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Pathogenesis and Early Management of Non–ST-segment Elevation Acute Coronary Syndromes

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In 2001, there were more than 5.6 million visits to United States emergency departments because of chest pain or related symptoms [1]. Of these, nearly 1.4 million patients were admitted with acute coronary syndromes (ACS) [2]. The term "ACS" has evolved into a useful descriptor of a collection of symptoms associated with acute myocardial ischemia caused by sudden restriction of coronary blood flow. It is used to describe collectively acute myocardial infarction (AMI), both with and without ST-segment elevation, and unstable angina. By definition, then, it is a deliberately broad term that encompasses a range of related clinical conditions with varying degrees of host response, injury, prognosis, and, therefore, treatment.

In its very lack of specificity, the term "ACS" reflects the difficulty often encountered in differentiating between myocardial infarction (MI) (especially without ST segment elevation) and unstable angina at the time of presentation. As reflected by its name, non–ST-segment elevation MI (NSTEMI) is defined as presence of myocardial damage (typically detected by biochemical markers of myocardial necrosis) in the absence of ST segment elevation, true posterior MI, or new left bundle branch block on 12-lead ECG [3]. Its pathogenesis, clinical presentation, even angiographic appearance are virtually indistinguishable from those of unstable angina, save for evidence of myocardial necrosis, which is usually not apparent at initial presentation [4,5]. Therefore, the combined entity of unstable angina/NSTEMI is often referred to as non–ST-segment elevation ACS (NSTE ACS). There are subtle but important differences in the pathogenesis of NSTE ACS and ST-segment elevation MI (STEMI); more crucial are differences in treatment, specifically in urgency of reperfusion therapy.

This article focuses on pathogenesis and early management of NSTE ACS. Because atherosclerotic coronary artery disease represents the typical substrate for NSTE ACS, the discussion would be incomplete without an overview of the development of the atherosclerotic plaque. The article then reviews the specific pathologic pathways leading to NSTE ACS, with particular attention to disruption of the vulnerable plaque and ensuing nonocclusive thrombosis. Finally, it addresses appropriate early management based on the current understanding of the underlying pathophysiology and on a review of available clinical data.

Pathogenesis of coronary artery disease

In 1986, Ross [6] proposed the "response to injury" hypothesis of atherogenesis implicating endothelial injury and subsequent intimal smooth muscle cell proliferation and inflammation as the initiating events in atherosclerosis. This article presents an overview of the proposed mechanisms of endothelial injury and the molecular and cellular responses to such injury that lead to plaque

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formation, progression, and ultimately rupture. It is useful, first, to review the histologic characteristics of the developing plaque at various stages.

Histology of atherosclerotic lesions

Stary and colleagues [7] have proposed a classification scheme of atherosclerotic lesions based on distinct morphologic characteristics. They describe two types of precursor or early lesions, two types of advanced lesions, and a linking stage between the two groups. The first three lesion types are characterized by being focal and lacking evidence of intimal disruption. More advanced lesions demonstrate intimal disruption and even modification of underlying media and adventitia.

Initial or type I lesions are microscopic collections of isolated macrophage foam cells (MFC)—macrophages containing lipid droplets—within arterial intima; these lesions have been found in as many as 45% of infants aged 8 months [8]. By the time of puberty, type II lesions are present [9]. These display a more organized pattern of MFC, arranged in adjacent layers and accompanied by smooth muscle cells that also contain lipid droplets, as well as small quantities of dispersed lipid droplets in the extracellular matrix (ECM) [7]. The preatheroma or type III lesion represents a transitional stage between early lesions and advanced atheroma. Its morphologic composition is marked by the presence of extracellular lipid pools between layers of smooth muscle cells. This lesion type still contains layers of MFC and non–lipid-containing macrophages [7]. The lipid pools eventually coalesce to form the lipid core that is characteristic of atheroma or type IV lesion [10]. In this lesion, the lipid core disrupts intimal structure but generally does not narrow the arterial lumen; instead there is compensatory eccentric expansion of the external boundary of the vessel, a process known as positive arterial remodeling (Fig. 1) [11,12]. Type V lesions also have a lipid core, now surrounded by layers of fibrous tissue [10]. These lesions are quite heterogeneous but generally are composed of varying proportions of collagen-rich ECM (also with proteoglycans and elastic fibers), a lipid core, smooth muscle cells, inflammatory cells (MFC and T lymphocytes), thrombi, and calcium deposits [10,13]. It is this advanced lesion that is generally prone to disruption.

Endothelium and endothelial injury

More than being simply a selectively permeable vascular inner layer, the endothelium is a dynamic organ with paracrine and autocrine functions that has a central role in regulating vascular hemodynamics and vascular hemostasis [14]. Endothelial regulation of vasomotion is performed by a balance in synthesis and release of vasodilators such as nitric oxide and prostacyclin, as well as vasoconstrictors such as endothelin-1 and platelet activating factor (PAF). The synthesis and release of these substances is controlled locally, modulated by a variety of biologically active molecules and mediators that allow an appropriate response to mechanical or chemical injury. In addition to their vasomotor effects, nitric oxide and prostacyclin are also central in inhibiting platelet activation, thereby preventing thrombosis. When disrupted, however, endothelial cells become procoagulant in an effort to stop blood flow and restore vascular integrity [14].

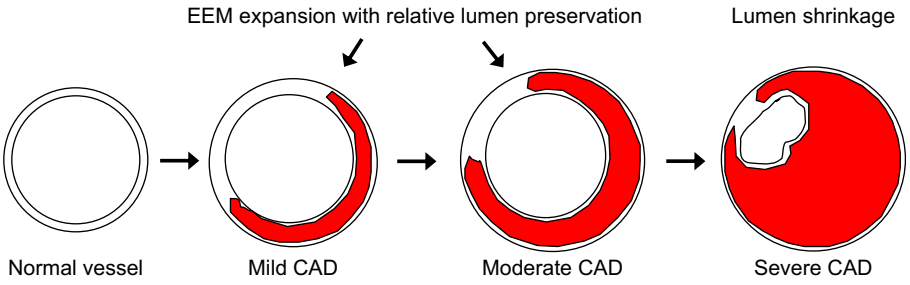

Fig. 1. Positive remodeling. In early atherosclerosis, plaque growth is compensated for by eccentric expansion of the external elastic membrane (EEM) with relative preservation of luminal area. As atherosclerosis progresses, the EEM does not expand further, and plaque growth results in luminal shrinkage. CAD, coronary artery disease. (*Adapted from* Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Eng J Med 1987;316:1371; with permission.)

A number of mechanisms of endothelial injury leading to dysfunction have been proposed. Chronic minimal injury caused by turbulent flow at bending points, chronic exposure to elevated low-density lipoprotein (LDL) cholesterol levels, smoking, diabetes, hypertension, oxidative stress, and infectious factors may all contribute to alterations in the function of endothelial cells (Fig. 2) [4,6]. This altered response includes a decrease in nitric oxide biosynthesis, increase in endothelin-1 production, and activation of the transcription factor nuclear factor κB [6,15]. This transcription factor has been implicated in the regulation of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and macrophage colony-stimulating factor; chemokines such as macrophage chemoattractant protein 1 (MCP-1); and adhesion molecules such as intercellular adhesion molecule 1 and vascular cell adhesion molecule-1 [16]. These factors serve to attract blood monocytes [17], which migrate into the subendothelial space and transform into macrophages. In turn, these activated macrophages internalize oxidized LDL to become MFC and release mitogens that lead to smooth muscle cell proliferation [6]. They also amplify the effect of nuclear factor κB by releasing MCP-1, IL-1β, TNF-α, and various other inflammatory cytokines, perpetuating the inflammatory cell recruitment process [17,18]. Plaque macrophages are stimulated to produce cytokines and collagen-degrading enzymes by a variety of factors, including angiotensin II [19], oxidized LDL [20], and the very inflammatory cytokines they express [21]. TNF-α, IL-1β (both expressed primarily by macrophages), and interferon gamma (IFN-γ) are overexpressed in atherosclerotic lesions but not in normal arteries [22]. IFN-γ is uniquely expressed by the activated T-helper type 1 lymphocyte, induced primarily by a combination of IL-18 and IL-12, both produced by macrophages [18,23]. These inflammatory cells and cytokines play a central role in the development of atherosclerosis and in the pathogenesis of ACS.

Pathogenesis of the acute coronary syndromes

Myocardial ischemia occurs when myocardial oxygen demand exceeds supply. In ACS this occurrence is typically because of a sudden reduction in coronary blood flow, and therefore of oxygen supply, relative to oxygen demand. Braunwald [24] recognizes five general circumstances in which this scenario can occur. The most common,

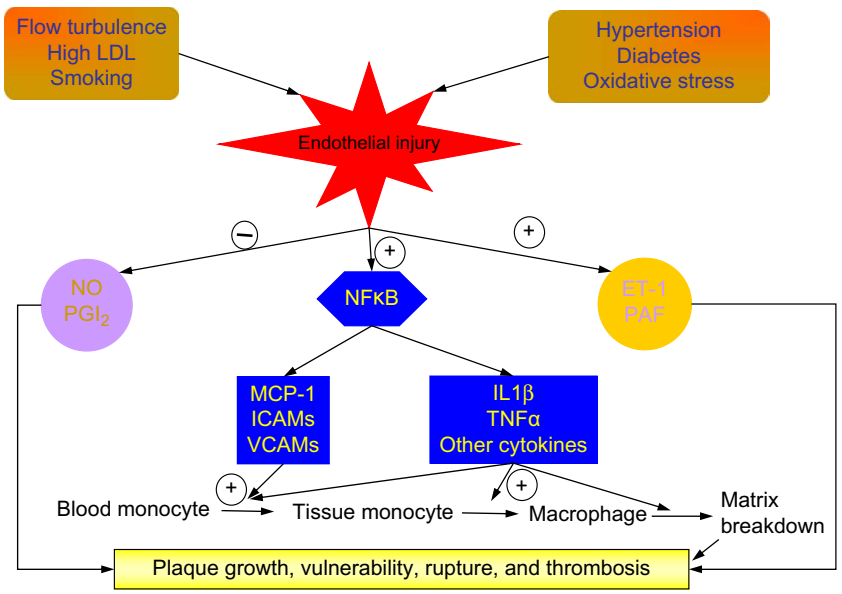

Fig. 2. Endothelial injury results in decreased vasodilator production, increase in vasoconstrictors, and increase in proinflammatory mediators that ultimately result in plaque growth and vulnerability. ET-1, endothelin-1; ICAMs, intercellular adhesion molecules; IL1β, interleukin 1 beta; MCP-1, macrophage chemoattractant protein-1; NO, nitric oxide; PAF, platelet-activating factor; PGI_2, prostacyclin; TNFα, tumor necrosis factor alpha; VCAMs, vascular cell adhesion molecules.

and most clinically important, involves disruption of the advanced atherosclerotic plaque with formation of a thrombus that partially or completely occludes the arterial lumen, thus reducing myocardial perfusion. A second cause is progressive narrowing of the arterial lumen caused by advancing chronic atherosclerosis. Vasospasm, or sudden contraction of vascular smooth muscle cells, results in a sudden narrowing of a focal segment of coronary artery, producing impaired myocardial perfusion. Arterial inflammation may lead to arterial narrowing or to plaque destabilization with ensuing plaque rupture and thrombosis. Finally, any systemic condition that increases myocardial oxygen demand (eg, fever, thyrotoxicosis), decreases overall coronary blood flow (eg, systemic hypotension), or decreases oxygen delivery (eg, profound anemia) can cause myocardial ischemia. Because of its clinical significance, plaque disruption and ensuing arterial thrombosis are the focus of this discussion.

The vulnerable plaque

Traditionally, the vulnerable plaque has been defined as one that is prone to rupture [25]. Recent pathologic findings suggest that, although rupture is the leading cause of arterial thrombosis, other processes can also result in thrombus formation. The comprehensive term of "high-risk plaque" provides a more complete description of the vulnerable plaque—one that may result in thrombus through rupture, cap erosion, or calcified nodules [26]. A significant limitation in the understanding of the pathology behind the ACS in humans is that histologic sections are available only after death. Most patients who have ACS do not die, and it is unclear if the pathologic process is identical in survivors.

Plaque rupture

Under appropriate circumstances the protective fibrous cap covering an atheromatous lesion can rupture, exposing the thrombogenic lipid core to coagulation factors and platelets in the bloodstream, which in turn leads to thrombosis [25,27]. Autopsy studies have shown that plaque rupture is associated with 60% to 80% of coronary thrombi in patients who have died of AMI [25,28]. Plaques prone to rupture seem to share common morphologic characteristics: a thin fibrous cap (<65 μm thick), an abundant population of macrophages, a relative scarcity of smooth muscle cells, and a soft extracellular lipid core [22,29–31]. Plaques of this type are referred to as "thin-cap fibroatheromas." The clinical significance of thin-cap fibroatheromas was confirmed by an angioscopic study of coronary arteries in 63 patients demonstrating a relationship between yellow, lipid-rich plaques with thin fibrous caps and acute ischemic events [32]. Circumstances that lead to rupture are complex and are not completely understood; however, a combination of inflammatory factors and mechanical stress seems to be central in the development of plaque disruption.

Why does the fibrous cap fracture? Rather than being static, the fibrous cap is a metabolically active structure, constantly undergoing remodeling by means of synthesis and degradation of collagen and other ECM components (Fig. 3) [33]. Fibrillar interstitial collagen, synthesized by smooth muscle cells, is the principal determinant of the fibrous cap's biomechanical strength [27]. Inflammatory cytokines and inflammatory cells, specifically, macrophages and T lymphocytes, seem to exert significant control over the level of collagen and thus the cap's mechanical integrity. Dysregulation of normal ECM remodeling, mediated by inflammation, represents an attractive (although as yet unproven) hypothesis to explain aspects of fibrous cap rupture: an imbalance favoring breakdown of collagen over its synthesis results in structurally compromised areas of the fibrous cap.

Given that they play a central role in the progression of atherosclerosis, it is no surprise that macrophages and activated T lymphocytes have been found in abundance at the sites of plaque rupture [28,34]. These cells and the cytokines and enzymes they produce are responsible for detrimental effects to ECM composition. When appropriately activated by cytokines and other signals, macrophages degrade ECM through expression of a variety of matrix metalloproteinases (MMPs) that catalyze the critical initial steps of collagen breakdown. Certain MMPs, notably MMP-2 (also known as 72kD gelatinase), are present constitutively in nonatherosclerotic vessels and function in normal ECM metabolism; additionally, MMP-2 is secreted mainly in an inactive complex with its endogenous inhibitors (tissue inhibitor of metalloproteinase -1 and -2, TIMP-1 and -2) [35]. In contrast, atherosclerotic plaques demonstrate overexpression of activated MMP-1 (interstitial collagenase-1), MMP-3 (stromelysin), MMP-9 (92kD gelatinase), and MMP-13 (interstitial collagenase-3), especially at the shoulder

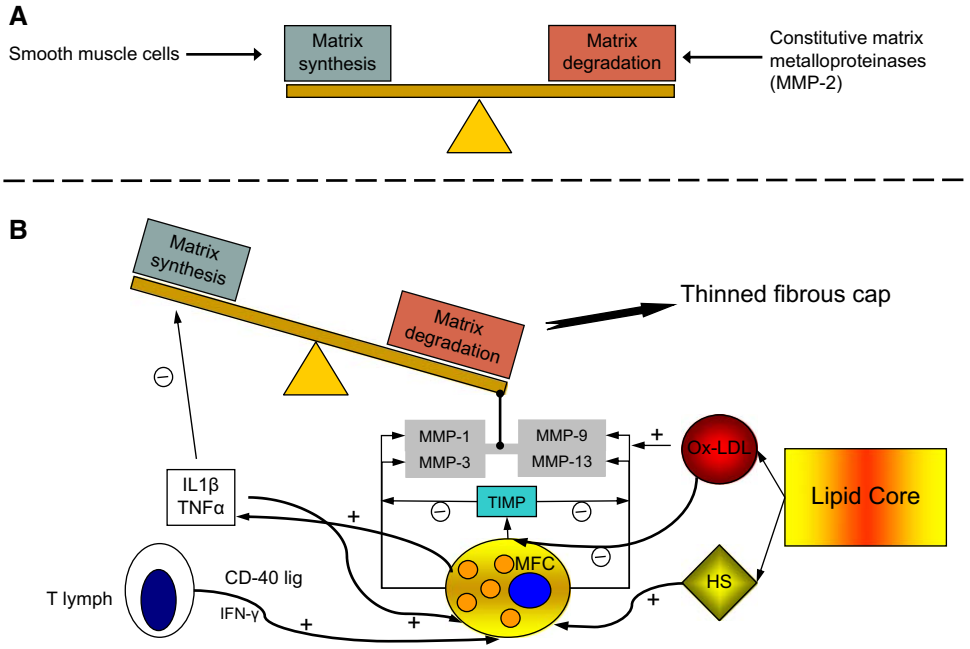

Fig. 3. (*A*). Balanced atherosclerotic cap homeostasis. (*B*) Activated macrophage foam cells (MFC) stimulated by T lymphocytes, inflammatory cytokines, oxidized LDL (ox-LDL), and circumferential hemodynamic stress (HS) overexpress matrix metalloproteinases (MMP) which leads to matrix degradation and cap thinning See text for details. IL1β, interleukin-1 beta; IFN-γ, interferon gamma; TIMP, tissue inhibitor of metalloproteinase.

region of the fibrous cap (the junction of the plaque with normal vessel) and surrounding the lipid core, where ruptures most often occur [22,35]. Macrophage expression of MMPs is induced by a variety of factors, including IL-1β, TNF-α, and IFN-γ [36], by activation by T lymphocytes through CD40 ligand [37], and by circumferential hemodynamic stress [38]. Induction of MMP is also accomplished by neutrophils and oxidized LDL. As is the case with macrophages and activated T lymphocytes, neutrophil infiltration has been noted in ruptured plaques [39]. Neutrophils express MMP-8, or neutrophil collagenase, which preferentially degrades type I collagen [40]. Oxidized LDL, present within the lipid core, stimulates the expression of MMP-9 by macrophages and inhibits the production of the MMP inhibitor TIMP-1 [41]. Even smooth muscle cells, when stimulated by IL-1β and IFN-γ, can degrade ECM by releasing activated MMPs [35] and the elastolytic proteases cathepsin S and K [42].

Protease-mediated degradation is complemented by reduced ECM production in the thin-cap fibroatheromas. IFN-γ has been shown to inhibit collagen gene expression in smooth muscle cells [27]. Additionally, the combination of IL-1β, TNF-α, and IFN-γ promotes smooth muscle cell apoptosis, which results in decreased collagen synthesis [43].

Inflammation in ACS may not be limited to a strictly local phenomenon. Evidence of neutrophil activation by reduced blood levels of neutrophil myeloperoxidase was found in samples from the aortic and great coronary veins of patients who had unstable angina [44]. This activation was found whether the culprit lesion was in the left anterior descending artery (which is drained selectively by the great coronary vein) or in the right coronary artery (which is not drained by the great coronary vein). Additionally, evidence of neutrophil activation was absent in patients who had chronic stable angina or variant angina. The presence of generalized coronary artery inflammation in the setting of ACS and the contribution of inflammation to the pathogenesis of ACS have led some to postulate that multiple unstable coronary lesions should be evident during an acute coronary event. In an intravascular ultrasound study of 24 patients who had initial ACS, there was evidence of multiple plaque ruptures at sites other than the culprit lesion, suggesting a generalized level of plaque instability [45]. Other evidence

suggests that the extent of inflammation is not just regional but systemic. In a study of 36 patients admitted with AMI, the group that had preinfarction unstable angina had higher levels of the systemic inflammatory markers C-reactive protein, serum amyloid protein A, and IL-6, than did those with unheralded infarctions [46].

Mechanical factors can affect plaque's susceptibility to inflammatory assault. High circumferential stress has been associated with increased expression of MMP-1 [38]. A significant determinant of this stress is the eccentric, soft, lipid core, the presence of which has been shown to concentrate high circumferential stresses at the shoulder regions of the plaque [47]. Most plaques rupture at these regions of elevated tensile stress [48]. Shear stresses can also have an impact on plaque disruption. A study of carotid plaques at autopsy demonstrated that areas of plaque exposed to high flow and high shear forces had an abundance of plaque macrophages relative to the density of smooth muscle cells compared with areas of plaque exposed to low shear forces and low flow [49]. There seems to be increased susceptibility to rupture in areas with a higher concentration of inflammatory cells [50]. The thinness of the fibrous cap itself can have negative mechanical repercussions. A mathematical model of arterial vessels suggests that for a given luminal area, decreasing thickness of the fibrous cap is associated with increased circumferential stress [51]. Furthermore, repetitive exposure to pulsatile flow at these areas of high circumferential stress may result in plaque fatigue [51]. Another important aspect of the influence of mechanical stress on plaque rupture is positive arterial remodeling. Intravascular ultrasound studies in human coronaries have shown that positive remodeling is more common in patients who have unstable angina, whereas negative remodeling (in which the plaque encroaches on the lumen) is more common in patients who have chronic stable angina [52]. Positive remodeling also correlates with a larger lipid core and increased macrophage content, both of which promote plaque vulnerability [53]. Additionally, positive remodeling may influence plaque distensibility, that is, the softness of the plaque, which in turns makes it more prone to rupture [54]. Finally, positive arterial remodeling has been correlated with decreased density of collagen fibers [55]. The finding that positive arterial remodeling can increase plaque vulnerability while preserving luminal area may account for the observation that, in a majority of patients presenting with ACS, recent prior coronary angiography fails to demonstrate culprit lesion stenoses exceeding 70% [56,57].

The thin cap fibroatheroma is uniquely susceptible to rupture. In the setting of inflammation and matrix degradation, a structurally unstable fibrous cap exposed to both transient and steady mechanical disturbances leads to increases in tensile stress and ultimately to fracture. A variety of triggers of plaque rupture have been proposed, including air pollution [58], marijuana use [59], cocaine use [60], sexual activity, and emotional or physical stress [61], among others. The exact mechanism by which these activities prompt rupture in the susceptible plaque is not well understood.

Other mechanisms of plaque vulnerability

Although plaque rupture is the most important precipitating event for thrombosis in ACS, other mechanisms of thrombosis without rupture have been proposed. In one series of 125 cases of sudden coronary death caused by confirmed acute epicardial thrombosis, only 74 (59%) had histologic evidence of plaque rupture; 45 (36%) showed thrombus overlying a smooth muscle cell–rich, proteoglycan-rich plaque denuded of endothelial cells, and 6 (5%) showed a calcified nodule at the site of thrombus [26]. Additionally, compared with thrombosis associated with plaque rupture, cases with thrombosis caused by erosion were more likely to be younger than 50 years, women, and smokers [26,62]. These findings were confirmed in an autopsy series of 291 patients who died of AMI and had confirmed coronary thrombosis. In 25% of cases, thrombosis was caused by plaque erosion [63].

Although some have proposed repeated focal vasospasm as the underlying cause for the endothelial denudation seen in plaque erosion, this process has not been confirmed [26]. The observed absence of endothelial cells in these lesions has generated the attractive hypothesis that severe endothelial apoptosis as a response to mechanical or chemical injury leads to thrombosis. Cell membrane microparticles derived from apoptotic cells in atherosclerotic plaque have been shown to increase local levels of thrombogenic (TF) [64]. The same study showed, however, that most of these microparticles were derived from apoptotic macrophages and T lymphocytes, not from endothelial cells; it is unclear if endothelial apoptosis is always associated with thrombosis.

The most unusual lesion associated with thrombosis is the calcified nodule, a superficial

fibrous-rich calcified lesion that erupts from the intima into the lumen [26]. The processes leading up to this lesion, or the way in which it induces thrombosis, are not known.

Arterial thrombosis

Plaque rupture or erosion both result in thrombus formation. This process is dynamic, and it is the balance of systemic and local procoagulant and fibrinolytic factors that ultimately determines the extent of thrombus formation and thus the clinical outcome [4].

Thrombus formation

The mechanisms behind thrombus formation associated with plaque disruption are better understood than those associated with plaque erosion. Davies [65] describes three stages of thrombosis. The first is characterized by platelet adhesion within the thrombogenic lipid core, the second by extension of the thrombus into the lumen with an increase in fibrin content and distal microembolization of activated platelets, and the third, by a growing thrombus composed of loose fibrin networks and entrapped red cells. This progression of stages is not deterministic and can be affected by host factors and clinical intervention.

Once plaque rupture occurs, the disrupted edges of the fibrous cap as well as the lipid core are exposed to blood-borne coagulation factors and platelets. Disruption of the normal endothelial layer transforms the endothelium from its constitutive antithrombotic state to a procoagulant state. It does so mainly by increased production of PAF and von Willebrand factor (vWF), a large multimeric protein with binding sites for subendothelial collagen [14]. Potentiated by arterial shear stress, platelets adhere to exposed subendothelium by platelet membrane glycoprotein Ib/IX-V complexed with vWF [66]. Adherent platelets then become activated under the influence of various mediators. Activation involves a shape change in the platelet, as well as release of alpha granules and dense granules containing potent platelet activation agents, including adenosine diphosphate and serotonin. Activation is also enhanced by circulating epinephrine and thrombin and by subendothelial collagen and vWF [67]. Additionally, activated platelets synthesize and release thromboxane A_2, a potent vasoconstrictor and platelet activator, which is increased in patients who have unstable angina [68]. The final step of activation is aggregation: expression of the platelet membrane Gp IIb/IIIa receptor allows platelet–platelet interactions whereby adherent platelets recruit circulating platelets to form an occlusive thrombus. Platelet aggregation is mediated by fibrinogen or vWF, either of which can bind to the Gp IIb/IIIa receptor, thus linking the platelets. The platelet thrombus is then stabilized by a fibrin mesh, the result of the simultaneously ongoing coagulation cascade [67].

Fernandez-Ortiz and colleagues [69] demonstrated that, at least in vitro, it is the lipid core that acts as the most significant substrate for the formation of the platelet thrombus. The exact source of the thrombogenic properties of the lipid core is not known. It has been suggested that lipids themselves and acellular debris found in the core may activate hemostasis [70]. This suggestion is an incomplete explanation and overlooks the significant role of TF. TF is a transmembrane glycoprotein that initiates the extrinsic clotting cascade. Its relationship to ACS was demonstrated in a study showing that TF is present in significantly greater amounts in the tissue of patients who have unstable angina than in those who have stable angina [71]. Despite its thrombogenicity, however, the lipid core is the source of surprisingly little TF. In fact, in patients who have unstable angina, TF is located predominantly in the cellular component of the plaque [71]. How can this apparent discrepancy be explained? Inflammatory cytokines, activated T cells, and oxidized LDL in the lipid core induce TF expression by plaque macrophages, smooth muscle cells, and endothelial cells [37,71,72]. At the time of plaque rupture, most TF seems to be associated with apoptotic cell fragments (mainly from macrophages and endothelial cells) that form part of the necrotic debris in the lipid core [64]. Thus, although there is no intrinsic TF expression within the lipid core, TF activity is found there in the setting of plaque rupture. Using an in vitro perfusion model, Toschi and colleagues [72] demonstrated the presence of active TF-VIIa complex within the lipid core, as well as a correlation between this complex and platelet adhesion.

TF, of course, is also responsible for initiating the plasma coagulation system that leads to the structural fibrin network of the thrombus. TF forms a high-affinity complex with coagulation factors VII and VIIa; this latter complex activates factors IX and X, and this activation in turn leads to thrombin generation and thrombosis [73]. Not only does thrombin serve to activate platelets, it

converts fibrinogen to fibrin and activates factor XIII, which in turn stabilizes the fibrin clot [67].

Factors that mediate the extent of thrombosis

Not all thrombi or all plaque ruptures result in MI; they may, however, contribute to the progression of atherosclerotic disease. In his series of 25 cases of sudden cardiac death caused by acute coronary thrombosis, Falk [74] found that 81% of the thrombi had a layered appearance, suggesting alternating episodes of thrombus formation and fragmentation preceding the fatal infarction. Other investigators have suggested that healing of repeated plaque ruptures leads to progression of atherosclerosis: the thrombus organizes and heals by migration and proliferation of smooth muscle cells. This healing fibromuscular response incorporates the mural thrombus and worsens luminal stenosis [75]. Finally, even though fibrotic lesions lack a thrombogenic lipid core, erosion of these plaques has been associated with thrombus formation [26]. A number of factors, both local and systemic, have been implicated in determining the extent to which an arterial thrombus develops at the site of endothelial disruption.

Increased shear stress produces a conformational change in the platelet Gp Ib/IX-V receptor and vWF resulting in more avid platelet adhesion [66]. The clinical importance of this observation was demonstrated by a study that demonstrated increased platelet adhesion at the apex of a disrupted lesion; furthermore, it showed that the extent of platelet adhesion corresponded directly with the extent of stenosis following plaque rupture [76]. The same group also showed that increasing the extent of plaque disruption resulted in a larger, more stable, platelet thrombus [77]. This finding is hardly surprising, because more extensive plaque injury leads to greater exposure of blood to thrombogenic TF within the lipid core and to endothelial platelet activators such as PAF and vWF and thus results in more widespread activation of the coagulation cascade. Finally, the presence of a mural thrombus from prior plaque ruptures, such as those described by Falk [74], seems to contribute to extensive thrombosis. Not only does a mural thrombus increase the degree of luminal stenosis, it provides for a rich source of potent platelet activation in the form of thrombin. This scenario was observed in a pig model of vessel injury with mural thrombus in which the direct thrombin inhibitor hirudin prevented extension of thrombus, whereas aspirin and heparin did not [78]. In summary, the extent of stenosis, plaque disruption, size of the lipid core, and the presence of a mural thrombus are local factors that seem to increase thrombogenicity in the disrupted plaque.

Several systemic factors, including elevated cholesterol levels, increased catecholamine levels, smoking, and hyperglycemia, have been associated with increased thrombogenicity [4]. LDL-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to decrease blood thrombogenicity and thrombus growth [79]. Although some of this effect may be caused by pleiotropic effects of statins, it is clear that LDL, and in particular oxidized LDL, plays a role in increased thrombotic activity. LDL promotes TF expression in plaque macrophages and expression of prothrombotic plasminogen activator inhibitor-1 in endothelial cells [14,71]. Elevated catecholamines are associated with increased platelet activation; activities that increase circulating catecholamines, such as cigarette smoking, [80] cocaine use [60], and increased physical activity [61], have been associated with triggering acute cardiovascular events. Smoking seems to be of particular importance in young patients who have underlying plaque erosion, reflecting the significance of increased systemic thrombogenicity in these patients whose lesions lack a lipid core [62]. Hyperglycemia associated with poor diabetic control results in increased blood thrombogenicity, caused in part by increased platelet activation and also by activation of the TF pathway [81,82]. Other metabolic abnormalities may also increase blood thrombogenicity. Activation of the renin-angiotensin-aldosterone system increases activity of plasminogen activator inhibitor-1, mediated by angiotensin II [27]. Lipoprotein (a) is structurally similar to plasminogen and may competitively inhibit its fibrinolytic activity [4]. It is also likely that several proinflammatory cytokines promote both atherosclerosis and plaque rupture and thrombogenesis, suggesting a role for systemic inflammation in the development of ACS [27].

Early management of the non–ST-segment elevation acute cardiac syndromes

The most recent update of the American College of Cardiology/American Heart Association guidelines for NSTE ACS highlights several areas of management, including early risk

stratification, early use of aspirin and clopidogrel, indications for early invasive strategy, and use of Gp IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) based on risk. Additionally, the guidelines recommend an algorithm for use of specialized chest pain units to manage patients who have possible and low-risk ACS while avoiding unnecessary hospitalizations [3]. This section discusses the early management of NSTE ACS, that is, management during the patient's initial stay in the chest pain unit.

Risk assessment

Patient management in ACS begins with risk stratification based on clinical history, physical examination, and ancillary data such as 12-lead ECG and biomarkers of cardiac injury. Based on this initial assessment, patients can be categorized into one of four groups: noncardiac chest pain, chronic stable angina, possible ACS, and definite ACS. Those who have possible or definite ACS are observed in a chest pain unit until the diagnosis is confirmed or discounted [3].

Given the wide range of presentations subsumed within ACS, risk assessment is essential in determining the choice of therapy, specifically the use of Gp IIb/IIIa inhibitors and of early invasive therapy. Gp IIb/IIIa inhibitors bind the platelet receptor and prevent platelet aggregation [83]. Their use has been shown to reduce the frequency and duration of ischemia [83] and the rate of the combined endpoint of death, reinfarction, or refractory angina in patients who have NSTE ACS [84]. Early invasive therapy consists of coronary angiography and angiographically guided revascularization within 48 hours of symptom onset. This approach, compared with conservative therapy of medical management and noninvasive evaluation of ischemia, has also been shown to reduce rates of the combined endpoint of death, reinfarction, or 6-month rehospitalization [85]. Although these trials suggest an overall benefit for aggressive therapy in NSTE ACS, there is such a wide range of clinical presentations that the risk–benefit ratio for these therapies may also vary greatly, depending on individual patient's risk.

Obviously, the presence of hemodynamic instability, pulmonary edema, prolonged rest chest pain, or sustained ventricular tachycardia portends a poor short-term outcome and should be addressed with early institution of aggressive therapy [3]. Many patients who do not have these clear high-risk features upon presentation may benefit from aggressive therapy, however. To predict risk in these patients a variety of schema has been proposed. Among the easiest to use and best-validated is the Thrombolysis in Myocardial Infarction (TIMI) risk score (Box 1) [86]. A score exceeding 4 in this equally weighted seven-item scale allows identification of the patients who benefit most from early invasive and Gp IIb/IIIa inhibitor therapies based on short- and long-term risks [87]. Many investigators, citing the direct relationship between rising cardiac troponin levels and poor outcomes, have suggested that elevated troponin levels alone should be considered markers of high risk [3].

Treatment

Initial treatment for NSTE ACS includes continuous ECG monitoring for ischemia and possibility of arrhythmia. Additionally, anti-ischemic therapy should be initiated promptly, tailored to the level of patient risk. Finally, the mainstay of initial therapy is directed at addressing arterial thrombus: antiplatelet and anticoagulant therapy (Table 1).

Box 1. Thrombolysis in Myocardial Infarction (TIMI) risk score prediction variables

Age greater than 65 years
Three or more risk factors for coronary artery disease
Known coronary artery stenosis greater than 50%
ST-segment deviation on presenting ECG
Two or more episodes of angina within the preceding 24 hours
Use of aspirin within the preceding 7 days
Elevated serum cardiac biomarker levels

Adapted from Gluckman TJ, Sachdev M, Schulman SP, et al. A simplified approach to the management of non-ST elevation acute coronary syndromes. JAMA 2005;293(3):349; with permission.

Table 1
Summary of cardiovascular disease management in NSTE ACS

Intervention	Agent(s)/Treatment Modalities	Comments
Antiplatelet therapy	Aspirin	All patients indefinitely Initially with 162–325 mg followed by 75–160 mg daily thereafter
	ADP receptor antagonist (clopidogrel)	All patients, unless anticipated need for urgent CABG surgery or within 5 days of electively scheduled CABG surgery Duration up to 1 year
	GP IIb/IIIa inhibitor (abciximab, eptifibatide, tirofiban)	All patients with continuing ischemia, an elevated troponin level, a TIMI risk score $>$ 4, or anticipated PCI Avoid abciximab if PCI is not planned
Anticoagulation	Unfractionated heparin	Alternative to LMWH for patients managed with early invasive strategy
	Low molecular weight heparin	Preferred anticoagulant if managed conservatively Alternative to unfractioned heparin for patients managed with an early invasive strategy Avoid if creatinine clearance $<$ 60 mL/min (unless anti-Xa levels are to be followed) or CABG surgery within 24 hours
ACE inhibition	No clear preferred agent	All patients with left ventricular systolic dysfunction (ejection fraction $<$ 40%), heart failure, hypertension, or other high-risk features
Angiotensin receptor blockade	No clear preferred agent	All patients intolerant to ACE inhibitors Avoid combination therapy with ACE inhibitors acutely, but consider in patients with chronic left ventricular systolic dysfunction (ejection fraction $<$ 40%) and heart failure
Beta blockade	No clear preferred agent	All patients
Blood pressure control	ACE inhibitors and beta blockers first line	Goal BP at least $<$ 130/85 mm Hg

Abbreviations: ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; BP, blood pressure; CABG, coronary artery bypass graft; LMWH, low molecular weight heparin; PCI, percutaenous coronary interventions.

Adapted from Gluckman TJ, Sachdev M, Schulman SP, et al. A simplified approach to the management of non-ST elevation acute coronary syndromes. JAMA 2005;293(3):349; with permission.

Anti-ischemic therapy

Beta blockade reduces cardiac workload and oxygen demand, and the use of beta-blockers in the acute setting has been associated with a 13% relative risk reduction in progression to AMI [87]. The current recommendation is for prompt initiation of beta-blocker therapy unless contraindicated (eg, by marked first-degree atrioventricular block, second- or third-degree atrioventricular block, history of asthma, left ventricular dysfunction with congestive heart failure) [3]. A recommended initial regimen for high-risk patients is intravenous metoprolol, 5 mg every 5 minutes to a total of 15 mg; if tolerated, 25 to 50 mg oral metoprolol should be administered 15 minutes after the last intravenous dose and given every 6 hours for the first 48 hours. Patients at lower risk may be managed with oral therapy [3]. For patients in whom beta-blockers are contraindicated, the nondihydropyridine calcium antagonists verapamil and diltiazem may be used. One trial using intravenous verapamil in 3447 patients who had suspected MI showed a trend toward lower risk of death or nonfatal MI [88]. Guidelines recommend the use of long-acting nondihydropyridine calcium antagonists either in the setting of beta-blocker intolerance or if ischemic pain persists despite full use of beta blockade and nitrate administration [3].

Nitroglycerin is an endothelium-independent arterial vasodilator that increases myocardial blood flow through coronary vasodilation and decreases myocardial oxygen demand through venodilation and reduced preload [89]. In the absence of contraindications such as hypotension or concurrent use of sildenafil, tadafil, or vardenafil within 24 hours, intravenous nitroglycerin is recommended for the patient who has ongoing chest pain despite three doses of sublingual nitroglycerin and administration of beta-blockers [3]. The purpose of nitroglycerin is to relieve ischemic pain, because it has not been demonstrated to improve survival [90,91]. American College of Cardiology guidelines currently recommend the use of intravenous morphine sulfate at doses of 1 to 5 mg if nitrate and beta-blocker therapy fail to relieve pain and in patients who have acute pulmonary edema, with care taken to avoid hypotension [3]. Recent registry data regarding 57,039 patients treated for NSTE ACS at 443 United States hospitals, however, showed that the 17,003 patients who received intravenous morphine within 24 hours of presentation had a higher adjusted risk of death (odds ratio, 1.48; 95% CI, 1.33–1.64), even though patients receiving morphine were also more likely to receive acute evidence-based therapies and to be treated by a cardiologist. These data suggest that morphine sulfate in acute NSTE ACS may not be as safe as previously thought and that randomized trials are needed [92].

HMG-CoA reductase inhibitors have been shown to decrease blood thrombogenicity [79], and early aggressive therapy with these agents in the setting of AMI reduced the risk of a combined endpoint of death, MI, unstable angina rehospitalization, revascularization, and stroke [93]. This therapy was instituted 10 days after presentation, however. It is unclear if administration of statins in the acute setting is of additional benefit.

Antiplatelet therapy

Given the central role of platelet activation and aggregation in thrombus formation, it is reasonable to expect that antiplatelet therapy would be at the core of NSTE ACS management. Recommended agents include aspirin, which inhibits platelet aggregation and activation primarily by inhibiting thromboxane A_2 synthesis, clopidogrel, which inhibits platelet activation by blocking the adenosine diphosphate receptor, and the Gp IIb/IIIa inhibitors.

Aspirin has been shown to reduce the rates of death or nonfatal MI by 51% (5% versus 10.1%; $P = .0005$) in patients who have unstable angina, without an increase in gastrointestinal symptoms [94]. Current guidelines recommend an initial dose of 162 to 325 mg followed by a daily dose of 75 to 160 mg [3].

In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, 12,562 patients who had NSTE ACS were randomly assigned to clopidogrel (300 mg loading dose followed by 75 mg daily for 9 months) and aspirin (75–325 mg daily) versus aspirin alone [95]. The group receiving clopidogrel had a relative risk reduction of 20% in the combined endpoint of cardiovascular death, nonfatal MI, or stroke (9.3% versus 11.4%; $P < .001$). The benefit was driven primarily by a reduction in risk of subsequent MI (5.2% versus 6.7%; relative risk, 0.77; 95% CI, 0.67–0.89). The benefit of clopidogrel also holds for patients undergoing percutaneous coronary interventions (PCI). The PCI-CURE study randomly assigned 2658 patients who had NSTE ACS and who were scheduled for PCI to pretreatment with clopidogrel plus aspirin versus aspirin alone; treatment was initiated a median of 6 days before PCI and continued for 8 months [96]. Patients who received clopidogrel experienced a 30% relative risk reduction in the combined endpoint of cardiovascular death, nonfatal MI, or urgent target vessel revascularization at 30 days and a 31% relative risk reduction of cardiovascular death or nonfatal MI at study end. Although clopidogrel is clearly beneficial in NSTE ACS, there are caveats to its use. In the CURE trial, major bleeding was significantly more common in the clopidogrel arm (3.7% versus 2.7%; $P = .001$), although there was no significant increase in life-threatening bleeding [95]. Additionally, use of clopidogrel within 5 days of surgery can increase bleeding risk [97]. Current guidelines recommend prompt initiation of clopidogrel, with use for at least 1 month and up to 9 months, withheld 5 to 7 days before coronary artery bypass grafting. Additionally, patients who have intolerance or hypersensitivity to aspirin should be given clopidogrel instead [3].

Benefit from Gp IIb/IIIa inhibitors is closely tied to patient risk and therefore to concomitant use of an early invasive strategy. A meta-analysis of six trials including 31,402 patients who had NSTE ACS and who were managed with conservative strategy found that benefit of Gp IIb/IIIa inhibitor use was limited to those who had elevated troponin

levels or who needed early revascularization, that is, higher-risk patients [98]. Furthermore, in patients who had NSTE ACS and who were treated conservatively, the Gp IIb/IIIa inhibitor abciximab demonstrates no benefit and may be harmful [99]. In patients undergoing PCI, however, there is clear benefit to Gp IIb/IIIa inhibitor use. A meta-analysis of eight trials (14,644 patients) of any Gp IIb/IIIa inhibitor versus placebo in patients undergoing PCI showed a reduction of both MI rate (5% versus 7.8%; $P < .001$) and need for urgent revascularization (3.4% versus 5.9%; $P < .001$) [100]. Subgroup analysis in study showed that only abciximab resulted in a significant reduction in AMI after PCI. This effect may reflect the timing of PCI relative to drug administration. Data suggest that abciximab is the Gp IIb/IIIa inhibitor of choice for PCI within 4 hours of presentation, whereas tirofiban and eptifibatide should be used if PCI is deferred [87]. Based on these data, current guidelines recommend administration of eptifibatide or tirofiban (but not abciximab) to high-risk patients (ie, those who have elevated troponin levels, a TIMI risk score greater than 4, continuing ischemia) who have NSTE ACS and are undergoing conservative therapy [3,87]. Because the decision to proceed to PCI and the timing thereof are not always clear at the time of initial presentation, the choice of agent in this setting may be deferred until the time of PCI [3].

In summary, all patients who have NSTE ACS should receive aspirin and clopidogrel on presentation, unless there is anticipated need for urgent surgical revascularization. Gp IIb/IIIa inhibitors are clearly recommended in high-risk patients and those referred to PCI (ie, those with high-risk clinical features, TIMI score greater than 4, or elevated troponin levels). Unfortunately, there are no large-scale studies that evaluate the incremental benefit of combined use of all three proposed antiplatelet therapies versus strategies using only two agents.

Anticoagulation

Heparin potentiates thrombin inactivation by circulating antithrombin III, thus preventing thrombus extension [101]. In a meta-analysis of six trials of patients who had unstable angina treated with unfractionated heparin (UFH) for 2 to 5 days plus aspirin versus aspirin alone, there was a 33% relative risk reduction in the incidence of death or MI (7.9% versus 10.4%; $P = .06$) [102]. Unfortunately, UFH requires frequent monitoring of the activated partial thromboplastin time (aPTT) and has been associated with delays in achieving appropriate anticoagulation, an aPTT 1.5 to 2.5 times control [103]. Low molecular weight heparin (LMWH) has more predictable pharmacokinetics, is more readily bioavailable, and is administered subcutaneously [103]. A recent meta-analysis of six trials encompassing 21,946 patients sought to compare the efficacy and safety of the LMWH enoxaparin at 1 mg/kg every 12 hours and UFH in patients who had NSTE ACS. At 30 days, there was no statistically significant difference in mortality and a small difference in the combined endpoint of death or MI favoring enoxaparin (10.1% versus 11.0%; 95% CI, 0.83–0.99), without significant difference in major bleeding [104]. The analysis showed benefit of LMWH over UFH in patients treated conservatively. Current guidelines recommend the use of LMWH in addition to aspirin in patients who have NSTE ACS unless coronary artery bypass grafting is planned within 24 hours [3]. For patients who have renal insufficiency or in whom early invasive strategy is planned, UFH is probably a better choice [87].

Another parenteral anticoagulant, the direct thrombin inhibitor hirudin, has been studied in NSTE ACS. In the trial by the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2), 10,141 patients who had NSTE ACS were randomly assigned to receive a 72-hour infusion of UFH or hirudin [105]. At 7 days those in the hirudin group had a lower (but not statistically significant) rate of the combined endpoint of death or new MI (3.6% versus 4.2%; relative risk, 0.84; 95% CI, 0.69–1.02, $P = .077$). Most of the benefit occurred during the drug infusion period, suggesting that the outcome of the therapies equalizes with time. A meta-analysis of 11 randomized trials consisting of 35,790 patients compared the use of any direct thrombin inhibitor (hirudin, bivalirudin, argatroban, efegatran, or inogatran) with UFH in patients who had ACS. At 30 days, there was a lower rate of death or MI in the group treated with direct thrombin inhibitors (7.4% versus 8.2%; relative risk, 0.91, 95% CI, 0.84–0.99, $P = .02$) [106]. The use of direct thrombin inhibitors along with aspirin and clopidogrel or Gp IIb/IIIa inhibitors in NSTE ACS has not been studied in large-scale trials; thus their incremental benefit is not known. Furthermore, hirudin has been shown to increase bleeding risks compared with heparin [105]. Although more studies are expected, routine use of direct thrombin inhibitors in NSTE ACS is not currently recommended [3].

Patients in the chest pain unit who have suspected NSTE ACS should be given UFH if early PCI is planned or if severe renal insufficiency (creatinine clearance $<$ 60 mL/minute) is present. Otherwise, LMWH should be used in addition to aspirin and clopidogrel. The role for direct thrombin inhibitors is unclear at present.

Summary

NSTE ACS is a clinically significant problem. Endothelial dysfunction triggered by traditional cardiovascular risk factors (and perhaps by other as yet unidentified risks) in the susceptible host leads to the formation and development of atherosclerotic plaque. Inflammatory mediators and mechanical stresses contribute to plaque rupture by disrupting the protective fibrous cap. In about 25% of patients who have ACS, typically those who are younger, female, or smokers, plaque erosion seems to be the main underlying pathologic mechanism. Endothelial alteration, inflammation, or exposure of the lipid core results in the release of TF, vWF, and PAF. The release of these factors leads to platelet activation and aggregation as well as to the formation of a fibrin clot, resulting in arterial thrombosis that occludes the vessel. A variety of factors, including circulating catecholamines, LDL levels, blood glucose levels, and systemic thrombogenic factors, can affect the extent and stability of the thrombus, thereby determining whether the occlusion is complete and fixed, labile and nonocclusive (NSTE ACS), or clinically silent resulting in a mural thrombus and plaque growth. The acute treatment of NSTE ACS is directed at interrupting the prothrombotic environment surrounding the ruptured plaque; thus, antiplatelet agents such as aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists, as well as anticoagulants such as heparin, are the mainstays of early therapy.

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