Acute coronary syndromes represent a complex phenotype involving the interplay of many elements. The risk of developing an acute coronary syndrome and related complications has been defined by variables such as age, diabetes, smoking history, serum creatine phosphokinase, or electrocardiographic findings. However, in the past 5 years the wide-scale acceptance of a protein—troponin—has changed the diagnostic profile. With advances in molecular medicine, this protein is a segue to a panel of molecular assays that will improve screening and tailored intervention. We expound upon some of these factors and the potential they may carry in changing clinical medicine. (J Am Coll Cardiol 2007;49:279–89) © 2007 by the American College of Cardiology Foundation

 Coronary artery disease (CAD) is increasing in prevalence and is predicted to become the dominant cause of mortality worldwide by 2020. A burgeoning body of literature exists that implicates inflammation as being central to atherogenesis and, ultimately, atherothrombosis (1). In fact, the inflammatory process appears to be more extensive than previously thought and may involve multiple vulnerable plaques within the coronary bed and, in many patients, other arterial trees simultaneously (2). That an integral link among inflammation, atherogenesis, and atherothrombosis exists is fundamental to understanding acute coronary syndromes (ACS). Translating this understanding and the emerging concept of differential genetic heritability between myocardial infarction (MI) and atherosclerosis (3) into the development of quantifiable molecular risk factors in otherwise healthy, asymptomatic individuals is a major goal for prevention.

 As the mechanisms and pathways involved in the processes of plaque rupture, thrombosis, and response to injury are defined, a logical evolution would be to use this opportunity to better define risk of future events and complications. Use of molecular markers of inflammation after ACS to predict the likelihood of recurrence or even appropriate response to therapy may facilitate targeted therapeutic strategies based on a comprehensive molecular risk profile (4) rather than on demographic and clinical characteristics.

 The goal of this review is to provide insight into the complex interactions between the inflammatory and cellular mechanisms involved in the pathogenesis of ACS and the response to injury. The prognostic value of some of these novel markers and relevant data on proposed therapeutic interventions will be addressed so that in time we can use these markers to prevent ACS events or, at least improve, clinical outcomes.

**Endothelium**

Compromise of endothelial integrity is felt to be fundamental, not only to the initiation and progression of atherosclerotic disease, but also to the onset of ACS. Leukocytes are believed to contribute to direct endothelial damage in this setting. Irrespective of the underlying contributor, endothelial damage and dysfunction remain integral to atherogenesis and the development of an ACS.

**Circulating endothelial cells as a marker of panvascular injury.** Circulating endothelial cells are a marker of arterial injury in vascular disease. Notably, significantly elevated levels of circulating endothelial cells have been observed in patients with ACS compared with those with stable angina (5). More recently, it was discovered that elevated levels of circulating endothelial cells measured in patients within 48 h of an ACS independently predict subsequent short- and long-term outcomes (6).

**Role of the subendothelial matrix von Willebrand factor (vWF) in ACS.** Through the actions of a key component, vWF, on factor VIII activity, the matrix contributes to modulation of the coagulation cascade and to the pathogenesis of ACS. Beyond its role in facilitating coagulation protein interaction, vWF binds to subendothelial collagen via its A3 domain and initiates platelet adhesion via the glycoprotein (GP) 1b receptor (7). Experimental evidence suggests that both vWF and high shear stress may be responsible for platelet aggregation in acute MI. Conversely, inhibition of the GP1b receptor from serum of patients with an acute MI or unstable angina by a vWF antibody results in reduced shear-induced platelet aggregation (8). Ultimately, increased levels of vWF
have been associated with suboptimal angiographic results and increased adverse events across the spectrum of ACS (9,10).

**Platelets**

The importance of platelets in thrombosis and ACS is well established. Through release of various constituents, expression of various receptors, and interactions with leukocytes and the endothelium, platelets function as inflammatory mediators in patients with ACS (Fig. 1). Platelets provide a pivotal link between inflammation and thrombosis in ACS.

**CD40 and CD40L.** CD40 and CD40L have been found on platelets and several other cell types in functional-bound and soluble (sCD40L) forms. Although many platelet-derived factors have been identified, recent evidence suggests that CD40L is actively involved in the pathogenesis of ACS. Through direct platelet-to-cell stimulation, most notably the interaction between CD40L on activated platelets and the CD40 receptor on endothelial cells, CD40L, drives the inflammatory response. Such interactions facilitate increased expression of adhesion molecules on the surface of endothelial cells and release of various stimulatory chemokines. These events, in turn, facilitate activation of circulating monocytes as a trigger of atherosclerosis (11).

Both CD40L and sCD40L contain separate domains allowing for direct binding to the αIIbβ3-receptor on platelets. It has been suggested that this CD40L-platelet αIIbβ3 receptor interaction is important for stability of platelet-based thrombus (12). Stimulation of the αIIbβ3 receptor is known to release sCD40L from within platelets (13) in addition to activating other platelets.

Beyond known proinflammatory and thrombotic properties of CD40L, experimental evidence suggests that CD40L-induced platelet activation leads to the production of reactive oxygen and nitrogen species, which are able to prevent endothelial cell migration and angiogenesis (14). As a consequence of inhibiting endothelial cell recovery, the risk of subsequent coronary events may be greater.

Clinical studies have supported the involvement of CD40L in ACS and the prognostic value in ACS populations. Levels of sCD40L have been shown to be an independent predictor of adverse cardiovascular events after ACS (15) with increased levels portending a worse prognosis (16,17). Importantly, specific therapeutic strategies have shown to be beneficial in reducing risk associated with sCD40L (Table 1) (16–22). The interaction of sCD40L and glycoprotein IIb/IIIa receptor is important in thrombosis and thrombus stability. Glycoprotein IIb/IIIa inhibitors such as abciximab may provide benefit in this high-risk population (17), with the caveat being the increased levels of sCD40L and potential worsening of the proinflammatory state and increased mortality seen with GP IIb/IIIa inhibitor underdosing (23,24).

These observations support the premise that platelet activity is central to the proinflammatory and prothrombotic states in ACS. CD40L and sCD40L seem to link these processes and underscore the need to identify those at risk.


**Table 1**

Effect of Medical Therapy on CD40L

<table>
<thead>
<tr>
<th>Study</th>
<th>Medical Intervention</th>
<th>CD40L vs. sCD40L</th>
<th>Clinical Outcome</th>
<th>Patient Type</th>
<th>Patients (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACL (16)</td>
<td>Atorvastatin</td>
<td>sCD40L</td>
<td>Composite of adverse cardiovascular events</td>
<td>UA/NSTEMI</td>
<td>2,352</td>
<td>Atorvastatin resulted in a significant reduction in adverse cardiac events, notably in those with higher sCD40L levels</td>
</tr>
<tr>
<td>CAPTURE (17)</td>
<td>Abciximab</td>
<td>sCD40L</td>
<td>6 months composite of death or nonfatal MI</td>
<td>ACS</td>
<td>1,088 ACS 626 CP</td>
<td>Abciximab use was of more benefit in those with higher sCD40L levels</td>
</tr>
<tr>
<td>Schonbeck et al. (18)</td>
<td>HMG-CoA reductase inhibitors</td>
<td>sCD40L</td>
<td>Plasma levels of sCD40L</td>
<td>Primary prevention</td>
<td>Statin therapy led to a reduction in sCD40L</td>
<td></td>
</tr>
<tr>
<td>Sanguigni et al. (19)</td>
<td>Atorvastatin</td>
<td>sCD40L, platelet-bound CD40L, F1 + 2 (marker of thrombin generation)</td>
<td>Primary prevention</td>
<td>30</td>
<td>Abciximab reduced sCD40L, platelet-bound CD40L and F1 + 2 suggesting antiinflammatory and antithrombotic mechanisms at play</td>
<td></td>
</tr>
<tr>
<td>Vare et al. (20)</td>
<td>Troglitazone</td>
<td>sCD40L</td>
<td>sCD40L levels after 12 weeks of therapy</td>
<td>Type 2 DM</td>
<td>48</td>
<td>Troglitazone therapy resulted in a reduction in sCD40L over a 12-week period</td>
</tr>
<tr>
<td>Semb et al. (21)</td>
<td>Atorvastatin 80 mg/day vs. simvastatin 40 mg/day</td>
<td>sCD40L</td>
<td>sCD40L after 2 yrs of therapy</td>
<td>Familial hypercholesterolemia</td>
<td>Reduction in sCD40L seen with statin therapy was independent of effect on cholesterol</td>
<td></td>
</tr>
<tr>
<td>Furman et al. (22)</td>
<td>Abciximab vs. eptifibatide vs. control</td>
<td>sCD40L</td>
<td>sCD40L leukocyte-platelet aggregates 18–24 h after PCI</td>
<td>ACS patients undergoing PCI</td>
<td>98</td>
<td>Reduction in sCD40L with abciximab and eptifibatide vs. control</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndromes; CAD = coronary artery disease; CAPTURE = CITE 3 Fab AntiPlatelet Therapy in Unstable REFractory angina; CP = chest pain; DM = diabetes mellitus; MI = myocardial infarction; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.

**Leukocytes**

The inflammatory responses leading to the disruption of plaque and subsequent events in ACS is characterized by a varied cellular presence. The relationship between atherothrombotic coronary artery disease (CAD) and the pathogenesis of atherosclerotic plaque has been well studied. In addition to macrophages, the importance of other leukocytes in these processes has become apparent. Dichotomizing cell types involved in atherogenesis compartmentalization of culprit lesions from acute MI patients demonstrated that in these without ACS (31). At the other end of the spectrum, infiltration of the atherosclerotic plaque with monocytes and eventual upregulation of oxidized low-density lipoprotein (LDL) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vital to acute plaque rupture with autopsy studies having shown higher concentrations of activated monocytes (IL-1) particles is thought to be vit
For example, myeloperoxidase, a powerful oxidant released from both neutrophils and monocytes, has been demonstrated in patients with coronary artery disease (52), has been implicated in having a role in plaque destabilization (50), and has been associated with a worse prognosis in patients presenting with an ACS (51). Although the majority of these leukocyte secretory products link inflammation and atherothrombosis, their clinical applicability has

### Table 2: Selected Leukocyte Secretory Products and Possible Involvement in ACS

<table>
<thead>
<tr>
<th>Leukocyte Secretory Product</th>
<th>Contribution to Atherogenesis/ACS</th>
</tr>
</thead>
</table>
| **Myeloperoxidase**         | Involved in low-density lipoprotein oxidation, nitric oxide breakdown, and endothelial homeostasis (32,33)  
Involved in plaque destabilization (50)  
Prognostic utility in those presenting with ACS (34,51)  
Involved in post-MI remodeling (35) |
| **Monocyte chemoattractant protein-1** | Essential for monocyte recruitment (36)  
Modulates inflammatory response in atherosclerosis, ACS, and postinfarct remodeling  
Higher levels associated with worse outcome post ACS (37) |
| **Interleukin (IL)-18**     | Induces production of IFN-γ, MMP, and adhesion molecules  
Associated with “vulnerable plaque” morphology (38,39)  
Increased IL-18/IL-10 ratio correlates strongly with risk of adverse events in those with ACS (40) |
| **Matrix metalloproteinases (MMPs)** | MMP-2 and MMP-9 associated with plaque instability (41)  
Elevated levels of MMP-2 and MMP-9 seen in patients with ACS (42)  
MMP-9 was associated with increased risk of cardiovascular death in patients with ACS (43)  
Several isoforms, both cardiac and noncardiac, exist |
| **Pregnancy-associated plasma protein-A (PAPP-A)** | Activates insulin-like growth factor-1  
Circulating PAPP-A significantly higher in patients with unstable coronary syndromes vs. those with stable angina (44)  
Elevated levels an independent predictor of 6-month major adverse cardiac events in patients with ACS (45)  
Several isoforms (both cardiac and non cardiac forms) exist |
| **Hepatocyte growth factor** | Related to thrombus generation in presence of mast cells (46)  
Significantly higher levels of hepatocyte growth factor demonstrated in patients with chest pain and evidence of acute thrombosis (47)  
Antiapoptotic  
Directly related to left ventricular function after MI (48) |
| **Interferon gamma (IFN-γ)** | Released from Th1 CD4+ cells  
Higher levels of Th1 CD4+ cells seen in patients with unstable angina vs. those with stable angina or controls (49)  
Activates monocytes/macrophages |

ACS = acute coronary syndrome; MI = myocardial infarction.
not been adequately defined. Nevertheless, there exists encouraging data that emphasize the potential future utility of some, if not all of these products.

**Progenitor Cells**

Derived from bone marrow sources and peripheral mononuclear cells, circulating endothelial progenitor cells (EPCs) have been shown to possess several characteristics that may facilitate the use of these cells as novel markers of endothelial dysfunction as well as of ongoing tissue repair and/or regeneration. Characteristics such as their pluripotency, ability to regenerate damaged endothelium, and the ability to “home” to damaged or ischemic tissue and contribute to neovascularization have elevated interest in these cells with novel prognostic and therapeutic goals in mind.

Endothelial progenitor cells represent a promising biomarker of endothelial dysfunction, one of the earliest stages of atherogenesis. In a study of patients with risk factors for CAD, reduced levels of EPCs correlated with higher degrees of endothelial dysfunction. Conversely, augmenting EPC volume through mechanisms, including transplantation, facilitates neovascularization and re-endothelialization and attenuates myocardial ischemia, supporting a role for EPCs in maintaining the homeostasis of the endothelial wall. Assessing for EPC levels may be more useful, given their correlation with established risk factors for CAD (53), their correlation with the presence of atherosclerosis (54), and with their prognostic ability in patients with established CAD (55). However, levels of circulating EPCs did not predict acute MI, suggesting a role for EPCs in atherosclerosis progression, but not in acute plaque rupture.

Although a natural, EPC-mediated repair mechanism that exists after myocardial injury has been demonstrated (56), this process occurs at a rate that precludes any meaningful functional recovery after MI. Experimental evidence has suggested that delivery of cytokine-expanded CD34+ EPCs via direct injection into the infarct border zone (57) may be able to augment the natural repair mechanisms and facilitate improvement in myocardial function. These observations highlight that a homing mechanism exists following myocardial injury, which, if harnessed, can contribute to myocardial repair facilitated, in part, by EPCs.

Although EPCs represent a promising biomarker of endothelial dysfunction, they also maintain an ability to participate in the repair process. In a healthy state, there is a role for progenitor cells in preservation of the endothelial wall. In states of endothelial dysfunction, reduced levels and functionality of EPCs and other circulating progenitor cells may impair these abilities and predispose to further injury. Manipulation of these progenitor cells may provide a therapeutic strategy for treating early stages of endothelial injury or preventing adverse remodeling after MI.

**Adipocytes**

Obesity has been identified as a risk factor for the development of the metabolic syndrome and subsequent cardiovascular disease. Specifically, visceral adipose tissue has been cited as the principal reservoir of adipocytes. Adipose tissue is a metabolically active organ that contains blood vessels and various active cell types. Acting through various endocrine and paracrine mechanisms, the relevance of adipose tissue to cardiovascular disease stems from its proinflammatory effects. Obesity, especially that which is associated with increased waist-to-hip ratio or increased visceral fat, leads to the up-regulation of various intercellular adhesion molecules, P-selectin, C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α, interleukin-18, tumor necrosis factor receptors, and plasminogen activator inhibitor-1, among others, are thought to result in a proinflammatory state that contributes to atherogenesis. Suppression of adiponectin, a protective adipokine, also appears to result from obesity.

Although adipocytes produce and secrete a variety of other factors, much is being learned about many of these factors and any relationship to coronary artery disease and ACS. Other examples include the transcription factor GATA2, resistin, CRP, serum amyloid A3, and leptin. Although these represent novel markers and may provide valuable insight with regard to atherosclerotic disease related to obesity, only CRP has been extensively studied in the context of coronary artery disease (Table 3) (58–80).

**CRP**. C-reactive protein is an acute phase reactant produced primarily by the liver in response to cytokines such as interleukin-6. It has gained attention not only as a marker of inflammation and cardiovascular risk but as an active participant in the process (81). C-reactive protein adds value beyond traditional cardiovascular risk factors such as LDL in predicting the risk of MI, stroke, need for revascularization, or death from cardiovascular causes (82). The significance of CRP is that it highlights the relationship between ongoing inflammation and future cardiac events. In those with unstable angina, discharge CRP levels predicted long-term risk of recurrent events (83).

Beyond prognostic value, evidence supports the direct involvement of CRP in the development of atherosclerotic plaque. C-reactive protein, identified in atherosclerotic plaque, has been shown to facilitate macrophage uptake of LDL particles (84) and to regulate both macrophage recruitment (85) and vascular adhesion molecule expression (86).

C-reactive protein has become an attractive target for medical therapy in coronary atherosclerosis (Table 4) (87–94). Therapeutic strategies in ACS have focused on modifiable risk factors, but none have focused on inflammation per se. It still remains to be seen what effect specifically targeting CRP will have upon hard clinical endpoints. A recent study in mice with experimental MI showed that CRP inhibition could markedly reduce infarct size (95). Although statin therapy has been touted for its ability to reduce levels of CRP (87–89,91) only now are studies under way examining
Adiponectin
- Important role in lipid and carbohydrate metabolism
- Modulates action of insulin
- Prevents lipid uptake by macrophages + inhibits transformation into foam cells (58)
- Acts to increase TIMP-1 expression in macrophages in vitro (59)
- Affects expression of various cellular adhesion molecules by affecting NF-κB signaling (60,61)

TNF-α
- Has a role in obesity-related insulin resistance
- A cytokine involved in many proinflammatory disease states
- In obesity, expression also increased on the surface of adipocytes
- Affects endothelial function by modulating expression of cellular adhesion molecules through NF-κB (78)
- Increases MMP activity (77)
- Inhibition of TNF-α in apoE knockout mice reduces disease progression (78)

IL-6
- Pro-inflammatory
- Increases production of CRP in the liver
- Leads to production of CRP, a marker known to be associated with risk of future CV events
- Has been shown to decrease lipoprotein lipase activity
- Elevated IL-6 levels in unstable angina patients predicted complicated in-hospital course (75)
- By mediating production of CRP, in addition to affecting the production of vascular cellular adhesion molecules and affecting coagulation, IL-6 may modulate many of the events that promote atherosclerotic disease.

PAI-1
- Functions to inhibit plasminogen activation and results in a balance favoring a prothrombotic state and may serve as a marker of impaired fibrinolysis
- Prothrombotic
- PAI levels are often increased in vascular disease, including DVT and AMI
- Balance between PA/PAI-1 is affected in states such as obesity and DM
- Small clinical study showing TnT and PAI-1 add prognostic information in the setting of ACS (67)
- In STEMI patients, acute rise in PAI-1 during first 24 hrs predicts 30-day mortality and risk for developing CHF (68)
- May potentially serve as a link between inflammation and thrombosis. It may provide adipocytes a mechanism by which to modulate the thrombotic state.

VEGF
- Angiogenic factor
- Levels of visceral adipose tissue correlate with VEGF levels
- VEGF-induced angiogenesis may contribute to atherosclerotic lesions (69)
- In experimental models, VEGF has been shown to hasten the progression of atherosclerotic plaque (70,71)
- Suggestions have been made about neovascularization being a factor in plaque instability and rupture (72)
- VEGF appears to modulate effect of angiotensin II-mediated inflammation (73)
- The significance of angiogenesis in the context of coronary artery disease remains controversial. There is phase I clinical trial data which show symptomatic benefit of VEGF via direct myocardial injection in those with refractory angina.

Plasminogen activator inhibitor-1; interleukin-6; tumor necrosis factor-alpha; troponin T

ACS = acute coronary syndrome; AMI = acute myocardial infarction; apo = apolipoprotein; CAD = coronary artery disease; CHF = congestive heart failure; CRP = C-reactive protein; CV = cardiovascular; DM = diabetes mellitus; DVT = deep venous thrombosis; HPFS = health professionals; IFN-γ = interferon gamma; IL-6 = interleukin-6; NF-κB = nuclear factor kappa B; PA = plasminogen activator; PAI-1 = plasminogen activator inhibitor-1; STEMI = ST-segment elevation myocardial infarction; TIMP-1 = Tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor-alpha; TnT = troponin T; VEGF = vascular endothelial growth factor.
the effects of various therapeutic modalities upon CRP levels as a marker of clinical cardiovascular risk (93,94).

It is apparent that inflammatory status is a variable that needs to be strongly considered. Whether currently available therapy will reduce inflammation and improve clinical end points has yet to be determined. Nevertheless, CRP provides valuable insight regarding the link between inflammation, CAD, and ACS.

Genetic Risk, Molecular Risk Factors, and Clinical Medicine

Genetic predisposition toward the development of MI is a concept that is only bluntly defined by traditional risk factors such as hypertension or hyperlipidemia. This common complex trait with extensive gene-environment and gene–gene interactions is in the early phase of being genomically unraveled. Complexity of the process is reflected in the number of single nucleotide polymorphisms. For example, the inhibition of the recently identified 5-lipoxygenase activating pathway with a 5-lipoxygenase activating protein pathway (FLAP) blocker in patients with a gain-of-function FLAP or leukotriene A4 haplotype has been shown to reduce the degree of inflammation as measured by various proinflammatory biomarkers, including CRP and leukotriene B4. Similarly, specific variants of PCSK-9 and USF-1, which affect lipoprotein handling, have been shown to provide marked protection from ACS events (96–99). This is a promising example of how such specific genomic information could facilitate individualized prevention.

With high-throughput genotyping of >500,000 key marker single nucleotide polymorphisms, the ability to identify the susceptibility factors for ACS such as FLAP or leukotriene A4 is greatly enhanced. High-throughput sequencing tools and microarrays will allow for examination and comparison of thousands of genes at once. The potential exists for developing profiles of risk based on genetic information. Ginsburg et al. (100) discuss the value of personalized cardiovascular medicine using not only large-scale genetic profiles but also gene products in revolutionizing the scope of clinical practice. Improved diagnostic sensitivity and refined prognostic value in combination with a tailored therapeutic approach would be the proposed outcome.

More and more genes and gene products are being considered as being valuable in providing information about patients at risk for ACS. As more candidates are introduced...
through proteomics and metabolomics, their pragmatic utility must be questioned in dedicated clinical trials. A standardized panel of markers used to assess inflammation, plaque vulnerability, and other features may become part of clinical practice, but the selection of which markers to use remains undecided, especially as the selection pool grows in size and complexity. Most of the markers that have been discussed have not yet been examined concurrently in large-scale clinical epidemiologic studies. Transitioning these markers directly into clinical practice without sufficient data stands only to create confusion. Furthermore, of the markers that hold promise in clinical medicine, there is still much to be learned about specific assays, measurement characteristics, and more precise pathophysiologic definitions. sCD40L is an excellent example of this as sample processing and temperature were found to affect measurements (101)—despite our current knowledge, our understanding still remains limited.

Although the discovery of such markers and subsequent studies proving association with ACS will likely continue to take place at an accelerated pace, the rate-limiting step should involve a rigorous process of systematically evaluating these markers prior to transitioning into clinical practice without sufficient data stands only to create confusion. Furthermore, of the markers that hold promise in clinical medicine, there is still much to be learned about specific assays, measurement characteristics, and more precise pathophysiologic definitions. sCD40L is an excellent example of this as sample processing and temperature were found to affect measurements (101)—despite our current knowledge, our understanding still remains limited.

Although the discovery of such markers and subsequent studies proving association with ACS will likely continue to take place at an accelerated pace, the rate-limiting step should involve a rigorous process of systematically evaluating these markers prior to transitioning into clinical practice. This would include reproducibility in large populations, a scrutiny of assay methods, cost effectiveness appraisals, an assessment of practicality, and determination of whether value is added beyond current methods of risk stratification.

**Conclusions.** It is apparent that a myriad of cellular and molecular mediators involved in the proinflammatory and prothrombotic phases of atherosclerosis and ACS exist. What determines any individual’s clinical manifestations may reflect the interplay of inflammatory components, environmental factors, and genetic susceptibility. Although our understanding of the inflammatory processes is only now expanding, we are just scratching the surface with regard to genetic susceptibility in acute coronary syndromes.

What remains wholly apparent, however, is the complexity of this disease process. It is no wonder, then, that many elements have been individually identified, characterized, and studied in the clinical setting in an effort to understand at least one potential pathway. Although no one entity has ever been found to be the holy grail of the ACS, the understanding of the complex interplay between these components seems to be most important.

In time, risk assessment may take the form of an evaluation of multiple molecular factors using a comprehensive pan-arterial analysis of carefully selected candidate genes and molecules that reflect the variety of cellular and molecular components actively involved in the pathogenesis of clinically apparent disease (Fig. 3).

Although using such a panel for disease risk stratification remains an objective, monitoring disease activity and pursuing individualized disease prevention are possible outgrowths of this work. In those with known disease, monitoring for evidence of ongoing inflammation, endothelial dysfunction, or platelet activation may help to identify those at higher risk requiring more intensive or more specific therapy to avert future events. Ultimately, real promise may turn out for primary prevention whereby the use of a panel of molecular markers and candidate genes may identify a particular segment of the population at risk for clinically significant CAD, otherwise undetectable. Screening for early evidence of endothelial dysfunction, up-regulation of inflammation, thrombosis, or genetic susceptibility will likely provide a new more precise assessment of risk for future cardiovascular disease beyond traditional clinical risk factors.
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