A Critical Appraisal of the Evolution of ST Elevation Myocardial Infarction (STEMI) Therapy and the Evidence Behind the Current Treatment Guidelines

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Abstract

In the United States cardiovascular disease is the leading cause of and is responsible for 26% of deaths each year. Half of the deaths due to heart disease in 2006 were women. In 2009, the Center for Disease Control (CDC) estimated that 785,000 Americans had a new myocardial infarction and about 470,000 had a recurrent attack. Nearly 400,000 Americans will die of CHD in 2010. The cost of heart disease in terms of health care services, medications, and lost productivity for 2010 has been estimated at $316.4 billion. The current therapeutic guidelines for the treatment of ST elevation myocardial infarction are reviewed from a historical perspective, and the scientific evidence behind such guidelines is systematically analyzed.

Prevalence and Scope of the Problem

In the United States cardiovascular disease has been the leading cause of death every year since 1900, except 1918, the year of the Spanish flu epidemic, and is responsible for 26% of deaths each year. Half of the deaths due to heart disease in 2006 were women. In 2009, the Center for Disease Control (CDC) estimated that 785,000 Americans had a new myocardial infarction, and about 470,000 had a recurrent attack. Nearly 400,000 Americans will die of CHD in 2010.[1-4] The cost of heart disease in terms of health care services, medications, and lost productivity for 2010 has been estimated at $316.4 billion.[2] The risk factors for coronary disease have been mapped out (5) and about 37% of American adults report two or more of these risk factors.[6] While heart disease is usually thought of as malediction of advanced societies and modern lifestyles, recent multidisciplinary studies of mummified remains have provided evidence of this particular phenotype among some elite classes of ancient Egyptians.[7-11]

Brief Historical Synopsis

Setting the Stage

Although William Heberden coined the term angina pectoris in 1768,[12] myocardial infarction remained mostly a medical curiosity until towards the end of the nineteenth century. For more than a hundred years after Heberden's clinical finding, the pathophysiology of acute myocardial infarction remained elusive until the German pathologist Carl Weigert in 1880 clearly correlated myocardial infarction as a disease of the coronary arteries and exhibiting specific myocardial changes.[13] William Osler[14] and George Dock[15] started teaching this possible clinical link. By 1910 two Russian clinicians, Obraztsov and Strazhesko, actually documented clinical features of myocardial infarction in a living patient.[16] However the evolution of modern day understanding and treatment of myocardial infarction began with James B. Herrick. In a landmark presentation to the Association of American Physicians in 1912, he coherently introduced the classic signs and symptoms of acute coronary artery occlusion.[17] Although that presentation is now universally hailed as the burgeoning of the clinical and pathophysiologic basis of coronary artery syndrome, it was met with indifference by his peers. Years later Herrick would reminisce, "My paper on the diagnosis of coronary thrombosis during life rather than only at autopsy, which I presented at the 19122 meeting of the Association of American Physicians, fell like a dud." In 1918 James Herrick was one of the first to encourage electrocardiography, which had been created by Einthoven in 1902, in the

diagnosis of myocardial infarction and has continued to be an indispensible major diagnostic tool for acute myocardial infarction up to the present time. Herrick also advocated bed rest as mainstay therapy for myocardial infarction. Bed rest was the only therapeutic option available at that time. Patients were essentially bedridden for up to six weeks and were not allowed to move or to feed themselves during the first post infarction week.[18, 19] This practice became established as a prime therapeutic cornerstone for the next 50 years.

The first clinical series of 19 patients with myocardial infarction by Wearn[20] appeared in the literature in 1923. By 1928, Parkinson and Bedford reported their series of 100 patients with acute myocardial infarction and detailed their experience with the use of morphine to relieve pain but advised against the use of nitrates because of the potential for hypotension.[21] A year later Samuel Levine in another series of 145 acute myocardial infarction patients noted the frequency and risk of various cardiac dysrhythmias and advocated the use of quinidine to treat ventricular tachycardia and intramuscular adrenaline for heart block and syncope. He further suggested that nurses be trained to use a stethoscope "to follow carefully the rate and rhythm of the apex beat," so that the dysrhythmias could be treated promptly even when a doctor was not present. This suggestion was at least three decades ahead of the arrival of coronary care units.[22] Levine and Lown also proposed "armchair treatment" of AMI in 1952 but were met with resistance and heated debate.[23] During the 1950s, the therapy of myocardial infarction included the administration of oxygen (in the presence of shortness of breath [rales] and cyanosis) and intravenous fluids (to prevent dehydration) as popularized by Tinsley Harrison, the founding editor and editor-in-chief of the first five editions of Harrison's Principles of Internal Medicine.[24] Subcutaneous atropine and papaverine, followed by sublingual nitroglycerine (glyceryl trinitrate) were routinely used to prevent or relieve coronary spasm. By 1920 it had become accepted by most that sudden occlusion of the coronary artery was the trigger for myocardial infarction. When the anticoagulants heparin and bishydroxy-coumarin (Dicumarol) were developed in the 1930s, they were adopted for use in treating AMI. In a report of 800 patients in 1948 Irving Wright advocated the use of anticoagulants in myocardial infarction to prevent reinfarction, mural thrombus, and pulmonary embolism.[25] These treatment modalities reigned supreme for many decades.

Arrival of the Main Pharmacological Characters

The latter half of the twentieth century brought reports that daily, low doses of aspirin appeared to be antithrombotic and could help prevent myocardial infarction and stroke. This finding was first reported by Lawrence Craven, a suburban general practitioner in Glendale, California. In 1950 Craven hypothesized that aspirin was preventive of coronary thrombosis. He cited evidence that aspirin prolonged prothrombin time. He also cited reports of more frequent hemorrhaging among patients who chewed aspirin gum after a tonsillectomy or a tooth extraction.

Craven then prescribed daily aspirin to 400 patients in 1948, and he reported in 1950 that none had suffered a myocardial infarction during that two-year period.[26, 27, 28] Unfortunately, Craven's work languished in obscurity, and it would be decades before his observations would be validated by clinical trials. Aspirin would play a large role and would be a cornerstone in antiplatelet therapy for acute myocardial infarction.

In 1933, while conducting an experiment at the Johns Hopkins Institutes Tillet and Garner accidentally found that Lancefield Group A beta-hemolytic streptococci were capable of producing a fibrinolytic substance, later named streptokinase.[29] Shortly thereafter Christiansen and MacLeod showed that this streptokinase could convert plasminogen to the proteolytic and fibrinolytic enzyme plasmin, which, in turn, was capable of degrading fibringen and fibrin. By 1947, Christiansen provided Tillet, Sherry, Hazelhurst, and Johnson with a crude preparation of streptokinase, which they used clinically to treat hemothorax, empyema, and abscess cavities with great success.[30, 31] Then Tillet and Johnson in 1952 reported lysing of experimental thrombi in rabbits' ears with streptokinase administered intravenously through a peripheral vein.[32] Once purified preparations of streptokinase were made available by Lederle Laboratories five years later in 1957, Sherry's group proposed a rational clinical strategy for intravenous fibrinolysis involving a loading dose of streptokinase, followed by a continuous infusion sufficient to maintain a plasma streptokinase concentration of about 10 μg/mL.[33] This proposal was subsequently followed by the first human study of intravenously administered streptokinase for the treatment of AMI.[34] Even at that time, interestingly enough, it was noted that the early administration of streptokinase (within 14 hours of symptom onset) resulted in low in-hospital mortality compared to those patients with delayed treatment whose in-hospital mortality was similar to untreated patients. However, the pathophysiological recognition of the open-artery hypothesis and the consequential universal adoption of thrombolytic agents as primary treatment of AMI would be delayed for decades because of a heated controversy over the exact role played by coronary thrombosis in the pathogenesis of AMI.

The Great Pathological Debate and the Dawn of a New Era

It is a strange twist of events in that while developments in thrombolytic therapy were beginning, a highly heated and voluble debate was brewing at the same time about the exact role coronary thrombosis played in the events leading to AMI. In 1939 Charles Friedberg and Henry Horn, pathologists from the Mount Sinai Hospital in New York, published an article in JAMA entitled, "Acute myocardial infarction not due to coronary obstruction." In their paper these authors argued that evidence of coronary thrombosis was only present in 31% of patients who had evidence of myocardial necrosis on autopsy.[35] Studies by other pathologists[36-40] appeared to collaborate this finding and called into question the cause-and-effect relationship between coronary thrombosis and AMI. The argument posed by these

anatomical pathologists was that if coronary thrombosis were the cause of myocardial infarction, it should be evident in virtually all the cases. The most significant and vocal proponent of this argument was William C. Roberts, the Section Chief of the Cardiac Pathology Heart Institute at the National Institutes of Health. He vehemently believed that coronary thrombosis was the result, rather than the cause, of myocardial necrosis: "Although it may play a major role in causing atherosclerosis, coronary thrombosis may well play a minor role or none at all, in precipitating a fatal coronary event… Evidence [has been] gathered suggesting that myocardial necrosis comes first and that coronary thrombosis is secondary."[41]

Within a few years Roberts and his cohorts had a resounding rebuttal to their hypothesis by Marcus DeWood and his colleagues from Spokane, Washington. In 1980, DeWood et al. published a landmark paper in the New England Journal of Medicine that grabbed the attention of everyone remotely involved in cardiac care.[42] After recognizing the inherent limitations of autopsy series in the study of AMI Pathophysiology, these researchers decided to perform coronary angiography in live patients within 24 hours of presentation with AMI. At that time this was indeed a revolutionary concept, since the perceived wisdom of the time was that injection of contrast media during AMI would inevitably result in fatal arrhythmia or hemodynamic compromise during the procedure. This study showed total coronary occlusion in 110 out of 126 patients (87%) presenting within four hours of the onset of symptoms suggestive of AMI. Thrombus was demonstrated angiographically in 59 patients. In addition DeWood was able to retrieve the thrombus in 52 (88%) of these patients using a Fogarty catheter. Finally, the debate was settled in favor of the "open artery hypothesis" and laid down the foundation and convincing argument for thrombolysis and percutaneous coronary intervention for the treatment of ST elevation myocardial infarction.

Decreasing Mortality from Acute Coronary Syndrome

In the past few decades mortality from acute coronary syndrome in the United States has been decreasing[43-46] (Table 1). Approximately 47% of the decrease in mortality has been attributed to therapeutic interventions and 44% to changes in the major risk factors for heart disease.[47] Studies from other countries have collaborated this welcome trend.[48-55]

One of the major innovations that brought down in-hospital mortality of AMI was the development of Coronary Care Units in the early sixties. Although Samuel Levine, as we have seen before, encouraged the treatment of cardiac dysrhythmias related to myocardial infarction and advocated the training of nurses to recognize such, his idea was not fully considered until the advent of coronary care units in the sixties. The very first description of the coronary care unit (CCU) was presented to the British Thoracic Society in July 1961 by Desmond Julian.[56] Within the year these units had spread all over the world.[57] The technique of closed-chest cardiopulmonary resuscitation

by Kouwenhoven, Jude, and Knickerbocker in 1960 at Johns Hopkins[58] and the adoption of a continuous telemetry monitoring system with an alarm,[57] laid the groundwork for coronary care units. To complete these developments patients with AMIs were clustered in a single hospital unit where trained personnel were in continuous attendance and where necessary equipment and drugs were also readily available. The training of specialized nurses to recognize and treat arrhythmias rapidly in the absence of a physician[59] revolutionized treatment in these units. By 1967 Killip and Kimball published their series of 250 patients with AMIs who had been treated in the CCU. Compared with other patients who had experienced AMIs, those treated in the CCU had better survival rates in the absence of cardiogenic shock.[60] Similar results were reported from other centers. The introduction of CCUs reduced the mortality rate of AMI from 30% to 15%.[61, 62, 63]

Table 1: Decreasing mortality of Acute Coronary Syndrome with time.

| MORTALITY FROM ACS	
Year	**Mortality**
1960s	30-40%
1975	27%
1984	19%
1994	10%
2009	6%

Pathophysiology of STEMI

Acute coronary syndrome consists of a spectrum of clinical conditions ranging from unstable angina, non-ST elevation MI (non-Q wave), and ST elevation MI (Q wave). All these conditions are characterized by the common pathophysiology of a disrupted atherosclerotic plaque (Figures 1 and 2). In the majority of cases the syndrome occurs when an atherosclerotic plaque ruptures, fissures, or ulcerates and precipitates thrombus formation, resulting in an acute total or near-total arterial occlusion. Alternatively, a piece of thrombus may break off leading to downstream vessel occlusion.

Platelets play a central role in the development of thrombi and subsequent ischemic events, and this process of platelet-mediated thrombus formation involves adhesion, activation, and aggregation. Plaque rupture exposes subendothelial collagen, a highly thrombogenic material, which serves as a site of platelet adhesion, activation, and aggregation. Activated platelets undergo a series of steps including: shape change, adhesion to endothelial cells of vessels, aggregation, and the secretion of granules that perpetuate the cycle.[64, 65, 66] Fibrinogen and thrombospondin are secreted from a-granules. Within one minute

of activation, the presence of fibrinogen and thrombospondin results in platelet aggregation through the linking of glycoprotein (GP) IIb/IIIa complexes.[65] An adhesive glycoprotein, von Willebrand factor (vWF), allows platelets to stay attached to the subendothelial vessel wall (via GP Ib) despite high shear forces. Following adhesion, platelets are activated to secrete a variety of agonists which are pro-aggregatory molecules, such as thrombin, serotonin, adenosine diphosphate (ADP), and thromboxane A_2 (TXA_2) (Figure 3). These agonists, which further augment the platelet activation process, bind to specific receptor sites on the platelets to activate the GP IIb/IIIa receptor complex, the final common pathway to platelet aggregation.[67, 68] Once activated, the GP IIb/IIIa receptor undergoes a conformational change that enables it to bind with fibrinogen (Figure 5). The shape of platelets changes from a discoid to spherical within seconds after activation once the concentration of ADP approaches 2–5 μM.[69,70] ADP binds to specific ADP receptors located on the platelet membrane including P2Y1, P2Y12 and P2X1.[66] Therefore, ADP is considered a natural agonist of platelet aggregation, as this molecule is involved in a positive feedback mechanism potentiating the process of platelet activation and thrombus formation. This role of ADP and ADP receptors as we will see has tremendous therapeutic implications and has been the subject of intensive research in the past three decades.

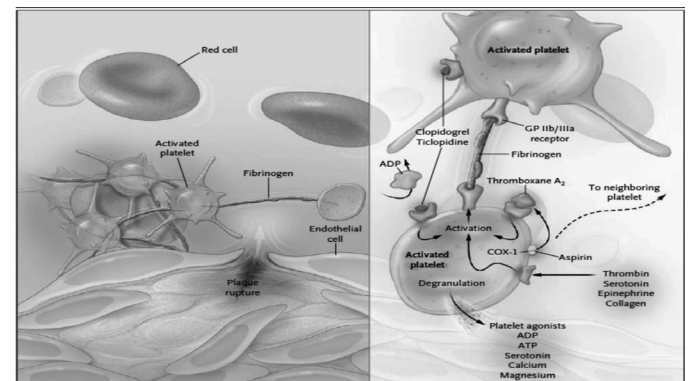**Figure 1:** The spectrum of Acute Coronary Syndrome.
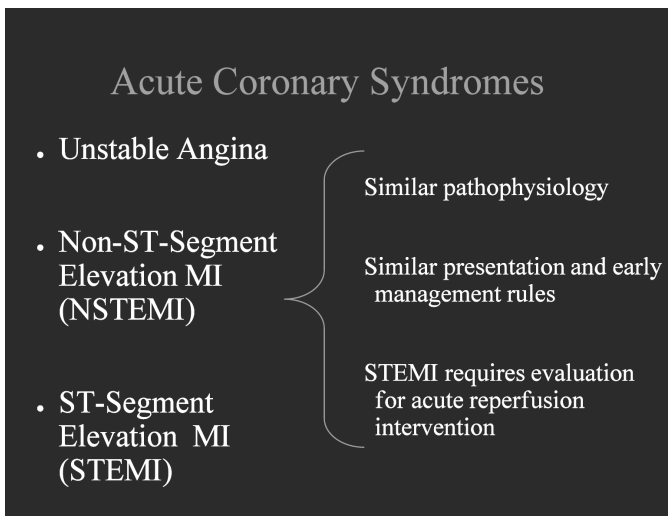
Reimer and Jennings, in the 1970s, performed a series of experimental studies in dogs after acute coronary occlusion, in which they examined the relation between duration of ischemia, area at risk, collateral blood flow, and final infarct size. Their results introduced the concept of "wave front phenomenon of myocardial death." This concept states that infarct size increases in a transmural wave front extending from the endocardium to the epicardium with increasing duration of coronary occlusions and with increasing severity of ischemia. Coronary occlusions lasting < 6 hours result in subendocardial infarcts, in which infarct size is smaller than the ischemic area at risk, because some epicardial rim of viable tissue is spared. When coronary occlusion exceeds six hours, infarcts become transmural with an infarct

size encompassing the entire area at risk.[71] This concept of Reimer and Jennings is fundamental to current revascularization therapy of acute ST-elevation myocardial infarcts (STEMI).[72] Indeed, modern therapeutic modalities for STEMI aimed at opening the infarct-related artery as quickly as possible in order to reduce the duration of ischemia and to save viable myocardium in the risk area are predicated on this concept.

Figure 2: Features and Characteristics of Acute Coronary Syndrome.

Figure 3: Atherosclerotic Plaque Disruption and Platelet Activation.

The disruption of an atherosclerotic plaque results in exposure of highly thrombogenic material. In patients with atherothrombosis, the activation of platelets and coagulation are inseparable, reciprocally self-amplifying processes. The inhibition of platelets alone does not block the coagulation activators. GP denotes glycoprotein, ADP adenosine diphosphate, and COX-1 cyclooxygenase-1. Adapted after *Mohler E R. N Engl J Med. 2007;357:293-296.*

Progression of postinfarct myocardial pathology can lead to the occurrence of possible characteristic complications at predictable times after the initial event. While there may be no apparent visible alterations in the gross morphological appearance of infarcted tissue for at least six hours after the onset of cell death, changes in cell biochemistry and ultrastructure begin to show abnormalities within 20 minutes of ischemia. Myocardial ischemia can cause an immediate loss of contractility in the affected myocardium, leading to hypokinesis. After about 15–30 minutes of sustained coronary occlusion, necrosis starts to develop in the subendocardium, with the necrotic region marching outward towards the epicardium within the next three to

six hours, eventually spanning the entire ventricular wall. In some areas (generally at the edges of the infarct) the myocardium is stunned (reversibly damaged) and can eventually recover if blood flow is restored. Contractility in the remaining viable myocardium increases, a process termed hyperkinesis. Cell damage is progressive, becomingly increasingly irreversible over about 12 hours. Therefore, this period can provide a window of opportunity during which thrombolysis and reperfusion may salvage some of the infarct. Between four and twelve hours after cell death starts, the infarcted myocardium begins to undergo coagulation necrosis, a process characterized by cell swelling, organelle breakdown, and protein denaturation. Between four and seven days following a STEMI the infarcted myocardium is especially soft and prone to rupturing, an event usually fatal, and can occur at any time during the initial first two weeks and is responsible for about 10% of STEMI mortality. By about two to three months following the infarction, the area has healed, leaving a thinned, firm and pale grey non-contracting region of the ventricular wall. Over the course of several months, there is progressive dilatation, not only of the infarct zone, but also of healthy myocardium. This process of ventricular remodeling is caused by an increase in end-diastolic wall stress. Infarct expansion puts patients at a substantial risk for the development of congestive heart failure, ventricular arrhythmias, and free wall rupture.

The Randomized Mega Trials and the Thrombolytic Era

In the 1970s, mortality rates for patients hospitalized with AMI ranged from 10% to 45% among different institutions.[73] Early attempts at using thrombolytic therapy for STEMI showed mixed results.[74-77] Rentrop demonstrated that local intracoronary infusion of streptokinase into the infarct artery could promptly recanalize the vessel and reestablish flow.[78] Anecdotal observations consistently found a high rate of spontaneous recanalization, but most often were too little, or appeared too late. In 1983 Schroder introduced and demonstrated the efficacy of a high-dose bolus intravenous infusion of streptokinase in achieving early recanalization of the infarct vessel.[79,80] Albeit the use of streptokinase appeared favorable, decisive conclusions appeared lacking because most of these series suffered from inadequate sample size or were performed in nonrandomized patient populations. In addition there were no universal protocols established at this time. By the early eighties a number of small series attempting to standardize a protocol ended up showing that improved reperfusion rates and better left ventricular function were dependent on time interval between onset of symptoms and streptokinase infusion, especially if streptokinase was administered early within one and one-half to three hours.[81-91]

Finally in 1986, a landmark study, GISSI-1 (First study of the *Gruppo Italiano per lo studio della strepochinasi ell' infarto Miocardio*) became the first large randomized international trial to convincingly and definitively show that intravenous thrombolytic therapy with streptokinase improved survival.[92] The objective of the trial was to evaluate the efficacy of a thrombolytic treatment with streptokinase (SK) on in-hospital mortality of patients with acute myocardial infarction (AMI). It was an open controlled clinical trial with central randomization of 11,712 patients to SK or control group of patients with AMI admitted within 12 hours from the onset of symptoms. Thrombolytic treatment significantly reduced mortality among patients treated with SK compared to controls, receiving conventional treatments: 10.7% SK vs. 13% controls, for an 18% reduction (p=.0002). The difference in survival produced by streptokinase and sustained up to one year was still significant at 10 years (log-rank test: p=0.02) with the absolute benefit of 19 lives saved per 1000 patients treated.

The GISSI-1 report was soon followed by a randomization of more than 100,000 patients in three large-scale trials directly comparing different thrombolytic agents. GUSTO (*Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries*),[93] GISSI -2 (*Gruppo Italiano per so Studio della Sopravvienza nell'Infarto Miocardico*),[94, 95] and ISIS-3 (Third International Study of Infarct Survival Collaborative Group).[96] These mega trials conclusively established the validity of the "open artery hypothesis" by demonstrating that opening up an occluded coronary artery within 90 minutes after treatment with intravenous thrombolytics resulted in a 15% reduction in mortality. Thus the concept of short "door-to-needle" mantra became a priority in the treatment of acute STEMI internationally. Other clinically relevant conclusions from GISSI-2, ISIS-3, and GUSTO-1 were that the choice of thrombolytic therapy was much less important to ultimate survival than was the delay time between onset of symptoms and initiation of treatment. In 1990 Kareiakes et al. showed that the average in-hospital delay for patients treated with thrombolytic agents is almost 90 minutes in the United States.97 Development of local protocols in emergency departments designed to decrease this time delay have gone a long way in saving more lives. In addition all three agents appeared to be effective even when given up to 12 hours after the onset of symptoms.

Indeed in the early 1990s some studies, such as EMERAS (*Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur)*[98] and LATE (Late Assessment of Thrombolytic Efficacy)[99] specifically looked at thrombolytic therapy in STEMI patients presenting six hours after the onset of symptoms. EMERAS found no significant differences in hospital mortality observed between the streptokinase and placebo groups (11.9% vs. 12.4%). The LATE (Late Assessment of Thrombolytic Efficacy) study (javascript:newshowcontent ['active','references']); showed no benefit for thrombolytic therapy in STEMI if administered 12 to 24 h after the symptoms.[99] A meta-analysis of all randomized fibrinolytic trials with greater than 1000 patients was performed by the Fibrinolytic Therapy Trialist (FTT) Collaborative group in 1994. This analysis revealed that the greatest mortality benefit was achieved in the first three hours of symptom onset, especially the first hour.[100] If treatment was within the first hour of symptoms, 39 lives were saved per 1000 patients treated. If treatment was within two to three hours, 30 lives were saved, while if treatment was within seven to twelve

hours after symptom treatment, 21 lives were saved. An absolute benefit reduction of 1.6 lives was cost by each hour delay in treatment (Figure 4).

Figure 4: Number of lives saved per 1000 patients treated with fibrinolytic at different treatment time delays from symptom onset.
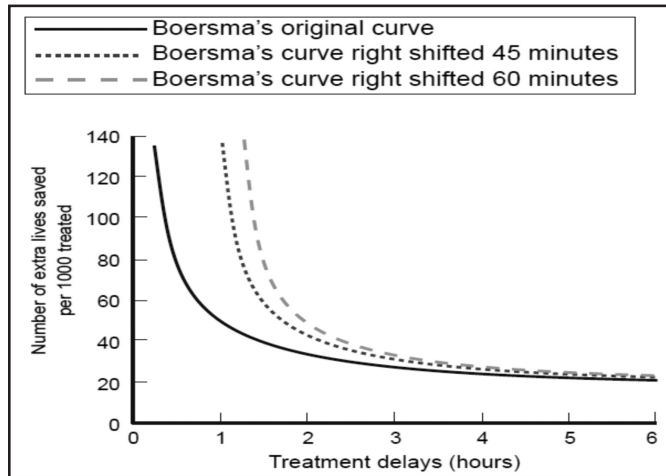
Adapted from Terkelsen TJ, Larsen JF, Norgaard BL et al. Are we understanding the full potential of early thrombolytic treatment in patients with acute myocardial infarction? *Heart.* 2003;89:483-484.

The ideal fibrinolytic agent is one that would achieve 100% patency in a short time period while having minimal bleeding complications and improve microvascular function and flow. It would have a prolonged half-life and slow plasma clearance and be easy to administer as a bolus. It would also be highly fibrin specific with little or no fibrinogen depletion. In addition, it would be easier to use. The thrombolytic agents currently available, such as rPA (reteplase) and TNKtPA (tenecteplase), are more fibrin specific and easier to use compared to the first generation agents.[101-105] Reteplase (r-PA) was one of the first bolus lytics and mutant variations of wild-t-PA. Tenecteplase or TNK-tPA is a deletion mutant of naturally occurring t-PA, which can be administered as a single bolus. TNK-PA is more fibrin specific than alteplase or reteplase. Lanoteplase (n-PA) is another deletion mutant of naturally occurring t-PA. The IN-TIME -2 trial (Intravenous nPA for Treatment of Infarcting Myocardium Early) was a large randomized equivalency trial testing 120KU/kg of lanoteplase with accelerated alteplase. The 30-day mortality rates were similar between the two agents, but intracranial hemorrhage was significantly higher with n-PA (1.13% vs. 0.62% p < [less than] 0.003) (106). As a result, the agent is not presently being developed for clinical use.

Antiplatelet Therapy

Platelet Physiology

Platelets are anucleate blood cells that form by fragmentation of megakaryocyte cytoplasm and have a maximum circulating life span of about ten days in man. Under normal physiological circumstances approximately ten[11]platelets are produced each day but can increase up to tenfold in times of stress and increased need. Platelets provide a circulating source of che-

mokines, cytokines, and growth factors that are preformed and packaged in storage granules. Platelet activation process involves the production of multiple activation agonists that include thrombin, thromboxane A2, and adenosine diphosphate (ADP), which amplify the platelet response and stimulate platelet aggregation. The purinergic receptors expressed on platelets consist of $P2X_1$, $P2Y_1$, and $P2Y_{12}$. Adenosine triphosphate (ATP) is the physiological agonist of $P2X_1$ ligand-gated cation channels involved in extracellular calcium influx and, thereby, changes in platelet shape and also helps to amplify platelet responses mediated by other agonists. ADP as a physiological agonist exerts its action on platelets through both G protein-coupled seven transmembrane domains purinergic receptors, $P2Y_1$ and P2Y12. The activation of the $P2Y_1$ receptor also leads to a transient change in platelet shape, intracellular calcium mobilization, granule release of other mediators and finally initiates a weak but transient phase of platelet aggregation. While both P2Y receptors are needed for complete aggregation, ADP-stimulated effects on platelets are upheld predominantly through the G_i-coupled $P2Y_{12}$ receptor. Thus activation of the $P2Y_{12}$ receptors causes a series of intracellular events that result in calcium mobilization, granules release, thromboxane A_2 generation, and activation of glycoprotein IIb/IIIa receptor, which leads to amplification of platelet aggregation and stabilization of the platelet aggregate. As a result, platelet $P2Y_{12}$ blockade is pivotal in attempting to inhibit thrombus formation by platelet activation and aggregation.

As demonstrated earlier in the pathophysiology of STEMI the nidus of an occlusive coronary thrombus is the adhesion of a small collection of activated platelets at the site of intimal disruption in an unstable atherosclerotic plaque. After an atherosclerotic plaque rupture, platelet- mediated thrombosis occurs through a tri-step process involving adhesion, activation, and aggregation. Each of these three phases represents a potential target for the development of pharmacologic antiplatelet agents. Inhibitors of platelet adhesion are still under investigation and not yet approved for clinical use. Inhibitors of platelet aggregation (i.e., intravenous glycoprotein IIb/IIIa inhibitors) are reserved only for the acute phase treatment of high risk ACS patients undergoing PCI. On the other hand inhibitors of platelet activation processes represent the mainstay treatment for the acute and long-term prevention of recurrent ischemic events in ACS and PCI patients.

Adenosine diphosphate stimulates platelet activation through two G-protein coupled receptors, $P2Y_1$ and $P2Y_{12}$.[107] Although binding of ADP to both receptors is required for complete platelet aggregation, $P2Y_{12}$ is the predominant receptor involved in ADP-stimulated platelet activation of the glycoprotein (GP) IIb/IIIa receptor.[108] Binding of ADP to $P2Y_1$ stimulates activation of the GP IIb/IIIa receptor resulting in calcium mobilization, platelet shape change, and transient platelet aggregation.[109,110] Binding of ADP to $P2Y_{12}$ stimulates activation of the GP IIb/IIIa receptor resulting in enhanced platelet degranulation and thromboxane production and prolonged platelet aggregation (Figure 5).[111-113] Moreover, activated platelets can synthesize prostanoids, primarily thromboxane $(TX)A_2$ from arachidonic

Figure 5: Mechanisms of platelet activation and potential receptor site blockage by various anti-platelet agents.
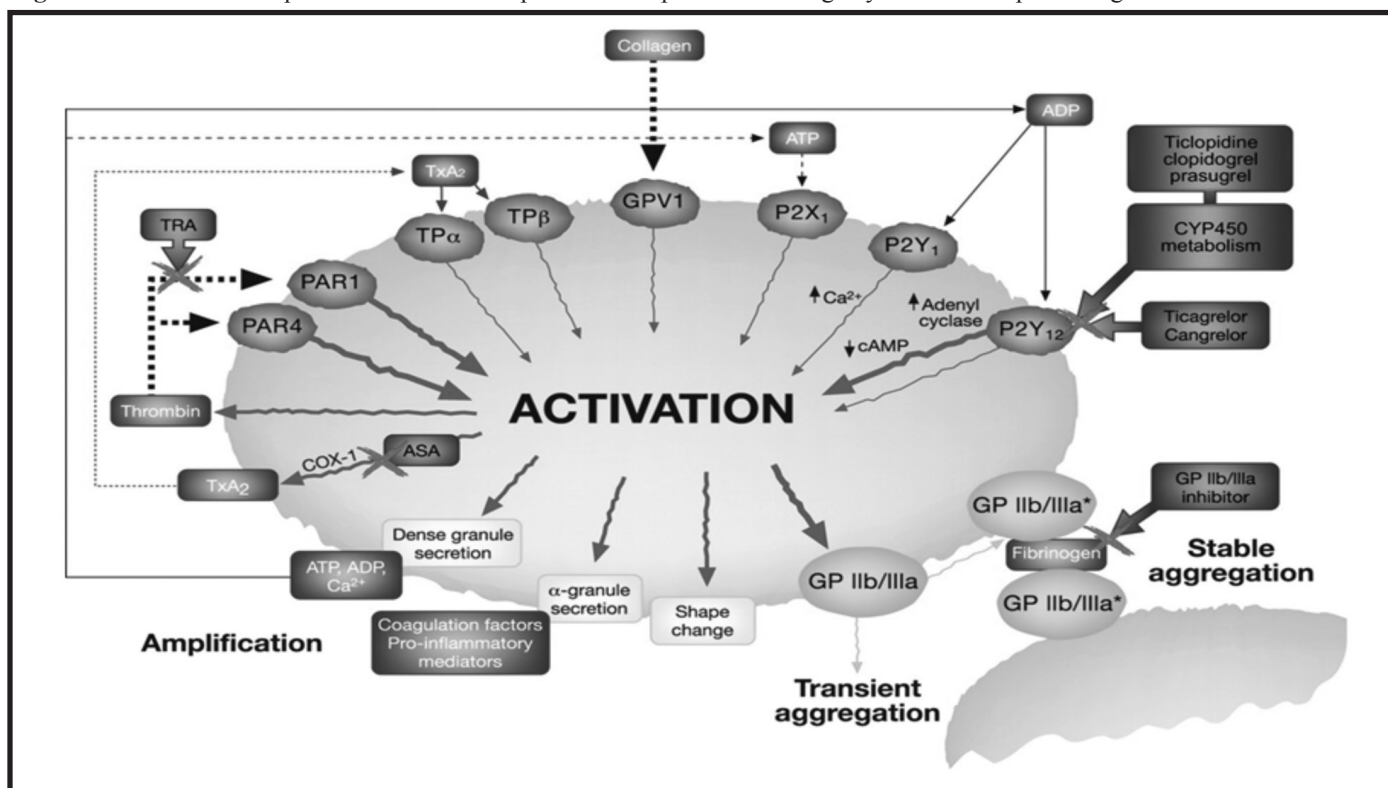
Wallentin L. *Eur Heart J.* 2009;30:1964-1977

acid released from membrane phospholipids through rapid coordinated activation of phospholipase(s), cyclo-oxygenase (COX)-1 and TX-synthase. At least four distinct platelet proteins represent the target of reversible and irreversible inhibitors with variable antiplatelet effects, i.e., COX-1, glycoprotein (GP)IIb/IIIa, the PGH_2/TXA_2(TP) receptor and the ADP receptor $P2Y_{12}$.[114-118]

Figure 6: Arachidonic acid metabolism via the cyclo-oxygenase (COX) pathways.
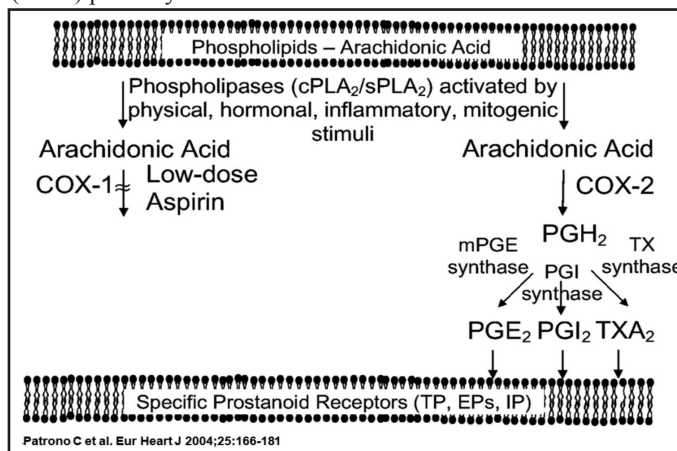
Low-dose aspirin is shown inhibiting the COX-1 pathway. This results in suppression of thromboxane (TX) A_2 and prostaglandin (PG) E_2 synthesis in platelets. However, the same products can be formed through the COX-2 pathway in an aspirin-insensitive fashion. PLA_2, phospholipase A_2; EP, PGE_2 receptor; IP, prostacyclin receptor; TP, thromboxane receptor.

An Aspirin a Day

Biochemically aspirin induces an irreversible functional defect in platelets, detectable clinically as a prolonged bleeding time. This appears to be primarily, if not exclusively, due to permanent inactivation by aspirin of a key enzyme in platelet arachidonate metabolism (Figure 6). Prostaglandin (PG) H-synthase, produces PGH_2, the precursor of thromboxane (TXA_2). Thromboxane A_2 is synthesized and released by platelets in response to a variety of stimuli (for example, thrombin, collagen, and adenosine diphosphate) and in turn induces irreversible platelet aggregation,[119-121] thereby providing a mechanism for amplifying the platelet response to such diverse agonists. Aspirin selectively acetylates the hydroxyl group of a single serine residue at position 529 within the polypeptide chain of platelet prostaglandin G/H synthase 1,[122-124] causing the irreversible loss of its cyclooxygenase activity. This enzyme exhibits two distinct catalytic activities: a bis-oxygenase (cyclo-oxygenase [COX]) involved in formation of PGG_2, and a hydroperoxidase allowing a net two-electron reduction in the 15-hydroperoxyl group of PGG_2, thus yielding PGH_2. Through O-acetylation of Ser[529] by aspirin, the cyclo-oxygenase activity is lost permanently, whereas the hydroperoxidase activity is not affected. An inducible form of PGH-synthase has been identified and termed PGH-synthase 2 or COX-2.[125] Aspirin inhibits the cyclo-oxygenase activity of PGH-synthase 2, but at higher concentrations than those required to inhibit PGH-synthase1or COX-1 (i.e., the constitutive enzyme).[126] This may account, at least in part, for the different dose requirements of analgesic and anti-inflammatory versus antiplatelet effects of the drug. Normally COX-

2 produces prostanoids, most of which are pro-inflammatory. Aspirin-modified COX-2 produces lipoxins, most of which are anti-inflammatory. Within minutes, aspirin prevents additional platelet activation and interferes with platelet adhesion and cohesion. Since platelets have no DNA, they are unable to synthesize new COX once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group was a multicenter, multinational, randomized, double-blind, placebo-controlled randomized trial of 17,187 cases of suspected acute myocardial infarction.[127] Patients were randomized to one of four groups involving streptokinase (SK) or aspirin.

1. **SK** (1.5 million U over 60 min) and **aspirin** (162.5 mg/day for one month).

2. **SK** (1.5 million U over 60 min) and **placebo** matching aspirin (enteric-coated starch).

3. **Placebo** matching SK (Hepatitis-B-antigen-free albumin) and **aspirin** (162.5 mg/day for one month).

4. **Placebo** matching SK and **placebo** matching aspirin.

The study results revealed that Streptokinase alone and aspirin alone each produced a highly significant reduction in five-week vascular mortality: 791/8592 (9.2%) among patients allocated streptokinase infusion vs. 1029/8595 (12.0%) among those allocated placebo infusion (odds reduction: 25% SD 4; 2p less than 0.00001); 804/8587 (9.4%) vascular deaths among patients allocated aspirin tablets vs. 1016/8600 (11.8%) among those allocated placebo tablets (odds reduction: 23% SD 4; 2p less than 0.00001) (Figure 6). The combination of streptokinase and aspirin was significantly (2p less than 0.0001) better than either agent alone. Their separate effects on vascular deaths appeared to be additive: 343/4292 (8.0%) among patients allocated both active agents vs. 568/4300 (13.2%) among those allocated neither (odds reduction: 42% SD 5; 95% confidence limits 34-50%) (Figure 7). There was evidence of benefit from each agent even for patients treated late after pain onset (odds reductions at 0-4, 5-12, and 13-24 hours: 35% SD 6, 16% SD 7, and 21% SD 12 for streptokinase alone; 25% SD 7, 21% SD 7, and 21% SD 12 for aspirin alone; and 53% SD 8, 32% SD 9, and 38% SD 15 for the combination of streptokinase and aspirin). The early survival advantages produced by fibrinolytic therapy and one month of aspirin started in acute myocardial infarction seem to be maintained for at least ten years.[128]

Aspirin alone has one of the greatest impacts on the reduction of MI mortality and has become the cornerstone of treatment in both acute coronary syndrome**s** and chronic coronary artery disease. Its beneficial effect is observed early in therapy and persists for years with continued use. The long-term benefit is sustained, even at doses as low as 75 mg/day. Some studies suggest that enteric coating may delay aspirin absorption,[129] making it preferable to give non-enteric coated aspirin in the setting of STEMI. While no large, prospective, random-ized trials randomizing STEMI patients to either low vs. high doses of aspirin in STEMI have been conducted, extrapolation from the GUSTO I and GUSTO III trials (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)[130] as well as results from non-randomized retrospective analysis of studies comparing 30-day mortality and bleeding risks associated with the administration of 162 mg versus 325 mg of aspirin among patients with STEMI treated with thrombolytic therapy shows that 162 mg of aspirin may be as effective as, and perhaps safer than, 325 mg for the acute treatment of STEMI. [131,132]

Figure 7: Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.
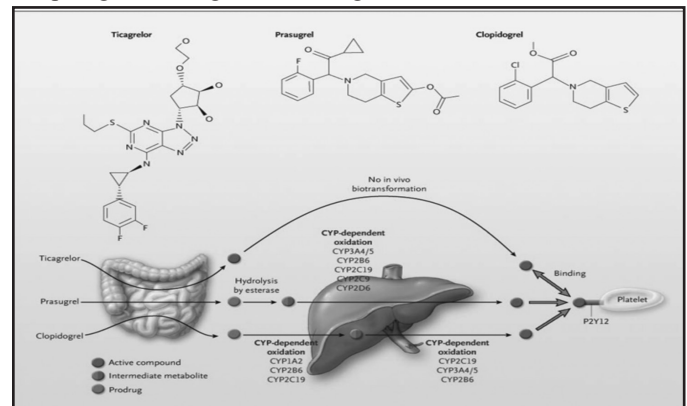
After Schömig A. *N Engl J Med.* 2009;361:1108-1111.

Recent reviews of a large database of randomized clinical trials[133,134] provide the most compelling evidence that prevention of myocardial infarction and ischemic stroke by aspirin is largely due to permanent inactivation of platelet COX-1. By testing the efficacy and safety of aspirin at daily doses ranging from as low as 30mg to as high as 1500mg, these studies have revealed that the anti-thrombotic effect of aspirin is saturable at doses in the range of 75 to 100mg, and that despite a half-life of approximately 20 minutes in the human circulation, the anti-thrombotic effect of aspirin is observed with dosing intervals of 24 to 48 hours, reflecting the permanent nature of platelet COX-1 inactivation and the duration of TXA_2 suppression following oral dosing in man.

Adenosine Diphosphate (ADP) Receptor Antagonists

The Case for Adding Thienopyridines to Aspirin.

Currently, platelet inhibitory treatment with a combination of aspirin (acetylsalicylic acid) and $P2Y_{12}$ receptor inhibition with the thienopyridine, clopidogrel is recommended for patients with acute coronary syndrome (ACS) as well as those undergoing percutaneous coronary intervention (PCI) with stent implantation. This dual antiplatelet therapy has received Class I recommendations in current clinical practice guidelines for unstable angina/non-STEMI (UA/NSTEMI), STEMI,

and PCI.[135,136] Thienopyridines are a subcategory of antiplatelet medications that prevent platelet aggregation through the binding of select, extracellular cysteine residues on the P2Y12 receptor located on the platelet membrane. Thienopyridine antiplatelet agents interfere with platelet activation and aggregation induced by ADP. Currently, three members of the thienopyridine class of antiplatelet agents, ticlopidine, clopidogrel and prasugrel, are available for clinical use. All three agents are prodrugs and require conversion to an active metabolite to exhibit an antiplatelet effect (Figure 8). The active metabolite of the thienopyridine binds irreversibly to the $P2Y_{12}$ receptor, blocking the binding of ADP and thereby inhibiting platelet activation and aggregation.

In addition to patients with STEMI thienopyridines have become a universally accepted cornerstone of treatment, particularly before, during, and after percutaneous coronary intervention (PCI), making a significant decrease in the rate of 30-day major adverse cardiac events (MACEs) in studies that initially compared ticlopidine and aspirin with aspirin alone or with warfarin and aspirin (p = 0.0001).[137] In time Clopidogrel showed a better tolerance profile than ticlopidine,[138] and the added benefit of a loading dose and long-term treatment for clopidogrel was suggested by the CREDO (Clopidogrel for Reduction of Events During Observation) study.[137-139] This was finally validated in a meta-analysis of combined registries and randomized studies.[140] Clopidogrel is currently the thienopyridine of choice.

The Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial,[141] a double-blind, randomized, placebo-controlled trial, randomized 3,491 STEMI patients treated with standard thrombolytic therapy, aspirin, and heparin to either clopidogrel 300-mg loading dose followed by 75 mg/day for 30 days or to placebo. This study showed that there was a 36% odds reduction in the clopidogrel group compared to placebo for the primary endpoint of infarct- related occlusion of arteries on angiography or death or MI recurrence before angiography which was performed two to eight days after lysis. In addition there was also a significant reduction of 20% in the major cardiovascular events (cardiovascular death, recurrent MI or recurrent ischemia requiring emergent revascularization) within 30 days of presentation. A sub study, PCI –CLARITY[142] also revealed that the clopidogrel treatment group was also effective in the reduction of major cardiovascular events in the 1,836 patients who underwent percutaneous coronary intervention (PCI) after fibrinolysis.

A more ambitious COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group study143 involved 45,852 patients admitted to 1,250 hospitals within 24 hours of suspected acute MI onset were randomly allocated clopidogrel 75 mg daily (n=22, 961) or matching placebo (n=22, 891) in addition to aspirin 162 mg daily. In the trial 93% of patients had ST-segment elevation or bundle branch block, and 7% had ST-segment depression. Patients allocated to the clopidogrel arm produced a highly significant 9% proportional reduction in death, reinfarction, or stroke (2121 [9·2%] clopidogrel vs. 2310 [10·1%] placebo; p=0·002), correspond-

ing to nine fewer events per 1000 patients treated for about two weeks. There was also a significant 7% (1-13) proportional reduction in any death (1,726 [7·5%] vs. 1845 [8·1%]; p=0·03) (Figure 9). These findings of death, reinfarction, and stroke seemed consistent across a wide range of patients and independent of other therapeutic modalities used. There appeared to be no significant excess risk noted with clopidogrel, either overall (134 [0·58%] vs. 125 [0·55%]; p=0·59), or in patients older than 70 years or in those given fibrinolytic therapy.

The metoprolol arm of COMMIT[144] showed that giving three intravenous doses of 5 mg metoprolol within 24 hours of the onset of a heart attack, followed by 200 mg daily oral doses while in the hospital, significantly reduced risk of reinfarction and ventricular fibrillation by 15–20%, but increased the relative risk of cardiac shock by about 30%. Risk of shock was elevated on the first two days but not subsequently. The overall balance of these different effects was about even, with no clear reduction in hospital mortality for any particular type of patient. Risk of harm with metoprolol was higher in patients ≥70 years of age, rated as Killip class III, or with systolic blood pressure <120 mm Hg or heart rate ≥110 beats/min where the hazards of early intravenous metoprolol appeared to outweigh any benefits.

Thienopyridine Metabolism, Pharmacokinetics and Polymorphic Genetic Variants

Despite the efficacy of this dual antiplatelet therapy treatment on both STEMI[145] and PCI patients[146,147] at least 15–40% of these patients are poor responders to treatment, in terms of ADP-induced platelet aggregation.[148-151] As a result such patients are at increased risk of myocardial infarction, stent thrombosis, and death as revealed in several trials.[152-155]

Active metabolites of the thienopyridine prodrugs (ticlopidine, clopidogrel, and prasugrel) metabolized in the liver and the intestines (Figure 7) to active metabolites that covalently bind to the $P2Y_{12}$ receptor, causing irreversible platelet inhibition. Although the thienopyridines require cytochrome P450 (CYP450) metabolism for generating active metabolites, the respective pathways differ among the prodrugs. Ticlopidine is metabolized by at least five main pathways resulting in at least 13, mostly inactive, metabolites[156,157] of which only one formed through a CYP-dependent pathway, appears to have antiplatelet activity[157,158] Clopidogrel is metabolized by two pathways. While one pathway de-esterifies most of the given dose to inactive metabolites,[159] the other pathway goes through at least two CYP-dependent steps to convert clopidogrel to its active metabolite.[160,161] Of the multiple CYP enzyme isoforms identified so far, the main contributors to active metabolite formation appear to be CYP1A2, CYP3A4/5, and CYP2C19 [162-164]). Defective genetic variants, CYP2C19 and possibly also CYP2C9 and CYP2B6, appear to be associated with decreased plasma concentrations (AUC and Cmax) of the active metabolite, lower platelet inhibition, and poor-responder status[165-167] (http://eurheartj.oxfordjournals.org/content/30/16/1964.full- ref-32)

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Genetic polymorphism in several genes involved in CYP450 metabolism and in the expression of platelet receptors have been proposed to explain part of the variability in clopidogrel responsiveness between individuals. The CYP2C19 defective genotypes, like CYPC19*2, appear to be common with frequencies ranging from 20 to 30% in Caucasians, 30 to 45% in African-Americans, but up to 50 to 65% in East Asians [164-166]. This translates to ethnic differences in clinical efficacy of clopidogrel in the larger population. In view of the above considerations on March 12, 2010, the US Food and Drug Administration (FDA) added a Boxed Warning (black box) to the label for clopidogrel (Plavix) regarding patients who do not effectively metabolize the drug and therefore may not receive the full benefits of the drug. Moreover, many physicians refrain from administering clopidogrel prior to obtaining coronary angiography, since this irreversible platelet inhibitor has been associated with an increased risk of perioperative bleeding should coronary-artery bypass grafting (CABG) be required rather than PCI.

The TRITON-TIMI 38 (Trials to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) trial in acute coronary syndrome (ACS) patients scheduled for percutaneous coronary intervention (PCI) trial[171] randomized 13,608 patients with acute coronary syndromes (with or without ST-segment elevation) who were scheduled for PCI and receiving aspirin were randomly assigned to receive either prasugrel or clopidogrel. Patients received prasugrel (60-mg loading dose and then 10-mg daily maintenance dose) or clopidogrel (300-mg/75-mg) for six to 15 months. The study found a significant decrease in the primary end point; the rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke with prasugrel (12.1% for clopidogrel vs. 9.9% for prasugrel, P<0.001). In addition, there was a significant decrease with prasugrel in the rate of myocardial infarction followed by death from cardiovascular causes, including arrhythmia, congestive heart failure, shock, and sudden or unwitnessed death (0.7% vs. 0.4%, P=0.02). Stent thrombosis, a complication of great recent concern, was reduced by approximately 50% in the prasugrel group as compared with the clopidogrel group (2.4% vs. 1.1%; P<0.001), not only for drug-eluting stents but also for bare-metal stents. However, in TIMI, there was a concerning excess major bleeding not related to coronary-artery bypass grafting that was life-threatening in the prasugrel group (1.4%, vs. 0.9% in the clopidogrel group; P=0.01), even fatally so (0.4% vs. 0.1%, P=0.002). For every 1000 patients treated with prasugrel as compared with clopidogrel, 23 MIs were prevented, but at a cost of an excess of six non-CABG-related TIMI major hemorrhages.

Thus, clopidogrel's delayed onset and variability in platelet inhibition appears to be associated with an increased risk of ischemic events and stent thrombosis in poorly responsive patients. Unlike clopidogrel metabolism, prasugrel, a novel third-generation thienopyridine P2Y12 receptor antagonist, first undergoes rapid de-esterification to an intermediate thiolactone, which is then converted to the active metabolite in a single CYP-dependent step.[171-174] In addition, the metabolism of prasugrel is not impacted by reduced function CYP polymorphisms[175,176] Therefore, in PCI-treated ACS patients, prasugrel seems to provide a better protection against thrombotic events but with a raised risk of major bleeding. Prasugrel's apparent higher efficacy is related to its simpler metabolism, more rapid conversion to the active metabolite, and the lack of influence of genetic variability. Prasugrel possesses more rapid, potent, and consistent platelet inhibition than clopidogrel. On July 10, 2009, the US Food and Drug Administration (FDA) approved the use of prasugrel in patients with ACS who are to be managed with PCI. However, much controversy surrounded the approval of prasugrel. There is still some uncertainty about the role this drug will play in the prevention of myocardial infarction, as well as its optimal dosing and adverse effects profile. It is possible that Prasugrel may be the preferred therapy in patients with diabetes mellitus. Prasugrel should not be used in patients with previous stroke, transient ischemic attack, or other intracranial pathology and is not recommended in patients 75 years or older, or in patients weighing less than 60 kg. The 2009 joint American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) STEMI/PCI focused update guidelines recommend administration of either clopidogrel (300 to 600 mg loading dose) as early as possible prior to, or at the time of, primary or non-primary PCI or prasugrel (60 mg loading dose) as soon as possible for primary PCI in STEMI patients undergoing planned PCI.

Direct-Acting P2Y$_{12}$ Inhibitors

As discussed above, thienopyridines (ticlopidine, clopidogrel, and prasugrel) are indirectly acting platelet inhibitors where the active metabolites of the thienopyridine prodrugs covalently and irreversibly bind to the P2Y$_{12}$ receptor during the entire lifespan of the platelet (See Table 2). Thus the delayed onset of action of these drugs is a disadvantage especially during PCI. Moreover, their irreversible antiplatelet effect represents a major disadvantage for patients who do not undergo PCI but are in need of urgent CABG. Because of this reason, many centers defer the administration of thienopyridines in patients with STEMI until angiography confirms the need for PCI. However newer, direct-acting P2Y$_{12}$ inhibitors like cangrelor and ticagrelor change the conformation of the P2Y$_{12}$ receptor resulting in reversible inhibition of the receptor. Ticagrelor (Brilinta, AstraZeneca) is the first in a new chemical class, the CPTPs (cyclopentyl-triazolo-pyrimidines) and is chemically distinct from the thienopyridines, such as clopidogrel and prasugrel. It is administered orally and has a reversible P2Y(12) receptor inhibitory effect and is chemically distinct from the thienopyridines, such as clopidogrel and prasugrel, but has a more rapid onset and with a more pronounced platelet inhibition that is nearly double that of clopidogrel.[177]

In the **PLAT**elet Inhibition and Patient **O**utcomes (PLATO) trial (178), 18,624 patients admitted to the hospital with ACS recruited from 862 sites in 43 countries between 2006 and 2008 and with or without ST-segment elevation were randomized to

receive either ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300- to 600-mg loading dose, 75 mg thereafter) in a double-blind, double-dummy fashion for one year. Patients left the study at their six- or nine-month visit if the targeted number of 1,780 primary end points had occurred by that time. Patients also received aspirin, at a dose of 75 mg to 100 mg day, unless they could not tolerate the drug. At 12 months, the primary end point, a composite of death from vascular causes, MI, or stroke, had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those taking clopidogrel (p<0.001). Overall mortality was reduced from 6% to 4.9%. Definite stent thrombosis was reduced from 2.6% in the clopidogrel group to 1.6% in the ticagrelor group. Major bleeding occurred in 9.3% of clopidogrel patients versus 9.0% of ticagrelor patients.

In the PLATO study, a subset of 8,430 patients who were in the midst of STEMI and were scheduled for primary percutaneous coronary intervention (PCI) with stenting received the investigational drug ticagrelor or clopidogrel in addition to aspirin.[179] Out of this clinical subset, 4,201 STEMI patients were allocated to ticagrelor 180 mg loading dose followed by 90 mg twice daily plus aspirin, and 4,229 to clopidogrel 300 mg loading dose (with provision for an extra 300 mg clopidogrel at PCI) followed by 75 mg daily for six to twelve months, plus aspirin. The sub-analysis revealed that the clopidogrel treatment arm compared to ticagrelor resulted in a reduction of cardiovascular events (composite of CV death, heart attack and stroke) for up to a year (ticagrelor vs. clopidogrel, 9.3% vs. 11.0%, P=0.02). There was a statistically significant reduction in myocardial infarction (4.7% vs. 6.1%, P=0.01). In addition no increase in major bleeding (9.0% vs. 9.3%, P=0.63) was observed. For these STEMI patients, the benefit observed with ticagrelor appeared to increase over time.

However, new side effects, particular to the use of ticagrelor but previously not seen with either clopidogrel or prasugrel, were more evident. These included dyspnea, bradyarrhythmia, and increased serum levels of uric acid and creatinine. As in the main trial, ticagrelor was associated with a significantly higher rate of dyspnea than was clopidogrel (12.9% vs. 8.3%, respectively; p<0.0001). On July 28, 2010, the FDA Cardiovascular and Renal Drugs Advisory Committee voted to recommend approval of antiplatelet drug ticagrelor in the management of STEMI and also unstable angina and NSTEMI.

Cangrelor is an adenosine triphosphate (ATP) analog which reversibly and directly, without any biotransformation, inhibits the P2Y$_{12}$ receptor.[180,181] This apparent dream drug in some respects is characterized by a) rapid onset of action, reaching steady-state concentrations within minutes; b) great degree of platelet inhibition (>90%); c) dose-dependent effects; and d) rapid onset of action, since it has an extremely short half-life (two to five minutes) due to rapid deactivation by plasma ecto-nucleotidases, with the platelet response approaching baseline within 60 minutes after discontinuation of the drug infusion and also appeared well tolerated during a prolonged infusion of up to 72 hours.[182,183] It is the first such drug to be administered intravenously. Harrington et al.[184] and Bhatt et al.[185] reported on the results of the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI trial and the CHAMPION PLATFORM trial respectively. Unfortunately, both CHAMPION trials had negative results and insufficient evidence for clinical effectiveness for cangrelor but questions about the flawed design and reporting of both these trials have been raised.[186] Although Cangrelor underwent these two phase-3 trials, which were stopped early for lack of efficacy, nevertheless, it is still being studied as a potential bridge for patients on clopidogrel who need to go off the drug to undergo surgery. There is a current ongoing study, BRIDGE (maintenance of platelet inihiBition with cangRelor after discontinuation of thienopyriDines in patients undergoing surgery) trial (NCT 00767507) to test this hypothesis.

Elinogrel (PRT060128), a quinazorinedione, is a reversible, potent and competitive inhibitor of the P2Y$_{12}$ receptor that can be administered by both oral and intravenous routes and rapidly achieves near complete platelet inhibition. At present Elinogrel is in the preliminary stages of development, with phase I studies showing some promising pharmacologic properties that include: a) rapid onset of action (almost immediate if administered intravenously); b) higher degree of platelet inhibition than clopidogrel; and c) rapid onset of action, with a half-life of 50 minutes and 12 hours for intravenously and oral administration, respectively.[187] In poor clopidogrel responders a single oral dose of elinogrel improved platelet inhibition in stable

Table 2: Platelet P2Y$_{12}$ inhibitors.

	Clopidogrel	Prasugrel	Cangrelor	Ticagrelor	Elinogrel
Group	Thienopyridine	Thienopyridine	ATP analog	Cyclopentyltriazolopyridine	Quinazolinedione
Development Status	Approved in 1997	Approved in 2009	Phase III completed in 2009	Phase III completed in 2009	Phase II ongoing
Administration	Oral	Oral	Parenteral	Oral	Oral and parenteral
Bioavailability	Prodrug	Prodrug	Direct-acting	Direct-acting	Direct-acting
Receptor inhibition	Irreversible	Irreversible	Reversible	Reversible	Reversible
Frequency	Daily	Daily	Bolus and infusion	Twice daily	Twice daily

ATP indicated adenosine triphosphate

Modified after Angiollio and Ferreiro. Rev *Esp Cardiol*. 2010; 63:60-76.

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patients with coronary artery disease.[188]   In the ERASE-MI trial (**E**arly **R**apid Revers**A**l of Platelet Thrombo**S**is with Intravenous PRT060128 Before PCI to Optimize R**E**perfusion in Acute **MI**), the initial phase 2 results, evaluating the safety and efficacy of intravenous elinogrel in patients with STEMI prior to primary PCI, showed that the incidence of bleeding events was infrequent and that no differences were demonstrated between elinogrel and placebo in serious adverse events, laboratory values, corrected Thrombolysis in Myocardial Infarction (TIMI) frame count, or ST resolution.[188] Currently, the ongoing INNOVATE (a Randomized, Double-Blind, Active-Controlled Trial to Evaluate Intravenous and Oral PRT060128, a Selective and Reversible P2Y12 Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-Urgent PCI) trial (NCT00751231) is evaluating clinical efficacy, biological activity, tolerability and safety of PRT060128 in patients undergoing non-urgent PCI, testing three doses of elinogrel (oral 50, 100, and 150 mg) twice daily, following an intravenous bolus.[189]

Anticoagulant Therapy

The American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend the use of intravenous unfractionated heparin, with the dose adjusted for the activated clotting time, during percutaneous coronary intervention (PCI).[189,190] On the basis of expert consensus, unfractionated heparin is recommended in patients undergoing primary PCI (class I =treatment should be administered). Unfractionated Heparins (UFH) are glycosaminoglycans (GAGS) consisting of chains of alternating residues of D-glucosamine and a uronic acid, either gluconic acid or iduronic acid. Heparin in particular is a heterogeneous polydispersed mixture of sulfated polysaccharides with a molecular weight range of 3000 to 30 000 Da (mean, 15 000 Da), whose anticoagu1ant activity is accounted for by a unique pentasaccharide with a high affinity binding sequence to antithrombin 111 (ATIII). Heparin produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin (AT)-dependent mechanism. Heparin binds to AT through the high-affinity pentasaccharide, which is present on about a third of heparin molecules. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition of factor Xa. Molecules of heparin with fewer than 18 saccharides lack the chain length to bridge between thrombin and AT and, therefore, are unable to inhibit thrombin. In contrast, very small heparin fragments containing the pentasaccharide sequence inhibit factor Xa via AT. By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and of factors V and VIII.

Historically, unfractionated heparin (UFH) has been widely used as an anti-coagulant in the treatment of STEMI for greater than 50 years. The benefits of UFH combined with fibrinolytic therapy have been established. Adding UFH to fibrinolysis with streptokinase (SK) has been shown to reduce death and re-

infarction,[192] while combining UFH with fibrin-specific agents is thought to help achieve and maintain coronary arterial patency.[193,194] However disadvantages to the use of UFH include its sometimes difficult-to-manage effects on coagulation because of its narrow therapeutic window, necessitating the need for continuous monitoring of coagulation, the potential for inducing platelet activation, and the risk of Heparin Induced Thrombocytopenia/Heparin Induced Thrombosis-Thrombocytopenia Syndrome (HIT/HITTS).

UFH can be fragmented and depolymerized to Low-molecular-weight heparins (LMWHs), by nitrous acid depolymerization (fraxiparin and fragmin), benzylation followed by alkaline depolymerization (enoxaparin=lovenox), or by enzymatic (heparinase) depolymerization (logiparin), LMWHs consisting of only short chains of polysaccharides having an average molecular weight of less than 8000 Da and for which at least 60% of all chains have a molecular weight less than 8000 Da. The resulting LMWHs contain the unique pentasaccharide required for specific binding to ATIII, but in a lower proportion than is contained in their parent UFH**.** Physiologically and clinically Low-molecular-weight heparins possess some pharmacological and pharmacokinetic advantages over unfractionated heparin. They have a predictable pharmacokinetic profile, high bioavailability, and long plasma half-life, all of which result in effective levels of anticoagulant activity after subcutaneous administration without need of constant laboratory monitoring.[195,196] Low-molecular-weight heparins, such as enoxaparin, are therefore an attractive potential replacement for UFH because of the convenient subcutaneous route of administration and reliable anticoagulation effects, eliminating the need for therapeutic monitoring. Five different LMWHs (Enoxaparin, Fragmin, Fraxiparin, Logiparin, and Lomoparin) have been approved for clinical use in Europe and three LMWHs (Enoxaparin, Logiparin, and RD heparin) and the heparinoid Lomoparin have been evaluated in large-scale randomized trials in North America.

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction Study 25 (ExTRACT-TIMI 25) trial demonstrated that enoxaparin as adjunctive anticoagulant therapy for the duration of the index hospitalization was superior to the standard two-day UFH regimen in patients with STEMI treated with fibrinolytic therapy.[197] In the ExTRACT-TIMI 25 trial, alteplase, tenecteplase, reteplase, or SK was administered to STEMI patients at the discretion of the treating physician, and 30-day outcomes were evaluated. In a pre-specified subgroup analysis of this study of patients with STEMI undergoing pharmacological re-perfusion, recurrent MI, and ischemic events leading to urgent revascularization were significantly reduced (12.0% vs. 9.9%, p < 0.001); with the enoxaparin strategy compared with UFH as adjunctive anticoagulant therapy in conjunction with fibrin-specific lytics. However, more major bleedings were observed in the enoxaparin group (1.4 vs. 2.1%, p < 0.001).[198]

Thrombin Inhibitors

Fondaparinux, a synthetic pentasaccharide, is the first of the selective Xa inhibitors with clinical importance. It is an indirect factor Xa inhibitor. It is a pentasaccharide designed specifically to bind to plasma antithrombin. This binding induces a conformational change in antithrombin which increases the affinity of antithrombin for factor Xa, potentiating the natural inhibitory effect of antithrombin against factor Xa. The Fifth Organization to Access Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial demonstrated that fondaparinux is an efficient and safe anticoagulant in the treatment of acute coronary syndromes without ST elevations.[199] The OASIS-6 trial[200] showed a reduction in mortality and reinfarctions by fondaparinux compared with unfractionated heparin in more than 10,000 patients with STEMI. Treatment of STEMI patients with fondaparinux was safe and not associated with an increase in bleedings or hemorrhagic strokes.

The data of the OASIS-6 trial suggest that selective factor Xa inhibition with fondaparinux is an attractive new antithrombotic strategy in the treatment of STEMI. Fondaparinux is easy to use. A single daily subcutaneous administration of 2.5 mg can provide a stable and predictable anti-coagulation without the need for laboratory control of coagulation parameters. Besides, it is not associated with the risk of heparin-associated thrombocytopenia. As a result it can be used in a wide range of settings for various patients. However, for primary PCI in STEMI patients, the actual data of the OASIS-6 trial suggested that at least during the intervention, unfractionated heparin is necessary in addition to fondaparinux to avoid catheter thrombosis and ischemic complications.

Bivalirudin (Angiomax or Angiox) is a synthetic congener of the naturally occurring drug hirudin (found in the saliva of the medicinal leech Hirudo medicinalis). It is a specific and reversible direct thrombin inhibitor (DTI). It does not have the many limitations seen with indirect thrombin inhibitors, such as heparin. Bivalirudin is a short, synthetic peptide that is potent, highly specific, and a reversible inhibitor of thrombin,[201,202] inhibiting both circulating and clot-bound thrombin,[203] as well as inhibiting thrombin-mediated platelet activation and aggregation.[202] Thrombin is a serine proteinase that plays a central role in the thrombotic process. It cleaves fibrinogen into fibrin monomers, activates Factor V, VIII, and XIII, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus. Thrombin also promotes further thrombin generation and activates platelets, stimulating aggregation and granule release. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin-Arg_3-Pro_4 bond, resulting in recovery of thrombin active site functions.

A subgroup analysis of 7,789 patients from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial[204] demonstrated that substitution of unfractionated heparin or enoxaparin with bivalirudin results in comparable clinical outcomes in patients with moderate and high-risk acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors and in whom percutaneous coronary intervention is done. Moreover, anticoagulation with bivalirudin alone suppresses adverse ischemic events to a similar extent as does heparin plus glycoprotein IIb/IIIa inhibitors, while significantly lowering the risk of major hemorrhagic complications.[205] For STEMI patients undergoing PCI there may soon be a transition from UFH or LMWH towards bivalirudin with or without GP IIb/IIIa inhibitor in the cardiac catheterization lab.

Glycoprotein IIb/IIIa Receptor Inhibitors

Integrins are cell surface receptors that transduce information between the cell and its extracellular matrix. They are obligate heterodimers with two distinct chains, called the α (alpha) and β (beta) subunits. Glycoprotein IIb/IIIa (gpIIb/IIIa, also known as integrin $α_{IIb}β_3$), is an integrin complex acting as a fibrinogen receptor on the platelet cell surface. It is the most abundant platelet membrane glycoprotein found in humans and is also involved in platelet activation as a key mediator of thrombus formation. The *sine qua non* of platelet activation is the conformational changes of the GP IIb/IIIa receptor—with subsequent transformation from a low- into a high-affinity state—allowing for binding of fibrinogen and vWF.[206] Inhibiting this process of platelet activation has been a recognized therapeutic modality in the past decade in ACS and particularly during percutaneous coronary interventions (PCI).

The glycoprotein IIb/IIIa receptor inhibitors, abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat), have all been approved by the FDA for use in ACS. They all have similar mechanisms of action to inhibit platelet aggregation. Abciximab is a large fragment of a mouse–human chimeric monoclonal antibody that interferes with platelet aggregation by steric hindrance. These huge molecules basically wrap around each platelet, thus preventing glycoprotein IIb/IIIa receptor binding but also the binding to other receptors responsible for platelet adhesion. However, by preventing both platelet adhesion and aggregation, abciximab may result in more bleeding complications than more specific GP IIb/IIIa inhibitors. On the other hand Tirofiban and eptifibatide are relatively small, synthetic molecules with high affinity for glycoprotein IIb/IIIa binding only and compete with fibrinogen for the glycoprotein IIb/IIIa receptor in a concentration-dependent fashion and thereby preventing platelet aggregation. Tirofiban and eptifibatide apparently are non-immunogenic and, therefore, suitable for repeat infusions. They also have a shorter half life (90-120 minutes) compared to abciximab (12 hours). Since they are mainly renally cleared, their doses should be adjusted in patients with renal impairment. To maximize clinical benefits all three drugs should at least achieve 80% inhibition of platelet aggregation.

GP IIb/IIIa blockers were launched in the 1990s with great fanfare on the assumption that the inhibition of the 'final common pathway' of platelet aggregation would translate into an improvement in prognosis of patients undergoing PCI or presenting with ACS.[207] Unfortunately, much of the evidence favoring the use of GP IIb/IIIa inhibitors for STEMI was established in

the era before dual oral antiplatelet therapy and largely by placebo-controlled comparisons.[208-210]

The three trials that have evaluated GP IIb/IIIa antagonists as adjuncts to oral antiplatelet therapy in the setting of primary PCI have not established whether GP IIb/IIIa antagonists provide significant additional benefit to STEMI patients who have received dual-antiplatelet therapy before catheterization. In the BRAVE-3 study,[211] the composite of death at 30 days, recurrent myocardial infarction (MI), stroke, or urgent revascularization of the infarct-related artery was not significantly different in the two groups (abciximab 5%, placebo 3.8%; P=0.4). A randomized, placebo-controlled, multicenter European trial ON-TIME 2[212] found no significant difference in death, recurrent MI, or urgent target-vessel revascularization (TVR) between the tirofiban and placebo groups at 30 days. In the HORIZONS-AMI trial,[213] patients undergoing primary PCI for STEMI and who had been given aspirin and a thienopyridine before catheterization were randomized to treatment with UFH plus a GP IIb/IIIa receptor antagonist (abciximab or double-bolus eptifibatide) or to bivalirudin alone with provisional IIb/IIIa. At 30 days, rates of major bleeding and total adverse events were higher among patients treated with GP IIb/IIIa antagonists and heparin than among those given bivalirudin alone.

In light of these findings the 2009 STEMI and PCI Focused Updates of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines advises that, in the setting of dual-antiplatelet therapy with UFH or bivalirudin as the anticoagulant, current evidence indicates that adjunctive use of a GP IIb/IIIa antagonist can be useful at the time of primary PCI but cannot be recommended as routine therapy.[214]

Percutaneous Coronary Intervention for Myocardial Revascularization

In 1929, Werner Forssmann, a young surgical resident from Eberswald, Germany, was tooling around in an attempt to find a safe and effective way to inject drugs for cardiac resuscitation. He anesthetized his left elbow, inserted a catheter into his antecubital vein, and confirmed the position of the catheter tip in the right atrium by use of radiography, thus performing the first documented human cardiac catheterization.[215] Forssmann further elaborated on his experiments to include intracardiac injection of contrast material through a catheter placed in the right atrium. By 1958, Mason Sones had performed selective coronary arteriography in a series of more than 1,000 patients.[216] Melvin Judkins, a radiologist who had studied coronary angiography with Sones, introduced a series of specialized catheters and created his own system of coronary imaging in 1967 and perfected the transfemoral approach.[217] These contributions coupled with the development of nontoxic contrast media paved the way for the development of coronary angiography.

Back in 1964, Charles Dotter and Melvin Judkins had described a new technique for relieving stenosis of the iliofemoral arter-

ies with rigid dilators.[218] Although this technique had been developed in Oregon, the procedure was largely ignored in the United States because of technical difficulties and complications but was widely adopted to treat large numbers of patients in Europe. Meanwhile in 1974 Andreas Gruentzig in Zurich substituted a balloon-tipped catheter for the rigid dilator and inaugurated the first peripheral balloon angioplasty in a human.[219] After perfecting coronary angioplasty in animals, Gruentzig then went on to perform intraoperative balloon angioplasty on the human heart for the first time.[220] Soon thereafter, Gruentzig and his colleagues described their technique of percutaneous transluminal coronary angioplasty (PTCA) as used in a series of 50 patients.[221] This Gruentzig technique was widely adopted and universally applied. The era of percutaneous coronary intervention had arrived. This technique quickly evolved into applications such as coronary atherectomy (1986) and coronary stenting (1987) and by 1997, angioplasty had become one of the most common medical interventions in the world.

In 1986 results from a small, randomized trial involving 56 patients suggested that percutaneous coronary intervention (PCI) could be superior to intracoronary streptokinase therapy in improving left ventricular function.[222] A systematic review of ten small trials involving a total of 2,606 patients and published in 1997[223] compared either streptokinase or tissue-type plasminogen activator with primary PCI. This revealed a statistically significant 34% reduction in mortality for PCI (6.5% v. 4.4%; p = 0.02), a 47% reduction in nonfatal reinfarction (5.3% v. 2.9%; p = 0.04), and a substantial reduction in hemorrhagic stroke (1.1% v. 0.1%; $p < 0.001$) at 30 days.[216] PCI, therefore, saved 21 more lives per 1000 patients compared with thrombolytic therapy (and 40 to 50 lives saved with PCI compared with no therapy). In addition PCI avoids increased rates of reinfarction and intracranial bleeds, two of the most serious complications of thrombolytic therapy. Multiple registries and randomized clinical trials have now solidly confirmed the benefits of PCI over thrombolysis.[224-228] The Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) trial enrolled 1,572 patients and randomized patients arriving at an invasive hospital within 12 hours of ST-segment elevation MI (STEMI) to fibrinolysis with tPA or primary PCI. In addition, patients who were admitted to noninvasive hospitals were randomized to immediate treatment with thrombolytic therapy in the local hospital or acute ambulance transfer for primary angioplasty.[229] Compared to fibrinolysis with front-loaded tPA, primary PCI in patients with STEMI reduced the combined incidence of death, recurrent MI, or stroke from 14% to 8% (relative risk reduction [RRR], 43%; p =0.0003). In transfer sites, the rate of combined end point was 14% in those treated with thrombolysis compared to 9% in those treated with PCI (RRR, 40%; p =0.003). In nontransfer sites, the combined end point was 12% in the thrombolytic group and 7% in the primary PCI group (RRR, 45%; p =0.048).

Again back in 1964, well before the introduction of coronary angioplasty by Grüntzig, Dotter and Judkins had proposed the use of percutaneously introduced prosthetic devices to maintain the luminal integrity of atheromatous vessels.[218] However, it was Palmaz et al.[230] who in 1985 introduced the use of balloon-

mounted stents in peripheral arteries. Schatz et al. subsequently modified the Palmaz stent, which led to the development of the first commercially successful stent, the Palmaz–Schatz stent.[231] However, it was Puel and Sigwart[232] who were the first to implant a self-expanding mesh device in humans in March 1986. The following year Sigwart and colleagues described the use of this particular stent for emergency vessel closure during balloon angioplasty.[233] The reasoning was that the device would act as a scaffold shunting intimal and medial flaps away from the lumen, thus maintaining radial support to offset vascular elastic recoil to obviate restenosis.[234] The most serious complication of PCI results when there is an abrupt closure of the dilated coronary artery within the first few hours after the procedure. Abrupt coronary artery closure occurs in 5% of patients after simple balloon angioplasty and is responsible for most of the serious complications related to percutaneous coronary intervention. Abrupt closure is due to a combination of tearing (dissection) of the inner lining of the artery, blood clotting (thrombosis) at the balloon site, and constriction (spasm) or elastic recoil of the artery at the balloon site.

Two important randomized clinical trials in 1993 compared the Palmaz–Schatz stent with balloon angioplasty. The Netherlands Stent (BENESTENT) study[235] and the North American Stent Restenosis Study (STRESS)[236] separately demonstrated that intracoronary stents significantly reduced the incidence of angiographic restenosis (defined as more than 50% narrowing of a previously stented site, as measured by quantitative coronary angiography) and repeated angioplasty in patients with discrete, new lesions in large target vessels. This firmly established the elective placement of coronary stents as a standard treatment for myocardial revascularization. By 1999, stenting constituted 84.2% of percutaneous coronary interventions.

Currently, mortality rates for PCI from experienced operators in large series range from 0.5 to 1.7 percent.[237-242] Overall, the improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incidence of major periprocedural complications of PCI in the last 20 to 25 years. This is evidenced by the fact that, the need for emergent coronary bypass surgery (CABG) decreased in two series from 1.5% in 1992 to 0.14% in 2000,[243] and from 2.9% in 1979 to 1994 to 0.3% in 2000 to 2003.[244]

Therefore, with respect to parameters utilized for assessment of success in primary PCI, which include TIMI flow, myocardial blush grades, and ST-segment resolution mechanical revascularization, (PCI) appears to perform better than lytic therapy. Primary percutaneous coronary intervention (PCI) to restore coronary blood flow is the current standard of care for ST-elevation myocardial infarction (STEMI) PCI. It carries a class IA recommendation from the American College of Cardiology (ACC)/American Heart Association (AHA) and 2005 Society for Cardiovascular Angiography and Interventions (SCAI) PCI guidelines. In addition the Centers for Medicare & Medicaid Services (CMS)/The Joint Commission have established a door-to-balloon time of less than 90 minutes as one of the core clinical performance measures.

Multiple "atherectomy" devices were also initially developed as adjuncts to percutaneous coronary intervention, including the excimer laser for photoablation of plaque, the use of a high-speed diamond-encrusted drill for rotational atherectomy for mechanical ablation of plaque, and directional atherectomy device for cutting and removal of plaque. These devices were initially thought to decrease the incidence of restenosis but in clinical trials were shown to be of little additional benefit and are now only used in selective cases as adjuncts to standard percutaneous coronary intervention.

It is self-evident that stent implantation would be inherently thrombogenic, initiating a complex interaction between the metal surface and blood components, resulting in activation of platelets, the complement system, and protein deposition. Indeed, this results in the deposition of thrombi over the surface of the stent (http://www.nejm.org/doi/full/10.1056/NEJM-ra051091 - ref15) and the establishment of a confluent endothelial monolayer,[245] a process leading to restenosis.

Drug-Eluting Stents (DES)

Drug-eluting stents are metal stents that have been coated with a polymer containing an antiproliferative agent, gradually released over time after the stent is inserted. Theoretically, this should provide sustained inhibition of the neointimal proliferation (the process that is responsible for restenosis) occurring as a result of vascular injury. The so-called first-generation drug-eluting stents released sirolimus, rapamycin, a natural cytostatic macrocyclic lactone with potent antiproliferative, anti-inflammatory, and immunosuppressive effects, acting by inhibiting the activation of the mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle, or paclitaxel, a chemotherapeutic agent that suppresses assembly and stabilization of microtubule.

The Randomized Study utilizing the Sirolimus-eluting Bx Velocity Balloon Expandable Stent (RAVEL) demonstrated a stupendous 0% rate of restenosis, as measured by angiography, and complete inhibition of neointimal hyperplasia in the group that received a sirolimus-eluting stent. While 23% of the control group at one year required percutaneous revascularization of the treated lesion, the study group that received a sirolimus-eluting stent group required 0% revascularization. This study led to the approval of the device in Europe.[246] The randomized, double-blind Sirolimus Eluting Stent in de Novo Coronary Lesions (SIRIUS) trial, involving 1,055 patients, similarly had favorable results that were used to gain approval of the device by the Food and Drug Administration (FDA) in the United States in 2003.[247] The SIRIUS trial confirmed the safety and efficacy of the sirolimus-eluting stent in single, previously untreated coronary artery lesions, with a lower rate of in-stent restenosis than found with otherwise identical bare-metal stents (3.2% vs. 35.4%, P<0.001). More studies confirmed that DES appeared to be superior to bare-metal stents (BMS) and to balloon angioplasty in reducing the magnitude of neointimal proliferation, the incidence of clinical restenosis, and the need for vascular reintervention.[248,249]

Bridled with new found enthusiasm for DES, physicians extended the use of drug-eluting stents to patients with clinical and anatomical features beyond those of patients in the FDA-approval trials. The use of drug-eluting stents in this context is called "off-label." In order to address this concern, in December 7-8, 2006, the FDA convened a public meeting of the Circulatory System Devices Advisory Committee to specifically: (1) provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis, both when DES are used according to their label and when they are used off-label in more complex cases beyond their FDA approved uses; and (2) address the appropriate duration of the use of clopidogrel with DES patients. The FDA panel observed that at least 60% of current DES use is off-label, and off-label use is associated with increased events. However, the panel acknowledged that "with more complex patients there is an expected increased risk in adverse events" and also noted that the FDA does "not regulate how [DES] are used by individual clinicians in the practice of medicine."[250]

Late stent thrombosis (i.e., thrombosis occurring 30 days or more after stent implantation) is more likely to occur with drug-eluting stents than with bare-metal stents.[251] As a result of continued gradual release of the antiproliferative agent, endothelialization of the stent struts is effectively inhibited. This then allows the struts to continue serving as a focus for platelet aggregation and thrombus formation. Indeed, there is angioscopic evidence that three to six months after stent deployment bare-metal stents were completely endothelialized, whereas 87% of drug-eluting stents were not, and thrombi were present in 50% of the drug-eluting stents.[252] While the risk of late stent thrombosis with drug-eluting stents is relatively small (0.5 to 3.1%), it does not diminish with time and its occurrence is unpredictable, often catastrophic, with fatal myocardial infarction occurring in up to 65% of such patients.[253]

Second-generation drug eluting stents differ from the first-generation stents in the shape of the stent frame and the nature of the polymer layer, a reservoir which delivers the antiproliferative agent.[254] In the second-generation drug-eluting stents, a semi-synthetic sirolitmus analogue, everolimus, is released from a cobalt-chromium stent frame with thin struts coated by a biocompatible fluoropolymer. In contrast, paclitaxel is released from a polymer coating affixed to less flexible thicker stainless steel struts in the older drug-eluting stents. Stone et al. recently showed that a second-generation everolimus-eluting stent is superior to a first-generation paclitaxel-eluting stent in preventing the clinical manifestations of stent thrombosis and restenosis.[255] However, it is not yet clear which of these two differences is responsible for the improved outcomes with the second-generation stents. Perhaps these newer stents have improved efficacy or delivery of the antiproliferative drug (everolimus) resulting in less neointimal proliferation and restenosis.

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