REVIEW

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME

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ABSTRACT

The high prevalence of heart disease puts many Americans at risk for an acute coronary attack. Their likelihood of survival will depend upon the extent and severity of their coronary artery disease. Current understanding of atherosclerosis suggests that the disease begins early in life and progresses until clinical symptoms develop. Inflammation caused by the presence of chronic disease or modifiable risk factors is increasingly viewed as an important mechanism of atherosclerotic disease progression. Inflammation is implicated in arterial plaque formation, plaque rupture, and clot formation during subclinical and symptomatic coronary events. Patients who have had an acute coronary attack often do not receive evidence-based treatments. Studies of treatment for acute coronary syndrome have reflected suboptimal adherence to treatment guideline recommendations and differences in adherence to guidelines by facility type. Although it is unclear whether increased adherence to treatment guidelines alone will reduce in-hospital mortality rates from acute coronary syndrome, increased adherence to guideline recommendations coupled with improved health profiles may have a beneficial effect on patient outcomes. (Adv Stud Pharm. 2006;3(3):100-105)

Heart disease is the major cause of death in the United States. Many Americans with heart disease will present at the hospital with an acute coronary syndrome (ACS) that will put them at significant risk of death and morbidity. Although timely and appropriate treatment reduces the risk of an immediate or subsequent poor outcome, the high prevalence of risk factors for coronary artery disease (CAD) ensures that the prevalence of future ACS will also be high. Unfortunately, the prevalence of risk factors is stratified by economics, education level, and cultural differences, among other factors, which puts patients who may be least likely or the least able to seek skilled care at the most risk for poor outcomes.

The presence of multiple risk factors increases the risk of developing CAD. However, theories of atherosclerotic plaque formation have changed such that cholesterol is no longer the lone culprit in CAD. Inflammation is increasingly implicated in the initiation and progression of atherosclerotic plaques. Plaques have been shown to develop early in life and remain subclinical for years or decades, depending on the accelerating effects that risk factors and genetic predisposition to CAD will have on disease progression. This article reviews the pathophysiology of ACS and identifies areas of need that, if addressed, may help reduce the high rate of morbidity and mortality in patients presenting with ACS.

Epidemiology

According to the American Heart Association (AHA), 71.3 million Americans had some form of cardiovascular disease (CVD) in 2003. CVD was responsible for nearly 1 million deaths in 2003 and is projected to result in $403.1 billion in direct and indirect healthcare costs in 2006. Among Americans with CVD, 13.2 million are estimated to have CAD, which
is responsible for the majority of deaths attributed to CVD (Figure 1).

ACS is a manifestation of CAD that encompasses acute myocardial infarction (AMI) and unstable angina (UA), the dangerous middle ground between stable angina and myocardial infarction. The AHA estimates that 700,000 Americans will have their first coronary event in 2006, and 500,000 will have a recurrent event. Although the death rate from CAD has been declining since 1950, approximately 40% of Americans who experience a coronary event this year will die as a result. For those who experience a recurrent coronary event, the risk of death is 4 to 6 times that of the general population.

Mortality in patients with AMI has been observed to increase for each 30 minutes that passes before appropriate intervention. Timely treatment upon presentation contributed to the reduced in-hospital mortality (11.2% to 9.4%) observed in the 1990s, and “median door-to-drug time” was reduced by nearly 50% for patients requiring thrombolytic therapy.

Despite efforts to improve patient management, there is no evidence suggesting that the risk of developing CAD is declining. The INTERHEART study, for example, found that 9 modifiable risk factors accounted for 90% of first AMIs. A 2003 Centers for Disease Control and Prevention study of adults showed that the prevalence of respondents with 2 or more CVD risk factors correlated with increased age, lower levels of education, and lower levels of income. Prevalence also varied according to psychosocial factors, race, and state of residence. African Americans and Native Americans had the highest prevalence of multiple risk factors at >46%, whereas Asian Americans had the lowest prevalence at <26%. Approximately 26% of college graduates had multiple risk factors, whereas more than 50% of those who did not complete high school had multiple risk factors. Respondents with a household income of $50,000 or greater had a 29% prevalence of multiple risk factors, whereas more than 50% of respondents with a household income of $10,000 or less had multiple risk factors. Disabled respondents reported approximately a 70% prevalence of multiple risk factors compared with only 34% of those who were homemakers or employed.

Winkleby et al reported health profiles among young adults who were 18 to 24 years old that were particularly alarming. Between 1990 and 2000, this group showed large increases in the prevalence of smoking and obesity with corresponding low rates of physical activity and fruit and vegetable intake. The high prevalence of major modifiable CVD risk factors among young Americans is expected to exacerbate the healthcare crisis anticipated to follow the aging of the baby boomers. It is estimated that 40 million Americans will be age 65 or older by 2010. Coupled with the increased prevalence of obesity and diabetes across age groups, the aging population and poor health profiles among young adults are driving an increase in CVD and the most potent risk factors for poor cardiovascular outcomes, such as hypertension and dyslipidemia.

PATHOPHYSIOLOGY

PLAQUE FORMATION

The accumulation of atherosclerotic plaques is no longer considered to be the simple result of cholesterol storage. Inflammation is increasingly implicated in plaque formation. At the cellular level, plaque accumulates in response to many signals that cause blood cells, such as monocytes, to adhere to the endothelium of the arterial lumen. Inflammatory responses to insults such as bacterial toxins, in addition to traditional risk factors, such as dyslipidemia, hypertension, hyperglycemia, and obesity, can initiate monocyte adherence. Once adhered to the endothelium, monocytes migrate into the vascular wall to the arterial intima, the muscular layer closest to the vessel lumen. At this point, they transform into macrophages and begin to ingest the...
modified lipoprotein particles, which accumulate in the intima naturally and at an accelerated rate in people with hyperlipidemia. These lipid-filled macrophages are also known as foam cells, which are the hallmarks of atherosclerotic plaques. Foam cells typically come together to form a plaque within the intima. Many foam cells die by apoptosis, disintegrate with debris becoming membrane-bound, and then are eliminated by phagocytosis or by shedding. The original modified lipoproteins, macrophages, foam cells, and apoptotic debris, in addition to other important factors, such as collagen and von Willebrand factor, form the core of the plaque (Figure 2).7

**PLAQUE PROGRESSION**

Ultrasound studies have shown that atherosclerotic plaques are widely distributed in the coronary arteries and that these plaques begin to form early in life.8,9 Therefore, atherosclerotic plaques only become clinically evident when they gain enough bulk to obstruct coronary circulation, often resulting in stable angina, or they become physically disrupted and form an acute clot at the site, resulting in UA or AMI (Figure 3). Studies using serial observations by angiography have suggested that plaque progression is not a linear process and more likely occurs as the result of physical disruption of plaques.

Many patients who present with ACS will have more than 1 disrupted plaque that may have become symptomatic through several mechanisms.10 First, erosion of the epithelial monolayer, separating the intima from the vessel blood flow, can produce a thrombus by exposing collagen and von Willebrand factor—factors that promote platelet aggregation (one of the first steps in thrombus formation).11 Endothelial monolayer erosion can be initiated by cell death or subendothelial basement membrane (a supportive layer that exists in between the endothelium and elastic lamina in the intima) degradation. Inflammatory activation of T cells subjects the endothelial cells to attack in addition to local signaling that may increase apoptosis.12 Secondly, plaque growth also results from intraplaque hemorrhages. Inflammatory cells within the plaque promote angiogenesis (the creation of new blood vessels that will deliver nutrients to the plaque) by secreting mediators.13 These small, fragile new vessels are prone to rupture. Thrombin production upon rupture stimulates the release of platelet-derived growth factor and transforming growth factor beta, which are potent stimulants for smooth muscle growth, further increasing plaque bulk.14 A third mechanism of plaque growth occurs when a plaque's fibrous cap tears, permitting contact between the plaque core and circulating coagulation factors in the blood. Inflammatory mediators, such as interferon-gamma, inhibit new collagen production necessary to maintain cap integrity, weakening the cap.7 In addition to the decreased collagen production, exist-
ing collagen is usually weakened because collagenases are overexpressed in plaque tissue. These mechanisms leave the fibrous cap of many plaques vulnerable to physical insult. If this vulnerability results in a microtear, a small subclinical thrombus may be formed, reabsorbed into the plaque, and then covered by additional fibrous tissue that is stimulated to grow by the release of platelet-derived growth factor and transforming growth factor beta. This process results in a bulky, fibrous plaque instead of a fatty plaque. If the tear exposes a substantial amount of the plaque’s prothrombotic core, a large, fatal acute thrombus may result.

**THROMBUS FORMATION**

Disrupted plaques allow contact between the blood and collagen, which activates platelets. The tissue growth factors produced by macrophages and smooth muscle cells also initiate coagulation. Platelet activation results in the transformation of the glycoprotein IIb/IIIa receptors on the platelets. These receptors are vital to thrombus formation because they are the sites where fibrinogen connects, enabling a “mesh” or “aggregation” of platelets to grow, and initiating thrombus formation. These mechanisms work in conjunction to produce the interlinked, aggregated platelets that are the hallmarks of the coronary thrombus. Clot formation is augmented in the presence of factors that inhibit natural fibrinolytic action. Plasminogen-activating inhibitor-1 levels are increased in patients with conditions that predispose them to CAD, such as diabetes and hypertension. This fibrinolytic inhibitor weakens the body’s natural defense against clot formation and increases the potential for thrombi to form larger, more damaging occlusions.

**IMPROVING OUTCOMES**

Although ACS is a major cause of morbidity and mortality among patients with CVD, these patients often do not receive treatment with therapies that have been shown to improve outcomes. Studies that followed the 1996 American College of Cardiology (ACC)/AHA clinical practice guidelines for the evaluation and treatment of ST-elevation myocardial infarction (STEMI) showed poor patient outcomes that were associated with underutilization of recommended therapies, such as aspirin, beta blockers, and fibrinolytic agents. Although the use of evidence-based therapies appears to be on the rise, their utilization in eligible patients is not optimal, and in-hospital mortality is still high following STEMI.

Effective therapies for non-ST-elevation myocardial infarction (NSTEMI) and UA are also underutilized, although their use did increase between 1990 and 2002. Part of this underutilization may be attributed to the complex diagnosis of NSTEMI/UA, which involves risk stratification based on the clinical presentation, multiple test results, and patient history. The recent ACC/AHA guidelines recommend stratifying patients to high, moderate, or low risk, according to various factors, and the guidelines recommend different treatment strategies based on the level of risk. Despite the existence of treatment guidelines—which have been evolving over the past 10 to 12 years—in-hospital mortality rates remain high for these patients.

Clinical trials such as GUSTO-IIb, GRACE, and GAP have investigated the relationship between adherence to treatment guidelines and outcomes for patients with ACS. GUSTO-IIb studied adherence to the Agency for Health Care Policy and Research practice guidelines (the first published guidelines on ischemic management that preceded those by the ACC and AHA) for UA. The study assessed the use of aspirin, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers at discharge in patients with NSTEMI/UA who had no contraindications to treatment with these agents. Table 1 shows the percentages of patients with indications who received the guideline-recommended treatment at discharge. GUSTO-IIb found a similar rate of aspirin use, a lower rate of calcium channel blocker use, and a higher rate of beta-blocker use than in the TIMI III Registry. However, the difference in actual and recommended use of these agents could not be explained by the number of contraindications to treatment in

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**Table. Discharge Medication Use in the United States for Patients Without Contraindication**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Use</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
<td>83.9%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>58.7%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>54.6%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

this population. GUSTO-IIb suggests suboptimal adherence to treatment guidelines for patients with NSTEMI/UA, especially in patients who had no contraindication to recommended therapy.

The GRACE study assessed adherence to treatment guidelines during hospitalization and at discharge for patients presenting with ACS. Analysis of therapy use according to diagnosis reflected that aspirin use in patients with STEMI and NSTEMI/UA was consistent with guideline recommendations. Beta blockers were used in a high percentage of patients with UA, and low–molecular-weight heparins were used in a high percentage of patients with NSTEMI, consistent with guideline recommendations. However, the use of unfractionated heparin was still high, regardless of diagnosis, despite clinical evidence that low–molecular-weight heparins are more effective at relieving ischemia.

However, some treatment differences were observed when the GRACE data were stratified according to hospital type and the availability of an on-site cardiac catheterization laboratory. The use of percutaneous coronary intervention, glycoprotein IIb/IIIa inhibitors, calcium channel blockers, statins, beta blockers, antiplatelet therapies, and anticoagulants was higher in teaching hospitals and facilities with a catheterization laboratory ($P < .01$), whereas the use of low–molecular-weight heparins was lower in these facilities. The GRACE study showed that treatment guidelines for ACS are more likely to be followed at teaching hospitals and at facilities that perform cardiac catheterizations. This difference in adherence likely reflects the higher concentration of skilled cardiologists who would be expected to practice at more specialized facilities. Despite differences in treatment according to facility type, no differences in mortality rates were observed.

The GAP study measured the effects of a quality improvement initiative on adherence to treatment guideline recommendations at hospital admission and discharge for patients with ACS. Overall, the study reflected increased use of aspirin and beta blockers at admission and an increase in smoking cessation counseling at discharge ($P < .05$). The use of standard admission orders for AMI improved early administration of aspirin and early measurement of low-density lipoproteins ($P < .005$). Similarly, the use of an AMI standard discharge form increased the use of aspirin and/or beta blockers, smoking cessation counseling, dietary counseling, and cholesterol-lowering therapy ($P < .05$). These data suggest that standardized care delivery systems for patients presenting with ACS can improve adherence to evidenced-based treatment recommendations.

**CONCLUSIONS**

The prevalence of poor health profiles ensures that many Americans will develop clinically apparent atherosclerosis and that a large percentage of these patients will present with ACS at the hospital. Atherosclerotic plaques develop and progress through the complex interaction between the cellular-level insults that result from CVD risk factors and the body's inflammatory response to those insults. Although ACS is a major cause of morbidity and mortality, effective therapies are currently underused. The diagnosis of UA is complicated and may serve as a barrier to appropriate treatment. Underuse of effective treatments is thought to be at least partly responsible for the high rate of in-hospital mortality from ACS.

Studies of adherence to treatment guidelines for patients with NSTEMI/UA, such as GUSTO-IIb, have found suboptimal adherence to recommended therapies, especially in patients who had no contraindications to these treatments. The GRACE study found differences in adherence to treatment guidelines between teaching hospitals and facilities with catheterization laboratories compared with nonteaching hospitals and less specialized clinics. The GAP study found that the use of standard admission orders and standard discharge forms could increase the use of evidence-based treatment in patients with ACS.

However, as the GRACE study suggested, increased adherence to treatment guidelines does not necessarily translate to lower in-hospital mortality. This unfortunate outcome is likely the result of many factors that will require a multifaceted approach to correct. First, the trend toward poor health profiles among the young needs to be quickly reversed. Second, preventive healthcare for people who are most at risk of ACS needs to be aggressively pursued by the patients and healthcare professionals. Third, evidence-based treatment guidelines need to be more strictly adhered to at all healthcare facilities. The use of standard admission and discharge tools that reflect evidence-based treatment can improve adherence to guideline recommendations. With these improvements in prevention and treatment, it may be possible to reduce mortality rates from ACS.
REFERENCES


