The innate or natural immune response is the body’s rapid first line of defense for environmental threats (eg, trauma and infection), responding long before an immune defense is mounted. This response involves a series of reactions that have evolved to limit damage, isolate pathogens (noxious agents), and initiate repair processes. Cells distinguish between pathogen and self by using signals from pattern-recognition receptors, scavenger receptors (CD-36, SR-A), and Toll-like receptors (TLRs) on macrophage and dendritic cells. These receptors recognize pathogen-associated patterns in nucleic acids, proteins, carbohydrates, and lipids. Flow-dependent regulation of TLR2 surface expression in endothelial cells and ligation of TLR1, TLR2, and TLR4 in plaque result in recruitment of adaptor protein myeloid differentiation factor 88, followed by activation of nuclear factor-κB and mitogen-activated protein kinases. This results in a cascade of proinflammatory molecules such as interleukin (IL)-6 that drive C-reactive protein (CRP) production, chemokines that act as chemoattractants, and serine proteases that drive thrombosis, all of which contribute to inflammation and pathogen clearance.

Accumulating evidence supports a central role for inflammation in preclinical atherosclerosis, with acute coronary syndrome (ACS) as a principle clinical expression. Indeed, ACS, ischemic brain syndrome (stroke/transient ischemic attack), and peripheral arterial occlusion result from a chronic inflammatory process, as well as disorders of lipid metabolism, modified by genetic and environmental factors. Arterial wall function and structure are modulated by interactions between injurious agents, blood vessel wall elements and monocytes, T lymphocytes, and platelets. Invading mononuclear cells release enzymes (eg, matrix metalloproteinases [MMPs]) that degrade collagen and elastin, thereby allowing cells to invade by disrupting matrix layers that otherwise stabilize developing plaque. Clot forming and inflammatory pathways then work in tandem to accelerate local macrophage and T-cell activation, which contributes to plaque erosion or rupture, forming a surface on which activated platelets may initiate thrombosis and microembolism and perhaps lead to continuing inflammation.

In vulnerable patients, atherosclerosis develops under the influence of conditions that traumatize the endothelium, eg, aging, elevated blood pressure, increased low-density lipoprotein (LDL) cholesterol, obesity, diabetes, smoking, and potentially infections. Inflammation is documented by increased temperature in unstable plaque and an increase in circulating leukocytes consistent with the rubor, calor, and tumor of classic description. Lesion susceptibility is greatest in vascular branches or curvatures with altered hemodynamics (Figure 1C and 1D) where endothelial proliferation, apoptosis, and permeability increase. Expression of adhesion molecules and chemokines facilitates recruitment of macrophages laden with oxidized lipid (foam cells) and weakening of the fibrous cap. Platelet and leukocyte microaggregates at sites of plaque erosion release cytokines and other factors (eg, CD40 ligand [CD40L] and receptor, CRP, local angiotensin II, tissue-type plasminogen activator and inhibitor, IL-1, IL-6, MMPs, chemokines, and cell adhesion molecules) are all important contributors to and/or
markers for inflammatory processes involved in atherothrombosis (Figure 2). What specifically initiates and maintains this inflammation is unclear, but it is intriguing that rates of ACS and stroke/transient ischemic attack increase during acute infections.2,4 Genetic predisposition to accelerated plaque growth and rupture also is under investigation. For example, Asp299Gly polymorphism in human TLR4 impairs signaling,5 and polymorphism in chemokine ligand 2, monocyte chemoattractant protein-1 (MCP-1), and 2578G and CX3CR1 chemokine receptor V249I alleles6 that direct monocyte and T cells to sites of arterial injury are associated with increased cardiovascular (CV) disease. Other recent work has identified high-risk genotypes associated with inflammation and restenosis. The inflammatory mediators discussed above, specifically leukocytes, CRP, IL-1, IL-6, MMPs, MCP-1, plasminogen activator and inhibitor, serum amyloid A, CD40L, tumor necrosis factor alpha,1–4 and a newer marker called LIGHT (lymphotoxinlike inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells), provide sensitive markers for ACS when combined with assessment of risk factors.

Antiinflammatory Actions of Therapies for ACS
The remainder of this review focuses on management strategies for ACS and their influences on inflammation. Each treatment is discussed with reference to a case study of ACS.

Case Study
Mrs C. is a 70-year-old woman admitted to the emergency department complaining of severe retrosternal chest discomfort that radiates to neck and arm with accompanying nausea and dyspnea. Details of clinical findings, treatment, and outcome are outlined in Figure 3.

Antiplatelet and Antithrombotic Therapy
Plaque erosion and rupture release extrinsic coagulation factors, tissue factor, and factor VII and activate platelets that also release inflammatory mediators such as CD40L. Prothrombotic and proinflammatory agents increase in concert with fibrinogen, a mediator of arterial thrombosis, and cardiac troponin, a marker of myocyte damage in ACS. These changes correlate with elevations in CRP.1,2,4 The antiplatelet agents aspirin, which is a cyclooxygenase inhibitor,7 and clopidogrel, which is a thienopyridine adenosine diphosphate receptor antagonist,8 as well as the glycoprotein (GP) IIb/IIIa antagonists9 and low-molecular-weight10 and unfractionated heparins, are beneficial and antiinflammatory in ACS patients. Studies confirming a clear association between inhibition of platelets and thrombosis, inflammation, and long- or short-term prognosis are ongoing. CRP levels are suppressed by aspirin,7 clopidogrel,8 and GP IIb/IIIa antagonists9; CD40L, tumor necrosis factor alpha,1–4 and a newer marker called LIGHT (lymphotoxinlike inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells), provide sensitive markers for ACS when combined with assessment of risk factors.

Figure 1. A and B, Coronary angiography in a patient with ACS/non-STEMI illustrating thrombotic right coronary artery stenosis, bracketed by yellow arrows, before (A) and after (B) stent implant. C through F, Altered blood flow dynamics in an arterial bifurcation phantom (courtesy of Dr David Steinman, Robarts Research Institute, London, Canada) (C) and modified Movat’s pentachrome–stained histological images of carotid arterial plaque buildup at a high-risk carotid bifurcation area (D) with thrombotic and fibrotic plaque (E), as well as an area of hemorrhagic plaque with adjacent fibrous and inflamed regions (macrophage/foam cells, T lymphocytes, apoptosis, and cytokine release) occurring where the fibrous cap region has collagen breakdown and smooth muscle cell apoptosis (F). Movat’s pentachrome stains nuclei and elastic fibers black, collagen and reticular fibers yellow, ground substance and mucin blue, fibrin intense red, and smooth muscle cells red. Th indicates thrombus; F, fibrosis; H, hemorrhage; and I, inflammation.
fit over the long term after PCI; however, clopidogrel and the GP IIb/IIIa antagonists may increase risk of bleeding with bypass surgery.

**Lipid-Lowering Therapy**

Excess lipids, particularly many of the neoepitopes that result from LDL oxidation, are immunogenic and lead to proatherogenic consequences such as endothelial cell dysfunction, thrombosis, and macrophage activation. These events may lead to plaque rupture.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce LDL and plaque progression in coronary arteries, along with risk of CV events.11 Statin use before PCI has the potential to reduce periprocedural myocardial infarction (MI) and improve 1-year survival. Statin-mediated immunomodulation assessed by reduction in inflammatory markers is, in part, independent of the magnitude of lipid lowering, and reduced inflammation may relate to the early benefit observed in ACS. Survival benefit after PCI is associated with reduced CRP levels, and high-dose statins are considered the preferred approach.

Studies using peroxisome proliferator–activated receptor-α (PPARα) agonists (eg, fibrates) have suggested antiinflammatory actions. These agents have antiatherogenic effects in experimental models, and some clinical trials (Veterans Administration HDL Intervention Trial [VA-HIT], Diabetes Atherosclerosis Intervention Study [DAIS])12 have shown a reduction in CV events. Large randomized trials in ACS, however, are lacking.

Additional reduction in lipids with combination therapy has been proposed with ezetimibe and niacin. Ezetimibe blocks cholesterol absorption and augments statin-mediated reduction in lipid and CRP levels, but data are lacking to document clinical outcome benefits. Experimentally, high-density lipoprotein has potent antiinflammatory actions and is increased by statins and high-dose nicotinic acid. A novel therapeutic approach in ACS with intravenous apolipoprotein A1 Milano as a synthetic high-density lipoprotein resulted in rapid resorption of coronary atheroma detected by intravascular ultrasound.13

In our case, there are no contraindications to lipid-lowering therapy, and statins, specifically high-dose statins, are clearly indicated to reduce early inflammation and plaque burden and to improve long-term outcomes.
stroke, and death in patients with (as documented by EURopean trial on re-
duction Of cardiac events with Perin-
dopril in patients with stable coronary Artery disease [EUROPAH] or at high risk for (as shown in the Heart Out-
comes Prevention Evaluation [HOPE] and HOPE–The Ongoing Outcomes [HOPE–TOO]) coronary artery dis-
ease. Angiotensin II drives inflamma-
tion, and ACE inhibitors reduce mark-
ers of inflammation and tissue factor. Associated with decreased mortality and CV morbidity is an early reduction of inflammatory markers, MMPs, IL-6, CRP, and platelet aggregation. Angiotensin receptor blockers provide an efficacy similar to that of ACE inhibitors for hypertension and heart failure with associated decreases in CRP, yet the relevance of CRP reduc-
tion to reduced adverse outcomes re-
mains uncertain. Information on angio-
tensin receptor blockers in ACS is lim-
ited. Aldosterone antagonists (eg, spironalactone, eplerenone) have ben-
efit in hypertension and heart failure early after acute MI with reduced ejection frac-
tion (as shown in the Random-
ized Aldactone (Spironolactone) Eval-
uation Study for Congestive Heart Failure [RALES] and Eplerenone Post-AMI Heart Failure Efficacy and Survival Study [EPHESUS]) and may reduce inflammatory markers. These agents, however, have not yet been examined in randomized trials of ACS patients without heart failure.

Mrs C. has no contraindication to angiotensin II active agents and has hypertension. Findings on physical examination suggest insulin resis-
tance, and she subsequently de-
veloped congestive heart failure. There-
fore, she is likely to benefit from angiotensin II and aldosterone active agents. The degree to which the an-
tiinflammatory actions of inhibitors of the renin-angiotensin-aldosterone system contribute to clinical benefit is unknown. Adding an aldosterone antagonist would have benefit if her heart failure is associated with re-
duced ejection fraction or if she re-
mains hypertensive.

**Antianginals: β-Blockers, Calcium Antagonists, and Nitrates**

Antiatherosclerosis effects have been suggested for all of these antianginal agents in multiple experimental models and some randomized, placebo-
controlled, double-blind clinical tri-
als. How this effect relates to antiinflammation pathways or the doc-
umented reduction in adverse out-
comes in patients with MI, heart fail-
ure, or hypertension with β-blockers is not clear. Observed antiatherogenic ef-
fects of β-blockers could be due to combined central nervous system ac-
tions leading to reduced peripheral sympathetic nerve discharge; hemody-
namic changes caused by reduced heart rate, blood pressure, and contrac-
tility; and biochemical systems leading to increased production of prostacyc-
ins, inhibition of platelet accumula-
tion, decreased affinity of LDL to pro-
teoglycans, decreased endothelial injury, and even inhibition of renin.

Most calcium antagonists have anti-
oxidant effects and reduce experimen-
tal inflammatory cell invasion. In re-

cions of inflamed atheroma, nitric oxide levels are low, leading to re-
duced vasodilatation; conversely, ex-
cess nitric oxide can form highly re-
active peroxynitrite. Dihydropyridine-
type calcium antagonists increase nitric oxide, block lipid peroxidation, and may be associated with reduction in CV events.

**Therapeutic Approaches to Diabetes, Insulin Resistance, and the Metabolic Syndrome**

Poor glycemic control is closely asso-
ciated with increased inflammation and a range of clinical events such as MI, stroke, hypertension, hyperlipid-
emias, and renal failure. Weight loss and improved glu-
cose control are cornerstones of treat-
ment, reducing microvascular but not necessarily macrovascular complica-
tions. This remains one of the more difficult long-term challenges.

Some newer glycemic control agents target PPARγ, improve insu-
lin resistance, and reduce inflamma-
tion and reperfusion injury after MI or stroke/transient ischemic attack. Evidence from observational, exper-
imental, and surrogate outcome stud-
s suggests these agents reduce macrovascular complications in type 2 diabetes, and several trials are testing this hypothesis. Prospective Piogli-
tazone Clinical Trial in Macrovascular Events (PROactive), the first to be reported, found that pioglitazone re-
duced the composite outcome all-
cause mortality, MI, or stroke with beneficial trends across all CV out-
comes except heart failure and edema. Other studies indicate that these agents also reduce CRP, MMP-9, and MCP-1 while reducing plaque progression in patients with-
out diabetes, independently of glyce-
mic control. More studies are needed in patients with and without diabetes to fully characterize the mechanism of benefit.

Our patient with diabetes would be a candidate for a PPARγ agonist, but her heart failure is a relative contraindication because of the risk of fluid retention.

**PCI and Coated Stent Implants**

PCI is frequently used in ACS to reperfusion patients with STEMI, control angina, and avert progression to vas-
cular occlusion in some cases. Al-
though vascular trauma from PCI de-

...
PCI of the right coronary artery stenosis in Mrs C. is certainly a reasonable approach, given her recent unstable symptoms.

Newer Experimental Treatments

Many new approaches aimed at inhibiting inflammation are under investigation. One pilot study using the cyclooxygenase-2 inhibitor meloxicam in ACS suggested evidence for benefit in clinical outcomes and reduction in inflammation, but more randomized trials are needed, especially in view of concerns about increased risk of CV events with nonsteroidal antiinflammatory drugs. Other early clinical approaches include the MPP inhibitors and more unique approaches such as endothelial progenitor cells or viral antiinflammatory proteins that can target chemokines and serine proteases or act as IL10 agonists.

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