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Breaking the Therapeutic Barriers: New Strategies for Acute Coronary Syndromes

CHRISTOPHER P. CANNON, M.D., Guest Editor

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ARTICLES IN BRIEF

Original Contributions

IV-3  Chest Pain Emergency Centers: Improving Acute Myocardial Infarction Care

J. P. Ornato, M.D.

Uncertainty and delay are common in the diagnosis of acute coronary syndromes (ACS). In the last 20 years, the need for faster, more accurate, and more cost-effective diagnosis gave rise to the concept of specialized treatment of patients with chest pain in emergency departments (EDs). The original strategy dedicated a separate section of the ED and a nursing staff to the task of rapid intervention in patients with acute myocardial infarction (MI) and triage of low-risk patients. Chest pain centers grew quickly in popularity but evolved with a variety of goals, staffing plans, diagnostic resources, and levels of commitment. Three existing centers—the University of Cincinnati Heart ER, Brigham and Women’s Hospital, and the Medical College of Virginia—have implemented chest pain strategies with the common aims of (1) screening for the entire spectrum of coronary artery disease, (2) avoiding unnecessary admissions, and (3) using multiple diagnostic modalities. Yet, they differ in the specifics of their approaches and diagnostic methods (e.g., echocardiography vs. treadmill vs. myocardial perfusion imaging). The safety and cost effectiveness of these centers are discussed.

IV-10 Prehospital Thrombolysis: An Idea Whose Time Has Come

C. P. Cannon, M.D., A. J. Sayah, M.D., R. M. Walls, M.D.

Aggressive reperfusion therapy for myocardial infarction (MI) characterized by acute ST-segment elevation leads to improved patient outcome. Furthermore, use of thrombolytic therapy is highly time-dependent: reperfusion therapy is beneficial within 12 h, but the earlier it is administered, the more beneficial it is. Thus, the focus of both prehospital and emergency department management of patients with acute MI is on rapid identification and treatment. There are many components to the time delays between the onset of symptoms of acute MI and the achievement of reperfusion in the occluded infarct-related artery. Time delays occur with both the patient and the prehospital emergency medical system, although patient delays are more significant. This article focuses on the prehospital management of acute MI, including (1) the rationale for rapid reperfusion in patients with acute MI, (2) the factors related to time delays in patient presentation to the hospital, and (3) strategies for reducing time delays, both patient- and medical system-based.

IV-20 Reperfusion Revisited: Beyond TIMI 3 Flow

J. P. Gassler, M.D. and E. J. Topol, M.D.

Therapy for acute myocardial infarction has advanced dramatically since the early 1980s with the use of early intravenous fibrinolytic therapy. Combining low-dose fibrinolysis and platelet lysis appears to provide an additional increase in infarct-related artery patency, but the large-scale mortality reduction trials evaluating this strategy are just getting under way. Recently, considerable attention has shifted away from the epicardial arteries to the microvasculature. Contemporary evidence suggests that epicardial patency does not necessarily translate to actual perfusion at the myocardial level. Techniques to evaluate beyond thrombolysis in myocardial infarction (TIMI) epicardial flow are now available and validated. In addition, we have promising treatments for the prevention or alleviation of certain forms of microvascular obstruction. This review attempts to clarify the confusion surrounding epicardial flow and “myocardial malperfusion” and to provide some insight into the next direction in acute myocardial infarction therapeutics.

(continued on page A6)
IV-30  Incorporating Platelet Glycoprotein IIb/IIIa Inhibition in Critical Pathways: Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction

C. P. CANNON, M.D.

Platelet glycoprotein (GP) IIb/IIIa inhibitors have been shown to be effective in reducing thrombotic events in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) and when used as medical therapy in patients with unstable angina/non–ST-segment elevation myocardial infarction (MI). Recent findings include dramatic preventive benefits in the setting of coronary stent deployment and a significant long-term preventive effect on mortality. The benefits of GP IIb/IIIa receptor inhibition suggest the utility of adopting routine use of these agents in critical pathways for unstable angina/non–ST-segment elevation MI and PCI. Because cost constraints may limit use of these agents, however, targeting treatment based on patient risk assessment may be warranted.

IV-37  Combination Therapy for Acute Myocardial Infarction: Glycoprotein IIb/IIIa Inhibitors plus Thrombolysis

C. P. CANNON, M.D.

Although thrombolytic therapy has been a major advance in the treatment of acute ST-segment elevation myocardial infarction (MI), new thrombolytic agents have been unable to improve early reperfusion. Because aspirin has been shown to be a very effective adjunctive agent in patients with acute MI, it has been hypothesized that the use of platelet glycoprotein (GP) IIb/IIIa receptor inhibitors combined with thrombolytic agents would lead to more effective platelet inhibition and improved angiographic and clinical efficacy. Emerging experimental and clinical data, including the Thrombolysis in Myocardial Infarction (TIMI)-14 trial, suggest that combining GP IIb/IIIa receptor inhibition with reduced-dose thrombolytic therapy improves early infarct-related artery patency without increasing bleeding risk. Thus, given the strong clinical and physiologic rationale, clinical investigation in patients with acute ST-segment elevation MI is currently focused on combining GP IIb/IIIa receptor inhibitors with reduced-dose fibrinolytic agents in acute MI.

IV-44  Future Directions in Thrombolysis

J. T. WILLERSON, M.D. AND P. ZOLDHELYI, M.D.

An extensive body of research conducted in the past 25 years has helped foster understanding of the mechanisms and pathogenesis of the acute coronary syndromes and occlusive disease. Thus, it is well established that thrombosis is caused by vascular injury and that immediate lysis of the arterial thrombus and subsequent prevention of thrombotic reocclusion are critical to the treatment of these disorders. Remarkable progress in the understanding of the biological and molecular mechanisms involved in vascular-wall–platelet interactions, platelet–platelet interactions, and coagulation has led to the identification of multiple targets for drug discovery and the development of numerous antithrombotic drugs. The purpose of this article is to review emerging antithrombotic therapies, introduce potential future molecular targets for drug discovery efforts, and discuss novel strategies for managing patients with coronary disease.
Breaking the Therapeutic Barriers:
New Strategies for Acute Coronary Syndromes

Introduction

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This is truly an exciting and dynamic time in cardiovascular medicine. Reperfusion therapy remains the standard of care for patients who present within 12 h of symptom onset of acute ST-segment elevation myocardial infarction (MI). Determination of biological, cellular, and molecular mechanisms involved in vascular-wall–platelet interactions, platelet–platelet interactions, and coagulation has led to the identification of multiple targets for drug discovery and the development of numerous fibrinolytic and antithrombotic drugs. These drugs reduce mortality by rapidly restoring normal blood flow in the occluded infarct-related coronary artery and maintaining patency once thrombolysis is successful. As evident in this supplement’s articles, two major trends are emerging to reduce mortality related to acute MI: (1) time to treatment is being reduced and (2) new medical treatments—fibrinolytics such as tissue plasminogen activators, antiplatelet agents such as glycoprotein IIb/IIIa receptor inhibitors, or a combination of these—are being optimized.

In November 1998, a panel of internationally recognized experts in reperfusion therapy was convened at a symposium entitled Thrombolysis ’98 to discuss emerging trends and recently developed treatment options for the medical management of acute coronary events. The topics included in the symposium form the basis for the articles in this supplement and further information is available at www.chestpainonline.org.

Two articles address recent efforts to improve care for patients with acute MI, with the overall goals of improving the speed and accuracy of the triage of patients with chest pain, reducing the time to treatment of patients, and reducing the costs. In the first article, Dr. Ornato considers the emerging role of specialized emergency departments. He includes a description of the origin and evolution of chest pain centers and offers a critical assessment of three leading models: the University of Cincinnati, Brigham and Women’s Hospital, and the Medical College of Virginia. The uniquely effective attributes of these models illustrate how institutions can use an array of available diagnostic tools to implement cost-effective and practical modalities to evaluate and treat patients who present to the emergency department with chest pain.

In the second article, Drs. Sayah, Walls, and I focus on the prehospital management of patients with acute MI. We summarize three important aspects of this issue: (1) the rationale for rapid reperfusion in patients with acute MI, (2) the factors related to time delays in patient presentation to the hospital, and (3) the strategies for reducing time delays. Included are the results of the Myocardial Infarction and Triage Intervention (MITI), the Grampian Region Early Anistreplase Trial (GREAT), and the European Myocardial Infarction Project clinical trials in prehospital thrombolysis, as well as a summary of the recent European Society of Cardiology and the European Resuscitation Council recommendations for prehospital thrombolysis. A new trial, Thrombolysis in Myocardial Infarction (TIMI) 19, is also mentioned.

Drs. Gassler and Topol introduce emerging concepts and treatments that are likely to play an important role in future approaches to the management of patients with acute MI. They present a cogent, enlightened summary of the potential reasons for continued failure of thrombolytic treatment in patients with acute MI, concentrating on the recent shift away from a concern for patency of the epicardial arteries toward consideration of the critical role of microvascular patency in myocardial perfusion. The clinical relevance of the newly recognized entity of platelet microembolism-induced microvascular occlusion, diagnostic methods to evaluate myocardial microvascular flow, and treatment options are reviewed to help clarify the confusion surrounding the concepts of epicardial flow and myocardial malperfusion.

The next two articles explore the potential of the platelet glycoprotein IIb/IIIa receptor inhibitors to effect a radical change in the approach to myocardial reperfusion in the treatment of patients with acute MI and unstable angina. Included are descriptions of experiences in incorporating GP IIb/IIIa receptor inhibitors into critical pathways for the treatment of acute MI and unstable angina. The results of major clinical trials that demonstrate improved outcomes with administration of GP IIb/IIIa receptor inhibitors alone or in combination with thrombolytic therapy to patients with acute coronary syndromes are also presented.
In the final article, Dr. Willerson looks toward the future with a summary of new developments in antithrombotic therapy. He summarizes the fundamentals of the pathophysiology of occlusive thrombosis, emphasizing the respective roles of platelets and inflammation. He follows this with a review of recent advances in pharmacologic therapy: In addition to underscoring the importance of GP IIb/IIIa receptor inhibitors, he discusses the potential of adenosine diphosphate inhibitors, antithrombins, and anti-inflammatory therapy for future medical management of acute coronary syndromes. Finally, he introduces new directions in thrombosis research and describes potential new molecular targets for future drug development efforts.

The availability of increased treatment options will produce more innovative, effective, and individualized strategies for improved management of patients with acute coronary syndromes.
Chest Pain Emergency Centers: Improving Acute Myocardial Infarction Care

JOSEPH P. ORNATO, M.D.

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Summary: Uncertainty and delay are common in the diagnosis of acute coronary syndromes (ACS). In the last 20 years, the need for faster, more accurate, and more cost-effective diagnosis gave rise to the concept of specialized treatment of patients with chest pain in emergency departments (EDs). The original strategy dedicated a separate section of the ED and a nursing staff to the task of rapid intervention in patients with acute myocardial infarction (MI) and triage of low-risk patients. Chest pain centers grew quickly in popularity but evolved with a variety of goals, staffing plans, diagnostic resources, and levels of commitment. Three existing centers—the University of Cincinnati Heart ER, Brigham and Women’s Hospital, and the Medical College of Virginia—have implemented chest pain strategies with the common aims of (1) screening for the entire spectrum of coronary artery disease, (2) avoiding unnecessary admissions, and (3) using multiple diagnostic modalities. Yet, they differ in the specifics of their approaches and diagnostic methods (e.g., echocardiography vs. treadmill vs. myocardial perfusion imaging). The safety and cost effectiveness of these centers are discussed.

Key words: acute coronary syndrome, myocardial infarction, chest pain, triage, emergency

Introduction

The diagnosis of acute coronary syndromes (ACS) by conventional assessment in an emergency department (ED) has long been a source of uncertainty and error. More than 90 million patient visits to EDs occur in the United States annually,1 of which an estimated 8 million are related to complaints of chest pain or an equivalent symptom complex that suggests potential or acute cardiac ischemia.2 Erring on the side of caution, physicians have tended to overestimate the incidence of acute myocardial infarction (MI) in this population and admit a large number of patients to the coronary care unit (CCU); almost two thirds of patients with chest pain are admitted, but only 13 to 15% ultimately are ruled in for acute MI. On the other hand, traditional assessment has also resulted in a high rate of “missed” MIs: Of the 40% of patients with chest pain who are discharged from the ED, 1 to 5% actually have MI.3–5

These diagnostic errors are costly in many ways. The rule-in process generates at least $600 million per year in unnecessary inpatient expenses.5 Worse, patients whose MI is “missed” have a mortality rate of about 16%5; their complications account for approximately 21% of malpractice awards against emergency physicians6 even though patients with chest pain make up only 3 to 5% of a typical emergency physician’s practice. Certainly the problem is not limited to emergency physicians: cardiologists also are vulnerable to misdiagnosis of MI when they see patients in their offices. Primary care physicians, internists, and family physicians account for about two thirds of missed MIs with adverse outcomes, largely because they collectively see large numbers of patients in the office, a phenomenon that will only worsen as a result of the national shift from specialty care to primary care.

Clinical, economical, and technological influences have converged in the last 2 decades to force change in acute MI care, and many EDs in the United States have explored ways to improve both the speed and accuracy of triage of patients with chest pain and reduce costs in the process. These have come to be known as “chest pain centers.” The objective of the current paper is to describe the evolution of chest pain centers and focus on several innovative models that vary in both labeling and substance, not only among themselves but also from the original concept of chest pain centers.

Origin of the Chest Pain Center Concept

Beginning in the early 1980s, when the importance of rapid treatment of acute MI was becoming evident and diagnostic technology was advancing, the goal of faster care in the ED gave rise to the concept of a separate, specialized system for
dealing with patients with chest pain. The concept, known as the chest pain center strategy, is still evolving today but is unquestionably popular: an estimated 700 to 1,000 chest pain centers are in place in the United States; growth has tended to double every 10 months.

In essence, the chest pain center is a system for treating the cardiac patient separately and differently from the general flow of adult emergencies by managing suspected cardiac patients in a subsection of (or addition to) the ED. No single model is defined or regulated, so centers can and do vary in mission, staffing, size, physical arrangement, and diagnostic and invasive capabilities. The prototype chest pain center was established in 1981 by Dr. Raymond Bahr of St. Agnes Hospital in Baltimore, Maryland. It opened in a 6,000-square-foot addition to the ED, sharing physicians and registration staff with the ED but dedicating a nursing staff and the space itself to patients with chest pain regardless of the intensity of the patient load.

Prior work in CCUs had highlighted the clinical importance of prodromal symptoms of acute MI—intermittent, “stuttering” chest pain that precedes prolonged chest pain and is believed to occur in 50% of patients presenting with acute MI. Based on the belief that intervention during the prodromal stage could stop an evolving infarction, the St. Agnes center was modeled to serve, in large measure, as a “damage control area” for rapid intervention and the conversion of patients with acute MI to “prodromal patients who have not yet had an MI.” Beyond this role, the center focuses on triage and definitive rule-out of acute MI in low-risk patients and on educating patients and the community about cardiac risk factors, prevention, chest pain awareness, and the importance of early treatment.

Evolution of Chest Pain Centers

The chest pain center concept was eagerly embraced as the principles of thrombolytic therapy and myocardial salvage became clearer in the last 15 years. However, during the period of exponential growth of new centers, Bahr’s original concept evolved into many variations. Common names that have been adopted include “chest pain emergency room,” “chest pain emergency department,” “chest pain evaluation unit,” “chest pain attack unit,” “heart emergency room,” and “short-stay coronary care unit.” While these labels today can represent a substantive, efficient unit with advanced technology for the evaluation of cardiac patients, they can also mean a barely specialized space that amounts to little more than a marketing effort on the part of the hospital. Hospital marketing leaders learned about a decade ago that merely adding the label to a facility could greatly increase market share, and under a fee-for-service reimbursement structure, the increase could mean a revenue windfall. That situation is changing now that capital and managed care are factors in most communities. On the other hand, the potential for a well-run chest pain center to be a cost-effective “gatekeeper” for inpatient admissions is highly attractive in the managed care environment.

Among current models of chest pain centers, some focus strictly on the initial triage and treatment of patients with possible acute MI. Others provide comprehensive testing for acute MI and other coronary syndromes using short-term observation, serial electrocardiogram (ECG), and biochemical markers of myocardial injury [e.g., creatine kinase (CK)-MB or troponins]. If acute MI and unstable angina are ruled out, some units conduct treadmill or pharmacologic provocation of ischemia and assess risk by means of ECG, echocardiography, or radionuclide perfusion imaging. Centers are staffed by emergency physicians, internists, cardiologists (or cardiology fellows), or some combination of the above. Some centers provide a wide range of therapeutic alternatives for patients with acute MI, including direct percutaneous coronary intervention (PCI). Others offer only pharmacologic management (e.g., thrombolytic therapy, heparin, aspirin, beta blocker). Like the original St. Agnes model, many chest pain centers maintain extensive community outreach and public education.

Despite their intuitive appeal, chest pain centers as a group have not yet been proven cost effective or clinically superior to standard ED care of cardiac patients. A widely cited analysis by Shesser and Smith suggests that, if adopted as a national strategy, chest pain centers would be strikingly inefficient. The authors estimated that an extra 1,029 lives per year would be saved (morbidity reductions were not analyzed) if chest pain centers were established in the country’s 5,400 hospital-based EDs: approximately 39 lives would be saved by reducing sudden “lobby deaths,” a little over 900 lives, by providing faster reperfusion, and approximately 89 lives by reducing “missed” heart attacks. The cost of realizing these benefits was estimated at $378 million to $3.78 billion, comprised of construction, staffing, equipment, and marketing costs. Therefore, the cost per life saved would total $378,000 to $3.78 million. Stressing that time to treatment remains the variable most critical to morbidity and mortality, the authors argue that unless chest pain centers accomplish treatment much faster than traditional EDs, they will not make a large difference in the effectiveness of care.

The Chest Pain Center in Practice

Nonetheless, prospective randomized data support the effectiveness of individual chest pain units when judged as alternatives to hospital admission of low-risk patients. Roberts et al. found at Cook County (Illinois) Hospital that costs for chest pain patients randomized to accelerated diagnostic protocols (ADPs) in the ED averaged $1,528 per patient versus $2,095 per control patient randomized to immediate admission (p < 0.001). Length of stay for the ADP patients averaged 33.1 h versus 44.8 h for control patients (p < 0.01). These results emerged even though ADP patients turned out to have more severe disease and more diagnostic tests than controls even though the 45% of ADP patients who were ultimately hospitalized had higher per-patient costs than controls. Of importance is the fact that this study, like oth-
ers,17, 18 found no increased short-term risks for patients who were discharged after ED evaluation.

Most recently, the Chest Pain Evaluation in the Emergency Room (CHEER) investigators reported that treatment in an ED-based chest pain observation unit was safe, effective, and associated with a significant reduction in resource utilization over 6 months compared with regular hospital admission in an intermediate-risk Virginia population.19 The study evaluated the outcomes of 424 patients and found a 45.8% reduction in the rate of hospital admission for patients with an intermediate risk of unstable angina and no increase in the rate of adverse events after a median stay in the chest pain observation unit of 9.2 h.

The remainder of this article will describe several existing models of chest pain centers that have evolved as variations on the original concept with uniquely effective attributes.

The University of Cincinnati Model: Chest Pain Evaluation Unit

In the early 1990s, a chest pain center concept began to emerge with a focus on the partnership between the ED and CCU to develop a more streamlined strategy involving cardiologists and emergency physicians. This concept of the chest pain evaluation unit (CPEU) was pioneered by Dr. Brian Gibler and colleagues at the University of Cincinnati. Known as the Heart ER, the distinguishing feature of the CPEU is that it augments the diagnostic capabilities of the ED itself. Although it functions as a specialized unit of the ED, the CPEU shares the ED nursing staff and can perform “fast-track” rule-out of acute MI in the ED 24 h a day, 7 days a week.

Patients with low to intermediate likelihood of unstable angina are eligible for the Heart ER fast-track protocol (patients at high risk or with a diagnostic ECG are treated and admitted) (Fig. 1). They are first evaluated by serial CK-MB measurements and continuous 12-lead ECG with serial ST-segment trend monitoring over 9 h.10, 17 An alarm on the ECG monitor sounds if there is a persistent ST change of 1 mm. A cardiologist is in-house at all times, so that at the end of any 9-h period, if MI has been ruled out in a patient but risk factors are present, the decision can be made to obtain further tests to exclude the possibility of a fixed coronary artery lesion. The first choice is a rest echocardiogram; if it is negative, the cardiologist might order an exercise treadmill test, which is available at all times in the ED. Other test options include cardiac catheterization, stress echocardiography, and outpatient exercise (or pharmacologic) thallium imaging. Patients evaluated in the CPEU are treated and billed as outpatients.

Evidence supports the Heart ER as a safe and highly cost-effective strategy for chest pain care. Gibler et al.17 reported on outcomes of 1,010 consecutive patients evaluated at the center. Of this group, 829 (82%) were discharged from the ED; 153 (15%) were admitted to the hospital, where cardiac diagnoses were confirmed in 52 (5%); and 28 (2.8%) went home against medical advice before evaluation was completed. One-month mortality data showed five deaths in total, but only one was definitely due to ACS (in a patient admitted directly to the CCU from the CPEU). A cost analysis comparing the CPEU protocol with inpatient evaluation of patients hospitalized because the ER was full during the same time period found that inpatient evaluation was more than twice as expensive: $2,810 per inpatient versus $1,368 per CPEU patient.20

The Brigham and Women’s Model: Critical Pathway/Checklist

The chest pain protocol in the ED at Brigham and Women’s Hospital in Boston, Massachusetts, uses a “critical pathway” approach to evaluation and treatment. Also known as clinical pathways or care paths, critical pathways identify the specific sequence and timing of the actions of physicians and nursing staff to achieve the desired outcomes for patients.21 At Brigham and Women’s, the chest pain pathway starts in the ED and carries on through the patient’s evaluation and disposition, with “checklists” on the critical pathway flowsheets that allow monitoring and feedback of information to the providers about achievement of patient outcomes. This allows adjustments to be made as the patient progresses along the pathway.22

The overall goal of the critical pathways program at Brigham and Women’s is to reduce admission rates, lengths of stay, and adverse outcomes for patients with chest pain at low risk of ACS.22 Patients whose ED evaluation indicates “possible ischemia” are first routed according to their ability to walk (Fig. 2). Those who are able to walk are observed for 6 h and then either treadmill tested, if they are stable, or observed further. Those who cannot walk are observed for 12 h and then discharged if stable. Clinical outcomes and timing of patient progress along the pathways are closely tracked and recorded by the physicians and nurses.

In a retrospective analysis, Nichol et al.22 applied eligibility criteria for the critical pathways to an existing cohort of patients with chest pain who presented to Brigham and Wom-
Critical Pathways Track Approach

The Medical College of Virginia (MCV) in Richmond, Virginia, is an institution with an 890-bed teaching hospital, a 65-bed ED, and 24 emergency physicians. The ED treats more than 85,000 patients per year, including two thirds of the city’s ambulance traffic. About 12 to 15 patients with chest pain present each day.

In 1994, MCV began a sophisticated approach to the triage and treatment of patients with chest pain in the ED. It is not termed a chest pain center but is a vertically integrated chest pain program with a track approach that starts in the prehospital care system, works its way through the critical pathways of the ED, CCU, or various diagnostic services, and ends by delivering the patient back into the hands of the primary care provider in the community. The approach has three major goals: (1) to rule out MI, (2) to rule out unstable angina, and (3) to screen (via next-day stress testing) for clinically significant coronary artery disease in patients believed to be at risk. If all of these clinical problems are ruled out, an additional goal is to identify noncardiac sources of chest pain through appropriate outpatient procedures. For example, if a stress test clears a patient of cardiac ischemia and the next most likely etiology is gastrointestinal, the patient can be referred for an immediate endoscopy that day.

Beginning in the field, multiple complementary technologies comprise the critical pathways at MCV. All of the city’s ambulances have prehospital 12-lead ECG capability. Depending on the ECG results, paramedics will or will not administer nitrates or follow a thrombolytic therapy checklist, based on standing orders; they will then tell the ED whether the incoming patient is a likely candidate for thrombolytic therapy or may require immediate cardiac catheterization. The ED immediately assigns a bed for the patient and prepares a preregistration packet for future completion.

Once in the ED, patients with chest pain bypass registration and are brought directly into the treatment unit, part of the adult acute treatment area of the ED. A nurse assesses vital signs and obtains an ECG, which is then assessed by one of the attending emergency physicians (five to seven attendings are on duty 24 h a day). The physician reviews the ECG, takes a brief history, examines the patient, and makes an immediate triage decision, assigning the patient to one of five critical pathways, or tracks (Fig. 3). Assignment is based on the probability of ACS and driven by specific interventional goals.

**Critical pathways:** Track 1 patients, who have an obvious acute MI and ST-segment elevation, are treated promptly with thrombolytic therapy or direct PCI and admitted to the CCU for further care. Track 2 patients typically have prolonged or intermittent chest discomfort with ST-segment depression and/or T-wave inversions, suggesting a high probability of unstable angina or non–Q-wave infarction; these patients are treated with heparin, aspirin, intravenous nitroglycerin, and (when indicated) a glycoprotein IIb/IIa receptor inhibitor and are admitted to the CCU for ECG monitoring and measurement of cardiac markers (CK-MB and troponin). At the other extreme are Track 5 patients, who have the lowest probability of ACS and are discharged after appropriate care. The typical patient in Track 5 is younger than age 30, has a normal ECG, no cocaine use or other cardiac risk factors, and, most important, an obvious noncardiac etiology of chest pain—for example, a basketball player who has been elbowed in the chest.

Less obvious cases are assigned to Track 3 or Track 4. These patients, who have intermittent chest discomfort and nondiagnostic ECGs, present the greatest diagnostic challenge in any ED. Track 3 patients are defined as having had at least one episode of discomfort suggesting probable unstable angina and lasting 20 to 30 min or more. These patients are fast-tracked in a 9-h observation period in the CCU, with accelerated measurement of cardiac markers (myoglobin and CK-MB) and an immediate technetium (99mTc) sestamibi rest study. If all tests are negative during the observation period, Track 3...
patients undergo a $^{99mTc}$ sestamibi exercise study. If it is negative, they are discharged. Track 4 patients, considered to be atypical low-risk patients with possible unstable angina, are evaluated in the ED with a $^{99mTc}$ sestamibi rest study. If the study is negative, the patient is released but is scheduled for a $^{99mTc}$ sestamibi exercise study in the ED for the following day.

**Evaluation of the MCV strategy:** At MCV, $^{99mTc}$ injection is available 24 h a day. Injection takes place as soon as possible after the patient arrives in the ED, and gated single-photon emission computed tomography (SPECT) imaging is performed within 60 to 90 min. Since the inception of MCV’s critical pathway track protocol in 1994, over 10,000 $^{99mTc}$ sestamibi studies have been performed in the ED. We have found a true false-positive rate based on coronary angiography in only 0.5% of Track 3 and 4 patients. Two thirds of acute MIs missed by ECG but detected by imaging have been posterior or lateral, where the ECG is most insensitive.

$^{99mTc}$ sestamibi rest imaging has been successful in discriminating risk levels at MCV, a result that can be credited to SPECT and to careful and consistent interpretation of images. Tatum et al. analyzed outcomes of 1,187 patients at MCV who received immediate $^{99mTc}$ rest studies after track assignment. Adverse cardiac outcomes were consistent with assignment, such that patients designated Track 1, 2, 3, and 4 had acute MI rates of 96, 13, 3, and 0.7%, respectively. Sensitivity for acute MI was 100% and specificity was 78%. At 1 year, the risk of acute MI, revascularization, or cardiac death was 42% in patients with abnormal images and 3% in those with normal images (relative risk 16.5; p < 0.0001). Despite such supportive findings, $^{99mTc}$ sestamibi is not necessarily superior to two-dimensional echocardiography at rapid risk assessment. Kontos et al. compared side-by-side echocardiograms and $^{99mTc}$ sestamibi images from 185 Track 3 and 4 chest pain patients at MCV and found the methods to be largely comparable in terms of sensitivity and specificity.

**Quality improvement and community outreach:** The MCV protocol is continuously reviewed and revised. A cardiology fellow leads weekly multidisciplinary continuous quality improvement (CQI) conferences where cases are reviewed. Emergency physicians have cardiac case reviews at least monthly. A Grand Rounds is dedicated each month to a case-by-case review to refresh ECG recognition skills and clarify the pathway process.

The MCV program has a full-time community outreach coordinator who communicates with the primary provider in Richmond. A system is in place that allows any physician in the community to refer patients directly from the office for $^{99mTc}$ sestamibi study 24 hours a day. Results are faxed back to the referring doctor. If the patient is discharged, the ED sends a letter to the doctor the next day, via the outreach coordinator, so that the patient can be followed appropriately.

**Cost:** Although more diagnostic testing is performed initially in the MCV approach, the number of pathway patients admitted to the hospital from the ED has decreased by about 20% compared with standard ED care. More patients with unstable angina but fewer with noncardiac chest pain have been admitted. Length of stay has decreased by 83% for noncardiac patients and is halved for unstable angina patients, resulting in savings in hospital charges (Table II). Overall, the critical pathway strategy is estimated to cost $300,000 for every 100
patients with chest pain evaluated, compared with an estimated $700,000 per patient evaluated in a standard ED strategy.

Conclusions

The picture emerging at the close of the twentieth century is one with no single, ideal approach to chest pain evaluation but rather an array of demonstrably or potentially effective approaches at individual institutions. The approaches described herein show how separate institutions can turn diagnostic tools and processes to their greatest advantage, tailoring a practical, safe, and cost-effective technique to evaluate patients who present to the ED with chest pain. It is likely that at any given moment at any given institution, any systematic and separate approach to patients with chest pain is better than the traditional ED strategy of ECG, physical exam, echocardiogram, and clinical judgment.

Nevertheless, the picture indicates that the most effective successful chest pain strategies should have several essential components. They should screen effectively for the entire spectrum of ACS—not just focus on the rule-out of acute MI but pursue equally the identification of cardiac ischemia, latent coronary artery disease, and risk factors. The most effective strategies should safely reduce unnecessary admissions and thereby rein in costs of care. They also should use multiple complementary diagnostic modalities, with the specific aim of detecting disease that might be overlooked with a more traditional approach. These modalities include $^{99m}$Tc myocardial perfusion imaging, two-dimensional echocardiography, and exercise treadmill testing, each of which is a mainstay of current chest pain evaluation protocols. Regardless of the strategy that is instituted, a quality improvement plan is another important part of the process.

It has been suggested that the true value of a chest pain center lies not in immediate dollar savings but in the institutional commitment to a high level of cardiac expertise, which inspires community confidence and economic well-being over time. While this commitment is indispensable, there is already evidence that individual programs can be cost effective even in the near term. As the concept of chest pain centers evolves in the twenty-first century, the hope is that both economic and community benefits will grow hand in hand.

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Prehospital Thrombolysis: An Idea Whose Time Has Come

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Summary: Aggressive reperfusion therapy for myocardial infarction (MI) characterized by acute ST-segment elevation leads to improved patient outcome. Furthermore, use of thrombolytic therapy is highly time-dependent: reperfusion therapy is beneficial within 12 h, but the earlier it is administered, the more beneficial it is. Thus, the focus of both prehospital and emergency department management of patients with acute MI is on rapid identification and treatment. There are many components to the time delays between the onset of symptoms of acute MI and the achievement of reperfusion in the occluded infarct-related artery. Time delays occur with both the patient and the prehospital emergency medical system, although patient delays are more significant. This article focuses on the prehospital management of acute MI, including (1) the rationale for rapid reperfusion in patients with acute MI, (2) the factors related to time delays in patient presentation to the hospital, and (3) strategies for reducing time delays, both patient- and medical system-based.

Key words: prehospital, reperfusion, acute myocardial infarction, patient presentation delay

Reperfusion Therapy: The Early Open Artery Theory

There are many components to the time delays between the patient’s onset of symptoms of acute myocardial infarction (MI) and the achievement of reperfusion in the occluded infarct-related artery (Fig. 1). The early open artery theory is the paradigm in which thrombolytic therapy is understood to be beneficial in patients with acute MI: early achievement of an open infarct-related artery is associated with improved patient outcome. Animal studies, initial angiographic studies in patients using intracoronary streptokinase, and numerous other angiographic studies over the subsequent 15 years have all lent strong support to this theory. An overview of angiographic studies in over 4,200 patients demonstrated that patients with a patent infarct-related artery 90 min after treatment with thrombolysis had a 50% lower mortality rate compared with patients who had a persistently occluded artery (p < 0.00001). Furthermore, patients who achieved thrombolysis in myocardial infarction (TIMI) grade 3 flow (defined as a patent artery with normal flow) at 90 min had a 66% lower mortality rate than patients who had an occluded artery (p < 0.00001). Thus, the modern management of acute MI appropriately focuses on rapid achievement of reperfusion of the infarct-related artery.

Importance of Time to Treatment

Achievement of early infarct-related artery patency is the cornerstone of acute MI management. One method of achieving an open artery early is to begin thrombolytic therapy as quickly as possible after onset of symptoms. As such, time can be considered an “adjunctive agent” in a thrombolytic or reperfusion regimen. The importance of time to treatment was highlighted initially by the first megatrial, Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI-1), which found that streptokinase led to a 19% reduction in mortality compared with placebo. However, patients who were treated within 1 h of the onset of chest pain had a 50% reduction in mortality. The TIMI-2 trial extended these observations and found that for each hour earlier that a patient was treated, the absolute mortality rate decreased by 1%, which translates into an additional 10 lives saved per 1,000 patients treated (Fig. 2A). This has also been observed in the Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial (Fig. 2B) and in an initial series of patients treated with primary percutaneous transluminal coronary angioplasty.

The mechanism of benefit of rapid time to treatment fits the paradigm of the early open artery theory. Rapid time to treatment has been shown to be associated with reduced infarct size...
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Thus, earlier treatment with either thrombolysis or primary angioplasty is associated with improved survival, emphasizing the need to speed treatment. With this goal in mind, rapid identification and transportation of the patient with MI to the hospital have been the main focus of prehospital management of patients with MI. Some variables that affect thrombolysis treatment when the patient is in the emergency department appear in Table I.

**National Heart Attack Alert Program**

In recognition of the need to expand the use of known therapies for acute MI, such as thrombolysis and early defibrillation, the National Heart, Lung, and Blood Institute (NHLBI) launched the National Heart Attack Alert Program (NHAAP) in June 1991. The NHAAP is a national education effort to promote the rapid identification and treatment of acute MI, with the overriding goal of reducing mortality and morbidity from acute MI, including sudden death. The NHAAP has divided the aspects of acute MI management into three phases, which provide a basis for improving care in the prehospital and hospital phases of management (Fig. 4). Phase I consists of the patient component of time delay. The NHAAP has several initiatives in this area. First, NHAAP personnel helped sponsor the Rapid Early Access to Coronary Treatment (REACT) trial of public education and also made a recommendation for patient/bystander recognition and action, that is, that the patient must recognize the symptoms and signs of a possible heart attack and seek help immediately. Phase II is the prehospital action component: emergency medical services (EMS) staff should be dispatched appropriately and respond, evaluate, and transport the patient in the shortest time possible, while providing needed life-sustaining measures. Phase III is the hospital action component: the emergency department staff of the hospital receives the patient and must be prepared to diagnose acute MI rapidly and promptly initiate reperfusion (and other) therapy as appropriate. The final component is reperfusion therapy, that is, the time from initiation of thrombolytic therapy to actual achievement of reperfusion.

**Patient Delays**

Studies of treatment delay indicate that the most common reason for delay is the patient not seeking care promptly. The median delay in seeking care after the onset of symptoms of acute MI ranges from 2 to 6.4 h. In the prethrombolytic era, an overview of 16 studies noted that the median delay was approximately 3 h. The median delay to thrombolytic treatment in the National Registry of Myocardial Infarction was

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**FIG. 1** Where and how to improve time to reperfusion in patients with acute myocardial infarction through thrombolysis or primary percutaneous coronary intervention. PCI = percutaneous coronary intervention, t-PA = tissue plasminogen activator, r-PA = recombinant tissue plasminogen activator. Adapted from Ref. No. 17 with permission.

**FIG. 2** Expedited time to thrombolytic treatment is associated with decreased levels of mortality, as evidenced by data from the TIMI-2 (A) and GUSTO-I (B) trials. t-PA = tissue plasminogen activator, SK = streptokinase. (A) Adapted from Ref. No 20 with permission. (B) Adapted from Ref. No. 40 with permission.
2.2 h, although presentation > 6 h after symptom onset was the most common reason for not treating the patient with thrombolytic therapy. In the TIMI-9 Registry of patients with MI characterized by ST-segment elevation, 12% of patients could not be treated with thrombolytics because of presentation > 12 h after the onset of symptoms. Conversely, very few patients are treated within the first hour of onset of symptoms: only 3% of patients in the GUSTO-I trial, 40 3% of patients in the TIMI-2 trial, 41 and 11% of patients in the GISSI-I trial 19 were treated within the first hour of symptom onset.

Demographic Factors

Table II shows the various demographic and clinical factors related to increased and decreased time to patient presentation. Women 43–46 and older patients 43, 47–49 tend to exhibit greater delay in presenting to the hospital with acute MI. Only preliminary information is available at present, but delays appear to be considerably greater in patients who are African-American 46, 50, 51 (up to 11.9 h in one urban study 50). In some studies, low socioeconomic status is associated with an increased delay. 52

Several clinical characteristics also affect patient delay. Severe chest pain is associated with reduced delay but only if it is sudden in onset 43, 48 Patients with a history of angina or diabetes are more likely to delay than patients without these conditions. 43, 44 It is amazing that patients already diagnosed with coronary artery disease, heart failure, or prior MI have the same or greater delay times as those without prior coronary disease. 37, 47

Other healthcare system factors also play a role. If the patient calls a physician, delay is significantly increased. 46, 53 Such delays may increase as health management organizations increasingly insist that patients contact their primary care physician prior to presenting to the emergency department. On the other hand, if the patient consults a friend, co-worker, or stranger, he/she presents to the emergency department more quickly than if consulting a family member/significant oth-

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### Table I Factors related to emergency department delays in initiating thrombolysis

- Patient volume
- Arrival by private vehicle
- Atypical symptoms
- Inconsistency of triage
- Patient initially seen by student/intern
- Hospitals without emergency department physicians
- Cardiology consult (some hospitals)
- Decision of thrombolysis versus primary angioplasty

### Table II Factors affecting prehospital delay in patients with symptoms and signs of acute myocardial infarction

**Factors contributing to increased delay**

- Older age
- Female gender
- African-American race
- Low socioeconomic status
- Low emotional or somatic awareness
- History of angina, diabetes, or both
- Consulting a spouse or other relative
- Consulting a physician
- Self-treatment

**Factors contributing to decreased delay**

- Hemodynamic instability
- Large infarct size
- Sudden onset of severe chest pain
- Recognition by patient that symptoms are heart-related
- Consulting a friend, co-worker, or stranger
er, possibly because family members or significant others are more easily dissuaded by the patient from calling 9-1-1. However, use of 9-1-1 to access EMS has been shown to decrease the time to reperfusion with thrombolytic therapy by as much as 60 min for individuals with symptoms and signs of an acute MI compared with patients who transport themselves. Patients who arrive by EMS are transported rapidly, bypass emergency department triage, have had vital signs, history, physical examination, and intravenous lines done in the field. In addition, the hospital is commonly notified of their condition prior to arrival and they are, in general, taken more seriously by the emergency department staff than are patients presenting by private transportation. Unfortunately, only half of patients with symptoms of a heart attack use the EMS system. In addition, as of 1995, EMS was only available in 83% of the United States. Furthermore, poor coordination between EMS and other first-response groups (e.g., fire rescue squads) in some communities may lead to inadvertent delays, which emphasizes the need for community planning in EMS to eliminate such delays.

Improving Time to Treatment and Survival

Reducing Patient Delays

Public awareness: The first component of reducing time delays is improving patient awareness of the symptoms of acute MI. Two approaches can be taken: (1) education of the general public (particularly people at risk for, but without, prior coronary artery disease); and (2) education of patients with stable coronary artery disease, that is, those at highest risk for a subsequent MI, who comprise a much smaller number compared with the general public. Patients with stable coronary artery disease or other significant risk factors for acute MI (e.g., peripheral vascular disease, diabetes, etc.) who are appropriately educated may present earlier to the hospital and have better outcomes. The NHAAP recommends that in both inpatient and outpatient settings, primary care physicians (and specialists) provide patients and their family members with advice about what actions to take in response to the symptoms of an acute MI (or unstable angina). The discussion should include the emotional aspects (e.g., fear and denial) that patients and those around them may experience in the acute MI setting, as well as barriers that may be associated with the healthcare delivery system (such as distance to the hospital or cost issues). Assistance from other healthcare providers, nurses, for example, should be solicited to initiate, reinforce, and supplement the counseling.

Physicians’ offices and clinics should devise a system to triage patients rapidly when they call or walk in seeking advice for possible symptoms of acute MI. This rapid response system should be able to activate EMS by calling 9-1-1 and/or notify the emergency department of an incoming patient with MI symptoms. They need to discourage patients from driving to the emergency department. Further research is needed to learn more about effective counseling strategies, symptom manifestation in high-risk groups (these include women and minorities), and healthcare delivery systems that enhance access to timely care for patients with acute MI.

Another practical issue is education of family members. Since family members can frequently be dissuaded by the patient from calling 9-1-1, it is important to educate spouses and other family members about the signs and symptoms of acute MI and to emphasize that they carry out the action plan developed. This can be done in a physician’s office during regular follow-up visits for patients with stable coronary artery disease.

Reducing transport and EMS delays: The next component of reducing time delays is focused on reducing transportation delays, which emphasizes the need for community planning in EMS to eliminate such delays.
time. Amazingly, only 50% of patients with acute MI present to the emergency department by ambulance. Since patients not transported by EMS do not have the benefit of cardiac monitoring and defibrillation in case of lethal arrhythmia, such patients do not receive optimal care. In addition, use of the 9-1-1 EMS system has been shown to reduce time to treatment with thrombolysis, and an ongoing goal is to make 9-1-1 service available throughout the United States.

One of the most important focuses of reducing delays and providing care is EMS dispatcher education and certification. These dispatchers need to have the skills to identify patients at risk for MI over the phone, dispatch a crew with appropriate training and equipment to care for the patient, provide the crew with precise directions to the patient’s location, and provide the patient/caller with pre-EMS arrival instructions, including when and how to perform cardiopulmonary resuscitation.

The next components of reducing time delays are improving response times for EMS, which has been a continuing priority in the United States and elsewhere, and developing symptom-specific protocols and treatment standing orders. These will allow EMS personnel to start the evaluation and treatment processes while contacting the hospital and communicating with an on-line physician. In addition, improved dialogue and communication between emergency medical technicians and hospital emergency departments have speeded the time to evaluation and treatment in many hospitals. The NHAAP has made recommendations for improving prehospital systems and the preparation of EMS personnel.

Community Planning

Taking a broader view that encompasses more than just EMS, it must be recalled that there are numerous providers of prehospital care and new concerns regarding where patients should be sent. Fire rescue vehicles provide a large proportion of prehospital care throughout the country, even where EMS are fully developed. Thus, in 1980, the American Heart Association proposed that the entire community be considered a coronary care unit. The rationale for this is that because heart attacks occur at home, at work, and in the community, and people die without potentially lifesaving care, identification and treatment of acute MI (and sudden death in particular, as well as acute coronary syndromes in general) should be community concerns. Therefore, it is critical that communities develop an action plan to ensure a consistent, appropriate, and coordinated response to the needs of patients who will be accessing their community’s coronary care system and to educate patients and the public about the need for early and appropriate treatment.

In addition, with the changes in healthcare insurance and preferred providers, some groups are proposing modifications in the longstanding policy that patients with acute MI be transported to the nearest hospital. Transport of very high risk patients with acute MI (e.g., those with cardiogenic shock or contraindications to thrombolysis) to a tertiary care facility with angioplasty capabilities does appear to be medically sound in systems where such facilities are available within a reasonable transport time. However, the criteria and action plan for such a policy need to be developed. The NHAAP has made recommendations on the essential components of a community plan to ensure a seamless response to the patient with acute cardiac symptoms that is the same as at the emergency department/hospital level. The similarities to regionalization of trauma care and categorization of hospital trauma care capabilities are readily apparent. Under these circumstances, patients are treated during transport. Early notification will enable the receiving hospital to prepare for the patient’s early reperfusion and lead to a shorter door-to-reperfusion time (and compensate for the longer transport time).

Prehospital Electrocardiograms

Prehospital electrocardiograms (ECGs) have been shown to decrease time to treatment and are associated with a lower mortality in one study. Prehospital ECGs usually involve both the performance of the ECG in the field and its transmission to a physician for interpretation. By this means, rapid identification of patients with acute ST-segment elevation MI is possible, and early evidence indicates that this speeds treatment and may improve the outcome of patients with acute MI. It is interesting that the time component that is reduced is the in-hospital time to treatment—that is, the door-to-needle time (Fig. 5). Since the ECG is already obtained and the patient is identified as having ST-segment elevation MI, there are fewer time delays in obtaining a history or performing an ECG, for example, and in some cases thrombolytic therapy can be readied at the bedside before the patient actually arrives in the emergency department. In one randomized trial, patients whose prehospital ECG was obtained and transmitted to the emergency department had a significantly reduced door-to-needle time (30 min compared with 50 min; p = 0.004) (Fig. 5).

A recent study in 66,995 patients in the multicenter National Registry of Myocardial Infarction-2 trial found that prehos-
hospital ECGs were associated with a 10-min decrease in door-to-needle time for thrombolysis (p<0.001) and a 23-min decrease in door-to-balloon time for primary angioplasty (p<0.001) (Fig. 6). In addition, patients who had a prehospital ECG performed were significantly more likely to receive reperfusion therapy, and more importantly, they had reduced mortality. Patients with a prehospital ECG had a mortality rate of 8% compared with 12% for those without a prehospital ECG. Even after correcting for differences in baseline characteristics in a multivariate model, the performance of a prehospital ECG was associated with improved survival (odds ratio 0.83, 95% confidence interval 0.71–0.96; p = 0.01).65

This study provides evidence that the prehospital ECG is an excellent rapid marker of acute MI that helps alert health professionals to treatment options (e.g., thrombolysis). It also suggests that other tests, such as a rapid bedside troponin T measurement66, 67 and other technologies,34 also might assist in the early identification and management of patients with acute MI. In addition, performing the ECG early in the course of the patient evaluation and identifying ST-segment elevation can help physicians focus on acute MI rather than other diagnoses. The limitations to implementation of prehospital 12-lead ECGs are (1) proximity to the hospital (if short, then transport time will be short—less than 15 min) and (2) cell phone communication availability (in which case, the paramedics can be trained to identify ST-segment elevation and communicate the findings to the hospital). Although the benefits of prehospital ECGs are likely to be somewhat dependent on the characteristics of the healthcare system, there is strong evidence pointing to improved system performance in patients with acute MI who have prehospital ECGs. Thus, healthcare systems should consider equipping and training the EMS personnel to perform prehospital ECGs.

**Prehospital Thrombolysis**

Even with the introduction of field 12-lead ECGs, the development of emergency department critical pathways for acute MI, and improving hospital efficiency, door-to-needle time remains in the range of 30 min.68 One way to further decrease the time from symptom onset to reperfusion is with prehospital initiation of thrombolytic therapy. By lysing patients in the field, some of the EMS transport time is saved in addition to eliminating door-to-needle time. Several trials of prehospital treatment with thrombolytic therapy have shown reductions in both time to treatment and mortality, especially in rural areas (Figs. 7–9).69, 70

The current EMS technological and logistical environments are ripe for the introduction of prehospital thrombolysis, beginning with field 12-lead ECG technology, which has proven effective and may decrease MI morbidity and mortality.24, 61, 65 Furthermore, communication technologies, such as widespread cell phone use and 800-MHz radio coverage, have been instrumental in improving field-to-hospital communication and 12-lead ECG transmission. In addition, the recent availability of bolus thrombolytic therapy has facilitated mixing and administration in the field.

Traditionally, the use of lytics in patients going on to planned percutaneous coronary intervention has been avoided. With the advent of thrombolytic therapy that can be administered as a double-bolus dose, this tradition may begin to be relaxed since giving the first bolus dose (injection) does not commit the patient to receiving the second. An agent like reteplase, which is administered as two 10 U injections, gives flexibility in patient treatment because there is no infusion required and, if the patient does require intervention after that, the second injection does not have to be given. Data on “facilitated intervention” from the Plasminogen Activator Coronary Angioplasty Trial (PACT) suggest that thrombolytic therapy can be administered safely in patients going on to catheterization laboratory.71 Early results from the ongoing Strategies for Patency Enhancement in the Emergency Department (SPEED) trial, the pilot study for GUSTO IV, indicated high rates of procedural success with earlier patency achieved when the thrombolytic was started in the emergency department prior to acute percutaneous coronary intervention.72

The Myocardial Infarction and Triage Intervention (MITI) trial compared prehospital versus hospital administration of thrombolytic therapy in the Seattle, Washington, area.24 Patients who were treated in the prehospital phase had a significant reduction in the time to treatment with thrombolytic therapy by 33 min (p<0.001) (Fig. 7).24 Although mortality was 31% lower, it was not a significant difference in this small trial.24 However, in MITI, patients who were treated within 70 min from the onset of chest pain had a significantly lower mortality rate than those treated later: 1.2 versus 8.7% (p = 0.04).

The Grampian Region Early Anistreplase Trial (GREAT), conducted in a rural area in England, compared prehospital or “home” thrombolysis with hospital-initiated thrombolytic therapy and documented a >2-h time saving by treatment with home thrombolysis (Fig. 8).69 Of importance, this 2-h savings in time to treatment was associated with a 50% reduction in mortality. At 1-year follow-up, mortality was 10.4% for patients treated at home compared with 21.6% for patients treated in the hospital (p = 0.007).69

<table>
<thead>
<tr>
<th>NRMI-2</th>
<th>Prehospital ECG</th>
<th>No prehospital ECG</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,768</td>
<td>66,995</td>
<td></td>
</tr>
<tr>
<td>Door-to-needle time (min)</td>
<td>30</td>
<td>40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Door-to-balloon time (min)</td>
<td>92</td>
<td>115</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Thrombolysis</td>
<td>43</td>
<td>37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Primary PTCA</td>
<td>11</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>8</td>
<td>12</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
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Fig. 6 The National Registry of Myocardial Infarction-2 study found that prehospital electrocardiograms were associated with a 10-min decrease in door-to-needle time for thrombolysis (p<0.001) and a 23-min decrease in door-to-balloon time for primary angioplasty (p<0.001). NRMI = National Registry of Myocardial Infarction, ECG = electrocardiogram, PTCA = percutaneous transluminal coronary angioplasty. Adapted from Ref. No. 65 with permission.
The European Myocardial Infarction Project was a large randomized trial of prehospital versus hospital-based thrombolytic therapy. A total of 5,469 patients were randomized to either prehospital administration of anistreplase or administration of thrombolytic therapy at the hospital. Investigators achieved a 55-min reduction in the time to treatment with prehospital thrombolysis, which was associated with a strong trend toward reduction in the overall 30-day mortality: 11.1 to 9.7% (p = 0.08). It is important to note that cardiovascular mortality was reduced from 9.8 to 8.3% (p = 0.05).

An overview of all the major prehospital thrombolysis trials is shown in Figure 9. Prehospital treatment across all trials was associated with a 17% reduction in mortality (p = 0.03). The recent consensus document of the European Society of Cardiology and the European Resuscitation Council recommends implementation of prehospital thrombolysis in any system where transport time (which includes time from ambulance arrival at the home to hospital arrival) exceeds 30 min or the aggregate of transport time and door-to-needle time in the hospital exceeds 60 min. If less time is involved, hospital-based thrombolysis is probably just as effective.

Prehospital Aspirin

Given the benefits of aspirin in patients with acute MI and those of rapid time to treatment with thrombolysis, it has been associated with a 17% reduction in mortality (p = 0.03). The recent consensus document of the European Society of Cardiology and the European Resuscitation Council recommends implementation of prehospital thrombolysis in any system where transport time (which includes time from ambulance arrival at the home to hospital arrival) exceeds 30 min or the aggregate of transport time and door-to-needle time in the hospital exceeds 60 min. If less time is involved, hospital-based thrombolysis is probably just as effective.

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thought that prehospital aspirin might improve patient outcomes. However, one study found no benefit of prehospital aspirin versus administration of aspirin in the hospital. A more recent report from an observational study has suggested benefit from prehospital aspirin. On the other hand, overall use of aspirin is lower than what is optimal, ranging from as low as 63% in one study to only 87% in others. Thus, standardized protocols or “checklists” that include aspirin in the prehospital phase will ensure that aspirin is not overlooked.

Additional Therapies

Although not yet studied in prehospital treatment of patients with acute MI or unstable angina, heparin is an approved drug in most interhospital advanced life support patient transfers, and future studies should address heparin’s prehospital role in patients with acute MI. In addition, the availability of glycoprotein IIb/IIIa receptor inhibitor opens the door to a whole new consideration of therapies and combinations of therapies while the patient is transported to the hospital for medical treatment or primary angioplasty. Further study is ongoing and should provide further recommendations and guidelines to optimize patient treatment.

Conclusions

The field of prehospital management of patients with acute MI has expanded rapidly in the past several years. It involves the patients in their own management by trying to educate them about the importance of rapid access to 9-1-1 for evaluation in case of symptoms suggestive of acute MI. In addition, emerging evidence supports the prehospital performance of ECGs for the rapid identification of patients who will benefit from reperfusion therapy. Prehospital thrombolytic therapy also appears to be beneficial, especially in areas where combined transport and in-hospital delays are long. Additional studies will help define the role of these strategies in a broad spectrum of prehospital emergency medical systems. For example, the current TIMI 19-ER study will address all the difficulties of implementing such a program, not in a single system setting but in 20 systems across the country. It also includes “facilitated intervention,” which should provide cutting-edge data on optimizing thrombolytic therapy regimens for the best patient outcomes.

References


Reperfusion Revisited: Beyond TIMI 3 Flow

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Summary: Therapy for acute myocardial infarction has advanced dramatically since the early 1980s with the use of early intravenous fibrinolytic therapy. Combining low-dose fibrinolysis and platelet lysis appears to provide an additional increase in infarct-related artery (IRA) patency, but the large-scale mortality reduction trials evaluating this strategy are just getting under way. Recently, considerable attention has shifted away from the epicardial arteries to the microvasculature. Contemporary evidence suggests that epicardial patency does not necessarily translate to actual perfusion at the myocardial level. Techniques to evaluate beyond TIMI epicardial flow are now available and validated. In addition, there are promising treatments for the prevention or alleviation of certain forms of microvascular obstruction. This review attempts to clarify the confusion surrounding epicardial flow and “myocardial malperfusion” and to provide some insight into the next direction in acute myocardial infarction therapeutics.

Key words: TIMI flow, perfusion, echocardiography, infarct-related artery

Introduction

Therapy for acute myocardial infarction (MI) has advanced dramatically since the early 1980s with the use of early intravenous fibrinolytic therapy. Current therapy provides an almost 30% mortality decrease in randomized, controlled trials,1–4 with infarct-related artery (IRA) patency rates of approximately 50% at 90 min.5, 6 Mechanical recanalization provides IRA patency rates of 75% [Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade], with a modest benefit in death and reinfarction rates compared with optimal fibrinolytic therapy.7

Combining low-dose fibrinolysis and platelet lysis appears to provide an additional increase in IRA patency,8–11 but the large-scale mortality reduction trials evaluating this strategy are just getting under way.

Recently, considerable attention has shifted away from the epicardial arteries to the microvasculature. Contemporary evidence suggests that epicardial patency does not necessarily translate to actual perfusion at the myocardial level. Techniques to evaluate beyond TIMI epicardial flow are now available and validated. In addition, we have promising treatments for prevention or alleviation of certain forms of microvascular obstruction. In this review, we will attempt to clarify the confusion surrounding epicardial flow and “myocardial malperfusion,” and provide some insight into the next direction in acute MI therapeutics.

Beyond Epicardial Patency

Coronary atherosclerotic plaque rupture and thrombosis of a major epicardial vessel are the underlying cause of acute ST-segment elevation MI. The ability to remove the occluding thrombus, by utilizing either fibrinolytic agents or mechanical techniques, and thus open the IRA, is referred to as “recanalization” or establishing IRA “patency.” “Reflow” is the visualization of contrast dye flowing beyond the site of the previous obstruction to the distal vessel. The quality of flow has been quantified by TIMI flow grade since the early days of intravenous fibrinolytic reperfusion therapy. “Myocardial perfusion” is the ultimate goal and reflects the distribution of blood to the capillary and tissue level. Despite the important differences in their meanings, these terms have unfortunately often been used interchangeably to characterize the outcomes of MI therapy.

The TIMI flow grades (Table I)12 were established to provide a semiquantitative categorization of epicardial blood flow, with the implicit assumption that this would reflect myocardial reflow. TIMI 0/1 flow was deemed to be failure of “reperfusion,” while TIMI 2 and 3 flow grades were considered to be similar and denote successful reperfusion. Subsequently, numerous trials have proven this categorization as faulty. Clinical outcomes, such as ejection fraction, regional wall motion, risk of congestive heart failure, and mortality, are all inferior with TIMI 2 flow compared with TIMI 3 flow.13–19 In fact, the clinical outcomes with TIMI 2 flow are much closer to TIMI 0/1 than to TIMI 3 flow outcomes.
Microcirculatory Malperfusion

There are two broad categories related to abnormal microcirculation in the setting of myocardial reperfusion. The early phase, referred to as microvascular obstruction, is due to platelet microembolism and de novo thrombosis. The later phase represents reperfusion injury and involves tissue edema, neutrophil aggregation, and free-radical release.

Microvascular obstruction: The initial event, acute microvascular obstruction due to platelet microemboli/thrombi, begins concurrently with fibrinolytic therapy. A combination of red (fibrin- and red blood cell-rich) and white (platelet-rich) clots is responsible for coronary obstruction after plaque rupture. Current MI therapy does not affect the platelet component, such that as fibrinolysis occurs (and fibrin is lysed), and fragments consisting of platelet aggregates may be dislodged and become microemboli, which can wedge in the microcirculation and cause obstruction to flow at that level. Furthermore, fibrinolysis generates elevated levels of free thrombin, which is one of the most potent platelet agonists known. In the setting of microcirculatory spasm, due to the release of platelet products (adenosine diphosphate, serotonin, thromboxane A2), and sluggish flow after an ischemic insult, these activated platelets are prone to aggregate, thus causing further microvascular obstruction.

Pathologic studies have found coronary microcirculatory thrombi in the hearts of patients who died of ischemic heart disease. Animal studies provide further evidence of microcirculatory thrombosis and embolization. Our neurology colleagues have provided the most convincing evidence for postischemic microvascular thrombosis in animal stroke models. Indium-111 (In)–labeled platelets have been shown to accumulate in the ipsilateral cerebral cortex in cat, rat, and dog models of stroke and reperfusion.

Reperfusion injury: The second cause of myocardial malperfusion is a manifestation of reperfusion injury. Beginning in the first few hours after recanalization of the IRA, and probably continuing for a few days, is the process of reperfusion injury “no reflow.” Described originally by Klomer et al. in 1974, this process involves the evolution of tissue level pathologic changes that hinder microvascular flow. On histologic examination, myocyte necrosis alone, or in combination with microvascular damage, is observed. However, microvascular damage in isolation is not found. This suggests that microvascular obstruction can be the result, not the cause, of tissue damage. Contraction band necrosis and tissue level edema are also characteristic features. In light of our recent understanding of the process of microvascular platelet embolism/thrombosis, the reason for the lack of isolated microvascular involvement is unclear. A possible explanation for the lack of microvascular thrombosis in the original work of Klomer et al. relates to the
mechanism of obstruction. Coronary obstruction was produced by an external snare; therefore, there would have been no fragmentation of thrombus or increased platelet activation.

Neutrophil accumulation appears to occur over the first 24 h after recanalization. Neutrophils and the inflammatory response play a role in normal healing after MI. In excess, neutrophils may accumulate in the microvasculature, further obstructing flow in the later hours after recanalization. Furthermore, with the release of inflammatory enzymes by the excess neutrophils, additional tissue damage and necrosis may occur. Neutrophil depletion has been shown to decrease reperfusion injury in animal models. Oxygen free radicals are generated soon after the release of the epicardial obstruction. Free-radical scavengers have proven to be effective in reducing reperfusion injury in animal models. Unfortunately, this success has not been replicated in clinical trials. Microvascular spasm, dysfunction, and hyperpermeability have been implicated in this process as well.

From this discussion it is clear that the term “no reflow” is being applied much too broadly and imprecisely. It was initially meant to refer to the pathologic changes associated with late reperfusion injury. Clinical trials of potential treatments for this process have thus far been consistently negative. Microvascular spasm, dysfunction, and hyperpermeability have been implicated in this process as well.

Clinical Diagnostic Evaluation

While TIMI flow grade is easily ascertained, it does not provide determination of actual myocardial perfusion status. Techniques that are more sensitive to microcirculatory flow have been developed and validated over the last decade. Four techniques are well studied and available in the clinical setting: myocardial contrast echocardiography (MCE), Doppler flow wire studies, magnetic resonance imaging (MRI), and nuclear scintigraphy. These techniques can not only define the presence or absence of myocardial perfusion, but also grade the degree of perfusion. An important clue to the mechanism of malperfusion (microembolism/de novo thrombosis versus reperfusion injury/necrosis) is the length of time between epicardial patency and microvascular imaging. Evaluation performed in the early hours would be indicative of microvascular obstruction by platelet emboli/thrombi. Evaluations after the first 2 to 3 h would reflect progressively more reperfusion injury.

MCE is a technique that provides significant amounts of information in patients with acute MI. Echo contrast injections prior to establishing patency of the infarct-related vessel can define the area of myocardium at risk and in doing so establish a baseline for determining the adequacy of myocardial reperfusion. MCE perfusion patterns have been correlated with TIMI flow grades. In a study by Ito et al., 18 of 18 patients with TIMI 2 flow after IRA recanalization displayed reduced myocardial perfusion on MCE, as defined by a ratio of contrast defect area (postrecanalization to prerecanalization) >25%. However, of greater significance is the fact that 11 of 68 patients (16%) with TIMI 3 flow also showed reduced myocardial perfusion. Patients with TIMI 3 epicardial flow, but reduced myocardial perfusion on MCE, had reduced wall-motion scores and ejection fraction at 28 days (Table II), similar to patients with TIMI 2 flow. Other studies have corroborated these findings. These studies verify that not only is there dissociation between epicardial flow and myocardial perfusion but there is significant correlation with myocardial performance parameters.

Ultimately, the goal of reperfusion therapy is to salvage the maximal amount of myocardium in an area of infarction. Several studies have evaluated the comparison of myocardial con-

![Fig. 2 Schematic demonstrating potential outcomes at the microvascular and myocardial level after fibrinolysis. * = The potential target for therapeutic intervention to increase myocardial salvage. PMN = polymorphonuclear monocytes.](image)

<table>
<thead>
<tr>
<th>Table II: Functional outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 3</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>WMS</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
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<tr>
<td></td>
</tr>
<tr>
<td>RWM.</td>
</tr>
<tr>
<td>SD/chord</td>
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</tbody>
</table>

<sup>a</sup> P < 0.05 versus TIMI 3/reflow.
<sup>b</sup> P < 0.001 versus TIMI 3/reflow.
<sup>c</sup> P < 0.001 versus Day 1.

Values are mean ± SD (standard deviation).

Contrast echo to dobutamine stress echo (DSE) in determining myocardial viability. The absence of MCE evidence of perfusion demonstrates a strong correlation with nonviable myocardium on DSE. Presence of contrast perfusion at the myocardial level shortly after recanalization indicates probable viability but does not predict it absolutely. Overall, the sensitivity and specificity for defining myocardial viability for MCE are 100 and 46%, and for DSE are 71 and 88%, respectively. This correlates with data from Bolognese et al. in a study using primary angioplasty for recanalization. The sensitivity and specificity for predicting viability with MCE were 96 and 18%, while for DSE they were 89 and 91%, respectively. This gives MCE a positive predictive value of 41% while DSE is 86%, along with a negative predictive value of 89% (MCE) and 93% (DSE). The reason for this discrepancy of nonviable tissue demonstrating perfusion is unclear. However, it probably represents areas of myocardium that will undergo further evolution from ischemic injury to reperfusion injury to necrosis. Further evidence for this phenomenon comes from Ito et al., who found that a moderate correlation between MCE and late functional improvement increased when the MCE was performed late (i.e., Day 28) (Fig. 3).

The largest drawback to the routine use of MCE is that intracoronary injection of echo contrast is needed. This would typically necessitate echocardiography personnel to be available around the clock or for the invasive catheterization to be performed during the usual hours of echo support availability. Porter et al. have recently demonstrated adequate coronary imaging with a new generation echo contrast agent, perfluorocarbon-exposed sonicated dextrose albumin (PESDA), during intravenous injection. Along with harmonic imaging, the use of this contrast agent would allow studies to be performed at a time separate from any angiography.

The second technique to evaluate microvascular flow is Doppler flow wire studies. In animal studies, basal flow in viable tissue is unimpaired but coronary flow reserve (CFR) decreases initially and then returns to normal within the first week. Intracoronary adenosine improves this flow reduction in viable tissue. Irreversibly damaged tissue shows a decrease in both basal flow and CFR, which does not improve with pharmacologic treatment.

Correlation between Doppler flow wire studies and MCE was demonstrated in a study by Iwakura et al. Patients with MCE perfusion defect and TIMI 2 or 3 epicardial flow exhibited three Doppler findings: (1) a reduction in systolic antegrade flow, (2) an abnormal early systolic retrograde flow, and (3) a rapid deceleration of the diastolic flow velocity. Other studies have found a decreased diastolic-to-systolic flow ratio or decreased CFR in coronary arteries even after successful recanalization for acute MI.

To understand these findings, we need to look closely at the pathophysiology involved in either microvascular obstruction from platelet emboli/thrombi or reperfusion injury. Coronary flow patterns consist of predominant antegrade flow during diastole with lesser flow during systole. This is due to the increased rate in tissue pressure with each cardiac systole, which in turn increases the downstream pressure against which blood must flow. In the absence of a flow-limiting lesion in the epicardial vessel, the microcirculation defines the flow rate of blood in the coronary circulation by autoregulation. In the presence of microvascular obstruction due to either platelet emboli/thrombi, vascular spasm, or injury, there will be a decrease in the aggregate cross-sectional area of the vessels. This decreased area will in turn increase the downstream pressure and decrease the velocity of blood flow. Upon evaluation of epicardial flow, the coronary reserve, diastolic-to-systolic...
flow ratio, and individual flow patterns will be affected. To distinguish between necrotic tissue and potentially reversible changes, the degree of abnormality, effects of pharmacologic treatments, and time course need to be evaluated.

The third diagnostic tool available is MRI. Most of the.data on the use of MRI for evaluating myocardial perfusion/microvascular integrity after coronary occlusion and reperfusion come from animal studies. Rat and canine studies using various contrast agents and techniques (first-pass signal, microvascular leak/tissue accumulation) have shown promise for application in clinical settings. MRI has been able to distinguish reversibly reperfused myocardium from irreversibly damaged myocardium, to evaluate the microvascular integrity, and to correlate defect size with infarct size. In a study by Wu et al., MRI-defined perfusion defects have been correlated with clinical outcomes.

The benefit of MRI is its ability to provide a measure of infarcted territory as well as to evaluate microvascular obstruction and reperfusion. Unfortunately, this means that the patient must be stable enough for transport and a prolonged study in a relatively insecure location. This limitation mandates that the study be performed days after the initial event. The obligatory time delay confounds the ability to distinguish between microvascular perfusion defects due to microvascular obstruction versus evolving reperfusion injury. As discussed earlier, we have been unsuccessful at reversing or altering the process of reperfusion injury. For a diagnostic tool to be clinically useful in tailoring therapy, it must provide the necessary information within the window of time when an intervention can affect the outcome. That window is the first 1 to 2 h of reperfusion, when a significant amount of microvascular obstruction can be expected to be attributable to platelet microemboli/thrombi.

Nuclear imaging with thallium/technetium or positron emission tomography (PET) is the fourth diagnostic modality available. This modality is also the least well investigated in terms of post-MI evaluation. Animal studies have shown that PET can demonstrate the presence or absence of microvascular flow. Schofer et al. were the first group to demonstrate abnormal microvascular perfusion in the setting of acute MI. Kondo et al. demonstrated that patients with normal reperfusion on technetium-99m scintigraphy immediately after recanalization had improved wall motion in the at-risk area on follow-up.

Nuclear evaluation of myocardial perfusion in the setting of acute MI has many of the same disadvantages as MRI. It requires that the patient be transported to a less medically secure environment. Furthermore, imaging must occur within 4 to 6 h of injection, which influences which form of microvascular obstruction (platelet-mediated or reperfusion injury) is being evaluated. Overall, each of these diagnostic tools has advantages and disadvantages, which are summarized in Table III.

**Clinical Relevance**

Among patients with “successful” infarct vessel recanalization (TIMI 3 flow), the reported incidence of myocardial malperfusion ranges from 22 to 50%, with the majority of studies reporting approximately 30%. Alterations in myocardial blood flow and microvascular function over time have been evaluated in both animals and humans. Coronary blood flow was originally measured with radiolabeled microspheres in animal models. Cobb et al. demonstrated that after 2 h of coronary occlusion in a dog model, vasodilation and hyperemia were seen at 15 min of reperfusion. However, by 4 h and again at 3 days, flow was significantly decreased in the previously ischemic region. Later animal studies corroborated these findings and provided comparisons utilizing PET imaging and MCE techniques.

The duration of follow-up has been extended to 2 weeks in patient trials. Neumann et al. demonstrated improvement in basal flow and coronary flow reserve between Doppler flow studies immediately after percutaneous transluminal coronary angioplasty (PTCA)/stent placement for acute MI at Day 14 follow-up. Studies utilizing MCE provide further evidence of improved myocardial perfusion over several weeks. Brochet et al. evaluated patients at Days 1 and 9 after recanalization for acute MI. They found three distinct patterns: sustained myocardial perfusion, sustained nonperfusion, and improved perfusion. The groups with sustained or improved perfusion exhibited the most improvement in wall-motion scores in the risk areas compared with areas of sustained perfusion defects (Fig. 4).

The available data suggest a rapid fall-off in myocardial perfusion after a brief period of hyperemia and vasodilation. This result is consistent with the development of microvascular thrombosis and microvascular spasm in the first several hours after recanalization of the IRA. This is followed by a period of evolution in the tissue and microvasculature. Some patients progress and maintain a level of microvascular obstruction. These are the patients with the most significant ischemic injury, either from the epicardial occlusion or microvascular obstruction in the first few hours, and have the least salvageable tissue and most necrosis. A second group of patients demonstrate a significant decrease in flow initially, with

### Table III: Quantitative comparison of the diagnostic techniques for evaluating myocardial malperfusion

<table>
<thead>
<tr>
<th>Early evaluation after MI</th>
<th>Strength of supporting data</th>
<th>Amount of data collected by study</th>
<th>Accessibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial contrast echo</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Doppler flow wire studies</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>MRI</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Nuclear imaging</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ = Highest rating; + = lowest rating.

**Abbreviations:** MI = myocardial infarction, MRI = magnetic resonance imaging.
subsequent improvement. These patients have resolution of the microvascular obstruction and salvage of a larger proportion of tissue. The last group of patients has evidence of myocardial perfusion that is stable throughout their follow-up. These patients have the most effective recanalization and myocardial salvage. If we can alleviate the initial microvascular obstruction, we can most likely increase the percentage of patients in the latter two groups and provide a better outcome in acute MI care.

The lack of myocardial perfusion after IRA recanalization affects functional improvement and myocardial viability. How does this translate into clinical outcomes? Three small patient series have evaluated the correlation between myocardial perfusion defects and clinical outcomes. Those results are summarized in Table IV. All reported comparisons attain statistical significance.

### Treatment Options

Treatment of myocardial malperfusion has to be directed at the potential mechanisms involved. Treatment of the newly recognized entity of platelet microembolism-induced microvascular obstruction demonstrates encouraging results. In contrast, therapeutic interventions for delayed reperfusion injury have provided limited, if any, benefit to date.

The most promising advance in the treatment of myocardial malperfusion is directed against the platelet microemboli/thrombi formation causing early microvascular obstruction. A murine model of ischemic stroke/reperfusion demonstrates a decrease in platelet accumulation in the ipsilateral hemisphere in mice treated with a novel IIb/IIIa receptor antagonist (SDZ GPI 562) (Fig. 6). Clinical anecdotal evidence also exists of the benefit of IIb/IIIa antagonists in reversing early malperfusion after coronary interventions. Neumann et al. reported the most convincing clinical evidence. Two hundred patients with acute MI undergoing primary PTCA/stent placement were randomized to receive abciximab or conventional therapy. The groups exhibited similar basal and peak flows immediately after recanalization; however, the abciximab group demonstrated a significantly greater increase in both basal and peak flows at the Day 14 evaluation (Fig. 7). Furthermore, the groups demonstrated significant improvement in wall motion scores in the treated group compared with controls (Fig. 8). A comparison of 30-day clinical outcome (death, nonlethal reinfarction, target lesion revascularization) demonstrated an 80% reduction with abciximab (odds ratio of 0.20 (confidence interval: 0.04-0.94); p = 0.031).

The utilization of IIb/IIIa antagonists as a treatment modality for early myocardial malperfusion has far-reaching implications. In addition to the benefits in maintaining epicardial vessel patency, IIb/IIIa antagonists can decrease or eliminate

### Table IV Summary of clinical outcomes on the basis of myocardial malperfusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Diagnostic modality</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakuma et al.</td>
<td>50</td>
<td>MCE</td>
<td>22 Months (median)</td>
<td>• Compared with patients with &lt;45% risk area and minimal defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Major cardiac events of death, MI, CHF, admission with relative risk of 10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Major cardiac events and target lesion revascularization with relative risk of 3.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Comparison with patients with MCE-defined reflow</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Reperfusion arrhythmia 19 vs. 14%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Any arrhythmia except reperfusion 10 vs. 6%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Early CHF 21 vs. 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Late CHF (after 3 days) 6 vs. 1%</td>
</tr>
<tr>
<td>Ito et al.</td>
<td>126</td>
<td>MCE</td>
<td>Hospital stay</td>
<td>• Cardiac death, reinfarction, CHF, stroke</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>44</td>
<td>MRI</td>
<td>16 Months (median)</td>
<td>• Comparison of patients with vs. without MRI defect (45 vs. 9%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** MCE = myocardial contrast echocardiography, MI = myocardial infarction, CHF = congestive heart failure, MRI = magnetic resonance imaging.
the downstream microembolization and thrombosis that cause early microvascular obstruction. In doing so, these agents should alleviate ongoing ischemia, reduce the evolution of reperfusion injury, and maximize myocardial salvage.

The treatment of the multiple mechanisms involved in reperfusion injury has been less successful than that for platelet microcirculatory obstruction. Vasodilators have been used in an attempt to target vasospasm as a potential contributor to early abnormal tissue perfusion. Nicorandil and papaverine have been utilized in small series, with improvement noted in perfusion grades. Verapamil administered via intracoronary injection has been reported to improve angiographic and MCE-defined abnormal perfusion.

Adenosine has been successful in animal models in reducing infarct size and improving regional myocardial blood flow. This benefit was initially considered a function of its vasodilatory effects. However, recent evidence from Min-

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**Fig. 5** Event-free survival (clinical course without cardiovascular death, reinfarction, congestive heart failure, or stroke) for patients with and without magnetic resonance imaging microvascular obstruction. Reproduced with permission from Wu K, et al.: Prognostic significance of microvascular destruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–772.

**Fig. 6** Indium-111–labeled platelet accumulation expressed as a ratio of ipsilateral/contralateral cpm in control (No stroke, n = 11) and experimental animals. Stroke + vehicle = saline (n = 10), Stroke + GPI = glycoprotein IIb/IIIa inhibitor (n = 10). Data are shown as mean ± SEM. *P < 0.005 versus No stroke and Stroke + GPI; p = not significant between No stroke and Stroke + GPI. Reproduced with permission from Choudhri TF, et al.: J Clin Invest 102:1301–1310 (1998).

**Fig. 7** Plot of the differences between 14-day follow-up and initial postinterventional study in basal flow velocity and in papaverine-induced peak flow velocity at treated lesion. Columns represent mean difference. Error bars indicate 95% confidence interval. Error bars not including zero indicate that change between initial study and follow-up is statistically significant at 0.05 level. P values above columns refer to differences between two treatment groups. ■ = abciximab, □ = heparin. Reproduced with permission from Neumann FJ, et al.: Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.

**Fig. 8** Plot of differences between 14-day follow-up and initial postinterventional study in wall-motion index (A) and in chords with hypokinesis (B). Columns represent mean difference. Error bars indicate 95% confidence interval. Error bars not including zero indicate that change between initial study and follow-up is statistically significant at 0.05 level. P values above columns refer to differences between the two treatment groups. ■ = abciximab, □ = heparin. Reproduced with permission from Neumann FJ, et al.: Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.
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13. Lincoff AM, Topol EJ, Sigmun KN, Lee KL, Ohman EM, Rosen-schein U, Ellis SG: Significance of a coronary artery with thrombus formation can be resolved, providing increased myocardial salvage. Tissue level perfusion is an evolving concept and platelet activation. Finally, work still needs to be done to decrease the delayed microvascular obstruction and tissue damage from reperfusion injury. It appears that the confus-

Conclusion

The realization has been reached that the static appearance of the epicardial artery is often dissociated from the underlying myocardial perfusion. Tissue level perfusion is an evolving process and early microvascular obstruction or de novo thrombus formation can be resolved, providing increased myocardial salvage. Both ongoing ischemia and the progression of reperfusion injury can lead to further myocardial necrosis, despite the angiographic appearance of a patent IRA.

In 1999, we have the ability to look beyond the epicardial vessel and evaluate the true tissue perfusion status. The understanding of the various tissue and microvascular level processes allows therapy to be tailored appropriately. Currently available IIb/IIIa receptor antagonists have been demonstrated to alleviate the early platelet-mediated microvascular obstruction, with subsequent increase in myocardial salvage. This has already proven to improve myocardial functional status and is associated with improved clinical outcomes as well.

The future of true myocardial reperfusion hinges on our ability to achieve a further decrease in microvascular obstruction in the early and delayed phases. Currently, the combination of low-dose fibrinolytics and platelet-lysis therapy is being evaluated for clinical outcomes. Further study of the impact of IIb/IIIa receptor antagonists on early microvascular obstruction should be evaluated to corroborate the initial trials. Direct thrombin antagonists or low–molecular-weight heparin can potentially have an additive benefit due to their ability to block the effects of thrombin on the coagulation cascade and platelet activation. Finally, work still needs to be done to decrease the delayed microvascular obstruction and tissue damage from reperfusion injury. It appears that the confusion surrounding myocardial reperfusion is gradually lifting and potential avenues of therapeutic intervention are being pursued.

min et al.23 supports an additional effect of adenosine on decreasing P-selectin–dependent platelet thromboembolism. Among patients with anterior wall MI, the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial80 demonstrated a decrease in infarct size in patients administered adenosine compared with placebo, when administered in conjunction with fibrinolytics.

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Incorporating Platelet Glycoprotein IIb/IIIa Inhibition in Critical Pathways: Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction

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Summary: Platelet glycoprotein (GP) IIb/IIIa inhibitors have been shown to be effective in reducing thrombotic events in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI) and when used as medical therapy in patients with unstable angina/non–ST-segment elevation myocardial infarction (MI). Recent findings include dramatic preventive benefits in the setting of coronary stent deployment and a significant long-term preventive effect on mortality. The benefits of GP IIb/IIIa receptor inhibition suggest the utility of adopting routine use of these agents in critical pathways of unstable angina/non–ST-segment elevation MI and PCI. Because cost constraints may limit use of these agents, however, targeting treatment based on patient risk assessment may be warranted.

Key words: Glycoprotein IIb/IIIa, pathway, unstable angina, coronary intervention

Introduction

Platelet glycoprotein (GP) IIb/IIIa receptor inhibitors preclude platelet function by occupying the fibrinogen binding site on the platelet surface, preventing cross-linking of platelets by fibrinogen during thrombus formation induced by plaque disruption or rupture.1–3 Inhibition of platelet aggregation with GP IIb/IIIa receptor inhibitors has been shown to improve clinical outcome in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI).4–8 GP IIb/IIIa receptor inhibitor treatment in patients undergoing PCI has been found to reduce the incidence of death, myocardial infarction (MI), and/or urgent revascularization in high-risk patients, those undergoing elective procedures, patients with unstable angina, patients with acute ST-segment elevation MI, and in those undergoing coronary stent deployment; use of GP IIb/IIIa receptor inhibitors in this setting has become a new therapeutic standard. In addition, GP IIb/IIIa receptor inhibitors are approved for use as initial treatment in patients with unstable angina/non–ST-segment elevation MI, having been associated with significant reductions in clinical endpoints regardless of whether patients are managed medically or subsequently undergo PCI or surgical intervention.

Overall, the benefits of platelet receptor inhibition shown by these agents in clinical trials have served to highlight the importance of acute thrombosis and platelet aggregation in acute coronary syndromes and have underscored the need to determine how GP IIb/IIIa receptor inhibition is to be best fit into critical pathways for the management of patients with acute coronary syndromes. The current article describes experience with GP IIb/IIIa receptor inhibitor treatment in interventional and medical therapy patient populations, focusing on use in the setting of unstable angina/non–ST-segment elevation MI and describing initial attempts to incorporate such treatment into critical pathways at the author’s institution. The use and potential role of GP IIb/IIIa receptor inhibitors in the setting of acute ST-segment elevation MI is extensively discussed in another article in this supplement.

Improved Clinical Outcomes with GP IIb/IIIa Receptor Inhibition in Interventional and Medical Management Trials

The benefits of GP IIb/IIIa receptor inhibitor treatment were initially demonstrated in trials of abciximab, a chimeric monoclonal antibody fragment, in patients undergoing PCI. The use of abciximab, combined with heparin and aspirin, was shown to be beneficial in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial of high-risk patients undergoing PCI,4, 9, 10 the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial in intervention patients across all risk strata,6 and the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial,11 in which abciximab treatment was used as medical therapy prior to intervention in patients with refractory unstable angina and was associated with significant reductions in the primary endpoint of death,
MI, or urgent revascularization at 30 days, compared with standard treatment with aspirin and heparin (Fig. 1A). These benefits have been shown to be durable (Fig. 1B), with significant prevention of thrombotic events observed up to 3 years in the EPIC population.10

The more recent Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial compared abciximab plus stenting or coronary angioplasty with stenting plus placebo in all patients receiving aspirin and heparin.5 The results of this trial, the largest stenting trial reported to date, are important because stenting has become common practice in coronary intervention in the past several years and now represents state-of-the-art interventional treatment. EPISTENT showed that the addition of abciximab to aspirin and heparin in patients undergoing coronary stent deployment resulted in a 50% relative reduction and a 5.5% absolute reduction in rates of death, MI, or urgent revascularization at 30 days (p < 0.001) compared with stenting alone (Fig. 2). These benefits have also proven to be durable. Compared with the stent group receiving placebo, patients receiving stent/abciximab exhibited a 5.7% absolute reduction in death, MI, or urgent revascularization, a 5.8% absolute reduction in death or MI, and a 5.3% absolute reduction in death, MI, or target vessel revascularization at 6 months.12 At 1 year, a mortality benefit was seen: mortality was reduced by 58% (2.4% for the placebo plus stent group vs. 1.0% for the abciximab plus stent group; p = 0.03).13

The benefits of GP IIb/IIIa receptor inhibition in patients with unstable angina undergoing PCI appear to result from both prevention of platelet aggregation during iatrogenic plaque disruption and stabilization of the complex plaques prior to intervention. As shown in the CAPTURE trial of abciximab,11 administration of abciximab for up to 24 h prior to intervention resulted in a significant reduction in rates of both preintervention MI and intraprocedural MI, the latter of which accounted for the majority of events (Fig. 3). The ability of these agents to reduce thrombotic events appears to be explained by their ability to resolve thrombi. For example, data from a subset of CAPTURE patients14 indicate that the addition of abciximab to aspirin and heparin resulted in a significantly greater frequency of thrombus resolution prior to coronary intervention (42.2 vs. 20.5%; p = 0.038).

Fig. 1 Rates of primary endpoints of death, myocardial infarction (MI), or urgent revascularization at 30 days (A) and rates of the composite endpoint (death, MI, or any intervention) at 6 months (B) in the EPIC, EPILOG, and CAPTURE trials of abciximab. Abciximab recipients in EPIC received bolus plus infusion; abciximab recipients in EPILOG received abciximab with low-dose, weight-adjusted heparin for 30-day results and all patients for 6-month results. Patients in EPIC and EPILOG received abciximab bolus immediately prior to PCI, with infusion continuing after intervention. Patients in CAPTURE received abciximab infusion for up to 24 h prior to intervention. Courtesy of Centocor, Inc.

Fig. 2 Patients from EPISTENT who experienced the primary endpoint of death, MI, or urgent revascularization at 30 days. Reproduced with permission from The EPISTENT Investigators: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998;352:87–92. © by The Lancet Ltd. 1998.

Fig. 3 Incidence of myocardial infarction before and after percutaneous coronary intervention in the CAPTURE trial. PTCA = percutaneous transluminal coronary angioplasty. Reproduced with permission from The CAPTURE Investigators: Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: The CAPTURE Study. Lancet 1997;349:1429–1435. © by The Lancet Ltd. 1997.
The notion that improved clinical outcome with these agents is consequent upon both inhibition of platelet aggregation and thrombus resolution is borne out by three major studies with other GP IIb/IIIa receptor inhibitors as medical therapy in patients with unstable angina/non–ST-segment elevation MI. In the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial, treatment with the GP IIb/IIIa receptor inhibitor tirofiban was associated with a reduction of 32% in the primary endpoint of death, MI, or recurrent ischemia at 48 h (3.8% for the tirofiban group vs. 5.9% for the heparin group; p = 0.007) compared with aspirin and heparin alone, with PCI being performed in only 1.9% of patients within this time period. By 30 days, however, there was no significant difference between groups with regard to rates of death and MI, or recurrent ischemia at 48 h (3.8% for the tirofiban group vs. 5.9% for the heparin group; p = 0.007) compared with aspirin and heparin alone, with PCI being performed in only 1.9% of patients within this time period. By 30 days, however, there was no significant difference between tirofiban and placebo groups with regard to rates of the composite endpoint (15.9 vs. 17.1% for tirofiban and placebo, respectively; p = 0.11). In the PRISM in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, which included patients with more severe clinical expression of unstable angina, tirofiban plus heparin and aspirin was associated with a 32% reduction in the primary endpoint of death, MI, or recurrent ischemia at 7 days (17.9 vs. 12.9%; p = 0.004), including results in patients who subsequently underwent intervention. Rates of the composite endpoint were also significantly reduced in the tirofiban group at 30 days and 6 months.

In the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, treatment with the GP IIb/IIIa receptor inhibitor eptifibatide was associated with a 10% reduction in the primary endpoint of death or MI at 30 days (14.2% for the eptifibatide group vs. 15.7% for the placebo group; p = 0.042).

A recent meta-analysis of the effect of GP IIb/IIIa receptor inhibitor treatment on the rate of death or MI in the interventional or medical management setting in trials reported by mid-1998 indicates a highly significant benefit of such treatment in a combined population of more than 30,000 patients (Fig. 4). The ability of GP IIb/IIIa receptor inhibition to reduce thrombotic events in both patients with acute coronary syndromes and in those undergoing PCI indicates the potential benefit of including treatment with these agents across the entire spectrum of patients with unstable angina/non–ST-segment elevation MI.

### Reduction in Mortality in Abciximab Trials

It is important to note that although GP IIb/IIIa receptor inhibitor treatment has been associated with reductions in thrombotic events in clinical trials, there has been no clear indication of reduced mortality alone until recently. Indeed a recent meta-analysis of all trials showed no benefit on mortality across all agents. However, a meta-analysis of 5,000 patients who received abciximab after PCI showed that abciximab treatment was associated with a 30% reduction in mortality over the course of follow-up (hazard ratio 0.70, 95% confidence interval 0.52–0.94; p = 0.016). The association of
abciximab treatment with reduced mortality indicated by this analysis has been strikingly borne out by recently reported long-term findings in the EPISTENT trial. These data show that abciximab/stent treatment was associated with a 58% relative reduction in mortality at 1 year compared with placebo/stent treatment among all randomized patients (1.0 vs. 2.4%, \( p = 0.03 \)). An updated mortality meta-analysis, including the EPISTENT outcomes (a total of more than 6,500 patients), indicates a 36% mortality risk reduction (\( p = 0.002 \)) among patients receiving abciximab (Fig. 5).18

There is some speculation on the etiology of abciximab’s mortality benefit when no other GP IIb/IIIa receptor inhibitors have shown such effect. Possibilities that have been raised include greater reductions in the occurrence of periprocedural MI, as well as physiologic responses that may be related to the vitronectin receptor or perhaps even MAC 1 as opposed to GP IIb/IIIa receptor blockade. Abciximab’s long duration of platelet inhibition may also be responsible for the reduction in long-term mortality.

It is noteworthy that such benefits do not occur at the cost of increased bleeding risk, the adverse effect that has been of primary concern with GP IIb/IIIa receptor inhibition. The results of EPISTENT also reconfirmed earlier data that showed that there is no increased risk of major bleeding with GP IIb/IIIa receptor inhibitor treatment when reduced-dose, weight-adjusted heparin regimens are used (Fig. 6). After observation of increased bleeding risk with standard heparin regimens in the EPIC trial,4 use of a lower dose heparin regimen in combination with abciximab in EPILOG6 was shown to result in bleeding rates comparable to those observed with placebo, and an important interaction of GP IIb/IIIa receptor inhibition with heparin was identified. This experience supports the general principle that dosing of components of an antithrombotic regimen must be reevaluated when an additional antithrombotic agent is added.

**Incorporation of GP IIb/IIIa Receptor Inhibitor Treatment in Critical Pathways**

The critical pathways for acute coronary syndromes currently in place at Brigham and Women’s Hospital in Boston are shown in Figure 7A; the newly revised critical pathway for unstable angina/non–ST-segment elevation MI is shown in Figure 7B. In terms of initial management, the focus for low-risk patients is on making a clear diagnosis. For those with unstable angina/non–ST-segment elevation MI, GP IIb/IIIa receptor inhibitor treatment has been incorporated into initial management. Options in the use of this treatment include beginning treatment upon admission or starting patients who will be rapidly moved to the catheterization laboratory on aspirin and heparin, with the GP IIb/IIIa receptor inhibitor added in those undergoing coronary intervention.

Much of the data shown for trials investigating GP IIb/IIIa receptor inhibition as medical management in unstable angina include outcomes in patients who subsequently underwent coronary intervention. Indeed, much of the benefit of GP IIb/IIIa blockade in the PRISM, PRISM-PLUS, and PURSUIT trials was driven by the subpopulation that underwent percutaneous revascularization.7 However, as shown by a breakdown of data from PRISM-PLUS,8 benefits in reducing 30-day rates of death or MI were observed in subsets of patients who received no intervention, underwent PCI, or required coronary artery bypass grafting (Fig. 8). A similar trend was observed in the PURSUIT trial.7 The ability of these agents to stabilize patients regardless of treatment strategy may be an important factor in deciding how such treatment is to be incorporated into management pathways.

**Cost Effectiveness**

The benefits observed with GP IIb/IIIa receptor inhibitor treatment across the spectrum of acute coronary syndromes...
argue for their routine use. However, cost constraints are often cited as a factor motivating limited use based on risk assessment. Currently, there are few published data on cost effectiveness of GP IIb/IIIa receptor inhibitor treatment. A cost analysis of treatment in patients in the EPIC trial\(^{19}\) showed that cost savings associated with reduced need for reintervention during initial hospitalization were virtually offset by cost of the excess bleeding complications observed in the trial. At 6 months, the lower rates of rehospitalization, catheterization, and reintervention in abciximab patients resulted in a cost savings that resulted in a net cost of $200 per patient when the abciximab drug cost was included.

Analysis of the 470 patients with unstable angina in EPIC showed a relative cost of $264 per patient during initial hospitalization and a net savings of $763 per patient including drug cost at 6 months.\(^{20}\) These findings suggest that cost effectiveness of abciximab may be relatively increased in patients with unstable angina. Indeed, a cost-effectiveness analysis combining data from major abciximab trials prior to EPISTENT indicates a cost of $18,000 per life-year-saved (data on file, Centocor, Inc.); this value compares quite favorably with cost per life-year-saved of other accepted standard therapies. For example, it is lower than the estimated $32,000 cost per life-year-saved for tissue plasminogen activator compared with streptokinase.

Despite the optimistic economic data and the demonstration of benefits of GP IIb/IIIa receptor inhibitor treatment across risk strata, there may be economic advantages to targeting the use of GP IIb/IIIa receptor inhibitors to high-risk patients. Several different approaches have been taken to assess risk in acute coronary syndrome patients. The Thrombolysis in Myocardial Infarction (TIMI)-III trial\(^{21, 22}\) and other trials have established ST-segment depression and transient ST-segment elevation as important risk factors. Troponin levels have also been shown to be useful in the identification of patients at elevated risk of adverse outcome. In the CAPTURE trial, prior to intervention, rates for death or MI for troponin-positive patients were 0% for the abciximab group versus 6.1% for the placebo group (\(p = 0.01\)).\(^{23}\) During intervention, all patients benefited equally from abciximab, and rates were 2% for the abciximab group versus 10% for the placebo group (\(p = 0.01\)). At 6 months, the benefit was sustained (9.5% for the abciximab group versus 25.5% for the placebo group; \(p = 0.004\)). Positive troponin status at baseline was predictive of risk of death or MI prior to intervention, with abciximab treatment associated with a dramatic decrease in event rate for up to 6

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Fig. 7 Critical pathways for patients with acute coronary syndromes at Brigham and Women’s Hospital (A). Critical pathways for patients with unstable angina/non–ST-segment elevation myocardial infarction at Brigham and Women’s Hospital (B). ECG = electrocardiogram, PTCA = percutaneous transluminal coronary angioplasty, MI = myocardial infarction, ED = emergency department, ETT = exercise treadmill test.

Fig. 8 Rates of death or myocardial infarction at 30 days in patients in the PRISM-PLUS trial who received medical therapy alone (i.e., no intervention), percutaneous transmural coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) for groups that received heparin and aspirin (ASA) alone or with tirofiban. CI = confidence interval. Adapted from Ref. No. 30 with permission.
months. Patients who were troponin negative had very few events and, as such, little benefit from abciximab, underscoring the need to identify patients appropriately who will derive the most benefit from the drug.

Other high-risk patients include those refractory to medical therapy and those with compromised left ventricular function. The CAPTURE trial demonstrated that GP IIb/IIIa blockade is beneficial as a pretreatment and as adjunctive treatment to percutaneous transluminal coronary angioplasty in refractory unstable angina patients.

As noted, data from the PRISM-PLUS and CAPTURE trials indicate that patients benefit from GP IIb/IIIa receptor inhibitor treatment during the preintervention period and in cases in which no intervention is performed. The issue of whether an invasive approach or conservative medical management results in superior clinical outcome in patients with unstable angina/non–ST-segment elevation MI remains undecided. The TIMI-IIIB trial showed that coronary intervention was associated with a significantly lower rate of rehospitalization for patients with angina than for patients who received conservative management, with no differences in the rates of death/MI or death at 1 year. The Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial showed no difference between the approaches in rates of death/MI at follow-up but did show a significant reduction in 1-year mortality in patients who received conservative management. It is important to note that stenting was not incorporated into the TIMI-IIIB and VANQWISH trials, and stenting is a prime consideration in clinical practice.

The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI-18 study is examining the issue of how best to triage patients to a treatment strategy when routinely incorporating GP IIb/IIIa receptor inhibition into their management. As shown in Figure 9, patients with unstable angina/non–ST-segment elevation MI are treated with aspirin, heparin, and the GP IIb/IIIa receptor inhibitor tirofiban and randomized to early invasive or conservative treatment.

It should be noted that the inclusion of low–molecular-weight heparin as potential treatment for unstable angina/non–ST-segment elevation patients in our critical pathway reflects recent findings indicating the superiority of low–molecular-weight heparin over standard unfractionated heparin. Several studies are currently under way to examine the combination of GP IIb/IIIa receptor inhibition with low–molecular-weight heparin.

It is expected that optimal antithrombotic therapy will involve the combination of a low–molecular-weight heparin and a GP IIb/IIIa receptor inhibitor to improve both the anticoagulant and antiplatelet therapy for patients with unstable angina/non–ST-segment elevation MI.

Conclusions

GP IIb/IIIa receptor inhibitors have been shown to be effective in reducing thrombotic events in patients with acute coronary syndromes and in those undergoing PCI. Recent findings include marked reductions in event rates in stented patients with GP IIb/IIIa receptor inhibition and significant reductions in mortality in patients undergoing PCI who receive abciximab. The ability of these agents to prevent thrombotic events in patients with unstable angina/non–ST-segment elevation MI across all risk strata and in both the medical management and interventional settings suggests that their use should be routinely adopted into critical pathways for such patients. However, in situations where costs are an issue, one means of optimizing the cost effectiveness of these agents is to utilize risk assessment so that therapy can be targeted at higher risk patients.

References


Combination Therapy for Acute Myocardial Infarction: Glycoprotein IIb/IIIa Inhibitors plus Thrombolysis

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Summary: Although thrombolytic therapy has been a major advance in the treatment of acute ST-segment elevation myocardial infarction (MI), new thrombolytic agents have been unable to improve early reperfusion. Because aspirin has been shown to be a very effective adjunctive agent in patients with acute MI, it has been hypothesized that the use of platelet glycoprotein (GP) IIb/IIIa receptor inhibitors combined with thrombolytic agents would lead to more effective platelet inhibition and improved angiographic and clinical efficacy. Emerging experimental and clinical data, including the Thrombolysis in Myocardial Infarction (TIMI)-14 trial, suggest that combining GP IIb/IIIa receptor inhibition with reduced-dose thrombolytic therapy improves early infarct-related artery patency without increasing bleeding risk. Thus, given the strong clinical and physiologic rationale, clinical investigation in patients with acute ST-segment elevation MI is currently focused on combining GP IIb/IIIa receptor inhibitors with reduced-dose fibrinolytic agents in acute MI.

Key words: thrombolysis, fibrinolysis, glycoprotein IIb/IIIa, acute coronary syndrome, combination

Introduction

While thrombolytic therapy has proven to be a major advance in the treatment of patients with acute myocardial infarction (MI),¹,² current thrombolytic regimens have several limitations: (1) failure of initial reperfusion,³,⁴ (2) inadequate perfusion with delayed Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow,³,⁴ (3) imperfect myocardial perfusion,⁵ and (4) infarct-related artery (IRA) reocclusion/reinfarction in significant percentages of patients.⁴,⁶ Even with the second- and third-generation plasminogen activators, rates of TIMI grade 3 flow in the IRA have remained at approximately 60%.⁷,⁸ Because these problems are associated with increased subsequent mortality⁵,⁶,⁹ and because platelets play a central role in coronary thrombosis, especially failed reperfusion, reocclusion, and reinfarction, attention has turned to the glycoprotein (GP) IIb/IIIa receptor inhibitors as a means of improving current reperfusion regimens.¹⁰

Mechanisms of Thrombolytic Resistance and Reocclusion

Rupture or erosion of a lipid-rich atherosclerotic plaque exposes the subendothelial plaque components to circulating blood.¹¹,¹² Platelet adhesion and aggregation at this site lead to the formation of a thrombus that can cause myocardial ischemia or infarction. Recent angioscopic studies have shown that a substantial portion of an occlusive coronary thrombus (which previously had been thought to consist only of fibrin-rich “red” clot) is made up of platelets (the so-called “white” clot).¹³ These findings also have been found in pathologic studies of ruptured plaques.¹⁴,¹⁵ Platelet-rich thrombi are more resistant to fibrinolytic therapy than are thrombi composed predominantly of fibrin and erythrocytes.¹⁶ Lack of initial reperfusion, which could be termed “thrombolytic resistance,” occurs due to several mechanisms (Table I): (1) Fibrinolytic agents act only on the fibrin portion of the thrombus, leaving activated platelets as a source of rethrombosis; (2) platelets elicit plasminogen activator inhibitor-1 (PAI-1), which inhibits the action of the thrombolytic agent, and platelets also release other agents such as thromboxane A₂, which causes local vasoconstriction;¹⁷,¹⁸ (3) lysis of clot-bound fibrin exposes clot-bound thrombin, which remains catalytically active and can cleave fibrinogen to fibrin, facilitating rethrombosis.¹⁹ In addition, thrombosis can stimulate further thrombin production and activation of platelets;²⁰ thrombolytic therapy also has a direct platelet-activating effect, leading to increased levels of thromboxane A₂ and platelet-activating factor (PAF).²¹ The presence of aspirin does not abolish the platelet-activating effect of fibrinolytic therapy.¹⁷,¹⁸ In summary, fibrinolysis promotes platelet activation and, therefore, actually creates an environment that may lead to subsequent rethrombosis and/or reocclusion.
Aspirin

Coadministration of aspirin addresses some of the limitations of thrombolytic agents. Aspirin has been shown to decrease the risks of IRA reocclusion,22 reinfarction,2, 23-25 and mortality,2 benefits additive to those achieved by thrombolytic therapy. These clinical observations highlight the pathophysiologic synergism of aspirin and thrombolytic therapy, which exists because each agent targets a separate part of the thrombus. Although aspirin is a relatively weak antiplatelet agent, its dramatic clinical benefits have increased awareness of the central role that platelets play in the thrombus formation process and rethrombosis after thrombolytic therapy. This has spurred the development of agents that have a more direct effect on platelet aggregation, such as the GP IIb/IIIa receptor antagonists, which bind directly to the receptors on the platelet surface that are responsible for platelet aggregation.

Platelets and Acute Myocardial Infarction

Acute MI is usually caused by the rupture or ulceration of an atherosclerotic plaque. The subendothelial matrix (i.e., collagen and tissue factor) is exposed to the circulating blood, and platelets mediate the “primary hemostasis” at the site of a ruptured plaque (Fig. 1). The first step is platelet adhesion via the GP Ib receptor, as well as via von Willebrand factor. This is followed by platelet activation, which leads to (1) a shape change in the platelet (from a smooth discoid shape to a spiculated form—this increases the surface area upon which thrombin generation can occur); (2) degranulation of the alpha and dense granules, thereby releasing thromboxane A₂, serotonin, and other platelet aggregatory and chemotactic agents; and (3) expression of GP IIb/IIIa receptors on the platelet surface in an “activated” state such that they can bind fibrinogen. The final step is platelet aggregation, that is, the formation of the platelet plug. Fibrinogen (or von Willebrand factor) binds to the activated GP IIb/IIIa receptors of platelets, thereby creating a growing platelet aggregate.

GP IIb/IIIa Receptor Inhibition

Fibrinogen and von Willebrand factor, as well as fibronectin and vitronectin, bind to platelet GP IIb/IIIa receptors via an arginine-glycine-aspartic acid (RGD) sequence. Although many agonists can activate platelets, the binding of adhesive proteins to integrins on adjacent platelets represents the final common pathway in the biological process of platelet aggregation. Thus, profound suppression of platelet aggregation may be achieved by direct blockade of the GP IIb/IIIa receptor that extends beyond the capabilities of aspirin, ticlopidine, and clopidogrel.

It was initially demonstrated in 1983 that GP IIb/IIIa receptor blockade by the murine monoclonal antibody 10E5 completely inhibited platelet aggregation induced by adenosine diphosphate, thrombin, and epinephrine.26 Removal of the Fc fragment of a similar antibody, 7E3, and subsequent recombinant Fab fragment with constant regions of human immunoglobulin resulted in the chimeric antibody c7E3 Fab, later named abciximab. Several peptide and pharmacologic GP IIb/IIIa receptor inhibitors, with varying affinity for the target integrin, were subsequently developed.

These nonantibody agents work by mimicking the RGD sequence on fibrinogen to inhibit the platelet GP IIb/IIIa receptor. Abciximab binds to the IIb/IIIa receptor and to a broader group of integrins, such as the α₃β₃ (vitronectin) receptor,
which appears to be important in neointimal proliferation. In addition, abciximab has been shown to inhibit thrombin generation by tissue factor, most likely due to its dual blockade of the GP IIb/IIIa and α,β3 receptors.27

Clinical Experience with GP IIb/IIIa Receptor Inhibitors

Percutaneous Coronary Intervention

Extensive research has been conducted on the prophylactic use of GP IIb/IIIa receptor blockers in a spectrum of patients undergoing percutaneous coronary intervention (PCI). The first agent to be studied was abciximab, in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial. For patients undergoing high-risk angioplasty or atherectomy, treatment with abciximab was associated with a significant 35% reduction in major ischemic events at 30 days.26 This benefit has been shown to be sustained at 3 years.29

Clinical benefit was also seen in the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial of high- and low-risk patients who received abciximab30 and in the Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombus (IMPACT)-II trial of eptifibatide, which also comprised patients from all risk strata,31 patients with refractory unstable angina treated with abciximab,32, 33 patients with ongoing or recent acute coronary syndromes who received tirofiban,34 patients undergoing coronary stenting,35 and patients undergoing "primary PCI" for acute ST-segment elevation MI.36–38

Mortality Benefit

The most recent data in the PCI setting come from the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial that compared stenting plus placebo with stenting plus abciximab and balloon angioplasty plus abciximab. The addition of abciximab led to a > 50% reduction in death, MI, and urgent revascularization at 30 days for the stenting plus abciximab group compared with the stenting plus placebo group (absolute reduction of 5.5%).39 At 1 year, there was a mortality benefit for abciximab: patients undergoing elective stenting had a mortality of 2.4% versus 1.0% (p = 0.03) for patients receiving abciximab plus stenting.39 These 1-year data are the only data from a single trial demonstrating a mortality benefit for the GP IIb/IIIa receptor inhibitor class. In addition, this benefit emerged over time, a phenomenon seen in the other trials of abciximab.

There is now a paradigm shift in the understanding of the benefit of IIb/IIIa receptor inhibitors. These agents inhibit platelets, increase resolution of coronary thrombus, improve coronary flow, thus preventing early recurrent ischemic events (MI or refractory ischemia/urgent revascularization). The recent data now suggest that these benefits translate into a late mortality benefit. These new data emphasize the importance of effective platelet inhibition in these syndromes.

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Glycoprotein IIb/IIIa receptor inhibitors also have been shown to be of benefit in the initial treatment of unstable angina and non–ST-segment elevation MI. In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, patients with unstable angina or non–ST-segment elevation MI who received tirofiban, heparin, and aspirin had reduced rates of death, MI, or refractory ischemia compared with patients who received heparin and aspirin alone at 7 days (12.9 vs. 17.9%; p = 0.004) and at 30 days (18.5 vs. 22.3%; p = 0.03).40 In the PRISM trial, tirofiban plus aspirin was compared with heparin plus aspirin in patients with unstable angina; tirofiban was associated with a 32% reduction in the composite endpoint of death, MI, or refractory ischemia at 48 h (3.8 vs. 5.6%; p = 0.01).41

In addition, the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, which studied patients with unstable angina, showed a significant reduction in the risk of death or MI at 30 days with eptifibatide compared with placebo (15.7% for the placebo group vs. 14.2% for the eptifibatide group; p = 0.04).42

Abciximab and lamifiban are each currently being tested in large phase III trials in patients with unstable angina and non–ST-segment elevation MI: abciximab in the Global Use of Strategies to Open Occluded Arteries (GUSTO)-IV trial and lamifiban in the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-B trial.

Thrombolytic Therapy in Combination with GP IIb/IIIa Receptor Inhibitors

Combining GP IIb/IIIa receptor inhibitors with thrombolytic therapy is the subject of current investigation. Preclinical studies were performed with this combination that first evaluated accelerated reperfusion time and reduction of the risk of reocclusion.43, 44 These studies have led to several clinical trials.

Full-Dose Thrombolytic Therapy plus GP IIb/IIIa Receptor Inhibition

TAMI-8: The first trial to evaluate GP IIb/IIIa receptor blockade with fibrinolytic therapy, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-8 pilot study,35 established the clinical feasibility of the combined treatment approach. After receiving a full-dose tissue plasminogen activator (t-PA) plus heparin and aspirin, patients received incremental doses of m7E3, a murine monoclonal antibody to the GP IIb/IIIa receptor. A consistent dose-dependent increase in platelet aggregation was observed, and a clear relationship between GP IIb/IIIa receptor occupancy and extent of platelet in-
Infarction flow grade. = tissue plasminogen activator, TIMI = Thrombolysis in Myocardial Infarction. *P = 0.006. Eptifib = eptifibatide, hem = hemorrhage, t-PA = tissue plasminogen activator, TIMI = Thrombolysis in Myocardial Infarction flow grade.

**IMPACT-AMI:** Results of the combination of eptifibatide and t-PA were reported from the Integrilin to Manage Platelet Aggregation and Combat Acute Myocardial Infarction (IMPACT-AMI) trial, which administered the two agents simultaneously. Patients who received the highest dose of eptifibatide showed a significantly increased rate of TIMI grade 3 IRA flow on angiography at 90 min (66%, compared with 39% in the placebo group; p = 0.006) (Fig. 2).  

No differences were seen in the rates of major or minor bleeding complications, including intracranial hemorrhage (ICH). It was noted subsequently, however, that the dosages of eptifibatide used achieved only 50 to 60% platelet inhibition. 

**Streptokinase-Eptifibatide Trial:** A subsequent trial was performed combining full-dose streptokinase with ascending dosages of eptifibatide. In the double-blind, placebo-controlled pilot study involving 181 patients with acute MI, streptokinase (1.5 MU/h) was combined with eptifibatide (a 180 µg/kg bolus followed by infusions of 0.75, 1.33, or 2.0 µg/kg/min for 24 h) without heparin. TIMI grade 3 flow in the IRA at 90 min was achieved by 53, 44, and 52% of patients randomized to the three dosage levels of eptifibatide, respectively, compared with 38% of patients in the placebo group (Fig. 2). Rates of TIMI grade 2 or 3 flow also tended to be higher in patients treated with eptifibatide, 75, 73, and 88%, respectively, compared with 65% in patients treated with placebo.

An increased incidence of bleeding, most often at the site of arterial puncture, was associated with increasing dosages of continuous infusion of eptifibatide. Rates of severe bleeding were 9, 9, and 15%, respectively, compared with 0% for placebo, which led to premature discontinuation of the highest dose of eptifibatide. There were no occurrences of ICH.

**PARADIGM:** The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial compared different lamifiban dosage levels with placebo in 353 patients presenting within 12 h of acute MI symptom onset. Patients received aspirin and heparin and either t-PA or streptokinase at standard doses. Lamifiban was associated with improved myocardial reperfusion as measured by early resolution of ST-segment elevation. However, no difference in the composite clinical endpoint was noted.

Lamifiban was associated with increased rates of gastrointestinal, coronary bypass-related, and catheterization access site bleeding complications.

In summary, the strategy of concomitant full-dose thrombolytic therapy and full-dose GP Ib/IIIa receptor inhibition has been a difficult one to balance efficacy and safety, and attention has turned to combining full-dose GP Ib/IIIa receptor inhibitors with reduced doses of thrombolytic agents.

**Reduced-Dose Thrombolytic Therapy plus GP Ib/IIIa Receptor Inhibition**

The combination of a reduced-dose thrombolytic agent and a GP Ib/IIIa receptor inhibitor is being tested in the TIMI-14 trial using t-PA, streptokinase, and reteplase and in the GUSTO-IV pilot trial Strategies for Patency Enhancement in the Emergency Department (SPEED) trial using reteplase.

**TIMI-14:** The international TIMI-14 trial dose-ranging phase enrolled 888 patients with MI characterized by ST-segment elevation who met standard eligibility criteria. The patients were randomized within 12 h of symptom onset to one of four reperfusion regimes (each encompassing several dosage levels): (1) standard-dose t-PA alone (the control arm), (2) reduced-dose t-PA plus abciximab, (3) reduced-dose streptokinase plus abciximab, or (4) abciximab alone. All patients received aspirin and heparin. The initial heparin dosage was a 70 U/kg bolus and a 15 U/kg/h infusion in the t-PA control arm, and a 60 U/kg bolus with a 7 U/kg/h infusion in the arms that included abciximab.

Abciximab alone was associated with 90 min TIMI grade 3 flow rates in 32% of patients (similar to the historic value seen with streptokinase) and 90 min patency in 48% of patients. The combination of streptokinase and abciximab produced only modest improvement in early TIMI grade 3 flow. TIMI grade 3 flow at 90 min was achieved in 42% of patients in the 0.5 MU group, 39% of patients in the 0.75 MU group, and 47% of patients in the 1.25 MU group. The 1.5 MU regimen, plus abciximab, was discontinued after four of six patients developed a major hemorrhage and one of whom developed an ICH.

The dose-ranging evaluation with t-PA found that the best angiographic results were obtained using a 50 mg dose given as a 15 mg bolus and a 35 mg infusion over 60 min. At 90 min, TIMI grade 3 flow was achieved in 77% of patients compared with 62% for t-PA alone (p = 0.01) (Fig. 3). Overall patency of the IRA was achieved in 94% of patients with the combination of abciximab and t-PA compared with 78% for t-PA (p = 0.09). An even greater difference was observed at 60
min when adding GP IIb/IIIa receptor inhibition. The standard t-PA dose achieved TIMI grade 3 flow at 60 min in 43% of patients compared with 72% of patients who received 50 mg of t-PA plus abciximab (p = 0.0009).

Major hemorrhage rates were similar among the t-PA-plus-abciximab and control groups, approximately 6% in each. In-hospital mortality was similar among all groups, ranging from 3 to 5%.

Thus, the addition of the GP IIb/IIIa receptor inhibitor abciximab to 50 mg of t-PA was able to increase the rate of TIMI grade 3 flow at 60 min by an absolute difference of 29%, representing a relative 67% improvement over standard therapy. At 90 min, the addition of the GP IIb/IIIa receptor inhibitor improved TIMI grade 3 flow by an absolute difference of 15% (a relative 25% improvement).

The TIMI-14 trial also included an arm evaluating the reteplase-abciximab combination in varying doses. Results thus far have been promising.

These results indicate that the combination of GP IIb/IIIa receptor inhibition with reduced-dose thrombolytic therapy appears to be a promising new regimen for enhancing both the speed and extent of reperfusion in patients with MI characterized by acute ST-elevation.

**SPEED:** Because of reteplase’s bolus dosing, it was the lytic of choice for this pilot trial of GUSTO-IV. Rather than an infusion, reteplase is given as a double-bolus injection, which gives unprecedented dosing flexibility in patients who may later go on to the catheterization laboratory. Because one bolus dose is given upon symptom presentation, there is no commitment made to the second bolus injection, allowing immediate lysis but not precluding later PCI if that is required. Ultimately, this allows the clinical practice team more options for patient treatment and encourages tailored therapy to optimize outcomes. Additionally, when combination therapy is administered, traditionally there are a number of infusions being given simultaneously. With reteplase’s bolus dosing, one of these infusions is eliminated.

In fact, results from the recent Plasminogen Activator Coronary Angioplasty Trial (PACT) indicated that patients treated with t-PA had significant improvement in vessel patency before undergoing angioplasty, with no adverse effect on procedural safety or outcome. The PACT study evaluated patients with acute MI presenting within 6 h and randomized patients to either a 50 mg t-PA bolus or placebo.

Preliminary results from the SPEED trial similarly demonstrated improvements in early TIMI grade 3 flow with reteplase, indicating that the combination of low-dose fibrinolytic therapy with reteplase appears to be a potentially promising new regimen for improving both the speed and extent of thrombolysis in patients with acute MI. Treatment arms evaluated in the “facilitated PCI” segment of SPEED were abciximab alone, abciximab plus reteplase (5 U + 5 U), and reteplase alone. The combination of abciximab and reteplase had the highest rate of TIMI grade 2 or 3 flow, 76%, compared with 73% for reteplase alone and 52% for abciximab alone. Postprocedural success (defined as < 50% diameter stenosis with TIMI grade 3 flow) for the three groups was 88% for the abciximab plus reteplase combination, compared with 85% for reteplase alone and 95% for abciximab alone.

**Other experience:** A number of other ongoing trials are exploring further the potential role of GP IIb/IIIa receptor inhibitors with reduced-dose thrombolytic therapy, and larger phase III trials are planned. It is hoped that these trials will help define a new era of myocardial reperfusion therapy of “true thrombolysis,” that is, lysis and inhibition of the platelet, thrombin, and fibrin components of occlusive thrombi.

**Safety**

A major concern with all regimens of thrombolytic therapy is bleeding, particularly ICH. Fortunately, GP IIb/IIIa receptor inhibitors generally have a low risk of ICH when used alone, and no apparent increase compared with aspirin and heparin in the major trials. The risk of ICH when combined with thrombolytic therapy may be due largely to the risk from the latter agent, but larger trials are needed to define the exact rate.

However, it appears that the third component of the regimen, heparin, also may modulate the risk of ICH with thrombolytic therapy. Reduced doses of heparin have been found to be associated with lower rates of ICH in several trials, including TIMI 9A/B, GUSTO IIA/B, TIMI 10B, and Assessment of the Safety of a New Thrombolytic (ASSENT) 1, 5, 6. Similarly, using reduced doses of heparin leads to lower rates of hemorrhage with GP IIb/IIIa receptor inhibitors, as seen in the EPIC versus EPILOG trials. Thus, use of lower doses of heparin and careful monitoring of the level of anticoagulation help avoid bleeding complications in patients receiving GP IIb/IIIa receptor inhibitors. The dose of adjunctive heparin also appears to influence bleeding with either fibrinolytic agents or GP IIb/IIIa receptor inhibitors. It is hoped that the combination of reduced-dose fibrinolytic therapy plus a GP IIb/IIIa receptor inhibitor and low-dose heparin will be associated with a potentially lower rate of ICH than are current regimens.
Conclusion

There is a strong rationale, both clinical and physiologic, for combining the potent GP IIb/IIIa receptor inhibitors with fibrinolytic agents in patients with acute ST-segment elevation MI. Current therapies need enhancement to achieve early reperfusion and decrease risk of reocclusion. Aspirin is a relatively weak platelet inhibitor yet has dramatic clinical benefits. GP IIb/IIIa receptor inhibitors have been shown to improve outcomes with a very low rate of ICH in other forms of acute coronary syndromes. It is hypothesized that the combination of GP IIb/IIIa receptor inhibitors and reduced-dose thrombolytic therapy will increase early and long-term patency rates and consequently survival, without increasing bleeding complications. Encouraging results have been observed in the dose-ranging trials to date, and the clinical benefits will be assessed in large-scale randomized trials. Although the improved TIMI 3 flow rates observed with this combination is progress, the greatest effects expected (on microvascular flow, proved TIMI 3 flow rates observed with this combination is assessed in large-scale randomized trials. Although the im-

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Future Directions in Thrombolysis

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Summary: An extensive body of research conducted in the past 25 years has helped foster understanding of the mechanisms and pathogenesis of the acute coronary syndromes and occlusive disease. Thus, it is well established that thrombosis is caused by vascular injury and that immediate lysis of the arterial thrombus and subsequent prevention of thrombotic reocclusion are critical to the treatment of these disorders. Remarkable progress in the understanding of the biological and molecular mechanisms involved in vascular-wall–platelet interactions, platelet–platelet interactions, and coagulation has led to the identification of multiple targets for drug discovery and the development of numerous antithrombotic drugs. The purpose of this article is to review emerging antithrombotic therapies, introduce potential future molecular targets for drug discovery efforts, and discuss novel strategies for managing patients with coronary disease.

Key words: acute coronary syndromes, thrombosis, occlusion, thrombolysis

Introduction

It is well established that the acute coronary syndromes [unstable angina, Q-wave myocardial infarction (MI), and non–Q-wave MI] are caused by thrombosis secondary to the disruption of an existing complex atherosclerotic plaque and that immediate lysis of the arterial thrombus, early reperfusion, and prevention of reocclusion are critical to preserving myocardial function.1–6 Similarly, restenosis following interventional revascularization procedures, such as percutaneous transluminal coronary angioplasty (PTCA), stent insertion, or coronary artery bypass grafting (CABG), is a manifestation of the physiologic thrombotic response to the vascular injury that commonly occurs during these procedures.

Although occlusive thrombi develop acutely in only a small percentage of patients following revascularization, longer-term effects of platelet activation (i.e., secretion of physiologic mediators that promote vascular smooth muscle cell proliferation, extracellular matrix accumulation, and development of a fibroproliferative lesion) contribute directly to symptomatic restenosis. As a result, inhibition of thrombosis represents an important therapeutic target for the prevention of acute coronary disease and restenosis following revascularization.

Recent research has helped elucidate the underlying mechanisms responsible for the thrombotic process, with increasing emphasis placed on the respective roles of platelets and inflammation. As medical science advances the understanding of these complex physiologic processes, new potential molecular targets for future drug development efforts will be uncovered. This article will explore several of these potential target areas, review recent advances in pharmacologic therapy, and point out new directions for research.

Mechanisms of Thrombus Formation Following Vascular Injury

To facilitate the discussion of therapeutic advances, a brief review of the mechanisms responsible for the fundamental aggregation response of platelets is provided, as is a review of mechanisms responsible for thrombin-induced fibrin generation activated by the coagulation cascade and the role of the inflammatory process in thrombosis. These three areas pose both challenges and opportunities in the treatment of acute coronary syndromes.

The cellular components of the normal vasculature and of atherosclerotic plaques synthesize and secrete a number of proteins into the subendothelial space, including von Willebrand factor, collagens, fibronectin, vitronectin, thrombospondin, and laminin.5 These proteins have within their sequences stretches of amino acids that make them sticky, or adhesive, and provide a mechanism for cells to interact with the matrix. In addition, smooth muscle cells, endothelial cells, and macro-
phages synthesize tissue factor, a powerful membrane-bound procoagulant protein that stimulates thrombin production and thereby induces fibrin formation to contribute to the development of the fibrin clot.\textsuperscript{7-11}

Normally, the endothelium does not react with either circulating platelets or coagulation factors. In fact, the endothelium produces substances, such as prostacyclin, thrombomodulin, heparan sulfate, tissue plasminogen activator (t-PA), and nitric oxide, that actually inhibit thrombosis and hemostasis.\textsuperscript{12-14}

However, injury to a blood vessel or disruption of an atherosclerotic plaque exposes blood elements to thrombogenic components of the subendothelium, such as adhesion and extracellular matrix proteins, and cell-associated tissue factor. Highly reactive platelets respond to and interact with the damaged vascular wall by a succession of rapid biochemical reactions and cellular changes leading to the formation of a platelet-rich thrombus on the damaged vascular wall.\textsuperscript{15, 16}

Adherence and Activation of Platelets

Platelets possess a number of specific membrane-bound glycoprotein (GP) receptors that enable them to bind to adhesive proteins and mediate their own adherence and aggregation.\textsuperscript{17} Platelet adherence is primarily achieved via simultaneous interaction of the multimeric subendothelial von Willebrand factor protein with the GP receptor Ib-IX on the platelet membrane and collagen within the subendothelium. The cytosolic portion of the transmembrane GP Ib-IX receptor is coupled in the platelet to actin-binding proteins. Binding of von Willebrand factor to the GP Ib-IX receptor results in actin-mediated activation of the platelet that leads to the platelet changing its shape from a smooth disc to a tiny sphere and to spreading of the platelet via multiple contact sites in the damaged vessel wall.

The change in platelet morphology has three major consequences: (1) The platelets release their granular contents, including adenosine diphosphate (ADP), serotonin, \(\beta\)-thromboglobulin, platelet-activating factor (PAF), fibrinogen, von Willebrand factor, platelet-derived growth factor (PDGF), and thromboxane A\(_2\); (2) the multimeric GP IIb/IIIa receptor conformation is altered, facilitating platelet-platelet aggregation through GP IIb/IIIa interaction with fibrinogen, fibronectin, and endothelial thrombospondin; and (3) the displacement of phosphatidylserine from the inside to the outside of the platelet membrane provides a surface for binding of the clotting factors.\textsuperscript{18}

Another consequence of the change in platelet shape following activation is that clotting factors become associated with the platelet membrane, which then serves as a procoagulant surface for the generation of thrombin, which further strengthens the clot.\textsuperscript{11, 12, 16, 19-21}

The Potential Role of Inflammation

Presently, there is much interest in the role of inflammation as a precursor of plaque rupture.\textsuperscript{23} The presence of inflammatory cells within complex plaque and detection of a wide variety of inflammatory mediators in and around unstable lesions support the hypothesis that inflammation correlates positively to plaque instability. Indeed, histological analysis at sites of plaque fissure or ulceration indicates that disruption correlates with the presence of inflammatory cells (macrophages, mast cells, and activated T lymphocytes) and suggests that plaque rupture generally occurs at the shoulder of the lesion, where the majority of the macrophages and mast cells reside.\textsuperscript{24-28}

Enzymes expressed by these cells, which digest extracellular matrix proteins, weaken the fibrous cap and precipitate cap disruption.\textsuperscript{23, 27} Furthermore, the reduced density of vascular smooth muscle cells within advanced atherosclerotic lesions predisposes the plaque cap to disruption on two levels: (1) The decreased density of the principal

\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig1}
\caption{The coagulation cascade illustrating the role of the tissue factor pathway in clot initiation, interactions between the pathways, and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HK = high–molecular-weight kininogen, PK = prekallikrein, PL = phospholipid, PT = prothrombin, TF = tissue factor, TH = thrombin. Reproduced from Ref. No. 22 by permission of Blackwell Science, Inc.}
\end{figure}
New Developments in Antithrombotic Therapy

As detailed above, platelet adhesion, activation, and aggregation play pivotal roles in thrombus generation following vascular injury. Thus, it stands to reason that pharmacologic intervention at any one of these steps may effectively reduce the incidence of thrombosis. Determination of the biological and molecular mechanisms involved in vascular-wall–platelet interactions, platelet-platelet interactions, and coagulation has identified multiple targets for drug discovery and has led to the development of numerous antithrombotic agents. Because of inherent redundancies in mechanisms leading to clot formation, interfering with any single aspect of platelet function fails to provide complete protection against the development of intravascular thrombosis, especially when the stimulus for thrombosis is strong, such as occurs with the disruption of an atherosclerotic plaque. Accordingly, successful prevention of thrombosis will likely require a multidimensional pharmacologic approach (Table I). It is not within the scope of this article to review all antithrombotic options; several comprehensive reviews on this subject have been published recently.12, 21, 32–38 Rather, the focus of this article is on platelet membrane GP receptor inhibitors (oral GP IIb/IIIa and GP Ib antagonists), ADP inhibitors (ticlopidine and clopidogrel), antithrombins (hirudin, argatroban, and hirulog), and anti-thrombotic and anti-inflammatory therapy (inhibition of P-selectin and cyclo-oxygenase type II). In addition, the application of adenovirus-mediated gene expression (gene therapy) to treat thrombotic disease is introduced.

GP IIb/IIIa Receptor Inhibitors

The platelet GP IIb/IIIa receptor has been identified as the pivotal mediator in the final common pathway of platelet aggregation. The critical role of the GP IIb/IIIa receptor is exemplified in persons with Glanzmann’s thrombasthenia, in whom there is a congenital defect or deficiency in intact GP IIb/IIIa on the platelets.32, 39 Platelets from these persons fail to bind fibrinogen and do not aggregate at all. The GP IIb/IIIa site is a member of a large family of receptors called integrins.32 All of these receptors are composed of two chains, an α subunit and a β subunit, which are held together by noncovalent bonds. Both α and β subunits are transmembrane proteins. The cloning of the cDNAs for GP IIb and GP IIIa30, 41 led to the identification of GP IIb as a typical α integrin and GP IIIa as a typical β subunit. The GP IIb/IIIa receptor is specific to platelets. It is activated and exteriorized when the platelets are stimulated.

The change in conformation of the GP IIb/IIIa receptor upon platelet activation is an absolute requirement for interaction with macromolecules.39 Fibrinogen and von Willebrand factor are the principal macromolecules that bind GP IIb/IIIa. These multivalent molecules can simultaneously bind more than one GP IIb/IIIa receptor and, as such, can link adjacent platelets together. As a result of multiple reactions of this type, the platelets become aggregated into a hemostatic plug.35 The conformational change and activation of the GP IIb/IIIa receptor occur regardless of the particular individual stimulus that activates the platelets, and therefore, GP IIb/IIIa is the final common pathway for platelet aggregation.32, 35, 39 This, together with the specificity of the GP IIb/IIIa receptor, renders the receptor an ideal target for development of a drug that will selectively inhibit platelet aggregation.

### Table I New developments in antithrombotic therapy

- **GP IIb/IIIa receptor inhibitors: intravenous**
  - Abciximab
  - Eptifibatide
  - Tirofiban
  - Lamifiban
- **GP IIb/IIIa receptor inhibitors: oral**
  - Xemilofiban
  - Orbofiban
  - Sibrafiban
- **GP Ib receptor inhibitors**
  - VCL
  - ATA
- **ADP inhibitors**
  - Ticlopidine
  - Clopidogrel
- **Thrombin inhibitors**
  - Hirudin
  - Hirulog
- **Anti-inflammatory agents**
  - COX-II inhibitor
  - P-selectin inhibitor
- **Gene therapy**

**Abbreviations:** GP = glycoprotein, VCL = von Willebrand factor comprising residues Leu-504 to Lys-728, ATA = aurintricarboxylic-acid, ADP = adenosine diphosphate, COX = cyclo-oxygenase.
Intense effort over the past decade has resulted in the development of a number of GP IIb/IIIa receptor antagonists, and to date, three of these agents are approved for use in the United States: abciximab, eptifibatide, and tirofiban; the fourth, lamifiban, is not approved for use. As reviewed in depth recently, 10 large clinical trials involving more than 32,000 patients have been performed with the intravenous formulations of monoclonal antibody (abciximab) or small-molecule (eptifibatide, tirofiban, and lamifiban) GP IIb/IIIa receptor inhibitors.

Five of these trials were in patients undergoing percutaneous coronary interventions: Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), 43–45 Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG), 46 c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), 47 Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT), 48 and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE). 49

Five trials were conducted in patients with unstable angina or non-Q-wave MI: Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), 50 Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM), 51 PRISM in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), 52 Canadian Lamifiban Study, 53 and Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON). 54

All 10 trials included standard background therapy with aspirin and heparin. Viewed in aggregate, these trials have demonstrated significant and consistent benefits in the reduction of death or nonfatal MI for the GP IIb/IIIa receptor blockers compared with placebo. Overall, there was a highly significant 20% reduction in death or MI. 57

Orally active GP IIb/IIIa receptor blockers are currently under development, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism. 58

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Orally active GP IIb/IIIa receptor blockers are currently under development, although initial reports have been discouraging. Oral forms allow more sustained receptor antagonism, thus offering the potential for greater long-term benefit and the secondary prevention of recurrent ischemic events. 55, 56 Large-scale clinical trials are now under way; however, development of two agents, xemilofiban and orbofiban, has been terminated.

Results of the Oral Glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis (ORBIT) trial, a randomized, 549-patient, multicenter, double-blind study of xemilofiban in the setting of percutaneous revascularization, were published recently. 55 Patients were randomized to one of three groups: placebo, 15 mg of xemilofiban, or 20 mg of xemilofiban. Following percutaneous intervention, the study medication was administered three times daily for 2 weeks and then twice daily for 2 weeks. All patients received concomitant aspirin and were followed clinically for 3 months. Xemilofiban therapy was well tolerated and did not increase serious bleeding events compared with placebo. Mild bleeding (particularly epistaxis) was observed more frequently in subjects who received xemilofiban and correlated with the degree of platelet inhibition on Day 1. Although this study was not powered for the definitive evaluation of differences in clinical outcomes between the treatment groups, there was a trend at 3 months toward a reduction in cardiovascular events in patients who received 20 mg of xemilofiban.

The larger scale phase III Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) study demonstrated no clinical benefit for the oral agent, and enrollment was halted in the Orbofiban Post Unstable Coronary Syndromes (OPUS) trial after an interim analysis found an excess of mortality in the treatment group. Results from the Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post Acute Coronary Syndromes (SYMPHONY) trial are awaited. Oral GP IIb/IIIa receptor inhibitors present dosing, efficacy, and safety challenges because their bioavailabilities are unpredictable from patient to patient and it is difficult to know what percentage of receptor blockade has been achieved and then to maintain receptor blockade levels.

Potential limitations of the GP IIb/IIIa receptor inhibitors include the facts that (1) there is generally no reduction in platelet adhesion; (2) there is no prevention of platelet activation and secretion; (3) there may not be effective inhibition of tissue factor or of the thrombus-bound thrombin, which may not be accessible to these inhibitors; and (4) the GP IIb/IIIa receptor inhibitors do not preclude inflammation. There also is some nuisance bleeding associated with the orally administered GP IIb/IIIa receptor antagonists, including bleeding from the gums, epistaxis, bleeding associated with shaving, and so forth. Thus, despite the optimism regarding the oral GP IIb/IIIa receptor antagonists, efforts are under way to inhibit the GP Ib integrin, to reduce platelet adhesion, and to inhibit tissue factor and thrombin. Clinical studies are under way to determine the effect of combinations of GP IIb/IIIa receptor inhibitors and other antithrombotic therapies, such as fibrinolytic agents.

A New Target: The GP Ib Receptor

The GP Ib receptor (a nonintegrin) exists in complex with GP V on the platelet surface and binds von Willebrand factor. GP Ib is the principal GP involved in the initial contact between platelets and the vessel wall, particularly in cases of high shear stress as exists in the coronary arteries. 35 The domain of the von Willebrand factor that interacts with the GP Ib receptor is composed of residues Val-449 to Lys-728. The same region contains the peptide-binding domains for heparin and collagen. 57 A recombinant peptide fragment of human von Willebrand factor comprising residues Leu-504 to Lys-728, named VCL, has been developed. Studies have demonstrated in canine and baboon models of arterial injury that VCL effectively inhibits cyclic flow variations, prolongs the time to development of intracoronary thrombus, enhances t-PA–induced thrombolysis, and delays coronary artery reclosure. 57, 58 More recently, in a rabbit model of arterial injury, aurointracarboxylic acid (ATA), a substance that inhibits platelet GP Ib–von Willebrand factor interaction, reduced the extent of neointimal hyperplasia measured 21 days after injury. 59 These studies confirm that inhibition of platelet ad-
hesion by blocking the GP Ib receptor is an attractive possibility for the prevention and treatment of acute coronary syndromes. In particular, the VCL peptide fragment may provide an effective and relatively specific inhibitor of thrombosis and may represent a new class of antithrombotic compound.

**Adenosine Diphosphate Inhibitors: Ticlopidine and Clopidogrel**

Ticlopidine and clopidogrel, less potent than GP IIb/IIIa receptor inhibitors as broad inhibitors of thrombosis, are thienopyridine derivatives that inhibit platelet aggregation via selective noncompetitive inhibition of platelet membrane ADP receptors. This interference with a specific ADP-dependent step of GP IIb/IIIa complex activation results in less platelet aggregation and, thus, ultimately impairs thrombus formation. Both compounds are prodrugs that require breakdown in the liver to unidentified active metabolite(s). Ex vivo, the antiaggregation effect is concentration-dependent and recovery is linked to platelet survival, suggesting a permanent platelet effect consistent with a reduction in functional platelet membrane ADP receptors. Ticlopidine is approximately 40 times as active as ticlopidine in inhibiting ADP-induced platelet aggregation in animal models and about 6 times as potent as ticlopidine in inhibition of ADP-induced aggregation of human platelets.

These agents differ from aspirin in that they do not inhibit the cyclo-oxygenase pathway, and they have no effect on phospholipase A activity or thromboxane A2 and prostacyclin synthesis, as aspirin does. In addition, these compounds provide broader inhibition of platelet aggregation than aspirin. Ticlopidine inhibits most of the known stimuli to platelet activation when tested at physiologic concentrations, and clopidogrel inhibits thromboxane-, serotonin-, and arachidonic acid-mediated platelet aggregation as well as ADP-induced platelet aggregation.

Clopidogrel is approximately 40 times as active as ticlopidine in inhibiting ADP-induced platelet aggregation in animal models and about 6 times as potent as ticlopidine in inhibition of ADP-induced aggregation of human platelets.

Ticlopidine has been available for many years; it was initially approved for the secondary prevention of stroke and also has been shown to be beneficial for the prevention of MI secondary to unstable angina and the treatment of peripheral arterial obliterative disease. Food and Drug Administration approval for ticlopidine was obtained principally on the basis of the cyclo-oxygenase pathway, and they have no effect on phospholipase A activity or thromboxane A2 and prostacyclin synthesis, as aspirin does. In addition, these compounds provide broader inhibition of platelet aggregation than aspirin. Ticlopidine inhibits most of the known stimuli to platelet activation when tested at physiologic concentrations, and clopidogrel inhibits thromboxane-, serotonin-, and arachidonic acid-mediated platelet aggregation as well as ADP-induced platelet aggregation.

CATS was a double-blinded study of 1,072 patients with recent thromboembolic stroke randomly assigned to receive ticlopidine (250 mg, twice daily) or placebo. At 2-year follow-up, patients who received ticlopidine had a 23.3% reduction in the combined endpoint of stroke, MI, or vascular death compared with the placebo group (p = 0.02). Subsequent trials of ticlopidine for various indications, including transient ischemic attacks and stroke, peripheral arterial disease and stenting, or ischemic heart disease, are summarized in a recent review by Sharis et al. Adverse effects of ticlopidine administration include diarrhea, pruritis and urticaria, and epistaxis and ecchymosis. The most potentially serious problem is bone marrow suppression, particularly leukopenia, which necessitates careful monitoring for the first 12 weeks of ticlopidine therapy. Because of this adverse event profile, current recommendations suggest the use of ticlopidine in place of aspirin for secondary prevention of transient ischemic attack or stroke only when the patient cannot tolerate aspirin.

Clopidogrel, which lacks the bone marrow suppression side effect of ticlopidine, is better tolerated by most patients and was recently approved for use in the prevention of ischemic events. In the large Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, the incidence of severe neutropenia with clopidogrel was only 0.1%; this was similar to the rate seen with aspirin. CAPRIE was a phase III study conducted to assess the relative efficacy, safety, and tolerability of clopidogrel and aspirin in reducing the incidence of the composite outcome of ischemic stroke, MI, or vascular death among patients who had survived a recent ischemic stroke or MI, or who had symptomatic peripheral arterial disease. This trial was a randomized, stratified, multicenter, double-blind, parallel group design study, with 19,185 patients randomly assigned to receive either clopidogrel (75 mg/day) or aspirin (325 mg/day) for a maximum of 3 years. At least 5,000 patients were assigned to one of three clinical subgroups (recent stroke, recent MI, and peripheral arterial disease). CAPRIE was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups.

The intent-to-treat analysis showed an overall relative risk reduction of 8.7% (p = 0.043). It was concluded that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death. Future studies are needed to determine additional indications for clopidogrel (e.g., prevention of restenosis with stenting) and to confirm the safety of using clopidogrel in combination with aspirin.

Ticlopidine and clopidogrel each cost significantly more than aspirin ($1 to $3 compared with < $0.01/tablet). Nevertheless, the safer profile of clopidogrel and its promising clinical efficacy render this new drug an exciting new option in antithrombotic therapy, particularly for patients who are unable to tolerate aspirin.
Thrombin Inhibitors: Hirudin, Argatroban, and Hirulog

Fibrinolytic agents such as alteplase (t-PA), reteplase (r-PA), and streptokinase are used routinely to resolve occlusive thrombi and reperfuse occluded coronary arteries. However, the ability of thrombolytic agents to induce early reperfusion may be offset by an attendant increase in procoagulant activity.68 The addition of heparin and aspirin to thrombolytic regimens attenuates this activity and improves overall patency rates. However, the most effective regimens using heparin and aspirin achieve adequate reperfusion in only 55% of patients at 90 min, and acute arterial thrombotic reocclusion subsequently develops in 6% of patients.69 This failure of standard anticoagulant therapy to afford full protection from thrombotic phenomena is largely a result of heparin’s inability to inhibit thrombin that is bound to a fibrin clot and factor Xa that is complexed to activated platelets. This and other limitations of heparin and low–molecular-weight heparins (e.g., narrow therapeutic window, endogenous modulation by proteins and platelet factor 4, heparin-induced thrombocytopenia, and bleeding) prompted the search for and development of new classes of antithrombotic drugs to improve vessel patency in patients treated with thrombolytic agents.6,69

Hirudin is a 7 kd anticoagulant protein isolated from the salivary glands of medicinal leeches (Hirudo medicinalis) and first identified as an antithrombin in 1957.70 Quantities of purified native hirudin were limited because the medicinal leech was considered an endangered species. Thus, the successful cloning and expression of the gene encoding hirudin71 enabled large-scale production of pure recombinant protein (r-hirudin) to support preclinical and clinical research (phase I studies were initiated in 1990).

Hirudin is substantially different from other anticoagulants because it does not interfere with the biosynthesis of clotting factors and it is not inhibited by endogenous proteins such as platelet factor 4.72 Unlike heparin, which requires endogenous cofactors for activity (antithrombin III, heparin cofactor II), hirudin does not require the presence of cofactors or an intermediate enzyme to elicit its anticoagulant effect.68,72 Hirudin is an effective anticoagulant in patients who are antithrombin III–deficient.72 The thrombin-hirudin complex inhibits all proteolytic functions of thrombin and thereby prevents (1) fibrinogen clotting, (2) further thrombin-catalyzed hemostatic reactions (i.e., activation of clotting factors V, VIII, and XIII), and (3) thrombin-induced platelet activation with subsequent accelerated generation of additional thrombin.68 Hirudin is a highly specific inhibitor of α-thrombin. Accordingly, apart from its anticoagulant activity, it is pharmacologically inert.72

Hirudin binds tightly to multiple sites on thrombin. Detailed structure-function studies determined that the carboxyterminus of hirudin binds to the substrate recognition site of thrombin, whereas the aminoterminus binds and inactivates the catalytic domain of the enzyme.6 These findings led to the rational design of a new class of synthetic bivalent thrombin inhibitors, the hirulogs, which consist of these two binding domains separated by a short linker sequence that is sized to mimic the interatomic distance between thrombin’s recognition site and catalytic site.6

Results from two large trials, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb73 and Thrombolysis in Myocardial Infarction (TIMI) 9,74 and one pilot study, Organization to Assess Strategies for Ischemic Syndromes (OASIS),75 detail the relative efficacy of hirudin compared with heparin in patients with acute coronary syndromes.

GUSTO IIb was a multicenter trial with 12,142 patients randomly assigned to 72 h of therapy with either intravenous hirudin (0.1 mg/kg bolus, 0.1 mg/kg/h infusion) or heparin (5,000 U bolus, 1,000 U/h infusion). At 24 h, the incidence of death or MI was significantly reduced in the hirudin group (1.3 vs. 2.1%; p = 0.001). However, at 30 days, the incidence of the primary composite endpoint of death, MI, or reinfarction was 9.8% in the heparin group and 8.9% in the hirudin group (p = 0.06). There was no significant difference between the serious or life-threatening bleeding event rates, but hirudin was associated with more frequent moderate bleeding (8.8 vs. 7.7%; p = 0.03).

The TIMI-9 trial, which involved 3,002 patients with acute MI, found no statistically significant benefit of hirudin compared with heparin at 30 days. Thus, although the GUSTO-IIb trial was marginally positive for hirudin, the cumulative outcome of these two trials failed to demonstrate a superior effect of hirudin over heparin on the combined endpoint.30

The OASIS pilot trial did demonstrate a significant benefit for medium-dose hirudin infused over 72 h compared with heparin or a low-dose hirudin infusion in patients with unstable angina or suspected MI without ST elevation. Despite the initial disappointment of the GUSTO-IIb and TIMI-9 trials, this result suggests that direct thrombin inhibitors may still prove useful for the treatment of acute coronary syndromes.

In the PTCA setting, however, the Hirudin in a European Trial vs. Heparin in the Prevention of Restenosis After PTCA (HELVETICA) trial76 and the Hirulog Angioplasty Study77 did not show any durable benefit of hirudin or hirulog over heparin.

The recombinant hirudin variant and the trial design used may be critical to successful demonstration of a benefit with this class of drugs. Indeed, a number of recent reports indicate that direct thrombin inhibition by hirulog may improve early clinical outcome in patients undergoing angioplasty77,78 or receiving fibrinolytics.69,79 There continues to be potential for this class of drugs as an adjunct to fibrinolytics in the treatment of thrombotic disorders.

Anti-inflammatory Agents: COX-II and P-Selectin Inhibitors

Over the past 2 decades, the proinflammatory properties of platelets have gradually been elucidated.80 Platelet involvement in inflammation was previously thought to be restricted to a passive role, as a target for inflammatory mediators released by leukocytes, in particular PAF. It has become apparent, however, that platelets also play an active role in inflammation, releasing their own intracellular platelet factor 4, β-thromboglobulin, PDGF, and histamine-releasing growth factor, which are potent amplifiers of basophil, mast cell, and
neutrophil activity. As such, anti-inflammatory agents may prove useful in the prevention of cardiovascular disease, for example, infection as a possible source of atherosclerosis. Indeed, one recent prospective study of 1,086 apparently healthy men, the Physician’s Health Study, showed that the baseline plasma concentration of C-reactive protein (an acute-phase reactant that is a marker for underlying systemic inflammation) predicts the risk of future MI and stroke. Moreover, the reduction in the risk of a first MI associated with the use of aspirin correlated directly with the C-reactive protein level, suggesting that part of the benefits of aspirin is mediated through its anti-inflammatory effects and not strictly through its anti-platelet properties.

This supposition that inflammation plays a key role in the atherosclerotic processes is confirmed by observations that the inducible inflammatory COX-II enzyme is present in atherosclerotic plaques. The development and recent approval of COX-II–specific inhibitors affords the opportunity to test these compounds in animal models to determine their potential for cardiovascular indications. The outcome of such studies may not be as straightforward as initially hoped, given the recent evidence that COX-II induction in vascular cells (endothelial cells and platelets) may actually be desirable following endothelial injury because it may replace the protective effect of the constitutively expressed COX-I–mediated prostaglandin production lost upon endothelial damage.

P-selectin is a 140-kd GP member of the selectin family of vascular adhesion molecules. P-selectin is typically stored in the α granules of platelets and the Weibel-Palade bodies of endothelial cells until cellular activation (e.g., treatment with thrombin, histamine, or oxygen-derived free radicals; ischemia and reperfusion) induces rapid (within minutes) mobilization of P-selectin to the cell surface. Because of the central role of thrombin in thrombosis and coagulation, subsequent induction of P-selectin is involved in the thrombotic process associated with acute coronary events. Demonstration of antibody blockade of P-selectin–attenuated fibrin deposition and clot formation in an in vivo animal model confirmed the role of P-selectin in the thrombotic process.

Willerson et al. have shown that a low–molecular-weight molecule that has combined inhibitory activity for P-., E-., and L-selectins inhibited thrombosis and inflammation in animal models with interventional injury. These authors also have demonstrated both in vitro (clot lysis assay) and in vivo (rat mesenteric artery cyclic flow protocol) that a chimeric P-selectin-t-PA fusion protein is an effective thrombolytic agent. In vitro cell adhesion assays indicated that the chimeric proteins retain P-selectin binding activity. The chimeric protein targeted t-PA to the thrombotic region where the t-PA actively lysed the clot and, perhaps, the P-selectin binding properties attenuated nascent fibrin deposition and clot formation as well.

Gene Therapy for the Prevention of Thrombosis

The much-anticipated future of antithrombotic therapy is likely to include transferring genes to the site of vascular injury to reduce the incidence of coronary thrombus associated with acute or recurrent ischemic episodes. Great optimism exists that gene therapy will prove effective in the management of thrombotic disorders. This optimism is based upon combined emerging successes with gene therapy in the treatment of other diseases and from laboratory data indicating this as a viable approach for inhibiting thrombosis. For example, the Zoldhelyi-Willerson laboratory has demonstrated that adenovirus-mediated delivery of the gene for human cyclo-oxygenase I enzyme to porcine carotid arteries restored prostacyclin production and abolished cyclic flow variations for at least 10 days following arterial injury (crush or balloon). Histological examination of the arteries verified that the vessels that overexpressed COX-I were devoid of thrombus. It is hoped that human trials using gene therapy to prevent thrombosis in humans with arterial injury will begin in late 1999.

Alternatively, one may inhibit tissue factor, which accumulates in the media and intima of injured arteries, with an endogenous inhibitor of tissue factor pathway inhibitor (TFPI). The Zoldhelyi-Willerson laboratory has used similar gene therapy with an adenoviral vector and the human cDNA for TFPI to prevent thrombosis after vascular injury in experimental animal arteries. This laboratory plans future studies in humans in which COX I and TFPI are overexpressed together in the hope of preventing or markedly attenuating vascular thrombosis after injury.

Conclusion

Acute coronary syndromes result from the onset of platelet activation, thrombosis, and fibrin generation after disruption of vulnerable atherosclerotic plaques or vascular injury following interventional revascularization. Given the substantial knowledge gained over the past several years regarding cellular and molecular biology of thrombosis/hemostasis and coagulation, the mechanisms through which selected pharmacologic interventions reduce new and recurrent coronary events are better appreciated.

In 1995, a workshop was held by the National Heart, Lung, and Blood Institute to survey what is known about mechanisms precipitating acute cardiac events and to assess the potential of advances in this field leading to new preventive methods. Among the recommendations made at the workshop were the following: (1) It is important to identify methods that inhibit the multiple mediators of acute thrombosis, and (2) it is important to develop means to express antithrombotic substances at local sites of injury.

The development of and continued research to find effective and safe GP IIb/IIIa receptor antagonists, GP Ib receptor antagonists, ADP inhibitors, thrombin inhibitors, and anti-inflammatory agents as described herein have contributed significantly to fulfilling the first recommendation. The application of gene therapy to treat thrombosis will hopefully meet the second recommendation. Thus, despite the remarkable progress made in antithrombotic therapy in the past decade, there is still much to be done and additional, exciting therapies remain undiscovered.
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