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Review

Does timing matter? Upstream or downstream administration of antiplatelet therapy

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Abstract Current treatment guidelines recommend an early, aggressive strategy in patients with non–ST-elevation acute coronary syndromes. Administration of antiplatelet therapy—a glycoprotein IIb-IIIa inhibitor with or without clopidogrel—before catheterization in patients with high-risk features confers substantially reduced risk of ischemic events while potentially increasing bleeding risk. Strategies for risk stratification are therefore important in the emergency department, with appropriate pharmacotherapy. This review will examine implications of the new guidelines for management of patients with unstable angina/non–ST-elevation myocardial infarction for emergency physicians, review current risk stratification paradigms, and evaluate appropriate use and timing of administration of glycoprotein IIb-IIIa inhibitors and clopidogrel for patients at varying levels of risk. We will also examine mechanisms for generating institutional care pathways that can enhance consistency and quality of care as well as communication among members of the medical team responsible for caring the patient with acute coronary syndrome.

1. Introduction

The pathogenesis of acute coronary syndromes, as well as the many complications arising from percutaneous coronary interventions, primarily results from coronary thrombosis; thus pharmacologic therapy to prevent periprocedural thrombotic complications is an integral part of treatment for these patients. Through their treatment choices, emergency physicians' decisions play a pivotal role in mitigating the thrombotic effects of the patient's diseased coronary vessels. The concept of "upstream" (before diagnostic angiography) advanced (beyond aspirin) platelet therapy to confer antipatient protection in the cardiac catheterization laboratory may not be fully appreciated by emergency physicians; however, this protection represents an important component of the acute treatment of patients with acute coronary syndrome. Despite evidence indicating that an early, aggressive treatment strategy improves outcomes in this patient population, especially in the precatheterization laboratory environment, adherence to guidelines recommending the use of advanced antiplatelet therapies remains low for the patients who are most likely to benefit from them, that is, those with high-risk features at presentation [1].

This article will examine the implications of the new American College of Cardiology/American Heart Association guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction. We will also review current risk stratification paradigms, with an emphasis on balancing risk for bleeding against risk for ischemic events. This will include evaluation of the evidence for and against the use of platelet glycoprotein

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IIb-IIIa inhibitors and clopidogrel, in terms of both appropriateness for patients at varying levels of risk and timing of administration. In addition, where detailed recommendations from the guidelines are lacking, we will examine mechanisms for generating institutional care pathways that can enhance consistency and quality of care as well as communication among various members of the medical team.

2. The new American College of Cardiology/American Heart Association guidelines for management of unstable angina/non–ST-segment-elevation myocardial infarction

The latest iteration of the American College of Cardiology/American Heart Association guidelines, released in August 2007, contains substantial and significant changes that shift treatment paradigms for acute coronary syndrome patients. Current algorithms for management using an invasive or conservative strategy are illustrated in Figs. 1 and 2 [2], respectively.

2.1. Risk stratification recommendations

The new guidelines place greater emphasis on the importance of risk stratification. All patients who present with chest discomfort or other ischemic symptoms should undergo early evaluation for risk of cardiovascular events, with a focus on history (eg, anginal symptoms), physical findings, electrocardiographic findings, and cardiac biomarkers [2]. Of critical importance, a 12-lead electrocardiographic should be performed as soon as possible after arrival in the emergency department (ED), preferably within 10 minutes of admission, and serial electrocardiographics at 15- to 30-minute intervals should be performed in patients in whom the initial electrocardiographic is not diagnostic. Troponins should be measured in all patients with chest discomfort consistent with acute coronary syndromes and should be repeated within 8 to 12 hours after symptom onset among patients who have negative cardiac biomarkers within 6 hours of the onset of symptoms. The guidelines also note that the use of risk stratification models (discussed later) can assist with clinical decision making.

2.2. Antiplatelet therapy recommendations

As with previous guidelines, aspirin should be administered to unstable angina and non–ST-segment-elevation myocardial infarction patients as soon as possible [2]. Clopidogrel (loading dose, 300 mg, followed by daily maintenance dose, 75 mg) is indicated in patients who are unable to take aspirin due to intolerance or hypersensitivity.

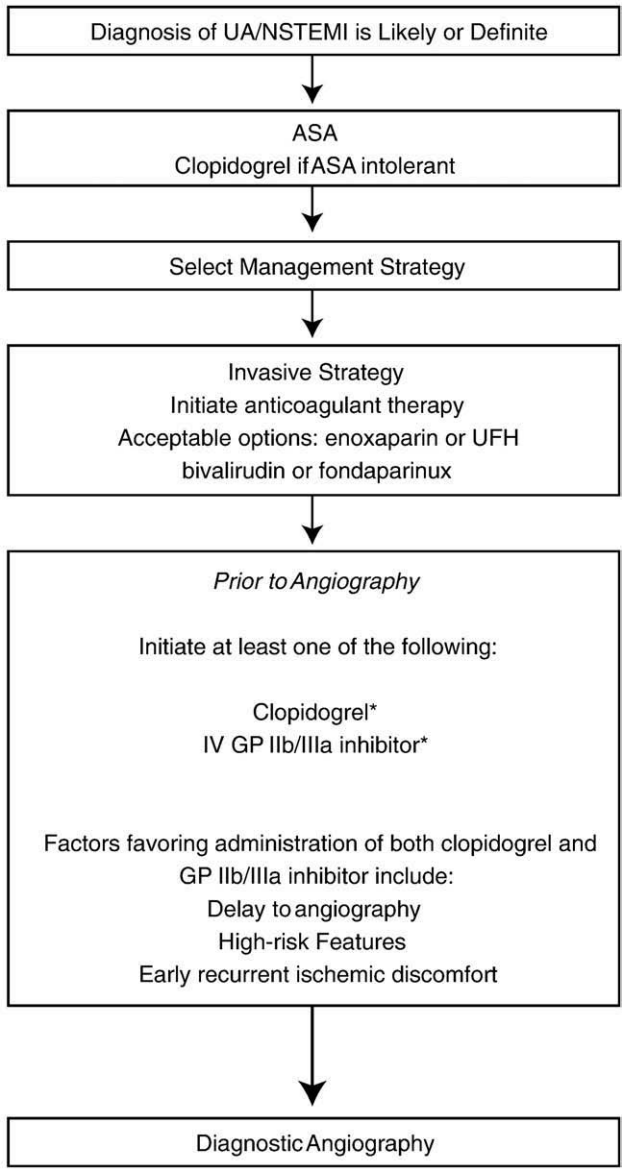

Fig. 1 Algorithm for patients with unstable angina and non–ST-segment-elevation myocardial infarction managed by an initial invasive strategy [2] (adapted from Anderson et al [2], with permission from the American College of Cardiology). *Evidence exists that glycoprotein IIb-IIIa inhibitors may not be necessary if the patient received a preloading dose of >300 mg clopidogrel at least 6 hours earlier, and bivalirudin has been selected as the anticoagulant. ASA indicates aspirin; GP, glycoprotein; IV, intravenous; US/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Among patients qualifying for an initial invasive strategy, defined in the guidelines as "diagnostic angiography with intent to perform revascularization," administration of clopidogrel and/or a glycoprotein IIb-IIIa inhibitor should be initiated before diagnostic angiography (class 1A recommendation). Due to the increased risk of bleeding during major surgery in patients receiving clopidogrel, the guidelines recommend that clopidogrel should not be

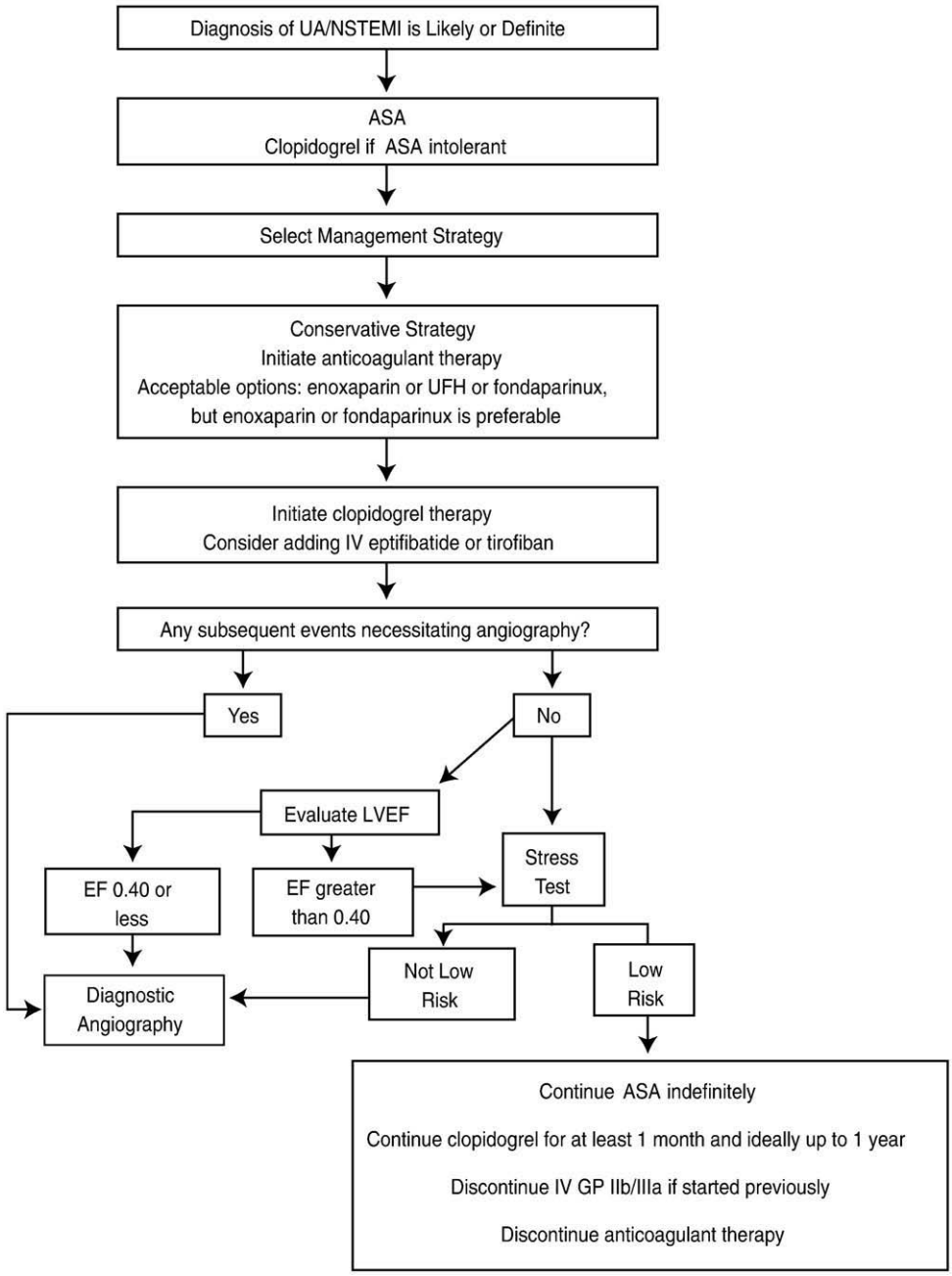

Fig. 2 Algorithm for patients with unstable angina and non–ST-segment-elevation myocardial infarction managed by an initial conservative strategy [2] (adapted from Anderson et al [2], with permission from the American College of Cardiology). Abbreviations are explained in Fig. 1.

administered for at least 5 days before surgery in patients in whom elective coronary artery bypass grafting is anticipated. The guidelines recommend initial upstream clopidogrel when angiography is delayed [2]. (See our discussion of clopidogrel in patients undergoing coronary artery bypass grafting later in this article.)

The guidelines note that abciximab is only indicated as upstream glycoprotein IIb-IIIa therapy if there is no appreciable delay to angiography (ie, the patient is emergently going to angiography from the ED) and percutaneous coronary interventions are likely to be performed; otherwise, either eptifibatide or tirofiban is the preferred glycoprotein IIb-IIIa inhibitor. The guidelines also provide a class IIa recommendation (reasonable treatment) for the anticoagulant bivalirudin in place of a glycoprotein IIb-IIIa inhibitor, if at least 300 mg of clopidogrel has been administered at least 6 hours before intervention.

Among patients who will be treated with an initial conservative (noninvasive) strategy, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission and continued for at least 1 month to 1 year. Among patients who have recurrent ischemic discomfort

while receiving clopidogrel, aspirin, and anticoagulant therapy, the guidelines suggest that it is reasonable to add a glycoprotein IIb-IIIa inhibitor before diagnostic angiography.

2.3. Anticoagulant therapy recommendations

As in previous versions, the new guidelines recommend that anticoagulant therapy should be added to antiplatelet therapy in patients with unstable angina and non–ST-segment-elevation myocardial infarction as soon as possible after presentation [2]. The anticoagulants with the strongest evidence for efficacy in patients for whom an invasive strategy is selected include enoxaparin and unfractionated heparin; both bivalirudin and fondaparinux may also be used in this application. Among patients who qualify for conservative management, enoxaparin and fondaparinux are recommended, with the latter preferred in patients at high risk for bleeding.

3. Rationale for stratifying risk

Patients frequently present to the ED with undifferentiated chest pain. Unlike most other specialties, the unique challenge in emergency medicine is to quickly identify the highest-risk acute coronary syndrome patients while simultaneously considering and excluding other life-threatening causes of chest pain. The most urgent goal of risk stratification of the patient with chest pain in the ED is to identify those with ST-segment-elevation myocardial infarction who need immediate reperfusion. The next priority is to identify and aggressively treat patients with non–ST-segment-elevation acute coronary syndromes because of their high morbidity and mortality. During the non–ST-elevation acute coronary syndromes, emergent pharmacologic therapies are given to counter the 3 important pathophysiological processes (platelet activation, platelet aggregation, thrombin activation/formation) involved in the thrombotic cascade that occurs after plaque rupture of culprit arterial lesions. In addition to the ischemic injury that can occur because of thrombosis and microvascular embolization, it is recognized that these patients also have an added risk of periprocedural ischemia and infarction at the time of percutaneous coronary interventions [3]. Although periprocedural complications may result from a variety of events during intervention (eg, embolization of the clot burden to downstream side-branch arteries (<3%), transient or abrupt vessel closure (<1%), or ischemic time related to balloon inflation), these factors are not believed to account for the majority of increased risk associated with percutaneous coronary intervention. Diffuse atherosclerotic disease and invasiveness of the revascularization technique are the 2 main factors that have been identified, and it is hypothesized that microvascular embolization plays a predominant role in the development of periprocedural infarction [3]. This supports the upstream use of glycoprotein IIb-IIIa inhibitors, anticoagulation, and clopidogrel. Choices must be made early in treatment, often with limited patient history and without knowledge of a patient's coronary anatomy, that can profoundly influence both outcomes as well as later procedural and pharmacologic options. Rapid, accurate risk stratification in patients with chest pain is therefore critical in the ED. Table 1 [4-10] details various tools that are available for this purpose.

The Thrombolysis in Myocardial Infarction risk score offers a convenient and emergency- department–pertinent means of quantifying risk. This score integrates various clinical factors and markers in a single, comprehensive risk stratification tool (Table 2) [11] that is predictive of death, reinfarction, and the need for target vessel revascularization. It has been validated both in clinical trials and in a nontrial-based ED population with chest pain [9].

Release of cardiac biomarkers is a well-understood phenomenon that reflects the extent of myocardial damage and predicts outcomes; in particular, cardiac troponin T is a powerful, independent marker of risk in patients with acute myocardial infarction [12] and acute coronary syndrome [13]. In the current American College of Emergency Physicians guidelines, the use of cardiac serum marker tests to exclude non–ST-segment-elevation myocardial infarction has a level B recommendation (reflecting moderate clinical certainty) [14]. These guidelines indicate that a diagnosis of non–ST-segment-elevation myocardial infarction (but not coronary artery disease) can be excluded with (1) a single negative creatine kinase–muscle type subunit (MB) mass, troponin I, or troponin T level measured 8 to 12 hours after symptom onset; (2) negative myoglobin in conjunction with a negative creatine kinase–MB mass or negative troponin when measured at baseline and at 90 minutes in patients presenting <8 hours after symptom onset; and (3) a negative 2-hour change in creatine kinase–MB mass in conjunction with a negative 2-hour change in troponin in patients being treated <8 hours after symptom onset. However, according to American College of Emergency Physicians guidelines, if symptom onset is unknown, unreliable, or more consistent with preinfarction angina, then the reference period for time of symptom onset should begin at the time of ED presentation. In contrast, as noted, current American College of Cardiology/American Heart Association guidelines indicate that biomarkers of cardiac injury (preferably troponin) should be measured in all patients who present with chest discomfort or related symptoms consistent with acute coronary syndrome [2].

Determining risk level on the basis of electrocardiographic readings is a cornerstone of stratification in the ED. Optimally, this should be the first step of chest-pain risk stratification in the ED. The presence of ischemic changes on electrocardiographic at presentation accurately predicts unfavorable outcomes in patients with acute chest pain. In the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) study, outcomes were assessed for 12 142 patients who reported symptoms of cardiac ischemia at rest within 12 hours of admission and with signs of myocardial ischemia confirmed by electrocardiographic, to determine the prognostic value of various

Table 1 Stratification tools are available to help assess patient risk upon presentation in the ED and shortly afterward [4-10]

Study	Outcomes evaluated	Patients	Factors for analysis/ score calculation	How score was calculated	Risk strata	Outcomes by Risk
CAD risk stratification model [4]	CAD: positive diagnostic study, death, MI	Women without ACS at initial ED evaluation	●Age ≥60 y ●History of diabetes, CAD, angina, and/or hypertension ●Tobacco use (current or within 5 y) ●Family history of CAD ●High clinical suspicion of ACS	Risk level assigned by summing and categorizing cumulative risk score	CAD risk: ●Low risk: score = 0 ●Moderate risk: score = 1-2 ●High risk: score ≥ 3	Evidence of CAD: ●Low risk: 1.8% ●Moderate risk: 4.9% ●High risk: 16.8%
GRACE ACS Risk Model [5,6]	Death, MI	Patients with ACS	●Age ●History of CHF and/or MI ●At presentation: SBP, resting heart rate, ST-segment depression ●During hospitalization: serum creatinine, elevated cardiac enzymes, PCI	Different points given to each factor	The greater the total number of points, the greater the total risk score and thus the probability of all-cause mortality or MI	NA
Erlanger Chest Pain Evaluation Protocol [7]	ACS, AMI?	Patients with suspected ACS	Patients assigned to 1 of 4 groups: ●I: ACS with clinical and ECG criteria for emergency reperfusion ●II: probable ACS, no clinical or ECG criteria for emergency reperfusion ●III: possible ACS ●IV: probable non-ACS chest pain but preexisting disease or significant risk factors for CAD	2-h evaluation period (CK-MB and troponin I monitoring, automated SECG)	Patients recategorized by likelihood of ACS: ●II: intermediate to high risk (clinical diagnosis of ACS or abnormal serum markers [CK-MB, troponin I], SECG, or both) ●III: low risk (possible ACS with negative SECG and serum markers) ●IV: very low risk (probable non-ACS chest pain with negative SECG and no elevated serum markers)	30-d ACS (based on initial groups): ●I: 100% ●II: 69.1% ●III: 13.5% ●IV: 3.3% 30-d ACS (recategorization after 2 h): ●I: 0% ●II: 14.5% ●III: 43.9% ●IV: 10.1%
Modified TIMI risk score [8]	All-cause mortality, nonfatal MI, coronary revascularization	Patients in ED with undifferentiated chest discomfort	TIMI risk score has 7 components: ●Age ≥65 y ●Elevated cardiac markers	1 point if factor is present, 0 if absent	Modified score, based on 4 components independently associated with worse prognosis: ● Elevated cardiac markers	Event rate, patients with ACS: ●Score 0: 4.7% ●Score 1: 10.3% ●Score 2: 29.3%

			•ST-segment deviation ≥0.5 mm •≥2 separate episodes of angina within 24 h •≥3 CAD risk factors •Aspirin use within 7 d •History of revascularization or ≥50% coronary stenosis at angiography		•ST-segment elevation or depression ≥0.5 mm •Coronary stenosis ≥50% •Age ≥65 y	•Score 3/4: 60.9% Event rates, patients without ACS: •Score 0: 2.4% •Score 1: 7.4% •Score 2: 11.4%
TIMI risk score in the ED [9]	AEs at 30 d (death, MI, revascularization)	Unselected ED chest pain population	TIMI risk score components	•Presentation ECGs used to calculate TIMI risk score •Presentation (or earlier) biomarkers, if known	Higher TIMI score indicates increased risk/rates of AEs at 30 d	TIMI score rates: •0: 2.1% •1: 5.7% •2: 10.1% •3: 19.5% •4: 22.1% •5: 39.2% •6: 45% •7: 100%
Predictors of poor outcomes risk score [10]	Composite of all-cause mortality or nonfatal MI at 1 y	Patients with acute chest pain without ST-segment deviation and with normal troponin concentrations	•Chest pain score ≥10 points •≥2 pain episodes in 24 h •Age ≥67 y •Diabetes •Prior PTCA	Each variable = 1 point except diabetes (2 points)	•Very low risk: 0 •Low risk: 1 •Intermediate risk: 2 •High risk: 3 •Very high risk: ≥4	Death or MI at 1 y (%): •Very low risk: 0% •Low risk: 3.1% •Intermediate risk: 5.4% •High risk: 17.6% •Very high risk: 29.6%

ACS, acute coronary syndrome; AEs, adverse events; CAD, coronary artery disease; CHF, congestive heart failure; CK-MB, creatine kinase–MB fraction; ECG, electrocardiogram; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; SECG, serial 12-lead electrocardiogram, TIMI, Thrombolysis in Myocardial Infarction.

Table 2 TIMI Risk Score includes age ≥65 years, ≥3 risk factors for coronary heart disease, prior coronary stenosis of 50% or more, ST-segment deviation, ≥2 anginal events in the prior 24 hours, use of aspirin in the prior 7 days, and elevated levels of serum cardiac markers) in a single, comprehensive risk stratification tool [4]

TIMI Risk Score
◆ Age older than 65 y
◆ 3 or more risk factors for CAD*
◆ Established CAD**
◆ Elevated serum cardiac markers
◆ Use of aspirin in the past 7 days
◆ ST depression ≥0.5 mm
◆ 2 or more angina events in the past 24 h

*Family history of CAD, hypertension, hypercholesterolemia, diabetes, current smoking; **prior coronary stenosis of 50% or more. CAD=coronary artery disease; TIMI=Thrombolysis in Myocardial Infraction.

electrocardiographic presentations of myocardial ischemia (Table 3) [15]. Multivariate analysis adjusting for factors associated with an increased risk for 30-day death or reinfarction indicated that compared with patients with T-wave inversion, the risk for 30-day death or reinfarction was 1.68-fold higher in patients with ST-segment elevation, 1.62-fold higher for those with ST-segment depression, and 2.27-fold higher for those with combined elevation and depression.

Although electrocardiographics at presentation accurately predict prognosis when they are diagnostic, acute coronary syndrome is a dynamic, evolving process. Accordingly, current American College of Emergency Physicians guidelines provide guidance on the use of serial electrocardiographics and regimens for serum marker testing for exclusion of non–ST-segment- elevation myocardial infarction. These guidelines indicate that repeat electrocardiographic or automated serial electrocardiographics (at 30- to 60-minute intervals) should be performed during evaluation of patients in whom the initial electrocardiographic is nondiagnostic for injury but who have symptoms consistent with ongoing ischemia [14].

3.1. Stratifying by bleeding risk

To optimally balance the risks and benefits of pharmacologic treatment among patients with acute coronary syndrome, it is necessary to weigh the risk for bleeding conferred by administration of antithrombotic and antiplatelet regimens. Based on this assessment, modification of either the agents or the dosing regimens may be appropriate. Risk factors for bleeding that may affect treatment decisions in the ED and indicate a need to modify downstream pharmacologic treatment include—but are not limited to—age, renal insufficiency, sex, race, and weight.

Age seems to be an important, consistent, and direct predictor of bleeding risk. In a retrospective analysis using pooled data form 4 multicenter, randomized clinical trials enrolling 26 452 patients with acute coronary syndrome, 27.6% had 1 or more bleeding episodes, with a stepwise increase in degree of bleeding according to age, ranging from no bleeding among patients with a median age of 63.8 years to severe bleeding among patients with a median age of 70.0 years o(P for trend, <.001) [16]. A similar pattern was seen in a retrospective study in which patients experiencing major bleeding were older than patients with no bleeding (67.8 years vs 63.6; $P < .001$) [17].

In part, the relationship between age and increased risk for bleeding is a result of age-related decline in renal function. In a subanalysis of the Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events (REPLACE-2) trial, a 1.72-fold increase in risk for bleeding complications was observed among patients with creatinine clearance levels <60 mL/min [18]. In a second study, in patients with acute myocardial infarction undergoing primary percutaneous coronary interventions, baseline renal impairment was found to be associated with a markedly increased risk for moderate to severe bleeding among those with preprocedure renal impairment (defined as creatinine clearance level ≤60 mL/min) compared with those with normal renal function (6.7% vs 2.8%; $P = .03$) [19]. Similarly, data from the Global Registry of Acute Coronary Events indicate that renal insufficiency is independently associated with a higher risk for bleeding ($P < .0062$ for patients with non–ST-segment-elevation myocardial infarction and $P = .0045$ for patients with unstable angina) [20].

Additional risk factors include sex, ethnicity, and weight. The influence of sex on bleeding risk is debatable, with some studies showing that female sex is associated with increased risk for bleeding [16] and others not showing this association [21]. Ethnicity has also been shown to have a marginal influence on bleeding risk, with an approximately 1.32-fold increased risk among African Americans as compared with white patients ($P = .030$) [22]. Finally, weight may influence outcomes by increasing risk for excess dosing of antiplatelet/antithrombotic agents [23].

Table 3 Occurrence of acute myocardial infarction in GUSTO-IIb, as measured by creatinine kinase levels [9]

	T-wave inversion	ST-segment elevation	ST-segment depression	ST-segment elevation/depression
At admission	22%	28%	35%	15%
MI 16 h postadmission	32%	81%	48%	89%

GUSTO-IIb indicates Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes; MI, myocardial infarction.

3.2. Ensuring accurate dosing to decrease risk

In fact, the increased bleeding risk associated with these factors may be at least partly related to failure to adjust dosages of antithrombotic/antiplatelet agents for patients with these characteristics. Recent data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology and American Heart Guidelines (CRUSADE) registry indicate that approximately 42% of patients with non–ST-segment-elevation myocardial infarction who are administered antithrombotic agents receive 1 or more doses outside the recommended range; factors associated with excess dosing agents included older age, female sex, renal insufficiency, low body weight, diabetes, and congestive heart failure [23]. Excess dosing can have important consequences, conferring an increase in bleeding risk between 1.08- and 1.36-fold that increases relative to the degree of excess dosage and the number of agents administered in excess. These data are supported by a retrospective analysis of the randomized trial to evaluate the relative PROTECTion against post-PCI microvascular dysfunction and post-PCI ischemia among antiplatelet and antithrombotic agents–Thrombolysis in Myocardial Infarction 30 (PROTECT-TIMI 30) trial, which suggests that failure to adjust eptifibatide infusion in patients with reduced creatinine clearance is associated with a relatively higher risk for bleeding [24].

Accurate dosing, which is dependent on patient age, weight, and other factors, decreases bleeding risk. Obtaining correct patient weights is therefore vital, as is regular estimation of creatinine clearance (often related to patient age). The Cockcroft-Gault formula is useful to estimate creatinine clearance:

$$\text{Creatine clearance (males)} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

For women, the result (glomerular filtration rate) is multiplied by 0.85.

In addition, having preprinted, weight-based medication orders or computerized entry forms decreases reliance on memory. Best practices at some institutions include integration of a clinical pharmacist into the ED team, although this is not common (3% of EDs) [25]. These emergency pharmacists serve as an immediate reference source and may provide guidance and oversight regarding critical medication dosing [26,27].

4. Glycoprotein IIb-IIIa inhibitors in high- vs low-risk patients

The recently updated American College of Cardiology/American Heart Association guidelines continue to support an early, aggressive approach in patients with non–ST-elevation acute coronary syndromes. This includes administration of a glycoprotein IIb-IIIa inhibitor in patients with high-risk features (eg, elevated troponin levels) [2]. Data from clinical trials and meta-analyses support the benefit of glycoprotein IIb-IIIa inhibitors even when used in the context of established oral antiplatelet therapies. In a meta-analysis of 6 pivotal trials of these agents in patients with non–ST-segment-elevation myocardial infarction enrolling a total of 31 402 patients, glycoprotein IIb-IIIa inhibitors were associated with a statistically significant 16% relative risk reduction in death or myocardial infarction ($P = .0003$), with absolute risk reduction of 1% compared with placebo or control (10.8% vs 11.8%; $P = .015$) maintained through 30 days of follow-up [28]. However, these trials did not differentiate between patients at high and low risk.

The Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) trial examined outcomes in a lower-risk population of 2159 patients undergoing elective percutaneous coronary interventions after pretreatment with 600 mg of clopidogrel with or without concomitant abciximab, administered 2 hours before the procedure [29]. Notably, the incidence of the primary end point—a composite of death, myocardial infarction, and urgent target-vessel revascularization within 30 days of randomization—was identical in the abciximab (4%) and placebo groups (4%) in this low-risk patient population.

The follow-up ISAR-REACT 2 trial evaluated outcomes in high-risk patients with acute coronary syndrome undergoing percutaneous coronary intervention after pretreatment with clopidogrel [30]. Like the ISAR-REACT trial, patients in this study received clopidogrel (600 mg) at least 2 hours before percutaneous coronary interventions, with preprocedure intravenous or oral aspirin (500 mg) before undergoing early percutaneous coronary intervention stenting (within 6 hours of diagnosis of acute coronary syndrome). Patients were randomly assigned to receive abciximab plus heparin or a placebo infusion plus heparin. The primary end point was a composite of death, myocardial infarction, or urgent target vessel revascularization within 30 days of randomization.

A total of 2022 patients entered the study, of whom 1012 were randomly allocated to abciximab and 1010 received placebo [30]. The composite primary end point was reached by 8.9% of patients in the abciximab arm, compared with 11.9% of patients receiving placebo, yielding a significant 25% reduction in risk with abciximab ($P = .03$) that was primarily due to reduction in the risk for death and myocardial infarction. In an analysis based on troponin levels, patients with elevated troponins (defined in this study as >0.03 μg/mL)—a population that represented >50% of the total study cohort— derived the most benefit, with reductions in risk of 29% ($P = .02$). In contrast, among patients without elevated troponins, the risk of the primary composite end point was 4.9% in both the abciximab and

placebo groups. Notably, the benefit seen among higher-risk patients was not offset by an increase in bleeding risk.

These data suggest that the benefit of glycoprotein IIb-IIIa inhibitors may largely be confined to patients with elevated troponin levels, at least among patients who are pretreated with clopidogrel, and also suggest that pretreatment with clopidogrel attenuates differences among antiplatelet/antithrombotic regimens. If one accepts that the population enrolled in ISAR-REACT 2 is representative of the typical population with non–ST-elevation acute coronary syndromes undergoing percutaneous coronary interventions, this study suggests that at least half of this patient population (those with elevated troponins) can benefit from glycoprotein IIb-IIIa inhibitors. The ISAR-REACT series of trials is also notable in that all patients in both study groups received 600 mg clopidogrel. In real-world clinical practice, however, it is often unknown at presentation whether the patient will undergo percutaneous coronary intervention or coronary artery bypass grafting. In the case of patients undergoing coronary artery bypass grafting, clopidogrel—particularly at the high dosage used in the ISAR-REACT studies—may be contraindicated due to increased bleeding risk. To put the situation in perspective, it is helpful to look at the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial involving 13 819 patients with acute coronary syndrome, of whom 1539 (11%) underwent coronary artery bypass grafting [31], and the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, in which 1865 of 10 027 (19%) high-risk patients with non–ST-elevation acute coronary syndromes underwent coronary artery bypass grafting. In the SYNERGY trial, most excess bleeding events were associated with this surgical procedure [32].

5. Does timing matter?

Optimal timing of administration of glycoprotein IIb-IIIa inhibitors remains a matter of controversy, even after the release of the new unstable angina and non–ST-segment-elevation myocardial infarction guidelines. In fact, the current United States guidelines provide the option of initiating these agents before diagnostic angiography, and European guidelines do not specify the timing of initiation [2,33].

Recent registry data indicate—consistent with current guideline recommendations—that glycoprotein IIb-IIIa inhibitors are primarily initiated in the catheterization laboratory and that there is a wide gap between the recommendations and clinical practice in terms of use of these agents at any time [34]. A large retrospective observational analysis from the CRUSADE registry evaluated selection patterns for early (within 24 hours of presentation) glycoprotein IIb-IIIa inhibitor use in 56 804 patients with high-risk non–ST-segment-elevation myocardial infarction (defined as ischemic chest pain of <24 hours in duration and ischemic electrocardiographic changes or positive cardiac markers) [34]. Of these patients, only 20 092—or approximately 36%—received glycoprotein IIb-IIIa inhibitors within 24 hours of admission, and of these patients, only about a third received them in the ED. Notably, early use of glycoprotein IIb-IIIa inhibitors was associated with improved in-hospital outcomes, including reduced rates of death (2.7% vs 4.7% for early vs late, respectively), death or myocardial infarction (7.7% vs 5.7%), congestive heart failure (6.3% vs 9.4%), and shortened hospital stay (3 vs 4 days).

The early effects of platelet glycoprotein IIb-IIIa inhibition in patients with non–ST-segment-elevation myocardial infarction have also been examined in a meta-analysis using pooled data from the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trials [35]. These studies compared the use of the glycoprotein IIb-IIIa inhibitors abciximab, eptifibatide, and tirofiban, respectively, with placebo in large populations of patients with recurrent ischemia under medical management (CAPTURE), or with recent ischemic chest pain and electrocardiographic or enzymatic evidence of myocardial ischemia (PURSUIT and PRISM-PLUS); these studies confirmed the association of glycoprotein IIb-IIIa inhibition with significant reductions in event rates both before and immediately after percutaneous coronary intervention. The pooled analysis of these trials indicated a 34% reduction in the composite of death or nonfatal myocardial infarction before percutaneous coronary intervention and a 41% reduction in percutaneous coronary intervention-related events during pharmacologic therapy. Overall and procedure-related mortality, although low in all arms, was also reduced by 50% and 45%, respectively, among patients who received glycoprotein IIb-IIIa inhibitors. These data suggest that the benefit of glycoprotein IIb-IIIa inhibitors can be maximized through early initiation.

Registry data support this conclusion. A recent (2003) analysis of National Registry of Myocardial Infarction (NRMI) data examined the effects on mortality of early administration of glycoprotein IIb-IIIa inhibitors in >60 000 patients with non–ST-segment-elevation myocardial infarction at >1100 sites [36]. The authors compared outcomes in patients receiving “early treatment” (defined as administration of glycoprotein IIb-IIIa inhibitors within 24 hours of hospital arrival) with those in patients not receiving early treatment (no treatment or treatment only after 24 hours, including glycoprotein IIb-IIIa inhibitors after elective percutaneous coronary intervention).

In this study, only 25% of eligible patients received early treatment with glycoprotein IIb-IIIa inhibitors [36]. Early treatment with these agents was associated with a substantial

reduction in mortality compared with no early treatment (3.3% vs 9.6%, respectively; $P < .001$); early treatment was also associated with a substantial reduction in risk for the composite of death or myocardial infarction (4.5% vs 10.3%; $P < .001$) and in risk for stroke (0.7% vs 1.2%; $P < .001$). When adjusted by baseline risk characteristics, early glycoprotein IIb-IIIa inhibitor use remained associated with lower in-hospital mortality (3.5% vs 3.9%; $P < .03$). For nonfatal complications, including shock, cardiac arrest, and reinfarction, rates were similar or slightly higher in patients receiving a glycoprotein IIb-IIIa inhibitor; patients who received glycoprotein IIb-IIIa inhibitors also had a significantly higher risk for bleeding (although other factors associated with bleeding risk were not uniformly controlled across trials). Using the NRMI non–ST-elevation myocardial infarction risk score, risk for in-hospital mortality was lower across all strata among patients who received glycoprotein IIb-IIIa inhibitors, suggesting that the benefit of early treatment is not confined to higher-risk patients (Fig. 3) [36].

More recently, the results of the ACUITY Timing trial suggest that early administration is associated with benefit [37]. In this subrandomization of the ACUITY trial, 9027 moderate- to high-risk patients with acute coronary syndrome were randomly assigned to receive either routine upstream or deferred selective glycoprotein IIb-IIIa inhibitor administration; the primary outcome was noninferiority of deferred vs upstream use in the prevention of the composite of death, myocardial infarction, or unplanned revascularization for ischemia at 30 days [37].

The primary composite end point was seen in 7.9% of patients who received deferred selective treatment and 7.1%

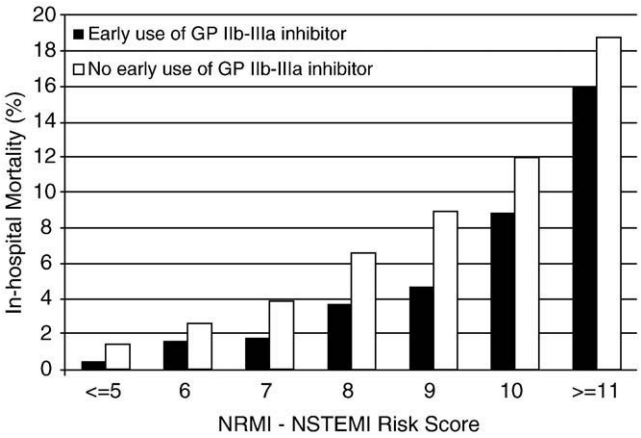

Fig. 3 Non–ST-elevation myocardial infarction risk score of NRMI. In-hospital mortality for patients receiving early glycoprotein IIb-IIIa inhibitor treatment vs those not treated, by the non–ST-elevation myocardial infarction risk score of NRMI. Among all risk strata, in-hospital mortality rates were lower in patients treated with a GP IIb-IIIa inhibitor than in those not so treated. In particular, the absolute treatment differences tended to be widest among those with intermediate to high baseline risk [36] (reprinted from Peterson et al [36], with permission from the American College of Cardiology). Abbreviations are explained in Fig. 1.

of those who received routine upstream administration of glycoprotein IIb-IIIa inhibitors ($P = .13$ for superiority) [37]. Routine upstream use was associated with fewer unplanned revascularizations for ischemia ($P = .03$ for superiority), but no difference was seen in rates of death or myocardial infarction [37]. The rate of minor, but not major, thrombolysis in myocardial infarction bleeding was also higher in the group receiving early glycoprotein IIb-IIIa inhibitor use. The new American College of Cardiology/American Heart Association guidelines assign a class IIa recommendation (level of evidence: B) to bivalirudin monotherapy before diagnostic angiography if clopidogrel (≥300 mg) is given 6 or more hours before planned catheterization or percutaneous coronary intervention [2], due to problems with bleeding and with time for this medication to become effective. This is a problematic recommendation for emergency physicians because it is usually not apparent when the patient will go to catheterization. Furthermore, there is often pressure from the cardiothoracic surgery service to avoid loading with clopidogrel before definition of the coronary anatomy, and so, this recommendation may be at crossed purposes with existing acute coronary syndrome protocols. Finally, this recommendation does not take into account the patient's risk level; in ACUITY [31], there was a strong trend toward an increased incidence in ischemic events among troponin-positive patients not receiving glycoprotein IIb-IIIa inhibitors.

On balance, these data suggest that early glycoprotein IIb-IIIa inhibitor use is associated with improved outcomes. However, questions regarding the impact of early initiation of glycoprotein IIb-IIIa inhibitors will be definitively answered by the ongoing Early Glycoprotein IIb-IIIa inhibition in non–ST-segment-elevation acute coronary syndrome (EARLY-ACS) trial [38]. This prospective, randomized, double-blind, placebo-controlled, multicenter trial will compare the efficacy and safety of early use of eptifibatide compared with placebo in reducing the composite of death and major ischemic complications in patients with high-risk non–ST-segment-elevation myocardial infarction. Patients with ischemia and 2 or more high-risk characteristics (elevated myocardial enzymes, new ST-segment deviation ≥1 mm, or age ≥60 years) will be randomly assigned, within 8 hours of presentation, to either eptifibatide at the currently recommended dosage, adjusted for creatinine clearance, or matching placebo, with provisional use of eptifibatide in the catheterization laboratory, with catheterization scheduled no sooner than the next calendar day after randomization. Oral or intravenous aspirin will be administered to all patients; other concomitant medications will be used in accordance with existing practice guidelines and local practice. In addition, investigators may administer clopidogrel at the time of randomization or defer its initiation until after the procedure, and analyses will be stratified accordingly to permit evaluation of the incremental benefit of early clopidogrel in patients who are managed with aspirin, glycoprotein IIb-IIIa inhibitors, and an early invasive strategy.

American College of Emergency Physicians guidelines provide a level B recommendation for administration of these agents, indicating that they should be given before percutaneous coronary intervention to patients with positive troponin levels or ischemic ST-segment depression in whom an early interventional strategy is anticipated, and suggest that the greatest benefit is derived in patients in whom treatment is initiated within 6 hours of presentation and in those in whom there will be a delay in percutaneous coronary intervention [14]. In addition, these guidelines suggest that glycoprotein IIb-IIIa inhibitors should be considered in patients with positive troponin levels or ischemic ST-segment depression in whom a noninterventional strategy is planned.

6. Where does clopidogrel fit in?

Current American College of Emergency Physicians guidelines indicate that clopidogrel is an option in patients with elevated troponin levels or ischemic ST-segment elevation in whom a noninterventional approach is planned and in patients undergoing percutaneous coronary interventions who are not expected to undergo coronary artery bypass grafting [14]. This approach is supported by data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, a multicenter, randomized, double-blind, placebo-controlled trial that evaluated the effects of clopidogrel with aspirin vs aspirin alone in 12 562 patients with non–ST-segment-elevation myocardial infarction [39]. In these patients, the combination of clopidogrel (300 mg) with aspirin provided substantial reductions in the composite outcome of death from cardiovascular causes, stroke, and nonfatal reinfarction compared with aspirin alone (9.3% vs 11.4%, respectively; relative risk, 0.80). Reductions in risk for ischemic events emerge early after treatment with clopidogrel, with up to a 33% reduction in relative risk for ischemic end points within 24 hours of randomization, arguing for early administration of this agent (Fig. 4) [40]. Among patients undergoing percutaneous coronary interventions, clopidogrel pretreatment was associated with significantly less cardiovascular death, acute myocardial infarction, and

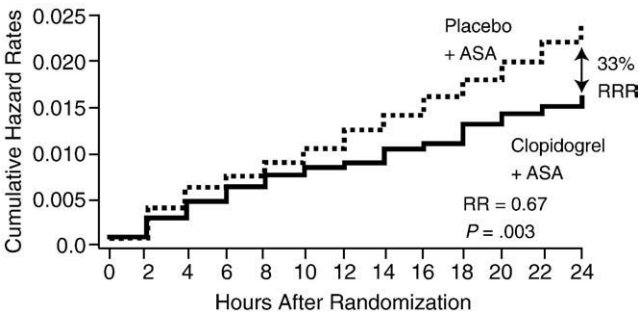

Fig. 4 Ischemic end points in the CURE trial were reduced within 24 hours of randomization [40] (adapted from Yusuf et al [40]). RR, relative risk; RRR, relative risk reduction.

urgent revascularization within 30 days compared with aspirin alone (4.5% vs 6.4%, respectively; relative risk, 0.70) [41]. Clopidogrel provides important periprocedural protection to patients who undergo percutaneous coronary intervention; however, guidelines suggest that optimal benefit occurs only if clopidogrel is administered long enough before percutaneous coronary interventions to achieve maximal platelet inhibition. Although the dosage is currently off-label, both the American College of Cardiology/American Heart Association [2] and European Society of Cardiology [42] guidelines discuss the option of giving a 600-mg loading dose to achieve more rapid platelet inhibition, but it is recognized that larger-scale trials are needed to rigorously establish the optimal loading dose.

6.1. Determining risk for coronary artery bypass grafting

Questions remain regarding who should receive a loading dose of clopidogrel in the ED. Although it is clear from the CURE trial that clopidogrel can provide substantial early and late reductions in risk among patients with non–ST-segment-elevation myocardial infarction and those undergoing percutaneous coronary interventions, current American College of Cardiology/American Heart Association guidelines recommend that clopidogrel be withheld for at least 5 days in patients in whom coronary artery bypass grafting is planned, to reduce bleeding risk [2]. Despite the isolation of 13 clinical characteristics that were significantly associated with the likelihood of coronary artery bypass grafting, it remains difficult to identify these patients in advance of diagnostic angiography [43].

Because it is difficult in the ED setting to prospectively identify patients who will require coronary artery bypass grafting, the use of clopidogrel upstream remains somewhat limited; however, it is clear that substantial early benefit can be derived from upstream administration in patients without significant risk for urgent coronary artery bypass grafting [40]. In the absence of clear institutional multidisciplinary protocols directing ED administration for non–ST-segment-elevation acute coronary syndrome patients, however, decisions regarding the use of clopidogrel should be deferred to the interventionalist who can administer the medication after the culprit coronary anatomy is known.

A system for scoring risk of going to coronary artery bypass grafting [44] has been developed that incorporates factors including elevated troponin levels, prior stable angina, ST-segment deviation ≥0.5 mm, male sex, and history of peripheral arterial disease (Table 4) [44]. Among 2220 patients with unstable angina and non–ST-segment-elevation myocardial infarction enrolled in the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction-18 (TACTICS–TIMI-18) trial, a significant increase in rates of coronary artery bypass grafting was seen with increasing risk scores: 6% of patients with a score <3 went to

Table 4 Risk score for likelihood of CABG [37]

Variable	OR of CABG	Risk score
Elevated troponin	3.9	3
Prior stable angina	1.8	1
ST deviation ≥0.5 mm	1.7	1
Male	1.6	1
PVD history	1.6	1
Previous CABG	0.35	-2

CABG=coronary artery bypass graft; OR=odds ratio; PVD=peripheral vascular disease.

coronary artery bypass grafting, as did 22% of patients with a score of 3 to 5, and 55% of patients with a score >5 [44].

Other patients who may qualify for upstream loading include those with previously implanted stents or with known single- or double-vessel disease who have previously been managed medically. In these patients, the anatomy of the target vessel(s) is usually known, and their acute coronary syndrome presentation is often a result of stent occlusion of the initial culprit artery(s). In addition, patients with suspected acute coronary syndrome who are known to have been noncompliant with recommendations for clopidogrel may benefit from upstream administration. In the absence of clear, agreed-upon institutional protocols regarding the administration of clopidogrel in non–ST-elevation acute coronary syndromes patients, it is prudent to make decisions in conjunction with the patient's cardiologist or the cardiologist on call when treating those with stents, known culprit artery anatomy, and medical noncompliance. Combined therapy with clopidogrel and glycoprotein IIb-IIIa inhibitors provides both platelet antiactivation and antiaggregation protection, and this dual therapy confers important periprocedural protection for patients destined for angiography and percutaneous coronary intervention; worries of increased bleeding risk can be lessened with attention to proper dosing of these agents, as discussed earlier in this review.

In notable contrast with the approach recommended by the American College of Cardiology/American Heart Association guidelines—to withhold clopidogrel from patients who are expected to be treated with coronary artery bypass grafting—the 2007 European Society of Cardiology guidelines [42] recommend clopidogrel in all patients with non–ST-elevation acute coronary syndromes, based on the viewpoint that the benefits of this agent outweigh the bleeding risks associated with it. If surgery is deemed necessary, the excess bleeding risk is ameliorated by a washout period of 5 days.

7. Improving care: generating institutional protocols for treatment of acute coronary syndrome patients

Optimal management of patients with acute coronary syndrome requires coordination across a broad range of care providers. Emergency physicians play a critical role in this process by providing early care and by identifying patients who are appropriate candidates for upstream therapies; thus, choices made in the ED can have a profound effect on downstream procedural and pharmacologic treatment choices as well as on outcomes. Because current guidelines do not yet provide specific recommendations on the timing of administration and dosing of antiplatelet/antithrombotic drugs, it remains critical to develop and initiate institution-wide protocols to foster decision making that takes into consideration the needs of all disciplines—emergency medicine, internal medicine, cardiology, and cardiovascular surgery—involved in the care of acute coronary syndrome patients [45]. Such collaboration and protocol development should decrease treatment variation among acute coronary syndrome patients, minimize reliance on individual cardiologists' preferences, and enable emergency physicians to initiate agreed-upon therapies to those highest-risk acute coronary syndrome patients.

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