times 10^9/\text{liter}$ ) thrombocytopenia. Both thrombocytopenia and severe thrombocytopenia were more frequent in the bolus-plus-infusion arm (5.2% and 1.6%, respectively) than in the bolus-only and placebo arms combined ( $p = 0.020$  and  $p = 0.025$ , respectively). Acute profound thrombocytopenia developed in two patients in the bolus-plus-infusion arm. Patients with thrombocytopenia experienced more unfavorable clinical outcomes than those who did not develop thrombocytopenia, regardless of treatment assignment, but those with thrombocytopenia who received abciximab had fewer worse outcomes at 30 days. Multivariable logistic modeling revealed a lower baseline platelet count, older age and lighter weight to be important predictors of thrombocytopenia. In a logistic regression model, bolus-plus-infusion treatment was a significant predictor of thrombocytopenia ( $p = 0.016$ ) and remained so after adjustment for procedures and baseline risk factors ( $p = 0.0077$ ).

**Conclusions.** Thrombocytopenia was associated with adverse clinical outcomes and excessive bleeding, but patients receiving abciximab fared better than those receiving placebo.

The American Journal of Cardiology, 81:2:147-151

#### Clinical Outcome at Six Months of Coronary Stenting Followed by Ticlopidine Monotherapy

Mathias Elsner, MD, Alfred Peifer, MD, Michael Drexler, MD, Christian Wenzel, Christian Hebbeker, Wolfgang Kasper, MD

Antiplatelet therapy has been shown to be superior to oral anticoagulation after coronary stent implantation. Different regimens for postinterventional antiplatelet therapy have been proposed. A combination of ticlopidine and aspirin has gained the most widespread use. The relative merit of the different compounds in this combination remains unclear. There are several, partly conflicting, reports on coronary stent implantation followed by aspirin alone, but data on ticlopidine monotherapy are scarce. We conducted a prospective trial of elective coronary stenting followed by ticlopidine monotherapy in 263 consecutive, unselected patients. One-, 2-, and 3-vessel disease was present in 42.9%, 42.6%, and 14.5% of patients, respectively. We deployed a total of 322 stents. All patients received 250 mg of ticlopidine twice daily for up to 6 months. The clinical end points encountered during the hospital stay and at  $5.9 \pm 2.9$  months, respectively, were: death (2 [0.8%] and 2 [0.8%]); myocardial infarction (5 [1.9%] and 4 [1.5%]); target vessel occlusion (2 [0.8%] and 4 [1.5%]); bypass surgery (0 and 2 [0.8%]); and repeat angioplasty (2 [0.8%] and 52 [19.8%]). There was 1 vascular surgery (0.4%) and 4 (1.5%) non-procedure-related ischemic cerebrovascular events at follow-up. We conclude that coronary stent deployment followed by ticlopidine monotherapy is safe and effective in an unselected population. The overall clinical outcome at 6 months is good and comparable to that of patients treated with combined antiplatelet

therapy. Ticlopidine monotherapy may be a safe alternative for patients with contraindications to aspirin.

Circulation, 1998; 98: 734-741.

### Randomized, Placebo-Controlled Trial of Platelet Glycoprotein IIb/IIIa Blockade With Primary Angioplasty for Acute Myocardial Infarction

Sorin J. Brener, Lawrence A. Barr, J. E. B. Burchenal, Stanley Katz, Barry S. George, Ancil A. Jones, Eric D. Cohen, Phillip C. Gainey, Harvey J. White, H. Barrett Cheek, Jeffrey W. Moses, David J. Moliterno, Mark B. Efron, and Eric J. Topol

**Background-**The benefit of catheter-based reperfusion for acute myocardial infarction (MI) is limited by a 5% to 15% incidence of in-hospital major ischemic events, usually caused by infarct artery reocclusion, and a 20% to 40% need for repeat percutaneous or surgical revascularization. Platelets play a key role in the process of early infarct artery reocclusion, but inhibition of aggregation via the glycoprotein IIb/IIIa receptor has not been prospectively evaluated in the setting of acute MI.

**Methods and Results-**Patients with acute MI of <12 hours' duration were randomized, on a double-blind basis, to placebo or abciximab if they were deemed candidates for primary PTCA. The primary efficacy end point was death, reinfarction, or any (urgent or elective) target vessel revascularization (TVR) at 6 months by intention-to-treat (ITT) analysis. Other key prespecified end points were early (7 and 30 days) death, reinfarction, or urgent TVR. The baseline clinical and angiographic variables of the 483 (242 placebo and 241 abciximab) patients were balanced. There was no difference in the incidence of the primary 6-month end point (ITT analysis) in the 2 groups (28.1% and 28.2%,  $P=0.97$ , of the placebo and abciximab patients, respectively). However, abciximab significantly reduced the incidence of death, reinfarction, or urgent TVR at all time points assessed (9.9% versus 3.3%,  $P=0.003$ , at 7 days; 11.2% versus 5.8%,  $P=0.03$ , at 30 days; and 17.8% versus 11.6%,  $P=0.05$ , at 6 months). Analysis by actual treatment with PTCA and study drug demonstrated a considerable effect of abciximab with respect to death or reinfarction: 4.7% versus 1.4%,  $P=0.047$ , at 7 days; 5.8% versus 3.2%,  $P=0.20$ , at 30 days; and 12.0% versus 6.9%,  $P=0.07$ , at 6 months. The need for unplanned, "bail-out" stenting was reduced by 42% in the abciximab group (20.4% versus 11.9%,  $P=0.008$ ). Major bleeding occurred significantly more frequently in the abciximab group (16.6% versus 9.5%,  $P=0.02$ ), mostly at the arterial access site. There was no intracranial hemorrhage in either group.

**Conclusions-**Aggressive platelet inhibition with abciximab during primary PTCA for acute MI yielded a

substantial reduction in the acute (30-day) phase for death, reinfarction, and urgent target vessel revascularization. However, the bleeding rates were excessive, and the 6-month primary end point, which included elective revascularization, was not favorably affected.

Circulation, 1998; 97: 2386-2395

International, Randomized, Controlled Trial of Lamifiban (a Platelet Glycoprotein IIb/IIIa Inhibitor), Heparin, or Both in Unstable Angina

**Background**-Unstable angina and non-Q-wave myocardial infarction involve coronary arterial plaque rupture, platelet activation, and thrombus formation. This study tested the benefit of different doses of lamifiban (a platelet IIb/IIIa antagonist) alone and in combination with heparin in patients with these conditions to select the most promising lamifiban regimen for subsequent evaluation.

**Methods and Results**-At 273 hospitals in 20 countries, 2282 patients were randomly assigned to lamifiban (2x2 factorial design: low-dose [1 µg/min] with and without heparin versus high-dose [5 µg/min] with and without heparin) or to standard therapy (placebo and heparin). All patients received aspirin. The composite primary end point of death or nonfatal myocardial infarction at 30 days occurred in 11.7% of those receiving standard therapy, 10.6% receiving low-dose lamifiban, and 12.0% receiving high-dose lamifiban (P=0.668). By 6 months, this composite was lowest for those assigned to low-dose lamifiban (P=0.027) and intermediate for those assigned to high-dose lamifiban (P=0.450) compared with control (13.7%, 16.4%, and 17.9%, respectively). Compared with control, the combination of high-dose lamifiban and heparin resulted in more intermediate or major bleeding (12.1% versus 5.5%; P=0.002) and a similar rate of ischemic events. Conversely, low-dose lamifiban and heparin yielded similar bleeding rates as in the control group but fewer ischemic events at 6 months (12.6% versus 17.9%; P=0.025).

**Conclusions**-In unstable angina and non-Q-wave infarction, platelet IIb/IIIa antagonism with lamifiban reduces adverse ischemic events at 6 months beyond that of aspirin and heparin therapy. The role of conjunctive heparin remains uncertain but appears more favorable with low-dose IIb/IIIa antagonism. Larger-scale study is needed to more reliably estimate these effects.

Circulation, 1998; 98: 1358-1364

## Reduction of Recurrent Ischemia With Abciximab During Continuous ECG-Ischemia Monitoring in Patients With Unstable Angina Refractory to Standard Treatment (CAPTURE)

Peter Klootwijk, Simon Meij, Rein Melkert, Timo Lenderink, and Maarten L. Simoons

**Background**-In the CAPTURE (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina) trial, 1265 patients with refractory unstable angina were treated with abciximab or placebo, in addition to standard treatment from 16 to 24 hours preceding coronary intervention through 1 hour after intervention. To investigate the incidence of recurrent ischemia and the ischemic burden, a subset of 332 patients (26%) underwent continuous vector-derived 12-lead ECG-ischemia monitoring.

**Methods and Results**-Patients were monitored from start of treatment through 6 hours after coronary intervention. Ischemic episodes were detected in 31 (18%) of the 169 abciximab and in 37 (23%) of the 163 placebo patients (NS). Only 9 (5%) of abciximab versus 22 (14%) of placebo patients had 2 ST episodes ( $P<0.01$ ). In patients with ischemia, abciximab significantly reduced total ischemic burden ( $P<0.02$ ), which was calculated alternatively as the total duration of ST episodes per patient, the area under the curve of the ST vector magnitude during episodes, or the sum of the areas under the curves of 12 leads during episodes. Twenty-one patients (6%) suffered a myocardial infarction (MI) (18) or died (3) within 5 days of treatment. The presence of asymptomatic and symptomatic  $\geq$ ST episodes during the monitoring period preceding coronary intervention was associated with an increased relative risk of these events of 3.2 (95% CI 1.4, 7.4) and 4.1 (95% CI 1.4, 12.2), respectively.

**Conclusions**-Recurrent ischemia predicts MI or death within 5 days of follow-up. Treatment with abciximab is associated with a reduction of frequent ischemia and a reduction of total ischemic burden in patients with refractory unstable angina. As such, patients with ischemia derive particularly high benefit from abciximab.

Journal of the American College of Cardiology, 31:1:31-36

## Does Intracoronary Thrombus Influence the Outcome of High Risk Percutaneous Transluminal Coronary Angioplasty? Clinical and Angiographic Outcomes in a Large Multicenter Trial

M. Musa Khan, MD, Stephen G. Ellis, MD, FACC, Frank V. Aguirre, MD, FACC, Harlan F. Weisman, MD, FACC, Nancy M. Wildermann, BA, Robert M. Califf, MD, FACC, Eric J. Topol, MD, FACC, Neal S. Kleiman,

MD, FACC for the EPIC Investigators

**Objectives.** We sought to evaluate the impact of angiographically visible thrombus on short- and long-term clinical outcomes after percutaneous transluminal coronary angioplasty (PTCA).

**Background.** Intracoronary thrombus is frequently seen on angiography in patients with acute ischemic coronary syndromes or complex lesion morphology, or both, and is often considered to predict a higher rate of complications in patients undergoing PTCA.

**Methods.** Prospectively collected data from 2,099 patients undergoing high risk PTCA in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial were analyzed. In addition to aspirin and heparin, patients were randomized to receive either abciximab bolus and infusion, abciximab bolus alone or placebo. Based on an angiographic core laboratory interpretation, patients were classified into three groups: thrombus absent, thrombus possible or thrombus present. The primary end point at 30 days was the composite of death, myocardial infarction or urgent revascularization. The 6-month end point was the composite of death, myocardial infarction or any revascularization.

**Results.** Although abrupt closure was most common in patients with thrombus present compared with thrombus absent or possible (13%, 10.0% and 7.4%, respectively), neither the 30-day nor the 6-month clinical end points were different among the three groups (9%, 11% and 11.7%, respectively, and 30%, 34% and 31%, respectively). Most notably, the benefit of treatment with abciximab was present in all three thrombus groups, and the magnitude of benefit was not different among the thrombus groups.

**Conclusions.** In high risk patients undergoing percutaneous coronary revascularization, features of thrombus on the preprocedure angiogram do not indicate an augmented risk of adverse clinical outcomes. Abciximab therapy reduces the rate of adverse outcomes regardless of the presence of thrombus and should therefore not necessarily be reserved for patients whose angiograms have features of intraluminal thrombus.

Journal of the American College of Cardiology, 32:5:1366-1370

The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non-Q-wave myocardial infarctions

Steven R. Steinhubl, Michael S. Lauer, Debabrata P. Mukherjee, David J. Moliterno, A. Michael Lincoff, Stephen G. Ellis, Eric J. Topol

**Objectives.** This study sought to determine whether the duration of pretreatment with the adenosine diphosphate receptor antagonist ticlopidine prior to intracoronary stenting is associated with the incidence of procedure-related non-Q-wave myocardial infarctions (MIs).

**Background.** Dual antiplatelet therapy with ticlopidine and aspirin is routinely used with stenting, although ticlopidine is commonly not begun until the day of the procedure. Periprocedural MIs are at least partially platelet-dependent events. As the maximal platelet inhibitory effects of this drug take 2 to 3 days to be realized, we hypothesized that longer treatment prior to stenting would be associated with lower rates of procedure-related MIs.

**Methods.** We reviewed outcomes in 175 consecutive patients treated with ticlopidine prior to stenting at the Cleveland Clinic Foundation. Those patients with an elevation in creatine kinase above our laboratory normal ( $>210$  IU/L) with  $\geq 4\%$  MB fraction on routine evaluation were defined as having a non-Q-wave MI.

**Results.** There were 28 patients (16%) who had a non-Q-wave MI. Longer duration of ticlopidine pretreatment was strongly associated with a lower incidence of procedure-related non-Q-wave MIs (duration of pretreatment  $<1$  day, 29% had MI; 1 to 2 days, 14%;  $\geq 3$  days, 5%; chi-square for trend = 9.6;  $p = 0.002$ ). Ticlopidine pretreatment of  $\geq 3$  days was associated with a significant reduction in the risk of non-Q-wave MI (unadjusted odds ratio 0.18, 95% confidence interval = 0.04 to 0.78,  $p = 0.01$ ) compared with pretreatment of  $<3$  days.

**Conclusions.** Among patients undergoing intracoronary stenting, beginning ticlopidine therapy several days prior to the procedure is associated with a reduced risk of procedural non-Q-wave MIs.

Circulation, 1998 ;98: 1860-1868

#### Acute Coronary Syndromes in the GUSTO-IIb Trial : Prognostic Insights and Impact of Recurrent Ischemia

Paul W. Armstrong, Yuling Fu, Wei-Ching Chang, Eric J. Topol, Christopher B. Granger, Amadeo Betriu, Frans Van de Werf, Kerry L. Lee, and Robert M. Califf

**Background-**Recurrent ischemia after an acute coronary syndrome portends an unfavorable outcome and has major resource-use implications. This issue has not been studied systematically among the spectrum of patients with acute coronary presentations, encompassing those with and without ST-segment elevation.

**Methods and Results-**We assessed the 1-year prognosis of the 12 142 patients enrolled in the GUSTO-IIb trial by the presence (n=4125) or absence (n=8001) of ST-segment elevation. This latter group was further categorized into those with baseline myocardial infarction (n=3513) or unstable angina (n=4488). We also assessed the incidence of recurrent ischemia and its impact on outcomes. Recurrent ischemia was significantly rarer in those with ST-segment elevation (23%) than in those without (35%; P<0.001). Mortality at 30 days was greater among patients with ST-segment elevation (6.1% versus 3.8%; P<0.001) but less so at 6 months; by 1 year, mortality did not differ significantly (9.6% versus 8.8%). Patients with non-ST-segment-elevation infarction had higher rates of reinfarction at 6 months (9.8% versus 6.2%) and higher 6-month (8.8% versus 5.0%) and 1-year mortality rates (11.1% versus 7.0%) than such patients who had unstable angina.

**Conclusions-**Refractory ischemia was associated with an approximate doubling of mortality among patients with ST-segment elevation and a near tripling of risk among those without ST elevation. This study highlights not only the substantial increase in late mortality and reinfarction with non-ST-segment-elevation infarction but also the opportunities for better triage and application of therapeutic strategies for patients with recurrent ischemia.

The American Journal of Cardiology, 1998;81:2:147-151

#### Clinical Outcome at Six Months of Coronary Stenting Followed by Ticlopidine Monotherapy

Mathias Elsner, MD, Alfred Peifer, MD, Michael Drexler, MD, Christian Wenzel, Christian Hebbeker, Wolfgang Kasper, MD

Antiplatelet therapy has been shown to be superior to oral anticoagulation after coronary stent implantation. Different regimens for postinterventional antiplatelet therapy have been proposed. A combination of ticlopidine and aspirin has gained the most widespread use. The relative merit of the different compounds in this combination remains unclear. There are several, partly conflicting, reports on coronary stent implantation followed by aspirin alone, but data on ticlopidine monotherapy are scarce. We conducted a prospective trial of elective coronary stenting followed by ticlopidine monotherapy in 263 consecutive, unselected patients. One-, 2-, and 3-vessel disease was present in 42.9%, 42.6%, and 14.5% of patients, respectively. We deployed a total of 322 stents. All patients received 250 mg of ticlopidine twice daily for up to 6 months. The clinical end points encountered during the hospital stay and at 5.9 ± 2.9 months, respectively, were: death (2 [0.8%] and 2 [0.8%]); myocardial infarction (5 [1.9%] and 4 [1.5%]); target vessel occlusion (2 [0.8%] and 4 [1.5%]); bypass surgery (0

and 2 [0.8%]); and repeat angioplasty (2 [0.8%] and 52 [19.8%]). There was 1 vascular surgery (0.4%) and 4 (1.5%) non-procedure-related ischemic cerebrovascular events at follow-up. We conclude that coronary stent deployment followed by ticlopidine monotherapy is safe and effective in an unselected population. The overall clinical outcome at 6 months is good and comparable to that of patients treated with combined antiplatelet therapy. Ticlopidine monotherapy may be a safe alternative for patients with contraindications to aspirin.

Journal of the American College of Cardiology, 1998;31:289-293

### High Dose Bolus Heparin as Initial Therapy Before Primary Angioplasty for Acute Myocardial Infarction: Results of the Heparin in Early Patency (HEAP) Pilot Study

Freek W. A. Verheugt, MD, FACC, Aylee Liem, MD, Felix Zijlstra, MD, Randall C. Marsh, MD, FACC, Gerrit Veen, MD, Jean G. F. Bronzwaer, MD

**Objectives.** We sought to determine the effect of high dose intravenous bolus heparin on early coronary patency before primary angioplasty.

**Background.** Early coronary angiography after thrombolysis for acute myocardial infarction has shown better patency when intravenous heparin is used as an adjunct. The present study explores whether heparin alone can induce reperfusion.

**Methods.** In the Heparin in Early Patency (HEAP) pilot study, 108 patients with signs and symptoms of acute myocardial infarction <6 h eligible for primary angioplasty received a single intravenous bolus of 300 U/kg of heparin together with aspirin (160 mg chewed) in the emergency room. The median dose of bolus heparin given was 27,000 U. Patency of the infarct-related artery (IRA) was assessed by coronary angiography at a median of 85 min after the heparin bolus.

**Results.** In 55 patients (51%, 95% confidence interval 38% to 64%), Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 was observed at 90 min: TIMI flow grade 3 in 33 patients (31%); TIMI flow grade 2 in 22 (20%). Thirty-two (64%) of 50 patients with symptoms  $\leq 2$  h had TIMI flow grade 2 or 3 versus 23 (40%) of 58 patients with symptoms  $> 2$  h ( $p = 0.02$ ). No significant bleeding was seen. Two patients (2%) died in the hospital. The patency results obtained in patients treated with the high dose bolus heparin were compared with those in 108 patients from a large primary angioplasty database, who were treated with standard therapy, including aspirin but not intravenous heparin, and were matched for clinical and angiographic characteristics with the HEAP pilot study patients. They showed an 18% patency rate ( $p < 0.001$ ) of the IRA (TIMI flow grade 3

in 9%, TIMI flow grade 2 in 9%) before primary angioplasty.

**Conclusions.** Early therapy with high dose heparin is associated with full coronary reperfusion in a considerable number of patients with acute myocardial infarction, especially in those treated early (<2 h). This simple, inexpensive, probably safe and easily antagonizable treatment may be an attractive first treatment of acute myocardial infarction both before and during the hospital stay in conjunction with primary angioplasty

Circulation, 1998; 98: 2695-2701

#### Effect of Glycoprotein IIb/IIIa Receptor Blockade on Recovery of Coronary Flow and Left Ventricular Function After the Placement of Coronary-Artery Stents in Acute Myocardial Infarction

Franz-Josef Neumann, Rudolf Blasini, Claus Schmitt, Eckhard Alt, Josef Dirschinger, Meinrad Gawaz, Adnan Kastrati, and Albert Schomig

**Background-**Apart from its established effects on vessel patency after percutaneous coronary revascularization, glycoprotein IIb/IIIa receptor blockade by abciximab may improve myocardial perfusion by inhibition of the interaction of platelets and platelet aggregates with the microvasculature. We investigated the effect of abciximab with stent placement in acute myocardial infarction.

**Methods and Results-**In a prospective randomized trial, patients undergoing stenting in acute myocardial infarction within 48 hours after onset of symptoms were randomly assigned to receive either standard-dose heparin or abciximab plus low-dose heparin. Immediately after the procedure and at 14-day angiographic follow-up, we assessed flow velocity in the recanalized vessel with the Doppler wire and regional wall motion by the centerline method. End points were changes in papaverine-induced peak flow velocities and in wall motion indices. We assigned 98 patients to standard heparin and 102 to abciximab. We obtained 152 paired flow measurements and 151 paired left ventricular function studies. Residual stenoses of the treated lesions did not differ between the 2 groups. Improvement of peak flow velocity (mean [95% CI]: 18.1 cm/s [13.6 to 22.6 cm/s], n=80, versus 10.4 cm/s [5.4 to 15.4 cm/s], n=72, P=0.024) and wall motion index (0.44 SD/chord [0.29 to 0.59 SD/chord], n=79 versus 0.15 SD/chord [0.00 to 0.30 SD/chord], n=72, P=0.007) was significantly greater in patients assigned to abciximab than in those on heparin alone. At follow-up, the abciximab group had a higher global left ventricular ejection fraction than the heparin group (62% [59% to 65%] versus 56% [53% to 59%], P=0.003).

**Conclusions-**Abciximab had important effects beyond the maintenance of large-vessel patency. It improved the recovery of microvascular perfusion and concomitantly enhanced the recovery of contractile function in the

area at risk.

Circulation. 1998;97:857-864

### Abciximab Therapy and Unplanned Coronary Stent Deployment: Favorable Effects on Stent Use, Clinical Outcomes, and Bleeding Complications

Dean J. Kereiakes, MD; A. Michael Lincoff, MD; Dave P. Miller, MS; James E. Tchong, MD; Catherine F. Cabot, MD; Keaven M. Anderson, PhD; Harlan F. Weisman, MD; Robert M. Califf, MD; Eric J. Topol, MD; for the EPILOG Trial Investigators

**Background** The clinical and angiographic demographics of patients requiring unplanned coronary stent deployment and the optimal adjunct pharmacotherapy in this population are not well described. This report details the EPILOG trial experience with unplanned coronary stent deployment and the effect of abciximab platelet glycoprotein IIb/IIIa blockade to improve clinical outcomes during 6 months of follow-up.

**Methods and Results** After randomization in the EPILOG double-blind, placebo-controlled trial of abciximab therapy during percutaneous coronary intervention, 326 (12%) of 2792 patients required unplanned coronary stent deployment. Although stented patients were not distinguished by clinical variables, they had greater coronary lesion complexity by American Heart Association/American College of Cardiology criteria ( $P=.003$ ) and greater incidence of lesion length  $>10$  mm ( $P=.002$ ), lesion eccentricity ( $P=.027$ ), irregular lesion contour ( $P=.001$ ), and bifurcation involvement ( $P=.019$ ) than nonstented patients. Unplanned stents were required less often in patients treated with abciximab and low-dose, weight-adjusted heparin than in patients receiving placebo and standard-dose heparin (9.0% versus 13.7%;  $P=.001$ ). Although adverse clinical outcomes including target-vessel revascularization and bleeding events were more frequent in patients requiring unplanned coronary stent deployment, abciximab therapy reduced adverse outcomes in these patients at 30 days and 6 months to a greater extent than was observed in patients not requiring stent placement. Among stented patients, abciximab therapy did not increase bleeding events.

**Conclusions** Patients requiring unplanned coronary stent deployment have more complex coronary lesion morphology and a more complicated clinical course after coronary intervention. Abciximab therapy both reduces the need for unplanned stent deployment and confers clinical benefit to patients requiring an unplanned stent, without increasing bleeding complications.

JACC 1998;32:1996-2002

Abciximab in primary coronary angioplasty for acute myocardial infarction improves short- and medium-term outcomes

Rabih R. Azar, Raymond G. McKay, Paul D. Thompson, Jeffrey A. Hirst, Joseph F. Mitchell, Daniel B. Fram, David D. Waters and Francis J. Kiernan

**Objectives.** The purpose of this study was to compare the outcome of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction (MI) when performed with or without the platelet glycoprotein IIb/IIIa antibody, abciximab.

**Background.** Abciximab improves the outcome of angioplasty but the effect of abciximab in primary angioplasty has not been investigated.

**Methods.** Data were collected from a computerized database. Follow-up was by telephone or review of outpatient or hospital readmission records.

**Results.** A total of 182 consecutive patients were included; 103 received abciximab and 79 did not. The procedural success rate was 95% in the two groups. At 30-day follow-up, the composite event rate of unstable angina, reinfarction, target vessel revascularization and death from all causes was 13.5% in the group of patients who did not receive abciximab, 4% ( $p < 0.05$ ) in the abciximab group and 2.4% ( $p < 0.05$ ) in the subgroup of patients ( $n = 87$ ) who completed the 12-h abciximab infusion. At the end of follow-up (mean  $7 \pm 4$  months), the composite event rate was 32.4%, 17% ( $p < 0.05$ ) and 13.1% ( $p < 0.01$ ) in these three categories respectively. Abciximab bolus followed by a 12-h infusion was an independent predictor of event-free survival, in a Cox proportional hazards model (relative risk 0.49; 95% confidence interval 0.24 to 0.99;  $p < 0.05$ ).

**Conclusions.** Abciximab given at the time of primary angioplasty may improve the short- and medium-term outcome of patients with acute MI, especially when a 12-h infusion is completed.

AJC 1998;82:705-709

Abciximab administration and outcome after intracoronary stent implantation

David Hasdai, Charanjit S. Rihal, Malcolm R. Bell, Peter B. Berger, Diane E. Grill, Kirk N. Garratt and David R.

Holmes Jr

Although adjunctive abciximab therapy improves outcome after angioplasty or atherectomy, there are few data demonstrating its benefit for intracoronary stent implantation. We characterized patients receiving abciximab for stent placement in our practice and determined the impact of abciximab on outcome. Abciximab was introduced to our practice in April 1995 for percutaneous revascularization. Demographic, clinical, and angiographic variables that were independently associated with the use of abciximab for stent placement through 1996 (abciximab era) were examined. We then examined among all patients receiving stents from 1992 through 1996 (preabciximab and abciximab eras) whether the use of abciximab was independently associated with improved outcome (death, nonfatal Q-wave myocardial infarction, coronary bypass surgery, or target vessel percutaneous revascularization) in the hospital and at 30 days. The 30-day event rate was 7% for those who did or did not receive abciximab. The following characteristics were independently associated with the use of abciximab for stent placement in the abciximab era: thrombus before stent placement (chi-square 50.5),  $\geq 2$  stents implanted (chi-square 10.8), stent in venous graft (chi-square 7.4), calcific lesion (chi-square 5.8), and hypertension (chi-square 5.5). Among all patients receiving stents in the preabciximab and abciximab eras (n = 1,859), the presence of these characteristics was independently associated with worse outcome. Abciximab, however, did not improve outcome in the hospital (odds ratio [95% confidence interval] = 0.96 [0.58 to 1.58]) or at 30 days (0.87 [0.53 to 1.41]), even after adjusting for these characteristics. Abciximab for stent placement was used in high-risk patients in our practice but was not associated with improved outcome.

[Circulation ,1998; 97: 1912-1920.](#)

[Diabetes Mellitus, Glycoprotein IIb/IIIa Blockade, and Heparin : Evidence for a Complex Interaction in a Multicenter Trial](#)

[Neal S. Kleiman, A. Michael Lincoff, Dean J. Kereiakes, Dave P. Miller, Frank V. Aguirre, Keaven M. Anderson, Harlan F. Weisman, Robert M. Califf, and Eric J. Topol](#)

[Background](#)

[After angioplasty, major complications and ischemic events occur more frequently in diabetic than nondiabetic patients. To determine whether treatment with abciximab is effective in reducing these events in diabetics, we](#)

analyzed characteristics and outcomes of diabetic patients enrolled in a large multicenter study (EPILOG).

#### Methods and Results

Of 2792 patients enrolled, 638 (23%) were diabetic. Diabetic patients were older, shorter, and heavier; more likely to be female and have three-vessel disease, prior coronary artery bypass graft surgery, a history of hypertension, or a recent myocardial infarction; and less likely to be current smokers than their nondiabetic counterparts. During hospitalization, death, myocardial infarction, or urgent revascularization occurred in 7.1% of diabetics and 7.5% of nondiabetics. By 6 months, the composite of death and myocardial infarction had occurred in 8.8% of diabetic patients and 7.4% of nondiabetics, whereas death, myocardial infarction, or revascularization had occurred in 27.2% and 22.6%, respectively. Abciximab treatment reduced death or myocardial infarction among diabetic and nondiabetic patients (hazard ratios, 0.28 [95% confidence interval (CI), 0.13 to 0.57] and 0.47 [95% CI, 0.33 to 0.70] at 30 days for diabetics and nondiabetics, respectively, and 0.36 [95% CI, 0.21 to 0.61] and 0.60 [95% CI, 0.44 to 0.82] at 6 months for diabetics and nondiabetics, respectively). Abciximab reduced target vessel revascularization among nondiabetic patients (hazard ratio, 0.78 [95% CI, 0.63 to 0.96]) but not among diabetics (hazard ratio, 1.4 [95% CI, 0.94 to 2.08]). When standard- and low-dose heparin adjuncts were compared, diabetics receiving abciximab with standard-dose heparin had marginally greater reductions in the composite of death and myocardial infarction and in target vessel revascularization than diabetics assigned to abciximab with low-dose heparin.

#### Conclusions

Abciximab treatment in diabetic patients led to a reduction in the composite of death and myocardial infarction, which was at least as great as that seen in nondiabetic patients. However, target vessel revascularization was reduced in nondiabetic but not diabetic patients. This effect may be associated in part with lower doses of heparin. These differences may be related to differences in the platelet and coagulation systems between diabetics and nondiabetics, the greater extent of coronary artery disease in diabetics, or patient selection and management factors.

Cathet. Cardiovasc. Diagn. 44:267-274, 1998

Local and systemic delivery of low molecular weight heparin following PTCA: Acute results and 6-month follow-up of the initial clinical experience with the porous balloon (PILOT-study)

Martin Oberhoff, Andreas Baumbach, Thomas Hermann, Claudia Diehl, Rita Maier, Anastasios Athanasiadis, Christian Herdeg, Armin Bohnet, Karl K. Haase, Wolfram Voelker, Reinhard Baildon, Susan Veldhof, Karl R. Karsch

The purpose of this study was to assess safety and feasibility of intracoronary delivery of reviparin using a porous balloon following percutaneous transluminal coronary angioplasty.

The 2.7 mm porous balloon used in this study had 35 holes arranged in a spiral pattern. Eighteen patients (male n = 10, female n = 8, age  $63 \pm 9$  years) undergoing successful PTCA in coronary arteries with a vessel diameter of 2.5 to 3.0 mm determined by online QCA (LAD = 11, RCX = 3, RCA = 4) were included. They received a bolus of 7,000 anti-Xa-IU reviparin followed by local delivery of 1,500 anti-Xa-IU in 4 ml with an injection pressure of 2 atm. The patients received additionally 10500 anti-Xa-units intravenously during the following 24 hours and a daily dose of 7000 anti-Xa-units reviparin subcutaneously for the following 28 days. Angiograms were obtained before and after PTCA, directly after local delivery, at 24 hours postintervention and after 6 months. The primary success rate was 100%. Quantitative coronary angiography showed a minimum luminal diameter of  $0.42 \pm 0.14$  mm before PTCA,  $1.87 \pm 0.45$  after PTCA,  $1.67 \pm 0.43$  after LDD,  $1.63 \pm 0.46$  after 24 hours, and  $1.06 \pm 0.6$  after 6 months. Angiographic follow-up was obtained in all patients. No major complications occurred during the 6-month follow-up period. The angiographic restenosis rate was 28% (5/18) at follow-up.

This study demonstrates safety and feasibility of local intracoronary delivery of reviparin with a porous balloon following PTCA even in smaller diameter coronary arteries

Circulation, 1998; 98: 2829-2835

Clinical Outcomes of Therapeutic Agents That Block the Platelet Glycoprotein IIb/IIIa Integrin in Ischemic Heart Disease

David F. Kong, Robert M. Califf, Dave P. Miller, David J. Moliterno, Harvey D. White, Robert A. Harrington, James E. Tchong, A. Michael Lincoff, Vic Hasselblad, and Eric J. Topol

Background-Several platelet glycoprotein (GP) IIb/IIIa receptor antagonists have been evaluated in clinical trials. We conducted a systematic overview (meta-analysis) to assess the effect of these compounds on death, myocardial infarction (MI), and revascularization.

Methods and Results-ORs were calculated for 16 randomized, controlled trials of GP IIb/IIIa inhibitors. An

empirical Bayesian random-effects model combined the outcomes of 32 135 patients. There was a significant mortality reduction by GP IIb/IIIa inhibitors at 48 to 96 hours, with an OR of 0.70 (95% CI, 0.51 to 0.96;  $P < 0.03$ ), equivalent to a reduction of 1 death per 1000 patients treated. Mortality benefits at 30 days (OR, 0.87; 95% CI, 0.74 to 1.02;  $P = 0.08$ ) and 6 months (OR, 0.97; 95% CI, 0.86 to 1.10;  $P = 0.67$ ) were not statistically significant. For the combined end point of death or MI, there was a highly significant ( $P < 0.001$ ) benefit for GP IIb/IIIa inhibitors at each time point. The 30-day OR was 0.76 (95% CI, 0.66 to 0.87), or 20 fewer events per 1000 patients treated. For the composite end point of death, MI, or revascularization, there was also a highly significant ( $P < 0.001$ ) benefit for GP IIb/IIIa inhibitors. At 30 days, the OR was 0.77 (95% CI, 0.68 to 0.86), or 30 fewer events per 1000 patients treated. The risk differences for death, death or MI, and composite outcomes were similar at 6 months, indicating a sustained absolute improvement. Similar benefit was seen when trials were subgrouped by therapeutic indication (percutaneous intervention versus acute coronary syndromes).

**Conclusions**-Application of this new therapeutic class to clinical practice promises substantial benefit for both indications.

Circulation, 1999 ;99: 3050-3055

### Plasminogen Activator Inhibitor-1 Is a Major Determinant of Arterial Thrombolysis Resistance

Yanhong Zhu, Peter Carmeliet, and William P. Fay

**Background**-Platelet-rich thrombi are resistant to lysis by tissue plasminogen activator (tPA). Plasminogen activator inhibitor-1 (PAI-1), a rapid inhibitor of tPA, may contribute to arterial thrombolysis resistance. However, few data are available regarding the effect of PAI-1 on arterial thrombolysis in animals. We used a murine carotid injury model to test the hypothesis that PAI-1 inhibits thrombolysis mediated by pharmacological concentrations of tPA.

**Methods and Results**-Platelet-rich thrombi were induced in wild-type mice (PAI-1  $+/+$ ;  $n = 11$ ) and PAI-1-deficient mice (PAI-1  $-/-$ ;  $n = 11$ ) with ferric chloride. Baseline carotid blood flows and mean occlusion times did not differ between PAI-1  $+/+$  and PAI-1  $-/-$  mice. Clot lysis was induced by infusion of heparin (200 U/kg bolus, 70 U $\cdot$ kg $^{-1}$  $\cdot$ h $^{-1}$  drip), human plasminogen (50 mg/kg), and tPA at 20 ( $n = 10$ ) or 100 ( $n = 12$ )  $\mu$ g $\cdot$ kg $^{-1}$  $\cdot$ min $^{-1}$ . Mean plasma tPA antigens were 2.7  $\mu$ g/mL (tPA infusion, 20  $\mu$ g $\cdot$ kg $^{-1}$  $\cdot$ min $^{-1}$ ) and 5.5  $\mu$ g/mL (tPA infusion, 100  $\mu$ g $\cdot$ kg $^{-1}$  $\cdot$ min $^{-1}$ ), with no significant differences between PAI-1  $+/+$  mice and PAI-1  $-/-$  mice. Reperfusion after tPA 20  $\mu$ g $\cdot$ kg $^{-1}$  $\cdot$ min $^{-1}$  occurred in 1 of 5 PAI-1  $+/+$  mice versus 5 of 5 PAI-1  $-/-$  mice ( $P = 0.0006$ ). Reperfusion occurred in

all mice that received tPA 100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , but reperfusion times were significantly shorter in PAI-1  $-/-$  mice ( $17.8\pm 2.6$  minutes,  $n=6$ ) than in PAI-1  $+/+$  mice ( $35.7\pm 5.1$  minute,  $n=6$ ;  $P=0.01$ ). Histological analyses confirmed that carotid thrombi were platelet rich and that PAI-1 was distributed uniformly throughout thrombi from PAI-1  $+/+$  mice. Lysates of PAI-1  $+/+$  platelets inhibited human tPA, whereas PAI-1  $-/-$  platelet lysates did not. Conclusions-PAI-1 is a major determinant of the resistance of platelet-rich arterial thrombi to lysis by pharmacological concentrations of tPA. Strategies to inhibit or resist PAI-1 may enhance thrombolysis.

Journal of the American College of Cardiology, 33:634-639

Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial

Kenneth A. Ault, Christopher P. Cannon, Jane Mitchell, John McCahan, Russell P. Tracy, William F. Novotny, James D. Reimann, Eugene Braunwald

#### OBJECTIVES

This study was designed to determine the magnitude and time course of platelet activation during therapy of acute coronary syndromes with an oral platelet antagonist.

#### BACKGROUND

Platelet activation and aggregation are central to the pathogenesis of the acute coronary syndromes (ACS). However, few data are available on levels of platelet activation over time in patients with ACS, especially in the setting of chronic glycoprotein (GP) IIb/IIIa inhibition.

#### METHODS

The Thrombolysis in Myocardial Infarction (TIMI) 12 trial was a phase II, double-blind trial evaluating the effects of sibrافiban, an oral, selective antagonist of the platelet glycoprotein IIb/IIIa receptor in patients stabilized after an ACS. A subset of 90 of the 329 patients in the study had measurement of platelet activation as assessed by the expression of platelet associated P-Selectin on days 0, 7 and 28. Platelet activation was measured in blood samples that were fixed either immediately (spontaneous activation) or after 5 minute incubation with 0, 1 M or 5 M ADP in order to assess platelet responsiveness to very low or moderate stimulation.

#### RESULTS

At baseline there was a significant elevation of spontaneous platelet activation as compared to samples obtained from normal donors or from patients who did not have acute coronary syndromes (ACS patients 27.6

$\pm 18.7\%$ , Normal controls  $8.5 \pm 4.4\%$ , Patient controls  $10.9 \pm 7.1\%$ ,  $p < 0.005$  for both). In addition, there was a significant decrease in the levels of platelet activation with time during the 28 days of treatment with sibrافiban. Nevertheless, even on day 28, the TIMI-12 patients continued to show elevated platelet activation in comparison to the control groups ( $p < 0.05$  for both).

#### CONCLUSIONS

These results suggest that platelets remain activated long after clinical stabilization post ACS. Although platelet activation decreased after one month of oral GPIIb/IIIa inhibition, levels remained higher than normal, suggesting the need for long-term antiplatelet therapy following ACS.

Circulation, 1999 ;99: 1951-1958

#### Sustained Suppression of Ischemic Complications of Coronary Intervention by Platelet GP IIb/IIIa Blockade With Abciximab : One-Year Outcome in the EPILOG Trial

Kelly, Gerald C. Timmis, Neal S. Kleiman, Joan E. Booth, Craig Balog, Catherine F. Cabot, Keaven M. Anderson, Harlan F. Weisman, and Eric J. Topol

Background-Blockade of the platelet glycoprotein IIb/IIIa receptor with the monoclonal antibody fragment abciximab was shown in a placebo-controlled randomized trial to reduce the incidence of acute ischemic complications within 30 days among a broad spectrum of patients undergoing percutaneous coronary revascularization. The durability of clinical benefit in this setting has not been established.

Methods and Results-A total of 2792 patients enrolled in the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) trial were followed with maintenance of double-blinding for 1 year. Patients had been assigned at the time of their index coronary interventional procedure to receive placebo with standard-dose, weight-adjusted heparin (100 U/kg initial bolus), abciximab with standard-dose, weight-adjusted heparin, or abciximab with low-dose, weight-adjusted heparin (70 U/kg initial bolus). The primary outcome was the composite of death, myocardial infarction, or urgent repeat revascularization by 30 days; this composite end point and its individual components were also assessed at 6 months and 1 year. Rates of any repeat revascularization (urgent or elective), target vessel revascularization, and a composite of death, myocardial infarction, or any repeat revascularization were also reported. Follow-up at 1 year was 99% complete for survival status and 97% complete for other end points. By 1 year, the incidence of the primary composite end point was 16.1% in the placebo group, 9.6% in the abciximab with low-dose heparin group ( $P < 0.001$ ), and 9.5% in the abciximab with standard-dose heparin group ( $P < 0.001$ ). Each of the components of this composite end point was reduced to a similar extent. Nonurgent or target vessel repeat revascularization rates were not significantly decreased by abciximab therapy. Mortality rates over 1 year increased with

increasing levels of periprocedural creatine kinase MB fraction elevation.

Conclusions-Acute reductions in ischemic events after percutaneous coronary intervention by abciximab are sustained over follow-up to at least 1 year. Early periprocedural myocardial infarctions suppressed by this therapy are associated with long-term mortality rates.

Circulation, 1999 ;100: 1667-1672

Ticlopidine and Clopidogrel

Martin J. Quinn and Desmond J. Fitzgerald

Abstract-The thienopyridines ticlopidine and clopidogrel are inhibitors of platelet function in vivo. Their mode of action has not been defined, but it appears that they require conversion to as yet unidentified metabolites that are noncompetitive antagonists of the platelet ADP receptor. Inhibition of platelet aggregation with these compounds is delayed until 24 to 48 hours after administration. Maximum inhibition occurs after 3 to 5 days, and recovery is slow after drug withdrawal. Ticlopidine is effective in preventing cardiovascular events in cerebrovascular, cardiovascular, and peripheral vascular disease, with an efficacy that is similar to aspirin. However, its use is associated with significant and sometimes fatal adverse reactions, specifically neutropenia and bone marrow aplasia. Gastrointestinal side effects and skin rashes are common and result in discontinuation of therapy in up to 10% of patients. Clopidogrel is at least as effective as aspirin in preventing cardiovascular events in patients with a history of vascular disease. It appears to be safer than ticlopidine, although its efficacy in acute coronary syndromes or post-coronary-stent insertion has not been reported. Important outstanding issues are whether clopidogrel adds to the benefit of aspirin and whether the combination of these agents is safe. If so, this combination may become the standard for antithrombotic therapy in cardiovascular disease.

Circulation ,1999 ;99: 2720-2732.

Abciximab Facilitates the Rate and Extent of Thrombolysis : Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial

Elliott M. Antman, Robert P. Giugliano, C. Michael Gibson, Carolyn H. McCabe, Patrick Coussement, Neal S. Kleiman, Alec Vahanian, A. A. Jennifer Adgey, Ian Menown, Hans-Jurgen Rupprecht, R. Van der Wieken, John Ducas, Joel Scherer, Keaven Anderson, Frans Van de Werf, and Eugene Braunwald

**Background-**The TIMI 14 trial tested the hypothesis that abciximab, the Fab fragment of a monoclonal antibody directed to the platelet glycoprotein (GP) IIb/IIIa receptor, is a potent and safe addition to reduced-dose thrombolytic regimens for ST-segment elevation MI.

**Methods and Results-**Patients (n=888) with ST-elevation MI presenting <12 hours from onset of symptoms were treated with aspirin and randomized initially to either 100 mg of accelerated-dose alteplase (control) or abciximab (bolus 0.25 mg/kg and 12-hour infusion of 0.125  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) alone or in combination with reduced doses of alteplase (20 to 65 mg) or streptokinase (500 000 U to 1.5 MU). Control patients received standard weight-adjusted heparin (70-U/kg bolus; infusion of 15 U $\cdot$ kg $\cdot$ 1-h $\cdot$ 1), whereas those treated with a regimen including abciximab received low-dose heparin (60-U/kg bolus; infusion of 7 U $\cdot$ kg $\cdot$ 1-h $\cdot$ 1). The rate of TIMI 3 flow at 90 minutes for patients treated with accelerated alteplase alone was 57% compared with 32% for abciximab alone and 34% to 46% for doses of streptokinase between 500 000 U and 1.25 MU with abciximab. Higher rates of TIMI 3 flow at both 60 and 90 minutes were observed with increasing duration of administration of alteplase, progressing from a bolus alone to a bolus followed by either a 30- or 60-minute infusion (P<0.02). The most promising regimen was 50 mg of alteplase (15-mg bolus; infusion of 35 mg over 60 minutes), which produced a 76% rate of TIMI 3 flow at 90 minutes and was tested subsequently in conjunction with either low-dose or very-low-dose (30-U/kg bolus; infusion of 4 U $\cdot$ kg $\cdot$ 1-h $\cdot$ 1) heparin. TIMI 3 flow rates were significantly higher in the 50-mg alteplase plus abciximab group versus the alteplase-only group at both 60 minutes (72% versus 43%; P=0.0009) and 90 minutes (77% versus 62%; P=0.02). The rates of major hemorrhage were 6% in patients receiving alteplase alone (n=235), 3% with abciximab alone (n=32), 10% with streptokinase plus abciximab (n=143), 7% with 50 mg of alteplase plus abciximab and low-dose heparin (n=103), and 1% with 50 mg of alteplase plus abciximab with very-low-dose heparin (n=70).

**Conclusions-**Abciximab facilitates the rate and extent of thrombolysis, producing early, marked increases in TIMI 3 flow when combined with half the usual dose of alteplase. This improvement in reperfusion with alteplase occurred without an increase in the risk of major bleeding. Substantial reductions in heparin dosing may reduce the risk of bleeding even further. Modest improvements in TIMI 3 flow were seen when abciximab was combined with streptokinase, but there was an increased risk of bleeding.

## Usefulness of subcutaneous low molecular weight heparin (ardeparin) for reduction of restenosis after percutaneous transluminal coronary angioplasty

Lawrence W. Gimple, Howard C. Herrmann, Michael Winniford, Eberhard Mammen for the Ardeparin and Restenosis Study Group

In addition to its anticoagulant effects, heparin is known to have antiproliferative effects on vascular smooth muscle cells. Ardeparin is a partially depolymerized (low molecular weight) heparin that has a longer half-life than unfractionated heparin. Following successful coronary balloon angioplasty, 565 patients were randomized to treatment with twice-daily subcutaneous ardeparin 50 anti-Xa U/kg (low dose) or 100 anti Xa U/kg body weight (high dose), or placebo for 3 months. Follow-up angiography was performed in 415 patients at 4 months, or earlier if clinically indicated. Additionally, patients underwent treadmill exercise electrocardiography at 2 weeks and 4 months. This study was designed to test the hypothesis that 3 months of subcutaneous dosing of ardeparin would reduce angiographic restenosis after coronary balloon angioplasty. Ardeparin had no effect on the incidence of angiographic restenosis (prespecified definition:  $\geq 50\%$  luminal diameter narrowing plus a loss of 50% of initial gain or absolute decrease of 20% of luminal diameter). Neither the mean luminal diameters nor mean percent diameter stenoses were different among the treatment groups before, after, or 4 months after balloon angioplasty. On exercise electrocardiography at 2 weeks and 4 months, patients in all treatment groups had similar exercise tolerance, incidence of angina, and frequency of ST depression. Thus, ardeparin treatment given subcutaneously for 3 months after successful balloon angioplasty does not reduce either angiographic or clinical measures of restenosis.

Circulation ,1999 ;99: 620-625

## Rapid Platelet-Function Assay : An Automated and Quantitative Cartridge-Based Method

Jeffrey W. Smith, Steven R. Steinhubl, A. Michael Lincoff, Jacqueline C. Coleman, Theodore T. Lee, Robert S. Hillman, and Barry S. Collier

**Background-**The platelet glycoprotein (GP) IIb/IIIa receptor is important in mediating platelet thrombus formation, and the GP IIb/IIIa antagonist abciximab (c7E3 Fab; ReoPro) is effective in preventing thrombotic ischemic cardiovascular complications of unstable angina and percutaneous coronary interventions. Small-molecule antagonists of GP IIb/IIIa based on the Arg-Gly-Asp (RGD) sequence show similar benefit, and some of these agents are orally active. However, there may be significant interindividual variation in response to such antagonists, especially with chronic oral therapy. It will be essential to balance the beneficial antithrombotic effect of these drugs with their potential for causing bleeding. In response to this need, we have developed a rapid platelet-function assay (RPFA), a point-of-care system that provides a quantitative measure of the competence of the GP IIb/IIIa receptor as reflected in the ability of platelets to agglutinate fibrinogen-coated beads.

**Methods and Results-**Polystyrene beads were coated with fibrinogen and placed in a cartridge along with a lyophilized peptide that activates the thrombin receptor. Anticoagulated whole blood was added to the cartridge, and then a microprocessor-controlled operation mixed the reagents and detected agglutination between platelets and coated beads. Quantitative digital results were displayed within 3 minutes. Because there is no dilution of the blood, the assay can be used to measure platelet activity in samples that have been treated with GP IIb/IIIa antagonists with high dissociation rates. RPFA results of whole-blood samples treated with different GP IIb/IIIa antagonists correlated well with both conventional turbidimetric platelet aggregation ( $r^2=0.95$ ) and the percentage of free GP IIb/IIIa molecules in the sample ( $r^2=0.96$ ). The mean difference in measurements between RPFA and aggregometry was  $-4\%$  ( $\pm 4\%$  SD), and the mean difference in measurements between RPFA and free GP IIb/IIIa receptors was  $-2\%$  ( $\pm 6\%$  SD).

**Conclusions-**The RPFA provides rapid information on platelet function that mirrors turbidimetric platelet aggregation and reflects GP IIb/IIIa receptor blockade.

Circulation ,1999; 99: 73-80

**Recombinant Hirudin (Lepirudin) Provides Safe and Effective Anticoagulation in Patients With Heparin-Induced Thrombocytopenia : A Prospective Study**

A. Greinacher, H. Volpel, U. Janssens, V. Hach-Wunderle, B. Kemkes-Matthes, P. Eichler, H. G. Mueller-Velten, and B. Potzsch

**Background-**The immunological type of heparin-induced thrombocytopenia (HIT) is the most frequent drug-

induced thrombocytopenia. This study evaluated the efficacy of recombinant hirudin (r-hirudin or lepirudin), a potent thrombin inhibitor, for anticoagulation in patients with confirmed HIT.

**Methods and Results**-Eighty-two patients in this prospective, multicenter study received 1 of 4 intravenous r-hirudin regimens: A1, HIT patients with thrombosis (n=51), 0.4-mg/kg bolus and then 0.15 mg·kg<sup>-1</sup>·h<sup>-1</sup>; A2, HIT patients with thrombosis receiving thrombolysis (n=5), 0.2-mg/kg bolus and then 0.1 mg·kg<sup>-1</sup>·h<sup>-1</sup>; B, HIT patients without thrombosis (n=18), 0.1 mg·kg<sup>-1</sup>·h<sup>-1</sup>; and C, during cardiopulmonary bypass surgery (n=8), 0.25-mg/kg bolus and then 5-mg boluses as needed. Response criteria were increase in platelet count by ≥30% to >109/L and activated partial thromboplastin time (aPTT) values 1.5 to 3.0 times baseline values achieved with a maximum of 2 dose increases. No placebo control was used for ethical reasons. Outcomes of a subset of r-hirudin-treated patients who met predefined inclusion criteria (n=71) were compared with those of a historical control group (n=120) for combined and individual incidences of death, amputations, new thromboembolic complications, and incidences of bleeding. Platelet counts increased rapidly in 88.7% of r-hirudin-treated patients with acute HIT. In regimens A1 and A2, the 25% and 75% quartiles of the aPTT were within the target range at all but 1 time point. The incidence of the combined end point (death, amputation, new thromboembolic complications) was significantly reduced in r-hirudin patients compared with historical control patients (P=0.014). During first selected treatment, the adjusted hazard ratio for r-hirudin patients versus historical control was 0.279 (95% CI, 0.112 to 0.699; P=0.003). Bleeding rates were similar in both groups.

**Conclusions**-r-Hirudin treatment is associated with a rapid and sustained recovery of platelet counts, sufficient aPTT prolongations, and true clinical benefits for patients with HIT.

Circulation, 1999 ;100: 1609-1615

**Intracoronary Thrombus and Platelet Glycoprotein IIb/IIIa Receptor Blockade With Tirofiban in Unstable Angina or Non-Q-Wave Myocardial Infarction : Angiographic Results From the PRISM-PLUS Trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)**

Xue-Qiao Zhao, Pierre Theroux, Steven M. Snapinn, and Frederic L. Sax

**Background**-The present study describes the effects of tirofiban, a nonpeptide platelet glycoprotein (GP) IIb/IIIa receptor blocker, on the characteristics of culprit lesions in patients with unstable angina (UA) or non-Q-wave myocardial infarction (NQWMI).

**Methods and Results-**Of 1915 patients enrolled in PRISM-PLUS, 1491 had a readable film obtained a median of 65 hours after randomization. A core laboratory examined the culprit lesions for intracoronary thrombus burden (primary end point) and for TIMI flow grade distribution and severity of the obstruction and of underlying coronary artery disease (secondary end points). The combination of tirofiban plus heparin compared with heparin alone significantly reduced the intracoronary thrombus burden of the culprit lesions (OR=0.77, P=0.022), improved the perfusion grade (OR=0.65, P=0.002), and decreased the severity of the obstruction (P=0.037), but it did not influence the severity of the underlying plaque. Persistence of a thrombus in 45% of patients was associated with a 2.4-fold increase in the odds of death at 30 days (P=0.005) and a 2-fold increase in the odds of myocardial infarction (P=0.002).

**Conclusions-**The addition of tirofiban to heparin reduced the thrombus burden of the culprit lesion and improved distal perfusion in patients with UA or NQWMI, which supports the clinical benefit observed with the combination treatment.

Circulation, 1999; 99: 2231-2238

Quantifying GPIIb/IIIa Receptor Binding Using 2 Monoclonal Antibodies : Discriminating Abciximab and Small Molecular Weight Antagonists

Martin Quinn, Adele Deering, Maura Stewart, Dermot Cox, Brendan Foley, and Desmond Fitzgerald

**Background-**Dosing of glycoprotein (GP) IIb/IIIa receptor antagonists is frequently based on the inhibition of platelet aggregation, which may be influenced by the agonist used or concurrent medications. Here we describe a monoclonal antibody-based technique to quantify total and ligand-occupied GPIIb/IIIa receptors.

**Methods and Results-**In vitro binding of monoclonal antibodies, LYP18 (Mab1) and 4F8 (Mab2), to the GPIIb/IIIa complex, was characterized using purified receptor and to platelets by flow cytometry. Patients undergoing coronary angioplasty received a single 20 mg dose of the oral GPIIb/IIIa antagonist, xemilofiban, or matching placebo, and antibody binding was compared with inhibition of platelet aggregation. Mab1 and Mab2 were bound to purified GPIIb/IIIa and to unoccupied, inactivated receptor on platelets. Mab2 identified the  $\beta_3$  subunit, whereas Mab1 was complex-specific. Neither antibody interfered with the other's binding, suggesting that they identified distinct sites. Mab1 identified  $53\ 300 \pm 5423$  GPIIb/IIIa sites per platelet, whereas Mab2 identified  $50\ 120 \pm 5066$  sites per platelet. Mab1 binding was inhibited by abciximab in a dose dependent manner (IC<sub>50</sub>,  $0.85 \pm 0.1$   $\mu\text{g/mL}$ ), whereas Mab2 binding was unaffected. In contrast, the 2 small molecular weight antagonists, SC-57101A (IC<sub>50</sub>,  $0.22 \pm 0.06$   $\mu\text{mol/L}$ ) and eptifibatide (IC<sub>50</sub>,  $0.35 \pm 0.14$   $\mu\text{mol/L}$ ) inhibited

Mab2 but not Mab1 binding. In patients treated with xemilofiban, Mab1 binding was unaltered but Mab2 binding decreased from  $37\,930 \pm 2061$  sites per platelet at baseline to  $8318 \pm 870$  sites per platelet 6 hours after dosing ( $P < 0.0001$ ). Platelet aggregation to adenosine diphosphate ( $20\ \mu\text{mol/L}$ ) fell to  $3 \pm 3\%$  of baseline in line with the inhibition of Mab2 binding (correlation coefficient 0.8,  $P < 0.0001$ ).

Conclusions-Mab1 and Mab2 bind to GPIIb/IIIa and are differentially displaced by abciximab and small molecular weight antagonists. These antibodies may be used to monitor receptor number and occupancy during administration of a GPIIb/IIIa antagonist.

The American Journal of Cardiology, 83:7:1006-1011

Timing of coronary stent thrombosis in patients treated with ticlopidine and aspirin

Stephanie H. Wilson, Charanjit S. Rihal, Malcolm R. Bell, James L. Velianou, David R. Holmes, Jr., Peter B. Berger

In patients receiving coronary stents treated with aspirin and coumadin, the peak incidence of stent thrombosis occurs on the fifth and sixth days following the implantation procedure. Little is known about the timing of stent thrombosis in patients treated with aspirin and ticlopidine. We compared the timing of coronary stent thrombosis in patients treated with ticlopidine and aspirin with the timing in those receiving coumadin and aspirin. A retrospective databank analysis was performed and 39 patients were identified who experienced stent thrombosis after successful coronary stent implantation. Of these, 21 had been treated with ticlopidine and aspirin and 18 with coumadin and aspirin therapy. The median time from stent implantation to stent thrombosis in the ticlopidine and aspirin group was 12 hours (interquartile range 6 to 72 hours) compared with 4 days in the coumadin and aspirin group (interquartile range 21 to 68 hours) ( $p < 0.0001$ ). There was no significant difference between the timing of stent thrombosis in patients treated with abciximab in addition to ticlopidine and aspirin (median 17 hours, interquartile range 6 to 29) versus ticlopidine and aspirin patients who did not receive abciximab (median 11 hours, interquartile range 9 to 12,  $p = 0.57$ ). Thus, in patients who receive coronary stents, stent thrombosis occurs much earlier after the procedure in patients treated with ticlopidine and aspirin than in patients treated with anticoagulation therapy.

Journal of the American College of Cardiology, 1999;34:2:461-467

Heparin after percutaneous intervention (HAPI): a prospective multicenter randomized trial of three heparin regimens after successful coronary intervention

Maher Rabah, Denise Mason, David W.M. Muller, Randal Hundley, Aaron D. Kugelmass, Bonnie Weiner, Louis Cannon, William W. O'Neill, Robert D. Safian

**OBJECTIVES** The purpose of this study was to determine the incidence of bleeding, vascular, and ischemic complications using three different heparin regimens after successful intervention.

**BACKGROUND** The ideal dose and duration of heparin infusion after successful coronary intervention is unknown.

**METHODS** Patients were randomized to one of three heparin strategies after coronary intervention: Group 1 (n = 157 patients) received prolonged (12 to 24 h) heparin infusion followed by sheath removal; Group 2 (n = 120 patients) underwent early removal of sheaths, followed by reinstitution of heparin infusion for 12 to 18 h; Group 3 (n = 137 patients) did not receive any further heparin after intervention with early sheath removal. The primary end point of the study was the combined incidence of in-hospital bleeding and vascular events. Secondary end points included in-hospital ischemic events, length of stay, cost and one-month outcome.

**RESULTS** After successful coronary intervention, 414 patients were randomized. Unstable angina or postinfarction angina was present in 83% of patients before intervention. The combined incidence of bleeding and vascular events was 21% in Group 1, 14% in Group 2 and 8% in Group 3 (p = 0.01). The overall incidence of in-hospital ischemic complications was 2.2%; there were no differences between groups. Length of hospital stay was shorter (p = 0.033) and adjusted hospital cost was lower (p < 0.001) for Group 3. At 30 days, the incidence of delayed cardiac and vascular events was similar for all three groups.

**CONCLUSIONS** Heparin infusion after successful coronary intervention is associated with more minor bleeding and vascular injury, prolonged length of stay and increased cost. In-hospital and one-month ischemic events rarely occur after successful intervention, irrespective of heparin use. Routine postprocedure heparin is not recommended, even in patients who present with unstable ischemic syndromes.

Circulation ,1999 ;99: 2364-2366

Effectiveness of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis After

## Coronary Stent Implantation

Issam Moussa, Mathew Oetgen, Gary Roubin, Antonio Colombo, Xangdong Wang, Sriram Iyer, Roberta Maida, Michael Collins, Edward Kreps, and Jeffrey W. Moses

**Background-**Ticlopidine has been shown to reduce the incidence of stent thrombosis compared with warfarin, but it may cause serious hematological side effects. Clopidogrel, a new thienopyridine derivative, may be a safe alternative to ticlopidine. The aim of this study was to compare the safety and efficacy of clopidogrel and aspirin with those of ticlopidine and aspirin in patients undergoing coronary stent implantation.

**Methods and Results-**The population of this study consisted of 2 groups: patients who underwent coronary stenting and were treated with ticlopidine and aspirin (TA group, n=1406), and patients who underwent coronary stenting followed by treatment with clopidogrel and aspirin (CA group, n=283). At 1-month follow-up, there was no difference in stent thrombosis (1.5% versus 1.4%, P=1.0) or major adverse cardiac events (3.1% versus 2.4%, P=0.85) between the TA and CA groups, respectively. The probability of any side effect (neutropenia, diarrhea, rash) was significantly higher in the TA group (10.6% versus 5.3%, P=0.006; relative risk, 0.53; CI, 0.32 to 0.86).

**Conclusions-**These data suggest that clopidogrel may be an effective pharmacological regimen after coronary stent implantation. Furthermore, the simpler dosing regimen, the absence of neutropenia, and the lower frequency of other side effects make it a safe alternative to ticlopidine.

Circulation, 1999; 100: 1593-1601

**Enoxaparin Prevents Death and Cardiac Ischemic Events in Unstable Angina/Non-Q-Wave Myocardial Infarction : Results of the Thrombolysis In Myocardial Infarction (TIMI) 11B Trial**

Elliott M. Antman, Carolyn H. McCabe, Enrique P. Gurfinkel, Alexander G. G. Turpie, Peter J. L. M. Bernink, Diana Salein, Antonio Bayes de Luna, Kim Fox, Jean-Marc Lablanche, David Radley, Jerome Premmereur, and Eugene Braunwald

**Background-**Low-molecular-weight heparins are attractive alternatives to unfractionated heparin (UFH) for

management of unstable angina/non-Q-wave myocardial infarction (UA/NQMI).

**Methods and Results**-Patients (n=3910) with UA/NQMI were randomized to intravenous UFH for 3 days followed by subcutaneous placebo injections or uninterrupted antithrombin therapy with enoxaparin during both the acute phase (initial 30 mg intravenous bolus followed by injections of 1.0 mg/kg every 12 hours) and outpatient phase (injections every 12 hours of 40 mg for patients weighing <65 kg and 60 mg for those weighing 65 kg). The primary end point (death, myocardial infarction, or urgent revascularization) occurred by 8 days in 14.5% of patients in the UFH group and 12.4% of patients in the enoxaparin group (OR 0.83; 95% CI 0.69 to 1.00; P=0.048) and by 43 days in 19.7% of the UFH group and 17.3% of the enoxaparin group (OR 0.85; 95% CI 0.72 to 1.00; P=0.048). During the first 72 hours and also throughout the entire initial hospitalization, there was no difference in the rate of major hemorrhage in the treatment groups. During the outpatient phase, major hemorrhage occurred in 1.5% of the group treated with placebo and 2.9% of the group treated with enoxaparin (P=0.021).

**Conclusions**-Enoxaparin is superior to UFH for reducing a composite of death and serious cardiac ischemic events during the acute management of UA/NQMI patients without causing a significant increase in the rate of major hemorrhage. No further relative decrease in events occurred with outpatient enoxaparin treatment, but there was an increase in the rate of major hemorrhage.

Circulation, 1999 ;100: 2049-2053

#### Clinical Outcomes of Bivalirudin for Ischemic Heart Disease

David F. Kong, Eric J. Topol, John A. Bittl, Harvey D. White, Pierre Theroux, Vic Hasselblad, and Robert M. Califf

**Background**-Current treatment strategies for percutaneous coronary revascularization and acute coronary syndromes incorporate thrombin inhibition with either unfractionated or fractionated heparin. The peptide bivalirudin (Hirulog) is a direct thrombin inhibitor whose pharmacological properties differ from those of heparin. We conducted a systematic overview (meta-analysis) to assess the effect of bivalirudin on 4 end points: death, myocardial infarction, major hemorrhage, and the composite of death or infarction.

**Methods and Results**-Six trials (5674 patients) represent the randomized, controlled bivalirudin experience, including 4603 patients undergoing elective percutaneous coronary revascularization and 1071 patients with acute coronary syndromes. ORs for the 4 clinical end points were calculated for each trial. Four trials (4973

patients) that compared bivalirudin with heparin were combined with the use of a random-effects model. In these trials, bivalirudin was associated with a significant reduction in the composite of death or infarction (OR 0.73, 95% CI 0.57 to 0.95; P=0.02) at 30 to 50 days, or 14 fewer events per 1000 patients so treated. There also was a significant reduction in major hemorrhage for the same trials (OR 0.41, 95% CI 0.32 to 0.52; P<0.001, or 58 fewer events per 1000 patients so treated). A similar analysis combined 2 dose-ranging trials (701 patients) that compared therapeutic (activated partial thromboplastin time more than twice the control time) with subtherapeutic bivalirudin anticoagulation (activated partial thromboplastin time less than twice the control time).

Conclusions-Bivalirudin is at least as effective as heparin, with clearly superior safety. Thus, it provides an unprecedented net clinical benefit over heparin in patients with ischemic heart disease.

JACC, 1999;33:1528-32

Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty : Results of the glycoprotein receptor antagonist patency evaluation (GRAPE) pilot study

Lambert F.M. van den Merkhof, Felix Zijlstra, Hans Olsson, Lars Grip, Gerrit Veen, Frits W.H.M. Bar, Marcel J.B.M. van den Brand, Maarten L. Simoons and Freek W.A. Verheugt

#### OBJECTIVES

We sought to study the effect of early infusion of abciximab on coronary patency before primary angioplasty in patients with acute myocardial infarction.

#### BACKGROUND

Glycoprotein IIb/IIIa antagonists have proved to be effective in reducing ischemic events associated with coronary angioplasty. The present study explores whether abciximab alone, without administration of thrombolytic therapy, may induce reperfusion in patients with acute myocardial infarction.

#### METHODS

In the Glycoprotein Receptor Antagonist Patency Evaluation pilot study 60 patients with less than 6 h signs and symptoms of acute myocardial infarction eligible for primary angioplasty received in the emergency room a bolus of abciximab 250 µg/kg followed by a 12-h infusion of 10 µg/min. All patients were also treated with an oral dose of 160 mg aspirin and 5,000 IU of heparin intravenously. As soon as possible a diagnostic angiography was performed to evaluate the patency of the infarct-related artery.

#### RESULTS

The median time between onset of symptoms and the administration of the abciximab bolus was 150 min (range 45 to 345), and the median time between abciximab bolus and first contrast injection in the infarct-

related artery was 45 min (range 10 to 150). In 24 patients (40%, 95% confidence interval 28% to 52%) Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 was observed at a median time of 45 min (range 10 to 150) after abciximab bolus; TIMI flow grade 3 was observed in 11 patients (18%, 95% confidence interval 9% to 28%). There was no difference in percentage of TIMI flow grade 2 or 3 between patients who received abciximab within 2.5 h after onset of symptoms or thereafter.

#### CONCLUSIONS

Abciximab therapy given in the emergency room in patients awaiting primary angioplasty is associated with full reperfusion (TIMI flow grade 3) in about 20% and with TIMI flow grade 2 or 3 in about 40% of the patients at a median time of 45 min. These figures are higher than those in primary angioplasty trials without such pretreatment. Randomized controlled trials of very early infusion of abciximab, either prehospital or in-hospital, in patients eligible for angioplasty are warranted.

Circulation, 1999; 100: 1602-1608

Assessment of the Treatment Effect of Enoxaparin for Unstable Angina/Non-Q-Wave Myocardial Infarction :  
TIMI 11B-ESSENCE Meta-Analysis

Elliott M. Antman, Marc Cohen, David Radley, Carolyn McCabe, Janet Rush, Jerome Premmereur, and Eugene Braunwald

**Background-**Two phase III trials of enoxaparin for unstable angina/non-Q-wave myocardial infarction have shown it to be superior to unfractionated heparin for preventing a composite of death and cardiac ischemic events. A prospectively planned meta-analysis was performed to provide a more precise estimate of the effects of enoxaparin on multiple end points.

**Methods and Results-**Event rates for death, the composite end points of death/nonfatal myocardial infarction and death/nonfatal myocardial infarction/urgent revascularization, and major hemorrhage were extracted from the TIMI 11B and ESSENCE databases. Treatment effects at days 2, 8, 14, and 43 were expressed as the OR (and 95% CI) for enoxaparin versus unfractionated heparin. All heterogeneity tests for efficacy end points were negative, which suggests comparability of the findings in TIMI 11B and ESSENCE. Enoxaparin was associated with a 20% reduction in death and serious cardiac ischemic events that appeared within the first few days of treatment, and this benefit was sustained through 43 days. Enoxaparin's treatment benefit was not associated with an increase in major hemorrhage during the acute phase of therapy, but there was an increase in the rate of minor hemorrhage.

**Conclusions-**The accumulated evidence, coupled with the simplicity of subcutaneous administration and

elimination of the need for anticoagulation monitoring, indicates that enoxaparin should be considered as a replacement for unfractionated heparin as the antithrombin for the acute phase of management of patients with high-risk unstable angina/non-Q-wave myocardial infarction.

Am J Cardiol 1999 Dec 15;84(12):1391-5

Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris.

Rabah MM, Premmereur J, Graham M, Fareed J, Hoppensteadt DA, Grines LL, Grines CL

This pilot study was designed to determine whether the low molecular weight heparin, enoxaparin, could be used for elective percutaneous coronary intervention (PCI) to provide antithrombotic effects without the full systemic anticoagulation that occurs with the use of unfractionated heparin. Sixty patients were randomized to receive intravenous enoxaparin (1 mg/kg bolus dose) or unfractionated heparin at the time of coronary intervention. Laboratory testing was performed at baseline, 5 minutes, and 4 hours after study drug to test if a single bolus dose of intravenous enoxaparin can consistently achieve therapeutic antithrombotic effect, thus eliminating the need for multiple doses of heparin and closely monitoring levels of anticoagulation during PCI. Thirty percent of patients who received unfractionated heparin required a second bolus of intravenous heparin to achieve the target-activated clotting time of 300 seconds before PCI. Enoxaparin showed antithrombotic properties comparable to that of unfractionated heparin as measured by anti-Xa levels, with less inhibition of thrombin (factor IIa) at the time points measured ( $p < 0.0001$ ). Angioplasty success rates, in-hospital ischemia, bleeding, and vascular complications were similar in both groups. Thus, intravenous enoxaparin has predictable and effective antithrombotic effects during elective PCI. Although the level of anticoagulation attained with enoxaparin is significantly lower than that after unfractionated heparin, no increase in ischemic complications were noted. The use of a single bolus of intravenous enoxaparin, without the need for measuring the activated clotting time or titrating heparin anticoagulation, has the potential for simplifying the performance and perhaps enhancing the safety of PCI.

Summary

J Am Coll Cardiol , 1999 ;34:1884-90

Clopidogrel as adjunctive antiplatelet therapy during coronary stenting.

Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL

**OBJECTIVES:** We examined the procedural and 30-day clinical outcomes among patients receiving aspirin and either ticlopidine or clopidogrel during coronary stenting. **BACKGROUND:** Ticlopidine-plus-aspirin has become standard antiplatelet therapy for the prevention of thrombotic complications after coronary stenting. Clopidogrel has a similar mechanism of action as ticlopidine, but both its efficacy and its safety as a pharmacologic adjunct to coronary stenting have not been well described. **METHODS:** This single-center, prospective analysis examined the in-hospital procedural and 30-day clinical outcomes among 875 consecutive patients undergoing coronary stenting who received adjunctive aspirin and either clopidogrel (n = 514; 58.7%) or ticlopidine (n = 361; 41.3%) therapy. **RESULTS:** Procedural success rates were similar among the clopidogrel- (99.6%) and ticlopidine-treated patients (99.4%). Subacute stent thrombosis (i.e., >24 h < or =30 days) occurred in one clopidogrel-treated (0.2%) and in one ticlopidine-treated (0.3%) patient (p = 0.99). By 30 days following the index procedure, the combined rates of death, nonfatal myocardial infarction and need for target vessel revascularization were similar among patients who received either clopidogrel (2.1%) or ticlopidine (1.4%; p = 0.57) therapy. **CONCLUSIONS:** In this analysis the antiplatelet combination therapy of aspirin-plus-clopidogrel was an effective regimen for preventing thrombotic complications and major adverse cardiovascular events among a broad spectrum of patients undergoing coronary artery stenting.

Summary

Catheter Cardiovasc Interv 1999 ;48(4):430-4

Effect of glycoprotein IIb/IIIa inhibition without thrombolytic therapy on reperfusion in acute myocardial infarction: results of ReoMI pilot study.

Makkar R, Goff B, Eigler N, Sebastian M, Fischell T, Barr L, D'Haem C, Shah PK, Effron MB, Litvack F

The efficacy of abciximab and moderate dose heparin in attaining reperfusion in acute MI was tested in a multicenter pilot study. Patients with acute MI of less than 6-hr onset triaged to primary PTCA received intravenous abciximab bolus and infusion and heparin (70 u/kg) in the emergency room. Mean time to angiography from administration of abciximab was 34 +/- 23 min. TIMI flow rates were: grade 0-62%, grade I-20%, grade II-9%, and grade III-9%. Primary PTCA was performed with 100% success rate. Access site bleeding occurred in 10% of patients with no incidence of intracranial bleeding. TIMI II/III flow rates were 50% in a patient subset where angiography was delayed by 45 min. While not an alternative to thrombolytics in AMI, abciximab administration in the emergency room in patients triaged to PTCA may be beneficial in situation where door to needle time is delayed as TIMI II/III flows may be attained in some patients.

#### Summary

1. TIMI flow rates : grade 0-62%, grade I-20%, grade II-9%, and grade III-9%.
2. Access site bleeding:10% of patients, no incidence of intracranial bleeding.
3. TIMI II/III flow rates were 50% in a patient subset where angiography was delayed by 45 min.

Circulation , 1999 ;100(20):2045-8

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.

Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML

**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% versus 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.

### Summary

Am J Cardiol , 1999 ;84(7):779-84

Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). Global Use of Strategies To Open occluded coronary arteries.

Duke Clinical Research Institute, Durham, North Carolina 27715, USA.

We evaluated the effects of abciximab treatment during early angioplasty after clinically failed thrombolysis for acute myocardial infarction. In the Global Use of Strategies To Open occluded coronary arteries (GUSTO-III) trial of reteplase versus alteplase for acute infarction (n = 15,059), 392 patients underwent angioplasty a median of 3.5 hours after thrombolysis and had complete procedural data. We compared 30-day mortality and in-hospital outcomes between patients who received abciximab (n = 83) and those who did not (n = 309), and (among patients given abciximab) between those randomized to alteplase versus reteplase. Patients given abciximab had anterior infarction less often, but were more often in Killip classes III or IV. The 30-day mortality rate tended to be lower with abciximab (3.6% vs 9.7%, p = 0.076), more so after adjustment for baseline differences (p = 0.042). The composite of death, stroke, or reinfarction did not differ significantly with abciximab treatment (12% vs 14%, p = 0.7), but it occurred less often among abciximab-treated patients who had been randomized to reteplase (n = 55) versus alteplase (n = 28) (7% vs 21%, p = 0.08). Severe bleeding was increased among abciximab-treated patients (3.6% vs 1.0%, p = 0.08), despite less heparin use. No intracranial hemorrhages occurred with abciximab. The use of abciximab for early angioplasty after clinically failed thrombolysis resulted in trends toward lower 30-day mortality and increased bleeding.

## Summary

Am J Cardiol , 1999 ;84(6):728-30

Effect of abciximab on the pattern of reperfusion in patients with acute myocardial infarction treated with primary angioplasty. RAPPORT investigators. ReoPro And Primary PTCA Organization and Randomized Trial.

Brener SJ, Barr LA, Burchenal JE, Wolski KE, Effron MB, Topol EJ

We investigated the effect of platelet fibrinogen receptor blockade on infarct size after primary angioplasty. Abciximab significantly reduced the time-to-peak creatine kinase without affecting enzymatic infarct size, suggesting a beneficial effect on the pattern and speed of reperfusion.

Time-to-peak CK values in patients receiving abciximab (white bars) and placebo (black bars) in the 25th to 75th interquartile range.

Median AUC for CK in patients receiving abciximab (white bars) and placebo (black bars) in the 25th to 75th interquartile range.

Am J Cardiol , 1999 ;84(5):511-4

Comparison of cilostazol versus ticlopidine therapy after stent implantation.

Park SW, Lee CW, Kim HS, Lee HJ, Park HK, Hong MK, Kim JJ, Park SJ

The aim of this study was to evaluate the efficacy of cilostazol for prevention of stent thrombosis compared with ticlopidine. Cilostazol is a potent antiplatelet agent with less serious side effects. However, few data are available about the effect of cilostazol in preventing stent thrombosis after coronary stent implantation. Four hundred ninety patients selected for elective stent placement were randomized to receive aspirin plus ticlopidine (n = 243) or aspirin plus cilostazol (n = 247) for 1 month. Clinical and laboratory evaluations were performed at regular interval. There were no differences in baseline characteristics between the 2 groups. During the first 30 days after stent implantation, major cardiac events or adverse drug effects were similar

between the 2 groups: ticlopidine (2.9%) vs cilostazol (1.6%) group,  $p = \text{NS}$ ; stent thrombosis (0.4% vs 0.8%,  $p = \text{NS}$ , respectively), myocardial infarction (0.4% vs 0.8%,  $p = \text{NS}$ ), severe leukopenia (1.2% vs 0%,  $p = \text{NS}$ ), severe thrombocytopenia (0.4% vs 0%,  $p = \text{NS}$ ), and cerebral hemorrhage (0.4% vs 0%,  $p = \text{NS}$ ). Adverse effects led to drug withdrawal in 7 patients in the ticlopidine group (2.9%) and in 5 in the cilostazol group (2.0%). There was no death during the follow-up period. Thus, aspirin plus cilostazol may be an effective antithrombotic regimen with comparable results to aspirin plus ticlopidine after elective coronary stenting.

There were no differences between the 2 groups.

Circulation, 1999 ;100(8):799-806

Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). The ERASER Investigators.

**BACKGROUND:** Although stents reduce restenosis compared with balloon angioplasty, their long-term efficacy is limited by neointimal hyperplasia. Platelet and  $\alpha(v)\beta(3)$  integrin receptor inhibition limits neointimal proliferation in animal models of arterial injury. **METHODS AND RESULTS:** We tested whether the dual  $\beta(3)$  integrin blocking agent abciximab, administered for 12 or 24 hours at the same intravenous dose as that shown to reduce adverse clinical events (death, infarction, and revascularization) after angioplasty, would reduce restenotic tissue volume, as measured by intravascular ultrasound at 6 months. Two hundred twenty-five patients were randomly allocated to placebo or abciximab before coronary intervention. Of the 215 patients who received stents and study drug, 191 (88.8%) returned for late ( $\geq 4$  months) coronary evaluation. Tissue volume, expressed as a percentage of stent volume, did not differ:  $25 \pm 15\%$ ,  $27 \pm 15\%$ , and  $29 \pm 14\%$  for the patients in the placebo and the 12- and 24-hour abciximab groups, respectively. Lack of abciximab benefit was confirmed by quantitative coronary angiography (dichotomous restenosis: 11.6%, 18.9%, and 19.4%; loss index: 0.33, 0.52, and 0.47, respectively,  $P = \text{NS}$ ). **CONCLUSIONS:** Potent platelet inhibition with abciximab, as administered in this study, does not reduce in-stent restenosis. The interrelationship between stents, platelets, and neointimal proliferation requires further study.

Summary

Am Heart J,1999 ;138(1 Pt 2):S33-8

Readministration of abciximab: interim report of the ReoPro readministration registry.

Tcheng JE, Kereiakes DJ, Braden GA, Jordan RE, Mascelli MA, Langrall MA, Effron MB

Even with continued improvements in the technology of percutaneous coronary intervention (PCI), approximately 10% to 20% of patients undergoing PCI will require repeat procedures within 1 year. Furthermore, because of the chronic nature of coronary artery disease, many patients will require additional treatment with PCI well after an initial episode of care. Abciximab (ReoPro), a chimeric (murine/human) monoclonal antibody fragment (c7E3 Fab), has been shown to significantly improve periprocedural and long-term outcomes associated with PCI and to reduce the need for repeat target vessel revascularization. However, because the structure of abciximab is derived from an antibody, concern has been raised about subsequent repeat administration. To prospectively evaluate the safety and efficacy of abciximab readministration, we established the ReoPro Readministration Registry with the intent to determine the efficacy, human antichimeric antibody response and rates of thrombocytopenia, bleeding, intracranial hemorrhage, and anaphylaxis in at least 500 patients being retreated with abciximab. The study was conducted at 19 centers beginning in March 1997. This article details interim data that are based on the first 329 patients. Data to date indicate that readministration with abciximab is safe and efficacious and that the same indications for first-time use should apply to subsequent readministration. There were 12 cases of thrombocytopenia (3.6%), defined as a decline in platelet count to less than  $100 \times 10^9/L$  with at least a decrease of 25% from baseline.

Rates of thrombocytopenia with readministration of abciximab

HACA: human antichimeric antibody

[Am Heart J , 1999 ;138\(1 Pt 1\):49-54](#)

[Effects of platelet glycoprotein IIb/IIIa inhibition with abciximab on thrombin generation and activity during percutaneous coronary intervention.](#)

[Dangas G, Marmur JD, King TE, De Leon J, Sharma SK, Vidhun R, Feldman D, Stoyanov MY, Badimon JJ, Ambrose JA](#)

**BACKGROUND:** Antagonists of the platelet glycoprotein IIb/IIIa decrease acute ischemic complications after percutaneous coronary interventions (PCI). Abciximab (c7E3 Fab, ReoPro) has been reported to decrease thrombin generation in vitro. We investigated in vivo the effect of abciximab therapy on thrombin generation, thrombin activity, and the activated clotting time (ACT) during PCI. **METHODS:** We studied 32 consecutive patients who underwent PCI for unstable coronary syndromes. Group I (n = 11) was treated with heparin plus aspirin, and group II (n = 21) was treated with heparin plus aspirin plus standard-dose abciximab, administered 5 minutes after the initial heparin bolus. Patients received a standardized heparin bolus at time 0, and arterial blood specimens for prothrombin fragment F1.2, fibrinopeptide A (FPA), and ACT were obtained from the guiding catheter at 5 minutes, 10 minutes (ACT only), 20 minutes, and at the end of the PCI. Standard-dose abciximab was administered in group II only. Each patient served as his or her own control, and the changes against the baseline were compared between the 2 groups. **RESULTS:** There were no significant differences between the 2 groups regarding baseline characteristics, hematocrit, and platelet count. Group I patients had higher ACT and lower F1.2 and FPA compared with group II at baseline. Subsequent measurements demonstrated a gradual decrease in FPA and F1.2 in group II; the end of procedure versus baseline changes that occurred in F1.2 were significantly different compared with group I (decrease of 0.59 +/- 0.22 nmol/L in group II vs increase of 0.22 +/- 0.3 nmol/L in group I, P =.04), and a trend in the same direction was evident for FPA changes (decrease of 1.46 +/- 1.16 ng/mL in group II vs increase of 2.25 +/- 1.58 ng/mL in group I, P =.07). The ACT response to abciximab was variable, but a 6.3% increase (+20 sec) in ACT was documented 5 minutes after abciximab bolus in group II compared with the 3.4% decrease (-10 sec) observed in group I at the same time point (P =.1). **CONCLUSION:** Addition of abciximab to heparin plus aspirin during PCI was associated with a significant decrease in thrombin generation and a borderline decrease in thrombin activity.

F1.2: Prothrombin fragment F1.2(nmol/L)

FPA: Fibrinopeptide A(ng/mL)

Am J Cardiol ,1999 ;83(9):1308-13

Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators.

Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, Ishikawa K, Masuda Y, Yamaguchi T, Motomiya T, Tamura Y

Aspirin therapy confers conclusive net benefits in the acute phase of evolving myocardial infarction, but no clear evidence of benefit from the long-term use of aspirin after acute myocardial infarction (AMI) has been shown in any single study. This multicenter study, the Japanese Antiplatelets Myocardial Infarction Study, was performed to find out whether aspirin or trapidil would improve clinical outcome compared with no antiplatelets in postinfarction patients. The study was a multicenter, open-label, randomized controlled trial of aspirin 81 mg/day, trapidil 300 mg/day, and no antiplatelets in patients with AMI admitted within 1 month from the onset of symptoms. Seven hundred twenty-three patients were enrolled at 70 hospitals in 18 prefectures of Japan; 250 were randomly assigned to treatment with 81 mg aspirin (aspirin group), 243 to that with trapidil (trapidil group), and 230 were not given antiplatelet agents. The mean follow-up period was 475 days. This study demonstrated that long-term use of aspirin at the dose of 81 mg/day reduced the incidence of recurrent AMI compared with the group receiving no antiplatelets after AMI ( $p = 0.0045$ ) and that trapidil also reduced the occurrence of reinfarction compared with the group receiving no antiplatelets, but the difference was not significant ( $p = 0.0810$ ). The incidence of cardiovascular events including cardiovascular death, reinfarction, uncontrolled unstable angina requiring admission to hospital, and nonfatal ischemic stroke was reduced in the group receiving 300 mg trapidil daily compared with the group receiving no antiplatelets ( $p = 0.0039$ ). The use of aspirin 81 mg/day provided almost no benefit over no antiplatelets therapy in the incidence of cardiovascular events. In conclusion, low-dose aspirin (81 mg) effectively prevented recurrent AMI in postinfarction patients after thrombolysis or coronary angioplasty when used over a long term. Furthermore, the long-term use of trapidil resulted in a significant reduction in the incidence of cardiovascular events.

J Am Coll Cardiol, 1999 ;33(5):1248-56

Antithrombin activity during the period of percutaneous coronary revascularization: relation to heparin use, thrombotic complications and restenosis.

Matthai WH Jr, Kurnik PB, Groh WC, Untereker WJ, Siegel JE

**OBJECTIVES:** This study evaluated changes in antithrombin (AT) activity around the time of percutaneous transluminal coronary revascularization (PTCR) with unfractionated heparin anticoagulation and the effects these changes had on major thrombotic complications of PTCR. **BACKGROUND:** Heparin is used during PTCR to prevent thrombosis. However, heparin, a cofactor for AT, causes AT activity to fall. AT activity <70% is associated with thrombosis. There is a prothrombotic state after heparin discontinuation that has not been well explained. **METHODS:** Antithrombin activity was sampled at the start and end of PTCR and the next two mornings in 250 consecutive patients. We recorded occurrence of major thrombotic events, defined as 1) major thrombotic complications of PTCR; 2) major in-lab thrombus formation; or 3) subacute occlusion. Discriminant analysis was employed to evaluate the relationship of AT activity to these events. Change in AT activity and its relationship to heparin was evaluated. Evidence of restenosis at six months was obtained. **RESULTS:** There were 14 major thrombotic events. Antithrombin activity <70% was strongly ( $p = 0.006$ ) associated with these events. The AT activity fell significantly through the morning after PTCR when 21% of patients had AT activity <70%; AT activity did not normalize until >20 h after heparin discontinuation. Pre-PTCR use of heparin led to lower AT activity in proportion to duration of heparin use. There was no relationship between AT activity and restenosis. **CONCLUSIONS:** Low AT activity may contribute to major thrombotic complications of PTCR. The way heparin is used before and after PTCR is important to development of low AT activity.

Association with antithrombin activity with primary outcome events

#### Summary

Circulation, 1999;99(2):248-53

Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement.

Berger PB, Bell MR, Hasdai D, Grill DE, Melby S, Holmes DR Jr

**BACKGROUND:** In patients receiving intracoronary stents, stent thrombosis is reduced when ticlopidine therapy is combined with aspirin after the procedure. However, ticlopidine causes neutropenia in 1% of patients when administered for >2 weeks, and little is known about the duration that ticlopidine needs be administered to prevent stent thrombosis. **METHODS AND RESULTS:** We analyzed 827 patients undergoing successful stent placement in 1061 coronary segments at Mayo Clinic who were treated between May 1, 1996, and October 31, 1997. Chronic warfarin therapy, cardiogenic shock, and enrollment in research protocols requiring 4 weeks of ticlopidine were exclusion criteria; ticlopidine was discontinued after 14 days in all remaining patients. The mean age of the study population was 64+/-11 years; 49% had suffered a prior infarction, 20% had undergone coronary artery bypass surgery, and 65% had multivessel disease. The

indication for stent placement was dissection or abrupt closure in 31% of patients and suboptimal results from balloon angioplasty in 18%. Placement was elective in 51% of patients, and 10.3% of patients were treated within 12 hours of an acute myocardial infarction. Mean nominal stent size was 3.3±0.5 mm. High-pressure inflations (≥12 atm) were performed in all patients (mean, 17±4 atm). Intravascular ultrasound was used to facilitate stent placement in 8.8% of patients. Abciximab was administered to 38% of patients; 11% of patients who were at increased risk of stent thrombosis were treated with enoxaparin for 10 to 14 days. Adverse cardiovascular events in the 14 days after stent placement occurred in 11 patients (1.3%). Two patients died of nonischemic causes (sepsis and renal failure) in the 15th through 30th days after ticlopidine was stopped. However, there were no cardiovascular deaths, myocardial infarctions, coronary artery bypass operations, or repeat angioplasty procedures between the 15th and 30th days; stent thrombosis did not occur in any patient after ticlopidine had been stopped. No patient developed neutropenia, although 1.8% of the first 489 patients who were closely monitored for side effects from ticlopidine developed side effects requiring its discontinuation, and milder side effects occurred in 4.7%. CONCLUSIONS: In patients receiving intracoronary stents, the discontinuation of ticlopidine therapy 14 days after stent placement is associated with a very low frequency of stent thrombosis and other adverse events

#### Summary

1. Adverse cardiovascular events in the 14 days after stent placement: 11 patients (1.3%).
2. No cardiovascular deaths, myocardial infarctions, coronary artery bypass operations, or repeat angioplasty procedures between the 15th and 30th days, No stent thrombosis
3. No patient developed neutropenia

Circulation, 2000 ;102: 1901-1905

Platelet PIA2 Allele and Incidence of Coronary Heart Disease : Results From the Atherosclerosis Risk In Communities (ARIC) Study

Nena Aleksic, Harinder Juneja, Aaron R. Folsom, Chul Ahn, Eric Boerwinkle, Lloyd E. Chambless, and Kenneth K. Wu

Background-The major platelet integrin glycoprotein IIb-IIIa plays a primary role in platelet aggregation and acute thrombus formation at the site of vascular injury. A genetic polymorphism of glycoprotein IIb-IIIa (PIA) has recently been proposed as a potential genetic factor linking to platelet hyperaggregability and increased risk of myocardial infarction. Despite numerous, mostly nonprospective studies, the role of this polymorphism as a clinically relevant, inherited risk factor for coronary heart disease (CHD) is still controversial. The purpose

of this study was to determine whether PIA2 is a risk factor for incident CHD and whether it is correlated with increased platelet activation in a case-cohort study nested within a prospective epidemiologic investigation.

**Methods and Results**-Blood samples were collected and processed from the Atherosclerosis Risk in Communities Study cohort at the baseline examination (1987 to 1989). They were stored at -80°C. PIA1/A2 genotype and plasma  $\beta$ -thromboglobulin levels were determined in 439 incident CHD cases and a reference cohort sample of 544 (of whom 18 were also CHD cases). The prevalence of the PIA2 allele was not different in cases versus noncases. No significant correlation between CHD risk factors and the PIA2 allele was noted either. Platelet activation, as measured by plasma  $\beta$ -thromboglobulin levels, was not enhanced in individuals with the PIA2 allele.

**Conclusions**-This prospective study indicates that healthy individuals carrying the PIA2 allele do not have an increased risk of CHD.

The American Journal of Cardiology, 85:1060-1064

The benefit of abciximab in percutaneous coronary revascularization is not device-specific

Deepak L. Bhatt, A. Michael Lincoff, Robert M. Califf, Maarten L. Simoons, James E. Tchong, Sorin J. Brener, Katherine E. Wolski, Eric J. Topol

Abciximab has been shown to decrease adverse outcomes after percutaneous coronary interventions, but it is unclear whether this beneficial effect is more or less pronounced with specific devices. This study sought to determine the relative magnitude of the benefit of abciximab among different interventional devices. Data from the 5 placebo-controlled trials of abciximab during coronary intervention were pooled. Patients were divided into groups based on whether they received balloon angioplasty alone, elective stenting, bailout stenting, or directional coronary atherectomy. In the patients undergoing balloon angioplasty, the 30-day hazard ratio for death or myocardial infarction (MI) in the group randomized to abciximab versus the placebo-treated group was 0.52 ( $p < 0.001$ ), for elective stenting the hazard ratio was 0.51 ( $p < 0.001$ ), for bailout stenting the hazard ratio was 0.38 ( $p < 0.001$ ), and for directional coronary atherectomy the hazard ratio was 0.38 ( $p = 0.007$ ). A Cox proportional-hazards model revealed that overall, the use of abciximab decreased the composite end point of 30-day death or MI rates (hazard ratio 0.55, 95% confidence interval 0.43 to 0.69,  $p < 0.001$ ). However, bailout stenting and directional coronary atherectomy were associated with increased rates of death or MI compared with balloon angioplasty, as was elective stenting in women compared with men. There was no significant increase in major bleeding episodes associated with abciximab in any of the device categories. These findings

from all the controlled coronary revascularization trials using abciximab demonstrate that a decrease in death and MI is achieved with abciximab regardless of the type of device used, without an increase in significant bleeding complications.

Circulation, 2000; 102: 2051-2057

### Novel, Bedside, Tissue Factor-Dependent Clotting Assay Permits Improved Assessment of Combination Antithrombotic and Antiplatelet Therapy

Michael B. Holmes, David J. Schneider, Michael G. Hayes, Burton E. Sobel, and Kenneth G. Mann

**Background-**Because optimal use of combinations of antiplatelet and antithrombotic drugs requires improved methods for assessment of therapeutic efficacy, we developed an assay designed to increase sensitivity that is based on initiation of clotting by tissue factor in minimally altered whole blood.

**Methods and Results-**Blood samples were obtained from healthy subjects, and the contact pathway of coagulation was inhibited with corn trypsin inhibitor (a specific factor XIIa inhibitor without effect on other coagulation factors). Clotting was initiated with relipidated tissue factor and detected with a Hemochron ACT instrument. Results were reproducible with samples from 25 healthy volunteers (mean time to clot, 125±17 seconds). Blood was also exposed to pharmacological concentrations of antithrombotic and antiplatelet agents *in vitro*. Heparin (0.25 anti-IIa/Xa U/mL) prolonged the time to clot by 2.4-fold (172 seconds, P<0.05); hirudin (1.0 anti-IIa U/mL), by 3-fold (250 seconds P<0.05); and enoxaparin (0.6 anti-Xa U/mL), by 2 -fold (123 seconds, P<0.05). Additive effects of antiplatelet agents were readily detectable with both heparin and hirudin. Thus, addition of 3 µg/mL abciximab to 1.0 anti-IIa/Xa U/mL heparin and to 1.0 anti-IIa U/mL hirudin further prolonged the times to clot by 140 and 67 seconds, respectively (P<0.05 for each). Addition of abciximab to enoxaparin did not further prolong the time to clot (increment, 13 seconds; P=NS).

**Conclusions-**The assay developed should facilitate improved dose selection, titration, and monitoring of combination antithrombotic and antiplatelet treatment regimens.

Lancet, 1999; 353: 429-38

Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial

Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators\*

**Background** Despite the use of heparin and aspirin, 510% of patients with unstable angina develop myocardial infarction or refractory angina in hospital. We tested the hypothesis that recombinant hirudin (lepirudin), a direct thrombin inhibitor, would be superior to heparin, an indirect thrombin inhibitor, in patients with acute ischaemic syndromes who were receiving aspirin.

**Methods** 10141 patients with unstable angina or suspected acute myocardial infarction without ST elevation were randomly assigned heparin (5000 units bolus then 15 units kg<sup>-1</sup> h<sup>-1</sup>; n=5058) or hirudin (0.4 mg/kg bolus then 0.15 mg kg<sup>-1</sup> h<sup>-1</sup> infusion; n=5083) for 72 h in a double-blind trial. The primary outcome measure was cardiovascular death or new myocardial infarction at 7 days. Analysis was by intention to treat.

**Findings** At 7 days, 213 (4.2%) patients in the heparin group and 182 (3.6%) in the hirudin group had experienced cardiovascular death or new myocardial infarction (relative risk 0.84 [95% CI 0.691-0.02]; p=0.077). The numbers with cardiovascular death, new myocardial infarction, or refractory angina at 7 days were 340 (6.7%) with heparin and 284 (5.6%) with hirudin (0.82 [0.700-0.96]; p=0.0125). These differences were primarily observed during the 72 h treatment period (cardiovascular death or myocardial infarction relative risk 0.76 [0.590-0.99], p=0.039; cardiovascular death, myocardial infarction, or refractory angina 0.78 [0.630-0.96], p=0.019). Although there was an excess of major bleeding requiring transfusion with hirudin (59 [1.2%] vs 34 [0.7%] with heparin; p=0.01), there was no excess in life-threatening episodes (20 in each group) or strokes (14 in each group).

**Interpretation** The data from OASIS-2 suggest that recombinant hirudin is superior to heparin in preventing cardiovascular death, myocardial infarction, and refractory angina with an acceptable safety profile in patients with unstable angina or acute myocardial infarction without ST elevation. Thus, a direct thrombin inhibitor is more effective than an indirect thrombin inhibitor.

The American Journal of Cardiology, 85:953-956

Minimal heparinization in coronary angioplasty-how much heparin is really warranted?

Edo Kaluski, Ricardo Krakover, Gad Cotter, Alberto Hendler, Itzhak Zyssman, Olga Milovanov, Alex Blatt, Ester Zimmerman, Edna Goldstein, Vera Nahman, Zvi Vered

The purpose of the study was to assess the results of percutaneous transluminal coronary angioplasty (PTCA), performed with a single intravenous bolus of 2,500 U of heparin, in a nonemergency PTCA cohort. Three hundred of 341 consecutive patients (87.9%) undergoing PTCA were prospectively enrolled in the study. They received heparin, 2,500-U intravenous bolus, before PTCA, with intention of no additional heparin administration. Patient and lesion characteristics as well as PTCA results were evaluated independently by 2 physicians. Patients were followed up by structured telephone questionnaires at 1 and 6 months after PTCA. Mean activated clotting time obtained 5 minutes after heparin administration was  $185 \pm 19$  seconds (range 157 to 238). There were 3 (1%) in-hospital major adverse cardiovascular events: 2 deaths (0.66%), 1 (0.33%) Q-wave myocardial infarction. Emergency coronary surgery and stroke were not reported. Six patients (2%) experienced abrupt coronary occlusion within 14 days after PTCA, warranting repeat target vessel revascularization. Angiographic and clinical success were achieved in 96% and 93.3%, respectively. No bleeding or vascular complications were recorded. Six-month follow-up (184 patients) revealed 3 cardiac deaths (1 arrhythmic, 2 after cardiac surgery), 1 Q-wave myocardial infarction, and 9.7% repeat target vessel revascularization. This study suggests that very low doses of heparin and reduced activated clotting time target values are safe in non-emergency PTCA, and can reduce bleeding complications, hospital stay, and costs. Larger, randomized, double-blind heparin dose optimization studies need to confirm this notion.

Circulation, 2000 ;102: 1093-1100

Management of Patients With Acute Coronary Syndromes in the United States by Platelet Glycoprotein IIb/IIIa Inhibition : Insights From the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial

A. Michael Lincoff, Robert A. Harrington, Robert M. Califf, Judith S. Hochman, Alan D. Guerci, E. Magnus Ohman, Carl J. Pepine, Steven L. Kopecky, Neal S. Kleiman, Cynthia M. Pacchiana, Lisa G. Berdan, Michael M. Kitt, Maarten L. Simoons, and Eric J. Topol

Background-A multinational, randomized, placebo-controlled trial (Platelet Glycoprotein IIb/IIIa in Unstable

Angina: Receptor Suppression Using Integrilin Therapy, PURSUIT) demonstrated that the platelet glycoprotein IIb/IIIa receptor antagonist eptifibatide reduced the incidence of death or myocardial infarction among patients with acute ischemic syndromes without ST-segment elevation. Because of expected differences in practice patterns, a prospectively planned analysis of outcomes as a function of regions of the world was performed. The current study provides a detailed assessment of eptifibatide among the subgroup of patients enrolled within the United States.

**Methods and Results**-Patients presenting with chest pain within the previous 24 hours and ischemic ECG changes or creatine kinase-MB elevation were eligible for enrollment. Of the 10 948 patients randomized worldwide, 4035 were enrolled within the United States. Patients were allocated to placebo or eptifibatide infusion for up to 72 to 96 hours. Other medical therapies and revascularization strategies were at the discretion of the treating physician. Eptifibatide reduced the rate of the primary end point of death or myocardial infarction by 30 days from 15.4% to 11.9% (P=0.003) among patients in the United States. The treatment effect was achieved early and maintained over a period of 6 months (18.9% versus 15.2%; P=0.004). Bleeding events were more common in patients receiving eptifibatide but were predominantly associated with invasive procedures. The magnitude of clinical benefit from eptifibatide was greater among patients in the United States than elsewhere in the world.

**Conclusions**-Platelet glycoprotein IIb/IIIa receptor blockade with eptifibatide reduces the incidence of death or myocardial infarction among patients treated for acute ischemic syndromes without ST-segment elevation within the United States.

Journal of the American College of Cardiology, 36:5:1507-1513

Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST segment monitoring substudy

Shaun G. Goodman, Aiala Barr, Anatoli Soltchouk, Marc Cohen, Gregg J. Fromell, Luc Laperriere, Carol Hill, Anatoly Langer for the Canadian Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) ST Segment Monitoring Substudy Group

#### OBJECTIVES

The goal of this study was to determine whether enoxaparin was more effective than heparin in reducing recurrent ischemic episodes.

## BACKGROUND

Continuous ST segment monitoring is a simple tool for assessment of ischemia and identifies patients with a worse prognosis. Little is known about the impact of low molecular weight heparin on ST segment shift.

## METHODS

Patients were randomized to receive enoxaparin or heparin (mean 3.4 days). Three-lead ST segment monitoring was performed for the first 48 h (n = 220) and an additional 48 h (n = 174) after intravenous study drug discontinuation (mean 1.9 days later).

## RESULTS

During initial monitoring, ischemia rates were similar among the heparin and enoxaparin groups (27.2% vs. 22.6%, P = 0.44); however, the time to first ischemic episode was earlier among heparin-treated patients ( $11 \pm 11$  vs.  $25 \pm 18$  min, P = 0.001). After drug discontinuation, ischemic episodes occurred more frequently (44.6% vs. 25.6%, P = 0.009), and the total ischemic duration was greater among heparin patients ( $18 \pm 39$  vs.  $5 \pm 12$  min/24 h, P = 0.005). Recurrent ischemia occurred more frequently after discontinuation in the heparin (46% vs. 31%, P = 0.043), but not the enoxaparin, group (18.4% vs. 25%, P = 0.33). Regardless of treatment, patients with ischemia were more likely to die or experience (re)infarction at one year (18.4% vs. 8.3%, P = 0.023).

## CONCLUSIONS

ST segment shift occurs frequently in unstable angina/non-Q-wave myocardial infarction despite antithrombotic therapy and is associated with worse one-year prognosis. Enoxaparin is a more effective antithrombotic treatment than unfractionated heparin and leads to greater prevention of rebound ischemia.

N Engl J Med, 2000;342:1316-24

## Long-Term Treatment with a Platelet Glycoprotein-Receptor Antagonist after Percutaneous Coronary Revascularization

William W. O'Neill, Patrick Serruys, Merrill Knudtson, Gerrit-Anne van Es, Gerald C. Timmis, Coen van der Zwaan, Jay Kleiman, Jianjian Gong, Ellen B. Roecker, Roger Dreiling, John Alexander, Robert Anders, for the EXCITE Trial Investigators

Background. When administered intravenously at the time of percutaneous coronary revascularization, glycoprotein IIb/IIIa receptor antagonists decrease the incidence of death and nonfatal myocardial infarction and the need for urgent revascularization. We hypothesized that long-term administration of oral glycoprotein

IIB/IIIa antagonists, which block the aggregation of platelets, might stabilize intravascular plaque and prevent additional ischemic cardiac events.

**Methods.** We conducted a prospective, double-blind trial in which 7232 patients were randomly assigned to receive 20 mg of oral xemilofiban or placebo 30 to 90 minutes before undergoing percutaneous coronary revascularization, with maintenance doses of 10 or 20 mg of xemilofiban or placebo administered three times daily for up to 182 days. There were two primary composite end points: one was death, nonfatal myocardial infarction, or urgent revascularization at 182 days, and the other was death or nonfatal myocardial infarction at 182 days.

**Results.** Death, myocardial infarction, or urgent revascularization occurred within 182 days in 324 patients who received placebo (Kaplan-Meier cumulative event rate, 13.5 percent), 332 who received 10 mg of xemilofiban (13.9 percent,  $P=0.82$  for the comparison with placebo), and 306 who received 20 mg of xemilofiban (12.7 percent,  $P=0.36$  for the comparison with placebo). The incidence of death or myocardial infarction was also similar in all three groups. Clinically significant hemorrhagic complications and thrombocytopenia were infrequent.

**Conclusions.** The administration of the glycoprotein IIB/IIIa antagonist xemilofiban before percutaneous coronary revascularization and for up to six months thereafter does not significantly reduce the incidence of important clinical end points.

#### Postmenopausal Hormone Therapy Increases Risk for Venous Thromboembolic Disease. The Heart and Estrogen/progestin Replacement Study

D. Grady, N.K. Wenger, D. Herrington, S. Khan, C. Furberg, D. Hunninghake, E. Vittinghoff, and S. Hulley, for the Heart and Estrogen/progestin Replacement Study Research Group

Postmenopausal therapy with estrogen plus progestin increases risk for venous thromboembolism in women with coronary heart disease. This risk should be considered when the risks and benefits of therapy are being weighed. **Background:** Oral contraceptive use increases risk for venous thromboembolism, but data on the effect of postmenopausal hormone therapy are limited.

**Objective:** To determine the effect of therapy with estrogen plus progestin on risk for venous thromboembolic events in postmenopausal women.

**Design:** Randomized, double-blind, placebo-controlled trial.

**Setting:** 20 clinical centers in the United States.

**Participants:** 2763 postmenopausal women younger than 80 years of age (mean age, 67 years) who had coronary heart disease but no previous venous thromboembolism and had not had a hysterectomy.

**Intervention:** Conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg, in one tablet

(n = 1380) or placebo that was identical in appearance (n = 1383).

Measurements: Documented deep venous thrombosis or pulmonary embolism.

Results: During an average of 4.1 years of follow-up, 34 women in the hormone therapy group and 13 in the placebo group experienced venous thromboembolic events (relative hazard, 2.7 [95% CI, 1.4 to 5.0] [ P = 0.003]; excess risk, 3.9 per 1000 woman-years [CI, 1.4 to 6.4 per 1000 woman-years]; number needed to treat for harm, 256 [CI, 157 to 692]). In multivariate analysis, the risk for venous thromboembolism was increased among women who had lower-extremity fractures (relative hazard, 18.1 [CI, 5.4 to 60.4]) or cancer (relative hazard, 3.9 [CI, 1.6 to 9.4]) and for 90 days after inpatient surgery (relative hazard, 4.9 [CI, 2.4 to 9.8]) or nonsurgical hospitalization (relative hazard, 5.7 [CI, 3.0 to 10.8]). Risk was decreased with aspirin (relative hazard, 0.5 [CI, 0.2 to 0.8]) or statin use (relative hazard, 0.5 [CI, 0.2 to 0.9]).

Conclusions: Postmenopausal therapy with estrogen plus progestin increases risk for venous thromboembolism in women with coronary heart disease. This risk should be considered when the risks and benefits of therapy are being weighed.

Am Heart J 2000;139:962-70.

Predictors of recurrent ischemic events and death in unstable coronary artery disease after treatment with combination antithrombotic therapy

Marc Cohen, MD, Sandra S. Stinnett, DrPH, Beth D. Weatherley, MS, Enrique P. Gurfinkel, MD, Gregg J. Fromell, MD, Shaun G. Goodman, MD, Keith A.A. Fox, MBChB, Robert M. Califf, MD, for the ESSENCE study group

Philadelphia and Collegeville, Pa; Durham, NC; Buenos Aires, Argentina; Toronto, Ontario, Canada; and Edinburgh, United Kingdom

Background. Patients with non-Q-wave acute coronary syndromes (ACS) have substantial rates of recurrent ischemic events, but prognostic studies have been small or preceded the routine use of aggressive combination antithrombotic therapy. We sought to identify predictors of these events after antithrombotic treatment of non-Q-wave ACS.

Methods. We assessed 30-day rates of a composite triple end point (death, infarction, or refractory angina) and double end point (death or infarction) among 3171 patients with non-ST-segment elevation ACS randomly assigned to enoxaparin or heparin, plus aspirin, for 2 to 8 days. We created multivariable regression models to predict these end points from baseline factors.

Results. Overall, 682 patients (21%) reached the triple end point and 220 (6.8%) reached the double end point. Independent predictors of the triple end point were admission with myocardial necrosis, ST-segment

depression, prior angina severity, symptom duration, and allocation to enoxaparin treatment in patients with ST-segment depression (significant interaction). Independent predictors of the double end point were admission with myocardial necrosis, ST-segment depression, enrollment region, age >75 years, prior angina severity, and rales. By deciles, the average predicted risk for the double end point ranged from 2% to 20%: a patient aged <75 years with no risk factors had a 3.5% risk, whereas a patient aged >75 years with 2 additional high-risk features (myonecrosis and ST depression) had a risk of death or reinfarction of 26%.

**Conclusions.** Patients with non-ST-segment elevation ACS exhibit a broad range of risk of adverse recurrent ischemic events. The predictive power of the model for the triple end point, using baseline variables, was modest. However, a subgroup at very low risk of the double end point (average 2%) can be identified with baseline variables.

Am Heart J 2000;139:1061-70.

**Heparin Infusion Prior to Stenting (HIPS) trial: Final results of a prospective, randomized, controlled trial evaluating the effects of local vascular delivery on intimal hyperplasia**

Robert L. Wilensky, MD, Jean-Francois Tanguay, MD, Shigenori Ito, MD, Antonio L. Bartorelli, MD, Jeffrey Moses, MD, David O. Williams, MD, Steven R. Bailey, MD, Jack Martin, MD, Theresa A. Bucher, RN, Pam Gallant, RN, Ann Greenberg, RN, Jeffrey J. Popma, MD, Neil J. Weissman, MD, Gary S. Mintz, MD, Aaron V. Kaplan, MD, Martin B. Leon, MD, for the HIPS investigators

**Background.** Local delivery of pharmacologic agents or genes at the site of angioplasty is a promising approach to reduce restenosis. However, there are unresolved questions concerning the safety and feasibility of local vascular delivery in clinical practice as well as the efficacy of delivered drug. To this end, the safety, feasibility, and efficacy of local delivery of heparin were evaluated in the Heparin Infusion Prior to Stenting (HIPS) trial.

**Methods and Results.** A total of 179 patients were enrolled in this multicenter, randomized, prospective, core laboratory-evaluated trial. Patients were randomly assigned to 5000 U heparin either administered to the coronary artery lumen or infused into the arterial wall immediately after angioplasty and before stent placement. End points included procedural events and clinical, angiographic, and intravascular ultrasound events at 6 months. Patient groups were evenly matched. There was no difference in the incidence of arterial injury, defined as an increase in arterial dissection, acute closure, or decrease in Thrombolysis In Myocardial Infarction grade blood flow in the group receiving local delivery. At follow-up there was no difference in the major adverse event rate between intraluminal (22.7%) and local groups (24.7%). There was no difference

between intraluminal and local therapy in the angiographic in-stent restenosis rate (12.5%, 12.7%) or the in-stent volumetric analysis by intravascular ultrasound (IVUS) ( $37.19 \pm 20.86 \text{ mm}^3$  vs  $43.79 \pm 25.52 \text{ mm}^3$ ).

Conclusions. Local delivery of 5000 U heparin into the arterial wall before stent implantation is safe and feasible. There was not a favorable effect of locally delivered heparin on clinical, angiographic, or IVUS end points of restenosis. The use of IVUS to measure volume of intimal hyperplasia in a multicenter, core laboratory-controlled trial is feasible.

N Engl J Med 2000;342:1622-6.

### Hemodynamic Effects of Sildenafil in Men with Severe Coronary Artery Disease

Howard C. Herrmann, Gene Chang, Bruce D. Klugherz, Paul D. Mahoney

**Background.** The cardiovascular effects of sildenafil are important because of the frequent presence of underlying cardiac disease in men with erectile dysfunction and reports indicating serious cardiac events temporally associated with the use of this drug.

**Methods.** We assessed the systemic, pulmonary, and coronary hemodynamic effects of oral sildenafil (100 mg) in 14 men (mean [ $\pm$ SD] age,  $61 \pm 11$  years) with severe stenosis of at least one coronary artery (stenosis of  $>70$  percent of the vessel diameter) who were scheduled to undergo percutaneous coronary revascularization. Blood-flow velocity and flow reserve were assessed with a Doppler guidewire in 25 coronary arteries, including 13 severely diseased arteries (mean degree of stenosis,  $78 \pm 7$  percent) and 12 arteries without stenosis, used as a reference; maximal hyperemia was induced (to assess flow reserve) with the intracoronary administration of adenosine both before and after sildenafil.

**Results.** Oral sildenafil produced only small decreases ( $<10$  percent) in systemic arterial and pulmonary arterial pressures, and it had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. There were no significant changes in average peak coronary flow velocity, coronary-artery diameter, volumetric coronary blood flow, or coronary vascular resistance. Coronary flow reserve at base line was lower in the stenosed arteries ( $1.26 \pm 0.26$ ) than in the reference arteries ( $2.19 \pm 0.44$ ) and increased about 13 percent in both groups of arteries combined after the administration of sildenafil (from  $1.70 \pm 0.59$  to  $1.92 \pm 0.72$ ,  $P=0.003$ ). The ratio of coronary flow reserve in coronary arteries with stenosis to that in the reference arteries ( $0.57 \pm 0.14$ ) was not affected by sildenafil.

**Conclusions.** No adverse cardiovascular effects of oral sildenafil were detected in men with severe coronary artery disease.

Circulation 2000 102: 1490-1496.

### Flow Cytometric Monitoring of Glycoprotein IIb/IIIa Blockade and Platelet Function in Patients With Acute Myocardial Infarction Receiving Reteplase, Abciximab, and Ticlopidine : Continuous Platelet Inhibition by the Combination of Abciximab and Ticlopidine

Karlheinz Peter, Benedikt Kohler, Andreas Straub, Johannes Ruef, Martin Moser, Thomas Nordt, Manfred Olschewski, Magnus E. Ohman, Wolfgang Kubler, and Christoph Bode

**Background-**Improvement of thrombolysis may be achieved by concomitant strong platelet inhibition. To monitor platelet function in patients with myocardial infarction (n=46) who were treated with the fibrinolytic agent reteplase, the glycoprotein (GP) IIb/IIIa blocker abciximab, and the ADP receptor antagonist ticlopidine, we developed a flow cytometric assay.

**Methods and Results-**Binding of abciximab to platelets was directly monitored as the percentage of platelets stained by a goat anti-mouse antibody. Blood drawn 10 minutes and 2 hours after the start of therapy with reteplase and abciximab and during the 12-hour infusion of abciximab demonstrated a maximal blockade of GP IIb/IIIa (10 minutes,  $86.2 \pm 10.3\%$ ; 12 hours,  $85.8 \pm 7.1\%$ ). Starting at 24 hours, abciximab binding gradually decreased (24 hours,  $74.6 \pm 16.2\%$ ; 48 hours,  $66.8 \pm 14.9\%$ ; 72 hours,  $60.5 \pm 16.7\%$ ; 96 hours,  $49.4 \pm 17.8\%$ ; 120 hours,  $35.8 \pm 16.4\%$ ; and 144 hours,  $29.9 \pm 15.3\%$ ). Binding of a chicken anti-fibrinogen antibody to platelets, indicating the level of functional blockade of GP IIb/IIIa, was inversely correlated with the binding of abciximab ( $r = -0.72$ ,  $P < 0.0001$ ). In blood drawn at 10 minutes, platelet aggregation was maximally inhibited but recovered within 48 hours even if the majority of GP IIb/IIIa receptors were still blocked by abciximab. Reteplase did not influence abciximab binding and did not activate platelets, as measured by P-selectin expression, fibrinogen binding, and platelet aggregation. Platelet inhibition that was achieved during the first 24 hours by abciximab was directly maintained by additional treatment with ticlopidine.

**Conclusions-**Flow cytometric monitoring of platelet function allows differentiation of the effects of reteplase, abciximab, and ticlopidine. The combination of abciximab and ticlopidine is an attractive therapeutic strategy that provides a fast and continuous platelet inhibition.

Journal of the American College of Cardiology, 2000;36:3:699-705

## Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy

Khatereh Moshfegh, Maurice Redondo, Friedgard Julmy, Walter A. Wuillemin, Mathias U. Gebauer, Andre Haerberli, Beat J. Meyer

### OBJECTIVES

We sought to compare the inhibitory effects of the combination of two doses of aspirin plus clopidogrel with either drug alone on platelet aggregation and activation.

### BACKGROUND

Enhanced platelet inhibitory effects of clopidogrel by aspirin on platelet aggregation and activation are suggested by experimental studies but have not been shown in humans.

### METHODS

The effects of clopidogrel 75 mg or aspirin 100 (300) mg on platelet aggregation and activation by flow cytometry after stimulation with various agonists were determined in 30 patients with a past history of myocardial infarction.

### RESULTS

Clopidogrel alone or in combination with aspirin markedly inhibited adenosine diphosphate (ADP)-mediated platelet aggregation compared with monotherapy with aspirin ( $24.6 \pm 3.3\%$  or  $26.6 \pm 2.7\%$  vs.  $44.7 \pm 2.9\%$ ;  $p < 0.001$ ). Combined treatment significantly inhibited collagen-induced aggregation compared with aspirin and clopidogrel ( $16.4 \pm 2.4\%$ ,  $36.5 \pm 4.2\%$  and  $59.3 \pm 5.1\%$ , respectively;  $p < 0.001$ ) and resulted in considerable inhibition of aggregation induced by thrombin receptor agonist peptide (TRAP,  $p < 0.03$ ). Clopidogrel with or without aspirin significantly suppressed expression of platelet activation markers CD 62p, CD 63 and PAC-1 after stimulation with ADP or thrombin ( $p < 0.001$ ). In addition, the combined treatment was more effective than either agent alone after activation with low dose thrombin ( $p < 0.05$ ). Both doses of aspirin equally potentiated the platelet inhibitory effects of clopidogrel.

### CONCLUSIONS

In this prospective clinical ex vivo platelet study, clopidogrel was more effective than aspirin in inhibiting ADP-mediated platelet aggregation and activation. Clopidogrel in combination with aspirin showed synergistic inhibitory effects after stimulation with collagen and thrombin compared with monotherapies. Thus, this dual antiplatelet treatment strategy deserves further evaluation in clinical trials for secondary prevention of acute myocardial infarction or unstable angina.

Circulation 2000 101: 1122-1129.

Effects of Abciximab, Ticlopidine, and Combined Abciximab/Ticlopidine Therapy on Platelet and Leukocyte Function in Patients Undergoing Coronary Angioplasty

Becky J. Fredrickson, Nancy A. Turner, Neal S. Kleiman, Nikki Graziadei, Kelly Maresh, Mary Ann Mascelli, Mark B. Effron, and Larry V. McIntire

**Background-**Abciximab and ticlopidine reduce adverse cardiovascular events after percutaneous transluminal coronary angioplasty (PTCA). The goal of the current study was to determine if combined abciximab/ticlopidine therapy inhibits arterial thrombosis more effectively than either treatment alone. The effect of each therapy on platelet-leukocyte interactions was also investigated.

**Methods and Results-**Whole blood samples from 14 patients undergoing PTCA who received abciximab therapy, ticlopidine therapy, or both treatments were evaluated using dynamic experimental systems. Mural thrombus formation under arterial shear conditions (1500 S-1) was determined in a parallel plate flow chamber. Shear-induced platelet aggregation was evaluated using a cone-and-plate viscometer at a shear rate of 3000 S-1. Of the 3 treatments, combined abciximab/ticlopidine therapy produced the most consistent reduction in shear-induced platelet aggregation and the most prolonged inhibition of mural thrombosis. Three days after PTCA, abciximab/ticlopidine treatment decreased mural thrombus formation to 50% of baseline values. Abciximab treatment alone inhibited mural thrombosis for only 1 day after PTCA, whereas ticlopidine treatment alone had no significant effect. Two hours after PTCA, abciximab therapy significantly decreased the number of circulating platelet-neutrophil aggregates but significantly enhanced P-selectin-mediated leukocyte adhesion on the collagen/von Willebrand factor-platelet surface.

**Conclusions-**Combined therapy with abciximab and ticlopidine has a prolonged inhibitory effect on mural thrombosis formation relative to either treatment alone. Further, we demonstrated an unexpected effect of abciximab in enhancing P-selectin-mediated leukocyte adhesion.

Journal of the American College of Cardiology, 2000;35:4:915-921

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

Franz-Josef Neumann, Adnan Kastrati, Claus Schmitt, Rudolf Blasini, Martin Hadamitzky, Julinda Mehilli, Meinrad Gawaz, Michael Schleef, Melchior Seyfarth, Josef Dirschinger, Albert Schomig

## OBJECTIVES

In the Intracoronary Stenting and Antithrombotic Regimen-2 trial (ISAR-2), we sought to investigate the effect of abciximab on angiographic and clinical restenosis after stenting following acute myocardial infarction (AMI). We also intended to assess the impact of abciximab on clinical outcome in this setting.

## BACKGROUND

It is unclear whether abciximab reduces neointima formation after stenting. Such an effect may be particularly prominent in thrombus-containing lesions.

## METHODS

Patients undergoing stenting within 48 h after onset of AMI were randomly assigned to receive either standard-dose heparin or abciximab plus reduced-dose heparin. Of 401 patients randomized, 366 without 30-day adverse events were eligible for six-month angiographic follow-up. Scheduled angiography was performed in 80% of these patients.

## RESULTS

By 30 days, the composite clinical end point of death, reinfarction, and target lesion revascularization (TLR) was reached in 5.0% of the abciximab group and in 10.5% of the control group ( $p = 0.038$ ). At one year, absolute reduction in the composite clinical end point by abciximab was still 5.7% but had lost its statistical significance. Our primary end point, late lumen loss, was  $1.26 \pm 0.85$  mm with abciximab and  $1.21 \pm 0.74$  mm with standard heparin ( $p = 0.61$ ), and binary angiographic restenosis rates were 31.1% and 30.6%, respectively ( $p = 0.92$ ).

## CONCLUSIONS

In patients undergoing stenting following AMI, abciximab exerted beneficial effects by substantially reducing the 30-day rate of major adverse cardiac events. During one-year follow-up, there was no additional benefit from a reduction in TLR nor did abciximab reduce angiographic restenosis.

Journal of the American College of Cardiology, 35:4:922-928

Abciximab reduces mortality in diabetics following percutaneous coronary intervention

Deepak L. Bhatt, Steven P. Marso, A. Michael Lincoff, Katherine E. Wolski, Stephen G. Ellis, Eric J. Topol

## OBJECTIVES

We sought to determine whether abciximab therapy at the time of percutaneous coronary intervention (PCI) would favorably affect one-year mortality in patients with diabetes.

## BACKGROUND

Diabetics are known to have increased late mortality following PCI.

## METHODS

Data from three placebo-controlled trials of PCI, EPIC, EPILOG, and EPISTENT, were pooled. The one-year mortality rate for patients with a clinical diagnosis of diabetes mellitus was compared with the rate for nondiabetic patients treated with either abciximab or placebo.

## RESULTS

In the 1,462 diabetic patients, abciximab decreased the mortality from 4.5% to 2.5%,  $p = 0.031$ , and in the 5,072 nondiabetic patients, from 2.6% to 1.9%,  $p = 0.099$ . In patients with the clinical syndrome of insulin resistance-defined as diabetes, hypertension, and obesity-mortality was reduced by abciximab treatment from 5.1% to 2.3%,  $p = 0.044$ . The beneficial reduction in mortality with abciximab use in diabetics classified as insulin-requiring was from 8.1% to 4.2%,  $p = 0.073$ . Mortality in diabetics who underwent multivessel intervention was reduced from 7.7% to 0.9% with use of abciximab,  $p = 0.018$ . In a Cox proportional hazards survival model, the risk ratio for mortality with abciximab use compared with placebo was 0.642 (95% confidence interval 0.458-0.900,  $p = 0.010$ ).

## CONCLUSIONS

Abciximab decreases the mortality of diabetic patients to the level of placebo-treated nondiabetic patients. This beneficial effect is noteworthy in those diabetic patients who are also hypertensive and obese and in diabetics undergoing multivessel intervention. Besides its potential role in reducing repeat intervention for stented diabetic patients, abciximab therapy should be strongly considered in diabetic patients undergoing PCI to improve their survival.

Journal of the American College of Cardiology, 2000;35:4:895-902

Early angiography versus conservative treatment in patients with non-ST elevation acute myocardial infarction

Grant S. Scull, Jenny S. Martin, W. Douglas Weaver, Nathan R. Every for the MITI Investigators

## OBJECTIVES

To compare short- and long-term outcome after early invasive or conservative strategies in the treatment of non-ST segment elevation acute myocardial infarction (AMI).

#### BACKGROUND

It is uncertain whether or not there is benefit from emergent invasive diagnosis and treatment of AMI in patients without ST segment elevation on the admission electrocardiogram (ECG).

#### METHODS

In a cohort of 1,635 consecutive patients with AMI who presented to hospitals without ST segment elevation on their admission ECG, we compared treatments, hospital course and outcome in 308 patients who presented to hospitals whose initial strategy favored early angiography and appropriate intervention when indicated versus 1,327 similar patients who presented to hospitals that favor a more conservative initial approach.

#### RESULTS

At baseline, patients admitted to hospitals favoring an early invasive strategy were younger, more predominately Caucasian and had less comorbidity. Early coronary angiography occurred in 58.8% versus 8% ( $p < 0.001$ ), and early angioplasty was performed in 44.8% versus 6.1% ( $p < 0.001$ ) in the two different cohorts. Patients treated in hospitals favoring the early invasive strategy had a lower 30-day (5.5% vs. 9.5%,  $p = 0.026$ ) and four-year mortality (20% vs. 37%,  $p < 0.001$ ). Multivariate analysis showed a trend towards lower hospital mortality (OR = 0.56, 95% CI: 0.29 to 1.09) and a significant lower long-term mortality (hazard ratio = 0.61, 95% CI: 0.47 to 0.80) in patients admitted to hospitals favoring an early invasive strategy.

#### CONCLUSIONS

These data suggested that an early invasive strategy in patients with AMI and nondiagnostic ECG changes is associated with lower long-term mortality.

Eur Heart J 2000;21:1440-9

The ENACT study: a pan-European survey of acute coronary syndromes

K.A.A. Fox, D.V. Cokkinos, J. Deckers, U. Keil, A. Maggioni, G. Steg

**Aim.** The European Network for Acute Coronary Treatment (ENACT) study was designed to collect prospective information across Europe on the relative frequency, diagnosis and management of the whole spectrum of acute coronary syndromes.

**Methods.** Cardiologists, who were respondents to mailings sent out to 17 European countries with the target of reaching one centre per million inhabitants, completed a prospective patient record, each physician providing

information on 10 consecutive patients with a working diagnosis on admission of acute coronary syndrome, and a questionnaire.

**Results.** A total of 390 responses were received (0.91/106 population) with data on 3092 patients in 29 countries. The patient population comprised 1431 (46%) with an initial working diagnosis of unstable angina/non-ST-segment elevation myocardial infarction, 1205 (39%) with myocardial infarction and 445 (14%) with suspected acute coronary syndrome. The ratio of unstable angina to myocardial infarction was 1.2:1 and this was similar across Europe. An initial diagnosis of myocardial infarction was more likely to be confirmed than unstable angina or suspected acute coronary syndrome. There were wide variations in the rates of angiography and percutaneous coronary intervention across Europe. Most unstable angina patients received aspirin, nitrates and heparin (unfractionated heparin 44% intravenous, 16% subcutaneous; low-molecular-weight heparin 50%). Overall, 50% of unstable angina patients and 34% of myocardial infarction patients received low-molecular-weight heparin and 6% and 8% respectively received a glycoprotein IIb/IIIa inhibitor, but there were large inter-country differences. There were also national differences in the use of calcium antagonists, angiotensin-converting enzyme inhibitors and beta-blockers.

**Conclusion.** The ENACT study provides robust data, for the first time, on the relative frequency of unstable angina and acute myocardial infarction across Europe. It provides insight into differences in management across Europe and a reference benchmark of current treatment.

Circulation 2000 Feb 22;101(7):751-7

Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. PURSUIT Investigators.

Kleiman NS, Lincoff AM, Flaker GC, Pieper KS, Wilcox RG, Berdan LG, Lorenz TJ, Cokkinos DV, Simoons ML, Boersma E, Topol EJ, Califf RM, Harrington RA

**BACKGROUND:** Platelet glycoprotein (GP) IIb/IIIa antagonists prevent the composite end point of death or myocardial infarction (MI) in patients with acute coronary syndromes. There is uncertainty about whether this effect is confined to patients who have percutaneous coronary interventions (PCIs) and whether PCIs further prevent death or MI in patients already treated with GP IIb/IIIa antagonists. **METHODS AND RESULTS:** PURSUIT patients were treated with the GP IIb/IIIa antagonist eptifibatide or placebo; PCIs were performed according to physician practices. In 2253 of 9641 patients (23.4%), PCI was performed by 30 days. Early (<72 hours) PCI was performed in 1228 (12.7%). In 34 placebo patients (5.5%) and 10 treated with eptifibatide (1.7%)

( $P=0.001$ ), MI preceded early PCI. In patients censored for PCI across the 30-day period, there was a significant reduction in the primary composite end point in eptifibatide patients ( $P=0.035$ ). Eptifibatide reduced 30-day events in patients who had early PCI (11.6% versus 16.7%,  $P=0.01$ ) and in patients who did not (14.6% versus 15.6%,  $P=0.23$ ). After adjustment for PCI propensity, there was no evidence that eptifibatide treatment effect differed between patients with or without early PCI ( $P$  for interaction= $0.634$ ). PCI was not associated with a reduction of the primary composite end point but was associated with a reduced (nonspecified) composite of death or Q-wave MI. This association disappeared after adjustment for propensity for early PCI. CONCLUSIONS: Eptifibatide reduced the composite rates of death or MI in PCI patients and those managed conservatively.

#### Summary

1. In patients censored for PCI across the 30-day period, there was a significant reduction in the primary composite end point in eptifibatide patients ( $P=0.035$ )
2. Eptifibatide reduced 30-day events in patients who had early PCI (11.6% versus 16.7%,  $P=0.01$ )
3. After adjustment for PCI propensity, there was no evidence that eptifibatide treatment effect differed between patients with or without early PCI ( $P$  for interaction= $0.634$ ).

Circulation 2000 Feb 15;101(6):590-3

A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents.

Muller C, Buttner HJ, Petersen J, Roskamm H

**BACKGROUND:** The introduction of an effective antiplatelet therapy with aspirin and ticlopidine after the placement of coronary-artery stents has decreased the risk of thrombotic stent occlusions (TSO) and hemorrhagic complications. However, the use of ticlopidine is limited by hematological and gastrointestinal adverse effects. The safety and efficacy of clopidogrel after stenting remains to be established. **METHODS AND RESULTS:** After successful coronary stenting during elective or emergency percutaneous transluminal coronary angioplasty, 700 patients with 899 lesions were randomly assigned to receive a 4-week course of either 500 mg ticlopidine ( $n=345$ ) or 75 mg clopidogrel ( $n=355$ ), in addition to 100 mg aspirin. All the following clinical events reflecting TSO were included in the prespecified primary cardiac endpoint: cardiac death, urgent target vessel revascularization, angiographically documented TSO, or nonfatal myocardial infarction within 30 days. The primary noncardiac endpoint was defined as noncardiac death, stroke, severe peripheral vascular or

hemorrhagic events, or any adverse event resulting in discontinuation of study medication. Cardiac events occurred in 17 patients [11 (3.1%) with clopidogrel and 6 (1.7%) with ticlopidine (P=0.24)]. The primary noncardiac endpoint was observed in 16 patients (4.5%) assigned to receive clopidogrel versus 33 patients (9.6%) assigned to receive ticlopidine (P=0.01). CONCLUSIONS: After the placement of coronary-artery stents in unselected patients, antiplatelet therapy with aspirin and clopidogrel seems to be comparably safe and effective as aspirin and ticlopidine. Noncardiac events were significantly reduced with clopidogrel.

#### Summary

The American Journal of Cardiology, 2000;85:9:1065-1070

Long-term outcome in patients treated by intracoronary stenting with ticlopidine and aspirin, and deleterious prognostic role of unstable angina pectoris

Michael Angioi, Nicolas Danchin, Francois Alla, Catherine Gangloff, Henri Sunthorn, Rosa-Maria Rodriguez, Jean-Philippe Preiss, Alain Grentzinger, Philippe Houplon, Yves Juilliere and Francois Cherrier

Compared with stable clinical conditions, unstable angina carries an increased risk of immediate and delayed cardiac adverse events after balloon coronary angioplasty. The influence of stent use in reducing these differences remains unknown. We analyzed the early (30 days) and late outcome of a cohort of 459 consecutive patients who underwent stent placement with ticlopidine and aspirin as antithrombotic regimen according to the presence (group 1, n = 151) or absence (group 2, n = 308) of unstable angina at rest (Braunwald classes II and III). Group 1 patients were older and more likely to be current or former smokers. In group 2, prior myocardial infarction was more frequent. Procedural, in-hospital results, and early outcome were similar in the 2 groups. However, over the long term, the incidence of myocardial infarction (11% vs 6%, p <0.04), target lesion revascularization (19% vs 13%, p <0.04), or any revascularization (30% vs 20%, p <0.01) was significantly higher in group 1. Kaplan-Meier probabilities of survival without myocardial infarction (85% vs 91%, p <0.05), survival without revascularization of the target lesion (73% vs 83%, p <0.01), survival without any revascularization (65% vs 77%, p <0.006), and survival without any events (61% vs 73%, p <0.009) were significantly worse in group 1. In addition, Cox multivariate analysis showed that unstable angina at rest was an independent predictor of target lesion revascularization, of survival without any revascularization, and without any events. Thus, unstable angina at rest remains an adverse prognostic indicator in patients treated with intracoronary

stents, particularly with regard to subsequent requirement of revascularization procedures and event-free survival.

Figure 1. Kaplan-Meier curves of survival without myocardial infarction, survival without target lesion revascularization, survival without any revascularization, and event-free survival.

AHJ September 2000, Volume 140, Number 3, 483 ~491

Clopidogrel for prevention of major cardiac events after coronary stent implantation: 30-day and 6-month results in patients with smaller stents

Alison L. Calver, MD, MRCP, Lucy J. Blows, MBBS, MRCP, Sue Harmer, RGN, Keith D. Dawkins, MD, FRCP, Huon H. Gray, MD, FRCP, John H. Morgan, MD, FRCP, Iain A. Simpson, MD, FRCP

**Objectives.** We developed this study to assess the procedural outcome, complications, and clinical follow-up in patients treated with different antiplatelet regimens after intracoronary stent implantation with small stents. Three hundred sixty-one consecutive patients, in whom at least one 3.0-mm intracoronary stent was implanted, were studied.

**Methods.** The study was a prospective, observational registry of unselected consecutive patients treated in our institution. Patients who underwent stent implantation between December 1997 and July 1998 were treated with aspirin and ticlopidine; those who received stents between August 1998 and February 1999 were treated with aspirin and clopidogrel.

**Results.** In the group treated with ticlopidine, there were 190 patients who had 253 lesions treated with 274 stents. Mean age was 59.1 years, 72% were male, 31% had unstable angina, 64% had 1 stent, 36% had >1 stent, and 23% had multivessel intervention. In the group treated with clopidogrel, there were 171 patients who had 226 lesions treated with 245 stents. Mean age was 60.4 years, 79% were male, 26% had unstable angina, 70% had 1 stent, 30% had >1 stent, and 26% had multivessel intervention. Complications at 30 days in the ticlopidine group were death in 1 (0.5%), stent occlusion in 3 (1.6%; all reopened with repeat angioplasty), non-Q-wave myocardial infarction in 2 (1%), and urgent revascularization in 4 (2%). Complications at 30 days in the clopidogrel group were noncardiac death in 1 (1.2%), cardiac death in 1 (1.2%), stent occlusion in 0, non-Q-wave myocardial infarction in 3 (1.8%), and urgent revascularization in 0. Follow-up was available in 100% of patients in both groups (mean  $253 \pm 75$  days in the ticlopidine group,  $198 \pm 53$  days in the clopidogrel group). Complications at >30 days in the ticlopidine group were death in 1 and clinical restenosis in 11 (5.8%); 1 additional patient had an admission with unstable angina to the local hospital. Hence, recurrent angina as a consequence of target lesion restenosis occurred in 5.8%. Complications at >30 days in the clopidogrel group were death in 0 and clinical restenosis in 8 (4.7%); 2 additional patients were admitted with unstable angina to the local hospital, and 1 patient had a myocardial infarction 164 days after stent implantation. Hence, recurrent

angina as a consequence of target lesion restenosis occurred in 4.7%. There were no significant differences in complications between the 2 groups.

**Conclusions.** Our observations suggest that clopidogrel can be used instead of ticlopidine in patients treated with stents with a diameter of 3.0 mm, without any increase in major adverse cardiac events, both within the first 30 days and at medium-term follow-up. Clopidogrel has significant cost advantages over ticlopidine, and carries a superior side-effect profile. We suggest that, in combination with aspirin, clopidogrel should replace ticlopidine as standard antiplatelet therapy after intracoronary stent implantation.

Table VI. Complications  $\leq 30$  days

MI, Myocardial infarction; MACE, major adverse cardiac event; CI, confidence interval.

Table VII. Complications  $>30$  days

MI, Myocardial infarction.

Table VIII. Major adverse cardiac events (MACE)

American Heart Journal January 2001 ? Volume 141 ? Number 1 ? p124 to p130

Effects of cilostazol on late lumen loss and repeat revascularization after Palmaz-Schatz coronary stent implantation

Ken Kozuma, MDa, Kazuhiro Hara, MD, FACCb, Masao Yamasaki, MD<sub>b</sub>, Yoshihiro Morino, MD<sub>b</sub>, Seiji Ayabe, MD<sub>b</sub>, Yuzo Kuroda, MD<sub>b</sub>, Kengo Tanabe, MD<sub>b</sub>, Yuji Ikari, MD<sub>b</sub>, Tsutomu Tamura, MD<sub>b</sub>

**Background** Cilostazol is an antiplatelet agent that increases the intracellular concentration of cyclic adenosine monophosphate by inhibiting phosphodiesterase III; it has been shown to reduce neointimal hyperplasia in animal balloon injury models.

**Methods** One hundred thirty patients who underwent elective stenting (Palmaz-Schatz stent) were randomly assigned to cilostazol treatment 200 mg/d (n = 65) or to ticlopidine treatment 200 mg/d (n = 65). Angiographic follow-up was performed at 6 months, and clinical follow-up was continued up to 1 year.

**Results** One sudden death and one myocardial infarction resulting from subacute occlusion were observed in the ticlopidine group. Drug adverse effects were observed in 3 patients in the cilostazol group, as opposed to 6 patients in the ticlopidine group. In the intention-to-treat analysis, 56 patients (61 lesions) in the cilostazol group and 58 patients (58 lesions) in the ticlopidine group were assessed with quantitative coronary angiography. Late loss in the cilostazol group was smaller ( $0.58 \pm 0.52$  mm vs  $1.09 \pm 0.65$  mm,  $P < .0001$ ) than

in the ticlopidine group. The restenosis rate was lower in the cilostazol group than in the ticlopidine group (16% vs 33%,  $P = .044$ ). The target vessel revascularization rate at 1 year was 23% in the cilostazol group and 42% in the ticlopidine group ( $P = .03$ ).

**Conclusions** The results of this study suggest that cilostazol may be a safe medication that is effective in preventing restenosis after stent implantation.

Fig. 2. Target vessel revascularization-free survival curves.

Table IV. Linear regression predictors for late lumen loss

CI, Confidence interval.

AHJ October 2000, part 1, Volume 140, Number 4, 637 ~ 642

Superiority of enoxaparin versus unfractionated heparin for unstable angina/non-Q-wave myocardial infarction regardless of activated partial thromboplastin time

Gerardo E. Bozovich, MDa, Enrique P. Gurfinkel, MD, PhD<sup>b</sup>, Elliott M. Antman, MD<sup>b</sup>, Carolyn H. McCabe, BS<sup>b</sup>, Branco Mautner, MDa

**Background** Whether the clinical superiority of enoxaparin versus unfractionated heparin (UFH) depends on a more stable antithrombotic effect or the proportion of patients not reaching the therapeutic level with UFH has not been addressed.

**Methods** All patients participating in the Thrombolysis In Myocardial Infarction 11B trial who received UFH and had sufficient activated partial thromboplastin time (aPTT) data ( $n = 1893$ ) were compared with patients who received enoxaparin ( $n = 1938$ ). Patients receiving UFH were divided into 3 categories depending on mean aPTT values throughout 48 hours: subtherapeutic, for those in whom the average aPTT fell below 55 seconds; therapeutic, between 55 and 85 seconds; and supratherapeutic, longer than 85 seconds. Events and bleeding rates were determined at 48 hours.

**Results** A small portion of patients (6.7%) had a subtherapeutic average aPTT value ( $n = 127$ ). Forty-seven percent of patients ( $n = 891$ ) fell within the therapeutic range, and 46% were in the supratherapeutic level ( $n = 875$ ). Event rates were 7.0% in the UFH group versus 5.4% with enoxaparin ( $P = .039$ ). Events rates were higher in every aPTT strata compared with enoxaparin and statistically significant in the supratherapeutic group (odds ratio 0.65; 95% confidence interval, 0.47-0.89). Major bleeding rates were 0%, 0.6%, and 0.9% for the subtherapeutic, target, and supratherapeutic strata, respectively, and 0.8% with enoxaparin. Minor

hemorrhages occurred in 5.1% of patients receiving enoxaparin versus 3.9%, 2%, and 2.3%, respectively, for the UFH subgroups ( $P < .001$  for all UFH groups vs enoxaparin).

Conclusions Enoxaparin showed a better clinical profile compared with every level of anticoagulation with UFH. Potential mechanisms for enoxaparin superiority are stable antithrombotic activity, lack of rebound thrombosis, and intrinsic superiority. (*Am Heart J* 2000;140:637-42.)

Fig. 1. Odds ratios and 95% confidence intervals for treatment effect of enoxaparin compared with individual aPTT subgroups. Entire enoxaparin group is compared with aPTT strata calculated as mean aPTTs throughout 48 hours. There is significant benefit in favor of enoxaparin vs suprathreshold UFH group. Lower half of figure compares patients within and out of range with enoxaparin. Combined subtherapeutic and suprathreshold strata have a significantly higher event rate.

*The American Journal of Cardiology*, 2000;85:9:1054-1059

Increased platelet aggregability in response to shear stress in acute myocardial infarction and its inhibition by combined therapy with aspirin and cilostazol after coronary intervention

Takashi Tanigawa, Masakatsu Nishikawa, Tamaki Kitai, Yuji Ueda, Tsutomu Okinaka, Katsutoshi Makino, Masaaki Ito, Naoki Isaka, Yasuo Ikeda, Hiroshi Shiku and Takeshi Nakano

Although antiplatelet therapy with a specific inhibitor of phosphodiesterase-3 cilostazol improves stent patency compared with use of aspirin (ASA) alone, the specific role of cilostazol on platelet aggregation in patients with acute myocardial infarction (AMI) is less well understood. Thirty-six patients with AMI who were successfully treated with primary angioplasty were randomized to 3 antiplatelet regimens: ASA alone ( $n = 12$ ), ASA + ticlopidine ( $n = 12$ ), and ASA + cilostazol ( $n = 12$ ). We measured shear stress-induced platelet aggregation (SIPA) using a modified cone-plate viscometer on admission and on day 7, and evaluated the inhibitory effects of combination therapy with ASA + cilostazol on SIPA. Compared with cases of stable coronary artery disease, significant increases in SIPA and plasma von Willebrand factor activity were observed in patients with AMI before they received antiplatelet therapy. On day 7 after primary angioplasty, ASA did not inhibit SIPA ( $65 \pm 15\%$  vs  $57 \pm 11\%$ ,  $p = 0.086$ ), whereas both combination therapies of ASA + ticlopidine and ASA + cilostazol significantly inhibited SIPA in patients with AMI (ASA + ticlopidine:  $61 \pm 15\%$  vs  $45 \pm 13\%$ ,  $p < 0.0001$ ; ASA + cilostazol:  $64 \pm 14\%$  vs  $43 \pm 9\%$ ,  $p < 0.005$ ). There was a significant correlation of SIPA with adenosine diphosphate (ADP)-induced platelet aggregation ( $r = 0.412$ ,  $p = 0.003$ ) and with plasma von Willebrand factor activity ( $r = 0.461$ ,  $p = 0.0008$ ). These data suggest that patients with AMI have increased platelet aggregability in response to high shear stress. Combined antiplatelet therapy with ASA + cilostazol appears to be as effective as therapy with ASA + ticlopidine for reducing SIPA in patients with AMI who are undergoing primary

angioplasty.

Figure 2. Effects of ASA, ASA + ticlopidine, and ASA + cilostazol on platelet aggregation induced by ADP (A), epinephrine (B), collagen (C), and arachidonate (D) in AMI patients after coronary intervention. Box and whisker plots show mean value (plus signs), median (horizontal lines), 25th and 75th percentiles (box), and 10th and 90th percentiles (error bars). Pre- and day 7 indicate the data obtained for patients who received no medication before coronary intervention and on day 7 of each treatment, respectively. CIL = cilostazol; TIC = ticlopidine. \* $p < 0.05$ ; † $p < 0.005$ ; # $p < 0.0001$ .

Thrombosis Research, 2000;100:6:479-488

Abciximab treatment in vitro after aspirin treatment in vivo has additive effects on platelet aggregation, ATP release, and P-selectin expression

Alejandra Scazziota, Raul Altman, Jorge Rouvier, Claudio Gonzalez, Zulfiqar Ahmed, Walter P. Jeske, Jeanine M. Walenga and Jawed Fareed

To prevent arterial thrombosis, abciximab is administered together with aspirin. However, whether or not there are benefits to combine abciximab with aspirin is not yet well defined. Healthy volunteers were studied for the effect of aspirin+abciximab using sodium arachidonate and adenosine diphosphate (ADP) alone or in combination to induce platelet activation/aggregation. Abciximab produced complete inhibition of platelet

aggregation induced with ADP but only 40% inhibition of aggregation induced by 0.75-mmol/l sodium arachidonate. Abciximab added in vitro to platelet-rich plasma (PRP) from platelets from aspirin-treated donors produced an almost complete inhibition of platelet aggregation. Aspirin, and abciximab alone, did not inhibit adenosine triphosphate (ATP) release as thoroughly as aspirin+abciximab did. Abciximab (3-5 $\mu$ g/ml) produced inhibition of P-selectin expression induced with 5 (from 46.2 $\pm$ 6.0% to 27.4 $\pm$ 7.0%, P=.002) and 20- $\mu$ g mol/l ADP (from 53.1 $\pm$ 8.1% to 35.1 $\pm$ 11.0%, P=.019), but no effect was observed when 0.75-mmol/l sodium arachidonate was used (P=.721). Aspirin diminished P-selectin expression in sodium arachidonate-stimulated platelets (from 77.7 $\pm$ 11.8% to 40.2 $\pm$ 3.6%, P<.0001) in non-aspirinated and platelets from aspirin-treated donors, respectively. Abciximab (3, 4, and 5 $\mu$ g/ml) added to platelets from aspirin-treated donors decreased P-selectin expression in platelets stimulated with sodium arachidonate from 40.2 $\pm$ 8.6% to 25.6 $\pm$ 11.5% (P=.027), to 20.5 $\pm$ 3.5% (P<.0001), and to 22.5 $\pm$ 1.8% (P<.0001). We concluded that the antiplatelet effect of abciximab is greatly increased by aspirin.

Fig. 4. P-selectin expression in platelets from aspirin-treated donors from volunteers after 100-mg/day aspirin for 7 days (200 mg on the first day). Results represent mean $\pm$ S.D. values from five volunteers. Abciximab significantly decreased P-selectin expression obtained in aspirinated platelet activated with sodium arachidonate. The indicated P values result from comparing saline and 5-g/ml abciximab, and were calculated by the Student's t test

The American Journal of Cardiology, 2000;85:5:527-531

Effect of aspirin and ticlopidine on plasma tissue factor levels in stable and unstable angina pectoris

Jean Marco a, Robert A.S. Ariens b, Jean Fajadet a, Irene M. Bossi a, Isabelle Marco a, Monique Bernies a, Salvatore M. Romano b, Francesco Donatelli b, Gabri M. Brambilla b, Francesco Somalvico b, Daniela Mari b and Luisa Gregorini bA

Patients with unstable angina have an increased activation of the coagulation system. Aspirin and ticlopidine given in combination may potentiate each other by the combination of different action mechanisms and may reduce the risk of coronary occlusion and clinical instability. Plasma tissue factor (TF) levels collected into the stenotic coronary artery may be an index of TF expression within the vasculature. In 160 patients undergoing angioplasty for a 81  $\pm$  5% coronary lesion, we measured TF in blood samples collected from a vein and from the coronary ostium. Immediately after and 10 minutes after the dilation procedures the samples were withdrawn also beyond the lesion. Heparin 150 U/kg was given as an anticoagulant. All patients were

pretreated with 250 mg/day of aspirin. One hundred twenty patients were randomly assigned to receive 24, 48, or 72 hours of ticlopidine treatment (250 mg/twice daily). TF levels did not increase during angioplasty but there was a significantly higher TF expression in unstable than in stable patients, irrespective of the invasiveness of debulking procedures. When ticlopidine was given for 72 hours, TF levels were similar to normal laboratory values both in stable and unstable patients. This combined antiplatelet pretreatment may be of benefit in unstable angina patients, with a favorable cost/benefit ratio.

Figure 1. Mean plasma TF levels (pg/ml  $\pm$  SD) collected before PTCA and soon after dilation procedures. TF normal laboratory values: 141  $\pm$  45 pg/ml. h = hours of ticlopidine pretreatment; S = stable; T = ticlopidine; U = patients with unstable angina

Journal of the American College of Cardiology, 2000;36:3:699-705

Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy

Khatereh Moshfegh, Maurice Redondo, Friedgard Julmy, Walter A. Wuillemin, Mathias U. Gebauer, Andre Haerberli and Beat J. Meyer

**OBJECTIVES:** We sought to compare the inhibitory effects of the combination of two doses of aspirin plus clopidogrel with either drug alone on platelet aggregation and activation. **BACKGROUND:** Enhanced platelet inhibitory effects of clopidogrel by aspirin on platelet aggregation and activation are suggested by experimental studies but have not been shown in humans. **METHODS:** The effects of clopidogrel 75 mg or aspirin 100 (300) mg on platelet aggregation and activation by flow cytometry after stimulation with various agonists were determined in 30 patients with a past history of myocardial infarction. **RESULTS:** Clopidogrel alone or in combination with aspirin markedly inhibited adenosine diphosphate (ADP)-mediated platelet aggregation compared with monotherapy with aspirin ( $24.6 \pm 3.3\%$  or  $26.6 \pm 2.7\%$  vs.  $44.7 \pm 2.9\%$ ;  $p < 0.001$ ). Combined treatment significantly inhibited collagen-induced aggregation compared with aspirin and clopidogrel ( $16.4 \pm 2.4\%$ ,  $36.5 \pm 4.2\%$  and  $59.3 \pm 5.1\%$ , respectively;  $p < 0.001$ ) and resulted in considerable inhibition of aggregation induced by thrombin receptor agonist peptide (TRAP,  $p < 0.03$ ). Clopidogrel with or without aspirin significantly suppressed expression of platelet activation markers CD 62p, CD 63 and PAC-1 after stimulation with ADP or thrombin ( $p < 0.001$ ). In addition, the combined treatment was more effective than either agent alone after activation with low dose thrombin ( $p < 0.05$ ). Both doses of aspirin equally potentiated the platelet inhibitory effects of clopidogrel. **CONCLUSIONS:** In this prospective clinical ex vivo

platelet study, clopidogrel was more effective than aspirin in inhibiting ADP-mediated platelet aggregation and activation. Clopidogrel in combination with aspirin showed synergistic inhibitory effects after stimulation with collagen and thrombin compared with monotherapies. Thus, this dual antiplatelet treatment strategy deserves further evaluation in clinical trials for secondary prevention of acute myocardial infarction or unstable angina. Figure 4. Changes in the expression of platelet activation epitopes after administration of aspirin (100 mg/day, black bars), clopidogrel (75 mg/day, white bars) and aspirin (100 mg/day) plus clopidogrel (75 mg/day, hatched bars). In figures A to C, platelets were stimulated with adenosine diphosphate (ADP; 0.01, 0.1, 1, 10, 100 mol/L) and in D to F with thrombin (0.01, 0.05, 0.1, 0.5 U/mL). After stimulation, activated platelets were detected by flow cytometry with monoclonal antibodies directed against CD62p (P-selectin), which recognizes alpha-granule release, CD63 recognizing lysosome secretion and PAC-1 detecting activated GP IIb-IIIa complex. Results (n = 30) are expressed as the percentage of the total platelet population binding each monoclonal antibody and represent mean  $\pm$  SEM. \*p < 0.05 versus aspirin; #p < 0.05 versus clopidogrel; §p = 0.054; ¶p = 0.065 versus clopidogrel (Wilcoxon signed rank test).

The American Journal of Cardiology, 2000;86:5:499-503

#### Effects of cilostazol on angiographic restenosis after coronary stent placement

Seong-Wook Park, Cheol Whan Lee, Hyun-Sook Kim, Nae-Hee Lee, Deuk Young Nah, Myeong-Ki Hong, Jae-Joong Kim and Seung-Jung Park

This study evaluates the impact of cilostazol on poststenting restenosis. Cilostazol is a potent antiplatelet agent with antiproliferative properties. Few data are available about the effect of cilostazol on poststenting restenosis. Four hundred nine patients (494 lesions) who were scheduled for elective stenting were randomized to receive aspirin plus ticlopidine (group I, n = 201, 240 lesions) or aspirin plus cilostazol (group II, n = 208, 254 lesions), starting 2 days before stenting. Ticlopidine was given for 1 month and cilostazol for 6 months. Follow-up angiography was performed at 6 months, and clinical evaluation at regular intervals. Baseline characteristics were similar between the 2 groups. The procedural success rate was 99.6% in group I and 100% in group II. There were no cases of stent thrombosis after stenting. Angiographic follow-up was performed in 380 of the 494 eligible lesions and the angiographic restenosis rate was 27% in group I and 22.9% in group II (p = NS). However, diffuse type in-stent restenosis was more common in group I than in group II (54.2% vs 26.8%, respectively, p < 0.05). In diabetic patients, the angiographic restenosis rate was 50% in group I and 21.7% in group II (p < 0.05). Clinical events during follow-up did not differ between the 2 groups. In conclusion, aspirin

plus cilostazol seems to be an effective antithrombotic regimen with comparable results to aspirin plus ticlopidine, but it does not reduce the overall angiographic restenosis rate after elective coronary stenting.

Figure 1. Comparison of the cumulative distribution of the minimal lumen diameter for the ticlopidine and cilostazol groups before (Pre), immediately after coronary stenting (Post), and at follow-up (FU). As shown, the minimal lumen diameter at 6-month follow-up was greater in the cilostazol group than in the ticlopidine group ( $p < 0.05$ ).

Journal of the American College of Cardiology, 2000;36:1:75-83

#### Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy

David C. Sane , Lakshmi V. Damaraju, Eric J. Topol, Catherine F. Cabot, Mary Ann Mascelli , Robert A. Harrington , Maarten L. Simoons and Robert M. Califf EPIC EPILOG CAPTURE and EPISTENT Study Groups

**OBJECTIVES:** This study determined the incidence of pseudothrombocytopenia during abciximab therapy administered for percutaneous coronary interventions and compared the clinical course of patients with pseudothrombocytopenia with the clinical courses of patients with thrombocytopenia and patients with normal platelet counts. **BACKGROUND:** Although pseudothrombocytopenia has been previously reported during therapy with abciximab, the incidence and significance of this occurrence are unknown. The failure to differentiate pseudothrombocytopenia from thrombocytopenia could lead to unnecessary interruption of abciximab infusions or to platelet transfusions. **METHODS:** The incidences of pseudothrombocytopenia and thrombocytopenia were determined in four large placebo-controlled abciximab trials: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome of c7E3 GpIIb/IIIa Receptor Blockade (EPILOG) and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT). The clinical features, bleeding complications and major clinical outcomes of patients with pseudothrombocytopenia and those with thrombocytopenia were compared with each other and with those of patients with normal platelet count. **RESULTS:** Pseudothrombocytopenia occurred in 2.1% (95% confidence intervals [CI]: 1.7%, 2.5%) of abciximab-treated patients and in 0.6% of placebo-treated patients ( $p < 0.001$ ). Thrombocytopenia occurred in 3.7% (95% CI: 3.2%, 4.2%) of abciximab-treated patients and in 1.8% (95% CI: 1.3%, 2.3%) of placebo-treated patients ( $p < 0.001$ ). Patients with thrombocytopenia had significantly higher rates of major bleeding, major decreases in hemoglobin and increased transfusion requirements of both blood and platelets compared with those without thrombocytopenia. By contrast, pseudothrombocytopenic patients

did not differ from patients with normal platelet counts in any of the measures of blood loss or transfusion requirements. Thrombocytopenic patients, but not those with pseudothrombocytopenia, had increased rates of revascularization at 30 days and six months. As previously reported, there was also a higher rate of death and myocardial infarction in the thrombocytopenic patients. CONCLUSIONS: Pseudothrombocytopenia is the cause of more than one third (36.3%) of low platelet counts in patients undergoing coronary interventions who are treated with abciximab. This study demonstrates that pseudothrombocytopenia is a benign laboratory condition that does not increase bleeding, stroke, transfusion requirements or the need for repeat revascularization. It is important to recognize pseudothrombocytopenia so that the beneficial effects of abciximab are not lost by premature termination of therapy.

Table 5. 30-Day Clinical Outcomes legend Clinical

[\*]There is a significant association between thrombocytopenia and MI in both the placebo and abciximab group (p value < 0.001);

[†]there is a significant association between thrombocytopenia and repeat revascularization, in both the placebo and abciximab group (p value < 0.001);

[‡]there is a significant association between thrombocytopenia and CABG, in both the placebo and abciximab group (p value < 0.001);

[§]analysis of revascularization excludes patients with staged PCI.

[legend]CABG = coronary artery bypass grafting; MI = myocardial infarction; Hem = hemorrhagic stroke; Nonhem = non hemorrhagic stroke; Re Rev = repeat revascularization; Re PCI = repeat PCI

Journal of the American College of Cardiology, 200035:7:1699-1712

Low molecular weight heparin in acute coronary syndrome: evidence for superior or equivalent efficacy compared with unfractionated heparin?

Sanjay Kaul and Prediman K. Shah

This article will review the results of recent clinical trials evaluating low molecular weight heparins (LMWHs) in the management of patients with acute coronary syndromes of unstable angina and non-ST segment elevation MI. Low molecular weight heparins are a new class of anticoagulants that have a number of advantages over unfractionated heparin (UFH) leading to their increasing use for thrombotic vascular disorders. There is convincing evidence that LMWH is more effective than placebo and at least as effective as UFH in reducing the hard end points of death and recurrent myocardial infarction. Convincing evidence for a superior efficacy is mostly limited to the least robust but most prevalent end point of recurrent angina, and

benefits appear to be confined predominantly to high-risk patients. The benefits are sustained long-term, but there appears to be no incremental benefit with prolonged treatment. The risk for major bleeding is approximately equivalent to UFH, but minor hemorrhage is clearly increased, especially with vascular instrumentation. The increased bleeding risk together with its long half-life and absence of specific antidote warrants exercising caution when using LMWH with coronary intervention. Low molecular weight heparins have the potential of being cost-neutral or even cost-saving by reducing resource utilization, especially in the setting of aggressive interventional practice pattern. Last, the issue of whether one LMWH preparation is more effective and cost-effective than others remains an open question that can be answered only by direct head-to-head comparison of different LMWH preparations in randomized trials. In conclusion, subcutaneous weight-adjusted LMWH is as effective and safe as intravenous UFH in the management of patients with acute coronary syndromes. The logistic ease of administration without the need for monitoring anticoagulation appears to be the major advantage over UFH.

[legend]D = death; MI = myocardial infarction; NQMI = non-Q-wave myocardial infarction; RA = recurrent angina; Revasc. = revascularization (CABG, PTCA); RR = relative risk; UA = unstable angina; UHF = unfractionated heparin.

Circulation 2000 102: 157-165

#### Long-Term Effects on Clinical Outcomes of Aggressive Lowering of Low-Density Lipoprotein Cholesterol Levels and Low-Dose Anticoagulation in the Post Coronary Artery Bypass Graft Trial

Genell L. Knatterud, Yves Rosenberg, Lucien Campeau, Nancy L. Geller, Donald B. Hunninghake, Sandra A. Forman, James S. Forrester, Fredarick L. Gobel, J. Alan Herd, Ann Hickey, Byron J. Hoogwerf, Michael L. Terrin, and Carl White

**Background-**The Post Coronary Artery Bypass Graft Trial, designed to compare the effects of 2 lipid-lowering regimens and low-dose anticoagulation versus placebo on progression of atherosclerosis in saphenous vein grafts of patients who had had CABG surgery, demonstrated that aggressive lowering of LDL cholesterol (LDL-C) levels to <100 mg/dL compared with a moderate reduction to 132 to 136 mg/dL decreased the progression of atherosclerosis in grafts. Low-dose anticoagulation did not significantly affect progression.

**Methods and Results-**Approximately 3 years after the last trial visit, Clinical Center Coordinators contacted each patient by telephone to ascertain the occurrence of cardiovascular events and procedures. The National Death Index was used to ascertain vital status for patients who could not be contacted. Vital status was

established for all but 3 of 1351 patients. Information on nonfatal events was available for 95% of surviving patients. A 30% reduction in revascularization procedures and 24% reduction in a composite clinical end point were observed in patients assigned to aggressive strategy compared with patients assigned to moderate strategy during 7.5 years of follow-up,  $P=0.0006$  and  $0.001$ , respectively. Reductions of 35% in deaths and 31% in deaths or myocardial infarctions with low-dose anticoagulation compared with placebo were also observed,  $P=0.008$  and  $0.003$ , respectively.

**Conclusions-**The long-term clinical benefit observed during extended follow-up in patients assigned to the aggressive strategy is consistent with the angiographic findings of delayed atherosclerosis progression in grafts observed during the trial. The apparent long-term benefit of low-dose warfarin remains unexplained.

Circulation 2000 101: 590 - 593.

A Randomized Comparison of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin After the Placement of Coronary-Artery Stents

Christian Muller, Heinz J. Buttner, Jens Petersen, and Helmut Roskamm

**Background-**The introduction of an effective antiplatelet therapy with aspirin and ticlopidine after the placement of coronary-artery stents has decreased the risk of thrombotic stent occlusions (TSO) and hemorrhagic complications. However, the use of ticlopidine is limited by hematological and gastrointestinal adverse effects. The safety and efficacy of clopidogrel after stenting remains to be established.

**Methods and Results-**After successful coronary stenting during elective or emergency percutaneous transluminal coronary angioplasty, 700 patients with 899 lesions were randomly assigned to receive a 4-week course of either 500 mg ticlopidine ( $n=345$ ) or 75 mg clopidogrel ( $n=355$ ), in addition to 100 mg aspirin. All the following clinical events reflecting TSO were included in the prespecified primary cardiac endpoint: cardiac death, urgent target vessel revascularization, angiographically documented TSO, or nonfatal myocardial infarction within 30 days. The primary noncardiac endpoint was defined as noncardiac death, stroke, severe peripheral vascular or hemorrhagic events, or any adverse event resulting in discontinuation of study medication. Cardiac events occurred in 17 patients [11 (3.1%) with clopidogrel and 6 (1.7%) with ticlopidine ( $P=0.24$ )]. The primary noncardiac endpoint was observed in 16 patients (4.5%) assigned to receive clopidogrel versus 33 patients (9.6%) assigned to receive ticlopidine ( $P=0.01$ ).

**Conclusions-**After the placement of coronary-artery stents in unselected patients, antiplatelet therapy with aspirin and clopidogrel seems to be comparably safe and effective as aspirin and ticlopidine. Noncardiac events were significantly reduced with clopidogrel.

Circulation 2000 102: 28 - 34

## Pronounced Benefit of Coronary Stenting and Adjunctive Platelet Glycoprotein IIb/IIIa Inhibition in Complex Atherosclerotic Lesions

Fernando A. Cura, Deepak L. Bhatt, A. Michael Lincoff, Samir R. Kapadia, Philippe L. L'Allier, Khaled M. Ziada, Katherine E. Wolski, David J. Moliterno, Sorin J. Brener, Stephen G. Ellis, and Eric J. Topol

**Background**-Previous trials testing stents compared with balloon angioplasty excluded patients with complex lesions and did not assess the effect of adjunctive platelet IIb/IIIa inhibition. This analysis sought to assess the effect of stenting and abciximab specifically for patients with complex lesions.

**Methods and Results**-Patients with complex lesions (long, tandem, severely calcified, restenotic, thrombotic, or ostial; total occlusions; bifurcations; saphenous vein grafts; and multivessel interventions) from the Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade (EPILOG) and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trials were included in the analysis. The 1-year combined death or myocardial infarction rates in the 4 treatment groups were as follows: balloon angioplasty/placebo, 14.2%; stent/placebo, 15.8%; balloon angioplasty/abciximab, 7.6%; and stent/abciximab, 8.0% ( $P<0.001$ ). Death rates were 3.2%, 3.1%, 2.1%, and 0.5%, respectively ( $P=0.03$ ). The incidence of target vessel revascularization at 1 year was 30.5%, 18.0%, 24.4%, and 19.7% in the 4 groups, respectively ( $P<0.001$ ). After adjustment for baseline differences, multivariate analysis demonstrated that the rate of death or myocardial infarction was independently reduced by balloon angioplasty/abciximab (hazard ratio, 0.51;  $P<0.001$ ) and stent/abciximab (hazard ratio, 0.60;  $P=0.02$ ) but was not affected by the use of stents alone. Conversely, target vessel revascularization was reduced by stent/placebo (hazard ratio, 0.53;  $P<0.001$ ), stent/abciximab (hazard ratio, 0.58;  $P<0.001$ ), and balloon angioplasty/abciximab (hazard ratio, 0.74;  $P=0.006$ ) compared with balloon angioplasty/placebo, respectively.

**Conclusions**-The combination of stenting and abciximab during percutaneous coronary interventions for patients with angiographically complex lesions confers additive long-term benefit with respect to death, myocardial infarction, and target vessel revascularization.

Circulation 2000 102: 149 - 156

## Oral Glycoprotein IIb/IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes (OPUS-TIMI 16) Trial

Christopher P. Cannon, Carolyn H. McCabe, Robert G. Wilcox, Anatoly Langer, Abraham Caspi, Peter Berink, Jose Lopez-Sendon, Jiri Toman, Andrew Charlesworth, Robert J. Anders, John C. Alexander, Allan Skene, and Eugene Braunwald

**Background-**Although intravenous glycoprotein IIb/IIIa inhibitors are beneficial in patients with acute coronary syndromes, prolonged oral IIb/IIIa inhibition might provide an additional reduction in recurrent events.

**Methods and Results-**Investigators at 888 hospitals in 29 countries enrolled 10 288 patients with acute coronary syndromes, which was defined as ischemic pain at rest within 72 hours of randomization, associated with positive cardiac markers, electrocardiographic changes, or prior cardiovascular disease. Patients received aspirin and were randomized to receive, for the duration of the trial, (1) 50 mg of orbofiban twice daily (50/50 group), (2) 50 mg of orbofiban twice daily for 30 days followed by 30 mg of orbofiban twice daily (50/30 group), or (3) a placebo. The primary composite end point was death, myocardial infarction, recurrent ischemia requiring rehospitalization, urgent revascularization, or stroke. The trial was terminated prematurely because of an unexpected increase in 30-day mortality in the 50/30 orbofiban group. Mortality through 10 months was 3.7% for the placebo group versus 5.1% in the 50/30 group ( $P=0.008$ ) and 4.5% in the 50/50 group ( $P=0.11$ ). There were no differences in the primary end point (22.9%, 23.1%, and 22.8%, for the placebo, 50/30, and 50/50 groups, respectively). Major or severe bleeding (but not intracranial hemorrhage) was higher with orbofiban; it occurred in 2.0%, 3.7% ( $P=0.0004$ ), and 4.5% ( $P<0.0001$ ) of patients, respectively. Exploratory subgroup analyses found that patients who underwent percutaneous coronary intervention had a lower mortality and a significant reduction in the composite end point ( $P=0.001$ ) with orbofiban.

**Conclusions-**Fixed-dose orbofiban failed to reduce major cardiovascular events and was associated with increased mortality in this broad population of patients with acute coronary syndromes; however, a benefit was observed among patients who underwent percutaneous coronary intervention.

Circulation 2000 102: 1093 - 1100

Management of Patients With Acute Coronary Syndromes in the United States by Platelet Glycoprotein IIb/IIIa Inhibition : Insights From the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using

## Integrilin Therapy (PURSUIT) Trial

A. Michael Lincoff, Robert A. Harrington, Robert M. Califf, Judith S. Hochman, Alan D. Guerci, E. Magnus Ohman, Carl J. Pepine, Steven L. Kopecky, Neal S. Kleiman, Cynthia M. Pacchiana, Lisa G. Berdan, Michael M. Kitt, Maarten L. Simoons, and Eric J. Topol

**Background-**A multinational, randomized, placebo-controlled trial (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy, PURSUIT) demonstrated that the platelet glycoprotein IIb/IIIa receptor antagonist eptifibatide reduced the incidence of death or myocardial infarction among patients with acute ischemic syndromes without ST-segment elevation. Because of expected differences in practice patterns, a prospectively planned analysis of outcomes as a function of regions of the world was performed. The current study provides a detailed assessment of eptifibatide among the subgroup of patients enrolled within the United States.

**Methods and Results-**Patients presenting with chest pain within the previous 24 hours and ischemic ECG changes or creatine kinase-MB elevation were eligible for enrollment. Of the 10 948 patients randomized worldwide, 4035 were enrolled within the United States. Patients were allocated to placebo or eptifibatide infusion for up to 72 to 96 hours. Other medical therapies and revascularization strategies were at the discretion of the treating physician. Eptifibatide reduced the rate of the primary end point of death or myocardial infarction by 30 days from 15.4% to 11.9% ( $P=0.003$ ) among patients in the United States. The treatment effect was achieved early and maintained over a period of 6 months (18.9% versus 15.2%;  $P=0.004$ ). Bleeding events were more common in patients receiving eptifibatide but were predominantly associated with invasive procedures. The magnitude of clinical benefit from eptifibatide was greater among patients in the United States than elsewhere in the world.

**Conclusions-**Platelet glycoprotein IIb/IIIa receptor blockade with eptifibatide reduces the incidence of death or myocardial infarction among patients treated for acute ischemic syndromes without ST-segment elevation within the United States.

Circulation 2000 102: 2466 - 2472

Glycoprotein IIb/IIIa Receptor Blockade Improves Outcomes in Diabetic Patients Presenting With Unstable Angina/Non-ST-Elevation Myocardial Infarction : Results From the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study

Pierre Theroux, Joe Alexander, Jr, Chantal Pharand, Eliav Barr, Steven Snapinn, Asma F. Ghannam, and Frederic L. Sax

**Background-**Diabetic patients who present with unstable angina or non-ST-elevation myocardial infarction suffer a substantially greater incidence of subsequent infarction or death compared with nondiabetic patients. The present study was undertaken to examine whether diabetic patients in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study appeared to benefit from platelet glycoprotein IIb/IIIa receptor-mediated inhibition of platelet aggregation by tirofiban.

**Methods and Results-**Of the 1570 PRISM-PLUS patients treated with either tirofiban plus heparin (n=773) or heparin alone (n=797), 23% in each treatment group were diabetic. A comparison of treatment outcomes in the diabetic subgroup revealed that the combination therapy compared with heparin alone was associated with reductions in the incidence of the composite primary end point of death, myocardial infarction (MI), or refractory ischemia at 2, 7, 30, and 180 days (7.7% versus 8.3%, 14.8% versus 21.8%, 20.1% versus 29.0%, and 32.0% versus 39.9%, respectively; P=NS) and in the incidence of MI or death (0.0% versus 3.1%, P=0.03; 1.2% versus 9.3%, P=0.005; 4.7% versus 15.5%, P=0.002; and 11.2% versus 19.2%, P=0.03). Tests for quantitative interaction between tirofiban therapy and diabetic status were significant.

**Conclusions-**The addition of tirofiban to heparin and aspirin appears effective in the prevention of major ischemic events, particularly MI or death, in diabetic patients presenting with unstable angina and non-ST-elevation MI.

Circulation 2001 103: 201 - 206.

Increased Mortality With Oral Platelet Glycoprotein IIb/IIIa Antagonists : A Meta-Analysis of Phase III Multicenter Randomized Trials

Derek P. Chew, Deepak L. Bhatt, Shelly Sapp, and Eric J. Topol

**Background-**Numerous clinical trials have established the benefits of intravenous glycoprotein IIb/IIIa inhibition in the management of coronary artery disease. In contrast, the recent large-scale, placebo-controlled, randomized trials of the oral glycoprotein IIb/IIIa antagonists have failed to provide commensurate reductions in late composite ischemic end points despite potent inhibition of platelet aggregation.

Methods and Results-The ORs for death, myocardial infarction, urgent revascularization, and major bleeding from the 4 large-scale, placebo-controlled, randomized trials with oral glycoprotein IIb/IIIa inhibitors were calculated and combined. Stratification by low-dose or high-dose therapy and the use of concurrent aspirin was also undertaken. In 33 326 patients followed for >30 days, a consistent and statistically significant increase in mortality was observed with oral glycoprotein IIb/IIIa therapy (OR, 1.37; 95% CI, 1.13 to 1.66; P=0.001). This effect was evident regardless of aspirin coadministration and treatment with either low-dose or high-dose therapy. Although a reduction in urgent revascularization was observed with oral glycoprotein IIb/IIIa inhibition, pooled analysis favored an increase in myocardial infarction that did not demonstrate statistical significance.

Conclusions-Although we found a highly significant excess in mortality consistent across 4 trials with 3 different oral glycoprotein IIb/IIIa inhibitor agents, this was associated with a reduction in the need for urgent revascularization and no increase in myocardial infarction. These findings suggest the potential for a direct toxic effect with these agents and argue against a prothrombotic mechanism. Further investigation to elucidate the cause of this increased fatality risk is warranted.

#### Anticoagulation and antiplatelet therapy

##### 1. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia.

Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, Bartholomew J, Sham R, Lerner RG, Zeigler ZR, Rustagi PK, Jang IK, Rifkin SD, Moran J, Hursting MJ, Kelton JG; ARG-911 Study Investigators.

Circulation 2001 Apr 10;103(14):1838-43

##### 2. Oral Anticoagulant Therapy During and After Coronary Angioplasty : The Intensity and Duration of Anticoagulation Are Essential to Reduce Thrombotic Complications.

Berg JM, Hutten BA, Kelder JC, Verheugt FW, Plokker HW.

Circulation 2001 Apr 24;103(16):2042-2047

##### 3. Antiplatelet effects of abciximab, tirofiban and eptifibatide in patients undergoing coronary stenting.

Neumann FJ, Hochholzer W, Pogatsa-Murray G, Schomig A, Gawaz M.

J Am Coll Cardiol 2001 Apr;37(5):1323-8

##### 4. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis.

Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP; Investigators of the ?uree Optimale du Traitement AntiVitamines K?(DOTAVK) Study.

Circulation 2001 May 22;103(20):2453-60

5. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS).

Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, Taaffe M, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KK, Lindsay J.

Circulation 2001 May 15;103(19):2332-5

6. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study.

Steinhubl SR, Talley JD, Braden GA, Tcheng JE, Casterella PJ, Moliterno DJ, Navetta FI, Berger PB, Popma JJ, Dangas G, Gallo R, Sane DC, Saucedo JF, Jia G, Lincoff AM, Theroux P, Holmes DR, Teirstein PS, Kereiakes DJ.

Circulation 2001 May 29;103(21):2572-8

7. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatid in coronary stent intervention: the ESPRIT trial: a randomized controlled trial.

O'hea JC, Hafley GE, Greenberg S, Hasselblad V, Lorenz TJ, Kitt MM, Strony J, Tcheng JE; ESPRIT Investigators (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial).

JAMA 2001 May 16;285(19):2468-73

8. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization.

Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L; TARGET Investigators. Do Tirofiban and ReoPro Give Similar Efficacy Trial.

N Engl J Med 2001 Jun 21;344(25):1888-94

9. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery.

Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S.

Circulation 2001 Jun 26;103(25):3069-74

10. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population.

Taniuchi M, Kurz HI, Lasala JM.

Circulation 2001 Jul 31;104(5):539-43

11. Abciximab suppresses the rise in levels of circulating inflammatory markers after percutaneous coronary revascularization.

Lincoff AM, Kereiakes DJ, Mascelli MA, Deckelbaum LI, Barnathan ES, Patel KK, Frederick B, Nakada MT, Topol EJ.

Circulation 2001 Jul 10;104(2):163-7

12. Pharmacodynamics and pharmacokinetics of higher-dose, double-bolus eptifibatide in percutaneous coronary intervention.

Gilchrist IC, O'Hea JC, Kosoglou T, Jennings LK, Lorenz TJ, Kitt MM, Kleiman NS, Talley D, Aguirre F, Davidson C, Runyon J, Tcheng JE.

Circulation 2001 Jul 24;104(4):406-11

13. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators.

N Engl J Med 2001 Aug 16;345(7):494-502

14. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study.

Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators.

Lancet 2001 Aug 18;358(9281):527-33

15. Abciximab readministration: results of the ReoPro Readministration Registry.

Tcheng JE, Kereiakes DJ, Lincoff AM, George BS, Kleiman NS, Sane DC, Cines DB, Jordan RE, Mascelli MA, Langrall MA, Damaraju L, Schantz A, Efron MB, Braden GA.

Circulation 2001 Aug 21;104(8):870-5

16. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: A propensity analysis.

Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS.

JAMA 2001 Sep 12;286(10):1187-94

17. Does ticlopidine reduce reocclusion and other adverse events after successful balloon angioplasty of occluded coronary arteries? Results from the Total Occlusion Study of Canada (TOSCA).

Berger PB, Dzavik V, Penn IM, Catellier D, Buller CE.

Am Heart J 2001 Nov;142(5):776-81

18. Oral anticoagulation thresholds.

Brummel KE, Paradis SG, Branda RF, Mann KG.

Circulation 2001 Nov 6;104(19):2311-7

19. A randomized, placebo-controlled trial of enoxaparin after high-risk coronary stenting: the ATLAST trial.

Batchelor WB, Mahaffey KW, Berger PB, Deutsch E, Meier S, Hasselblad V, Fry ET, Teirstein PS, Ross AM, Binanay CA, Zidar JP; The ATLAST Trial Investigators.

J Am Coll Cardiol 2001 Nov 15;38(6):1608-13

20. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial.  
White H; The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators.  
Lancet 2001 Dec 1;358(9296):1855-63
21. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.  
BMJ 2002 Jan
22. Long-term mortality benefit with the combination of stents and abciximab for cardiogenic shock complicating acute myocardial infarction.  
Chan AW, Chew DP, Bhatt DL, Moliterno DJ, Topol EJ, Ellis SG.  
Am J Cardiol 2002 Jan 15;89(2):132-6
23. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting.  
Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, Dangas G, Taniuchi M, Lasala JM, Holmes DR, Ellis SG, Topol EJ.  
J Am Coll Cardiol 2002 Jan 2;39(1):9-14
24. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials.  
Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML.  
Lancet 2002 Jan 19;359(9302):189-98
25. Bivalirudin as a replacement for unfractionated heparin in unstable angina/non-ST-elevation myocardial infarction: observations from the TIMI 8 trial. The Thrombolysis in Myocardial Infarction.  
Antman EM, McCabe CH, Braunwald E.  
Am Heart J 2002 Feb;143(2):229-34
26. Abciximab improves 6-month clinical outcome after rescue coronary angioplasty.  
Petronio AS, Musumeci G, Limbruno U, De Carlo M, Baglioni R, Paterni G, Grazia Delle Donne M, Caravelli P, Nardi C, Mariani M.  
Am Heart J 2002 Feb;143(2):334-41
27. Heparin and coumadin versus acetylsalicylic acid for prevention of restenosis after coronary angioplasty.  
Garachemani AR, Fleisch M, Windecker S, Pfiffner D, Meier B.  
Catheter Cardiovasc Interv 2002 Mar;55(3):315-20
28. Use of a Monoclonal Antibody Directed against the Platelet Glycoprotein IIb/IIIa Receptor in High-Risk Coronary Angioplasty  
The EPIC Investigators  
(N Engl J Med 1994;330:956-61.)
29. A Comparison of Continuous Infusion of Alteplase with Double-Bolus Administration for Acute Myocardial

## Infarction

The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators  
(N Engl J Med 1997;337:1124-30.)

### 30. 'Rescue' Utilization of Abciximab for the Dissolution of Coronary Thrombus Developing as a Complication of Coronary Angioplasty

Joseph B. Muhlestein, MD, FACC, Labros A. Karagounis, MD, FACC, Sanjeev Treehan, MD, Jeffrey L. Anderson, MD, FACC

Journal of the American College of Cardiology, 30:7:1729-1734

### 31. 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

Circulation 1997 96: 1445-1453.

### 32. Bivalirudin Compared With Heparin During Coronary Angioplasty for Thrombus-Containing Lesions

Pinak B. Shah, MD, Waqar H. Ahmed, MD, FACC, Peter Ganz, MD, FACC, John A. Bittl, MD, FACC

Journal of the American College of Cardiology, 1997;30:5:1264-1269

### 33. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction

The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators

(N Engl J Med 1997;337:1118-23.)

### 34. Platelet Glycoprotein IIb/IIIa Receptor Blockade and Low-Dose Heparin during Percutaneous Coronary Revascularization

The EPILOG Investigators

(N Engl J Med 1997;336:1689-96.)

### 35. 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

A. Michael Lincoff, MD, FACC, Robert M. Califf, MD, FACC, Keaven M. Anderson, PhD, Harlan F. Weisman, MD, FACC, Frank V. Aguirre, MD, FACC, Neal S. Kleiman, MD, FACC, Robert A. Harrington, MD, FACC, Eric J. Topol, MD, FACC for the EPIC Investigators

Journal of the American College of Cardiology, 30:1:149-156

### 36. Effect of Nadroparin, a Low-Molecular-Weight Heparin, on Clinical and Angiographic Restenosis After Coronary Balloon Angioplasty : The FACT Study

Jean-Marc Lablanche, Eugene P. McFadden, Nicolas Meneveau, Jean Rene Lusson, Bernard Bertrand, Jean-Philippe Metzger, Victor Legrand, Gilles Grollier, Carlos Macaya, Bernard de Bruyne, Alec Vahanian, Alain Grentzinger, Christiane Masquet, Jean-Eric Wolf, Gerard Tobelem, Sylvie

Fontecave, Andre Vacheron, Pascal d'Azemar, and Michel E. Bertrand

Circulation 1997 96: 3396-3402.

37. First Chronic Platelet Glycoprotein IIb/IIIa Integrin Blockade : A Randomized, Placebo-Controlled Pilot Study of Xemilofiban in Unstable Angina With Percutaneous Coronary Interventions  
Conrad Simpfendorfer, Kandice Kottke-Marchant, Marsha Lowrie, Robert J. Anders, Daniel M. Burns, Dave P. Miller, Christopher S. Cove, Anthony C. DeFranco, Stephen G. Ellis, David J. Moliterno, Russell E. Raymond, Joseph M. Sutton, and Eric J. Topol  
Circulation 1997 96: 76-81.
38. Effect of Platelet Glycoprotein IIb/IIIa Receptor Inhibition on Distal Embolization During Percutaneous Revascularization of Aortocoronary Saphenous Vein Grafts  
Koon-Hou Mak, MBBS, Ram Challapalli, MD, Mark J. Eisenberg, MD, MPH, Keaven M. Anderson, PhD, Robert M. Califf, MD, Eric J. Topol, MD for the EPIC Investigators  
The American Journal of Cardiology, 1997;80:8:985-988
39. Sustained Platelet Glycoprotein IIb/IIIa Blockade With Oral Xemilofiban in 170 Patients After Coronary Stent Deployment  
Dean J. Kereiakes, Neal Kleiman, James J. Ferguson, John Paul Runyon, Thomas M. Broderick, Nancy A. Higby, Linda H. Martin, Gary Hantsbarger, Shawn McDonald, and Robert J. Anders  
Circulation 1997 96: 1117-1121.
40. Ticlopidine and Aspirin Pretreatment Reduces Coagulation and Platelet Activation During Coronary Dilation Procedures  
Luisa Gregorini, MD, Jean Marco, MD, Jean Fajadet, MD, Monique Bernies, MD, Bernard Cassagneau, MD, Philippe Brunel, MD, Irene M. Bossi, MD, Pier Mannuccio Mannucci, MD  
J Am Coll Cardiol 1997;29:13-20
41. Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting : The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study  
Michel E. Bertrand, Victor Legrand, Jean Boland, Eckart Fleck, Johannes Bonnier, Hakan Emmanuelson, Matty Vrolix, Luc Missault, Sergio Chierchia, Michele Casaccia, Luigi Niccoli, Ali Oto, Christopher White, Michael Webb-Peploe, Eric Van Belle, and Eugene P. McFadden  
Circulation 1998 98: 1597-1603.
42. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) Trial  
The Paradigm Investigators  
Journal of the American College of Cardiology, 32:7:2003-2010
43. Inhibition of Platelet Glycoprotein IIb/IIIa with Eptifibatide in Patients with Acute Coronary Syndromes  
The PURSUIT Trial Investigators  
. (N Engl J Med 1998;339:436-43.)

44. 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)

Philip Urban, Carlos Macaya, Hans-Jurgen Rupprecht, Ferdinand Kiemeneij, Hakan Emanuelsson, Alessandro Fontanelli, Michael Pieper, Thea Wesseling, and Luc Sagnard Background-Although the association of ticlopidine and aspirin has been shown to be superior to anti-vitamin K agents and aspirin after coronary stent implantation in low-risk patients, the latter combination has remained an unproven reference regimen for high-risk patients until recently  
Circulation 1998 98: 2126-2132.

45. Vasoeseal hemostasis following coronary interventions with Abciximab

Leo Lunney, Khalid Karim, Thomas Little  
Cathet. Cardiovasc. Diagn. 44:405-406, 1998.

46. A Comparison of Aspirin plus Tirofiban with Aspirin plus Heparin for Unstable Angina

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators  
(N Engl J Med 1998;338:1498-505.)

47. Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-Wave Myocardial Infarction

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators  
(N Engl J Med 1998;338:1488-97.)

48. Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization

Scott D. Berkowitz, David C. Sane, Kristina N. Sigmon, Jane H. Shavender, Robert A. Harrington, James E. Tchong, Eric J. Topol, Robert M. Califf for the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) Study Group  
Journal of the American College of Cardiology, 32:2:311-319

49. Clinical Outcome at Six Months of Coronary Stenting Followed by Ticlopidine Monotherapy

Mathias Elsner, MD, Alfred Peifer, MD, Michael Drexler, MD, Christian Wenzel, Christian Hebbeker, Wolfgang Kasper, MD  
The American Journal of Cardiology, 81:2:147-151

50. Randomized, Placebo-Controlled Trial of Platelet Glycoprotein IIb/IIIa Blockade With Primary Angioplasty for Acute Myocardial Infarction

Sorin J. Brener, Lawrence A. Barr, J. E. B. Burchenal, Stanley Katz, Barry S. George, Ancil A. Jones, Eric D. Cohen, Phillip C. Gainey, Harvey J. White, H. Barrett Cheek, Jeffrey W. Moses, David J. Moliterno, Mark B. Efron, and Eric J. Topol  
Circulation 1998 98: 734-741.

51. International, Randomized, Controlled Trial of Lamifiban (a Platelet Glycoprotein IIb/IIIa Inhibitor), Heparin, or Both in Unstable Angina  
Circulation 1998 97: 2386-2395.
52. Randomized, Placebo-Controlled Trial of Platelet Glycoprotein IIb/IIIa Blockade With Primary Angioplasty for Acute Myocardial Infarction  
Sorin J. Brener, Lawrence A. Barr, J. E. B. Burchenal, Stanley Katz, Barry S. George, Ancil A. Jones, Eric D. Cohen, Phillip C. Gainey, Harvey J. White, H. Barrett Cheek, Jeffrey W. Moses, David J. Moliterno, Mark B. Efron, and Eric J. Topol  
Circulation 1998 98: 734-741.
53. Reduction of Recurrent Ischemia With Abciximab During Continuous ECG-Ischemia Monitoring in Patients With Unstable Angina Refractory to Standard Treatment (CAPTURE)  
Peter Klootwijk, Simon Meij, Rein Melkert, Timo Lenderink, and Maarten L. Simoons  
Circulation 1998 98: 1358-1364.
54. Does Intracoronary Thrombus Influence the Outcome of High Risk Percutaneous Transluminal Coronary Angioplasty? Clinical and Angiographic Outcomes in a Large Multicenter Trial  
M. Musa Khan, MD, Stephen G. Ellis, MD, FACC, Frank V. Aguirre, MD, FACC, Harlan F. Weisman, MD, FACC, Nancy M. Wildermann, BA, Robert M. Califf, MD, FACC, Eric J. Topol, MD, FACC, Neal S. Kleiman, MD, FACC for the EPIC Investigators  
Journal of the American College of Cardiology, 31:1:31-36
55. The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non-Q-wave myocardial infarctions  
Steven R. Steinhubl, Michael S. Lauer, Debabrata P. Mukherjee, David J. Moliterno, A. Michael Lincoff, Stephen G. Ellis, Eric J. Topol  
Journal of the American College of Cardiology, 32:5:1366-1370
56. Acute Coronary Syndromes in the GUSTO-IIb Trial : Prognostic Insights and Impact of Recurrent Ischemia  
Paul W. Armstrong, Yuling Fu, Wei-Ching Chang, Eric J. Topol, Christopher B. Granger, Amadeo Betriu, Frans Van de Werf, Kerry L. Lee, and Robert M. Califf  
Circulation 1998 98: 1860-1868.
57. Clinical Outcome at Six Months of Coronary Stenting Followed by Ticlopidine Monotherapy  
Mathias Elsner, MD, Alfred Peifer, MD, Michael Drexler, MD, Christian Wenzel, Christian Hebbeker, Wolfgang Kasper, MD  
The American Journal of Cardiology, 1998;81:2:147-151
58. High Dose Bolus Heparin as Initial Therapy Before Primary Angioplasty for Acute Myocardial Infarction: Results of the Heparin in Early Patency (HEAP) Pilot Study  
Freek W. A. Verheugt, MD, FACC, Aylee Liem, MD, Felix Zijlstra, MD, Randall C. Marsh, MD, FACC, Gerrit Veen, MD, Jean G. F. Bronzwaer, MD

Journal of the American College of Cardiology, 1998;31:2:289-293

59. Effect of Glycoprotein IIb/IIIa Receptor Blockade on Recovery of Coronary Flow and Left Ventricular Function After the Placement of Coronary- Artery Stents in Acute Myocardial Infarction

Franz-Josef Neumann, Rudolf Blasini, Claus Schmitt, Eckhard Alt, Josef Dirschinger, Meinrad Gawaz, Adnan Kastrati, and Albert Schomig

Circulation 1998 98: 2695-2701.

60. Abciximab Therapy and Unplanned Coronary Stent Deployment

Favorable Effects on Stent Use, Clinical Outcomes, and Bleeding Complications

Dean J. Kereiakes, MD; A. Michael Lincoff, MD; Dave P. Miller, MS; James E. Tcheng, MD; Catherine F. Cabot, MD; Keaven M. Anderson, PhD; Harlan F. Weisman, MD; Robert M. Califf, MD; Eric J. Topol, MD; for the EPILOG Trial Investigators

(Circulation. 1998;97:857-864.)

61. Abciximab in primary coronary angioplasty for acute myocardial infarction improves short- and medium-term outcomes

Rabih R. Azar, Raymond G. McKay, Paul D. Thompson, Jeffrey A. Hirst, Joseph F. Mitchell, Daniel B. Fram, David D. Waters and Francis J. Kiernan

JACC 1998;32:1996-2002

62. Abciximab administration and outcome after intracoronary stent implantation

David Hasdai, Charanjit S. Rihal, Malcolm R. Bell, Peter B. Berger, Diane E. Grill, Kirk N. Garratt and David R. Holmes Jr

AJC 1998;82:705-709

63. Diabetes Mellitus, Glycoprotein IIb/IIIa Blockade, and Heparin : Evidence for a Complex Interaction in a Multicenter Trial

Neal S. Kleiman, A. Michael Lincoff, Dean J. Kereiakes, Dave P. Miller, Frank V. Aguirre, Keaven M. Anderson, Harlan F. Weisman, Robert M. Califf, and Eric J. Topol

Circulation 1998 97: 1912-1920.

64. Local and systemic delivery of low molecular weight heparin following PTCA: Acute results and 6-month follow-up of the initial clinical experience with the porous balloon (PILOT-study)

Martin Oberhoff, Andreas Baumbach, Thomas Hermann, Claudia Diehl, Rita Maier, Anastasios Athanasiadis, Christian Herdeg, Armin Bohnet, Karl K. Haase, Wolfram Voelker, Reinhard Baildon, Susan Veldhof, Karl R. Karsch

Cathet. Cardiovasc. Diagn. 44:267-274, 1998.

65. Effect of Glycoprotein IIb/IIIa Receptor Blockade on Recovery of Coronary Flow and Left Ventricular Function After the Placement of Coronary- Artery Stents in Acute Myocardial Infarction

Franz-Josef Neumann, Rudolf Blasini, Claus Schmitt, Eckhard Alt, Josef Dirschinger, Meinrad Gawaz, Adnan Kastrati, and Albert Schomig

Circulation 1998 98: 2695-2701.

66. Clinical Outcomes of Therapeutic Agents That Block the Platelet Glycoprotein IIb/IIIa Integrin in Ischemic Heart Disease

David F. Kong, Robert M. Califf, Dave P. Miller, David J. Moliterno, Harvey D. White, Robert A. Harrington, James E. Tcheng, A. Michael Lincoff, Vic Hasselblad, and Eric J. Topol

Circulation 1998 98: 2829-2835.

67. Plasminogen Activator Inhibitor-1 Is a Major Determinant of Arterial Thrombolysis Resistance

Yanhong Zhu, Peter Carmeliet, and William P. Fay

Circulation 1999 99: 3050-3055.

68. Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial

Kenneth A. Ault, Christopher P. Cannon, Jane Mitchell, John McCahan, Russell P. Tracy, William F. Novotny, James D. Reimann, Eugene Braunwald

Journal of the American College of Cardiology, 33:3:634-639

69. Sustained Suppression of Ischemic Complications of Coronary Intervention by Platelet GP IIb/IIIa Blockade With Abciximab : One-Year Outcome in the EPILOG Trial

Kelly, Gerald C. Timmis, Neal S. Kleiman, Joan E. Booth, Craig Balog, Catherine F. Cabot, Keaven M. Anderson, Harlan F. Weisman, and Eric J. Topol

Circulation 1999 99: 1951-1958.

70. Ticlopidine and Clopidogrel

Martin J. Quinn and Desmond J. Fitzgerald

Circulation 1999 100: 1667-1672.

71. Abciximab Facilitates the Rate and Extent of Thrombolysis : Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial

Elliott M. Antman, Robert P. Giugliano, C. Michael Gibson, Carolyn H. McCabe, Patrick Coussement, Neal S. Kleiman, Alec Vahanian, A. A. Jennifer Adgey, Ian Menown, Hans-Jurgen

Rupprecht, R. Van der Wieken, John Ducas, Joel Scherer, Keaven Anderson, Frans Van de Werf, and

Eugene Braunwald

Circulation 1999 99: 2720-2732.

72. Sustained Suppression of Ischemic Complications of Coronary Intervention by Platelet GP IIb/IIIa Blockade With Abciximab : One-Year Outcome in the EPILOG Trial

A. Michael Lincoff, James E. Tcheng, Robert M. Califf, Dean J. Kereiakes, Thomas A. Kelly, Gerald C. Timmis, Neal S. Kleiman, Joan E. Booth, Craig Balog, Catherine F. Cabot, Keaven M. Anderson, Harlan F. Weisman, and Eric J. Topol

Circulation 1999 99: 1951-1958.

73. Usefulness of subcutaneous low molecular weight heparin (ardeparin) for reduction of restenosis after percutaneous transluminal coronary angioplasty

- Lawrence W. Gimple, Howard C. Herrmann, Michael Winniford, Eberhard Mammen for the Ardeparin and Restenosis Study Group  
The American Journal of Cardiology, 83:11:1524-1529
74. Rapid Platelet-Function Assay : An Automated and Quantitative Cartridge-Based Method  
Jeffrey W. Smith, Steven R. Steinhubl, A. Michael Lincoff, Jacqueline C. Coleman, Theodore T. Lee, Robert S. Hillman, and Barry S. Collier  
Circulation 1999 99: 620-625.
75. Recombinant Hirudin (Lepirudin) Provides Safe and Effective Anticoagulation in Patients With Heparin-Induced Thrombocytopenia : A Prospective Study . Greinacher, H. Volpel, U. Janssens, V. Hach-Wunderle, B. Kemkes-Matthes, P. Eichler, H. G. Mueller-Velten, and B. Potzsch  
Circulation 1999 99: 73-80.
76. Recombinant Hirudin (Lepirudin) Provides Safe and Effective Anticoagulation in Patients With Heparin-Induced Thrombocytopenia : A Prospective Study  
A. Greinacher, H. Volpel, U. Janssens, V. Hach-Wunderle, B. Kemkes-Matthes, P. Eichler, H. G. Mueller-Velten, and B. Potzsch  
Circulation 1999 99: 73-80.
77. Intracoronary Thrombus and Platelet Glycoprotein IIb/IIIa Receptor Blockade With Tirofiban in Unstable Angina or Non-Q-Wave Myocardial Infarction : Angiographic Results From the PRISM-PLUS Trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)  
Xue-Qiao Zhao, Pierre Theroux, Steven M. Snapinn, and Frederic L. Sax  
Circulation 1999 100: 1609-1615.
78. Quantifying GPIIb/IIIa Receptor Binding Using 2 Monoclonal Antibodies : Discriminating Abciximab and Small Molecular Weight Antagonists  
Martin Quinn, Adele Deering, Maura Stewart, Dermot Cox, Brendan Foley, and Desmond Fitzgerald  
Circulation 1999 99: 2231-2238.
79. Timing of coronary stent thrombosis in patients treated with ticlopidine and aspirin  
Stephanie H. Wilson, Charanjit S. Rihal, Malcolm R. Bell, James L. Velianou, David R. Holmes, Jr., Peter B. Berger  
The American Journal of Cardiology, 83:7:1006-1011
80. Heparin after percutaneous intervention (HAPI): a prospective multicenter randomized trial of three heparin regimens after successful coronary intervention  
Maher Rabah, Denise Mason, David W.M. Muller, Randal Hundley, Aaron D. Kugelmass, Bonnie Weiner, Louis Cannon, William W. O'Neill, Robert D. Safian  
Journal of the American College of Cardiology, 1999;34:2:461-467
81. Effectiveness of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin in Preventing Stent Thrombosis

After Coronary Stent Implantation

Issam Moussa, Mathew Oetgen, Gary Roubin, Antonio Colombo, Xangdong Wang, Sriram Iyer, Roberta Maida, Michael Collins, Edward Kreps, and Jeffrey W. Moses

Circulation 1999 99: 2364-2366.

82. Enoxaparin Prevents Death and Cardiac Ischemic Events in Unstable Angina/Non-Q-Wave Myocardial Infarction : Results of the Thrombolysis In Myocardial Infarction (TIMI) 11B Trial

Elliott M. Antman, Carolyn H. McCabe, Enrique P. Gurfinkel, Alexander G. G. Turpie, Peter J. L. M. Bernink, Diana Salein, Antonio Bayes de Luna, Kim Fox, Jean-Marc Lablanche, David Radley, Jerome Premmereur, and Eugene Braunwald

Circulation 1999 100: 1593-1601.

83. Clinical Outcomes of Bivalirudin for Ischemic Heart Disease

David F. Kong, Eric J. Topol, John A. Bittl, Harvey D. White, Pierre Theroux, Vic Hasselblad, and Robert M. Califf

Circulation 1999 100: 2049-2053.

84. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty : Results of the glycoprotein receptor antagonist patency evaluation (GRAPE) pilot study

Lambert F.M. van den Merkhof, Felix Zijlstra, Hans Olsson, Lars Grip, Gerrit Veen, Frits W.H.M. Bar, Marcel J.B.M. van den Brand, Maarten L. Simoons and Freek W.A. Verheugt

JACC 1999;33:1528-32.

85. Assessment of the Treatment Effect of Enoxaparin for Unstable Angina/Non-Q-Wave Myocardial Infarction : TIMI 11B-ESSENCE Meta-Analysis

Elliott M. Antman, Marc Cohen, David Radley, Carolyn McCabe, Janet Rush, Jerome Premmereur, and Eugene Braunwald

Circulation 1999 100: 1602-1608.

86. Abciximab Facilitates the Rate and Extent of Thrombolysis

Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial

Elliott M. Antman, MD; Robert P. Giugliano, MD, SM; C. Michael Gibson, MS, MD; Carolyn H. McCabe, BS; Patrick Coussement, MD; Neal S. Kleiman, MD; Alec Vahanian, MD; A. A. Jennifer Adgey, MD; Ian Menown, MD; Hans-Jurgen Rupprecht, MD; R. Van der Wieken, MD;

John Ducas, MD; Joel Scherer, MD; Keaven Anderson, PhD; Frans Van de Werf, MD, PhD; Eugene Braunwald, MD; for the TIMI 14 Investigators<sup>1</sup>

Circulation 1999;99:2720-32

87. Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris.

Rabah MM, Premmereur J, Graham M, Fareed J, Hoppensteadt DA, Grines LL, Grines CL

Am J Cardiol 1999 Dec 15;84(12):1391-5

88. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting.  
Mishkel GJ, Aguirre FV, Ligon RW, Rocha-Singh KJ, Lucore CL  
J Am Coll Cardiol 1999 Dec;34(7):1884-90
89. Effect of glycoprotein IIb/IIIa inhibition without thrombolytic therapy on reperfusion in acute myocardial infarction: results of ReoMI pilot study.  
Makkar R, Goff B, Eigler N, Sebastian M, Fischell T, Barr L, D'Haem C, Shah PK, Effron MB, Litvack F  
Catheter Cardiovasc Interv 1999 Dec;48(4):430-4
90. 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.  
Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML  
Circulation 1999 Nov 16;100(20):2045-8
91. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). Global Use of Strategies To Open occluded coronary arteries.  
Duke Clinical Research Institute, Durham, North Carolina 27715, USA.  
Am J Cardiol 1999 Oct 1;84(7):779-84
92. Effect of abciximab on the pattern of reperfusion in patients with acute myocardial infarction treated with primary angioplasty. RAPPORT investigators. ReoPro And Primary PTCA Organization and Randomized Trial.  
Brener SJ, Barr LA, Burchenal JE, Wolski KE, Effron MB, Topol EJ  
Am J Cardiol 1999 Sep 15;84(6):728-30, A8
93. Comparison of cilostazol versus ticlopidine therapy after stent implantation.  
Park SW, Lee CW, Kim HS, Lee HI, Park HK, Hong MK, Kim JJ, Park SJ  
Am J Cardiol 1999 Sep 1;84(5):511-4
94. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). The ERASER Investigators.  
Circulation 1999 Aug 24;100(8):799-806
95. Readministration of abciximab: interim report of the ReoPro readministration registry.  
Tcheng JE, Kereiakes DJ, Braden GA, Jordan RE, Mascelli MA, Langrall MA, Effron MB  
Am Heart J 1999 Jul;138(1 Pt 2):S33-8
96. Effects of platelet glycoprotein IIb/IIIa inhibition with abciximab on thrombin generation and activity during percutaneous coronary intervention.  
Dangas G, Marmur JD, King TE, De Leon J, Sharma SK, Vidhun R, Feldman D, Stoynov MY, Badimon JJ, Ambrose JA  
Am Heart J 1999 Jul;138(1 Pt 1):49-54

97. Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators.  
Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, Ishikawa K, Masuda Y, Yamaguchi T, Motomiya T, Tamura Y  
Am J Cardiol 1999 May 1;83(9):1308-13
98. Antithrombin activity during the period of percutaneous coronary revascularization: relation to heparin use, thrombotic complications and restenosis.  
Matthai WH Jr, Kurnik PB, Groh WC, Untereker WJ, Siegel JE  
J Am Coll Cardiol 1999 Apr;33(5):1248-56
99. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement.  
Berger PB, Bell MR, Hasdai D, Grill DE, Melby S, Holmes DR Jr  
Circulation 1999 Jan 19;99(2):248-53
100. Platelet PIA2 Allele and Incidence of Coronary Heart Disease : Results From the Atherosclerosis Risk In Communities (ARIC) Study  
Nena Aleksic, Harinder Juneja, Aaron R. Folsom, Chul Ahn, Eric Boerwinkle, Lloyd E. Chambless, and Kenneth K. Wu  
Circulation 2000 102: 1901-1905.
101. The benefit of abciximab in percutaneous coronary revascularization is not device-specific  
Deepak L. Bhatt, A. Michael Lincoff, Robert M. Califf, Maarten L. Simoons, James E. Tchong, Sorin J. Brener, Katherine E. Wolski, Eric J. Topol  
The American Journal of Cardiology, 85:9:1060-1064
102. Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared With Ticlopidine in Combination With Aspirin After Coronary Stenting : The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)  
Michel E. Bertrand, Hans-Jurgen Rupprecht, Philip Urban, Anthony H. Gershlick, and for the CLASSICS Investigators  
Circulation 2000 102: 624-629.
103. Novel, Bedside, Tissue Factor-Dependent Clotting Assay Permits Improved Assessment of Combination Antithrombotic and Antiplatelet Therapy  
Michael B. Holmes, David J. Schneider, Michael G. Hayes, Burton E. Sobel, and Kenneth G. Mann  
Circulation 2000 102: 2051-2057.
104. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial  
Lancet 1999; 353: 42938
105. Minimal heparinization in coronary angioplasty-how much heparin is really warranted?

Edo Kaluski, Ricardo Krakover, Gad Cotter, Alberto Hendler, Itzhak Zyssman, Olga Milovanov, Alex Blatt, Ester Zimmerman, Edna Goldstein, Vera Nahman, Zvi Vered

The American Journal of Cardiology, 85:8:953-956

106. Management of Patients With Acute Coronary Syndromes in the United States by Platelet Glycoprotein IIb/IIIa Inhibition : Insights From the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial

A. Michael Lincoff, Robert A. Harrington, Robert M. Califf, Judith S. Hochman, Alan D. Guerci, E. Magnus Ohman, Carl J. Pepine, Steven L. Kopecky, Neal S. Kleiman, Cynthia M. Pacchiana, Lisa G. Berdan, Michael M. Kitt, Maarten L. Simoons, and Eric J. Topol

Circulation 2000 102: 1093-1100.

107. Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST segment monitoring substudy

Shaun G. Goodman, Aiala Barr, Anatoli Soltchouk, Marc Cohen, Gregg J. Fromell, Luc Laperriere, Carol Hill, Anatoly Langer for the Canadian Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) ST Segment Monitoring Substudy Group

Journal of the American College of Cardiology, 36:5:1507-1513

108. Long-Term Treatment with a Platelet Glycoprotein-Receptor Antagonist after Percutaneous Coronary Revascularization

William W. O'Neill, Patrick Serruys, Merrill Knudtson, Gerrit-Anne van Es, Gerald C. Timmis, Coen van der Zwaan, Jay Kleiman, Jianjian Gong, Ellen B. Roecker, Roger Dreiling, John Alexander, Robert Anders, for the EXCITE Trial Investigators

(N Engl J Med 2000;342:1316-24.)

109. Postmenopausal Hormone Therapy Increases Risk for Venous Thromboembolic Disease. The Heart and Estrogen/progestin Replacement Study

D. Grady, N.K. Wenger, D. Herrington, S. Khan, C. Furberg, D. Hunninghake, E. Vittinghoff, and S. Hulley, for the Heart and Estrogen/progestin Replacement Study Research Group

110. Predictors of recurrent ischemic events and death in unstable coronary artery disease after treatment with combination antithrombotic therapy

Marc Cohen, MD, Sandra S. Stinnett, DrPH, Beth D. Weatherley, MS, Enrique P. Gurfinkel, MD, Gregg J. Fromell, MD, Shaun G. Goodman, MD, Keith A.A. Fox, MBChB, Robert M. Califf, MD, for the ESSENCE study group

(Am Heart J 2000;139:962-70.)

111. Heparin Infusion Prior to Stenting (HIPS) trial: Final results of a prospective, randomized, controlled trial evaluating the effects of local vascular delivery on intimal hyperplasia

Robert L. Wilensky, MD, Jean-Francois Tanguay, MD, Shigenori Ito, MD, Antonio L. Bartorelli, MD, Jeffrey Moses, MD, David O. Williams, MD, Steven R. Bailey, MD, Jack Martin, MD,

Theresa A. Bucher, RN, Pam Gallant, RN, Ann Greenberg, RN, Jeffrey J. Popma, MD, Neil J.

Weissman, MD, Gary S. Mintz, MD, Aaron V. Kaplan, MD, Martin B. Leon, MD, for the HIPS investigators

(Am Heart J 2000;139:1061-70.)

112. Hemodynamic Effects of Sildenafil in Men with Severe Coronary Artery Disease

Howard C. Herrmann, Gene Chang, Bruce D. Klugherz, Paul D. Mahoney

(N Engl J Med 2000;342:1622-6.)

113. Flow Cytometric Monitoring of Glycoprotein IIb/IIIa Blockade and Platelet Function in Patients With Acute Myocardial Infarction Receiving Reteplase, Abciximab, and Ticlopidine : Continuous Platelet Inhibition by the Combination of Abciximab and Ticlopidine

Karlheinz Peter, Benedikt Kohler, Andreas Straub, Johannes Ruef, Martin Moser, Thomas Nordt, Manfred Olschewski, Magnus E. Ohman, Wolfgang Kubler, and Christoph Bode

Circulation 2000 102: 1490-1496.

114. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy

Khatereh Moshfegh, Maurice Redondo, Friedgard Julmy, Walter A. Wuillemin, Mathias U. Gebauer, Andre Haeberli, Beat J. Meyer

Journal of the American College of Cardiology, 2000;36:3:699-705

115. Effects of Abciximab, Ticlopidine, and Combined Abciximab/Ticlopidine Therapy on Platelet and Leukocyte Function in Patients Undergoing Coronary Angioplasty

Becky J. Fredrickson, Nancy A. Turner, Neal S. Kleiman, Nikki Graziadei, Kelly Maresh, Mary Ann Mascelli, Mark B. Effron, and Larry V. McIntire

Circulation 2000 101: 1122-1129.

116. 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

Franz-Josef Neumann, Adnan Kastrati, Claus Schmitt, Rudolf Blasini, Martin Hadamitzky, Julinda Mehilli, Meinrad Gawaz, Michael Schlee, Melchior Seyfarth, Josef Dirschinger, Albert Schomig

Journal of the American College of Cardiology, 2000;35:4:915-921

117. Abciximab reduces mortality in diabetics following percutaneous coronary intervention

Deepak L. Bhatt, Steven P. Marso, A. Michael Lincoff, Katherine E. Wolski, Stephen G. Ellis, Eric J. Topol

Journal of the American College of Cardiology, 35:4:922-928

118. Early angiography versus conservative treatment in patients with non-ST elevation acute myocardial infarction

Grant S. Scull, Jenny S. Martin, W. Douglas Weaver, Nathan R. Every for the MITI Investigators

Journal of the American College of Cardiology, 2000;35:4:895-902

119. The ENACT study: a pan-European survey of acute coronary syndromes  
K.A.A. Fox, D.V. Cokkinos, J. Deckers, U. Keil, A. Maggioni, G. Steg  
Eur Heart J 2000;21:1440-9
120. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. PURSUIT Investigators.  
Kleiman NS, Lincoff AM, Flaker GC, Pieper KS, Wilcox RG, Berdan LG, Lorenz TJ, Cokkinos DV, Simoons ML, Boersma E, Topol EJ, Califf RM, Harrington RA  
Circulation 2000 Feb 22;101(7):751-7
121. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents.  
Muller C, Buttner HJ, Petersen J, Roskamm H  
Circulation 2000 Feb 15;101(6):590-3
122. Long-term outcome in patients treated by intracoronary stenting with ticlopidine and aspirin, and deleterious prognostic role of unstable angina pectoris  
Michael Angioi aA, Nicolas Danchin a, Francois Alla b, Catherine Gangloff a, Henri Sunthorn a, Rosa-Maria Rodriguez a, Jean-Philippe Preiss a, Alain Grentzinger a, Philippe Houplon a, Yves Juilliere a and Francois Cherrier a  
[a]Service de Cardiologie, Hopitaux de Brabois, Vandoeuvre-les-Nancy, France[b]Service d' Epidemiologie et d'Evaluation Clinique, Hopital Marin, CHU de Nancy, Vandoeuvre-les-Nancy, France  
The American Journal of Cardiology, 2000;85:9:1065-1070
123. Clopidogrel for prevention of major cardiac events after coronary stent implantation: 30-day and 6-month results in patients with smaller stents  
Alison L. Calver, MD, MRCP, Lucy J. Blows, MBBS, MRCP, Sue Harmer, RGN, Keith D. Dawkins, MD, FRCP, Huon H. Gray, MD, FRCP, John H. Morgan, MD, FRCP, Iain A. Simpson, MD, FRCP  
American Heart Journal September 2000 ? Volume 140 ? Number 3 ? p483 to p491
124. Effects of cilostazol on late lumen loss and repeat revascularization after Palmaz-Schatz coronary stent implantation  
Ken Kozuma, MDa, Kazuhiro Hara, MD, FACCb, Masao Yamasaki, MDb, Yoshihiro Morino, MDb, Seiji Ayabe, MDb, Yuzo Kuroda, MDb, Kengo Tanabe, MDb, Yuji Ikari, MDb, Tsutomu Tamura, MDb  
American Heart Journal January 2001 ? Volume 141 ? Number 1 ? p124 to p130
125. Superiority of enoxaparin versus unfractionated heparin for unstable angina/non-Q-wave myocardial infarction regardless of activated partial thromboplastin time  
Gerardo E. Bozovich, MDa, Enrique P. Gurfinkel, MD, PhDb, Elliott M. Antman, MDb, Carolyn H. McCabe, BSb, Branco Mautner, MDa

American Heart Journal October 2000, part 1 ? Volume 140 ? Number 4 ? p637 to p642

126. Increased platelet aggregability in response to shear stress in acute myocardial infarction and its inhibition by combined therapy with aspirin and cilostazol after coronary intervention

Takashi Tanigawa a, Masakatsu Nishikawa bA, Tamaki Kitai a, Yuji Ueda a, Tsutomu Okinaka a, Katsutoshi Makino a, Masaaki Ito a, Naoki Isaka a, Yasuo Ikeda c, Hiroshi Shiku b and Takeshi Nakano a

The American Journal of Cardiology, 2000;85:9:1054-1059

127. Abciximab treatment in vitro after aspirin treatment in vivo has additive effects on platelet aggregation, ATP release, and P-selectin expression

Alejandra Scazziota a, Raul Altman aA, Jorge Rouvier a, Claudio Gonzalez a, Zulfiqar Ahmed b, Walter P. Jeske b, Jeanine M. Walenga b and Jawed Fareed

Thrombosis Research, 2000;100:6:479-488

128. Effect of aspirin and ticlopidine on plasma tissue factor levels in stable and unstable angina pectoris

Jean Marco a, Robert A.S. Ariens b, Jean Fajadet a, Irene M. Bossi a, Isabelle Marco a, Monique Bernies a, Salvatore M. Romano b, Francesco Donatelli b, Gabri M. Brambilla b, Francesco Somalvico b, Daniela Mari b and Luisa Gregorini bA

The American Journal of Cardiology, 2000;85:5:527-531

129. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy

Khatereh Moshfegh a, Maurice Redondo \*, Friedgard Julmy a, Walter A. Willemin \*, Mathias U. Gebauer a, Andre Haerberli a and Beat J. Meyer aA

Journal of the American College of Cardiology, 2000;36:3:699-705

130. Effects of cilostazol on angiographic restenosis after coronary stent placement

Seong-Wook Park a, Cheol Whan Lee a, Hyun-Sook Kim a, Nae-Hee Lee a, Deuk Young Nah a, Myeong-Ki Hong a, Jae-Joong Kim a and Seung-Jung Park

The American Journal of Cardiology, 2000;86:5:499-503

131. Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy

David C. Sane \*A, Lakshmi V. Damaraju †, Eric J. Topol ‡, Catherine F. Cabot †, Mary Ann Mascelli †, Robert A. Harrington , Maarten L. Simoons § and Robert M. Califf EPIC EPILOG CAPTURE and EPISTENT Study Groups

Journal of the American College of Cardiology, 2000;36:1:75-83

132. Low molecular weight heparin in acute coronary syndrome: evidence for superior or equivalent efficacy compared with unfractionated heparin?

Sanjay Kaul and Prediman K. Shah

Journal of the American College of Cardiology, 2000;35:7:1699-1712

133. Long-Term Effects on Clinical Outcomes of Aggressive Lowering of Low-Density Lipoprotein Cholesterol

- Levels and Low-Dose Anticoagulation in the Post Coronary Artery Bypass Graft Trial  
Genell L. Knatterud, Yves Rosenberg, Lucien Campeau, Nancy L. Geller, Donald B. Hunninghake,  
Sandra A. Forman, James S. Forrester, Fredarick L. Gobel, J. Alan Herd, Ann Hickey,  
Byron J. Hoogwerf, Michael L. Terrin, and Carl White  
Circulation 2000 102: 157-165
134. A Randomized Comparison of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin After the Placement of Coronary-Artery Stents  
Christian Muller, Heinz J. Buttner, Jens Petersen, and Helmut Roskamm  
Circulation 2000 101: 590 - 593.
135. Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared With Ticlopidine in Combination With Aspirin After Coronary Stenting : The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)  
Michel E. Bertrand, Hans-Jurgen Rupprecht, Philip Urban, Anthony H. Gershlick, and for the CLASSICS Investigators  
Circulation 2000 102: 624 - 629
136. Effects of Abciximab, Ticlopidine, and Combined Abciximab/Ticlopidine Therapy on Platelet and Leukocyte Function in Patients Undergoing Coronary Angioplasty  
Becky J. Fredrickson, Nancy A. Turner, Neal S. Kleiman, Nikki Graziadei, Kelly Maresh, Mary Ann Mascelli, Mark B. Effron, and Larry V. McIntire  
Circulation 2000 101: 1122 - 1129
137. Pronounced Benefit of Coronary Stenting and Adjunctive Platelet Glycoprotein IIb/IIIa Inhibition in Complex Atherosclerotic Lesions  
Fernando A. Cura, Deepak L. Bhatt, A. Michael Lincoff, Samir R. Kapadia, Philippe L. L'Allier, Khaled M. Ziada, Katherine E. Wolski, David J. Moliterno, Sorin J. Brener, Stephen G. Ellis, and Eric J. Topol  
Circulation 2000 102: 28 - 34
138. Oral Glycoprotein IIb/IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes (OPUS-TIMI 16) Trial  
Christopher P. Cannon, Carolyn H. McCabe, Robert G. Wilcox, Anatoly Langer, Abraham Caspi, Peter Berink, Jose Lopez-Sendon, Jiri Toman, Andrew Charlesworth, Robert J. Anders, John C. Alexander, Allan Skene, and Eugene Braunwald  
Circulation 2000 102: 149 - 156
139. Management of Patients With Acute Coronary Syndromes in the United States by Platelet Glycoprotein IIb/IIIa Inhibition : Insights From the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial  
A. Michael Lincoff, Robert A. Harrington, Robert M. Califf, Judith S. Hochman, Alan D. Guerci, E.

Magnus Ohman, Carl J. Pepine, Steven L. Kopecky, Neal S. Kleiman, Cynthia M. Pacchiana, Lisa G. Berdan, Michael M. Kitt, Maarten L. Simoons, and Eric J. Topol

Circulation 2000 102: 1093 - 1100

140. Glycoprotein IIb/IIIa Receptor Blockade Improves Outcomes in Diabetic Patients Presenting With Unstable Angina/Non-ST-Elevation Myocardial Infarction : Results From the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study

Pierre Theroux, Joe Alexander, Jr, Chantal Pharand, Eliav Barr, Steven Snapinn, Asma F. Ghannam, and Frederic L. Sax

Circulation 2000 102: 2466 - 2472

141. Increased Mortality With Oral Platelet Glycoprotein IIb/IIIa Antagonists : A Meta-Analysis of Phase III Multicenter Randomized Trials

Derek P. Chew, Deepak L. Bhatt, Shelly Sapp, and Eric J. Topol

Circulation 2001 103: 201 - 206.