Eur Heart J (2004);25:1903-10
High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability
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AIM: To assess platelet inhibitory effects, interindividual variability in platelet inhibition as well as response to a 600 mg, compared to a standard 300 mg, clopidogrel loading dose (LD) after coronary stenting METHODS AND RESULTS: Platelet function profiles were assessed in 50 patients undergoing coronary stenting receiving either a 300 mg (n=27) or 600 mg clopidogrel LD. ADP (6 microM) and collagen (6 microg/mL) induced platelet aggregation, as well as ADP (2 microM) induced glycoprotein (GP) IIb/IIIa activation and P-selectin expression were assessed at baseline and 4, 24, and 48 h following clopidogrel front-loading. A more intense and rapid inhibition of platelet activation (both GP IIb/IIIa activation and P-selectin expression) were achieved using a 600 mg, compared to a 300 mg, LD throughout the entire 48 hours ($p<0.001$). Although there were no differences in platelet aggregation, overall a 600 mg LD increased the number of clopidogrel responders and this was also achieved earlier compared to a 300 mg LD. A 600 mg LD did not reduce interindividual variability of platelet response. CONCLUSION: The use of a 600 mg clopidogrel LD in patients undergoing coronary stenting optimises platelet inhibitory effects early after intervention and may provide a more effective protection against early thrombotic complications.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15522469

Circulation (2004);109:2480-6
Pharmacoinvasive therapy: the future of treatment for ST-elevation myocardial infarction
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15173037

Circulation (2004);109:1704-6
Abciximab-supported infarct artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infarct artery stenting plus abciximab with stenting alone
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BACKGROUND: The impact on survival of routine use of abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction is not defined. We sought to determine the effect of abciximab on 1-year survival and other major adverse cardiac events of patients with acute myocardial infarction undergoing routine infarct artery stenting. METHODS AND RESULTS: The Abciximab and Carbostent Evaluation (ACE) Trial is an unblinded, randomized, controlled trial that compared abciximab with placebo in patients undergoing routine infarct artery stent implantation for acute myocardial infarction. At 1 year, the survival rate was 95+/-2% in the

abciximab group and 88+/-2% in the stent-alone group (P=0.017). The reinfarction rate was 1% in the abciximab group and 6.0% in the stent-alone group, whereas there were no differences between groups in target vessel revascularization rate (16.5% in the abciximab group, 17.5% in the stent-alone group). CONCLUSIONS: Abciximab as adjunctive treatment to routine infarct artery stenting for acute myocardial infarction resulted in improved 1-year survival and lower reinfarction rates.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15066943

Am J Cardiol (2004);93:830-5
Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival in non-ST-segment elevation acute coronary syndromes: a meta-analysis and review of the literature
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Current evidence suggests that routine invasive therapy in the setting of unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) reduces the incidence of composite end points (i.e., death, myocardial infarction, or angina.). The 2002 American College of Cardiology/American Heart Association guidelines recommend invasive therapy in high-risk patients, although it is unknown if such an approach improves survival. We conducted a meta-analysis on 5 studies in 6,766 UA/NSTEMI patients who were randomized to either routine invasive versus conservative therapy in the era of glycoprotein IIb/IIIa inhibitors and intracoronary stents. Compared with conservative therapy, an invasive approach suggested a reduction in mortality at 6 to 12 months (risk ratio [RR] 0.80, 95% confidence interval [CI] 0.63 to 1.03) and at 24 months (RR 0.77, 95% CI 0.60 to 0.99). The composite end point of death or myocardial infarction was reduced throughout all periods of follow-up: at 30 days (RR 0.61, 95% CI 0.45 to 0.84), at 6 months (RR 0.75, 95% CI 0.63 to 0.89), and at 12 months (RR 0.78, 95% CI 0.65 to 0.92). For the same composite end point at 6 to 12 months, men benefited from invasive therapy (RR 0.68, 95% CI 0.57 to 0.81), as did troponin-positive patients (RR 0.74, 95% CI 0.59 to 0.94). The results for women (RR 1.07, 95% CI 0.82 to 1.41) and troponin-negative patients (RR 0.82, 95% CI 0.59 to 1.14) were equivocal. Routine invasive therapy in UA/NSTEMI patients along with adjunctive use of glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival. Enhanced risk stratification is needed in women and troponin-negative patients so that invasive therapy may be more effectively recommended in these groups.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15050484

Catheter Cardiovasc Interv (2004);62:186-92
Increase of myocardial salvage and left ventricular function recovery with intracoronary abciximab downstream of the coronary occlusion in patients with acute myocardial infarction treated with primary coronary intervention
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abciximab administered intracoronarily, downstream of the coronary occlusion, leads to a greater degree of myocardial salvage and better left ventricular function recovery compared with the usual abciximab administration. Forty-five consecutive patients with first AMI and infarct-related artery TIMI flow 0-1 undergoing primary PCI were enrolled. Twenty-two patients were randomly assigned to the intracoronary treatment and 23 to the usual treatment. The initial perfusion defect, final infarct size, myocardial salvage, salvage index, and left ventricular function recovery were assessed by serial scintigraphic scans performed at admission and 7 days and 1 month after PCI. Angiographic myocardial blush grade, corrected TIMI frame count, and electrocardiographic ST segment elevation reduction were also assessed as markers of myocardial reperfusion. Final infarct size was significantly smaller (P = 0.043) and salvage index significantly higher (P = 0.003) in the intracoronary treatment group as a result of a greater degree of myocardial salvage (P = 0.0001). The increase of left ventricular ejection fraction at 1 month was significantly higher in the intracoronary treatment patients (P = 0.013). The markers of myocardial reperfusion were also significantly better in the intracoronary treatment group. In patients with AMI and occluded infarct-related artery treated with primary PCI, intracoronary abciximab given just before PCI downstream of the occlusion is associated to a greater degree of myocardial salvage than the usual abciximab protocol. This benefit is mainly related to a substantial reduction in final infarct size, which leads to an improvement in left ventricular ejection fraction.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15170708

Jama (2004);292:55-64
Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial
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CONTEXT: Enoxaparin or the combination of glycoprotein IIb/IIIa inhibitor tirofiban with unfractionated heparin independently have shown superior efficacy over unfractionated heparin alone in patients with non-ST-elevation acute coronary syndromes (ACS). It is not clear if combining enoxaparin with glycoprotein IIb/IIIa inhibitors is as safe or as effective as the current standard combination of unfractionated heparin with glycoprotein IIb/IIIa inhibitors. OBJECTIVE: To assess efficacy and safety of the combination of enoxaparin and tirofiban compared with unfractionated heparin and

experienced death, myocardial infarction, or refractory ischemia at 7 days compared with 184 (9.4%) of 1952 patients randomized to unfractionated heparin (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.71-1.08). This met the prespecified criterion for noninferiority. All components of the composite primary and secondary end points favored enoxaparin except death, which occurred in only 1% of patients (23 for enoxaparin and 17 for unfractionated heparin). Rates for any TIMI grade bleeding were low (3.0% for enoxaparin and 2.2% for unfractionated heparin; P =.13). Using a worst-case approach that combined 2 independent bleeding evaluations, use of enoxaparin was associated with 1 additional TIMI major bleeding episode for each 200 patients treated. CONCLUSIONS: In patients receiving tirofiban and aspirin, enoxaparin is a suitable alternative to unfractionated heparin for treatment of non-ST-elevation ACS. The 12% relative and 1% absolute reductions in the primary end point in favor of enoxaparin met criterion for noninferiority and are consistent with prior trials performed without the use of glycoprotein IIb/IIIa inhibitors.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15238591

Circulation (2004);109:861-6
Volumetric analysis of in-stent intimal hyperplasia in diabetic patients treated with or without abciximab: results of the Diabetes Abciximab steNT Evaluation (DANTE) randomized trial
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BACKGROUND: In diabetic patients in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, abciximab reduced target vessel revascularization by approximately 50% compared with placebo. Whether this is a result of a lower restenosis rate caused by inhibition of intimal hyperplasia remains to be defined. METHODS AND RESULTS: The purpose of this study was to determine whether abciximab at the time of stent implantation would reduce in-stent intimal hyperplasia measured by intravascular ultrasound at 6-month follow-up in type 2 diabetics. Ninety-six diabetic patients (96 lesions) who underwent elective stent implantation for a de novo lesion in a native coronary artery were randomly assigned to receive abciximab or no abciximab. In-stent intimal hyperplasia volume, expressed as percentage of stent volume, did not differ between groups: 41.3+/-21.0% for those treated with abciximab versus 40.5+/-18.3% for those treated without abciximab (P=0.9). There were also no significant differences in angiographic minimal luminal diameter at follow-up (1.74+/-0.69 versus 1.66+/-0.63 mm; P=0.6d-5.3iR4 v(avasc)-i.(vol5)0.2600stenosd-5.3iR49005.1(ere

percutaneous coronary intervention despite clopidogrel pretreatment
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OBJECTIVES: We sought to investigate the effect of aspirin resistance on the incidence of myonecrosis after non-urgent percutaneous coronary intervention (PCI) among patients pretreated with clopidogrel. BACKGROUND: Oral antiplatelet therapy using aspirin and a thienopyridine is the standard of care for preventing thrombotic complications of PCI. The effect of aspirin resistance on the outcomes of patients undergoing PCI is unknown. METHODS: We used the Ultegra Rapid Platelet Function Assay-ASA (Accumetrics Inc., San Diego, California) to determine aspirin responsiveness of 151 patients scheduled for non-urgent PCI. All patients received a 300-mg loading dose of clopidogrel >12 h before and a 75-mg maintenance dose in the morning of the PCI. The incidence of myonecrosis was measured by creatine kinase-myocardial band (CK-MB) and by troponin I (TnI) elevations after PCI. RESULTS: A total of 29 (19.2%) patients were noted to be aspirin-resistant. There was a significantly higher incidence of female subjects in the aspirin-resistant versus aspirin-sensitive groups. The incidence of any CK-MB elevation was 51.7% in aspirin-resistant patients and 24.6% in aspirin-sensitive patients ($p = 0.006$). Elevation of TnI was observed in 65.5% of aspirin-resistant patients and 38.5% of aspirin-sensitive patients ($p = 0.012$). Multivariate analysis revealed aspirin resistance (odds ratio [OR] 2.9; 95% confidence interval [CI] 1.2 to 6.9; $p = 0.015$) and bifurcation lesion (OR 2.8; 95% CI 1.3 to 6.0; $p = 0.007$) to be independent predictors of CK-MB elevation after PCI. CONCLUSIONS: Despite adequate pretreatment with clopidogrel, patients with aspirin resistance as measured by a point-of-care assay have an increased risk of myonecrosis following non-urgent PCI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028378

Am J Cardiol (2004);94:789-92

on peri-procedural myonecrosis
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AIMS: Although full platelet inhibition with aspirin and thienopyridines before coronary stenting has significantly reduced the risk of acute stent thrombosis, peri-procedural myonecrosis still occurs frequently and is associated with increased death rate. Whether further inhibition of platelet aggregation by a glycoprotein IIb/IIIa antagonist may provide an additional cardioprotection is unknown. METHODS AND RESULTS: A total of 200 patients pre-treated with aspirin and a loading dose of clopidogrel (450mg) were randomized just before coronary intervention (percutaneous coronary intervention, PCI) to treatment with or without abciximab. Platelet aggregation was assessed in samples collected during the procedure and the degree of platelet aggregation inhibition was correlated with cardiac enzyme release post-PCI. Abciximab treatment achieved a more complete inhibition of aggregation than dual oral antiplatelet therapy alone (median value of 1 vs. 50%, normal 100%). Any pathological increase in creatinine kinase-MB (CK-MB) post-PCI was present in 21% of the abciximab group and in 22% of the no-abciximab group (P = 0.9). Also the occurrence of clinically relevant myonecrosis [myocardial infarction (MI) = CK-MB >3x upper limit of normal] was not significantly influenced by treatment assignment: 9 vs. 10% (P = 0.9). In a multiple logistic regression model including clinical, angiographic, and procedural characteristics, post-PCI myonecrosis was not correlated with the degree of platelet aggregation inhibition but with procedural features (such as long inflation time) and with the presence of multi-vessel disease. There were no cases of acute or subacute stent thrombosis. At 6 months, major adverse cardiac events, including cardiac death, non-fatal MI, or target lesion revascularization occurred in 13% of abciximab patients and in 16% of the control patients (P = 0.6). CONCLUSIONS: In the studied patients scheduled for elective coronary stenting and pre-treated with aspirin and a loading dose of clopidogrel, further inhibition of platelet aggregation by abciximab does not afford additional cardioprotection. Our data suggest that distal athero-embolization rather than thrombo-embolization is involved in the phenomenon of myonecrosis post-elective stenting.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15618034

Circulation (2004);110:2361-7
Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes
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BACKGROUND: Oral antiplatelet agents (OAAs) can prevent further vascular events in cardiovascular disease. How prior use or recent discontinuation of OAA affects clinical presentation of acute coronary syndromes (ACS) and clinical outcomes (death, myocardial infarction [MI]) is unclear. METHODS AND RESULTS: We studied and followed up for up to 30 days a cohort of 1358 consecutive patients admitted for a suspected ACS; of these, 930 were nonusers, 355 were prior users of OAA, and 73 had recently withdrawn OAA. Nonusers were at lower risk, more frequently presented with

ST-elevation MI on admission, and more frequently had Q-wave MI at discharge than prior users (36.6% versus 17.5%, P<0.001; and 47.8% versus 28.2%, P<0.001, respectively). However, there was no difference regarding the incidence of death or MI at 30 days between nonusers and prior users (10.3% versus 12.4%, P=NS). In addition, prior users experienced more major bleeds within 30 days compared with nonusers (3.4% versus 1.4%, respectively; P=0.04). Recent withdrawers were admitted on average 11.9+/-0.8 days after OAA withdrawal. Interruption was primarily a physician decision for scheduled surgery (n=47 of 73). Despite a similar cardiovascular risk profile, recent withdrawers had higher 30-day rates of death or MI (21.9% versus 12.4%, P=0.04) and bleedings (13.7% versus 5.9%, P=0.03) than prior users. After multivariate analysis, OAA withdrawal was found to be an independent predictor of both mortality and bleedings at 30 days. CONCLUSIONS: Among ACS patients, prior users represent a higher-risk population and present more frequently with non-ST-elevation ACS than nonusers. Although patients with a recent interruption of OAA resemble those chronically treated by OAA, they display worse clinical outcomes.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15477397

Am Heart J (2004);147:655-61
Subcutaneous enoxaparin with early invasive strategy in patients with acute coronary syndromes
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Department of Cardiology, Pitie-Salpetriere Hospital, Paris, France.
BACKGROUND: Subcutaneous enoxaparin during at least 48 hours provides adequate anticoagulation and good clinical results in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention (PCI).
METHODS: In this nonrandomized retrospective study, we compared 347 patients with non-ST-segment elevation acute coronary syndromes who underwent rapid PCI after only 2 injections of subcutaneous enoxaparin (EI,

J Am Coll Cardiol (2004);44:305-12
Frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction
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OBJECTIVES: We sought to determine the prognostic importance of myocardial reperfusion after various contemporary interventional strategies in patients with acute myocardial infarction (AMI). BACKGROUND: The frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty in AMI have not been examined in a large-scale prospective study. Similarly, whether glycoprotein (GP) IIb/IIIa inhibitors and/or stents improve myocardial perfusion beyond balloon angioplasty has not been investigated. METHODS: Tissue-level perfusion assessed by the myocardial blush grade was evaluated in 1,301 patients with AMI randomized to balloon angioplasty versus stenting, each with or without abciximab. RESULTS: Despite Thrombolysis In Myocardial Infarction flow grade 3 restoration in 96.1% of patients, myocardial perfusion was normal in only 17.4% of patients, reduced in 33.9%, and absent in 48.7%. Myocardial perfusion status post-coronary intervention stratified patients into three distinct risk categories, with 1-year mortality rates of 1.4% (normal blush), 4.1% (reduced blush), and 6.2% (absent blush) ($p = 0.01$). Among patients randomized to angioplasty, angioplasty + abciximab, stenting, and stenting + abciximab, normal myocardial perfusion was restored in 17.7%, 17.0%, 17.5%, and 17.6%, respectively ($p = 0.95$), which was associated with similar 1-year rates of mortality in patients randomized to stenting versus angioplasty (4.5% vs. 4.8%, $p = 0.91$) and abciximab versus no abciximab (4.3% vs. 5.0%, $p = 0.63$). CONCLUSIONS: Restoration of normal tissue-level perfusion is a powerful determinate of survival after primary PCI in AMI and is achieved in a minority of patients. Neither stents nor GP IIb/IIIa inhibitors significantly enhance myocardial perfusion compared to balloon angioplasty alone, underlying the similar long-term mortality with these different mechanical reperfusion strategies.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15261923

Am J Cardiol (2004);94:279-83
Efficacy and safety of two unfractionated heparin dosing strategies with tenecteplase in acute myocardial infarction (results from Assessment of the Safety and Efficacy of a New Thrombolytic Regimens 2 and 3)
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We investigated the effect of smaller dose, weight-adjusted heparin with earlier monitoring of activated partial thromboplastin time on the incidence of ischemic and hemorrhagic complications in patients with ST-elevation myocardial infarction treated with full-dose tenecteplase. We compared the outcomes of patients enrolled in the Second Assessment of the Safety and Efficacy of a New Thrombolytic Regimen

received a 4,000-U bolus plus infusion at 800 U/hour) with patients in ASSENT-3 who received weight-adjusted heparin (60-U/kg bolus, maximum 4,000 U/hour, followed by a 12-U/kg/hour infusion, maximum 1,000 U/hour). Compared with patients in ASSENT-2, those in ASSENT-3 had similar rates of 30-day mortality, recurrent infarction, and intracranial hemorrhage, less major bleeding (2.2% vs 4.7%, p <0.001), and less refractory ischemia (6.5% vs 8.6%, p <0.001). After adjustment for baseline characteristics, patients in ASSENT-3 had similar rates of 30-day mortality (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.77 to 1.19) and intracranial hemorrhage (OR 1.02, 95% CI 0.61 to 1.69) but less major bleeding (OR 0.49, 95% CI 0.35 to 0.67) than did patients in ASSENT-2. These findings support the use of smaller dose, weight-adjusted heparin in patients with ST-elevation myocardial infarction treated with tenecteplase.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15276088

J Am Coll Cardiol (2004);43:162-8
Eptifibatide provides additional platelet inhibition in non-ST-elevation myocardial infarction patients already treated with aspirin and clopidogrel. Results of the platelet activity extinction in non-Q-wave myocardial infarction with aspirin, clopidogrel, and eptifibatide (PEACE) study
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OBJECTIVES: The present study hypothesis was that eptifibatide offered further antiplatelet efficacy above clopidogrel in non-ST-elevation myocardial infarction (NSTEMI) patients before an expeditive coronary intervention. BACKGROUND: Although thienopyridines and glycoprotein (GP) IIb/IIIa antagonists are often co-prescribed in the context of NSTEMI, the antiplatelet interaction of these agents is poorly described and the superiority of GP IIb/IIIa antagonists above thienopyridine treatment alone is not clear. METHOD: Thirty-two NSTEMI patients treated with aspirin and enoxaparin were studied using flow cytometry to define parameters of platelet activation with a panel of agonists before clopidogrel, after clopidogrel, and during an eptifibatide infusion following the clopidogrel load. RESULTS: After platelet activation with adenosine diphosphate, thrombin receptor-activating peptide, or U46-619, relative reductions in conformationally activated GP IIb/IIIa receptor expression (evaluated with PAC-1) of 48%, 43%, and 33%, respectively (all p < 0.0001), were seen with clopidogrel, but further 80%, 78%, and 72% (all p < 0.0001) reductions were seen with eptifibatide. With the same agonists, fibrinogen binding was significantly reduced after clopidogrel by 70%, 64%, and 81% (all p < 0.0001) and again further reduced with eptifibatide by 90%, 95%, and 69% (all p < 0.0001). The total number of GP IIb/IIIa receptors (measured as P2 expression) and P-selectin expression fell after clopidogrel, after ex vivo stimulation with the same agonists; however, both parameters increased slightly during the eptifibatide infusion. CONCLUSIONS: The activated GP IIb/IIIa expression and fibrinogen binding findings indicate that eptifibatide provides significant potent antiplatelet activity above aspirin and clopidogrel, suggesting additive immediate protection in the treatment of NSTEMI. The P2 and P-selectin findings suggest the possibility of a partial agonist and/or pro-inflammatory effect.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citatio

n&list_uids=14736431

Am J Cardiol (2004);94:983-8
Predictors of and outcomes of early thrombosis following balloon angioplasty versus primary stenting in acute myocardial infarction and usefulness of abciximab (the CADILLAC trial)
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We sought to identify the predictors and clinical outcomes of early thrombosis after primary angioplasty and stenting for acute myocardial infarction (AMI). Little is known about the correlates and prognosis of acute and subacute thromboses after percutaneous coronary intervention (PCI) for AMI. We therefore studied the frequency, clinical determinants, and implications of early thrombosis in a large trial of patients who had primary PCI. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, 2,082 patients who had AMI were randomized in a 2 x 2 factorial design to primary stenting or to balloon angioplasty, each with and without abciximab. Early thrombosis occurred in 19 patients (0.9%) at a median of 2 days (range 0 to 23). Maximal balloon diameter was smaller, and aneurysmal and bifurcation lesions were more prevalent in the group with early thrombosis. Early thrombosis occurred in 0.4% of patients who had been randomized to receive abciximab versus 1.5% of control patients ($p < 0.01$) and in 0.5% of patients who had been randomized to undergo stenting versus 1.4% of those who underwent balloon angioplasty ($p = 0.04$). By multivariate analysis, abciximab use was an independent predictor of no thrombosis (hazard ratio 0.27, 95% confidence interval 0.09 to 0.86, $p = 0.026$). Within 30 days, 5.3% of patients who had early thrombosis died, 32.9% developed reinfarction, and 89.5% required repeat target vessel revascularization (including bypass surgery in 11.1%). As a result, patients who had versus those who did not have early thrombosis had markedly higher rates of major adverse cardiac events at 30 days (94.7% vs 5.0%, $p < 0.0001$) and at 1 year (94.7% vs 16.9%, $p < 0.0001$). Patients who develop early thrombosis after primary PCI have a very high rate of major adverse cardiac events, including death and reinfarction, and usually require repeat coronary angioplasty or surgery for management. Complex baseline angiographic morphology and smaller maximal balloon diameter are predictors of early thrombosis after primary PCI for AMI. The incidence of early thrombosis after primary angioplasty and stenting is decreased by abciximab use.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15476608

Catheter Cardiovasc Interv (2004);61:179-84
Safety of a high bolus dose of tirofiban in patients undergoing coronary stent placement
G. B. Danzi

bleeding risk and 30-day clinical outcome in patients undergoing coronary stenting. We compared two cohorts of patients who underwent coronary stent placement between January 2000 and December 2002. In the first cohort, the only available IIb/IIIa receptor inhibitor was abciximab, which was given to 280 (34.9%) out of 802 stented patients; in the second cohort, tirofiban was administered to 274 (38.3%) out of 716 treated patients. The primary endpoints were the proportion of patients with major bleeding and the rate of site access complications; the 30-day incidence of major adverse cardiac events (MACE) was also assessed. After the procedure, the patients were given ticlopidine for 4 weeks and aspirin indefinitely. Major bleeding episodes were observed in four patients receiving abciximab and in none receiving tirofiban (1.4% vs. 0%; P = 0.12); the rates of site access complications were similar (3.6% vs. 3.3%; P = 0.96). The 30-day incidence of MACE was 7.1% in the abciximab group and 5.8% in the tirofiban group (P = 0.65). In patients undergoing coronary stenting, the high bolus dose of tirofiban is safe and not associated with an increased risk of major bleeding or site access complications in comparison with abciximab.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14755808

Am J Cardiol (2004);94:35-9
Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function
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In patients treated with primary coronary angioplasty, the use of abciximab improves microvascular perfusion and enhances the recovery of contractile function. This study compared the effects of the new dose regimen of tirofiban (25-microg/kg bolus followed by an 18-hour infusion at 0.15 microg/kg/min) on left ventricular function with those of abciximab in patients who underwent direct angioplasty. One hundred patients who underwent primary coronary angioplasty were randomized to receive a standard dose of abciximab or a large-dose bolus of tirofiban. The primary end point of the study was change in the infarct-zone wall motion score index between the initial and 30-day follow-up echocardiographic studies. The secondary end points were procedural evaluations before and after Thrombolysis In Myocardial Infarction (TIMI) grade flow, TIMI grade myocardial perfusion, and corrected TIMI frame count. Baseline global and regional ventricular functions were similar in the 2 treatment groups. After the procedure, a TIMI grade 3 flow was obtained in 86% of patients treated with abciximab and 88% of those receiving tirofiban (p = 1.0), whereas TIMI grade 3 myocardial perfusion was present in 70% and 76%, respectively (p = 0.65); corrected TIMI frame count was 22.5 +/- 1.9 and 22.1 +/- 2.5 (p = 0.37). After 30 days, we obtained 87 paired echocardiographic studies. The infarct-zone wall motion score index decreased from 2.20 +/- 0.3 to 1.99 +/- 0.2 in the abciximab group and from 2.18 +/- 0.3 to 1.95 +/- 0.3 in the tirofiban group (p = 0.67). Thus, in patients who had primary coronary angioplasty, abciximab, and the large-dose bolus of tirofiban showed similar effects on the initial angiographic results and 30-day recovery of left ventricular function.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15219505

Eur Heart J (2004);25:1688-94
Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial
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AIMS: In high risk patients with non-ST elevation acute coronary syndromes (ACS), enoxaparin is generally preferred to unfractionated heparin (UFH). However, less is known about the relative merits of these two forms of heparin in patients receiving concomitant glycoprotein IIb/IIIa inhibitors. METHODS AND RESULTS: The A phase of the A-to-Z trial was an open label non-inferiority trial in which 3987 patients with non-ST elevation ACS were randomised to receive either enoxaparin or UFH in combination with aspirin and tirofiban. Inclusion required either ST depression or cardiac biomarker elevation. While the selection of an early management strategy (invasive or conservative) was at the discretion of the local investigator, investigators were asked to designate their plans for an invasive or conservative strategy on the case record form. An early conservative strategy was specified for 1778 patients (45%); this subgroup forms the population for the present analyses. Among patients with a planned conservative strategy, baseline characteristics were similar between those randomised to UFH (n = 872) and those randomised to enoxaparin (n = 906). The primary endpoint of death, new MI, or documented refractory ischaemia within 7 days of randomisation occurred in 10.6% of patients randomised to UFH and 7.7% of patients randomised to enoxaparin (HR 0.72; 95% CI 0.53-0.99; p = 0.04). The combined rate of TIMI major, minor, or loss no-site bleeding was 1.3% in patients treated with UFH and 1.8% in those treated with enoxaparin (p = ns). CONCLUSIONS: When a conservative approach to catheterisation and PCI was planned for ACS patients receiving tirofiban and aspirin, enoxaparin was associated with superior efficacy and similar bleeding vs UFH.
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Am Heart J (2004);148:378-85
Combined Abciximab REteplase Stent Study in acua iooctgn = 906gn c 58611uor1 6sTni0kd6sTn =a(

(referring them for rescue PTCA only if needed) or to immediately send all patients for emergency coronary angioplasty. METHODS: The Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction (CARESS in AMI) is an open, prospective, randomized, multicenter clinical trial conducted in patients with high-risk ST-segment elevation AMI treated within 12 hours from symptom onset in hospitals without PTCA facilities or in a prehospital mobile intensive care unit. Apart from contraindications to thrombolysis, the main exclusion criteria are age > or =75 years and a past history of CABG surgery or a percutaneous coronary intervention procedure involving the infarct-related artery. Enrollment will be performed in hospitals without PTCA facilities or directly in the ambulance if a dedicated system is in place for prehospital diagnosis and treatment of AMI. Patients will receive half-dose reteplase and full-dose abciximab and will subsequently be randomized to conventional medical therapy (with referral for emergency rescue PTCA allowed in selected cases) or emergency angioplasty. The primary end point is the 30-day combined incidence of mortality, reinfarction, and refractory ischemia. In order to obtain a 95% power (2-sided) to detect a 42% reduction in the primary end point, 900 patients are required in each arm of the study. Secondary end points include the 1-year composite end point of mortality, reinfarction, refractory ischemia, and hospital readmission because of heart failure; resource use at 30 days and 1 year; and the incidence of inhospital stroke and bleeding complications in the 2 groups. RESULTS: Seventy-four patients have been randomized (as of March 10, 2004); results are expected in June 2005. CONCLUSION: This study will establish whether angioplasty must be started as soon as possible in all patients who receive combined pharmacologic reperfusion with the glycoprotein IIb/IIIa inhibitor abciximab and half-dose thrombolysis or whether it can be postponed or skipped in patients with signs of successful reperfusion, with obvious organizational advantages.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15389222

Eur Heart J (2004);25:720-2
Long-term clopidogrel therapy after percutaneous coronary intervention in PCI-CURE and CREDO: the "Emperor's New Clothes" revisited
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15120880

J Am Coll Cardiol (2004);44:1187-93
Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction
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OBJECTIVES: To evaluate the extent of platelet aggregation inhibition in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI), treated with different antiplatelet agents and dosages.

predictor of major cardiac events after elective PCI. In STEMI patients undergoing PCI, routine dose of antiplatelet agents may be associated with less effective platelet aggregation inhibition. METHODS: Patients were treated with clopidogrel before angiography and randomized to abciximab, tirofiban, high-dose tirofiban, or no glycoprotein (GP) IIb/IIIa inhibitor; GP IIb/IIIa inhibitor bolus, followed by maintenance infusion, was administered after angiography, but before PCI. Platelet aggregation inhibition was assessed before angiography, immediately after PCI, and 1 and 6 h afterwards. RESULTS: The total study population consisted of 112 patients. Platelet aggregation inhibition was variable for individuals and suboptimal for all agents, particularly in the periprocedural period. Only with high-dose tirofiban, mean periprocedural platelet aggregation inhibition exceeded 80%. Angiographic parameters after PCI were not different between the groups. No relationship was found between the level of platelet aggregation and parameters of PCI success (Thrombolysis In Myocardial Infarction frame count and myocardial blush grade), after combining the data from all four groups studied. CONCLUSIONS: Platelet aggregation inhibition in STEMI patients undergoing PCI, treated with antiplatelet agents, is variable and suboptimal for all agents and dosages studied. Only with high-dose tirofiban, mean periprocedural platelet aggregation inhibition exceeded 80%. However, no relationship of platelet aggregation inhibition and angiographic outcome was found in this patient cohort.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15364318

Jama (2004);292:45-54
Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial
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CONTEXT: Enoxaparin has demonstrated advantages over unfractionated heparin in low- to moderate-risk patients with non-ST-segment elevation acute coronary syndromes (ACS) treated with a conservative strategy. OBJECTIVES: To compare the outcomes of patients treated with enoxaparin vs unfractionated heparin and to define the role of enoxaparin in patients with non-ST-segment elevation ACS at high risk for ischemic cardiac complications managed with an early invasive approach. DESIGN, SETTING, AND PARTICIPANTS: The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was a prospective, randomized, open-label, multicenter, international trial conducted between August 2001 and December 2003. A total of 10 027 high-risk patients with non-ST-segment elevation ACS to be treated with an intended early invasive strategy were recruited. INTERVENTIONS: Subcutaneous enoxaparin (n = 4993) or intravenous unfractionated heparin (n = 4985) was to be administered immediately after enrollment and continued until the patient required no further anticoagulation, as judged by the treating physician. MAIN OUTCOME MEASURES: The primary efficacy outcome was the composite clinical end point of all-cause death or nonfatal myocardial infarction during the first 30 days after randomization. The primary safety outcome was major bleeding or stroke. RESULTS: The primary end point occurred in 14.0% (696/4993) of patients assigned to enoxaparin and 14.5% (722/4985) of patients assigned to unfractionated heparin (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.86-1.06).

No differences in ischemic events during percutaneous coronary intervention (PCI) were observed between enoxaparin and unfractionated heparin groups, respectively, including similar rates of abrupt closure (31/2321 [1.3%] vs 40/2364 [1.7%]), threatened abrupt closure (25/2321 [1.1%] vs 24/2363 [1.0%]), unsuccessful PCI (81/2281 [3.6%] vs 79/2328 [3.4%]), or emergency coronary artery bypass graft surgery (6/2323 [0.3%] vs 8/2363 [0.3%]). More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI (Thrombolysis in Myocardial Infarction) major bleeding (9.1% vs 7.6%, P =.008) but nonsignificant excess in GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Arteries) severe bleeding (2.7% vs 2.2%, P =.08) and transfusions (17.0% vs 16.0%, P =.16). CONCLUSIONS: Enoxaparin was not superior to unfractionated heparin but was noninferior for the treatment of high-risk patients with non-ST-segment elevation ACS. Enoxaparin is a safe and effective alternative to unfractionated heparin and the advantages of convenience should be balanced with the modest excess of major bleeding.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15238590

J Am Coll Cardiol (2004);44:635-41
Co-administration of nitric oxide-aspirin (NCX-4016) and aspirin prevents platelet and monocyte activation and protects against gastric damage induced by aspirin in humans
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OBJECTIVES: The goal of this study was to test the hypothesis that NCX-4016 may have broader anti-inflammatory and antithrombotic effects as well as better gastric tolerability than aspirin in humans. BACKGROUND: NCX-4016 is an aspirin derivative containing a nitric oxide-releasing moiety that prevents platelet activation and modulates tissue factor (TF) expression and cytokine release from lipopolysaccharide (LPS)-stimulated monocytes. METHODS: This was a blind-observer, placebo-controlled, parallel-group study in which 48 healthy subjects were randomized to receive NCX-4016 800 mg twice a day, NCX-4016 800 mg twice a day plus aspirin 325 mg, aspirin 325 mg, or placebo for 21 days. RESULTS: Similar to aspirin alone, NCX-4016 effectively inhibited platelet aggregation induced by 0.6 mmol/ arachidonic acid, clot-stimulated thromboxane (TX) B2 generation in whole blood, and urinary excretion of 11-dehydro-TXB2. Unlike aspirin alone, the administration of NCX-4016 significantly inhibited TF expression in monocytes stimulated ex vivo with 10 mic( )5.1(a(u)5.9(l)E(y)6.1u(t)-5.4(y T

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Jama (2004);292:3017-23
Aspirin sensitivity: implications for patients with coronary artery disease
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CONTEXT: Although acetylsalicylic acid (aspirin) is commonly used for patients with chronic cardiovascular disease, a minority of patients have a sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. OBJECTIVE: To provide a diagnostic strategy for evaluating and treating patients with aspirin sensitivity, with additional consideration for issues specific to patients with coronary artery disease (CAD). EVIDENCE ACQUISITION: Published articles were identified through a search of MEDLINE and the Cochrane databases using the dates 1966 to June 2004 and the search terms aspirin allergy, coronary artery disease, aspirin desensitization, and aspirin sensitivity. References of retrieved articles were also reviewed for pertinent studies. Articles were included in this review if they were controlled studies, published in the English language, and appeared in a peer-reviewed journal. EVIDENCE SYNTHESIS: The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10% and for aspirin-induced urticaria the prevalence varies from 0.07% to 0.2% of the general population. Aspirin sensitivity is most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase 1. The primary mechanism of sensitivity is less often related to drug-specific IgE antibody production leading to urticaria/angioedema and rarely to anaphylaxis. Most patients with acetylsalicylic acid sensitivity are able to undergo desensitization therapy safely and successfully except in cases of chronic idiopathic urticaria. However, there have not been any randomized trials that specifically focus on the efficacy of aspirin desensitization. Furthermore, experience with acetylsalicylic acid desensitization in patients with CAD is very limited. After successful desensitization, acetylsalicylic acid therapy must be indefinitely continued to prevent resensitization. CONCLUSIONS: Acetylsalicylic acid sensitivity is common and desensitization can be performed safely in many patients. Large-scale trials are warranted to determine the safety and efficacy of acetylsalicylic acid desensitization therapy in patients with concomitant CAD because data are currently limited to small case series.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15613671

Eur Heart J (2004);25:1898-902
Antiplatelet effects of a 600 mg loading dose of clopidogrel are not attenuated in patients receiving atorvastatin or simvastatin for at least 4 weeks prior to coronary artery stenting
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weeks prior to coronary artery stenting. METHODS AND RESULTS: Blood samples were obtained at least 2 h after receiving 100 mg aspirin and 600 mg clopidogrel and prior to coronary stenting from 90 patients without statin therapy and 90 patients with statin (atorvastatin and simvastatin) therapy for at least 4 weeks. Maximal and residual platelet aggregation was evaluated with optical aggregometry in response to ADP (5 and 20 micromol/l). Surface expression of IIb/IIIa (CD61) and P-selectin (CD62) was assessed with whole blood flow-cytometry at baseline and following stimulation (5 and 20 micromol/l ADP). Inhibition of ADP-induced platelet aggregation was not impaired in the presence of concomitant statin therapy. Moreover, patients with and without statin therapy did not differ in respect to all flow-cytometric parameters obtained. CONCLUSION: The antiplatelet effect of a high, 600 mg loading dose of clopidogrel is not diminished in patients receiving atorvastatin and simvastatin for at least 4 weeks prior to coronary stenting.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15522468

Lancet (2005);365:475-81
Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study
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BACKGROUND: Controversy has surrounded the question about whether high-dose rofecoxib increases or naproxen decreases the risk of serious coronary heart disease. We sought to establish if risk was enhanced with rofecoxib at either high or standard doses compared with remote non-steroidal anti-inflammatory drug (NSAID) use or celecoxib use, because celecoxib was the most common alternative to rofecoxib. METHODS: We used data from Kaiser Permanente in California to assemble a cohort of all patients age 18-84 years treated with a NSAID between Jan 1, 1999, and Dec 31, 2001, within which we did a nested case-control study. Cases of serious coronary heart disease (acute myocardial infarction and sudden cardiac death) were risk-set matched with four controls for age, sex, and health plan region. Current exposure to cyclo-oxygenase 2 selective and non-selective NSAIDs was compared with remote exposure to any NSAID, and rofecoxib was compared with celecoxib. FINDINGS: During 2302029 person-years of follow-up, 8143 cases of serious coronary heart disease occurred, of which 2210 (27.1%) were fatal. Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses), 1.59 (95% CI 1.10-2.32, p=0.015); for rofecoxib 25 mg/day or less, 1.47 (0.99-2.17, p=0.054); and for rofecoxib greater than 25 mg/day, 3.58 (1.27-10.11, p=0.016). For naproxen versus remote NSAID use the adjusted odds ratio was 1.14 (1.00-1.30, p=0.05). INTERPRETATION: Rofecoxib use increases the risk of serious coronary heart disease compared with celecoxib use. Naproxen use does not protect against serious coronary heart disease.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15705456

J Am Coll Cardiol (2004);43:542-8

Outcome of acute ST-segment elevation myocardial infarction in diabetics treated with fibrinolytic or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: lessons from the GUSTO V trial

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OBJECTIVES: We studied the outcome of diabetics enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) V trial to assess whether the combination of half-dose reteplase and abciximab provides any propitious benefits over standard fibrinolytic therapy in diabetic patients. BACKGROUND: Diabetics with acute ST-segment elevation myocardial infarction (MI) have a worse outcome compared with nondiabetics. Higher-risk patients are usually more likely to benefit from advances in medical therapy. METHODS: We analyzed diabetic patients enrolled in the GUSTO V trial to assess the outcome of those randomized to the combination of half-dose reteplase and abciximab versus those randomized to reteplase. We also evaluated whether any differences existed in presentation and outcome of MI among the diabetics versus the nondiabetics enrolled in the study. RESULTS: The trial enrolled 13782 nondiabetics and 2633 diabetics. Compared to nondiabetics, diabetics had a significantly higher mortality at 30 days (8.5% vs. 5.1%, $p < 0.001$) and at 1 year (12.7% vs. 7.5%, $p < 0.001$). Among the diabetic subset, no significant difference existed in the incidence of 30-day (8.8% vs. 8.2%, $p = 0.52$) or 1-year mortality (13.0% vs. 12.4%, $p = 0.62$) among patients randomized to reteplase compared to those receiving combination of abciximab and reteplase. The incidence of reinfarction (2.5% vs. 4.3%, $p = 0.013$), recurrent ischemia (11.8% vs. 14.9%, $p = 0.017$), and urgent revascularization (10.9% vs. 13.3%, $p = 0.055$) at seven days was lower in diabetics treated with the combination therapy. CONCLUSIONS: Compared to nondiabetics, diabetics continue to have a worse outcome with MI. Although combination therapy did not provide a survival benefit, nonfatal ischemic outcomes, including reinfarction, recurrent ischemia, and urgent revascularization, were substantially reduced.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14975461

Eur Heart J (2004);25:2125-33

Use of abciximab prior to primary angioplasty in STEMI results in early recanalization of the infarct-related artery and improved myocardial tissue reperfusion - results of the Austrian multi-centre randomized ReoPro-BRIDGING Study

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AIMS: The aim of the ReoPro-BRIDGING Austrian multi-centre study was to investigate the effects of abciximab (ReoPro(R)) on early reperfusion in ST-elevation myocardial infarction prior to or during primary percutaneous coronary angioplasty (pPCI).

stenosis (76.3 /63.5-100/ vs 100 /73.5-100/; median /interquartile range/, p=0.023), were significantly higher in Group 1 vs Group 2. Quantitative myocardial dye intensity measurement revealed a significantly higher grade of myocardial tissue perfusion (1 /0-9.25/ vs 0 /0-3.0/ grey pixel unit, p=0.048) in Group 1 before pPCI. Rapid release of cardiac enzymes was observed in Group 1 as compared with Group 2: rate of rise of CK was 210+/-209 vs 97+/-95 U/l/h (p=0.015). QRS score indicated a smaller infarct size in Group 1 (4.8+/-3.8 vs 7.6+/-3.5, p=0.011) on day 7. CONCLUSION: The use of abciximab in the organization phase for pPCI results in signs of early recanalization of the infarct-related artery and a subsequent improved myocardial tissue reperfusion.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15571828

Chest (2004);126:513S-548S
Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy
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This chapter about antithrombotic therapy for coronary artery disease (CAD) is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, CHEST 2004; 126:179S-187S). Among the key recommendations in this chapter are the following: For patients presenting with non-ST-segment elevation (NSTE) acute coronary syndrome (ACS), we recommend immediate and then daily oral aspirin (Grade 1A). For patients with an aspirin allergy, we recommend immediate treatment with clopidogrel, 300-mg bolus po, followed by 75 mg/d indefinitely (Grade 1A). In all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until > 5 days, we recommend clopidogrel as bolus therapy (300 mg), followed by 75 mg/d for 9 to 12 months in addition to aspirin (Grade 1A). In NSTE ACS patients in whom angiography will take place within 24 h, we suggest beginning clopidogrel after the coronary anatomy has been determined (Grade 2A). For patients who have received clopidogrel and are scheduled for coronary bypass surgery, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A). In moderate- to high-risk patients presenting with NSTE ACS, we recommend either eptifibatide or tirofiban for initial (early) treatment in addition to treatment with aspirin and heparin (Grade 1A). For the acute treatment of NSTE ACS, we recommend low molecular weight heparins over unfractionated heparin (UFH) [Grade 1B] and UFH over no heparin therapy use with antiplatelet therapies (Grade 1A). We recommend against the direct thrombin inhibitors as routine initial antithrombin therapy (Grade 1B). For patients after myocardial infarction, after ACS, and with stable CAD, we recommend aspirin in doses from 75 to 325 mg as initial therapy and in doses of 75 to 162 mg as indefinite therapy (Grade 1A). For patients with contraindications to aspirin, we recommend long-term clopidogrel (Grade 1A). For primary prevention in patients with at least moderate risk for a coronary event, we recommend aspirin, 75 to 162 mg/d, over either no antithrombotic therapy or vitamin K antagonist (VKA) [Grade

2A]; for patients at particularly high risk of events in whom the international normalized ratio (INR) can be monitored without difficulty, we suggest low-dose VKA (target INR, 1.5) [Grade 2A].
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15383483

Eur Heart J (2004);25:232-9
Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction; the LoWASA Study
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AIM: To evaluate whether long-term treatment with a fixed low dose of warfarin in combination with aspirin improves the prognosis compared with aspirin treatment alone after an acute myocardial infarction (AMI). METHODS: Patients who were hospitalized for AMI were randomized to either 1.25mg of warfarin plus 75mg of aspirin (n=1659) daily or 75mg of aspirin alone (n=1641). The study was performed according to the PROBE (Prospective Open Treatment and Blinded End Point Evaluation) design and was conducted at 31 hospitals in Sweden. The median follow-up time was 5.0 years. In the aspirin+warfarin group, 30.2% were permanently withdrawn as opposed to 14.0% in the aspirin group (P<0.0001). Analyses were performed on an intention-to-treat basis. RESULTS: The combination of cardiovascular death, reinfarction or stroke was registered in 28.1% in the aspirin+warfarin group versus 28.8% in the aspirin group (NS). Cardiovascular deaths occurred in 14.2% in the aspirin+warfarin group vs 15.7% in the aspirin group (NS). Whereas no difference was found with regard to total mortality or reinfarction, those randomized to aspirin+warfarin had a reduced occurrence of stroke (4.7% vs 7.1%; P=0.004). The percentage of patients who suffered a serious bleed was 1.0% in the aspirin group vs 2.2% in the combination group (P=0.0006). CONCLUSION: A fixed low dose of warfarin added to aspirin in the long term after AMI did not reduce the combined risk of cardiovascular death, reinfarction or stroke. The results did, however, indicate that a fixed low dose of warfarin added to aspirin reduced the risk of stroke, but this was a secondary end point. The combination of aspirin and warfarin was assoc(pirinondal rK an)-5.15.6(c(par)-6.7sraJal)6.6(t)0.6(s)-O8(ion ofTJ0 -1.rp5.1(wa)6.1(s)-8.wa)6op

after coronary stenting, which plays a key role on the mechanism of restenosis. Thus, cilostazol's potential inhibition of this process may lead to prevention of restenosis. METHODS: Using flow cytometric analysis of whole blood obtained from the coronary sinus, the expression of platelet membrane glycoproteins and neutrophil adhesion molecules was observed in 70 consecutive patients undergoing coronary stenting. The patients were randomly assigned to either a cilostazol or ticlopidine group before stent placement. RESULTS: The restenosis rate was lower (15% vs. 31%, $p < 0.05$) in the cilostazol group ($n = 34$) than in the ticlopidine group ($n = 32$). A stent-induced increase in platelet P-selectin (CD62P) expression and an increase in neutrophil Mac-1 (CD11b) expression were suppressed in the cilostazol group compared with the ticlopidine group. Angiographic late lumen loss was correlated with the relative changes in platelet P-selectin and neutrophil Mac-1 at 48 h after coronary stenting. CONCLUSIONS: Cilostazol may have effects on suppression of P-selectin-mediated platelet activation, platelet-leukocyte interaction, and subsequent Mac-1-mediated leukocyte activation, which might lead to a reduced restenosis rate after coronary stent implantation.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15464320

Am Heart J (2004);147:E15
A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after coronary stent implantation
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BACKGROUND: The combination of a thienopyridine and aspirin has become the standard of care after intracoronary stenting. Clopidogrel appears to be better tolerated than ticlopidine but may be associated with more adverse cardiac events. We assessed the tolerability and efficacy of 2 weeks of therapy with ticlopidine and aspirin in comparison to clopidogrel and aspirin after coronary stent implantation. METHODS: Patients with successful intracoronary stent implantation at our institution were randomly assigned, in addition to aspirin, to receive either ticlopidine or clopidogrel. Loading doses were administered immediately after the procedure, and the drugs were continued for 2 weeks. RESULTS: Three hundred seven patients were randomly assigned: 154 patients to clopidogrel and 153 to the ticlopidine group. The primary end point of early drug discontinuation occurred in 5 patients (3.3%) in the ticlopidine group and 1 patient (0.6%) in the clopidogrel group ($P = .121$). Within 30 days, thrombotic stent occlusion occurred in 1 patient (0.7%) in the ticlopidine group and 3 patients (1.9%) in the clopidogrel group ($P = .623$). A major adverse cardiac event occurred in 3 patients (approximately 1.9%; $P = 1.00$) in each group. CONCLUSIONS: There was a nonsignificant trend to improved tolerability of a 2-week regimen of clopidogrel and aspirin when compared with ticlopidine and aspirin in patients undergoing intracoronary stent implantation. The combination of clopidogrel and aspirin results in a comparably low incidence of major adverse cardiac events when compared with ticlopidine and aspirin.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15077098

J Am Coll Cardiol (2004);44:2133-6
Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization
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OBJECTIVES: We examined clinical outcomes in the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial based on the duration of pretreatment with a 600-mg loading dose of clopidogrel. BACKGROUND: The influence of the treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization on early outcomes remains uncertain. METHODS: Among 2,159 patients with coronary disease who underwent percutaneous coronary intervention (PCI) in the ISAR-REACT trial, we examined clinical outcomes relative to the duration of pretreatment with a 600-mg dose of clopidogrel: (2 to 3 h, 3 to 6 h, 6 to 12 h, or >12 h). Patients were randomly assigned to adjunctive therapy with abciximab or placebo at the beginning of the study. The primary end point was a composite of death, myocardial infarction, or urgent revascularization within 30 days after randomization. RESULTS: No significant differences were observed between patient groups regarding the duration of pretreatment, irrespective of assignment to abciximab or placebo (p = 0.27 for interaction among abciximab/clopidogrel and placebo/clopidogrel treatment at each time interval). Occurrence of major bleeding also did not differ according to time of initial clopidogrel dosing. CONCLUSIONS: For low-to-intermediate risk patients treated with a 600-mg loading dose of clopidogrel before PCI, incremental clinical benefit within the first 30 days from durations of pretreatment >2 to 3 h was not evident.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15582309

Am Heart J (2004);147:457-62
Improved clinical outcomes with abciximab therapy in acute myocardial infarction: a systematic overview of randomized clinical trials
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trends favoring a decrease in mortality alone and the composite of death or reinfarction. CONCLUSIONS: Treatment with abciximab significantly reduces early adverse ischemic events, a clinical benefit that is maintained at 6-month follow-up. These findings support the use of adjunctive GP IIb/IIIa inhibition in primary PCI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14999194

Jama (2004);291:947-54
Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial
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CONTEXT: The optimal pharmacological strategy for bridging the delay between admission and performance of percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (MI) is not known. OBJECTIVE: To assess whether early administration of reteplase plus abciximab produces better results compared with abciximab alone in patients with acute MI referred for PCI. DESIGN, SETTING, AND PATIENTS: Open-label, randomized controlled study conducted from May 3, 2001, through June 2, 2003, of 253 patients who were admitted to 13 community hospitals without catheterization facilities (n = 186) and to 5 hospitals with catheterization facilities (n = 67), with the diagnosis of an ST-segment elevation acute MI within 12 hours from onset of symptoms. INTERVENTIONS: Patients received intravenously either the combination of a half-dose reteplase (two 5-U boluses, 30 minutes apart) with a standard dose of abciximab (0.25 mg/kg bolus, 0.125 microg/kg per minute infusion [maximum 10 microg/min for 12 hours]) or the standard dose of abciximab alone; all patients were then transferred for PCI. MAIN OUTCOME MEASURE: Final infarct size according to a single-photon emission computed tomography study with technetium Tc 99m sestamibi performed between 5 and 10 days after randomization in 228 patients (90.1% of entire sample). RESULTS: Of the 253 patients enrolled, 125 were assigned to reteplase plus abciximab and 128 to abciximab alone. The median (interquartile range) of the final infarct size of the left ventricle was 13.0% (3.0%-28.0%) in the reteplase plus abciximab group and 11.5% (3.0%-26.3%) in the abciximab-alone group (P =.81). The mean difference in final infarct size of left ventricle between the reteplase plus abciximab group and the abciximab group was 1.3% (95% confidence interval [CI], -3.1% to 5.7%). Within 6 months after randomization, the composite secondary end point of death, recurrent MI, or stroke occurred in 8 patients (6.4%) in the reteplase plus abciximab group and 6 patients (4.7%) in the abciximab group (relative risk, 1.4; 95% CI, 0.5-3.9; log-rank P =.56). Major bleeding complications were observed in 7 patients (5.6%) in the reteplase plus abciximab group and 2 patients (1.6%) in the abciximab group (P =.16). CONCLUSION: Early administration of reteplase plus abciximab does not lead to a reduction of infarct size compared with abciximab alone in patients with acute MI referred for PCI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14982910

aggregation from 90+/-9% to 51+/-19% (P<0.001). In the chronic therapy group, loading with 600 mg clopidogrel yielded further inhibition of ADP 5 micromol/L-induced platelet aggregation in addition to that achieved by the maintenance dose of 75 mg/d, from 52+/-14% to 33+/-12% (P<0.001). In both groups, 600 mg clopidogrel loading significantly inhibited ADP-induced expression of glycoprotein IIb/IIIa and P-selectin receptors. CONCLUSIONS: Further platelet inhibition can be achieved with clopidogrel in addition to that provided by currently recommended loading and maintenance doses. Higher doses may be warranted after assessment of their clinical efficacy and safety.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15262828

J Am Coll Cardiol (2004);43:526-31
Optimal suppression of thromboxane A(2) formation by aspirin during percutaneous transluminal coronary angioplasty: no additional effect of a selective cyclooxygenase-2 inhibitor
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OBJECTIVES: We examined the contribution of cyclooxygenase (COX)-1 and -2 to the generation of prostacyclin, thromboxane (Tx) A(2), and 8-epi prostaglandin (PG) F(2alpha) during percutaneous transluminal coronary angioplasty (PTCA). BACKGROUND: Both TxA(2) and 8-epi PGF(2alpha) activate platelets and are mitogenic, whereas prostacyclin is a platelet inhibitor, and therefore may influence the outcome of PTCA. METHODS: Twenty-one patients undergoing PTCA while receiving aspirin 300 mg daily or aspirin plus the selective COX-2 inhibitor nimesulide were compared with 13 patients treated only with fradafiban, a glycoprotein IIb/IIIa antagonist. Urine was analyzed for the metabolites of TxA(2) (Tx-M) and prostacyclin (PGI-M) and for the isoprostane, 8-epi PGF(2alpha). RESULTS: In the fradafiban group, there was a marked increase in Tx-M during PTCA (mean, 1973; 95% confidence interval [CI] 112 to 3834 rising to mean 7645; 95% CI 2,009 to 13281 pg/mg creatinine, p = 0.018). The Tx-M excretion was similarly reduced by aspirin and the combination of aspirin and nimesulide. In contrast, the combination of nimesulide and aspirin inhibited PGI-M excretion to a greater extent than aspirin (p = 0.001). Urinary 8-epi PGF(2alpha) excretion was elevated following PTCA compared with normal subjects (p = 0.002) and appeared to be unaffected by any of the treatments. CONCLUSIONS: The increase in TxA(2) during PTCA is primarily COX-1 dependent, and aspirin alone is effective in suppressing its formation. In contrast, prostacyclin generation is both COX-1 and COX-2 dependent. The inhibition of COX-1 and COX-2 did not prevent the production of 8-epi PGF(2alpha), suggesting that this is not enzymatically derived. The persistent generation of 8-epi PGF(2alpha) may contribute to the thrombosis and restenosis that complicate PTCA.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14975458

J Am Coll Cardiol (2004);43:985-90
The effects of nonselective non-a and

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OBJECTIVES: This study was designed to determine if non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) are associated with lower odds of myocardial infarction (MI) and if NANSAIDs, particularly ibuprofen, interfere with aspirin's cardioprotective effect. BACKGROUND: The NANSAIDs may reduce the risk of MI but may also interfere with aspirin's cardioprotective effect. METHODS: A case-control study was conducted, with cases of first, nonfatal MI identified prospectively and controls identified randomly from the community. RESULTS: The use of NANSAIDs was associated with a significant reduction in MI among those not using aspirin (adjusted odds ratio [OR] 0.53; 95% confidence interval [CI]: 0.42 to 0.67). This was true for both ibuprofen (adjusted OR 0.52; 95% CI: 0.39 to 0.69) and naproxen (adjusted OR 0.48; 95% CI: 0.28 to 0.82). Although aspirin itself was associated with decreased odds of MI in those not also using NANSAIDs (adjusted OR relative to no aspirin use 0.79; 95% CI: 0.63 to 0.98), it was not associated with decreased odds of MI among those who were using NANSAIDs (OR 1.28; 95% CI: 0.85 to 1.94; p value for interaction = 0.026). The association of aspirin and reduced odds of MI diminished with increasing frequency of NANSAID use (test for interaction p = 0.006), particularly for ibuprofen (p = 0.018). Among frequent (4 times/week) NANSAID users, the OR for aspirin versus no aspirin was 2.04 (95% CI: 1.06 to 3.94). Users of prophylactic aspirin plus frequent ibuprofen had an OR relative to aspirin-only users of 2.03 (95% CI: 0.60 to 6.84). CONCLUSIONS: In the absence of aspirin use, NANSAIDs are associated with reduced odds of MI. In those using aspirin, NANSAIDs do not provide additional protection. Additional study is needed to determine the clinical impact of using NANSAIDs along with aspirin for cardioprotection.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028354

Am Heart J (2004);148:582-9
Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment
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BACKGROUND: Although clinical trials have found that enoxaparin clearance is prolonged in renal impairment, only one letter describes experience with adjusting doses. Only pharmacokinetic studies exist to guide dose adjustment in response to anti-Xa levels. Unfractionated heparin has comparable major bleeding in renal impairment compared with unadjusted enoxaparin. This necessitates a pharmacokinetic program to adjust enoxaparin with anti-Xa monitoring. METHODS: A pharmacokinetic program was created in response to adverse events and physician interest in a service. A program was designed providing all patients a loading dose of 1 mg/kg enoxaparin. Subsequent doses were 0.50 mg/kg per dose subcutaneously (SC) every 12 hours (q12h) for patients with a creatinine clearance (CrCl) < or =30 mL/min (severe group) and 0.75 mg/kg per dose SC q12h for patients with CrCl of 30 to 60 mL/min (moderate group). A 1-year review of 170 hospitalized patients is reported. RESULTS: The mean

+/- SD [95% CI] anti-Xa level 4 hours after the third dose was 0.65 +/- 0.19 [0.59 to 0.70] IU/mL for the severe group and 0.82 +/- 0.18 [0.79 to 0.85] IU/mL for the moderate group (P <.001). Eighty percent of patients with moderate renal failure and 60% of the patients with severe renal failure were in the therapeutic anti-Xa range after the third dose. A dose-adjustment ratio was used to adjust doses in patients whose levels were outside the therapeutic range: New dose = [(Current dose) x (Goal anti-Xa level)]/(Current anti-Xa level). An incidence of bleeding comparable to that found in normal patients was found. CONCLUSIONS: In high-risk patients, it is reasonable to limit the exposure of patients to low molecular weight heparins by using anti-Xa levels as a marker. The enoxaparin protocol for renally impaired patients successfully placed patients in the therapeutic range established by consensus guidelines. The dose-adjustment ratio adds significant understanding to the pharmacokinetics of dose adjustment.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15459586

J Am Coll Cardiol (2004);43:276-83
Effects of glycoprotein IIb/IIIa inhibition on microvascular flow after coronary reperfusion. A quantitative myocardial contrast echocardiography study
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Catheter Cardiovasc Interv (2004);61:52-5
Assessment of anticoagulation using activated clotting times in patients receiving intravenous enoxaparin during percutaneous coronary intervention
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Enoxaparin is being used more frequently in patients undergoing percutaneous coronary intervention (PCI). In this study, we determined the effect of intravenous enoxaparin on activated clotting time (ACT) measurements in the setting of PCI. In 67 consecutive patients, either 1 mg/kg intravenous enoxaparin alone was given for anticoagulation or 0.75 mg/kg given in patients receiving eptifibatide. ACT was measured before and 5 min following enoxaparin administration. After 1 mg/kg enoxaparin (n = 22), mean ACT increased from 122 +/- 22 to 199 +/- 20 sec. After 0.75 mg/kg enoxaparin and eptifibatide (n = 45), mean ACT increased from 125 +/- 22 to 194 +/- 24 sec. The mean increase in ACT was 77 +/- 26 sec in the 1 mg/kg group and 69

eptifibatide (83% to 89.7% reduction in the enoxaparin-eptifibatide group and 77.8% to 85.5% reduction in the UFH-eptifibatide group, inter-group differences not significant). Both groups also demonstrated marked reductions in thrombus formation, but the reductions achieved in the enoxaparin-eptifibatide group were significantly higher than those achieved in the UFH-eptifibatide group (HSR: 75.6% reduction vs. 63.9%, respectively, p = 0.01; LSR: 79.7% reduction vs. 66.1%, respectively, p = 0.0001). CONCLUSIONS: The combination of eptifibatide with enoxaparin appears to have a more potent antithrombotic effect than that of eptifibatide and UFH in the doses tested.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028351

Chest (2004);126:287S-310S
Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy
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This chapter about hemorrhagic complications of anticoagulant treatment is part of the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Bleeding is the major complication of anticoagulant therapy. The criteria for defining the severity of bleeding varies considerably between studies, accounting in part for the variation in the rates of bleeding reported. The major determinants of vitamin K antagonist-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy. There is good evidence that vitamin K antagonist therapy, targeted international normalized ratio (INR) of 2.5 (range, 2.0 to 3.0), is associated with a lower risk of bleeding than therapy targeted at an INR > 3.0. The risk of bleeding associated with IV unfractionated heparin (UFH) in patients with acute venous thromboembolism (VTE) is < 3% in recent trials. This bleeding risk may increase with increasing heparin dosages and age (> 70 years). Low molecular weight heparin (LMWH) is associated with less major bleeding compared with UFH in acute VTE. UFH and LMWH are not associated with an increase in major bleeding in ischemic coronary syndromes, but are associated with an increase in major bleeding in ischemic stroke. Information on bleeding associated with the newer generation of antithrombotic agents has begun to emerge. In terms of treatment decision making for anticoagulant therapy, bleeding risk cannot be considered alone, ie,

urgent revascularization were randomized in a large-scale pilot study to receive heparin (70 U/kg initial bolus) or bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/hour infusion during the procedure). All patients received aspirin; pretreatment with clopidogrel was encouraged, and glycoprotein (GP) IIb/IIIa blockade was at the physician's discretion. Stents were placed in 85% of patients; 72% received a GP IIb/IIIa inhibitor, and 56% were pretreated with clopidogrel. Activated clotting times were higher among patients randomized to bivalirudin than among those given heparin before device activation (median 359 vs 293 seconds, p <0.001). The composite efficacy end point of death, myocardial infarction, or repeat revascularization before hospital discharge or within 48 hours occurred in 5.6% and 6.9% of patients in the bivalirudin and heparin groups, respectively (p = 0.40). Major bleeding occurred in 2.1% versus 2.7% of patients randomized to bivalirudin or heparin, respectively (p = 0.52). This trial represents the largest prospective dataset of bivalirudin administered concomitantly with planned GP IIb/IIIa blockade and provides evidence of the safety and efficacy of this combined antithrombotic approach.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15110198

Jama (2004);292:696-703
Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial
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CONTEXT: In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, bivalirudin with provisional glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibition was found to be noninferior to heparin plus planned Gp IIb/IIIa blockade in the prevention of acute ischemic end points and was associated with significantly less bleeding by 30 days after percutaneous coronary intervention (PCI). OBJECTIVE: To determine whether the efficacy of bivalirudin remains comparable with that of heparin plus Gp IIb/IIIa blockade over 6 months and 1 year. DESIGN, SETTING, AND PARTICIPANTS: Follow-up study to 1 year of a randomized, double-blind 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 intravenously bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of PCI), with provisional Gp IIb/IIIa inhibition, or to receive heparin (65 U/kg bolus), with planned Gp IIb/IIIa inhibition (abciximab or eptifibatide). Both groups received daily aspirin and a thienopyridine for at least 30 days after PCI. MAIN OUTCOME MEASURES: Incidence of death, myocardial infarction, or repeat revascularization by 6 months and death by 12 months after enrollment. RESULTS: At 6 months, death occurred in 1.4% of patients in the heparin plus Gp IIb/IIIa group and in 1.0% of patients in the bivalirudin group (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.43-1.14; P =.15). Myocardial infarction occurred in 7.4% and 8.2% of patients, respectively (HR, 1.12; 95% CI, 0.93-1.34; P =.24), and repeat revascularization was required in 11.4% and 12.1% of patients, respectively (HR, 1.06; 95% CI, 0.91-1.23; P =.45). By 1 year, death occurred in 2.46% of patients treated

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CONTEXT: Glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors improve myocardial reperfusion and clinical outcomes of patients undergoing primary percutaneous coronary intervention (PCI), but optimal timing of administration remains unclear. No systematic reviews have comprehensively examined the effects of early vs delayed administration

benefit. The TIMI risk score was calculated for 1,570 patients randomized to tirofiban plus heparin versus heparin in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial. In high-risk patients (score > or =4) treated without PCI, tirofiban reduced the risk for death, myocardial infarction, and refractory ischemia at 30 days (28.8% vs 21.9%; odds ratio [OR] 0.69, p = 0.04). This benefit was similar in magnitude as that for patients who underwent PCI (32.4% vs 22.2%; OR 0.60, p = 0.06). No benefit was evident in low-risk patients.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15374786

Eur Heart J (2004);25:1635-40
Five-year outcome of patients with acute myocardial infarction enrolled in a randomised trial assessing the value of abciximab during coronary artery stenting
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AIMS: The aim of the study was to investigate the long-term (five years) efficacy of glycoprotein IIb/IIIa inhibition with abciximab given as an adjunct therapy to coronary stenting in patients with acute myocardial infarction (MI) using the patient cohort of the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) randomised trial. METHODS and RESULTS: The patient cohort of ISAR-2 trial (401 patients) was followed up for 5 years after enrollment. There were 201 patients in the abciximab group (stenting plus abciximab) and 200 patients in the control group (stenting without abciximab). The primary end-point of the study was mortality at 5 years. Recurrent MI and target vessel re-vascularisation were also assessed at 5 years after enrollment. On the basis of the Kaplan-Meier analyses, the 5-year mortality was 17.8% (35 patients) in the group with abciximab and 14.6% (29 patients) in the control group (relative risk, 1.20 [95% confidence interval, 0.73-1.96]; P=0.47). The 5-year combined incidence of death, recurrent MI and target vessel re-vascularisation was 38.2% (76 patients) in the group of abciximab and 37.7% (75 patients) in the control group (relative risk, 0.97 [95% confidence interval, 0.70-1.33]; P=0.83). Multivariable analysis showed no significant independent association of abciximab with 5-year mortality (adjusted hazard ratio, 1.16 [95% confidence interval, 0.70-1.92]; P=0.55). CONCLUSION: These findings are not in support of a sustained clinical benefit at 5 years with the use of abciximab during coronary artery stenting in patients with acute MI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15351163

Eur Heart J (2004);25:166-81
Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology
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n&list_uids=14720534

Circulation (2004);109:1476-81
Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy
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BACKGROUND: Postoperative thromboembolic stroke affects 2% to 3% of patients undergoing carotid endarterectomy (CEA) and is preceded by 1 to 2 hours of increasing cerebral embolization. Previous work has demonstrated that high rates of postoperative embolization are associated with increased platelet reactivity to adenosine 5'-diphosphate (ADP). Our hypothesis was that preoperative administration of the platelet ADP antagonist clopidogrel could reduce postoperative embolization. METHODS AND RESULTS: One hundred CEA patients on routine aspirin therapy (150 mg) were randomized to 75 mg clopidogrel (n=46) or placebo (n=54) the night before surgery. Platelet response to ADP was assessed by whole-blood flow cytometry. The number of emboli detected by transcranial Doppler within 3 hours of CEA was independently quantified. Time taken from flow restoration to skin closure was used as an indirect measure of the time to secure hemostasis. In comparison with placebo, clopidogrel produced a small (8.8%) but significant reduction in the platelet response to ADP ($P<0.05$) while conferring a 10-fold reduction in the relative risk of those patients having >20 emboli in the postoperative period (odds ratio, 10.23; 95% CI, 1.3 to 83.3; $P=0.01$, Fisher's exact test). However, in the clopidogrel-treated patients, the time from flow restoration to skin closure (an indirect marker of hemostasis) was significantly increased ($P=0.04$, Fisher's exact test), although there was no increase in bleeding complications or blood transfusions. CONCLUSIONS: This is the first study to show that a CEA patient's postoperative thromboembolic potential can be significantly reduced by targeted preoperative antiplatelet therapy without increasing the risk of bleeding complications.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15007001

Jama (2004);292:89-96
Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-Segment elevation acute coronary syndromes: a systematic overview
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CONTEXT: Antithrombin therapy has become a guidelines-recommended standard of

for TIMI 11B, ACUTE II, and INTERACT were provided by the principal investigator of each study. STUDY SELECTION: All 6 randomized controlled trials comparing enoxaparin and unfractionated heparin in non-ST-segment elevation ACS were selected for analysis. DATA EXTRACTION: Efficacy and safety end points were extracted from the overall trial populations and the subpopulation receiving no antithrombin therapy prior to randomization. DATA SYNTHESIS: Systematic evaluation of the outcomes for 21 946 patients was performed using a random-effects empirical Bayes model. No significant difference was found in death at 30 days for enoxaparin vs unfractionated heparin (3.0% vs 3.0%; odds ratio [OR], 1.00; 95% confidence interval [CI], 0.85-1.17). A statistically significant reduction in the combined end point of death or nonfatal MI at 30 days was observed for enoxaparin vs unfractionated heparin in the overall trial populations (10.1% vs 11.0%; OR, 0.91; 95% CI, 0.83-0.99; number needed to treat, 107). A statistically significant reduction in the combined end point of death or MI at 30 days was also observed for enoxaparin in the populations receiving no prerandomization antithrombin therapy (8.0% vs 9.4%; OR, 0.81; 95% CI, 0.70-0.94; number needed to treat, 72). No significant difference was found in blood transfusion (OR, 1.01; 95% CI, 0.89-1.14) or major bleeding (OR, 1.04; 95% CI, 0.83-1.30) at 7 days after randomization in the overall safety population or in the population of patients receiving no prerandomization antithrombin therapy. CONCLUSION: In a systematic overview of approximately 22 000 patients across the spectrum of ACS, enoxaparin is more effective than unfractionated heparin in preventing the combined end point of death or MI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15238596

Circulation (2004);110:1213-8
Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME)
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BACKGROUND: There are no prospective trial data on long-term outcomes in 80-year-old patients with chronic angina with regard to antiischemic therapy. METHODS AND RESULTS: To assess long-term survival and quality of life (QoL) in patients from the Trial of Invasive versus Medical Therapy in the Elderly (TIME), all 276 1-year survivors (of a total 301 patients) were contacted after a median of 3.1 years (range, 1.1 to 5.9 years). At baseline, patients were 80+/-4 years old, 42% were women, and they were designated as being in angina class 3.2+/-0.7, despite their taking 2.5+/-0.7

invasive-strategy versus medical-strategy patients (39% versus 20%, P<0.0001). CONCLUSIONS: Long-term survival was similar for patients assigned to invasive and medical treatment. The benefits of both treatments in angina relief and improvement in QoL were maintained, but nonfatal events occurred more frequently in patients assigned to medical treatment. Irrespective of whether patients were catheterized initially or only after drug therapy failure, their survival rates were better if they were revascularized within the first year.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15337691

Circulation (2004);109:641-6
Differential treatment benefit of platelet glycoprotein IIb/IIIa inhibition with percutaneous coronary intervention versus medical therapy for acute coronary syndromes: exploration of methods
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BACKGROUND: Although many believe that platelet glycoprotein IIb/IIIa inhibitors should be used only in acute coronary syndrome patients undergoing percutaneous coronary intervention, supporting data from randomized clinical trials are tenuous. The assumption that these agents are useful only in conjunction with percutaneous coronary intervention is based primarily on inappropriate subgroup analyses performed across the glycoprotein IIb/IIIa inhibitor trials. METHODS AND RESULTS: We describe the problems with these analytical techniques and demonstrate that different approaches to the question can result in opposing answers. CONCLUSIONS: Clinical-practice decisions and practice guidelines should be based on overall trial results and not analyses of post-randomization subgroups.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14769687

Chest (2004);126:576S-599S
Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy
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who undergo stent placement, we recommend the combination of aspirin and a thienopyridine derivative (ticlopidine or clopidogrel) over systemic anticoagulation therapy (Grade 1A). We recommend clopidogrel over ticlopidine (Grade 1A). For all patients undergoing PCI, particularly those undergoing primary PCI, or those with refractory unstable angina or other high-risk features, we recommend use of a glycoprotein (GP) IIb-IIIa antagonist (abciximab or eptifibatide) [Grade 1A]. In patients undergoing PCI for ST-segment elevation MI, we recommend abciximab over eptifibatide (Grade 1B). In patients undergoing PCI, we recommend against the use of tirofiban as an alternative to abciximab (Grade 1A). In patients after uncomplicated PCI, we recommend against routine postprocedural infusion of heparin (Grade 1A). For patients undergoing PCI who are not treated with a GP IIb-IIIa antagonist, we recommend bivalirudin over heparin during PCI (Grade 1A). In PCI patients who are at low risk for complications, we recommend bivalirudin as an alternative to heparin as an adjunct to GP IIb-IIIa antagonists (Grade 1B). In PCI patients who are at high risk for bleeding, we recommend that bivalirudin over heparin as an adjunct to GP IIb-IIIa antagonists (Grade 1B). In patients who undergo PCI with no other indication for systemic anticoagulation therapy, we recommend against routine use of vitamin K antagonists after PCI (Grade 1A).
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15383485

J Am Coll Cardiol (2004);43:979-84
Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients
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OBJECTIVES: We sought to investigate, during a two-year follow-up period, the effects of aspirin on platelet aggregation. BACKGROUND: The platelets of patients given aspirin may be less sensitive to antiplatelet treatment, although the extent of such phenomenon over long-term follow-up is unclear. METHODS: Adenosine diphosphate (ADP) and collagen-induced platelet aggregation was periodically monitored before and after 2, 6, 12, and 24 months of treatment with aspirin (n = 150) or ticlopidine (n = 80) in patients matched for gender, age, and risk factors for atherothrombosis. RESULTS: Compared with baseline values, two months of aspirin treatment significantly inhibited platelet aggregation; thereafter, this inhibitory effect progressively decreased. At 24-month follow-up, collagen-induced platelet aggregation was significantly higher than that observed at two months ($p < 0.05$); a more pronounced difference was observed when collagen-induced lag phase was considered ($p < 0.01$). Restoration of platelet aggregation was less evident when ADP was used as an agonist. Conversely, the inhibition induced by ticlopidine was constant throughout follow-up with both agonists. CONCLUSIONS: The study demonstrates that a long-term treatment with aspirin is associated with a progressive reduction in platelet sensitivity to this drug.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028353

J Am Coll Cardiol (2004);43:972-8

Aspirin dose and six-month outcome after an acute coronary syndrome
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OBJECTIVES: This study was designed to compare the efficacy of low and intermediate aspirin doses in acute coronary syndromes. BACKGROUND: Little is known of the comparative efficacy of low and intermediate aspirin doses in this setting. METHODS: We compared six-month death, myocardial infarction (MI), and stroke in patients with unstable angina or acute MI discharged while receiving low (<150 mg) or intermediate (> or =150 mg) aspirin therapy in the GUSTO IIb and PURSUIT trials (n = 20,521). We used multivariable analysis and performed a propensity analysis in order to adjust for baseline imbalances between the groups. RESULTS: Aspirin doses <150 mg were prescribed to 29.9% (6,128) of patients. By six months, 6.4% of the patients (1,310 of 20,521) had a primary event, 6.2% of the patients receiving <150 mg and 6.6% of the patients receiving aspirin doses > or =150 mg (hazard ratio [HR] 1.06 [95% confidence interval (CI) 0.94 to 1.19], p = 0.35). After adjusting for baseline imbalances and the propensity score for discharge aspirin dose, there was no effect of aspirin dose on the composite end point at six months (HR 0.92 [95% CI 0.79 to 1.07], p = 0.28). However, the higher aspirin dose was associated with a reduction in six-month MI (HR 0.79 [95% CI 0.64 to 0.98], p = 0.03). The outcome was similar when patients were matched on the basis of the propensity score for aspirin dose (HR for death/MI/stroke 0.94 [95% CI 0.80 to 1.12], p = 0.51), although stroke occurred significantly more frequently among patients receiving the higher aspirin dose (HR 1.74 [95% CI 1.01 to 3.02] p = 0.05) and the effect on MI was no longer apparent. CONCLUSIONS: Although these data are non-randomized, they suggest that the aspirin dose upon discharge may influence the clinical course after unstable angina or acute MI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028352

Circulation (2004);110:e1-4
Approach to "aspirin allergy" in cardiovascular patients
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15238467

J Am Coll Cardiol (2004);43:549-56
Improved speed and stability of ST-segment recovery with reduced-dose tenecteplase and eptifibatide compared with full-dose tenecteplase for acute ST-segment elevation myocardial infarction
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OBJECTIVES: This sub-study of the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) trial evaluated of the impact of combination reperfusion therapy with reduced-dose tenecteplase plus eptifibatide on continuous ST-segment recovery

and angiographic results. BACKGROUND: Combination therapy with reduced-dose fibrinolytics and glycoprotein IIb/IIIa inhibitors for ST-segment elevation myocardial infarction improves biomarkers of reperfusion success but has not reduced mortality when compared with full-dose fibrinolytics. METHODS: We evaluated 140 patients enrolled in the INTEGRITI trial with 24-h continuous 12-lead ST-segment monitoring and angiography at 60 min. The dose-combination regimen of 50% of standard-dose tenecteplase (0.27 microg/kg) plus high-dose eptifibatide (2 boluses of 180 microg/kg separated by 10 min, 2.0 microg/kg/min infusion) was compared with full-dose tenecteplase (0.53 microg/kg). RESULTS: The dose-confirmation regimen of reduced-dose tenecteplase plus high-dose eptifibatide was associated with a faster median time to stable ST-segment recovery (55 vs. 98 min, p = 0.06), improved stable ST-segment recovery by 2 h (89.6% vs. 67.7%, p = 0.02), and less recurrent ischemia (34.0% vs. 57.1%, p = 0.05) when compared with full-dose tenecteplase. Continuously updated ST-segment recovery analyses demonstrated a modest trend toward greater ST-segment recovery at 30 min (57.7% vs. 40.6%, p = 0.13) and 60 min (82.7% vs. 65.6%, p = 0.08) with this regimen. These findings correlated with improved angiographic results at 60 min. CONCLUSIONS: Combination therapy with reduced-dose tenecteplase and eptifibatide leads to faster, more stable ST-segment recovery and improved angiographic flow patterns, compared with full-dose tenecteplase. These findings question the relationship between biomarkers of reperfusion success and clinical outcomes.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14975462

Circulation (2004);109:874-80
Implications of upstream glycoprotein IIb/IIIa inhibition and coronary artery stenting in the invasive management of unstable angina/non-ST-elevation myocardial infarction: a comparison of the Thrombolysis In Myocardial Infarction (TIMI) IIIB trial and the Treat angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial
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interactions). After adjustment for baseline risk, an early invasive strategy tended toward a more favorable result in TACTICS-TIMI 18 than in TIMI IIIB (OR, 0.79; 95% CI, 0.56 to 1.11). CONCLUSIONS: Advances in the care of patients with UA/NSTEMI, including glycoprotein IIb/IIIa inhibition and stenting, were associated with lower rates of death, MI, and rehospitalization for acute coronary syndromes and a trend toward a greater benefit of an early invasive strategy.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14757697

J Am Coll Cardiol (2004);44:1194-9
Lack of clopidogrel pretreatment effect on the relative efficacy of bivalirudin with provisional glycoprotein IIb/IIIa blockade compared to heparin with routine glycoprotein IIb/IIIa blockade: a REPLACE-2 substudy
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OBJECTIVES: The purpose of this study was to assess if clopidogrel pretreatment affects the relative efficacy of bivalirudin versus heparin with glycoprotein (GP) IIb/IIIa blockade for percutaneous coronary interventions (PCI). BACKGROUND: Although thienopyridine pretreatment may improve clinical outcomes with PCI, it is unknown if bivalirudin's efficacy compared with heparin is dependent upon such pretreatment. METHODS: The Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events (REPLACE-2) trial was a double-blind, triple-dummy, randomized-controlled trial comparing heparin plus routine GP IIb/IIIa blockade (heparin group) with bivalirudin plus provisional GP IIb/IIIa blockade (bivalirudin group) during PCI. The primary end point was a composite of death, myocardial infarction (MI), urgent revascularization at 30 days, and major in-hospital bleeding. The secondary end point was a 30-day composite of death, MI, and urgent revascularization. Clopidogrel pretreatment was encouraged (300 mg loading, 75 mg/day). RESULTS: Of 6,010 patients enrolled, 5,893 received clopidogrel, with 85.8% in the bivalirudin and 84.6% in the heparin group receiving clopidogrel pretreatment. Bivalirudin (provisional GP IIb/IIIa blockade 7.2%) was noninferior to the heparin group for both primary and secondary end points. Clopidogrel pretreatment did not affect the relative efficacy of bivalirudin versus heparin with GP IIb/IIIa blockade, irrespective of pretreatment duration. Pretreatment was associated with significantly lower primary end point with bivalirudin (8.7% pretreatment vs. 12.9% no pretreatment, p = 0.007), and nonsignificantly with heparin (9.7% vs. 11.7%, respectively, p = 0.20). Multivariable models showed a trend toward lower primary and secondary end points with clopidogrel pretreatment. CONCLUSIONS: Clopidogrel pretreatment at the doses and time administered in this trial did not influence the relative efficacy of bivalirudin versus heparin plus GP IIb/IIIa blockade for PCI. However, pretreatment was associated with a trend towards lower clinical events after PCI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15364319

Am J Cardiol (2004);94:623-5
Comparison of long-term usefulness of clopidogrel therapy after the first percutaneous

coronary intervention or coronary artery bypass grafting versus that after the second or repeat intervention
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Patients in the Clopidogrel for the Reduction of Events During Observation trial were subgrouped according to whether they underwent index percutaneous coronary artery revascularization procedures only or this procedure plus subsequent percutaneous or surgical revascularization procedures during 1-year follow-up. The relative risk reduction in ischemic events associated with up-front and long-term clopidogrel compared with placebo was 2-fold greater in patients who required repeat revascularization procedures compared with those who did not (42.4% vs 21.7%).
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15342293

Am J Cardiol (2004);93:843-7
Tirofiban therapy for patients with acute coronary syndromes and prior coronary artery bypass grafting in the PRISM-PLUS trial
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The role of glycoprotein IIb/IIIa platelet receptor antagonist therapy for patients with an acute coronary syndrome (ACS) and a history of coronary artery bypass grafting (CABG) remains incompletely defined. We examined the outcomes of patients with an ACS and prior CABG who were treated with tirofiban versus placebo among subjects with prior CABG in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial. Of 1,570 patients treated with tirofiban plus heparin (n = 773) or heparin alone (n = 797), 231 had prior CABG. Compared with patients without prior CABG, those with prior CABG were

A dose-finding study of fondaparinux in patients with non-ST-segment elevation acute coronary syndromes: the Pentasaccharide in Unstable Angina (PENTUA) Study

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OBJECTIVES: In this dose-finding study, we sought to compare fondaparinux with enoxaparin in patients with acute coronary syndromes (ACS). BACKGROUND: Fondaparinux is a synthetic pentasaccharide that selectively inhibits activated clotting factor X. It has been demonstrated as effective in preventing thromboembolic complications in orthopedic surgery. METHODS: Four doses fondaparinux (2.5, 4, 8, or 12 mg once daily) and enoxaparin (1 mg/kg twice daily) were compared, both given for three to seven days, in patients with ACS without persistent ST-segment elevation. RESULTS: The rates of the combined primary end point of death, myocardial infarction, or recurrent ischemia after nine days were 27.9%, 35.9%, 34.7%, 30.3%, and 35.7% in patients allocated to fondaparinux doses of 2.5, 4, 8, and 12 mg and enoxaparin, respectively (p = NS). In the per-protocol analysis (929 patients who received adequate study drug and had adequate ST-segment monitoring), these figures were 30.0%, 43.5%, 41.0%, 34.8%, and 40.2%. Again, no dose response was observed. The lowest event rates were observed in the 2.5-mg fondaparinux group, which had significantly lower rates than the enoxaparin group as well as for 4 and 8 mg fondaparinux in the per-protocol analysis ($p < 0.05$). Bleeding rates were low and not different among the patient groups. No differences were observed in fondaparinux concentrations in patients with or without death, myocardial infarction, recurrent ischemia, or bleeding events. CONCLUSIONS: This dose-finding study revealed no dose response for different fondaparinux doses ranging from 2.5 to 12 mg subcutaneously and suggests that the efficacy and safety of fondaparinux may be similar to that of enoxaparin. Further studies with fondaparinux in ACS might include the lowest dose (2.5 mg) investigated in this study.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15193678

Am Heart J (2004);147:993-8

Efficacy of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: one-year follow-up results of the Assessment of the Safety of a New Thrombolytic-3 (ASSENT-3) randomized trial in acute myocardial infarction

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BACKGROUND: In the ASsessment of the Safety of a New Thrombolytic 3 (ASSENT-3) study, full-dose tenecteplase plus enoxaparin or half-dose tenecteplase plus abciximab reduced the frequency of ischemic complications of acute myocardial infarction, when compared to full-dose tenecteplase plus unfraca38Mf(0.1(rcTh)e0.004Bw[(P.)-5.4j5pquery)de.9(0.8(a)2(ep

166) in the enoxaparin group, and 9.3% (n = 188) in the abciximab group (P =.226). Overall, pairwise comparisons did not show a significant difference among treatment regimens: relative risk 1.03 (95% CI 0.82-1.30) for enoxaparin versus heparin (P =.794) and relative risk 1.18 (95% CI 0.95-1.47) for abciximab versus heparin (P =.144). However, 1-year outcome tended to be worse with abciximab in diabetic patients. CONCLUSION: Mortality at 1 year after acute myocardial infarction remains high. Despite a reduction in ischemic complications after acute myocardial infarction with the use of full-dose tenecteplase plus enoxaparin or half-dose tenecteplase plus abciximab, mortality at 1 year was similar in these treatment groups.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15199346

Circulation (2004);109:e9039-40
Rofecoxib use increases acute myocardial infarction risk
R. SoRelle
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15123542

Eur Heart J (2004);25:2187-94
DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction
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AIM: To determine whether late recanalization of an occluded infarct artery after acute myocardial infarction is beneficial. METHODS AND RESULTS: Two hundred and twelve patients with a first Q-wave myocardial infarction (MI) and an occluded infarct vessel were enrolled. After coronary and left ventricular contrast angiography, patients were randomized to percutaneous revascularization (PTCA, n=109), carried out 2-15 days after symptom onset or medical therapy (n=103). The primary endpoint was a composite of cardiac death, non-fatal MI, or ventricular tachyarrhythmia. The majority had single-vessel disease and less than one-third had involvement of the left anterior descending artery. The use of pharmacological therapy was high in both groups. At six months, left ventricular ejection fraction was 5% higher in the invasive compared with the medical group (P=0.013) and more patients had a patent artery (82.8% vs 34.2%, P<0.0001). Restenosis was seen in 49.4% of patients in the PTCA group. At a mean of 34 months of follow-up, the occurrence of the primary endpoint was similar in the

Chest (2004);126:600S-608S
Antithrombotic therapy in patients with saphenous vein and internal mammary artery bypass grafts: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy
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This chapter about prevention of coronary artery bypass occlusion is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, CHEST 2004; 126:179S-187S). Among the key recommendations in this chapter are the following: For patients undergoing coronary artery bypass grafting (CABG), we recommend aspirin, 75 to 162 mg/d, starting 6 h after operation over preoperative aspirin (Grade 1A). In patients in whom postoperative bleeding prevents the administration of aspirin at 6 h after CABG, we recommend starting aspirin as soon as possible thereafter (Grade 1C). For patients undergoing CABG, we recommend against addition of dipyridamole to aspirin therapy (Grade 1A). For patients with coronary artery disease undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d p.o. (Grade 1C+). In patients who undergo CABG for non-ST-segment elevation acute coronary syndrome (ACS), we recommend clopidogrel, 75 mg/d for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 1A). For patients who have received clopidogrel for ACS and are scheduled for CABG, we recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A). For patients undergoing CABG who have no other indication for vitamin K antagonists (VKAs), we suggest clinicians to not administer VKAs (Grade 2B). For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C). For all patients with coronary artery disease who undergo internal mammary artery (IMA) bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (Grade 1A). For all patients undergoing IMA bypass grafting without other indication for VKA, we suggest clinicians not use VKA (Grade 2C).
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15383486

Am J Cardiol (2005);95:1-7
Impact of stenting and abciximab in patients with diabetes mellitus undergoing primary angioplasty in acute myocardial infarction (the CADILLAC trial)
T. D. Stuckey*, et al.*

assigned to balloon angioplasty versus stenting, with or without abciximab. Diabetes was present in 346 patients (16.6%). The primary end point was the composite incidence of death, disabling stroke, reinfarction, and ischemic target vessel revascularization (TVR). The primary end point at 1 year occurred significantly more frequently in diabetic than nondiabetic patients (21.9% vs 16.8%, p <0.02), driven by increased rates of death (6.1% vs 3.9%, p = 0.04) and TVR (16.4% vs 12.7%, p = 0.07). Among patients with diabetes, TVR at 1 year was significantly reduced with routine stenting compared with balloon angioplasty (10.3% vs 22.4%, p = 0.004), with no differences in death, reinfarction, or stroke. Angiographic restenosis was also greatly reduced in diabetics randomized to stenting (21.1% vs 47.6%, p = 0.009). No beneficial effects were apparent with abciximab in diabetic patients at 1 year. Despite the improved outcomes with stenting in patients with diabetes, 1-year mortality remained increased in diabetic patients who received stents compared with nondiabetics (8.2% vs 3.6%, p = 0.005). Thus, routine stent implantation in diabetic patients with AMI significantly reduces restenosis and enhances survival free from TVR, independent of abciximab use, although survival remains reduced compared with survival in nondiabetic patients regardless of reperfusion modality.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15619385

Jama (2004);292:1867-74
Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease
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CONTEXT: Atherothrombosis is a pathophysiologic process that results in clinical ischemic events affecting the cerebral, coronary, and peripheral arterial circulation. Antiplatelet agents, used alone or in combination, are effective in preventing recurrent vascular events among individuals with established vascular disease. OBJECTIVE: To summarize the current state of evidence regarding oral antiplatelet treatment in patients with cerebrovascular disease, coronary artery disease (CAD), and peripheral arterial disease. EVIDENCE ACQUISITION: Using the key terms acute coronary syndrome, atherothrombosis, ischemic stroke, myocardial infarction, MI, peripheral arterial disease,

ticlopidine, clopidogrel, aspirin combined with clopidogrel, and aspirin combined with dipyridamole are effective in preventing recurrent vascular events among various subgroups of patients with vascular disease. Current clinical trial evidence favors the use of aspirin or clopidogrel as first-line agents for the majority of patients with vascular disease. Clinical trials evaluating combination antiplatelet therapies will direct future practice.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15494585

Eur Heart J (2004);25:837-46
Facilitation of primary coronary angioplasty by early start of a glycoprotein 2b/3a inhibitor: results of the ongoing tirofiban in myocardial infarction evaluation (On-TIME) trial
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AIM: Although primary angioplasty is effective despite additional transportation delay, improved patency before PCI might be obtained by starting pharmacological pre-treatment before transportation. METHODS AND RESULTS: From June 2001 to November 2002, 507 patients with acute myocardial infarction, who were transferred to a PCI centre, were randomised to early, pre-hospital initiation of Tirofiban (Early) or to initiation in the catheterisation laboratory (Late). The primary end-point was TIMI flow grade 3 of the infarct-related vessel (IRV) at initial angiography, as assessed by an independent core-lab. The effect of Tirofiban on each TIMI flow component, the presence of thrombus at initial angiography and pre-PCI myocardial blush grade were secondary end-points. A large proportion of patients (41%) was diagnosed and randomised in the ambulance, without intervention of a physician. In the Early group, Tirofiban was administered a median of 59 min (range 11-178 min) earlier than in the Late group. At initial angiography, TIMI 3 flow was present in 19% the Early group and in 15% in the Late group (P = 0.22). The combined incidence of TIMI 2 or 3 flow was present in 43% in the Early group and in 34% in the Late group, respectively (P = 0.04). Thrombus or a fresh occlusion was present in 60% and 73% in the Early and Late group, respectively (P = 0.002). A pre-PCI myocardial blush grades 2 or 3 was more often present in the Early group (30% vs. 22%, P = 0.04). However, no difference in TIMI 3

therapy in inhibiting flow- and lesion-dependent thrombosis in the porcine ex vivo model
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BACKGROUND: Acetylsalicylic acid (ASA), or aspirin, plus clopidogrel is becoming the standard antithrombotic treatment in people with coronary disease. Novel approaches such as the use of platelet-selective nitric oxide (NO) donors may provide additional protection against thrombosis. We evaluated the antithrombotic properties of a novel platelet-selective NO donor (LA816) administered alone and in combination with ASA, clopidogrel, or ASA+clopidogrel. METHODS AND RESULTS: Thrombogenicity was measured in the porcine experimental model and assessed as platelet-thrombus formation in the ex vivo Badimon perfusion chamber. Pigs were randomly divided into 4 groups: (1) placebo control, (2) clopidogrel, (3) ASA, and (4) ASA+clopidogrel (ASA and clopidogrel were given orally, 10 mg x kg(-1) x d(-1) for 3 d). The animals were anesthetized, heparinized, and catheterized, and the Badimon perfusion chamber was placed in an extracorporeal shunt. After baseline perfusions, all animal groups received the intravenous infusion of LA816 for 2 hours. Platelet aggregation, blood pressure, and heart rate also were evaluated during the experiments. LA816, clopidogrel, and ASA+clopidogrel produced a reduction of approximately 45% on thrombus mass versus placebo control perfusions (P<0.05). Combined treatment of oral ASA+clopidogrel and intravenous LA816 produced a significant further reduction of 25% in platelet deposition (70% from placebo controls; P<0.0001). LA816 intravenous treatment did not modify blood pressure or heart rate. CONCLUSIONS: Acute NO donation with LA816, without modifying hemodynamic parameters, provides the same inhibitory effect as that obtained with chronic treatment with clopidogrel+ASA. Moreover, LA816 provides platelet inhibitory effects in addition to those of the combined blockade of cyclooxygenase and P2y(12) receptor.
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combined lytic group before rescue angioplasty). There was no difference in overall treatment success between primary angioplasty and combined lytic group with rescue angioplasty (83% vs. 94%; P = NS). Major adverse cardiac events at 1 month were not significant (15% vs. 11%; P = NS), but there was a trend toward more events in the combined lytic group at 6 months (32% vs. 14%; P = 0.066), particularly in target vessel revascularization. In this feasibility pilot study, high rate of TIMI 3 flow was attained in patients with AMI with both combined fibrinolysis and primary angioplasty with adjunctive abciximab. A larger randomized trial is currently ongoing to compare these two strategies. Cathet Cardiovasc Intervent 2004;62:445-452. Copyright 2004 Wiley-Liss, Inc.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15274152