Delineating Potential Roles for Pharmacists in the Management of Acute Coronary Syndromes

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Acute coronary syndrome (ACS) is an umbrella term that includes unstable angina (UA) and acute myocardial infarction (AMI), both ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI).[1,2] ACS originates from the erosion or rupture of an unstable plaque within the coronary artery, which sets off a cascade resulting in the formation of an occlusive or nonocclusive thrombus.[3]

Despite advances in medical interventions such as percutaneous coronary intervention (PCI) and pharmacotherapy, cardiovascular disease still results in significant morbidity and mortality in the United States. According to the American Heart Association (AHA), ACS accounts for more than 733,000 hospital discharges (approximately 80% of these cases are either UA or NSTEMI, and about 20% are STEMI).[4] One-third of patients with STEMI die within 24 hours of onset of ischemia, and 15% of those with UA/NSTEMI either die or experience a reinfarction within 30 days of hospitalization.[5] Financially, ACS is exorbitantly expensive, costing Americans more than $150 billion annually.[5] Based on the findings from a multiemployer claims analysis for the time period 2001 to 2002, the mean length of hospitalization for a patient with ACS was 4.6 days, with a cost of approximately $23,000 per capita.[6] The analysis also showed that nearly 20% of patients with ACS are rehospitalized within 1 year and approximately 60% of the costs related to ACS are due to rehospitalization. Although these statistics appear dismal, mortality from ACS appears to be decreasing, which can be attributed in part to application of evidence-based pharmacotherapies.[7,8]

Based on data from the CRUSADE National Quality Improvement Initiative, which tracks guideline adherence, facilitates process improvement, and improves

health outcomes for patients with ACS, adherence to evidence-based guidelines remains imperfect, and significant variation in quality of care exists among hospitals nationwide.[9] From the standpoint of pharmacotherapy, the CRUSADE data suggest that care gaps exist for all major treatments but are most notable for use of glycoprotein (GP) IIB/IIIA inhibitors, clopidogrel, and lipid-lowering therapy. For every 10% increase in the overall composite guideline adherence at a hospital, there exists a 10% reduction in the overall risk for death at that hospital (adjusted odds ratio [OR], 0.90; 95% confidence interval (CI), 0.84-0.97; *P*<0.001).[10] Data from the GRACE (Global Registry of Acute Coronary Events) study also demonstrate that increased use of guideline-recommended pharmacotherapies in patients with ACS is associated with fewer adverse cardiac events and deaths.[11]

With this in mind, pharmacists within inpatient settings are uniquely positioned to impact the care of patients with ACS. With access to a patient's complete medical record and medication regimen, pharmacists can recommend pharmacotherapies based on risk stratification, evaluate and document whether a patient has received guideline-based pharmacotherapies, and provide patient-specific discharge counseling.

TIMI Risk Score: Using Risk To Your Advantage

Immediately on admission, patients with ACS should be evaluated and stratified with respect to risk for death and reinfarction, based on presenting signs and symptoms, past medical history, and echocardiogram (ECG) and cardiac biomarker changes. The first risk stratification method, introduced by Killip et al in 1967, was found to be a useful, convenient tool for early risk stratification for patients with STEMI.[12] Higher Killip class was found to be associated with increased in-hospital and 1-year mortality (Table 1). Since that time, many risk stratification tools have been developed and validated, such as the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk score and the GRACE risk score.[13] However, the most commonly used method for risk stratification has been the Thrombolysis in Myocardial Infarction (TIMI) risk score, which was introduced in 2000 and can be used to stratify risk in patients with either STEMI or UA/NSTEMI.[14,15] The TIMI risk score is a means of integrating all of a patient's clinical factors and markers into a comprehensive risk stratification tool. Table 1 summarizes the TIMI risk score,[16] and electronic versions for STEMI and UA/NSTEMI also are available at http://www.mdcalc.com/timi-risk-score-for-uanstemi and http://www.mdcalc.com/timi-risk-score-for-stemi.

For patients with STEMI, the higher the risk score, the greater the 30-day mortality rate. For UA/NSTEMI, TIMI scores of 5 to 7, 3 to 4, and 0 to 2 reflect a high, medium, and low risk for death, MI, or need for urgent coronary artery revascularization, respectively. A low-risk patient with negative cardiac biomarkers may undergo a noninvasive stress test or be discharged from the emergency department (ED) with further diagnostic testing scheduled for the near future. Moderate- to high-risk patients often are admitted to a coronary intensive care unit or cardiac step-down floor. Patients at high or moderate risk who have positive cardiac biomarkers should receive early coronary angiography within 12 to 24 hours of admission and possible revascularization if a coronary artery thrombosis or stenosis is detected. Moderate-risk patients with negative biomarkers may receive angiography with revascularization or undergo a noninvasive stress evaluation.

Case Study: Applying TIMI Scores

For example, suppose a 67-year-old man presented to the ED with chest tightness and shortness of breath. He gave a history of similar symptoms that lasted 20 minutes the prior day. He was given aspirin, intranasal oxygen, atorvastatin (Lipitor, Pfizer), metoprolol, and IV nitroglycerin; at that time, his blood pressure was 100/60 mm Hg, and his heart rate was 88 beats per minute. His ECG continued to show ST segment depression in the anterior leads and he had negative cardiac biomarkers. His past medical history was significant for coronary artery disease (CAD), hyperlipidemia, diabetes, and hypertension, and he smoked one pack of cigarettes daily. Based on his presentation, this patient was diagnosed with UA. Using the TIMI Risk Score for UA/NSTEMI, he had a risk score of 5 based on his age (1 point); at least 3 risk factors for CAD (1 point), prior CAD history (1 point), and ST segment deviation (1 point). Based on this TIMI risk score, this patient was at high risk for death and AMI, and had a high need for urgent coronary artery revascularization. Additionally, this patient would have received an invasive rather than a conservative approach to management, meaning that he would have proceeded directly to angiography and PCI.

The TIMI risk score can help direct treatment, particularly for patients with UA/NSTEMI. For example, the 2007 American College of Cardiology (ACC)/AHA guidelines recommend beginning anticoagulant therapy for all patients (without contraindications) as soon as possible after presentation.[17] The guidelines recommend 4 options: unfractionated heparin (UFH), enoxaparin, fondaparinux (Arixtra, GlaxoSmithKline), and bivalirudin (Angiomax, The Medicines Co; approved only for patients managed according to an invasive strategy such as PCI).

In the TIMI-11B trial, compared with UFH (70 U/kg bolus, followed by 15 U/kg per hour for 3-8 days), enoxaparin (30 mg IV bolus followed by 1 mg/kg subcutaneously twice daily for 8 days) reduced the composite end point of death, MI, or need for urgent revascularization at 8 days (*P*=0.048) and 43 days (*P*=0.048).[18] Based on subanalyses of this study, the benefit of enoxaparin appears to be greatest for high-risk subgroups, such as those with ST segment deviation, elevated troponins, and a high TIMI risk score (eg, ≥5).[14,18,19]

In patients with UA/NSTEMI, several large trials have demonstrated that the GP IIB/IIIA inhibitors are of benefit

Table 1. Risk Evaluation Using the TIMI Risk Score

TIMI Risk Score[a]	
NSTEMI	
Risk Factor	**No. of Points**
Age ≥65 y	1
≥3 risk factors for CAD[b]	1
Prior history of CAD[c]	1
Aspirin use in past 7 d	1
≥2 anginal events in past 24 h	1
ST segment deviation ≥0.5 mm	1
Elevation of cardiac markers[d]	1
STEMI	
Risk Factor	**No. of Points**
Age 65–74 y	2
Age ≥75 y	3
SBP <100 mm Hg	3
Heart rate >100 beats/min	2
Killip class II–IV (see box)[e]	2
Weight <67 kg	1
History of HTN, diabetes, or angina	1
Time to reperfusion therapy >4 h	1
Anterior ST segment elevation or left bundle branch block	1

Killip Class		
Class	**Symptoms**	**In-hospital and 1-y Mortality, %**
I	No heart failure	5
II	Mild heart failure, rales, S3, congestion on chest radiograph	21
III	Pulmonary edema	35
IV	Cardiogenic shock	67

[a] TIMI risk score data from references 14 and 15. A risk score is calculated by adding the total number of risk factors. Total points for STEMI are 0 to 14, in which risk scores of 0, 2, 4, 6, 7, and >8 correspond to a 30-day mortality rate of 0.8%, 2.2%, 7.3%, 16%, 23%, and 36%, respectively. Total points for NSTEMI are 0 to 7, in which scores of 0 or 1, 3, 5, and 7 correspond to a 3%, 5%, 12%, and 19% risk for death or repeat MI at 14 days, respectively.

[b] Risk factors include smoking, diabetes, HTN, family history of CAD, and hypercholesterolemia.

[c] Defined as a prior coronary stenosis ≥50%; history of previous MI, PCI, or CABG; or chronic stable angina pectoris associated with a positive exercise tolerance test or pharmacologically induced nuclear imaging or echocardiographic changes (positive nuclear imaging or echocardiographic changes required if female).

[d] Either troponin I or T or CK-MB.

[e] Killip class data from reference 12.

CABG, coronary artery bypass graft; **CAD,** coronary artery disease; **CK-MB,** creatine kinase-myocardial band; **HTN,** hypertension; **MI,** myocardial infarction; **NSTEMI,** non–ST segment elevation myocardial infarction; **PCI,** percutaneous coronary intervention; **SBP,** systolic blood pressure; **STEMI,** ST-segment elevation myocardial infarction; **TIMI,** thrombolysis in myocardial infarction

Modified from reference 16.

Table 2. 2008 ACC/AHA ACS Performance Measures

Quality Performance Measure	Measure Description
Aspirin at arrival	AMI patients who receive aspirin within 24 h before or after hospital arrival.
Aspirin prescribed at discharge	AMI patients who are prescribed aspirin at hospital discharge.
Statin at discharge	AMI patients who are prescribed a statin at hospital discharge.
β-blocker prescribed at discharge	AMI patients who are prescribed a β-blocker at hospital discharge without contraindications.
Evaluate LVSF	AMI patients with documentation that LVSF was evaluated during hospitalization or is planned after discharge.
ACE inhibitor or ARB for LVSD	AMI patients with LVSD, defined as an ejection fraction of 40% or less, who are prescribed an ACE inhibitor or ARB at hospital discharge.
Time to fibrinolytic therapy	AMI patients with STEMI or LBBB on the ECG should receive fibrinolytic therapy within 30 min of arrival at the hospital.
Time to PCI	AMI patients with STEMI or LBBB on the ECG should receive primary PCI within 90 min of arrival at the hospital.
Reperfusion therapy	AMI patients with STEMI or LBBB on ECG performed closest to arrival receiving either fibrinolysis or primary PCI or who are transferred to another facility for primary PCI.
Time from ED arrival at STEMI referral facility to ED discharge from STEMI referral facility in patients transferred for primary PCI[a]	In centers where PCI is not available on-site, patients may be transferred to another facility for treatment. Because delayed PCI may not be as beneficial as timely fibrinolysis, opting for transfer for PCI rather than fibrinolysis requires that transfer be performed in a timely manner.
Time from ED arrival at STEMI referral facility to primary PCI at STEMI receiving facility among transferred patients[a]	In centers where PCI is not available on-site, patients may be transferred to another facility for treatment. Because delayed PCI may not be as beneficial as timely fibrinolysis, opting for transfer for PCI rather than fibrinolysis requires that transfer be performed in a timely manner.
Smoking cessation advice/counseling	AMI patients with a history of smoking cigarettes who are given smoking cessation advice or counseling during the hospital stay.
Cardiac rehabilitation patient referral from an inpatient setting	All patients hospitalized with a primary diagnosis of AMI referred to an early outpatient cardiac rehabilitation program.

for patients considered high risk, those undergoing PCI, or both.[20,21] Patients who obtain the greatest advantage from these agents are those who have elevated troponins, diabetes, ST segment changes, recurrent angina, or a TIMI risk score of 4 or higher at presentation.[22-26] The 2007 ACC/AHA guidelines recommend that for patients with UA/NSTEMI who will be treated with an invasive initial strategy, either a GP IIB/IIIA inhibitor—abciximab (ReoPro, Lilly), eptifibatide (Integrilin, Schering), or tirofiban (Aggrastat, Medicure Pharma)—or clopidogrel (Plavix, Bristol-Myers Squibb) should be added to aspirin and anticoagulant therapy before diagnostic angiography is performed. The guidelines also state that considering use of both a GP IIB/IIIA inhibitor and clopidogrel is reasonable. Although not part of the guidelines, ticagrelor (Brilinta, AstraZeneca) was approved as an alternative to clopidogrel for reducing thrombotic cardiovascular events in patients with ACS in July. Unlike with other agents, with ticagrelor, aspirin doses should not exceed 100 mg per day because this can reduce the drugs effectiveness.

Based on our patient case and his TIMI risk score, this patient would be a candidate for enoxaparin and a GP IIB/IIIA inhibitor, as long as he does not have contraindications to either therapy.

Performance Measures: Applying and Documenting Evidence-based Guidelines

Since around 2000, there has been an enhanced acknowledgment that implementation of the ACC/AHA

Test Measure	Measure Description
LDL cholesterol assessment[a]	AMI patients with documentation of LDL cholesterol concentration in the hospital record or documentation that the LDL cholesterol testing was conducted during the hospitalization or is planned after discharge.
Excessive initial heparin dose[a]	AMI patients who receive excessive dosing of UFH initially.
Excessive initial LMWH dose[a]	AMI patients who receive excessive subcutaneous dosing of a LMWH initially.
Excessive initial GP IIB/IIIA dose[a]	AMI patients who receive excessive dosing of abciximab (ReoPro, Lilly), eptifibatide (Integrilin, Schering), or tirofiban (Aggrastat, Iroko) initially.
Clopidogrel prescribed at discharge for medically treated AMI patients[a]	Medically treated AMI patients who are prescribed clopidogrel (Plavix, Bristol-Myers Squibb), prasugrel (Effient, Lilly), or ticlopidine at hospital discharge.
Presence of an anticoagulation dosing protocol for ACS[a]	Presence of a protocol or other clinical aid (eg, nomogram, electronic order entry) in the hospital record of AMI patients that addresses dosing of anticoagulant therapy and parenteral antiplatelet agents (ie, UFH, LMWH, GP IIB/IIIA inhibitors)
Presence of an anticoagulant medication error tracking system[a]	Evidence of a tracking system for identifying dosing errors in anticoagulation therapy in the hospital record of AMI patients.

ACC, American College of Cardiology; **ACE,** angiotensin-converting enzyme; **ACS,** acute coronary syndrome; **AHA,** American Heart Association; **AMI,** acute myocardial infarction; **ARB,** angiotensin receptor blocker; **ECG,** eclectrocardiogram; **ED,** emergency department; **GP,** glycoproetin; **LBBB,** left bundle branch block; **LDL,** low-density lipoprotein; **LMWH,** low-molecular-weight heparin; **LVSD,** left ventricular systolic dysfunction; **LVSF,** left ventricular systolic function; **NSTEMI,** non-ST segment elevation myocardial infarction; **PCI,** percutaneous coronary intervention; **STEMI,** ST segment elevation myocardial infarction; **UFH,** unfractionated heparin

[a] New measure

Adapted from reference 29.

guideline recommendations for ACS can result in lower patient morbidity and mortality. These cardiovascular metrics, also referred to as quality core measures, evaluate the quality of care provided to patients with ACS and focus only on the strongest recommendations from the ACC/AHA guidelines. Performance measures, a subset of these core measures intended to be publicly reported to allow consumers to make more informed choices, are compared between institutions, and are used by third-party payers in pay-for-performance considerations.[27] For example, Medicare uses these performance measures when comparing hospitals.[28] Test measures, also known as candidate measures, are quality measures that do not meet the criteria for a performance measure but can be used by hospitals for quality improvement programs.

As seen in Table 2, the STEMI and UA/NSTEMI performance measures were revised by the ACC/AHA in 2008.[27] These measures, which are endorsed by multiple organizations such as the Leapfrog Group, the National Quality Forum, the Joint Commission, the Agency for Healthcare Research and Quality (AHRQ), and the American Public Health Association, are designed to ensure effective, timely, safe, efficient, and patient-centered medical care. The majority of these performance measures revolve around providing appropriate drug therapy, such as antiplatelet, β-blocker, statin, and angiotensin-converting enzyme inhibitor therapy, as well as smoking cessation programs.[29] For a hospital to receive credit for meeting these performance measures, it must document each measure as being met or document why the measure was not met in the patient's chart. Inpatient pharmacists can play a critical role in quality improvement within their health systems by

participating on protocol/guideline writing committees, anticoagulation subcommittees, and medication safety committees; assisting with design of computer order-entry sets; and facilitating and documenting implementation of these performance measures.

Providing Counseling: Targeting the 'Smoking' Gun

It is not surprising that smoking is associated with at least a 1.5- to 3-fold increased relative risk for MI due to its effects on coronary perfusion, myocardial oxygen demand, and thrombosis.[30-33] Recent data have suggested that smoking cessation after an AMI may be associated with as much as a 50% reduction in mortality after 1 to 3 years.[33-35] Mortality reduction is apparent within a few months and diminishes with time, with the risk for reinfarction approaching that of nonsmokers by 3 years of cessation.[31] As mentioned above, smoking cessation has been identified as an important performance measure for ACS, and the US Public Health Service guidelines highlight the importance of initiating smoking cessation treatments in hospitalized patients. However, many patients do not receive optimal smoking cessation counseling while they are in the hospital, which results in a missed opportunity for an intervention.[36]

In many hospitals, nurses or respiratory therapists may provide smoking counseling; however, pharmacists are well trained to provide this type of counseling. Beginning on the day of admission, inpatient pharmacists can obtain from the patient a complete history of tobacco use; discuss reasons/motivation to quit; elucidate triggers for tobacco use; highlight concerns about weight gain, withdrawal and relapse; set a quit date; refer patients for counseling support; and provide pharmacologic assistance. The AHRQ publishes an excellent resource for clinicians involved with smoking cessation at all levels of the care continuum.[37]

Conclusion: Taking It to the Next Level

Within inpatient health systems, pharmacists are the unsung heroes when it comes to the management of patients with ACS. Through their involvement with risk stratification and pharmacotherapy implementation, evaluation and documentation of performance core measures, and provision of comprehensive smoking cessation counseling at the bedside, pharmacists can expand their current roles and help improve the care of patients with ACS.

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