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Coronary Artery Revascularization in Patients with Sustained Ventricular Arrhythmias

ABSTRACT & COMMENTARY

Synopsis: *A combination of coronary artery revascularization and antiarrhythmic therapy is required in patients with prior myocardial infarctions who present with sustained ventricular arrhythmias and an indication for revascularization.*

Source: Brugada J, et al. *J Am Coll Cardiol.* 2001;37:529-533.

Brugada and colleagues from barcelona describe a series of 64 consecutive patients who had a sustained ventricular arrhythmia (sustained monomorphic ventricular tachycardia or ventricular fibrillation with cardiac arrest) in the chronic phase after myocardial infarction who subsequently underwent coronary artery revascularization. Coronary artery revascularization was performed using either coronary artery bypass grafting (46 patients) or single or double percutaneous transluminal coronary angioplasty (16 patients). Patients underwent electrophysiologic testing with programmed ventricular stimulation at the time of coronary angiography and then again 3-15 days after the coronary revascularization was performed. There were no changes in antiarrhythmic drugs or beta-adrenergic blocking agent usage between the first and second studies. Patients with an inducible arrhythmia at the second study were treated with either antiarrhythmic drugs or an implantable cardioverter defibrillator.

Fifty-eight of the 64 patients were men, and the mean age for the entire group was 65 ± 8 years. The mean ejection fraction was 38 ± 9%, with 13 of the patients having ejection fractions less than 30%. The presenting arrhythmia had been sustained monomorphic ventricular tachycardia in 55 patients and ventricular fibrillation in the remaining 9 patients. Percutaneous transluminal coronary angioplasty was successfully performed in 16 patients with single or uncomplicated double-vessel disease. Coronary artery bypass grafting was performed in the remaining 48 patients. Two of the patients who underwent surgical intervention died at the time of surgery.

At the initial electrophysiologic study, 53 of the 55 patients with a

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clinical presentation of monomorphic ventricular tachycardia had inducible ventricular tachycardia (47) or ventricular fibrillation (6). Only 2 of these patients had no inducible arrhythmia. Among the 9 patients with ventricular fibrillation, 6 had inducible ventricular tachycardia, 2 had inducible ventricular fibrillation and 1 patient had no inducible arrhythmia. Fifty-nine patients with an inducible arrhythmia (ventricular tachycardia, 51 patients; ventricular fibrillation, 8 patients) at the time of the first electrophysiologic study underwent a second electrophysiologic study. At the follow-up electrophysiologic study, 52 of these 59 (88%) patients again had an inducible sustained ventricular arrhythmia. Five of 53 patients with inducible ventricular tachycardia had no inducible arrhythmia at the follow-up study. Two of 8 patients with inducible ventricular fibrillation had no inducible arrhythmia at the follow-up study. Three patients who had no inducible arrhythmia at the first study had no inducible arrhythmia at the follow-up study as well.

Thirty-six patients received an implantable cardioverter defibrillator (ICD) prior to discharge, and 14 of these 36 also received amiodarone. The remaining 26 patients with an inducible arrhythmia after revascularization were treated with either amiodarone (18) or sotalol (8). Among the 52 patients with inducible arrhythmia at the follow-up study, recurrent arrhythmias were documented after discharge in 28 (54%). Four of the 10 patients (40%) who had no inducible arrhythmia at their second study also had recurrent events. Events were somewhat more common in patients with the lowest ejection fractions. Nine of 13 patients (69%) with an ejection fraction of less than 30% had a recurrent arrhythmic event compared with 23 of 49 (47%) with an ejection fraction greater than 30% (P = .02).

Brugada et al conclude that coronary artery revascularization does not improve the arrhythmia substrate in a significant proportion of patients who presented with sustained ventricular arrhythmias. Sustained arrhythmias remain inducible in most patients after revascularization, and there is a high recurrence rate of clinical arrhythmias during follow-up. Brugada et al conclude that a combination of coronary artery revascularization and antiarrhythmic therapy is required in patients with prior myocardial infarctions who present with sustained ventricular arrhythmias and an indication for revascularization.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The beneficial effect of coronary revascularization on survival in patients with multivessel disease and decreased left ventricular function is well accepted. Among patients who initially presented with ventricular tachycardia or ventricular fibrillation, Kelly and associates reported that surgical coronary revascularization was an independent predictor of an improved outcome.[1] However, the effect of revascularization on the risk of future arrhythmia remains poorly characterized. This paper is the largest study on this issue to date and it clearly indicates that revascularization alone does not favorably influence previously established stable arrhythmia substrates as identified by responses to programmed stimulation and clinical outcome.

Several years ago, the Coronary Artery Bypass Graft (CABG) Patch Trial reported that prophylactic ICD insertion at the time of bypass surgery did not favorably influence mortality during follow-up. A proposed explanation for that observation was that revascularization decreased the frequency of sustained ventricular arrhythmias. The difference from that study and this current one is that the patients in the current study by Brugada et al had already presented with ventricular arrhythmia. Therefore, they had previously defined themselves as a high-risk group with an established substrate for arrhythmia. The patients in the CABG Patch Trial had low ejection fractions but most probably had not yet developed a chronic substrate for ventricular arrhythmias. This study shows that once such a substrate becomes established, it is unlikely to be favorably affected by revascularization.

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The conclusion we should take from this paper is that although revascularization may be effective in preventing the development for a substrate of arrhythmia and in preventing arrhythmias due to ischemia, once a stable substrate has developed, revascularization alone is not adequate therapy. ❖

Reference

1. Kelly P, et al. *J Am Coll Cardiol.* 1990;15:267-273.

Platelet IIb/IIIa Inhibitors for Percutaneous Interventions

ABSTRACT & COMMENTARY

Synopsis: *Available data would suggest that abciximab is the superior agent for use in percutaneous coronary intervention and retains its potent anti-platelet effects despite pretreatment with tirofiban or eptifibatide.*

Source: Lev EI, et al. *Circulation.* 2001;37:84.

Three glycoprotein (gp) iib-iiia inhibitors, the long-acting monoclonal antibody, abciximab (ReoPro®—Centocor/Lilly), and 2 short-acting small molecules tirofiban (Aggrastat®—Merck), and eptifibatide (Integrilin®—Cor/Key), have been FDA approved for the treatment of patients with coronary artery disease. Tirofiban and eptifibatide have been shown to be effective in the prevention of ischemic complications in the medical therapy of patients with acute coronary syndromes (ACS) and, therefore, are being used with increasing frequency. Abciximab is the only GP IIb-IIIa inhibitor that has been shown to reduce short-and long-term ischemic complications in patients undergoing percutaneous coronary intervention (PCI) but, in contrast, appears to offer no benefit as medical therapy in ACS. However, in clinical practice, many patients who initially present with ACS, particularly those at highest risk, will eventually undergo PCI. Thus, it often remains difficult to predict which agent will ultimately provide the most beneficial for a given patient.

Lev and colleagues, therefore, sought to determine whether patients receiving medical therapy with a small-molecule GP IIb-IIIa inhibitor could subsequently be treated with abciximab. This small study was designed to assess the efficacy and safety of 20-24 hours of tirofiban or eptifibatide, overlapping with abciximab administration at the time of PCI.

Fifty patients with ACS or recent (< 2 weeks) MI, who were scheduled to undergo PCI within 24 hours, were enrolled in the study. All patients received heparin and aspirin. They were divided into 3 consecutive groups: 25 received tirofiban (bolus and 20-24 hour infusion) followed by abciximab at the time of PCI, 10 received eptifibatide (bolus and 20-24 hour infusion) followed by abciximab at the time of PCI, and 15 received only abciximab (control group) at the time of PCI. Heparin was discontinued after PCI, and all patients receiving stents were treated with 4 weeks of clopidogrel post-procedure.

Efficacy was assessed using several different assays of platelet function in vitro. GP IIb-IIIa receptor binding was measured to assess for any interference with abciximab binding by the small molecule agents. These assays were performed at multiple time points before, during, and after GP IIb-IIIa inhibitor administration. Safety was assessed by serial complete blood counts for evidence of bleeding or thrombocytopenia, need for transfusion, and evidence of clinical bleeding events, as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.

There were no significant differences in baseline demographics between groups. Forty-six patients received coronary stents, and all PCI procedures were deemed successful. The addition of abciximab to tirofiban resulted in additional antiplatelet effects by all assay methods. The addition of abciximab to eptifibatide resulted in additional reduction of platelet function by the surface deposition assay only. The degree of platelet inhibition was greater for either combination therapy than for abciximab alone. Neither tirofiban nor eptifibatide interfered with abciximab binding to the GP IIb-IIIa receptor.

There were no statistically significant differences in safety outcomes among the groups, and complication rates were comparable to or lower than those published in previous clinical trials. There were no major bleeding events or transfusions required in any of the groups. Mild mucocutaneous bleeding occurred in 5 tirofiban-abciximab treated patients, 1 eptifibatide-abciximab treated patient, and 1 control patient. No patient developed severe thromboytopenia (< 50,000 cells/mL). Mild thrombocytopenia developed in 1 patient receiving tirofiban-abciximab, 5 control patients, and in none of the patients receiving eptifibatide-abciximab.

COMMENT BY SARAH M. VERNON, MD

Available data would suggest that abciximab is the superior agent for use in PCI, given the magnitude and durability of benefit demonstrated in the EPIC,

EPLILOG, and EPISTENT trials, while both eptifibatide and tirofiban have been shown to have a more modest benefit in multiple trials for patients with ACS. Furthermore, in all of the previously published trials, each of these agents has proved to be of particular benefit for the highest risk subgroups of patients. Within the last several months, initial results of from GUSTO IV, evaluating abciximab in ACS, TACTICS (TIMI 18), and TARGET have become available. In the context of previously published literature, the results from these more recent clinical trials have raised almost as many questions as they answer. In GUSTO IV, 48 hours of abciximab as medical therapy resulted in no reduction in ischemic complications (and a concerning trend toward increased mortality) in patients with ACS. TACTICS demonstrated the superiority of an early invasive strategy vs. an early conservative strategy in the management of patients with ACS treated with tirofiban. TARGET demonstrated superior outcomes for abciximab compared with tirofiban, in the first published head-to-head comparison of GP IIb-IIIa inhibitors for patients undergoing PCI. Thus, there are more data supporting the use of the short-acting small molecule drugs (tirofiban and eptifibatide) in ACS and abciximab in PCI. However, given that the highest risk ACS patients, those most likely to suffer ischemic complications and most likely to benefit from GP IIb-IIIa inhibition, are also the most likely to ultimately require PCI, a conundrum arises. Despite large amounts of data from many randomized trials, it remains difficult to determine which agent to administer to which patient and in what time frame.

The study by Lev et al is important in that it is the first published to evaluate the combination of abciximab and intravenous GP IIb-IIIa inhibitor therapy in vivo. Lev et al acknowledge that this study has obvious and significant limitations, most notably small sample size and the consecutive (nonrandomized, nonblinded) pattern of treatment group assignment. Despite these limitations, the study suggests that abciximab retains its potent antiplatelet effects in the presence of pretreatment with tirofiban or eptifibatide. While the small sample size make the data assessing safety of combination therapy less convincing, the study also suggests that medical therapy with tirofiban or eptifibatide can be safely overlapped with abciximab should such a patient ultimately require PCI. These results, while preliminary, are compelling, and in time may be borne out when data from larger randomized trials assessing combination therapy become available. ❖

How Far to Lower LDL Cholesterol: Important New Data

ABSTRACTS & COMMENTARY

Synopsis: *Aggressive LDL cholesterol lowering of at least 45-50% is beneficial and safe in patients with familial hypercholesterolemia.*

Sources: Smilde TJ, et al. *Lancet.* 2001;367:577-581; Durrington PL. *Lancet.* 2001;367:574.

Asap, the effect of aggressive vs. conventional Lipid Lowering on Atherosclerosis Progression in Familial Hypercholesterolaemia, is a prospective randomized trial in individuals with familial hypercholesterolemia (FC) treated with aggressive vs. less aggressive statin therapy for 2 years. The primary end point was a change in carotid intima medial thickness (IMT), with a number of secondary end points at 24 months. Eligible patients were untreated (1/3) or were on therapy but still had an LDL-C greater than 175 mg/dL. After a run-in period of 2 months, with baseline measurements of IMT and a variety of lipoproteins, 325 patients (mean age, 48) were randomized to 80 mg of atorvastatin or 40 mg of simvastatin. One-third had overt cardiovascular disease, and one-third were smokers. A resin was added to therapy if total cholesterol remained greater than 320 mg/dL. All individuals were recommended to be on a standard low-fat diet. B-mode ultrasound was used, with measurements of the distal common corotid artery, carotid bifurcation, and the proximal internal carotid artery; IMT was determined for both anterior and posterior walls of the common carotid and bifurcation.

Results: 14% of patients did not complete the protocol for a variety of reasons. There was a low cardiovascular event rate; muscle aches and mild abdominal complaints were common in both groups (there was no placebo arm). Baseline TC was 400 mg/dL, and LDL-C was approximately 320 mg/dL. Lipid levels dropped dramatically. Atorvastatin (A) lowered LDL-C by 50% (P = .0001), with a reduction TC of 42%, TG 29%, and an increase in HDL of 13%. Simvastatin (S) lowered TC by 34%, LDL-C by 41%, TG by 18%, with a comparable increase in HDL-C. There was a marked change in the LDL/HDL ratios in both groups. Twenty-seven percent of A individuals had a fall in LDL-C below 120 mg/dL, but only 7% of the S patients achieved these levels. Lp(a) levels decreased by 15% in both groups. IMT changes were notable. Overall IMT was reduced in the A group but increased in the S group, with highly signifi-

cant *P*-values. Thus, regression of carotid IMT was noted in 66% of A patients and 42% of S patients. Overall changes in IMT were correlated with baseline IMT (thicker vessels demonstrated greater changes) and with the percentage of cholesterol reduction. Changes in HDL and Lp(a) did not correlate with changes in IMT. Smilde and associates conclude that aggressive LDL cholesterol lowering of at least 45-50% is warranted in patients with FH to modify IMT progression and produce regression. While HDL did not seem to relate to IMT, triglycerides did; they speculate that triglyceride rich LDL and small dense LDL particles may be favorably altered by aggressive statin therapy and play a role in favorable changes in IMT. They point out that their data are consistent with the Post CABG Trial, which compared a modest vs. high dose of lovastatin in patients with prior bypass surgery, and demonstrated a more favorable effect on slowing progression of saphenous graft disease in the high-dose lovastatin subjects, who achieved a final LDL-C of less than 90 mg/dL. They emphasize that the A subjects in ASAP not only had limited progression but actually reversed atherosclerosis, as assessed by IMT; the data are concordant and correlate LDL-C reduction to favorable changes in IMT. They point out that a yearly IMT progression rate of 0.03 mm or greater increases the risk of future events, based on data in the literature. The 0.07 mm difference in IMT between A and S at 2 years suggests that less effective LDL-C lowering did not achieve sufficiently favorable results in this high-risk subject. They concluded that IMT is an adequate surrogate end point for vascular disease, although there are significant limitations using this marker; "aggressive lipid lowering is indicated, beneficial, and safe in patients with FH."

COMMENT BY JONATHAN ABRAMS, MD

The data in this study are striking, suggesting for the first time that a large number of patients with FH can have their vascular disease stabilized and potentially even regressed. The comparison of 80 mg of atorvastatin to 40 mg of simvastatin is unfair, in one sense, as it is no surprise that greater LDL-C reductions can be achieved with high-dose atorvastatin. As to what is the best end point for lowering LDL cholesterol, the arguments remain: should it be a percentage reduction, achievement of a target level, or simply reaching a specific level, such as 125 mg/dL, as the CARE investigators recommend. This study clearly supports that greater lowering is more favorable, and the fact that IMT actually regressed over 2 years, associated with a 50% reduction in baseline LDL-C, is compatible with much other data. Thus, lower is better, certainly in FH patients, and probably in other individuals at high risk. These would include an elevated LDL-C in individuals who have established vascular disease and/or multiple other CAD risk factors. The absence of a placebo arm in this trial makes it difficult to know whether simvastatin slowed progression; this is likely but is unproven. In that the mean baseline total cholesterol in this FH cohort was 400 mg/dL, and the LDL-C was approximately 320 mg/dL, there is little to dispute over a target of LDL reduction of 50% or even greater.

The role of carotid IMT as a marker for vascular disease and atherosclerosis seems reasonably well founded. Multiple studies have or are using this technique. Meticulous attention to detail is necessary. The slope of change is important, and clearly a negative slope, as seen with the high dose atorvastatin group, is an exciting finding. I am unaware of other regression trials that show that the majority of individuals treated with lipid lowering actually regress as opposed to having stabilized disease and slowed progression. It is reasonable to extrapolate from the FH patients in this trial to high-risk individuals in general, from either a primary or secondary prevention perspective. In patients with established vascular disease, LDL-C should (and can) be brought to below 100 mg/dL and probably even lower. The actual levels achieved in the FH patients are much higher, of course. One can extrapolate from the 2-year differences in LDL and IMT between the simvastatin and atorvastatin groups that reducing high levels of total and LDL cholesterol to levels approaching "normal" is most beneficial for patients with high cardiovascular risk. ❖

Natriuretic Peptide B for Heart Failure Triage

ABSTRACT & COMMENTARY

Synopsis: *The B-type natriuretic peptide test appears sensitive and specific for diagnosing heart failure in the urgent care setting.*

Source: Dao Q, et al. *J Am Coll Cardiol.* 2001;37: 379-385.

B-type natriuretic peptide (bnp) is secreted from the ventricles in response to volume or pressure overload and is elevated in heart failure (HF). With the development of a new rapid assay, Dao and associates sought to determine the value of BNP in the urgent care setting. A sample of 250 of 438 patients presenting

to a VA urgent care center with dyspnea were studied. Patients whose dyspnea was clearly not due to HF ie chest trauma and patients with acute coronary syndromes were excluded. The patients were predominately male (94%) and most (70%) had dyspnea on exertion, but 50% had dyspnea at rest. Although the urgent care center physicians rated the probability of HF as high, medium, or low, the gold standard was 2 cardiologists who retrospectively reviewed all the available data including the hospital course and tests done after transfer from urgent care. During the initial evaluation in urgent care, blood for BNP, measured by the Biosite Diagnostics test, was obtained, but the urgent care doctors were not provided the results. The BNP results were evaluated against the cardiologists diagnosis. They diagnosed acute HF in 39%, LV dysfunction with no HF in 6%, and noncardiac dyspnea in 55%. BNP levels in the HF patients were 1076 vs. 38 pg/mL in the patients with noncardiac dyspnea ($P < .001$). Those with LV dysfunction but no HF had levels of 141 ≠ 31 pg/mL. At BNP levels greater than 80, HF was predicted with an accuracy of 95% and a negative predictive value of 98% for levels less than 80. Also, BNP levels were higher as the assessed severity of HF increased. In addition, BNP was highly accurate in separately pulmonary dyspnea vs. HF and noncardiac pedal edema from HF. Finally, BNP greater than 80 was the most accurate predictor of HF compared to all pertinent clinical variables available initially including ECG and chest x-ray; consideration on BNP levels would have prevented 15 unnecessary admissions, and 29 of 30 misdiagnosed cases would have been corrected. Dao et al concluded that the BNP test appears sensitive and specific for diagnosing HF in the urgent care setting.

COMMENT BY MICHAEL H. CRAWFORD, MD

As I was perusing the annotated table of contents of *Journal of the American College of Cardiology*, I saw a full page ad for The Triage BNP Test by Biosite Diagnostics. It touted a 15-minute result with 98% accuracy for the diagnosis of HF vs. "all significant variables in patients with or without disease history." My first reaction was this is ludicrous. I know how to diagnose HF and don't need some blood test. How accurate will it be in the real world? Will this be another "troponin" that results in endless, mindless consultations to the emergency department? Now in addition to seeing everyone with chest pain, we would have to see everyone with dyspnea. At this rate, ER doctors would soon just draw blood, await a battery of tests, then start calling consultants. I was appalled. Then I noticed the strategic placement of this ad next to the brief description of 2 studies in *Journal of the American College of Cardiology* using this test that suggested it was useful. As I started to calm down, I remembered those patients with COPD and CAD in whom COPD exacerbation vs. HF is always a difficult call on clinical grounds. And what about the patient who languishes intubated under the ineffectual care of intensivists in the ICU, in whom they finally order an echo, which shows an ejection fraction of 20%? Perhaps there is a use for this test. This study makes a good point that dyspnea is a nonspecific symptom, and HF is difficult to diagnose clinically in patients with pulmonary disease or in elderly deconditioned patients. The ECG and chest x-ray can be helpful but are not sufficiently diagnostic in many cases. Echocardiography is extremely useful but is logistically more difficult than a blood test and probably more costly. Thus, the rapid BNP test could be a useful triage test as this study showed. The 98% negative predictive value and sensitivity is just what the ER physicians like because it reduces missed diagnoses to a litiginously acceptable level. Fortunately, in this study the specificity and positive predictive value of BNP were also greater than 90%, which keeps the false positives that drive us consultants crazy to a minimum.

One of the major limitations of this study was that it was a convenient sample of mainly elderly men. Also, patients with obvious confounders such as acute coronary syndromes and obvious causes of dyspnea (ie pneumothorax) were excluded. Thus, the real world performance of this test is still an issue. Would it be elevated in other causes of ventricular enlargement or trauma such as hypertensive urgencies, pregnancy, and cardiac contusion? Clearly, more information is needed. However, this study suggests that this may be a useful test in selected patients. ❖

QT Dispersion in Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *QT dispersion has no significant prognostic value in patients with advanced heart failure and reduced left ventricular systolic function.*

Source: Brendorp B, et al. *Circulation.* 2001;103: 831-835.

Brendorp and colleagues tested the value of QT dispersion as a potential prognostic marker for arrhythmias and death in patients with advanced heart

failure. This study was a predefined substudy in the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (Diamond-CHF) trial. Diamond-CHF was a study to see if dofetilide would improve mortality in patients with congestive heart failure. Patients were eligible for the trial if they had severe left ventricular dysfunction with New York Heart Association functional class III or IV symptoms within the previous month. Patients were randomized between dofetilide and placebo. Since this was a trial involving dofetilide, an antiarrhythmic drug that prolongs the QT interval, patients with a corrected QT interval greater than 450 m/sec or one greater than 500 m/sec with bundle branch block were excluded from the trial. An analysis of the prognostic value of QT dispersion was a prespecified substudy in Diamond-CHF. QT dispersion could be determined on baseline electrocardiograms from 703 patients. The QT intervals were measured in all 12 leads using a computerized digitizer tablet. The QT dispersion was defined as the maximum minus minimum QT interval in the 12 leads measured. When U waves were present, the end of the QT interval was measured at the nadir between the T and U waves.

There were 285 deaths among the 703 patients in this study (41%). Of these deaths, 219 were classified as cardiac, and of these, 131 were arrhythmic and 81 nonarrhythmic deaths. The upper quartile for QT dispersion was greater than 102 m/sec. There was no difference between the survival curve in total mortality between those patients with QT dispersion greater than 102 m/sec and those with QT dispersion of 100 m/sec or less. Similarly, QT dispersion was not a significant predictor for any of the following end points: cardiac death, arrhythmic cardiac death, or nonarrhythmic cardiac death. The prognostic value of QT dispersion was also tested in various subgroups with stratifications by sex, age, ejection fraction, smoking status, presence of bundle branch block, renal function, New York Heart Association class, diabetes, ischemic heart disease, hypertension, or therapy with beta blockers, digoxin, or dofetilide. In all subgroups, the risk ratio for QT dispersion was found to be near 1.0 with small 95% confidence intervals. The 3 prognostic factors that were associated with increased risk for all-cause mortality, cardiac death, and cardiac arrhythmic death were increasing age, increasing New York Heart Association functional class, and decreasing ejection fraction or wall motion index. Brendorp et al conclude that QT dispersion has no significant prognostic value in patients with advanced heart failure and reduced left ventricular systolic function.

COMMENT BY JOHN P. DiMARCO, MD, PhD

In the last several years, several groups have proposed that QT dispersion may be a specific predictor for subsequent cardiac events in patients with various forms of heart disease. The most conclusive data come from patients with acute myocardial infarction and in patients with the congenital long QT syndrome. In patients without these diagnoses, however, the value of QT dispersion has been controversial. This study from the Diamond-CHF trial indicates that measurement of QT dispersion does not have prognostic value in patients with chronic congestive heart failure.

A possible limitation of this report is the fact that patients with obviously abnormal QT intervals or T wave morphologies were excluded from the study. In order to participate in Diamond-CHF, the patient had to be eligible for randomization to dofetilide. Certainly, patients with bizarre QT intervals or T wave morphologies were excluded by Brendorp et al. In these patients, large values for QT dispersion may be important to note. However, such patients are relatively uncommon and this study clearly indicates that the routine measurement of QT dispersion is of little prognostic value in unselected populations with chronic congestive heart failure.

The practical value of QT dispersion measurement remains limited. The QT interval may be difficult to measure reproducibly, and individuals show significant day-to-day and circadian variations. Patients with heart failure and depressed ejection fractions should all be considered to be a significant risk for arrhythmias. ❖

Lipoprotein (A) as a Marker for Coronary Risk

ABSTRACT & COMMENTARY

Synopsis: *Data confirm Lp(a) as an important coronary artery disease risk factor, and emphasize the point that their study used fresh serum samples as opposed to most of the data literature, which measured stored and frozen serum or plasma.*

Source: von Eckardstein A, et al. *J Am Coll Cardiol.* 2001;37:434-439.

Lipoprotein (a) has been a controversial risk factor for coronary artery disease (CAD) for many years, with varying recommendations as to whether Lp(a) should be measured in risk stratification for CAD. This is an interesting moiety, consisting of a cholesteryl

ester apoB particle, with an additional glycoprotein, apo(a), which homologous to plasminogen. This latter feature is believed to be responsible for the proatherogenic and proathrombotic characteristics of Lp(a). Elevations of Lp(a) have been correlated with increased CAD risk; however, it is not generally recommended to assay individuals for it, as data are conflicting and drug therapy to lower Lp(a) is difficult. Furthermore, there are no prospective studies showing that decreasing Lp(a) would improve outcomes. This report represents a substudy of the PROCAM study (Prospective Cardiovascular Münster), a long-term primary prevention study of 34,000 employees in Germany, recruited between 1979 and 1985. Ten-year follow-up data from a recently analyzed cohort of 5333 men, age 35-65 at entry, are now available. The Lp(a) data relate to a subgroup of 820 men who had Lp(a) measurements obtained from fresh serum. CAD risk factors and lipid levels were used to assess the role of the interaction of Lp(a) and traditional risk factors in predicting major CAD events. During the 10-year follow-up, 44 major coronary events occurred, including nonfatal MI, fatal MI, and stroke. The CAD risk factor profile of men with events was worse than those who did not have an event over 10 years. In addition, the median Lp(a) level was higher in those with events than in men without events (0.09 g/L vs 0.04 g/L; $P = .05$). Major CAD events were significantly increased in the highest quintile of baseline Lp(a), eg, a level greater than 0.17 g/L. For those individuals with a level greater than 0.2 g/L, there was almost a 3-fold increase risk of having a coronary event over the next 10 years. There was an adverse interaction of elevated Lp(a) on events with elevated LDL-C, low HDL-C, and hypertension. After correction of total LDL-C levels to take into account the cholesterol contained in the Lp(a) fraction, high Lp(a) levels actually increased risk in all men, irrespective of baseline LDL-C. An elevated Lp(a) did not increase risk in smokers or in individuals with elevated triglyceride levels, but it did impart risk in the absence of these risk factors. An Lp(a) level greater than 0.2 g/L was a risk marker for events in all men who were the top 40% of global CAD risk; in the majority of individuals with a more benign risk profile, Lp(a) elevations did not impart hazard. Eckardstein and associates conclude that their data confirm Lp(a) as an important CAD risk factor, and they emphasize the point that their study used fresh serum samples as opposed to most of the data in the literature, which measured stored and frozen serum or plasma. They suggest that assay difficulties may be the reason why Lp(a) has not always correlated with CAD risk. As in other studies, elevated Lp(a) increased risk in men with an elevated LDL-C but not in men with less than 160 mg/dL. Individuals with hypertension or low HDL-C were also at considerably higher risk with high Lp(a) concentrations. In summary, Lp(a) was a significant predictive risk factor in individuals with the greatest burden of overall CAD risk. Eckardstein et al state, "because Lp(a) increases the risk of coronary events strongly depending on the presence of additional coronary risk factors, it is imperative to strictly control additional risk factors in individuals with elevated Lp(a)."

COMMENT BY JONATHAN ABRAMS, MD

These data further support the argument that measurements of Lp(a) may be useful in primary prevention and suggest that in fresh plasma samples a level of 0.2 g/L or more increases CAD risk, particularly if the individual has other CAD risk factors present, such as an LDL-C above 160, low HDL, or hypertension. The suggestion that fresh samples may be more useful than frozen plasma could explain some of the discrepancies in the literature regarding this controversial matter. It does not appear that routine measurements of Lp(a) are indicated for prevention of CAD. Some lipid experts routinely use this assay, but the vast majority of physicians do not, nor do national guidelines support routine use of Lp(a) testing. However, when one is considering initiating pharmacologic therapy, such as a statin, a fibrate, or niacin, the measurement of Lp(a) may be useful in decision making. Statin therapy and estrogens lower Lp(a). However, there are no data to support that efforts to decrease levels of this compound are useful. Nevertheless, presence of high Lp(a) should trigger increased vigilance and a lower threshold for prescribing preventive measures, particularly drug therapy. ❖

Attention Subscribers

Enclosed with this issue is a special report on Acute Coronary Syndromes. Originally published in *Emergency Medicine Reports*, a sister publication to *Clinical Cardiology Alert*, we thought it would be of interest to our readers. Look for additional bonus reports inserted with the May and June issues. As always, we welcome your questions and comments. ❖

CME Question

16. Lp(a) should be measured:

a. in everyone.
b. in post-MI patients.
c. in familial hypercholesterolemia patients.
d. in selected high CAD risk men.

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Acute Coronary Syndromes (ACS): Pharmacotherapeutic Interventions—Treatment Guidelines for Patients With and Without Procedural Coronary Intervention (PCI)

Part I: Clinical Pathophysiology and Antiplatelet Agents

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Editor's Note: *Gideon Bosker, MD*

Editor's note—perhaps no aspect of emergency medicine is evolving more rapidly than the pharmacological and procedural landscape devoted to the management of patients with acute coronary syndromes (ACS). As every emergency physician and cardiologist understands, making the right choice—whether it is drug therapy, a procedural coronary intervention (PCI), or some combination of both strategies—can make the difference between a favorable and unfavorable outcome.

From an acute, clinical perspective, the challenge of formulating a management action plan that predictably yields optimal outcomes is compromised because there are many classes of agents (antiplatelet drugs, glycoprotein [GP] IIb/IIIa inhibitors, low molecular weight heparins [LMWHs], fibrinolytics), and many individual agents within those classes. More often than not, the trials evaluating the efficacy of specific pharmacotherapeutic interventions are difficult to compare, and the number of head-to-head studies contrasting the risks and benefits of individual agents within a class are almost nonexistent.

Complicating application of the trial data, some drugs may be more or less beneficial for a patient with ACS depending on whether a PCI is likely to be part of the treatment plan.

The multiplicity of interpretations regarding clinical trials, the variations among institutional protocols, proficiency or propensity for performing PCI, and personal preferences among physicians have produced a less-than-consistent approach to managing PCI patients. What's more, even consensus guidelines, such as those recently issued by the American Heart Association and American College of Cardiology for Unstable Angina/Non-ST Elevation Myocardial Infarction (UA/NSTEMI), provide a range of options that are amenable to interpretation and drug substitutions.

Despite these limitations, evidentiary trials continue to support an aggressive approach to managing patients with ACS—an approach that is multi-modal, algorithmic, and risk-strati-

fied driven, and that typically requires sequential administration of such agents as aspirin, beta-blockers, enoxaparin (or UFH), GP IIb/IIIa inhibitors, and/or fibrinolytic therapy. When PCI intervention is contemplated, the pharmacological cocktail for ACS may be modified as required, depending on whether a specific drug has demonstrated safety and efficacy in this setting. Outcome-effective management of patients with acute coronary ischemia requires prompt and accurate risk-stratification followed by a benefit-maximizing, risk-reducing combination of pharmacological and procedural interventions.

With these issues in clear focus, the purpose of this landmark review of ACS is to present a set of evidence-based guidelines and recommendations that emergency physicians and cardiologists can use to establish critical pathways for their institutions. Given the multiplicity of options and the profusion of recent literature on this subject, objectives of this three-part series include establishing an evidentiary infrastructure, presenting trial-based pathways, and providing an analysis base that can bring emergency physicians and their cardiology colleagues together on how best to manage life-threatening disorders characterized by acute coronary ischemia. In order to translate data and information into the world of practical, day-to-day clinical application, an evidence-based critical pathway for ACS has been generated for reader, academic, and institutional use. —gideon bosker, md

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Definition

Ischemic heart disease encompasses a wide spectrum of conditions, ranging from silent ischemia to acute myocardial infarction (AMI). Coronary ischemic syndromes have been classified into distinct diagnostic categories, including stable angina, unstable angina (UA), non-Q wave myocardial infarction (MI), and Q wave MI. Not surprisingly, the terminology for these conditions has evolved as new studies have shed light on the pathophysiology and natural history of these conditions.

On Sept. 8, 2000, The American College of Cardiology and American Heart Association (ACC/AHA) issued their Year 2000 ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. The guidelines have replaced the commonly used category, non-Q wave MI, with the clinical designation, Non-ST-segment Elevation Myocardial Infarction (NSTEMI). This change in terminology reflects the fact that among patients with MI, the presence or absence of ST-segment elevation does not always correlate with Q wave or non-Q wave MI, respectively. In other words, not all patients with ST-segment elevation develop Q waves, whereas some patients without ST-segment elevation on presentation eventually do develop Q waves.

From a practical perspective, this terminology also reflects that initial management of a patient with an ACS is based on the presence or absence of ST-segment elevation. While this review uses the new terminology, it must be recognized that most of the literature uses the term Q wave. UA includes many subtypes, including angina at rest, new-onset exertional angina, recent acceleration of angina, variant angina, and post-MI angina.[1] The term acute coronary syndrome (ACS) refers to conditions that share similar pathophysiology. These include UA, NSTEMI, and ST-segment elevation MI (STEMI).[1,2]

Epidemiology

Coronary artery disease (CAD) is present in more than 7 million Americans and is the cause of more than 500,000 deaths annually.[2] More than 1 million Americans have an AMI annually, and approximately 25% of all deaths are due to AMI.[2] In 1996 there were 750,000 admissions for AMI, approximately one-half of which had ST-segment elevation and one-half of which did not.[1,2]

UA is one of the leading causes of hospital admission for patients with CAD, with more than 1 million hospitalizations annually in the United States.[2,3] First year, direct medical costs associated with UA and AMI have been estimated at more than $12,000 per patient, which translates to an estimated national expenditure exceeding

$16 billion.[3] Among patients with UA who receive treatment, about 1-5% die and 2-10% experience an AMI within the first 28 days after hospital admission.[4]

Clinical Pathophysiology

Our understanding of the underlying lesions, pathophysiology, and natural history of ACS has evolved considerably during the past 25 years. It was hypothesized in the 1970s and early 1980s that the degree of vessel stenosis affected the frequency of ACS. However, it was later noted that the extent of luminal narrowing and severity of coronary stenonsis on angiography did not consistently correlate with the risk of thrombotic complications or the location of subsequent coronary artery occlusions.[5]

By the late 1980s, the concept of vulnerable atherosclerotic plaque had evolved, and it was observed that the presence of vulnerable lesions, some of which were associated with only minimal occlusion of the vessel, correlated with the development of ACS.[5] Subsequently, intravascular ultrasound techniques have revealed that arteries accommodate plaque growth through outward displacement of the vessel wall, thereby preserving much of the patency of the vessel lumen. Most MIs result from coronary artery occlusions associated with a degree of stenoses of less than 50% on angiography.[5] The unpredictable and episodic progression of plaques likely results from plaque disruption and subsequent thromboses, causing changes in plaque geometry and growth and intermittent ACS events.[1]

The natural history of ACS confirms that the pathogenesis of ischemic cardiovascular conditions is a complex process that is neither linear nor predictable. However, characteristic, pathologic phases that occur as part of the natural history of ACS include plaque formation (atherogenesis), plaque disruption (rupture or fissuring) or endothelial erosion, and thrombosis following plaque disruption. Inflammation contributes to the pathogenesis of ACS, as suggested by the fact that excised plaques from culprit lesions in UA patients have more inflammatory cell infiltration than do plaques from patients with stable angina.[6]

Atherogenesis: Atherogenesis frequently is initiated by endothelial cell changes, which may result from enhanced expression of adhesion molecules in intact cells. Factors that may initiate these changes include hypercholesteremia and certain constituents of cigarette smoke. It is postulated that endothelial cell changes permit blood monocytes to adhere to the altered endothelium and then enter the subendothelium. There, low-density lipoproteins (LDL-cholesterol) undergo oxidation, collect within the extracellular space, and bind to the macrophage receptors. This is the precursor phase to LDL sequestration by macrophages, which accumulate the LDLs (a process that results in the formation of foam cells).

Foam-laden macrophages and endothelial cells then secrete growth factors, resulting in smooth muscle cell proliferation. Subendothelial lipids eventually coalesce and form the lipid core of growing atherosclerotic plaques. Additional toxic products (among them, free radicals released by macrophages) produce local cell injury and denuding of endothelium. Platelets adhere to endothelial cell injury sites and release additional growth factors that result in more proliferation of intimal smooth muscle cells, promoting plaque growth. Smooth muscle cells also stimulate development of an extracellular matrix through collagen formation. This matrix consists of a fibrous cap that becomes an interface between the lipid core and the endothelium.

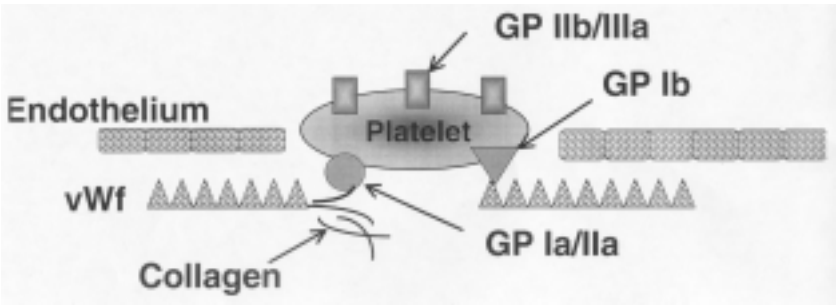
Upon analysis of excised plaques, angiographically-demonstrated lesions may consist primarily of smooth muscle proliferation. However, many plaques also have a thrombus incorporated within their matrix. It is postulated that thrombi are a potent stimulus for smooth muscle cell proliferation, as are cytokines or growth factors released from inflammatory cells. Other stimuli, including such infectious agents as Chlamydia pneumoniae and cytomegalovirus also have been identified as precipitants of atherogenesis.[6]

Plaque accretion and instability can result from disruptions to its various components. For example, a minor disruption might produce a small thrombus that becomes organized and may eventually lyse or, alternatively, be replaced by the vascular repair response. It should be emphasized that vascular repair can produce rapid plaque growth.[1,5] In this regard, serial angiograms performed before and after an episode of UA, without an intervening coronary intervention, have shown progression of CAD in about 75% of patients.[6]

Atherosclerotic plaques may be stable or vulnerable (i.e., prone to rupture). Vulnerable plaques often have a thin fibrous cap, a large lipid core, soft cholesterol ester lipids (rather than free cholesterol monohydrate), and an inflammatory cell infiltrate.[5,7] The arterial lumen may be well preserved at the site of a vulnerable plaque. Cap thickness results from the balance between new collagen production by smooth muscle cells and degradation secondary to inflammatory activity of macrophages.

Plaque Disruption: A number of mechanisms may cause plaque disruption. Plaques rich in extracellular matrix and smooth muscle cells may not necessarily be vulnerable or lipid rich, but they may, nevertheless, simply erode over time.[1] Passive or active forces may dis-

Figure 1. Platelet Adhesion



rupt vulnerable plaques. Propensity to rupture depends on circumferential wall stress or cap "fatigue"; location, size, and consistency of the atheromatous core; and blood flow characteristics, especially the effect of flow on the proximal aspect of the plaques (ie, configuration and angulation of the plaque).[1]

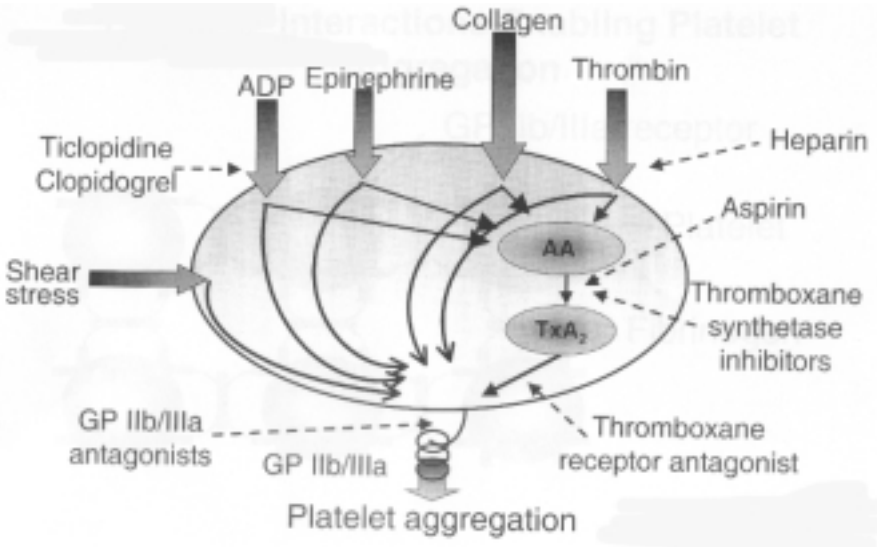
Passive physical forces typically cause disruption at the shoulder of the plaque, between the plaque and the adjacent vessel wall. The cap is weakest at the shoulder because it is thinner and more infiltrated with foam cells. Disruption may be triggered by myriad events, such as emotional stress or physical activity. A surge in sympathetic activity, with an increase in blood pressure, heart rate, force of cardiac contraction, and coronary blood flow, may lead to plaque disruption.[1] Vasospasm due to any cause may compress a plaque, causing rupture. Macrophages may induce active disruption. They degrade extracellular matrix by phagocytosis, and they secrete proteolytic enzymes such as plasminogen activators and matrix metalloproteinases (collagenases, gelatinases, and stromelysins) that may weaken the fibrous cap, predisposing it to rupture.[1]

Thrombosis: Initiated by plaque disruption or injury, thrombosis is a complicated process mediated by thrombin and platelets. The size of the thrombosis, and therefore, the degree of occlusion and clinical outcome, are affected by many factors. Thrombosis size is decreased by minor plaque disruption, high vessel blood flow, and increased fibrinolytic activity. Thrombosis is enhanced by larger plaque disruptions, low blood flow, hypercoagulable (such as increased fibrinogen) or hypofibrinolytic states, and increased platelet reactivity.[1,5,7] Thrombi may be labile, resulting in recurrent episodes of occlusion. Thrombosis may be intramural alone or may occlude the arterial lumen to varying extents.

After a plaque is disrupted, platelets adhere to denuded endothelium and form a monolayer. Platelets adhere via their GP Ia/IIa receptors binding to subendothelial collagen and their GP Ib receptors binding to the von Willebrand factor. (*See Figure 1*) The process of adhesion and thrombin formation both activate the adhered platelets, resulting in the secretion of adenosine diphosphate (ADP), thromboxane A2, and serotonin. These mediators, along with local shear forces, attract and activate other platelets.[1] (*See Figure 2*) Platelet activation includes activation of their GP IIb/IIIa receptors, one of the most densely expressed receptors known. Platelet activation results in a conformational change of the GP IIb/IIIa receptors, increasing their affinity for fibrinogen. Once adjacent platelets have activated GP IIb/IIIa receptors, fibrinogen can bridge between the platelets, and aggregation occurs. (*See Figure 3*) This is the "final common pathway" for platelet aggregation, resulting in a platelet plug at the subendothelial disruption site.

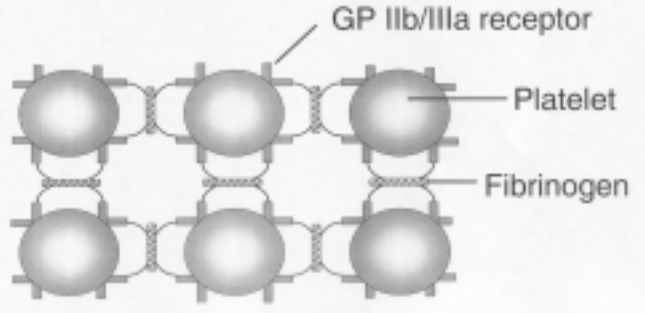
In addition to the aforementioned platelet-related events, plaque disruption also results in the release of tissue factor from foam cells, activating factor VII and the extrinsic coagulation pathway. (*See Figure 4*) Activation of the extrinsic coagulation pathway results in the production of thrombin and fibrin, which stabilize the

Figure 2. Affectors of Platelet Aggregation



AA = arachadonic acid; TxA_2 = Thromboxane A_2; ADP = Adenosine phosphate

Figure 3. Interactions Enabling Platelet Aggregation



platelet plug. Activated factor VII and tissue factor combine to also activate factor IX within the intrinsic pathway, initiating further production of thrombin and fibrin. (*See Figure 4*) In addition to converting fibrinogen to fibrin, thrombin also amplifies the coagulation cascade by activating factors V and VIII and is a powerful platelet agonist.[8]

Coronary artery thrombi vary both in content and location within the vessel and can be described in many ways, including being mural, occlusive, platelet-rich, fibrin-rich, organized, multi-layered, or re-endothelialized.[7] The differences in thrombi content may explain why fibrinolytic drugs benefit patients with MI but fail those with UA. Thrombus formation results in decreased blood flow through the occluded vessel, enabling fibrin to be added to the thrombus, which results in stabilization of the thrombus. The UA thrombi are likely to be relatively newer and smaller; primarily consist of platelets, with little fibrin; and look "white" on coronary angioscopy. Conversely, the thrombi associated with an AMI often are more complicated and evolved. They are more likely to have older thrombin deep within the clot, with loose and recently formed superficial layers, or to have undergone some reabsorption or reorganization. Because the coronary artery usually is occluded totally by thrombus in AMI, there is significant stasis of blood flow.

This stasis permits fibrin and red blood cells to become superimposed on the original platelet-rich thrombus. On angioscopy, the thrombi of AMI appear red because of the trapped red cells and fibrin.[6] Fibrinolytic agents target fibrin within the thrombus. The varied complexity and content of the thrombi associated with AMI likely reflects why normal (TIMI grade III) blood flow is achieved in only 50-60% of patients who receive fibrinolytics.[7] Within a thrombus is a catalytically active thrombin called clot-bound thrombin, which is likely of great importance. Thrombolysis re-exposes "clot-bound thrombin" to the circulation, reinitiating thrombosis by activating both platelets and thrombin. This process may contribute significantly to the vessel reocclusion that occurs after thrombolysis.

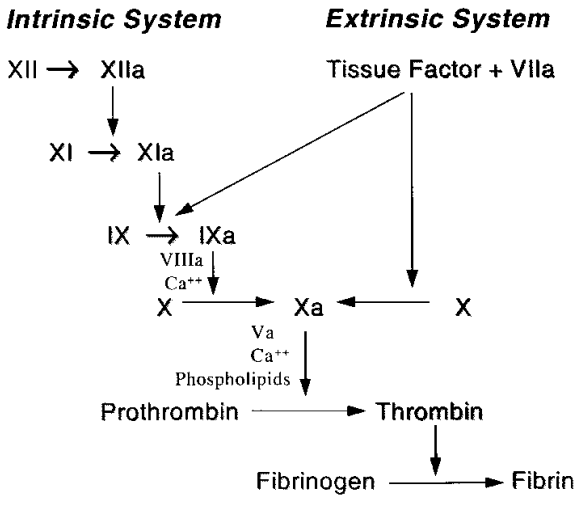
Clinical Presentation

Pathogenesis of CAD is linked to progression of atherosclerosis and, more specifically, to factors precipitating plaque disruption and subsequent thrombosis formation. Symptoms of ischemia, on the other hand, reflect an imbalance between myocardial blood (oxygen) supply and oxygen demand. Accordingly, ischemic coronary pain at rest can result from transient decreases in oxygen supply secondary to 1) thrombus formation; 2) embolization; or 3) transient increases in vasomotor tone producing diminished blood flow to the myocardium.

As principal mediators of ACS, activated platelets release several vasoactive substances that, in the presence of endothelial dysfunction (impaired vasodilation), can result in vasoconstriction near the lesion and a transient decrease in blood flow. Patient symptoms depend on many factors, including the degree of occlusion and the presence of collateral circulation. Plaque disruption, accompanied by isolated mural thrombosis formation, but without clinical symptoms, may be more common than once suspected. Patients with stable CAD may have angina or silent ischemia that results from increases in myocardial oxygen demand that outstrip the ability of a stenosed coronary artery to deliver the required oxygen load.

ACS patients present with variable symptomatology somewhere on the disease continuum that typically results from an abrupt reduction in coronary artery

Figure 4. The Coagulation Cascade



flow secondary to acute thrombosis. UA patients may have small erosions or fissuring on the plaques with small changes in plaque structure or small thromboses. Arterial occlusions, and accordingly, patient symptoms, may be transient if the thrombi are labile. NSTEMI may result from more severe plaque damage and a more persistent thrombotic occlusion. Patients with NSTEMI likely have high rates of spontaneous reperfusion as reflected by the fact that only 25% of this subgroup have complete coronary occlusions on early angiography. STEMI, with transmural necrosis of the involved myocardium, may be attenuated by spontaneous thrombolysis, resolution of vasoconstriction, or the presence of collateral circulation. Acute STEMI most likely results from larger plaque fissures and the formation of fixed and persistent thrombi.[1]

Table 1. Antithrombin and Antiplatelet Agents

ANTITHROMBIN AGENTS
AT III dependent
Heparin
LMWH
Dalteparin (Fragmin)
Enoxaparin (Lovenox)
Nadroparin (Fraxiparine)
AT III independent
Hirudin
Hirulog
ANTIPLATELET AGENTS
Cyclooxygenase inhibitor
Aspirin
GP IIb/IIIa inhibitors
Abciximab (Reopro)
Eptifabitide (Integrilin)
Tirofiban (Aggrastat)
ADP inhibitors
Ticlopidine (Ticlid)
Clopidogrel (Plavix)
Thromboxane synthetase inhibitor
Ridogrel
THROMBOLYTIC AGENTS
Alteplase (t-PA)
Reteplase (r-PA)
Streptokinase
Tenecteplase (TNK-tPA)

Acute Management

Overview: The goals of acute management of ACS are to relieve symptoms; prevent progression of the disease to AMI; minimize loss of myocardial muscle and function; reduce mortality; and treat specific complications of ischemia, such as dysrhythmias or pulmonary edema. Acute pharmacotherapeutic interventions aimed at minimizing or aborting pathogenic processes producing ischemic coronary events usually will require a multi-modal, "cocktail" approach—a polypharmacy strategy that addresses the complex pathogenesis of ACS. Accordingly, multiple agents will be required, each reflecting activity against a distinct precipitant of plaque disruption, thrombosis formation, or coronary vasoconstriction. This will include agents directed at thrombin generation, platelet aggregation, fibrin deposition, and inflammation.

Aspirin, heparin, and increasingly, LMWHs such as enoxaparin, routinely are used in the treatment of these syndromes. The need to target multiple pathogenic end points has stimulated the development of new antithrombotic drugs. Several new agents have been evaluated, particularly for the treatment of ACS. (*See Table 1*) Many trials have been conducted to evaluate these agents, used as monotherapy and in combination. Unfortunately, sorting out these trials and their implications for clinical practice has been difficult because the trial names lead to an "alphabet soup" of confusion, and they have reported on different patient groups evaluated with different protocols. (*See Table 2*) The relationships of some of these trials relative to different treatment modalities are summarized in Figure 5.

Antiplatelet Therapy

Overview: Platelet activation and aggregation involve multiple steps, each of which is a potential target for pharmacotherapeutic inhibition. Another goal of therapy is "passivation," which refers to the conversion of platelets that are already activated, highly reactive, and thrombogenic—to a non-reactive, non-thrombogenic state. Passivation occurs in approximately eight hours in a normal artery; however, an artery with atherosclerotic disease may require days or longer.[7] Aspirin has been the primary antiplatelet agent used in ACS. Other antiplatelet agents include inhibitors of GP IIb/IIIa receptors, ADP, and thromboxane synthetase.

Aspirin: Aspirin is the mainstay of ACS therapy. No other antiplatelet agent has a more impressive risk-benefit ratio and costs so little. Aspirin acts rapidly, achieving platelet inhibition within 1 hour. Aspirin dosages have varied among clinical trials, with 81-325 mg being the usual range. Clinicians should avoid enteric-coated aspirin in the setting of ACS because its onset of action is delayed 3-4 hours. Aspirin permanently inactivates the platelet enzyme cyclooxygenase for the eight- to 10-day

life of the platelet. This results in decreased production of thromboxane A2, which is pro-aggregatory and causes vasoconstriction. However, by blocking thromboxane A2 production at the cyclooxygenase level, prostacyclin (a vasodilator, platelet inhibitor, and protector of gastrointestinal mucosa integrity) synthesis also is inhibited.

The importance of platelet inhibition in MI was confirmed in ISIS-2, in which aspirin produced a 23% reduction in mortality and reduced the rate of hospital reinfarction from 2.9% to 1.9%.[9] Other trials also have demonstrated that aspirin decreases death and MI following UA by 31-50%.[10-12] In patients at high risk for atherosclerotic disease, regular aspirin use reduces eventual nonfatal MI by 30%, nonfatal stroke by 30%, and vascular deaths by 17%.[13]

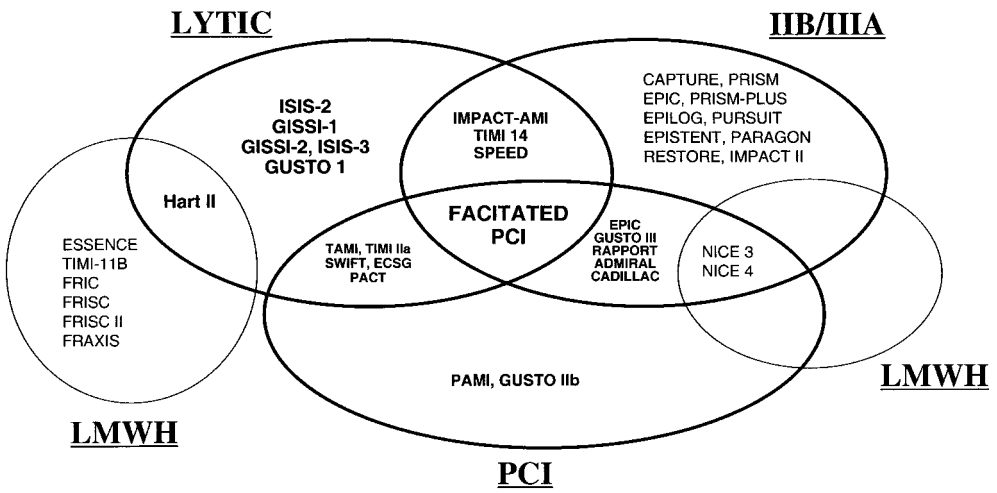
Despite its great benefits, aspirin has its limitations. It is a weak antiplatelet agent and does not inhibit platelet aggregation caused by thromboxane A2-independent pathways (eg, via ADP or collagen stimulation). Aspirin has no effect on thrombin, which likely plays a major role in platelet activation in acute ischemic syndromes. Aspirin also does not inhibit platelet adhesion or suppress platelet secretion of thrombogenic mediators. In addition, there are individual differences in patient response. Finally, aspirin, like most antiplatelet agents, increases the risk of bleeding complications.

Thromboxane Synthetase Inhibitors: Ridogrel selectively inhibits thromboxane synthetase, thereby lim-

Table 2. Abbreviations and Acronyms of Major Trials

ADMIRAL	=	Abciximab before Direct angioplasty and stenting in acute Myocardial Infarction Regarding Acute and Long-term follow-up
ASSENT	=	ASsessment of the Safety and Efficacy of a New Thrombolytic agent
ASSET	=	Anglo-Scandinavian Study of Early Thrombolysis
CADILLAC	=	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPTURE	=	C7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment
ECSG	=	European Cooperative Study Group
EPIC	=	Evaluation of c7E3 for Prevention of Ischemic Complications
EPILOG	=	Evaluation in PTCA to Improve Long-term Outcome by GP IIb/IIIa receptor blockade
EPISTENT	=	Evaluation of Platelet Inhibition in STENTing
ESSENCE	=	Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
FRAXIS	=	FRAXiparin in Ischemic Syndromes
FRIC	=	FRagmin In Coronary artery disease
FRISC	=	FRagmin during InStability in Coronary artery disease
GISSI	=	Gruppo Italiano per lo Studio della Streptochinasi nell' Infarcto miocardico
GUSTO	=	Global Utilization of Streptokinase and T-PA in Occluded arteries
HART	=	Hypertension Audit of Risk factor Therapy
IMPACT	=	Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis
NICE	=	National Investigators Collaborating on Enoxaparin
PACT	=	Plasminogen activator and Angioplasty Compatibility Trial
PAMI	=	Primary Angioplasty in Myocardial Infarction
PARADIGM	=	Platelet Aggregation Receptor Antagonist Dose Investigation for reperfusion Gain in Myocardial infarction
PARAGON	=	Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in the Global Organization Network
PRISM	=	Platelet Receptor Inhibition in ischemic Syndrome Management
PRISM PLUS	=	PRISM in Patients Limited by Unstable Signs
PURSUIT	=	Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
RAPPORT	=	Reopro And Primary PTCA Organization and Randomized Trial
RESTORE	=	Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis
SPEED	=	Strategies to Promote Early reperfusion in the Emergency Department
SWIFT	=	Should We Intervene Following Thrombolysis
TAMI	=	Thrombolysis and Angioplasty in Myocardial Infarction
TIMI	=	Thrombolysis In Myocardial Infarction
VANQWISH	=	Veterans Affairs Non-Q Wave Infarction Strategies in Hospital

Figure 5. Triple Pharmacotherapy for Acute Myocardial Infarction*



* = With various combinations of thrombolytic agents (LYTIC), low molecular weight heparins (LMWH), platelet glycoprotein IIb/IIIa inhibitors (IIB/IIIA), and percutaneous coronary intervention (PCI).

iting thromboxane production without affecting prostacyclin. Since inhibition of prostacylin synthesis has the potential to promote thrombogenesis, these more selective agents should, in theory, be more effective than aspirin. The effectiveness of ridogrel and aspirin for ACS were compared in the Ridogrel vs. Aspirin Patency Trial (RAPT).[14] All patients received streptokinase. The primary end point was arterial patency between seven and 14 days and secondary end points were clinical markers of reperfusion and safety. No differences in efficacy or safety were observed.[14]

Adenosine Diphosphate Inhibitors: ADP is secreted by activated platelets and stimulates additional platelet activation and aggregation via the platelet P2T cell surface receptor. Ticlopidine (Ticlid) and clopidogrel (Plavix) are structurally similar to P2T antagonists. These agents selectively and irreversibly inhibit ADP binding to the P2T cell surface receptor, stopping platelet activation via this route. However, they also interfere with a specific ADP-dependent step of GP IIb/IIIa complex activation, resulting in less platelet aggregation and, ultimately, less thrombus formation.[4] As a result, these agents provide broader inhibition of platelet aggregation than aspirin because they not only limit ADP-receptor stimulated aggregation but also aggregation triggered by a number of other stimuli. However, they are similar to aspirin in that their effect on platelet aggregation is incomplete and aggregation still occurs.[4]

The first ADP antagonist introduced, ticlopidine, has been shown to be better than placebo for reducing the risk of stroke, AMI, and vascular death in patients with atherosclerotic disease.[13] It is comparable to aspirin for reducing risk of stroke, MI, and vascular death.[13]

The Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial involved 19,185 patients in a randomized, double-blinded assessment of safety and efficacy.[15] Patients with ischemic stroke, AMI, or symptomatic atherosclerotic peripheral arterial disease were randomly assigned to receive aspirin or clopidogrel for 1-3 years. The combined end point of ischemic stroke, AMI, or vascular death occurred in 5.3% of the clopidogrel patients and in 5.8% of aspirin-treated cohort, a relative risk reduction of 8.7% (P = .043) in favor of the clopidogrel group.

Patients with peripheral arterial disease had particularly good benefit. Aspirin was associated with significantly more gastrointestinal hemorrhage, while clopidogrel caused significantly more rash. Severe neutropenia occurred in 0.1% of both treatment groups.[15] The CAPRIE trial suggested that clopidogrel is at least as effective as aspirin, if not more effective, for the secondary prevention of ischemic events. However, the efficacy of ADP-inhibitors for ACS is inferior to that of aspirin. Accordingly, clopidogrel should be used as a second-line agent for antiplatelet therapy, particularly in patients unable to tolerate aspirin therapy.

Thromboxane A2 receptor antagonists have numerous limitations. Compared to aspirin, these agents are relatively costly at $1 to $3 per tablet.[16] Moreover, ticlopidine requires 3-5 days for onset of action and, therefore, is not useful for ACS. Clopidogrel's onset is 2 hours, still slower than the 30-60 minute onset for aspirin. Complications with ticlopidine include diarrhea, pruritis, urticaria, and skin rash. Hepatocellular enzyme elevation occurs in as many as 8% of patients. Most significant are the hematologic side effects, particularly neutropenia. An absolute neutrophil count (ANC) of fewer than 1200

occurs in 2.4% of patients and an ANC of fewer than 450 in 0.8% of patients. While the neutropenia typically occurs between 3 weeks and 3 months after initiation of therapy, it may occur later and its onset may be sudden. Thrombocytopenia may occur and can present like immune thrombocytopenia or thrombotic thrombocytopenic purpura (TTP). Clopidogrel's side effect profile is safer and comparable to that of aspirin. Abdominal discomfort and rash each occur in approximately 4% of patients, while hematologic complications are rare.[16]

Glycoprotein IIB/IIIA Inhibitors: Pharmacology, Actions, and Side Effects

Overview: Many substances can activate platelet aggregation, especially GP IIb/IIIa receptors, which mediate the obligatory last step, or final common pathway, for platelet aggregation. GP IIb/IIIa receptors are platelet-specific, and there are approximately 50,000 per platelet.[17,18] Platelet activation causes these receptors to become activated and exteriorized, and to undergo a conformational change. The GP IIb/IIIa receptor is a functional receptor for such adhesive macromolecules as fibrinogen, fibronectin, vitronectin, and vWF. Each of these molecules can interact with multiple platelets via GP IIb/IIIa receptors.

Molecules that interact with GP IIb/IIIa receptors contain the arginine-glycine-aspartic acid (RGD) sequence, which serves as the minimal recognition sequence for the receptor. Fibrinogen contains this RGD sequence on each of its a-chains, as well as a dodecapeptide on its g-chain that also is capable of binding to the receptor. However, whereas the RGD

Table 3. Comparison of Parenteral GP IIb/IIIa Inhibitors

AGENT		ABCIXIMAB (REOPRO)	EPTIFIBATIDE (INTEGRILIN)	TIROFIBAN (AGGRASTAT)
Size		Large (~ 48 kDal)	Small (< 1 kDal)	Small (< 1 kDal)
Binding		High affinity	Competitive	Competitive
Clearance		Splenic and renal	Renal	Renal
Drug to receptor ratio		1.5-2.0	250-2500	> 250
Mechanism		Monoclonal antibody	Peptide inhibitor	Nonpeptide inhibitor
Antibody response		Yes	No	No
Binding to related integrins		Yes	No	No
Plasma T½ (mins)		10	150	120
Biologic[1] T½ (hours)		12-24	~ 2.5	~ 2
Indications (per the FDA)		PCI or refractory angina when PCI is planned within 24 hr	ACS (UA and non-Q MI) with or without PCI	ACS (UA and non-Q MI) with or without PCI
FDA approved dose	PCI	0.25 mg/kg bolus before PCI; 0.125 mcg/kg/min (max, 10 mcg/min) infustion × 12 hr after PCI	135 mcg/kg bolus, 0.5 mcg/kg/min infusion for 20-24 hr (IMPACT II dose)[3]	0.4 mcg/kg/min × 30 min, then 0.1 mcg/hg/min × 48-108 hr
	UA	0.25 mg/kg bolus and then 10 mcg/min infusion × 18-24 hrs. before PCI, continued 1 hr after PCI[2]	180 mcg/kg bolus, 2.0 mcg/kg/min infusion × 72-96 hr (PURSUIT dose)	

UA = unstable angina; NQMI = non-Q wave myocardial infarction; PCI = procedural coronary intervention; T½ = half-life

[1] Is the platelet-bound half-life

[2] This approval is for patients who are not responding to conventional medical therapy when PCI is planned within 24 hours.

[3] FDA approved dose may not be optimal. The larger dose of eptifibatide used in the PURSUIT trial is recommended for use in the setting of PCI.

sequence is recognized by many other integrin receptors, the dodecapeptide is specific for fibrinogen binding to platelets. During clot formation, activated platelets, with active GP IIb/IIIa receptors, recognize the RGD sequence in fibrinogen. Platelets and fibrinogen bind, initiating platelet aggregation, resulting in a

Table 4. Trials Using GP IIb/IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes with Mandated PCI‡

TRIAL	EPIC	EPILOG	EPISTENT	CAPTURE	IMPACT II	RESTORE
Agent	Abciximab	Abciximab	Abciximab	Abciximab	Eptifibatide	Tirofiban
Entry Criteria	Elective to emergent: MI w/i 12 hrs requiring rescue, early post-MI angina, UA w/i 24 hrs, or vessels at high risk for closure	Elective or urgent PCI pts w/ a stenosis of ≥ 60% (Not pts with acute ischemia)	Elective or urgent PCI pts w/ a stenosis of ≥ 60% (Not pts with acute ischemia)	Refractory UA defined as: CP + EKG Δ on admission, then more CP *or* EKG Δ despite medical Rx	Elective, urgent, or emergent PCI pts	Pts undergoing PCI w/i 72 hrs of presentation w/ UA, NQMI, or MI with ST ↑
Patient Number	2099	2792	2399	1265	4010	2141
Primary End Point	Death, MI, CABG, repeat emergent PCI, *or* stenting at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* any revasc (CABG or PCI) at 30 d
Drug Dosing	Abcix bolus (0.25 mg/kg) and inf (10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (0.125 mcg/kg/min to max of 10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (0.125 mcg/kg/min to max of 10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (10 mcg/min)	Eptif 135 mcg/kg bolus, then inf at: LD: 0.5 mcg/kg/min HD: 0.75 mcg/kg/min	Tirofiban bolus (10 mcg/kg) and inf (0.15 mcg/kg/min)
Drug Duration	12 hrs (started w/i 1 hr of PCI)	12 hrs (started w/i 1 hr of PCI)	12 hrs (started w/i 1 hr of PCI)	18-24 hrs *before* PCI then 1 hr after PCI	20-24 hrs beginning after access established	36 hrs after angioplasty guidewire was across the lesion
Vase Sheaths	Removed 6 hrs after end of inf	Early removal and meticulous wound care	Early removal and meticulous wound care	Removed 4-6 hrs after end of inf. Meticulous site care.	Removed 4-6 hrs after end of PCI	Early removal
Randomized Groups	Three Arms: Abcix bolus + abcix inf; Abcix bolus + placebo inf; Placebo bolus + placebo inf	Three Arms: Placebo + stand UFH; Abcix + stand UFH; Abcix + LD UFH	Three Arms: ST + placebo; ST + abcix; Angio + abcix	All with early angiography and had culprit lesions. Then, two arms: Abcix bolus + abcix inf; Placebo bolus + placebo inf. Then, PCI performed	Three Arms: LD Ept infusion; HD Ept infusion; Placebo bolus + placebo inf	Two Arms: Tiro bolus + tiro inf; Placebo bolus + placebo inf
1° End Point (30 d)						
IIb/IIIa	8.3*[3]	5.3* (Both abcix groups)		11.3*	LD: 9.2, HD: 9.9	10.3, 8.0[3]
Placebo	12.8	11.7		15.9	11.4	12.2, 10.5[5]
2° End Point (6 m)[2]						
IIb/IIIa	27.0*	22.8 (stand); 22.3* (LD)		31	LD: 10.5, HD: 10.1	
Placebo	35.1	25.8		30.8	11.6	
1° End Point (30 d)[1]						
ST + Placebo			10.8			
ST + IIb/IIIa			5.3*			
Angio + IIb/IIIa			6.9*			
Major/Intermediate Bleeding[4]						
IIb/IIIa	14*	3.5 (stand); 2.0 (LD)	1.5 (ST + angio groups)	3.8*	LD: 5.1, HD: 5.2	2.4
Placebo	7	3.1	2.2	1.9	4.8	2.1

Key: PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting; CABG, coronary artery bypass grafting; MI, myocardial infarction; Abcix, abciximab; Ept, eptifibatide; Tiro, tirofiban; inf, infusion; LD, low-dose; HD, high-dose; pts, patients; Angio, angioplasty; ST, stent; Vasc, vascular; Rx, treatment; UFH, unfractionated heparin; d, day(s); m, months; w, with; w/i, within; hrs, hours.

‡ All patients in the trials received aspirin and heparin.

* $P < 0.05$

1 Death, MI, or urgent revascularization.

2 Death, MI, or any revascularization (except IMPACT II which was only death or MI).

3 Data for abciximab bolus plus infusion group. The abciximab bolus only group was not different from placebo.

4 Major bleeding defined by TIMI criteria for all reported trial results.

5 These numbers reflect the combined end point when only emergent or urgent PTCA was considered ($P = 0.052$).

hemostatic plug.[17,18] (*See Figure 3.*)

Virtually all platelet aggregation can be stopped by inhibition of 80% of the GP IIb/IIIa receptors.[19] GP IIb/IIIa receptor antagonists—all of which contain the RGD sequence—include abciximab (ReoPro), tirofiban (Aggrastat), eptifibatide (Integrilin), and lamifiban. The first 3 have received FDA approval, while lamifiban has been used in Canada.

The GP IIb/IIIa receptor is an excellent target for inhibition of platelet aggregation because it is specific for platelets and it is the "final common pathway" for platelet aggregation, regardless of the specific mechanism responsible for platelet activation.[20] However, inhibition of the GP IIb/IIIa receptor does not abolish other platelet functions such as adhesion, activation, or secretion. These agents also do not block thrombin generation occuring on the surface of activated platelets. Consequently, IIb/IIIa antagonists may work best in combination with agents that block thrombin generation. They also do not affect tissue factor induced coagulation, and

Table 5.Trials Using GP IIb/IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes (PCI Not Mandated)‡

TRIAL	PARAGON	PURSUIT	PRISM	PRISM-PLUS
Agent	Lamifiban	Eptifibatide	Tirofiban	Tirofiban
Entry criteria	CP w/i 12 hrs + EKG Δ Δ (ST temp ↑ or ↓ or T ↓)	CP w/i 24 hrs + [EKG Δ (ST temp ↑ or ↓ or T ↓) *or* enzyme ↑]	CP w/i 24 hrs + [EKG Δ (ST temp ↑ or ↓ or T ↓) *or* enzyme ↑ *or* evidence prior CAD]	CP w/i 12 hrs + [EKG (ST or T ↓) or enzyme ↑]
Patients				
Number	2282	10948	3232	1915
EKG Δ (%)	100	92	75	90
Enzyme ↑ (%)	36	45	25	45
Revascularized	25	38	38	54
Primary end point	Death *or* nonfatal MI at 30 d	Death *or* nonfatal MI at 30 d	Death, MI, *or* refractory ischemia at 48 hrs	Death, MI, *or* refractory ischemia at 7 d[4]
Drug therapy	3-5 d[2]	≤ 72 hrs[2]	48 hrs	48 hrs[2]
Randomized groups	Five arms: Placebo Lam (LD or HD) (w/ or w/o UFH)	Three arms: Placebo HD or LD Ept (UFH)[3]	Two arms: Tiro UFH	Three arms: Tiro[5] UFH Tiro + UFH
Invasive procedures[1] hours	Discourages × 48 hours	Physician discretion	Discouraged during 48 hour infusion	Discouraged during 48 hour infusion; Encouraged 48-96
Outcome (primary end point) (%)	30 d: No difference 6 m: LD Lam ± UFH 13.7* Placebo 17.9	30 d: HD Ept 14.2* Placebo 15.7 (No difference between groups in those with only medical Rx)	2 d: Tiro 3.8 UFH 5.6 30 d: Tiro 15.9 UFH 17.1	7 d: Tiro + UFH 12.9 UFH 17.9 30 d: Tiro + UFH 18.5* UFH 22.3 6m: Tiro + UFH 27.7* UFH 32.1
Major/intermediate bleeding (%)	UFH 5.9* Lam 7.8 UFH + Lam 10.5	Ept 10.6 Placebo 9.1*	Tiro 0.4 Heparin 0.4	Tiro + UFH 4 UFH 3

Key: PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting; CP, chest pain; MI, myocardial infarction; CAD, coronary artery disease; LD, low-dose; HD, high-dose; w/, with; w/o, without; w/i, within; UFH, unfractionated heparin; Ept, eptifibatide; Lam, Lamifiban; Tiro, Tirofiban; hrs, hours; d, day(s); m, months; temp, temporary; Rx, treatment.

‡ All trials included aspirin for all patients and all contained patients with non-Q-MI. Some trials permitted patients who had temporary ST-segment elevation. PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting.

* $P < 0.05$

1 Includes diagnostic catheterization, PCI, CABG.

2 If intervention was performed at end of drug therapy, the study drug could be infused for an additional 24 hours (PURSUIT), 48 hours (PRISM PLUS), or 12-24 hours (PARAGON) after the procedure.

3 Heparin was optional.

4 The 30-day and 6-month end points also included rehospitalization.

5 Tirofiban alone arm dropped early in study because of increased adverse effects.

they do not prevent inflammation.[17,20]

From a clinical and pathophysiological perspective, early use of GP IIb/IIIa inhibitors (*see Table 3.*) prevents disrupted coronary arterial surfaces from supporting platelet deposition. This clinically advantageous event has been termed passivation. Heightened platelet activity associated with ACS is known to be associated with abrupt closure after angioplasty and coronary reocclusion after thrombolysis. Passivation may include limiting production of platelet-derived vasoconstrictors in the short term and growth factors in the long term. Decreased platelet aggregation may enable arterial surfaces to heal more favorably, reducing the likelihood of (re)infarction.[21]

Abciximab: Pharmacology and Antiplatelet Effects. Abciximab is a recombinant monoclonal antibody fragment (Fab) that blocks IIb/IIIa receptors. It has a high affinity for the GP IIb/IIIa receptor and, consequently, binds rapidly and irreversibly to platelets. Because of its large size, the unbound plasma fraction is rapidly cleared by the reticuloendothelial system. The rapid binding and clearance of abciximab results in a very short serum half-life and, therefore, it must be given as a continuous intravenous infusion. Maximum receptor blockade and inhibition of aggregation occurs two hours after a bolus injection and returns toward normal within 12 hours. However, because of its high affinity for the receptor, it has a long biologic half-life and aggregation may return toward baseline as late as 12-36 hours after discontinuation of the infusion.[20]

Abciximab undergoes gradual redistribution after administration, with antibody redistributing to newly produced platelets, prolonging the antihemostatic effect.[4] GP IIb/IIIa receptor occupancy by abciximab exceeds 30% at eight days and 10% at 15 days, and it has been found on receptors as far out as 21 days.[19,20] Recovery in platelet aggregability is gradual and smoothly transitioned after abciximab therapy. It is relatively rapid after tirofiban or eptifibatide discontinuation. The gradual tapering of antiplatelet effect theoretically could attenuate the propensity for rebound.

The pharmacology of abciximab could result in less of it being available to bind additional GP IIb/IIIa receptors expressed on platelet surfaces from the alpha granule storage pool. This may explain the erosion in the magnitude and the dispersion in consistency of platelet inhibition during a continuous 12-hour infusion of abciximab. Indeed, although greater than 95% of patients will exhibit more than 80% GP IIb/IIIa receptor inhibition after the bolus dose of abciximab, approximately 15% will be less than 80% inhibited at 8-10 hours into the continuous infusion.[20] However, despite this loss of receptor inhibition over time, the clinical benefit of adjunctive abciximab therapy during PCI is quite robust. This suggests that the benefit of abciximab might not be solely explained by the degree of GP IIb/IIIa platelet inhibition, but also may be related to other differences in pharmacodynamics such as the gradual redistribution or the nonspecific receptor affinity.

Abciximab is not very specific because it inhibits the GP IIb/IIIa receptor simply because of its size. In fact, it not only inhibits the b3 chain of the GP IIb/IIIa receptor, but also the receptor avb3 (vitronectin) and the leukocyte receptor MAC-1. The vitronectin receptor is found not only on platelets, but also on smooth muscle cells, endothelial cells (including those that overlie an atherosclerotic plaque) monocytes, and polymorphonuclear leukocyctes.[20,22] Of special interest, the vitronectin receptors on smooth muscle cells have been associated with an intimal hyperplasia response that follows vascular injury, including that associated with PCI.

As a result, it has been proposed that the vitronectin receptor may contribute to restenosis,[20] although it is uncertain whether inhibition of vitronectin contributes to the effectiveness of abciximab in humans. Animal studies demonstrate that vitronectin receptor inhibition can prevent intimal hyperplasia and the late vessel lumen loss after balloon angioplasty or stenting.[20] In laboratory animals, vitronectin blockade attenuates injury-induced smooth muscle migration and neointimal hyperplasia. Vitronectin receptors upregulate upon activation of smooth muscle and endothelial cells. These receptors may affect cell attachment, proliferation, migration, and survival; therefore, they may affect intimal hyperplasia and angiogenesis. These effects may play a role in new plaque formation and restenosis.[22]

Vitronectin receptors on activated platelets also have been implicated in both platelet adhesion to osteopontin (which is present in atherosclerotic plaques) and platelet-mediated thrombin generation. As a result, dual receptor blockade (GP IIb/IIIa and vitronectin) has been demonstrated to provide more potent inhibition of platelet-supported thrombin generation than monoreceptor blockade by specific monoclonal antibodies or after blockade by eptifibatide or tirofiban in combination with heparin.[20]

Abciximab also binds and inhibits the leukocyte MAC-1 (amb3) receptor, recognizing the am subunit. Activation of this receptor increases the intensity of interactions among white blood cells (WBCs) and platelets, thereby accelerating the inflammatory response to vessel injury. Following stent deployment, adhesion of WBCs is significantly reduced by abciximab, as is leukocyte accumulation in balloon-damaged

blood vessels. These inflammation-reducing effects may decrease the restenosis rate in patients undergoing PCI.[20,22]

Tirofiban and Eptifibatide: Pharmacology and Antiplatelet Effects. Other GP IIb/IIIa receptor inhibitors, eptifibatide and tirofiban, are peptide and nonpeptide agents, respectively. Unlike abciximab, they are small molecules that competitively, and specifically, inhibit the RGD sequence of the GP IIb/IIIa receptor. They do not affect other receptors such as vitronectin. Because the GP IIb/IIIa receptor affinity of these agents is lower than that of abciximab, they have a short duration of action at the platelet target receptor, a short biologic half-life, and their antiplatelet effect is readily reversible. They dissociate from the receptors within seconds (vs hours for abciximab). They also undergo slow hepatic and renal clearance. Because of their low affinity and their slow clearance, they have a relatively long plasma half-life.[20,22]

In vitro experiments have shown that tirofiban and eptifibatide, but not abciximab, enhance leukocyte-platelet aggregation in whole blood. Because leukocyte-platelet interactions affect atherogenesis, restenosis, and reperfusion injury, these agents may elicit a potentially deleterious cellular response despite their ability to inhibit platelet aggregation.[22] Eptifibatide is derived from the venom of the Southeastern pygmy rattlesnake while tirofiban is obtained from the venom of an African saw-scaled viper. Receptor inhibition is achieved within 15 minutes for eptifibatide and 5 minutes for tirofiban. Once the infusion is stopped, platelet aggregation function returns toward baseline within 30 minutes to 4 hours, much more rapidly than is the case with abciximab.[19] As expected, these agents require much larger molar concentrations (drug-to-receptor dose) to maintain receptor blockade than does abciximab.[18]

Oral agents in the GP IIb/IIIa inhibitor class also are being developed, among them xemilofiban, orbofiban, and sibrafiban. The clinical focus of these agents has been long-term therapy for the secondary prevention of ACS. Unfortunately, thus far, phase III trials have not demonstrated clinically significant efficacy; as a result, they have no role in the management of ischemic syndromes.[3]

Complications and Adverse Effects: The most important complications associated with GP IIb/IIIa inhibitors are bleeding, thrombocytopenia, and reactions to readministration. Abciximab is designated as a Pregnancy Class C agent while eptifibatide and tirofiban are designated as Class B agents.

Major bleeding was doubled in patients receiving GP IIb/IIIa inhibitors in the EPIC and CAPTURE trials. However, vascular sheaths were left in for hours after the trial drug infusions were stopped, venous access site management was not optimal, and weight-based heparin dosing was not used. Subsequent trials that corrected for the aforementioned problems demonstrated major bleeding rates comparable to placebo, ranging from 0.4-7.8%. Mild bleeding generally is slightly more common with the use of GP IIb/IIIa inhibitors.[23]

Prompt reversal of the effects of GP IIb/IIIa inhibitors may be required in patients who develop a bleeding diathesis and in those individuals who require immediate coronary artery bypass graft (CABG) surgery.[24] Eptifibatide and tirofiban have short biologic, but long plasma half-lives; they are cleared by the kidney. Normal hemostasis should return within hours of stopping an infusion of these agents if renal function is good. Hemodialysis may reverse the hemostasis defect, although this has not been tested. Platelet transfusion is of no benefit because the number of drug molecules overwhelms the number of GP IIb/IIIa receptors. Conversely, abciximab's long biologic and short plasma half-life results in slow elimination. Platelet transfusions may reverse the hemostatic defect despite the redistribution of drug onto the new platelets. This is because there are relatively few abciximab molecules and their effects will be diluted by the large number of new platelets that are introduced.[24]

In the GP IIb/IIIa trials, mild thrombocytopenia (< 100,000 platelets/mm^3) occurred in approximately 5% of patients while moderate thrombocytopenia (< 50,000 platelets/mm^3) occurred in 2% of the abciximab patients and in less than 1% of the eptifibatide and tirofiban patients. Severe thrombocytopenia (< 20,000 platelets/mm^3) rarely occurred with eptifibatide or tirofiban, but it did affect 0.7% of patients receiving abciximab. It has been proposed that abciximab is more likely to cause thrombocytopenia because it may have a complex interaction with heparin, leading to thrombocytopenia.[24]

The chimeric antibody fragments of abciximab are immunogenic. Low titers of antichimeric antibody develop in approximately 6-7% of patients receiving abciximab.[4,24] Titers peak 1 week to 1 month after administration and then gradually decline. Immunoglobulin G antibodies do not interfere with efficacy and are not associated with anaphylactic reactions. The significance of the antibody is unclear. Readministration of abciximab is not associated with an increased risk of anaphylaxis or altered benefit. However, severe thrombocytopenia has occurred in 2.4% of patients upon readministration of abciximab.[24]

Cost: Despite significant acquisition costs, GP IIb/IIIa inhibitors may be cost-effective by reducing the

need for revascularization and/or hospital stay. Economic analyses are just being released. The acquisition costs for 24-72 hour infusions of these medications range from $1260 to $2160. Abciximab costs approximately $1400 per patient for a standard 12-hour infusion. The infusion time for eptifibatide and tirofiban is variable and cost varies according to infusion time. Many trials have used 48- to 96-hour infusions, and the procurement cost is more than $1000 for these agents.[25]

Investigators have performed pharmacoeconomic analyses of GP IIb/IIIa inhibitors used in various PCI and ACS trials. In the PCI setting, the cost savings are secondary to reduced cardiac events with abciximab and tirofiban and partially offset drug acquisition costs. In general, it was concluded that only the very high-risk patients (elevated cardiac markers, persistent angina, etc.) have cost-effectiveness ratios that would be considered acceptable.[25]

GP IIb/IIIa Inhibitor Trials of Unstable Angina or NSTEMI With Mandated Procedural Coronary Intervention

The role of GP IIb/IIIa inhibitors in the setting of PCI has been established by 7 randomized, blinded, placebo-controlled trials involving a total of approximately 15,000 patients. The 6 larger trials are summarized in Table 4. All patients in these trials received aspirin and heparin. Except for CAPTURE, all trials administered the study drug or placebo as a bolus immediately before PCI, followed by infusions of variable durations. The rapidly reversible, small molecules, eptifibatide and tirofiban, were infused for 24 hours or 36 hours, respectively. Conversely, the slowly reversible abciximab was infused for only 12 hours. In the CAPTURE trial, the study drug was infused for 20-24 hours before angioplasty and 1 hour after. In EPISTENT, patients received ticlopidine for 4 weeks after stenting, according to standard practice for stent implantation.

EPIC Trial: The EPIC trial was the first major study evaluating the effectiveness and safety of a GP IIb/IIIa inhibitor. Its design was based on the concept that platelet aggregation may be triggered by revascularization procedures inasmuch as reocclusion is common following percutaneous transluminal coronary angioplasty (PTCA). The purpose of the EPIC trial was to determine if abciximab could reduce reocclusion following PTCA.[26] It included 2099 patients at high risk for vessel closure (UA, unfavorable coronary artery lesion morphology, AMI within 12 hours that needed rescue percutaneous intervention, or early postinfarction angina). Many of these patients did not have acute coronary ischemia. Patients were randomized to one of three treatment arms: 1) abciximab bolus without infusion; 2) abciximab bolus plus infusion; or 3) placebo bolus plus placebo infusion. Study drugs were initiated just prior to PCI and administered for 12 hours after the procedure. The primary end point was the composite of death, AMI, or need for revascularization at 30 days.

The absolute reduction (4.5%) in the composite end point by abciximab bolus plus infusion was significant compared to placebo.[26] The reduction in the composite end point was still evident at 6 months and at 3 years.[26,27] It should be noted that in the EPIC study, a doubling of major hemorrhage was observed with abciximab, primarily during CABG surgery or at the femoral puncture site. There was no difference in intracranial hemorrhage. Bleeding was more severe in patients who received relatively more of the fixed heparin dose. It was felt that bleeding resulted from the lack of weight-based heparin dosing, inadequate venous access care, and leaving the access sheath in place for several hours after the infusion had been completed.

EPILOG Trial: The purpose of the EPILOG trial was to see whether the efficacy of abciximab could be maintained while reducing the rate of major bleeding complications as compared to the results of EPIC.[28] To decrease hemorrhage, patients received weight-based heparin, meticulous access site care, and early sheath removal. Patients were less ill than in the EPIC trial because it was felt that the benefit of abciximab in those with more acute ischemic syndromes had already been demonstrated. As with EPIC, both elective and urgent PCIs were studied. Patients received one of the following three regimens: 1) placebo plus standard-dose heparin (100 units per kilogram with a maximum of 10,000 units); 2) abciximab with standard-dose heparin; or 3) abciximab plus low-dose heparin (70 units per kilogram with a maximum of 7000 units). Study drugs were started just before the PCI and infused for 12 hours after the procedure. The composite end point included death, AMI, and need for urgent revascularization.

The trial was suspended after enrolling only 2792 of the planned 4800 patients because both clinically significant superiority was demonstrated in both abciximab treatment arms. There was a significant reduction of the composite end point at both 30 days and 6 months. (*See Table 4.*) Of special clinical significance was the finding that major bleeding was comparable between the placebo group and both of the abciximab groups.[28]

EPISTENT Trial: The EPISTENT trial was performed to determine whether GP IIb/IIIa inhibitors would be beneficial in patients receiving intracoronary

stents (metal scaffolding devices inserted angiograpgically in vessel lumens).[29] Patients in the EPISTENT trial were similar to those in EPILOG (ie, they were not having an acute ischemic event, but were about to receive elective or urgent PCI).

In this trial, 2399 patients were randomized to receive one of the following three PCIs and pharmacotherapeutic agents: 1) stent plus placebo; 2) stent plus abciximab, or 3) angioplasty plus abciximab. The primary end point was death, AMI, or the need for urgent revascularization within the first 30 days. All patients also received ticlopidine for 4 weeks after stenting, according to contemporary post-interventional practice. The groups receiving abciximab reached the composite, morbid end point in significantly fewer patients (*see Table 4*) without a significant increase in major bleeding.[29]

CAPTURE Trial: The CAPTURE trial was unique among the abciximab trials for several reasons.[30] First, unlike other abciximab evaluations, all patients in CAPTURE presented with active UA within the previous 72 hours. This study assessed the effect of 18-24 hours of medical stabilization with abciximab prior to PTCA. Abciximab was given before PCI and continued for only one hour after the procedure was completed. All patients underwent angiography upon presentation and had significant CAD with a "culprit" lesion deemed suitable for angioplasty. However, angioplasty was not done at the time of the original angiography. Patients were randomized within 24 hours of angiography to receive placebo or abciximab during the 18-24 hours before angioplasty was performed and for 1 hour after the procedure. The primary end point was a composite of death due to any cause, AMI, or need for urgent revascularization at 30 days.

The end points were significantly improved in the abciximab group at 30 days, but the difference was not maintained at 6 months.[30] (*See Table 4.*) The decreased long-term efficacy in comparison to the EPIC trial may have resulted from the lack of post-procedural abciximab infusion. During the 18-24 hour infusion of drug prior to PCI, those who received abciximab had 67% fewer patients progress to AMI than did patients receiving placebo (2.1% vs 0.6%; $P = .029$). In comparison to placebo, major bleeding occurred twice as often in the abciximab group. (*See Table 4.*) However, major bleeding was less common in the CAPTURE trial than in the EPIC trial. This may have resulted from using a lower heparin dose and more meticulous access site care than that reported in the EPIC trial. Bleeding may have been reduced further in the CAPTURE trial by removing the sheath early. The authors recommended that the heparin dose be restricted to 70 IU/kg during PTCA.[30]

IMPACT-II Trial. The IMPACT-II trial assessed the role of eptifibatide in 4010 patients undergoing elective, urgent, or emergent PCI.[31] The trial included three arms: 1) bolus plus high-dose infusion; 2) bolus plus low-dose infusion; and 3) placebo. The primary end point was the composite of death, AMI, or need for urgent revascularization within the first 30 days. Although there was a significant reduction in coronary events at the end of the 24-hour infusion in the eptifibatide groups, there were no significant differences at 30 days.[31] (*See Table 4.*) The authors suggest that the lack of efficacy may have resulted from inadequate eptifibatide dosing or insufficient duration of infusion. There are, in fact, data suggesting that the dose may have achieved only 30-50% of platelet inhibition vs. the 80% required.[31]

RESTORE Trial: The RESTORE trial assessed the role of tirofiban in 2141 patients with ACS of 72 hours duration or less.[32] (*See Table 4.*) Patients were randomized to receive tirofiban or placebo for 36 hours after PCI. The primary end point was the composite of death, AMI, or need for urgent revascularization in the first 30 days. There was a significant reduction in coronary events at 2 and 7 days, but no significant difference at 30 days.[32] (*See Table 4.*) Major hemorrhage was comparable between groups. The authors indicated that the lack of efficacy at 30 days, as compared to abciximab in EPIC, may have resulted from different end point definitions between the trials. The composite end point in the EPIC trial included only emergency revascularization procedures, whereas the RESTORE trial considered all revascularizations ascribed to ischemia during the 30-day post-infusion period.[32]

GP IIb/IIIa Inhibitor Trials of Unstable Angina or Non-Q wave MI with Procedural Coronary Intervention not Mandated

The data for GP IIb/IIIa inhibitors in patients without PCI also suggest some possible advantages for one agent vs. another. The following trials (also know as the "Four Ps") targeted patients with ACS who did not have permanent ST-segment elevation. (*See Table 5.*) The objective of these investigations was to assess the role of the GP IIb/IIIa inhibitors in high-risk patients who were not necessarily going to have a PCI performed. One of the principal challenges when reviewing these studies is determining the outcome of patients who had PCI performed vs. those who did not. The use of PCI in these studies was not randomized. The preliminary results of GUSTO 4 ACS also address this issue.

PARAGON Trial: The PARAGON trial involved 2282 patients with UA, NSTEMI, or temporary ST-segment elevation who presented within 12 hours of onset and had ECG changes.[21] The 5 arms included a placebo group plus groups receiving lamifiban at both low and high doses, with or without heparin for 3-5 days of treatment. Percutaneous coronary intervention was discouraged during the first 48 hours. The primary end point was the composite of death due to all causes, AMI, or reinfarction within 30 days. There was no difference between groups at 30 days. (*See Table 5.*) However, at 6 months, low-dose lamifiban yielded a significantly lower composite end point than did placebo. Major bleeding occurred significantly more in patients who received heparin plus any dose of lamifiban. (*See Table 5.*) It was surprising that a very short-acting drug provided no benefits at 30 days but there was a significant difference at six months.[21]

PURSUIT Trial: The PURSUIT trial assessed the role of eptifibatide in 10,948 patients with ACS who presented with chest pain accompanied by either ECG changes or elevated markers.[33] Patients received either placebo, eptifibatide bolus plus a high-dose infusion, or eptifibatide bolus plus a low-dose infusion. Percutaneous coronary intervention was used at the discretion of the physicians. The primary end point was the composite of death or AMI at 30 days. The outcomes of patients who received only medical therapy vs. those who had PCI performed were difficult to differentiate. At 30 days, there was a significant reduction of the composite end point within the high-dose eptifibatide group. (*See Table 5.*)

It should be stressed, however, that outcomes were different among different regions of the world in this multinational trial. Patients enrolled in Latin America or Eastern Europe derived less benefit than those enrolled in Western Europe or the United States. The difference may have resulted from regional differences in the use of PCI. Patients had catheterization performed 79% of the time in North America, 58% in Europe, 46% in Latin America, and 20% in Eastern Europe. The observed treatment benefit varied directly with the frequency of catheterization. This suggests that the greatest benefits of eptifibatide were experienced by patients undergoing a PCI. More bleeding and more transfusions were required in the eptifibatide group, albeit most occurred at the femoral access site. Most major bleeding occurred in patients undergoing a CABG.[33]

PRISM Trial: The PRISM trial evaluated 3232 patients who were randomized to receive a 48-hour infusion of tirofiban or heparin.[34] Patients had onset of chest pain within 24 hours and either ECG changes, enzyme elevation, or prior documentation of CAD. PCI was discouraged during the 48-hour infusion. The primary end point was the composite of death, AMI, or refractory ischemia at two days. There was a significant reduction of the composite end point at 2 days; however, the difference was not maintained at 30 days. (*See Table 5.*) For patients who were treated with medical therapy alone, the rate of death or AMI was reduced from 6.2% in the heparin group to 3.6% in the tirofiban group at 30 days ($P < .01$). Bleeding complications were comparable between groups.[34]

PRISM PLUS Trial: The PRISM PLUS trial evaluated 1915 patients with very high-risk ACS without ST elevation, even more so than the patients in the PRISM trial.[35] Patients presented within 12 hours of symptom onset and were randomized to receive a 48-hour infusion of tirofiban, heparin, or of both. PCI was discouraged during the 48-hour infusion period but was encouraged thereafter. The study drug was used during interventions, unlike in PRISM. The primary end point was the composite of death from any cause, AMI, refractory ischemia at 7 days, or rehospitalization at 7 days, 30 days, or 6 months. The tirofiban-alone arm was discontinued early because of excess events (5% died during the first 7 days). The composite end point was significantly improved in the tirofiban plus heparin group vs. the heparin alone group at 7 and 30 days and at 6 months. (*See Table 5.*)

The primary difference between the groups was the occurrence of refractory ischemia. Among patients who were treated with medical management, those who received tirofiban and heparin had a lower composite end point at 30 days (14.8%) than did those treated with heparin alone (16.8%). Bleeding complications were comparable between groups.[35] The tirofiban-alone arm was stopped early because of excess mortality. This mortality was surprising because no such excess was observed in the composite end point or in refractory ischemia. In addition, the PRISM trial also had a tirofiban-alone arm that had a significant reduction in the composite end point at 2 days.

GUSTO 4 Trial: Initial data from the GUSTO 4 trial were presented August 2000 at the European Society of Cardiology Congress.[36] The trial involved 7800 patients with UA or NSTEMI, without a planned PCI, who were randomized to receive: 1) a 24-hour infusion of abciximab; 2) a 48-hour infusion of abciximab; or 3) placebo. The primary outcome was the composite of death or AMI at 30 days. There was no significant difference between groups, with the primary outcome occurring in 8.2%, 9.1%, and 8.0%, respectively. Major bleeding was

comparable between groups (0.6%, 1.0%, and 0.3%, respectively).[36]

Management of Unstable Angina and NSTEMI: Summary of Benefits Using GP IIb/IIIa Inhibitors

The aforementioned trials provide evidence-based support for management of subgroups of patients with ACS. In patients receiving PCI, abciximab has demonstrated consistent benefit. In contrast, neither eptifibatide nor tirofiban significantly decreased ischemic events after PCI in the RESTORE and IMPACT-II trials, respectively. In the EPIC, EPILOG, and EPISTENT trials, abciximab produced 4.5-6.4% absolute reductions in the 30-day composite end point, and these benefits persisted at 6 months in the EPIC and EPILOG trials (EPISTENT did not assess 6-month outcomes). The benefits also persisted at more extended follow-up. At one-year, patients in the EPILOG trial had a significant reduction of the composite end point from 16.1% in the placebo group to 9.6% in the abciximab groups ($P < .001$).[37] At 3 years, patients in the EPIC trial also had a significant reduction of the composite end point from 47.2% in the placebo group to 41.1% in the abciximab bolus plus infusion group ($P = .009$).[27] In the EPISTENT trial, the composite end point of mortality or AMI at 1 year was significantly reduced in the stent plus abciximab group (5.3%) compared to the stent plus placebo group (11.0%; $P < .001$).[38]

The CAPTURE trial, which evaluated abciximab and mandatory PCI, found significant benefit at 30 days but not at 6 months. Various factors may be responsible for the lack of enduring benefits. Patients received abciximab for only 1 hour after PCI in the CAPTURE trial vs. for 12 hours after PCI in both the EPIC and EPILOG trials. The 12-hour administration period post-procedure may be very important for establishing the long-term (6 months to 3 years) benefit of abciximab. This difference supports the concept of arterial passivation, in which the agent affects the vessel wall surface so as to inhibit further platelet-thrombin deposition. The significance of the pharmacologic differences between abciximab and the small molecule agents is unclear (*see Table 3*); however, they might contribute to the potential passivation associated with abciximab.

The GP IIb/IIIa inhibitors work comparably during the 12- to 36-hour intravenous infusions. The prolonged platelet-bound biologic half-life of abciximab might account for its prolonged effect on platelet function. The longer duration of action may have been the reason for abciximab's success with a 12-hour infusion vs. the 20- to 72-hour infusions used with eptifibatide or tirofiban. The highest risk for thrombotic events after PCI is within 48 hours. The prolonged and tapered effect of abciximab neutralizes platelets while the vessel heals itself, providing "artificial" passivation when the patient's thrombosis risk profile gradually progresses from high risk to low risk.[7]

The role of GP IIb/IIIa inhibitors in patients who are not necessarily having a PCI is controversial. All of the trials (PURSUIT, PRISM, PRISM-PLUS, and PARAGON) included patients who did and did not receive PCI and, importantly, the use of PCI was not randomized. Differentiating the outcomes of patients who received only medical therapy vs. those having a PCI is not easy. These groups were not differentiated in the PARAGON trial and no differences were found between the groups in the PURSUIT trial. As noted above, the PURSUIT trial also was interesting because the benefit among geographic locations varied directly with the frequency of catheterizations performed in the locations, supporting the concept that GP IIb/IIIa inhibitors might be optimal in the PCI population.

The PRISM trial noted a significant reduction in the combination of death and AMI at 30 days in those treated only medically with tirofiban. However, the data presented on the population receiving only medical therapy were limited. Patients treated with tirofiban and heparin, without PCI, had an improved 30-day composite outcome compared to those treated with only heparin in the PRIME-PLUS trial. Once again, the data pertaining to those treated only medically were limited. The CAPTURE trial, despite having mandated PCI, did start with an 18- to 24-hour infusion of abciximab before PCI. During this medical only treatment phase of the study, the AMI rate was reduced from 2.1% to 0.6% in the abciximab arm.

The GP IIb/IIIa inhibitors have not been compared directly in any trials. The first one planned is the Do Tirofiban and Abciximab for Revascularization Give Equivalent outcomes Trial (TARGET). It will be a randomized, double-blind comparison of these agents during PCI. Concerns exist that it may be too small to attain statistical power. In addition, there is a question that a 30-day end point may not be long enough to adequately assess the extended benefits noted in previous trials with abciximab. Indeed, benefits with tirofiban and eptifibatide have not been demonstrated at 30 days, let alone at 6 months, in trials involving mandated PCI.[20]

Major bleeding has not been a significant problem in most of the studies, except the EPIC and CAPTURE trials. However, these trials did not use the same safety considerations applied in later trials such as stopping the heparin infusion after the PCI, pulling the vascular

sheaths early, and performing meticulous access site care.

It must be emphasized that trials involving GP IIb/IIIa inhibitors have involved high-risk patients, many of whom had ischemic ECG changes or positive cardiac enzymes. This point applies especially to the four-P trials of patients without mandated PCI. Even if one felt there was evidence suggesting that patients not receiving PCI would benefit from treatment with GP IIb/IIIa inhibitors, many patients admitted to the emergency department with ACS would not be eligible for these agents according to the entry criteria of the trials. ❖

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