Are We Putting the Cart Ahead of the Horse: Who Determines the Standard of Care for the Management of Patients in the Emergency Department?

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In this issue of *Annals of Emergency Medicine*, Gibler et al[1] present an excellent summation of the 2002 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the initial management of patients with non–ST-segment elevation acute coronary syndromes. However, it is concerning that clinicians (and unfortunately lawyers) may equate some of the "class I" therapy recommendations for the "emergency department (ED) management" of acute coronary syndrome patients presented in this article with an established "standard of care" that is evidence based, which is not the case.

To put the ACC/AHA summary document in perspective, it is necessary to briefly review the methodology used in generating its recommendations. In the past, management recommendations were often developed that were based primarily on expert opinion and generally accepted as gospel even when there was no, or limited, supporting evidence. The limitations of this approach have been recognized by the scientific community as potentially perpetuating not only misinformation but at times even dangerous actions. Examples of the pitfalls implicit to consensus recommendations abound and include the use of calcium in the management of ventricular fibrillation, digoxin in acute decompensated heart failure, theophylline in acute asthma, military antishock trousers in hypotensive trauma patients, and hyperventilation in the management of severe traumatic brain injury. These are all treatments once supported by the experts and that have since been shown to either be of no benefit or dangerous. With recognition of the potential dangers inherent to consensus recommendations, evidence-based methodology requires that strong recommendations be based on the presence of strong evidence (ie, well-designed research that specifically addresses the question being asked). In other words, in therapeutics, the highest-level recommendations (levels "A," "I," "standard") require supporting evidence from randomized double-blind placebo-controlled studies with little or no bias. Consequently, there are few "level I," "level A," or "standard" recommendations in evidence-based literature. Most guideline methodologies do not allow opinion to drive a high-level recommendation no matter how strong a consensus exists with the experts; without evidence, nothing higher than the lowest level (level "III," "C," or "option") recommendation can be made.[2-4]

The ACC/AHA uses an unusual methodology that allows for a "class I" recommendation for therapeutics to be made based on "general agreement that a given procedure or treatment is useful and effective."[1] In other words, a high-level recommendation can be assigned to a treatment that has limited or no supporting research on its benefit if the "experts" deem it appropriate. This approach is surprising because it is counter to the evidence-based-medicine methodologies used by almost every other guideline development group. More concerning, this approach can mislead the unsuspecting reader into thinking that an intervention with an ACC/AHA class I (c) rating has strong evidence backing its recommendation, unless knowledgeable that the "c" stands for consensus.

In contrast to the ACC/AHA classification, the American College of Emergency Physicians (ACEP) and most other organizations believe that consensus opinion should never drive a class I, or even a class II, recommendation. ACEP uses an evidence-based system that has 3 levels of recommendation: A, B, and C.[5] Level A recommendations reflect generally accepted principles for patient management that reflect a high degree of clinical certainty based on the available evidence. Level B recommendations reflect management strategies based on moderate degree of clinical certainty, and level C recommendations reflect other strategies based on preliminary, inconclusive, or conflicting evidence or, in the absence of any published literature, based on panel consensus. It is important to recognize that the strength of evidence of individual studies used in creating an ACEP level of recommendation is highly dependent on whether the study directly addresses a particular management strategy as it applies to the ED. Thus, a large randomized controlled trial of a particular therapy may be a class I study when graded on its own merit but may be downgraded to a class II or class III study, depending on whether it addresses treatment in the ED as opposed to the inpatient or outpatient setting.

The summarization published in this month's *Annals* uses ACC/AHA evidence grading with the implication that what is a

class I ACC/AHA recommendation during the initial treatment phase of patients hospitalized with acute coronary syndrome translates into a class I recommendation for the treatment of these patients in the ED. In that many of the studies that support the high-level recommendation did not specifically examine ED populations, caution must be exercised in extrapolating to ED practice.

It is accepted that the emergency physician should aggressively manage ongoing chest pain and ischemia with aspirin, heparin, nitrates, and β-blockers. The literature also supports the use of angiotensin-converting enzyme inhibitors, clopidogrel, glycoprotein IIb/IIIa inhibitors, and other therapies in the initial management of hospitalized patients with acute coronary syndrome. However, evidence for initiation of many of these treatments in the ED is lacking and awaits further evidence before classifying these treatments as "class I" and making them standards of care in ED management.

In regard to ACC/AHA class I recommendations for the use of angiotensin-converting enzyme inhibitors, clopidogrel, and glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndrome, evidence for a treatment benefit from initiating these drugs in the ED is lacking. For angiotensin-converting enzyme inhibitors, there is absolutely no evidence that treatment initiated in the ED provides additional benefit compared to initiation in the inhospital setting and thus could never achieve higher than a "level C" ACEP recommendation. Gibler et al[1] share this sentiment in that they state "angiotensin-converting enzyme inhibitor initiation in the ED is appropriate; however, it does not necessarily need to be started in this setting."

For clopidogrel treatment, studies have demonstrated a benefit in high-risk acute coronary syndrome patients medically managed, as well as in patients undergoing early percutaneous intervention (PCI). The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial[6] demonstrated a reduction in the composite primary outcome of cardiovascular death, myocardial infarction, or stroke at 12 months in high-risk acute coronary syndrome patients randomized to receive clopidogrel within 24 hours of symptom onset. Benefit was seen within 24 hours of initiation of therapy and persisted throughout the ensuing 12 months.[7] Analysis of treatment benefit curves revealed the possibility of divergence in outcome as early as 4 hours after initiation of therapy, which does suggest that treatment should be initiated as soon as possible. However, no data are available for initiation of treatment in the ED versus inhospital, nor are any data available for initiation of therapy as a function of time of symptom onset. Furthermore, the median time to PCI in the PCI-CURE substudy[8] was 6 days (10 days if PCI after initial hospital stay was included), which is inconsistent with therapeutic strategies at PCI centers in the United States. The Clopidogrel for Reduction of Events During Observation (CREDO) study[9] demonstrated a trend for improved outcome in patients who receive the clopidogrel loading dose greater than 6 hours before PCI. However, it should be kept in mind that the CREDO population was undergoing elective PCI, and these findings may not be generalizable to the ED acute coronary syndrome population. Furthermore, the ED physician, who as of yet does not have access to a crystal ball, is faced with the dilemma of the mutually exclusive ACC/AHA class I recommendations to administer clopidogrel to acute coronary syndrome patients and to withhold clopidogrel 5 days before coronary artery bypass graft. In high-risk acute coronary syndrome patients who potentially are at risk for urgent coronary artery bypass graft surgery, clopidogrel treatment in the ED should be used cautiously until coronary anatomy has been defined. Pending further studies, it is premature to impose a class I recommendation for clopidogrel treatment as part of the ED management of acute coronary syndrome patients.

For glycoprotein IIb/IIIa inhibitors, it is clearly established that a benefit is seen in acute coronary syndrome patients undergoing early intervention and in select subgroups of patients medically managed. However, the optimum timing or location for initiation of therapy has not been clearly established. Subset analysis of the PURSUIT trial (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Supression Using Integrelin Therapy)[10,11] suggests that there is an incremental benefit of early administration of glycoprotein IIb/IIIa inhibitors in patients presenting at 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours from symptom onset, whereas subset analysis of the Platelet Receptor Inhibition in Ischemic Syndromes Management Trial[12] showed no such treatment benefit. Until results of the EARLY ACS (EARLY glycoprotein IIb/IIIa inhibition in non–ST-segment evaluation Acute Coronary Syndrome) trial are available, it also is premature to suggest that initiation of glycoprotein IIB/IIIa inhibitors by ED physicians is a class I recommendation.

In conclusion, assigning a class I classification to a treatment modality has significant implication to the practicing ED physician. Although it can be agreed that aggressive management of acute coronary syndrome with angiotensin-converting enzyme inhibitors, clopidogrel, glycoprotein IIb/IIIa inhibitors, and other newer treatments may represent best clinical practice for select subgroups of patients, it is imperative that class I recommendations for the practicing ED physician be based on evidence that directly addresses ED management and not on consensus opinion or on evidence that addresses only the inpatient or outpatient setting. Let us not put the cart before the horse and burden the ED physician with adhering to standards of care that are not yet clinically proven. Pending future studies that may help clarify these issues, appropriate use of these therapies in the ED should be based on institutional protocols or consensus created from a collaboration of ED physicians, primary care providers, cardiologists, and cardiothoracic surgeons.

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