Adjunctive Pharmacotherapy before Percutaneous Coronary Intervention in Non-ST-Elevation Acute Coronary Syndromes: The Role of Modulating Inflammation

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Abstract—Vascular inflammation is central to the pathogenesis of acute coronary syndromes (ACS) and the response to vascular injury after percutaneous coronary intervention (PCI). For both ACS and PCI, the magnitude of vascular inflammation is linked to adverse late clinical outcomes (e.g., death, recurrent myocardial infarction [MI] or ischemia, and restenosis). Many pharmacologic therapies with demonstrated efficacy for the treatment of ACS have anti-inflammatory properties, which are distinct from their perceived primary mechanism of action. The anti-inflammatory effects of aspirin, clopidogrel, low-molecular-weight heparin (LMWH), platelet glycoprotein (GP) IIb/IIIa receptor inhibitors, statins, and angiotensin converting enzyme (ACE) inhibitors are reviewed, and the hypothesis is generated that modulation of vascular inflammation at least in part contributes a common basis for the long-term clinical benefit ascribed to these medications. A therapeutic algorithm based on clinical risk stratification and coronary revascularization strategy is proposed for incorporating the current American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommendations for treatment of patients who present with non-ST-elevation ACS. (Circulation. 2003;108[suppl III]:III-22-III-27.)

Key Words: inflammation ■ angioplasty ■ pharmacology

Inflammation is central to the pathogenesis of atherothrombotic vascular events and thus, to ACS. As such, systemic markers of inflammation, such as C-reactive protein (CRP), have been correlated with both the presence and prognosis of non-ST-elevation ACS. The prevalence of elevation in high-sensitivity (hs) CRP depends on the clinical syndrome. Elevation in hs-CRP has been observed in <10% of normals, <20% of patients with stable angina, >65% of patients presenting with unstable angina (UA), <50% with MI who do not experience an UA prodrome, and >90% of patients with MI who have experienced an UA prodrome. CRP elevation is most marked in those patients with UA who experience a major adverse cardiovascular event (death, MI, or urgent revascularization).

Patients with non-ST-elevation ACS who have elevated CRP levels and who undergo PCI have an increased incidence of death or nonfatal MI to 6 months post-PCI compared with patients who have normal CRP levels. Indeed, marked elevation in CRP level before early revascularization for non-ST-elevation ACS predicts mortality to 5 years’ follow-up. Elevation of systemic CRP levels has been correlated with neutrophil activation, and reflects a generalized inflammatory arteritis. Recent three-vessel intravascular ultrasound study of patients presenting with non-ST-elevation ACS demonstrated that 80% of these patients have at least one detectable plaque rupture that is distinct and separate from the “culprit” lesion, which prompted their admission. In 71% of cases, the additional plaque ruptures were observed in “nonculprit” vessels.

Thus, patients with ACS have a multicentric, multivessel, generalized inflammatory process. From this perspective, the central “culprit” in the pathogenesis of ACS is macrophage infiltration of plaque. Indeed, the extent of macrophage infiltration of atherosclerotic plaque parallels coronary disease acuity (Figure 1).

Percutaneous Revascularization with Coronary Stenting

The majority of patients who undergo PCI for non-ST-elevation ACS have coronary stent deployment. The inflammatory response to coronary stenting in humans has demonstrated a prevalence of lymphocyte/macrophage infiltration both early and late during the sequence of thrombus formation, inflammation, and neo-intimal proliferation (Figure 2). Indeed, neo-intimal macrophage content has been directly correlated with subsequent in-stent restenosis. Depletion of the monocyte/macrophage pool with lysosomal chlodronate has been demonstrated to reduce neo-intimal proliferation after carotid balloon angioplasty in the hypercholesterolemic rabbit. These data suggest a central role for the macrophage in mediating the arterial response to injury. The time course of the inflammatory response to stent deployment, as reflected by elevation in CRP, demonstrates peak levels at 48–72 h after stent deployment. Elevation in CRP to >0.5 mg/dL at 72 h after stenting is associated with a higher subsequent occurrence of death, MI, or recurrent angina.
In patients with CRP levels >0.5 mg/dL at 72 h after stenting, the administration of anti-inflammatory therapy with prednisone has been demonstrated in a placebo-controlled randomized trial to improve event-free survival, and to reduce restenosis and late lumen loss by quantitative coronary angiography. Although this single trial will need to be replicated before it can be regarded as definitive, these data suggest that in patients who have a marked inflammatory response to coronary stent deployment, modulation of the inflammatory response with a potent anti-inflammatory agent may be effective in reducing neointimal proliferation and subsequent clinical/angiographic events.

Therapies for Non-ST-Elevation ACS

Many of the therapies with demonstrated efficacy for the treatment of non-ST-elevation ACS have anti-inflammatory properties (Figure 3). For example, the ACC/AHA 2002 guideline update for the treatment of UA identifies aspirin as a Class I indication, which should be administered as soon as possible after presentation and continued indefinitely (Level of Evidence A). In addition, clopidogrel should be administered to patients who are unable to take aspirin or in whom an early noninterventional approach is planned. Clopidogrel may also be given to those patients for whom PCI is planned and who are not at high risk for bleeding.

Both of these “antiplatelet” therapies, aspirin and clopidogrel, also possess anti-inflammatory effects. In low-density lipoprotein (LDL) receptor-deficient mice, low-dose (80 mg) aspirin administration is associated with marked reduction in the macrophage content of atherosclerotic plaque and suppression of inflammatory cytokine (intercellular adhesion molecule 1, membrane cofactor protein 1, and tumor necrosis factor α) production. These laboratory observations are supported by the clinical observation of a ~60% reduction in the relative risk of MI for those patients in the highest quartile of plasma CRP level versus a 14% reduction in risk for patients in the lowest quartile. Together, these observations suggest that at least a portion of the clinical benefit ascribed to aspirin may be secondary to its anti-inflammatory effects.

Similarly, in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, administration of clopidogrel in combination with aspirin versus aspirin alone reduced the cumulative occurrence of cardiovascular death, MI, or requirement for urgent target vessel revascularization in patients who presented with ACS and who subsequently had PCI. Interestingly, the effect of clopidogrel pretreatment on reduction in death or MI after coronary stent deployment is greatest for those patients in the highest quartile of serum CRP. Clopidogrel pretreatment has been demonstrated to suppress platelet inflammatory markers (CD62 and sCD40L) and to attenuate the rise in CRP that follows PCI. A recent CURE trial substudy demonstrated no differences in either markers of platelet activation (CD62 and von Willebrand factor) or coagulation (F1.2 and D-dimer) between patients randomly assigned to treatment with aspirin plus clopidogrel versus aspirin alone (plus placebo). This observation suggests both the need for more potent antithrombotic therapies in patients with ACS and that anti-inflammatory effects of clopidogrel, which are not explained by platelet inhibition, may contribute to the clinical benefit attributed to this agent.

Anticoagulation

The ACC/AHA 2002 UA guideline update gives anticoagulation with subcutaneous LMWH or intravenous unfractionated heparin (UFH) (added to antiplatelet therapy with aspirin and/or clopidogrel) a Class I recommendation (Level of Evidence A). A Class IIa recommendation is given to...
enoxaparin specifically as being preferable to UFH as an anticoagulant in patients with UA/non-ST-elevation MI in the absence of renal failure and unless coronary artery bypass surgery is planned within 24 h. The superiority of enoxaparin versus UFH in medically treated patients was demonstrated in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and Thrombolysis In Myocardial Infarction (TIMI) 11B randomized clinical trials of patients with non-ST-elevation ACS. The anticoagulation properties of enoxaparin with respect to the relative anti-factor Xa versus anti-factor IIa activities are well appreciated. However, enoxaparin has also been demonstrated to have anti-inflammatory effects on neutrophil-platelet interactions and complement activation.

In a randomized comparison with UFH, enoxaparin suppressed elastase and C5b9 elevation in response to simulated extracorporeal circulation.\textsuperscript{23} In addition, enoxaparin enhances tissue factor pathway inhibitor release and subsequent nitric oxide production.\textsuperscript{24} These anti-inflammatory properties of enoxaparin may work in concert with its anticoagulant effects to provide the preferential clinical benefit that was observed after enoxaparin administration to those patients who had PCI in the TIMI 11B/ESSENCE (TESSMA)-PCI meta-analysis.\textsuperscript{25} This meta-analysis evaluated the proportion of patients who underwent PCI in these predominately medically oriented trials. Patients who underwent PCI while receiving enoxaparin (versus UFH) had a marked reduction in the composite occurrence of death or nonfatal MI at 1-year follow-up (13\% UFH versus 5\% enoxaparin; \textit{P}=0.005). Furthermore, patients who underwent PCI “in hospital” and who were subsequently analyzed by their randomly allocated pharmacologic treatment regimen also manifested a highly significant reduction in the composite occurrence of death or nonfatal MI to 1 year in favor of enoxaparin (12\% UFH versus 6\% enoxaparin; \textit{P}=0.003).

The relative benefit of enoxaparin versus UFH has also been demonstrated in conjunction with aspirin and platelet GP IIb/IIIa inhibitor therapy by the Integrin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial.\textsuperscript{26} In INTERACT, patients with non-ST-elevation ACS received therapy with aspirin and intravenous eptifibatide. Patients were randomly allocated to either subcutaneous enoxaparin or intravenous UFH (dose titrated based on target activated partial thromboplastin time measurements 1.5–2\times control). After 48 h of pharmacotherapy, patients were eligible to undergo revascularization as clinically indicated. Enoxaparin therapy was associated with significant reductions in the incidence of major nonsurgical bleeding, ischemic events by continuous ECG monitoring, and in the composite occurrence of death or nonfatal MI to 30 days. The ongoing Superior Yield of the New strategy of Enoxaparin, Revascularization GIlycoprotein IIb/IIIa inhibitors (SYNERGY) and the Aggrestat to Zocor (A to Z) trials should definitively establish the role of enoxaparin versus UFH therapy for patients with non-ST-elevation ACS in whom an “invasive” treatment strategy is elected. In A to Z, patients with non-ST-elevation ACS received therapy with aspirin and tirofiban, and were randomly assigned to treatment with either subcutaneous enoxaparin (1.0 mg/kg every 12 h) or weight-adjusted intravenous UFH. The primary endpoint of A to Z (composite occurrence of death, MI, or refractory ischemia to 7 days after enrollment) was observed in 8.4\% of enoxaparin-treated patients and 9.4\% of UFH-treated patients. The primary hypothesis of A to Z, that enoxaparin is not inferior to UFH, was met, and all of the composite endpoints trended in favor of enoxaparin, particularly for higher-risk patients.\textsuperscript{27}

**Adjunctive Platelet GP IIb/IIIa Inhibitor Therapy**

The ACC/AHA 2002 UA guideline update recommends that “eptifibatide or tirofiban should be administered in addition to aspirin and LMWH or UFH to patients with continuing ischemia, with an elevated troponin, or with other high-risk features in whom an invasive management strategy is planned (Level of Evidence A).”\textsuperscript{15} Furthermore, a platelet GP IIb/IIIa antagonist should be administered to patients in whom catheterization and PCI are planned, and the GP IIb/IIIa antagonist may be administered at the time of PCI (Level of Evidence B). Indeed, the “upstream” administration of platelet GP IIb/IIIa inhibitor therapy is associated with a lesser degree of clinical benefit in the absence of early coronary revascularization.\textsuperscript{28}

A meta-analysis of 31,402 patients enrolled in six placebo-controlled, randomized trials of platelet GP IIb/IIIa inhibitor therapy administration for non-ST-elevation ACS demonstrated an 8.5\% relative reduction (11.5\% placebo \textit{versus} 10.7\% GP IIb/IIIa; \textit{P}=0.005) in death or nonfatal MI to 30 days. None of the individual trials showed a dramatic benefit, and the majority of the treatment effect occurred in those who went to early percutaneous intervention and those with an elevated troponin level.\textsuperscript{29} Whereas it appears that there was little benefit of GP IIb/IIIa inhibitor therapy in patients not undergoing PCI, it is important to note that almost half of the differences between GP IIb/IIIa and placebo groups occurred in the period before coronary intervention.\textsuperscript{30} Simply comparing those who had an intervention to those who did not is an inappropriate subgroup analysis because patients who die before intervention are counted in the medical group, and clinical events may precipitate interventions so that the censoring is informative (biased). A trial randomizing patients to immediate small-molecule GP IIb/IIIa inhibitor or delayed administration at the time of PCI would be required to provide a definitive answer to this debate.

Administration of platelet GP IIb/IIIa inhibitor therapy at the time of PCI is associated with a substantial clinical benefit in patients with ACS and those with stable angina. Indeed, abciximab has potent, direct, and sustained anti-inflammatory effects as demonstrated recently in a retrospective analysis of the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial angioplasty cohort.\textsuperscript{31} Patients randomly assigned to abciximab had significant suppression in both interleukin (IL) 6 and CRP levels at 48 h after PCI when compared with those patients who received placebo treatment. No evidence of rebound or re-elevation in levels of inflammatory cytokines was observed to 4 weeks after PCI. The durability of abciximab’s anti-inflammatory effects may be ascribed both to redistribution pharmacokinetics and to nonplatelet GP IIb/IIIa receptor affinity.\textsuperscript{32} Double-bolus intravenous eptifibatide in the
dose regimen utilized by the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrelin Therapy (ESPRIT) trial has been demonstrated to suppress IL6, CRP, and sCD40L during the time course of drug infusion.\textsuperscript{33,34} The durability of anti-inflammatory effect for this dose regimen of eptifibatide is uncertain as suggested by the observation of recurrent CRP elevation within 24 h of eptifibatide discontinuation.\textsuperscript{35} Indeed, longer durations of eptifibatide infusion (>22 h) have been reported to provide greater clinical benefit than shorter duration (<16 h) infusions.\textsuperscript{35}

A recent systematic overview of GP IIb/IIIa therapy administered at the time of PCI demonstrated a mortality benefit at 30 days, 6 months, and longer-term follow-up without significant heterogeneity.\textsuperscript{36} Heterogeneity was assessed as a function of trial, clinical indication (acute MI versus nonacute MI), and use of postprocedure heparin. However, only abciximab therapy (intravenous bolus and 12-h infusion) at the time of PCI has adequate outcome data to demonstrate a survival advantage in long-term (1–3 years) follow-up as an individual agent.\textsuperscript{37} A 22% relative reduction in mortality (6.4% placebo \textit{versus} 5.0% abciximab; \(P=0.030\)) was observed in a pooled analysis of \textasciitilde 6000 patients enrolled in placebo-controlled randomized trials of abciximab administration during PCI.\textsuperscript{37} Clinical benefit in late follow-up was most marked in those patients who presented with ACS. Interestingly, it appears that both clinical risk (composite occurrence of death or nonfatal MI) as well as the relative benefit of abciximab (\textit{versus} placebo) therapy may be predicted by the magnitude of elevation (quintile) in soluble CD40L, a marker of inflammation. Patients in the highest quintile of sCD40L had the greatest risk for adverse events and demonstrated the greatest benefit of abciximab therapy.\textsuperscript{38}

Although this clinical benefit may in part be ascribed to the demonstrated anti-inflammatory effect of abciximab as noted previously, a “cytoprotective” action of abciximab has been defined recently.\textsuperscript{39} Macrophage infiltration of plaque is directly associated with monocyte colony stimulating factor (MCSF) production. Thus, clusters of macrophages and MCSFs are in juxtaposition with vascular smooth muscle cells, which reside in the overlying cap of the plaque. Activated macrophages, in conjunction with MCSF, appear to mediate vascular smooth muscle cell death (apoptosis) through a mechanism modulated by the CD11b/CD18 (MAC1) receptor.\textsuperscript{39} Indeed, the addition of abciximab in physiological concentrations confers a protective effect (reduction in smooth muscle cell killing) similar to that observed after the administration of CD18, a human monoclonal antibody to the MAC1 receptor. The addition of eptifibatide or tirofiban in physiological concentrations (“pure” GP IIb/IIIa receptor inhibitors) provides no benefit with respect to smooth muscle cell preservation. Thus, the potential plaque stabilizing effect of abciximab on preserving smooth muscle cell content appears to be mediated by its affinity for the MAC1 receptor and is distinct from its platelet GP IIb/IIIa blocking effect. Abciximab inhibition of CD11b/CD18 receptor expression after PCI has been demonstrated.\textsuperscript{40} These observations are consistent with the results of postmortem exams, which have demonstrated that atherosclerotic plaques, which are etiologic in causing sudden cardiac death or MI, have an abundance of monocyte/macrophage infiltrate and are depleted in vascular smooth muscle cells.\textsuperscript{41}

**New Insights on Statin Therapy**

Recent data have demonstrated that an anti-inflammatory effect of statin therapy as reflected by CRP levels is evident early after administration and appears to be independent of cholesterol lowering effects. A significant reduction in CRP was observed within 14 days of simvastatin administration \textit{(versus} placebo) and was independent of the LDL lowering effect of this medication.\textsuperscript{42} Similarly, a significant increment in ischemic events (death or nonfatal MI) was observed within 15–30 days of discontinuing statin therapy in patients who presented with ACS.\textsuperscript{43} This “rebound” in ischemic events after statin withdrawal was also independent of cholesterol levels. The very early effect of statin therapy on the inflammatory response to coronary stenting as reflected by CRP levels at 24–48 h after coronary stent deployment has been reported recently.\textsuperscript{44} Patients who had never received statin therapy had the most marked inflammatory response to stenting as compared with those patients who had been receiving statins for 6 months before PCI. Remarkably, those patients who received atorvastatin 80 mg orally beginning at the time of stent deployment and daily thereafter (not previously statin treated) also manifested suppression in CRP levels over the subsequent 48 h. This observation is consistent with experimental data in the animal model (rat mesenteric venule) that simvastatin has an immediate inhibitory effect on leukocyte adherence, rolling and transmigration provoked by \textit{Staphylococcus aureus} α toxin.\textsuperscript{45} In these experiments, statin treatment was associated with an early (within 18 h) increment in endothelial cell nitric oxide synthase expression, a potent anti-inflammatory mediator. Similarly, a direct (white blood cell) anti-inflammatory effect of simvastatin was also demonstrated by a reduction in early (7 days) leukocyte accumulation and a reduction in neointimal area at 28 days after balloon angioplasty in LDL receptor-deficient mice.\textsuperscript{46} Thus, both basic science and clinical observations support the presence of direct anti-inflammatory effects of statin therapy that appear to be separate and distinct from cholesterol lowering.

These observations may have clinical relevance. For example, patients pretreated with statins before undergoing PCI have been demonstrated to have a reduction in periprocedural MI,\textsuperscript{47} as well as inhospital\textsuperscript{48} and long-term (6–12 months) mortality.\textsuperscript{49,50} The late (1-year) survival advantage attributable to statin therapy after coronary stent deployment is most evident for patients in the higher quartile of preprocedural CRP level.\textsuperscript{51} The benefit of statin therapy initiated early after presentation for ACS is being evaluated in the prospective, randomized A to Z trial mentioned previously. This trial should provide insight into the use of statins (simvastatin) as an acute pharmacologic intervention for ACS.

**ACE Inhibitor Therapy**

Treatment with ACE inhibitors has been associated with a reduction in the requirement for revascularization after coronary stent deployment.\textsuperscript{52} Interestingly, although ACE inhibitors are associated with a marked early reduction in serum
ACE activity, they also modulate inflammatory cytokine levels. Serum levels of tissue factor are reduced within 3–7 days of ACE inhibitor therapy. This likely reflects an anti-inflammatory effect of ACE inhibitors on macrophage and smooth muscle cells, as coronary tissue factor content is strongly correlated with both macrophage and smooth muscle cell areas in plaque tissue obtained from patients with UA. In fact, the relationship between tissue factor and macrophage areas in plaque from these patients is linear \((r = 0.98; P < 0.0001)\).

**Recommendations for Therapy**

In patients who present with non-ST-elevation ACS, therapy should be initiated with aspirin, LMWH, statin, ACE inhibitor, nitrates, and \(\beta\)-blockade. Clopidogrel therapy may be initiated at the time of presentation or may be deferred until coronary angiography and definition of coronary anatomy (Figure 4). Based on clinical risk stratification (positive serum troponin, ST-segment shift, TIMI risk score \(\geq 3\), recurrent/refractory ischemia, congestive heart failure, or prior revascularization), patients should be triaged to early coronary angiography to define the coronary anatomy. If the coronary anatomy is suitable for PCI, an intravenous GP IIb/IIIa inhibitor and oral clopidogrel loading dose may be administered immediately before PCI. The administration of clopidogrel before the definition of coronary anatomy may complicate early surgical coronary revascularization. At Christ Hospital in Cincinnati, OH, the Medicare database from January 1996 through June 2002 was queried for patients with a discharge diagnosis of UA/non-Q-wave MI. Notably, 20–27\% of those patients have undergone surgical coronary revascularization during their initial hospitalization. Furthermore, the preprocedural hospital length of stay for patients undergoing PCI for UA has fallen to \(<8\text{ h}^\text{.57}\). Although clopidogrel administration reduced the composite occurrence of death, MI, stroke, or severe recurrent ischemia within 24 h of enrollment into the PCI-CURE trial, in many United States institutions the coronary anatomy of high-risk patients can easily be defined within 12 h of presentation. Clopidogrel administration before coronary bypass surgery has been associated with an increased incidence of transfusion, blood product exposure, and a 10-fold increase in reoperation for bleeding.\textsuperscript{58}

Of note, the ACC/AHA guidelines also allow for early (“upstream”) administration of either clopidogrel or small-molecule GP IIb/IIIa inhibitors as a Class I indication. However, our practice (Ohio Heart Health Center) at Christ Hospital is to withhold clopidogrel until visualizing the coronary anatomy because of concern about operative bleeding in patients who need bypass surgery. We also prefer to administer abciximab at the time of PCI because it has the most convincing data in support of clinical benefit including enhanced survival.

**Conclusions**

Vascular inflammation is an underlying central mechanism determining coronary disease activity and the response to vascular injury (PCI or stenting). Most pharmacotherapies that are effective in improving outcomes for non-ST-elevation ACS and PCI have anti-inflammatory properties that are distinct from their perceived primary mechanisms of action. Coronary angiography should be performed early in patients presenting with non-ST-elevation ACS based on clinical risk stratification. Treatment with clopidogrel and platelet GP IIb/IIIa inhibitors can and should be initiated at the time of coronary angiography based on coronary anatomy and revascularization strategy.\textsuperscript{55,56}

**References**

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