Experimental models of atherogenesis have provided a growing body of information about molecular mechanisms of plaque growth; however, transition from coronary stability to instability is less well understood due to the lack of animal models reflective of human disease (1). The abrupt clinical presentation of acute coronary syndromes (ACS) gives a strong signal of discontinuity in the natural history of atherothrombosis. When primary prevention of atherosclerosis fails, the progression of coronary atherosclerosis can remain clinically silent for years, decades, or even for life, as indicated by the high prevalence of coronary atherosclerosis in subjects dying of noncardiac causes. In contrast, some patients, at a certain point in their life, exhibit ACS, followed by a period of stability that can be short or last for years or decades. These simple clinical observations suggest that the mechanisms responsible for plaque growth and for plaque instability are different and that the causes and mechanisms of plaque instability are multiple. Accordingly, the paradigm that implies a single type of culprit coronary plaque as a cause for instability does not adequately fit the findings of postmortem studies (2,3). Indeed, plaque fissure is frequently asymptomatic and contributes to stepwise, clinically silent plaque growth rather than precipitating an abrupt coronary occlusion; conversely, it is not observed in 30% to 50% of patients who have ACS. Furthermore, the notion that inflammatory cell activation plays a key role in the pathogenesis of ACS was promptly accepted by the scientific community, and it is now commonly believed that activation of inflammatory cells in the culprit stenosis is the cause of coronary instability in all patients (4,5). However, this notion is in sharp contrast with the observation that about 40% of patients with ACS have low or very low levels of C-reactive protein (CRP), a very sensitive marker of inflammation (6,7). Finally, coronary angiography fails to demonstrate obstructive atherosclerosis in up to one-third of patients with symptoms suggestive of ACS and raised troponin levels and/or ischemic-like ST-segment changes, thus suggesting that functional alterations of epicardial arteries and/or of coronary microcirculation play an important pathogenetic role (8).

Pathogenetic Classification of ACS

The complexity of postmortem and clinical observations suggests that it is unlikely to identify a common cause for the phenotype of ACS. To better understand the multiple causes of coronary instability, it would be desirable to construct a pathogenetic classification of ACS based on simple clinical descriptors.

In this review, the multiple causes of coronary instability are discussed in 3 homogeneous groups of patients with a similar clinical presentation: 1) patients who have obstructive atherosclerosis and systemic inflammation; 2) patients who have obstructive atherosclerosis without systemic inflammation; and 3) patients without obstructive atherosclerosis (Fig. 1).

We are not proposing here an alternative to the recent universal definition of myocardial infarction (MI) (9). Indeed, our classification of ACS provides a framework for understanding basic mechanisms responsible for coronary instability rather than a classification for immediate clinical use such as that provided by the universal definition of MI.
Our pathogenetic classification of ACS based on simple clinical descriptors, however, might help in the search for new diagnostic algorithms and therapeutic targets.

**ACS with obstructive atherosclerosis and systemic inflammation.** Although the presence of obstructive atherosclerosis can be promptly ascertained with coronary angiography, the evidence of systemic inflammation is less easy to define. Among the several inflammatory biomarkers tested in ACS, levels of C-reactive protein (CRP) assessed by using high-sensitivity CRP (hs-CRP) assays represent an obvious candidate because CRP is a prototypic marker of inflammation characterized by high sensitivity and a wide dynamic range (10). However, it is difficult to establish a cutoff at the present time. In primary prevention, hs-CRP levels ≥2 mg/l (and even ≥1 mg/l) might be helpful in guiding therapy (11); however, in patients with ACS, 2 different cutoffs have been suggested as clinically useful on the basis of our initial observations: an admission value ≥10 mg/l and a discharge value ≥3 mg/l. These cutoffs, although confirmed in larger studies (4), have not yet obtained general consensus.

Experimental studies have clarified the molecular mechanisms through which activation of inflammatory cells in the plaque can trigger thrombus formation. Notably, inflammation regulates the fragility of the fibrous cap, as well as the thrombogenic potential of the plaque. The main mediators of inflammation-induced activation of coagulation are proinflammatory cytokines. Several studies have shown, in particular, the importance of interleukin (IL)-6 in the initiation of coagulation activation and the role of tumor necrosis factor (TNF)-alpha and IL-1 in the modulation of anticoagulant pathways (12,13).

This clinical presentation of ACS has been carefully investigated over the past few years. Experimental observations and clinical studies have clarified key molecular pathways, some of which will probably become important therapeutic targets in the near future. The 3 main features of inflammation associated with ACS are: 1) widespread involvement of epicardial arteries, coronary microcirculation, and even myocardium; 2) activation of innate immunity; and 3) activation of adaptive immunity.

**WIDESPREAD CORONARY INFLAMMATION.** In patients with ACS and systemic evidence of inflammation, widespread coronary inflammation is suggested by transcardiac neutrophil activation in the effluent of myocardial regions not perfused by the culprit artery. This event seems unrelated to coronary atherosclerosis or recurrent ischemia, as it is not observed in patients with chronic stable angina and multivessel coronary disease or in patients with vasospastic angina (14). Widespread acute coronary inflammation is, therefore, the likely cause of multiple complex stenoses, multiple thrombi, and multiple fissured plaques involving different coronary artery branches observed in clinical studies in ACS, based on angiography and intravascular imaging (15–18). Of note, the number of disrupted coronary plaques correlates with systemic hs-CRP levels (17,18). The notion of widespread coronary inflammation has been confirmed by postmortem studies (19).

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**Abbreviations and Acronyms**

- **ACS** = acute coronary syndrome(s)
- **CRP** = C-reactive protein
- **hs-CRP** = high-sensitivity C-reactive protein
- **IL** = interleukin
- **INF** = interferon
- **MI** = myocardial infarction
- **PMN** = polymorphonuclear neutrophil
- **Th17** = type 17 helper T cells
- **TLR** = Toll-like receptor
- **TNF** = tumor necrosis factor
- **Treg** = regulatory T cells

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**Figure 1**

Classification of Acute Coronary Syndromes

The pathogenetic classification of acute coronary syndrome (ACS) based on simple clinical descriptors provides a framework for understanding basic mechanisms responsible for coronary instability in homogeneous groups of patients: 1) patients with obstructive atherosclerosis and systemic inflammation; 2) patients with obstructive atherosclerosis without systemic inflammation; 3) patients without obstructive atherosclerosis. This pathogenetic classification of ACS might help in the search of new diagnostic algorithms and therapeutic targets. ATS = atherosclerosis.
Both (A) innate immunity and (B) adaptive immunity play a key role in the pathogenesis of coronary plaque instability. (A) All types of inflammatory cells are present in atherosclerotic plaques. Macrophages and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows and where the risk of plaque rupture is higher. (B) T-cell infiltrates are always present in atherosclerotic lesions, and their activation may play a primary role in the transition from stable to unstable plaques. Such infiltrates are predominantly CD4 T cells, which recognize protein antigens (such as oxidized low-density lipoprotein, human heat shock protein 60, and chlamydial proteins) processed and presented by activated antigen-presenting cells (APCs). Recently, attention has been focused on the possible role of type 17 helper T cells (Th17), known to play critical roles in the development of autoimmunity and allergic reactions by producing interleukin (IL)-17 and, to a lesser extent, tumor necrosis factor (TNF)-beta and IL-6.

Another subset of Th1 cells in the plaque has the CD4 CD28null phenotype. These T cells have important plaque-destabilizing properties. Regulatory T cells (Treg) maintain the homeostasis of cell subsets involved in adaptive immunity. In human atherosclerotic lesions, Treg colocalize with IL-10 and transforming growth factor (TGF)-beta expression. Ang = angiotensin I; CCR = chemokine receptors; CRP = C-reactive protein; EC = endothelial cell; EDRF = endothelium-derived relaxing factor; ET1 = endothelin 1; IFN = interferon; IL12R = IL-12 receptor; KIR = killer immunoglobulin-like receptor; LTB-4 = leukotriene B-4; M-CSF = macrophage colony-stimulating factor; MMPs = metalloproteinases; MØ = macrophage; MPO = myeloperoxidase; MP-TF = tissue factor–bearing microparticles; PAF = platelet-activated factor; PAI = plasminogen activator; PLT = platelet; PMN = polymorphonuclear neutrophil; ROS = reactive oxygen species; sCD40L = soluble CD40 ligand; SMC = smooth muscle cell; TF = tissue factor; TLR = Toll-like receptor; TRAIL = TNF-related apoptosis-induced ligand.
ACTIVATION OF INNATE IMMUNITY. The notion that innate immunity plays an important role in ACS is supported by the demonstration of activated monocytes, polymorphonuclear neutrophils (PMNs), eosinophils, and mast cells not only at the site of plaque rupture but also in the whole coronary circulation of patients with ACS (Fig. 2A) (4,5).

Recently, we demonstrated high telomerase activity in PMN coming from the culprit coronary plaque of patients with ACS but not from the plaque of patients with stable angina or in the PMN from the peripheral blood. Telomerase activity is normally absent in differentiated cells such as PMN, but it can be reactivated under mitogenic stimulation and it might represent a way to overcome replicative senescence; the result would be a prolonged survival and toxic potential of these inflammatory cells (20). The only predictor of telomerase reactivation in coronary plaques of ACS patients was a short time interval from symptom onset to PMN sampling, supporting a possible role of telomerase reactivation in PMN persistence in the plaque in the very early phases of coronary instability. This mechanism is likely to maintain active the inflammatory process, as neutrophil apoptosis has been identified as 1 of the key mechanisms needed to switch off inflammation. Accordingly, we have recently reported on the delayed apoptosis of peripheral PMNs in patients with ACS (21).

Macrophages account for the majority of leukocytes in plaques. Plaque resident macrophages differentiate from monocytes recruited from circulating blood. However, monocytes represent a heterogeneous circulating population of cells, according to their differential expression of CD14 and CD16 (22,23). Human coronary artery lesions contain macrophage subpopulations with different gene expression patterns, which indicate heterogeneity (22). Patients with coronary atherosclerosis have higher numbers of circulating CD14+/CD16+ monocytes than healthy subjects. Furthermore, CD14+CD16+ count correlates negatively with the concentration of high-density lipoprotein and positively with levels of atherogenic lipids (23). Finally, peak levels of CD14hi/CD16lo monocytes after acute MI correlate negatively with the recovery of left ventricular ejection fraction 6 months after MI (24). Of note, in exploiting the functional differences in phagocytic activity between monocyte subsets, noninvasive imaging technologies have been developed to observe and quantify subpopulations of monocytes in patients (25).

Monocytes accumulated within thrombi, obtained during primary percutaneous coronary interventions, specifically overexpress Toll-like receptor (TLR)-4, together with specific patterns of locally expressed chemokines and cytokines compared with circulating monocytes (26,27). TLRs are key pattern-recognition receptors expressed by innate immunity cells, and they can recognize a large number of molecules named pathogen-associated molecular patterns; they are usually expressed by pathogens but are absent in normal mammal tissues. Interestingly, Niessner et al. (28) demonstrated that IFN-alpha produced by plasmacytoid dendritic cells in atherosclerotic plaques could enhance TLR-4 signaling by sensitizing these cells to lipopolysaccharide and other microbial molecules but also to (modified) endogenous molecules, all abundantly present in the atherosclerotic lesion microenvironment. These sensitized antigen-presenting cells strongly up-regulate the production of cytokines such as TNF-alpha, IL-12, IL-23, and metalloproteinase-9, thus enhancing plaque instability.

Recently, it has been demonstrated that human platelets express functional TLRs capable of recognizing bacterial components (29). TLR activation directly induces platelet aggregation and increased platelet adhesion to collagen under flow conditions. Moreover, TLR stimulation, in particular TLR2, induces a significant increase in platelet-leukocyte interactions and the amplification of platelet-derived inflammatory signals. These findings highlight the role of platelets as immunologic cells, critically participating in both inflammatory and thrombotic processes (29). Indeed, platelet TLR2 and related innate immune transcripts have been associated with cardiovascular disease and its risk factors (30). More recently, Beaulieu et al. (31) have shown expression of TLR2 in megakaryocytes and suggested that inflammatory processes, through TLR2 stimulation, can increase megakaryocyte maturation and modulate megakaryocyte phenotype, potentially influencing platelet function and thrombosis.

ACTIVATION OF ADAPTIVE IMMUNITY. The higher systemic frequency of activated T cells in patients with ACS compared with those with stable angina (32–35), and the higher prevalence of oligoclonal T-cell expansion in unstable coronary plaques compared with stable plaques (33,36), suggest that the sudden change leading to coronary instability might be related to mechanisms involving adaptive immunity (Fig. 2B).

In particular, the more recent acquisitions regarding the role of adaptive immunity suggest that T-cell repertoire perturbation might play a pivotal role in coronary instability. Indeed, we have consistently observed that patients with ACS have an increased frequency of autoaggressive CD4+ T cells characterized by defective cell surface expression of CD28, a major costimulatory molecule critically involved in determining the outcome of antigen recognition by T cells (32,33). In ACS, CD4+CD28null T cells are increased in the peripheral blood and infiltrate unstable coronary plaques where they undergo clonal expansion, probably triggered by specific antigens (37). They release large amounts of proinflammatory cytokines, in particular IFN-gamma (thus activating monocytes and macrophages), and have direct cytolytic effects on endothelial cells, amplified by hs-CRP (38), and on vascular smooth muscle cells (39). Apoptosis of vascular smooth muscle cells has been implicated in destruction of the plaque surface (40). By directly stimulating apoptosis of vascular smooth muscle or by coordinating and activating macrophages to kill these cells through the elevated production of IFN-gamma, CD4+CD28null T cells could weaken the fibrous cap and destabilize angiogenic
vessels, precipitating atherosclerotic plaque rupture (41). Moreover, CD4^+CD28null T cells, either isolated from plaque tissue or from peripheral blood of patients with ACS, spontaneously express IL-12 receptor and respond to IL-12 released by innate immunity cells with the up-regulation of chemokine receptors; thus, IL-12 can favor their tissue homing even in the absence of antigenic stimulation (42). Alternative costimulatory molecules regulate CD4^+CD28null T cells and their inflammatory and cytotoxic function can be inhibited by blocking these costimulatory receptors (43). We have recently shown that high frequencies of CD4^+CD28null T cells increase the risk of ACS, particularly in patients with diabetes (44,45).

Two other T cell subsets, type 17 helper T cells (Th17) and CD4^+CD25^+ regulatory T cells (Treg), are profoundly perturbed in ACS. Th17 cells expressing retinoic acid-related orphan receptor gamma t play critical roles in the development of autoimmunity and allergic reactions by producing IL-17 and, to a lesser extent, TNF-beta and IL-6 (46,47). Although the precise role of IL-17 in atherosclerosis remains controversial, recent experimental studies in mouse models have provided direct evidence that IL-17 is predominantly proatherogenic.

Treg expressing the forkhead/winged helix transcription factor (Foxp3) have been found to prevent atherosclerosis in mouse models (48). The normal function of Treg may be essential to maintain the homeostasis of cell subsets involved in adaptive immunity, including antigen-presenting cells and effector T cells, by contact-dependent suppression or by releasing anti-inflammatory cytokines, such as IL-10 and transforming growth factor–beta, (49). Consistently, a critical role for the anti-inflammatory cytokine IL-10 has been assumed in Treg-mediated atheroprotection, both in experimental models and in human atherosclerotic lesions, for which the expression of Treg colocalized with IL-10 expression. The balance between Th17 and Treg may be important in the development and prevention of inflammatory and autoimmune diseases (50).

Recently published data provide evidence of a defective Treg compartment in ACS. The number and the suppression efficiency of Treg were reduced in patients with ACS compared with patients with stable angina and healthy controls (51,52). A parallel increase in the circulating levels of Th17 has also been observed (53,54). Furthermore, in autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis characterized by CD4^+CD28null T-cell expansion, CD4^+CD28null T cells are only partially susceptible to the regulatory capacities of Treg.

Taken together, these findings support the notion that, at least in a subset of patients with ACS, the failure to mount a counter-regulatory response to the activation of aggressive effector T cells might play a key pathogenetic role and may represent an attractive therapeutic target.

The presence of activated T cells in ACS implies antigen stimulation. Indeed, T cells specific for antigens such as *Chlamydia pneumonia*, heat shock proteins, or oxidized low-density lipoproteins have been isolated from atherosclerotic plaques of patients with ACS (5).

**ACS with obstructive atherosclerosis without systemic inflammation.** In patients in whom coronary instability occurs in the absence of systemic evidence of inflammation, other mechanisms are likely to play a key pathogenetic role. These mechanisms include extreme emotional disturbance-ranging from external events of short duration, such as earthquakes and a beloved team’s loss of a football match, to acute manifestations of more long-lasting internal emotional dispositions—intense physical exertion, and local mechanical stress at the level of the artery wall, that is, both circumferential stress and shear stress. In addition, subclinical inflammation in the microenvironment of the culprit stenosis might play a role in the chain of events leading to coronary instability, although trigger and mechanisms of inflammation are probably different from those operating in patients with systemic evidence of inflammation. It is worth noting that while in the latter, a large number of studies have clarified the molecular mechanisms leading to coronary instability (4,5), patients without systemic evidence of inflammation have been investigated less extensively; consequently, the precise causes of instability are still poorly known, thus providing a strong stimulus for further research in this fascinating setting.

**ENVIRONMENTAL, PHYSICAL, AND EMOTIONAL STRESSORS.** The ability of environmental, physical, or emotional stressors to trigger MI has been attributed to the surge in sympathetic nervous system activation and catecholamine release that lead to increases in heart rate, blood pressure, and cardiac work as well as to local vasoconstriction at the site of vulnerable plaques, thereby precipitating plaque rupture (55). Activation of the sympathetic nervous system also leads to platelet activation, hypercoagulability, and intense coronary microvascular constriction (56). Obviously, environmental, physical, or emotional stressors per se are insufficient to cause coronary instability, but they might trigger instability in the presence of a vulnerable plaque, in particular if causing a severe stenosis (57). Indeed, under these circumstances, the direct hemodynamic effects on the vulnerable atherosclerotic plaque can cause mechanical rupture of the thin cap while thrombus formation is favored by prothrombotic effects as well as by the increased shear stress at the level of the vulnerable plaque (58).

Accordingly, a higher prevalence of plaque fissure has been found among patients dying of sudden coronary death during intense physical exercise compared with patients in whom death occurred at rest. Furthermore, plaque fissure triggered by environmental, physical, and emotional stressors exhibited a thinner cap compared with plaque fissure occurring at rest and was noted in the central region of the plaque. This finding suggests greater susceptibility to biomechanical forces rather than in the shoulder region of the plaque where inflammatory cells are more abundant (2).
ACUTE CHANGES OF PHYSICAL–CHEMICAL CHARACTERISTICS OF THE PLAQUE. Among patients who do not exhibit systemic evidence of inflammation or ACS triggered by environmental, physical, or emotional stressors, physical–chemical alterations of plaque composition might be a cause of instability. Abela et al. (59) proposed the intriguing working hypothesis that shifts in environmental factors, including local saturation of cholesterol, temperature, pH, and hydration status, could alone or in various combinations lead to cholesterol crystallization with sudden and forceful volume expansion causing plaque fissure and thrombosis (Fig. 3). Intraplaque hemorrhage can enhance this mechanism by triggering the crystallization of free cholesterol from erythrocyte membranes and causing abrupt enlargement of the necrotic core (60–62). Although postmortem images, obtained by vacuum dehydration to preserve cholesterol crystals, seem to suggest that needle-shaped cholesterol crystals might be able to perforate a thin fibrous cap (59), these observations are anecdotal and need to be confirmed in larger studies. The development of micro–optical coherence tomography with a 2 micron resolution will probably shed new light on this potential mechanism of instability by allowing assessment of its occurrence in vivo (63).

Interestingly, it has recently been shown that human monocytes and macrophages avidly phagocytose cholesterol crystals, resulting in a dose-dependent secretion of mature IL-1-beta, a potent proinflammatory cytokine, through an inflammasome-mediated pathway (64,65). This mechanism may represent an important link between cholesterol metabolism and local inflammation in the microenvironment of atherosclerotic lesions. In this setting, however, the causes of inflammation are likely to be different from those operating in patients with systemic evidence of inflammation.

ACS without obstructive atherosclerosis. Among patients who present with ACS in the absence of obstructive atherosclerosis, functional alterations of epicardial coronary arteries or of coronary microcirculation are the likely cause of instability. Plaque fissure has recently been observed in women with ACS and without obstructive atherosclerosis, potentially causing transient thrombus formation (66). However, its pathogenic role is difficult to establish because plaque fissure is frequently asymptomatic and is observed in a sizeable proportion of patients with stable ischemic heart disease (67).

FUNCTIONAL ALTERATIONS OF EPICARDIAL CORONARY ARTERIES. In some of these patients, instability is due to coronary spasm. In the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study, coronary angiography failed to show obstructive atherosclerosis in about 30% of patients with suspected ACS. More impor-
B.}

C.

D.

ACS

ACS

Figure 4 Functional Alterations of Coronary Microcirculation May Cause ACS in Patients Without Obstructive Coronary Atherosclerosis

Reversible intense coronary microvascular dysfunction has been demonstrated in Takotsubo or apical ballooning syndrome. A series of patients with apical ballooning syndrome underwent myocardial contrast echocardiography at baseline (Bsl); during infusion of adenosine (Adn) (140 μg/kg/min), a potent coronary microvascular vasodilator; and at 1-month follow-up (FUP). During Adn challenge, all patients exhibited a significant improvement of myocardial perfusion and of left ventricular (LV) function, which further improved at 1-month follow-up. (A) A clear perfusion defect is present at baseline within LV apical myocardium (arrow). (B) A striking decrease in the extent of the perfusion defect is evident during Adn infusion. Values of contrast score index and of LV ejection fraction in individual patients are shown at Bsl, at peak of Adn infusion, and at 1-month FUP in C and D, respectively. #p < 0.05 and *p < 0.001 versus baseline. ACS = acute coronary syndrome. Modified, with permission, from Galiuto et al. (72).

FUNCTIONAL ALTERATIONS OF CORONARY MICRO- CIRCULATION. Intense constriction of coronary microcirculation is a second mechanism that may cause ACS in patients who exhibit nonobstructive coronary atherosclerosis (70,71). This is the likely mechanism of instability in patients with Takotsubo syndrome, which is characterized by ischemic pain at rest, ST-segment elevation, cardiac enzyme release, and a characteristic regional akinesia more frequently affecting distal myocardial regions associated with hypercontractility of the remaining regions. Indeed, in these patients, using echocontrastography, we have recently found regional apical hypoperfusion that transiently improves during administration of adenosine, a potent arteriolar vasodilator; this transient improvement is associated with a transient improvement of regional wall motion abnormalities and of ejection fraction (Fig. 4) (72). Thus, reversible coronary microvascular dysfunction seems to be the common pathophysiological determinant of this syndrome. The causes of this intense microvascular constriction and the reasons for its peculiar locations are still largely unknown. Sympathetic hyperreactivity and myocarditis are potential, yet unproved, causes.

Parvovirus B19 genome has been found in myocardial biopsies of patients with angiographically normal coronary arteries who present with typical ischemic pain, ischemic ST-segment changes, cardiac necrosis enzyme increase, and various degrees of regional wall motion abnormalities (73). Its presence in the myocardium was associated with coronary vasoconstriction in response to acetylcholine, thus suggesting severe endothelial dysfunction (74).
Finally, microvascular constriction of lesser intensity occurring in the absence of regional wall motion abnormalities and associated with an unstable pattern of angina, ischemic ST-segment changes, and/or a cardiac necrosis enzyme increase has recently been proposed as the unstable counterpart of stable microvascular angina, which is more prevalent in women than in men (71). According, the prevalence of women who present with ACS in the absence of obstructive atherosclerosis is 2-fold higher than that of men (75). The mechanisms of this poorly defined presentation of coronary instability are unknown. Functional alterations of coronary microcirculation, similar to mechanisms described in women with stable microvascular angina, might be involved (76). There are a number of likely causes for impairment of coronary flow reserve in patients with nonobstructive atherosclerosis. Coronary flow is regulated by several endothelium-dependent and endothelium-independent factors influencing microvascular tone. Endothelium-independent factors include aortic pressure, myocardial compressive forces, neurohumoral substances, and myocardial metabolism. The endothelium regulates vasomotor tone by stimulating release of vasoactive factors. A major vasodilator substance is nitric oxide, originally identified as an endothelium-derived relaxing factor. In the WISE (Women’s Ischemia Syndrome Evaluation) study, coronary microvascular reactivity to adenosine predicted an adverse outcome in women evaluated for suspected ischemia (77,78).

Finally, it has recently been proposed that epicardial or microvascular spasm might promote coronary thrombosis at the site of a susceptible plaque, thus potentially also representing the primary cause of instability in some of the patients exhibiting obstructive atherosclerosis (79) (Fig. 1).

**Clinical Perspectives**

The large body of knowledge we have gained in the past 50 years in the field of cardiovascular diseases clearly indicates that our main goal is primary prevention. Indeed, more than 90% of acute vascular events are explained by environmental causes, which can theoretically be eradicated and thus prevent plaque growth (80). It is extremely important, therefore, to reduce the burden of cardiovascular risk factors. It is equally important, however, to improve our knowledge of the complex mechanisms responsible for sudden transition from coronary stability to instability. Indeed, when we fail with prevention of plaque growth, a subordinate goal is the preservation of plaque stability.

Coronary thrombosis is the final common pathway leading to coronary instability, and it is our current main therapeutic target. This goal has allowed us to considerably improve the outcome of ACS. However, more potent antithrombotic regimens have recently been found to increase the risk of major bleedings that are associated, in turn, with a higher risk of mortality (81). To identify new therapeutic targets, we need to know more about the different causes of coronary thrombosis.

The pathogenetic classification we propose is mainly conceived to stimulate innovative research on the causes of coronary instability, but it may also help in the management of patients presenting with ACS.

Several studies have shown that patients with ACS in whom obstructive atherosclerosis is associated with increased levels of CRP or other markers of inflammation have a worse outcome than patients with a similar severity of coronary atherosclerosis but normal levels of inflammatory markers (6,14,17,18,82,83). Thus, in the former, reassessment of the inflammatory status after discharge may help in the identification of patients at higher risk of recurrence of coronary instability. Although the assessment of the inflammatory status is currently based on biomarkers only, recently developed imaging techniques able to monitor inflammatory cell activity in atherosclerotic plaques might prove to be more predictive than biomarkers (84). In addition, an unmet need in this patient subset is a specific anti-inflammatory treatment based on the modulation of both innate and adaptive immunity (1,4,85). Although nonsteroidal anti-inflammatory drugs have been associated with a higher risk of cardiovascular events (probably related to inhibition of prostacyclin synthesis in endothelial cells), and steroid utilization is hampered by its well-known adverse effects (particularly in diabetic and hypertensive patients), disease-modifying anti-rheumatic drugs have been found in observational studies to be associated with a lower cardiovascular risk (85). Antagonism of key cytokines such as TNF-alpha is another potential approach, particularly in high-risk patients with high levels of CD4+CD28null T cells, although the high cost and the potential adverse effects make this approach difficult to pursue. Interestingly, statins have been found to modulate this aggressive subset of T cells, which might help explain the early beneficial effect of intensive statin treatment in patients with a recent ACS (86). Antagonists of IL-1-beta, agonist of IL-1Ra, or inhibitors of inflammasome activation are close to clinical testing. A recent pilot study in patients with acute MI has provided encouraging results, showing that IL-1 blockade with anakinra, a recombinant human IL1-Ra, is safe and favorably affects cardiac remodeling after acute MI without modifying either final infarct size or infarct healing (87).

Recently, at least 2 additional IL-1–targeted drugs, a recombinant protein with high affinity for IL-1-beta (known as IL-1 Trap or rilonacept) and a fully humanized anti–IL-1-beta monoclonal antibody (canakinumab), have proven effective in several chronic inflammatory diseases, including rheumatoid arthritis and diabetes, and might thus be of potential interest in ACS (88). Other ways to limit IL-1-beta activation are inhibition of caspase-1 or the inflammasome; some of these inhibitors have been tested in clinical trials (85). Another potential therapeutic target is regulatory T cells in those patients in whom their number or function is depressed. Putnam et al. (89) recently found that these cells can be isolated and expanded ex vivo for the treatment of autoimmune diseases. Finally, the identifica-
tion of the antigens triggering adaptive immunity may open
the way to specific vaccinations. Of note, the demonstration
that vaccination against influenza might be associated with
reduction of cardiovascular events is the first example of this
innovative approach (90,91).

In patients with ACS in whom obstructive atherosclerosis
is not associated with systemic inflammation, anatomic
(more than functional) features of the atherosclerotic plaque
are important in determining coronary instability. Accord-
ingly, in a recent trial, plaques characterized by a large
plaque burden, small lumen diameter, and a thin cap were
associated with a greater than 10-fold risk of causing ACS
during a 3-year follow-up than plaques not exhibiting any of
these 3 features (57,92).

Because it is difficult to limit environmental, physical, or
emotional triggers, an obvious target in this patient subset is
plaque stabilization as achieved by intensive statin treatment
(86). Another class of drugs that might help in plaque
stabilization is represented by inhibitors of phospholipase
A2. Indeed, darapladib, an antagonist of lipoprotein-bound
phospholipase A2, was found to reduce the necrotic core
(assessed by using virtual histology) compared with placebo
(93). Yet, a larger trial with clinical endpoints of varespladib,
an antagonist of secretory phospholipase A2, versus placebo
was halted prematurely because of lack of efficacy (94).
Another important but still elusive target to promote plaque
stabilization is enhancement of cholesterol efflux (95).

Among patients in whom obstructive atherosclerosis is
not associated with systemic inflammation and ACS occurs
in the absence of environmental, physical, or emotional
triggers, more needs to be learned about the mechanisms
modulating cholesterol crystallization, including the inflam-
masome pathway activated by cholesterol crystals, so that
new therapeutic targets can be identified.

Finally, epicardial and microvascular vasoconstriction is
the key therapeutic target when ACS is not associated with
obstructive atherosclerosis. Recently, data from clinical trials
suggest that the outcome of these patients is, on average,
better than that of patients with obstructive atherosclerosis;
however, about 10% of patients presenting with ACS in the
absence of coronary atherosclerosis have a major cardiac
event at 1-year follow-up (96).

Although nitrates and calcium antagonists are helpful in
patients with vasospastic angina, further efforts are needed
to identify the molecular alterations responsible for smooth
muscle cell hyperreactivity because a sizeable proportion of
patients with vasospastic angina are refractory to standard
doses of vasodilators (68). It has been observed that fasudil,
a specific rho-kinase inhibitor, reduces the rate of coronary
spasm episodes in patients with vasospastic angina (69).
Similarly, further efforts are warranted to unravel the mo-

cular mechanisms responsible for coronary microvascular
dysfunction in Takotsubo syndrome, in myocarditis, and in
unstable microvascular angina.

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REFERENCES
1. Libby P, Ridker PM, Hansson GK. Progress and challenges in
2. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of
vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol 2010;30:
1282–92.
3. Ferrante N, Nakano M, Prati F, et al. High levels of systemic
myeloperoxidase are associated with coronary plaque erosion in pa-
tients with acute coronary syndromes: a clinico-pathological study.
4. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis:
5. Hansson GK. Inflammation, atherosclerosis, and coronary artery
6. Liuzzo G, Biasucci LM, Gallimore JR. The prognostic value of
C-reactive protein and serum amyloid a protein in a severe unstable
protein is within normal levels at the very onset of first ST-segment
elevation acute myocardial infarction in 41% of cases a multiethnic
3-Year follow-up of patients with coronary artery spasm as cause of
acute coronary syndrome: the CASPAR (coronary artery spasm in
patients with acute coronary syndrome) study follow-up. J Am Coll
Cardiol 2011;57:147–52.
9. Thygesen K, Alpert JS, White HD. Universal definition of myocardial
10. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive
protein and coronary heart disease: a critical review. J Intern Med
11. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent
vascular events in men and women with elevated C-reactive protein.
12. Levi M, van der Poll T. Two-way interactions between inflamma-
13. Croce K, Libby P. Intertwining of thrombosis and inflammation in
2002;347:5–12.
15. Libby P. Act local, act global: inflammation and the multiplicity of
instability in patients with acute myocardial infarction as determined
inflammation and multiple complex stenoses (pancoronary plaque
vulnerability) in patients with non-ST segment elevation acute coro-
18. Tanaka A, Shimada K, Sano T, et al. Multiple plaque rupture and
C-reactive protein in acute myocardial infarction. J Am Coll Cardiol
inflammation occurs in both vulnerable and stable plaques of the entire
coronary tree: a histopathologic study of patients dying of acute

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