Balancing Ischemic Efficacy and Bleeding Risk in the Upstream Management of Non-ST-Segment Elevation Myocardial Infarction

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Abstract Pharmacologic treatment of non-ST-segment elevation acute coronary syndrome (ACS) has customarily focused on preventing or reducing ischemic complications through the use of potent antiplatelet and antithrombotic medications. From initial presentation in the emergency department, through hospitalization and possible intervention, preventing ischemia-related major adverse cardiac events (MACE), including death, recurrent myocardial infarction, urgent revascularization, and stroke, are the principal focus of health care providers. However, such reductions in ischemic events have come at the price of an increased risk of major bleeding, which is also associated with adverse clinical outcomes. Thus, attempts to improve anti-ischemic efficacy must be balanced against the increased risk of hemorrhage after ACS therapy is initiated. The objective of this article is to review evidence for a dual-risk stratification approach that centers on both ischemia and bleeding risks. The authors focused on the coherence of clinical trial data with respect to tools for reducing the risk of MACE as a result of early treatment, while maintaining awareness that such interventions can increase later bleeding risk.

Keywords Emergency and Hospital Medicine · Treatment of NSTEMI · Global Registry of Acute Coronary Events (GRACE) · Acute coronary syndrome ·

ACS · Preventing ischemia-related major adverse cardiac events (MACE) · Cardiovascular Risks · Cardiovascular Hazards · Heart Health

Abbreviations

ACTION	Acute Coronary Treatment and Intervention Outcomes Network
ACUTY	Acute Catheterization and Urgent Intervention Triage
ADP	Adenosine diphosphate
AHA	American Heart Association
ASA	Acetylic Salicylic Acid
AF	Atrial fibrillation
BUN	Blood urea nitrogen
BMS	Bare metal stent
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CKD	Chronic kidney disease
CV	Cardiovascular
CVA	Cerebrovascular accident
GPIIb/IIIa	Glycoprotein IIb/IIIa
GRACE	Global Registry of Acute Coronary Events
GUSTO-IIb	Global Use of Strategies to Open Occluded Coronary Arteries IIb
HF	Heart failure
LMWH	Low molecular weight heparin
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NSAIDs	Nonsteroidal Antiinflammatory Drugs
NSTEMI	Non-ST Elevation Myocardial Infarction
PCI	Percutaneous coronary intervention
STEMI	ST Elevation Myocardial Infarction
TIA	Transient ischemic attack

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TIMI Thrombolysis in Myocardial Infarction
Type 1 NSTEMI MI consequent to a pathologic process in the wall of the coronary artery (e.g., plaque erosion/rupture, fissuring or dissection)

Introduction

The decisions of emergency physicians and hospitalists, who are responsible for much of the upstream (i.e., prior to diagnostic coronary angiography and definition of the coronary anatomy) assessment and management of patients with non-ST segment elevation acute coronary syndrome (ACS), have broad future ramifications. Ideally, decisions made both before cardiac catheterization should be based on similar, consistently applied interpretations of evidence. An expert panel of emergency physicians and hospitalists met in Philadelphia, PA on 26 July, 2013 as part of the HEMI (Hospital-Emergency Medicine Interface) initiative to discuss the continuum of care for patients who present to the emergency department (ED) with non-ST Elevation Myocardial Infarction (NSTEMI). It should be noted here, that for the purposes of this document, NSTEMI refers to the universal definition of a type 1 NSTEMI [1•] characterized in early management by a clinical presentation consistent with an ACS presentation and an elevated troponin level (see Fig. 1).

Treatment of NSTEMI

Treatment of NSTEMI has customarily focused on preventing or reducing ischemic or thrombotic complications

with potent antiplatelet and antithrombotic medications. This strategy has demonstrated a clear benefit by markedly decreasing the risk of acute and long term mortality, as well as re-infarction. However, the reductions in ischemic events have come at the price of an increased risk of major bleeding, which is itself associated with adverse clinical outcomes [2]. In this report, the HEMI-ACS panel examined the rationale for dual risk stratification in the early patient care environment as a proactive means of directing therapy that balances anti-ischemic efficacy against the risk of bleeding in the management of these patients without knowledge of their coronary anatomy.

As examples of competing therapeutic concerns, we will present several cases for consideration. In the first we have a small (<60 kg), 72 year old Asian female who presents to the ED with chest pain syndrome. At presentation her blood pressure is 125/72 and her ECG is non-diagnostic. A review of her history reveals that she is a diabetic with a prior MI and a prior cerebrovascular accident (CVA), and she has an ejection fraction of 42 %. She also has chronic kidney disease (CKD) with a GFR of <30. Her troponin level is elevated and a diagnosis of NSTEMI is made. What is the proper course of action for this patient in the ED or after admission to the hospital? A typical response would be to administer anti-thrombotic therapy. However, we now must ask about the later effects of this intervention. Will she undergo catheterization? If so, when? If not, why not? Without knowing this patient's coronary anatomy, can her ischemic risk be calculated vis-à-vis her bleeding risk? What is the likelihood that she may require coronary artery bypass graft (CABG) surgery in the next several days? What is the correct course of immediate treatment if more attention needs to be paid to subsequent events?

Fig. 1 Balancing ischemic efficacy and bleeding risk in NSTEMI-ACS

- 1 All patients with NSTEMI are potential candidates for early dual antiplatelet therapy (DAPT)
- 2 Attempts to prevent ischemic outcomes should be made only after assessment of bleeding risk
- 3 Do not administer DAPT if the bleeding risk is high
- 4 Comparative data that guide the selection of specific antiplatelet agents for specific patients are available
- 5 Platelet GP IIb/IIIa antagonists remain therapeutic options and should be considered in the early setting under certain circumstances

Ideally, emergency physicians and hospitalists would collaborate with each other and with their cardiology colleagues to develop protocols for consistent, evidence-based, expeditious care of patients who are admitted to the hospital from the ED [3]. With this in mind, from the moment a NSTEMI patient presents to the ED, an emergency physician should consider a patient's potential hospital path, such as admission to the medical floor, catheterization with or without stenting, and possible CABG. Considerations should include anticipated time to diagnostic angiography, risk of bleeding in response to therapy in a systematic, perhaps quantitative, manner, and the impact of ED-administered therapies on decisions of downstream providers.

Hospitalists' approaches to NSTEMI patients are likewise important because not only do these physicians manage increasing numbers of such patients after admission—whatever their inpatient path may be—they must also deal with the consequences of emergency physicians' treatment decisions. Published guidelines call for a number of diagnostic and therapeutic actions that readily lend themselves to inclusion in a protocol that can be initiated in the ED and continued by hospitalists as a patient's path progresses to care by a cardiologist [4] (see Fig. 2).

Risk Assessment Tools

Ischemia

Ischemic risk in ACS refers to the likelihood of a major adverse clinical outcome, most frequently associated with ischemic recurrence, and its clinical sequelae. Recurrent ischemia, the need for urgent coronary revascularization, myocardial infarction (MI), death, and their combinations are the most frequently measured outcomes in ACS risk

analysis [5]. Baseline predictions of ischemic risk help to inform optimization of NSTEMI care. A number of risk scores have been developed to predict short-term and mid-term outcomes in patients with ACS. These scores assign a variable number of points for the presence of each risk factor identified by multivariable statistical techniques. These points then represent independent predictors of adverse outcomes (and with an additive contribution to overall risk), based on the observation of events in specific populations [5]. The section below reviews key guidelines that have been developed for assessing ischemia risk. According to the European Society of Cardiology (ESC), and based on direct comparisons of its discriminative power, the GRACE risk score appears to provide the most accurate currently available stratification of risk both on hospital admission and at discharge [6].

GRACE

The Global Registry of Acute Coronary Events (GRACE) risk score was developed to predict death, and death/MI, using a multivariable logistic regression model of 11,389 GRACE registry patients (including 509 in-hospital deaths) with ACS with and without ST-segment elevation, enrolled from 1 April 1999, through 31 March 2001. Validation data sets included a subsequent cohort of 3,972 GRACE patients and 12,142 enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries IIb (GUSTO-IIb) trial [7]. Eight factors based on the presenting clinical and biomarker characteristics were identified as independent predictors of death or a combined outcome of death and in-hospital MI and include age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine, initial cardiac biomarker findings, and heart rate (see Fig. 3).

Fig. 2 Different pathways in the continuum of care of NSTEMI patients

Fig. 3 Risk score and nomogram from the GRACE study, for predicting mortality due to any cause in the six months after discharge. *AMI* acute myocardial infarction, *HR* heart rate, *SAP* systolic arterial pressure. **P* values from the comparison between the three categories in each group. The comparison of the intermediate and low risk categories was 0.009 in the sample total, 0.02 in the STEMI group, and 0.6 in the NSTEMI-ACS group

Additional GRACE studies resulted in the development of a clinical risk prediction tool for estimating the cumulative six month risk of death and death or MI as a means of facilitating triage and management of patients with ACS [8]. In this analysis 43,810 patients were assessed (21,688 in derivation set; 22,122 in validation set) and nine factors independently predicted death and the combined end point of death or MI six months after discharge. These were age, development (or history) of heart failure, peripheral vascular disease, systolic blood pressure, Killip class, initial serum creatinine, elevated initial cardiac biomarkers, cardiac arrest on admission, and ST segment deviation (see Fig. 4).

TIMI

The Thrombolysis in Myocardial Infarction (TIMI) risk score for UA/NSTEMI patients was developed as a simple semi-quantitative score in a test cohort of patients derived

from two international, randomized, double-blind trials from the TIMI 11B trial 1,957 patients receiving unfractionated heparin were compared (and were validated) with 1,953 who received enoxaparin, and from Efficacy and Safety of Subcutaneous Enoxaparin in NonQ-wave Coronary Events (ESSENCE), the 1,564 receiving unfractionated heparin were compared to the 1,607 treated with enoxaparin [9].

The TIMI risk score includes seven variables to predict the 14-day risk of the composite end point of death, MI, or urgent revascularization. These variables are presented in figure X. Risk factors for coronary artery disease are defined as hypertension, diabetes, hypercholesterolemia, family history of coronary artery disease, or tobacco use. One point is assigned for the presence of each of the seven predictors, resulting in a score that ranges from 0 (lowest risk) to 7 (highest risk) that correlates well (*C*-statistic 0.65) with the selected outcome [5].

Fig. 4 Mortality at six months for the three risk categories in the total population, for STEMI and NSTACS [9, Fig. 2]

*Shows P-values from the comparison between the 3 categories in each group. The comparison of the intermediate and low risk categories was .009 in the sample total, .02 in the STEMI group, and .6 in the NSTE-ACS group.

Fig. 5 TIMI risk score for UA/NSTEMI [11]

The TIMI risk score has been validated and used frequently in several patient cohorts, including an all-comers, non-trial-based ED chest pain population. The TIMI risk score at ED presentation successfully risk-stratified this unselected cohort with respect to 30-day adverse outcome, with a range of 2.1 % adverse outcomes with a score of 0, to 100 % adverse events when the score was $\geq$ 7. The highest correlation of an individual TIMI risk indicator to adverse outcome was for an elevated cardiac biomarker at admission. Overall, the score had similar performance characteristics to that seen when applied to other databases of patients enrolled in clinical trials and registries using a 14-day end point [10••] (see Fig. 5).

The GRACE and TIMI risk scores are commonly employed in research studies, but not frequently in clinical practice. Calculators for both are easily obtainable on the internet. Although they both have been demonstrated to

predict risk, they use different characteristics (see Table 3). Neither risk score should be used as a diagnostic device; rather they predict risk in patients with presentations likely to represent ACS (see Table 1).

Bleeding Risk

Among other points of interest the panel focused on concerns about, and approaches in preventing, ischemia-related major adverse cardiac events (MACE), while minimizing the risk of bleeding. Although it is important to recognize the role of early antiplatelet agents and anticoagulation against both disease-related and procedural ischemic insults, if percutaneous coronary intervention is determined to be the course of action, appropriate therapy must balance the need for potent ischemic inhibition against the potential for increased bleeding [11]. In fact,

Table 1 Comparison of ischemia risk scores

GRACE	TIMI
Age	Age (<65 or >65 years)
Development (or history) of heart failure	≥3 risk factors for coronary artery disease ^a
Peripheral vascular disease	Known coronary artery disease (stenosis ≥50 %)
Systolic blood pressure	Aspirin use in the past 7 days
Killip class	Presentation factors
Initial serum creatinine concentration	Recent (≤24 h) severe angina
Elevated initial cardiac markers	ST segment deviation ≥0.5 mm
Cardiac arrest on admission	Positive cardiac markers
ST segment deviation	

^a Risk factors include family history of CAD, hypertension, hypercholesterolemia, diabetes, or being a current smoker [10••]

bleeding has emerged as a valuable predictor of early and late mortality in patients with ACS [12, 13]. These considerations and the interdependence of these factors suggest that a dual-risk stratification approach is imperative. As such, it implies that patients be simultaneously stratified with respect to their ischemic and bleeding risk.

Treatments for NSTEMI reduce ischemic events but at the cost of increased bleeding risk, the clinical relevance of which has been highlighted as detrimental to clinical outcomes. Patients who suffer a significant hemorrhagic event in the setting ACS not only suffer the consequences of blood loss, they also suffer the results of complications from the therapy required to treat it from an absolute

increase in mortality risk because significant bleeding precludes the use of ischemia prevention intervention. Hence, there has been growing interest in identifying predictors of bleeding, particularly major bleeding. Several risk scores have been created recently to help quantitatively assess the risk of major bleeding [5] (see Fig. 6).

CRUSADE

The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry enrolled more than 200,000 NSTEMI/ACS patients and served to derive the CRUSADE bleeding score. This model identifies eight independent baseline predictors of in-hospital major bleeding among community-treated NSTEMI patients [14••]. CRUSADE major bleeding was defined as intracranial hemorrhage, documented retroperitoneal bleed, hematocrit drop ≥12 % (baseline to nadir), any red blood cell transfusion when baseline hematocrit was ≥28 %, or any red blood cell transfusion when baseline hematocrit was <28 % with a witnessed bleed [2]. The CRUSADE bleeding score (range 1–100 points) was created by assigning weighted integers that corresponded to the coefficient of variables (see Table 4). The bleeding score was assessed as: very low risk <20; low risk 21–30; moderate risk 31–40; high risk 41–50; and very high risk >50. The rate of major bleeding increased by bleeding risk score quintiles: 3.1 % for those at very low risk; 5.5 % for those at low risk; 8.6 % for those at moderate risk; 11.9 % for those at high risk; and 19.5 % for those at very high risk (see Table 2).

Fig. 6 Potential relationship between bleeding and mortality [16]

Table 2 Algorithm used to determine the risk score of CRUSADE in-hospital major bleeding

Predictor	Score
Baseline hematocrit (%)	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance (mL/min)	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (bpm)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease	
No	0
Yes	0
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure (mmHg)	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

CHF congestive heart failure

Creatinine clearance was estimated with the Cockcroft-Gault formula

Prior vascular disease was defined as history of peripheral artery disease or prior stroke

BLEED-Myocardial Infarction (BLEED-MI)

The BLEED-MI prediction model derived and validated a score for the prediction of mid-term bleeding events following discharge for MI using collected baseline data at the time of MI diagnosis and outcome data from a cohort of 1,050 patients admitted with a MI, with an additional 852

Table 3 BLEED-MI risk scores [15]

Variable	Points assigned
Age (years)	
<65	0
65–74	1
≥75	2
GFR at admission (MDRD formula, mL/min)	
≥60	0
30–59.9	1
<30	2
History of stroke or transient ischemic attack	
No	0
Yes	1
Heart failure during hospitalization	
No	0
Yes	1
History of hypertension	
No	0
Yes	1
Antithrombotic therapy	
1 agent	1
2 agents	2
3 agents	3
Hemoglobin at admission (g/dL)	
≥12	0
10–11.9	1
<10	2
Blood urea nitrogen at admission (mg/dL)	
<10	0
10–25	1
>25	2
History of major hemorrhage or bleeding event during hospitalization	4
No	0
Yes	1
Smoking habits (until hospitalization)	
No	0
Yes	1
History of diabetes mellitus	
No	0
Yes	1

patients admitted at a later date. BLEED-MI showed good calibration, accuracy and discriminative performance for predicting post-discharge hemorrhagic episodes, and a composite endpoint of bleeding events plus all-cause mortality [12]. Importantly, an accurate prediction of bleeding events was shown to be independent of mortality. Moreover, progressively increasing risk of the primary and secondary endpoints was evident with increasing BLEED-

MI scores. Patients were grouped according to three risk categories: score 0–3 = low risk; 4–6 = intermediate risk; and ≥ 7 = high risk. The BLEED-MI results suggested a very high capability of the BLEED-MI rule in identifying low-risk patients; low-risk patients had an event rate of 1.2 %; intermediate risk patients has an event rate of 5.6 %; while high risk patients had an event rate of 12.5 %. The parameters of the BLEED-MI score are presented in Table 3.

ACTION

The ACTION (Acute Coronary Treatment and Intervention Outcomes Network) in-hospital major bleeding risk model was developed from the ACTION Registry-GWTG database to stratify patients with ST-segment Elevation Myocardial Infarction and non-ST-segment elevation (NSTEMI) myocardial infarction who were at elevated risk for bleeding. Derived from the ongoing ACTION-GWTG registry of MI, the model incorporated 12 baseline variables into a regression model. Variables are shown in Table 6. The risk model discriminated well in the derivation (C -statistic = 0.73) and validation (C -statistic = 0.71)

cohorts. A risk score for major bleeding corresponded well with observed bleeding: very low risk (3.9 %), low risk (7.3 %), moderate risk (16.1 %), high risk (29.0 %), and very high risk (39.8 %) [17] (see Table 4).

Overall, the various bleeding scores have significant overlap (see Table 8). Calculators for all are available on the internet. Whether one score is superior to any other is as yet not defined. Finally, scores are not diagnostic tools, but rather to assess risk. See Table 5 for a comparison of the different bleeding scores shows several identical or similar parameters used in risk calculation.

How Do Diverse Factors Enter into Treatment Decisions?

To begin to clarify the balance between risk of thrombotic and ischemic complications, which is usually emergent, and risk of hemorrhage, which is usually delayed, consistent methodologies amenable to the dearth of data available in the pre-angiography setting (particularly lack of knowledge of the coronary anatomy, which is defined only by angiography) must be established to facilitate risk/benefit analysis and treatment choices as they apply to individual patients. Differences among bleeding events add

Table 4 ACTION risk scores [15]

Age (years)	Points	Baseline serum creatinine (mg/dL)	Points	Systolic blood pressure on admission (mmHg)	Points	Baseline Hgb (g/dl)	Points	Heart rate on admission (beats/min)	Points
≤40	0	<0.8	0	≤90	4	<5	17	≤40	0
41–50	1	0.8–1.59	1	91–100	3	5–7.9	15	41–60	2
51–60	2	1.6–1.99	2	101–120	2	8–9.9	13	61–70	3
61–70	3	2.0–2.99	4	121–140	1	10–10.9	12	71–80	5
71–80	4	3.0–3.99	6	141–170	0	11–13.9	9	81–100	6
81–90	5	4.0–4.99	8	171–200	1	14–15.9	6	101–110	8
≥91	6	5.0–5.99	10	≥201	2	≥16	2	111–120	9
		≥6	11					121–130	11
								131–150	12
		On dialysis	11					>151	14
Weight (kg)		Points	Gender	Points	Home warfarin use		Points	Diabetes mellitus	Points
≤50		5	Female	4	No		0	No	0
51–70		4	Male	0	Yes		2	Yes	3
71–100		3							
101–120		2							
121–140		1							
≥141		0							
Heart failure ± shock on admission		Points	Electrocardiographic changes				Points	Previous peripheral artery disease	Points
None		0	No ST-segment changes				0	No	0
Heart failure only		3	ST-segment depression or transient elevation				3	Yes	3
Heart failure with shock		15	ST-segment elevation				7		

Table 5 Comparison of major bleeding risk scoring

CRUSADE	BLEED-MI	ACTION
Baseline hematocrit Creatinine clearance Heart rate SexSigns of CHF Diabetes mellitus Prior vascular disease Systolic blood pressure	Baseline hemoglobinGFRAgeHF during hospitalization DiabetesHistory of stroke/TIA Antithrombotic therapy Smoking BUNHistory of major bleed	Baseline hemoglobin Baseline serum creatinine Heart rate Female gender Age Heart failure or shock Diabetes PADSystolic blood pressure Home warfarin use ECG changes Body weight

to this challenge in that, for example, compressible bleeds in the groin differ from non-compressible bleeds in the retroperitoneum. In addition, both access-site and non-access-site bleeding events occurring within 30 days of PCI are independently associated with increased risk of 1-year mortality. Non-access-site bleeding correlates more clearly with mortality than does access-site bleeding, so this differentiation improves the discriminatory power of models for mortality prediction [15]. Ultimately, this leads us to the conclusion that mortality risk from an NSTEMI must be balanced against mortality risk associated with a major bleeding event that could occur up to 30 days after treatment.

Attempting to balance ischemia treatment and bleeding risk creates a conundrum because data to provide direction are scarce, and subjective clinical judgment based on empirical data is the driving force in the early management of NSTEMI, where the traditional course of action is to combat ischemia initially and to worry about bleeding later. While validated tools for estimating the risk of both ischemia and bleeding are available, these schemes are usually not applied in the pre-angiographic environment. Furthermore, there is overlap in the elements of these scores (see Table 6) as many of the same predictors appear in both the bleeding and ischemic risk calculators, further complicating the issue.

Patient Phenotypes

So let's revisit that hypothetical case of the small 72-year-old woman with a history of CVA, renal failure, and diabetes, who presents to the ED with chest pain and is ultimately diagnosed with a NSTEMI. Based on a qualitative review, she is at high risk for ischemia as a result of her prior MI, but she is also at high risk for bleeding based her on prior CVA and her GFR. Quantitatively, using on-line risk calculators, this patient has a 19.2 % bleed risk as

Table 6 Comparison of key factors in ischemic risk and bleeding risk

Key prognostic factors for ischemia	Key prognostic factors for bleeding risk
Older age	Older age
Male gender	Female gender
Diabetes	Diabetes
Renal failure	Renal failure
Anemia	Anemia
ST segment deviation	ST segment deviation
Elevated cardiac biomarkers	Elevated cardiac biomarkers
Hemodynamics on presentation (systolic bp, h)	History of bleeding
Clinical instability (shock, v-tac)	Invasive cardiac interventions
HF—past or present	Intensity of antithrombotic treatment
Prior vascular disease	

calculated by CRUSADE [16] and a 14.0 % risk of death/MI as calculated by GRACE [17]. With her risk scores calculated and the determination that she is high risk for both an ischemic event as well as a major bleeding incident, a course of action becomes evident. First, she should go to the catheterization lab as soon as possible, and a cardiologist consult should occur sooner than later. She should also immediately receive 325 mg of aspirin and unfractionated heparin, but she should not receive enoxaparin or bivalirudin because she has CKD and these drugs' longer half-lives could increase bleeding risk. She should also not receive clopidogrel because of its long clinical effect and her high likelihood of multivessel disease potentially requiring coronary artery bypass grafting, ticagrelor because of her prior CVA, nor a GPIIb/IIIa antiplatelet agent because of her significant renal failure.

Now let's take a look at another patient whose case is the polar opposite of the previous one; a patient who presents at the ED with low ischemic risk and low risk of developing a bleed. This is a 55-year-old African American male who presents with prior chest pain that resolved without treatment at the ED. He is obese, hypertensive, and smokes. Upon calculation, his CRUSADE bleeding risk is 5.9 % and his GRACE risk of death/MI equals 7.0 %. An appropriate course of action would be aspirin 325 mg and a P2Y₁₂ antiplatelet therapy (ticagrelor, prasugrel, or clopidogrel 600 mg) since his bleeding risk is low. P2Y₁₂ is in question, since the ESC guidelines recommend that ticagrelor be used and not clopidogrel due to genetic polymorphism and platelet reactivity [6] while the ACCF/AHA Guidelines do not distinguish between the two [18] but favor ticagrelor based on results from the PLATO trial [19•]. The use of a low molecular weight heparin

Table 7 Case study phenotypes

High ischemic risk/high bleeding risk	High ischemic risk/low bleeding risk
72 year old Asian female	66 year old female Hispanic
Diabetes	AF on rivaroxaban
Prior MI	Mild CKD—eGFR 50 mL/min
Prior stroke	Hypertension
CKD—eGFR < 30 mL/min	Diet controlled diabetes
Low ischemic risk/high bleeding risk	Low ischemic risk/low bleeding risk
58 white male	55 year old male African American
Bare metal stent 13 months ago	No more chest pain
Smoker	Obese
Hyperlipidemia	Smoker
Obese	Hypertensive
Killip 2—HF	
Hypertensive	
Non-compliant	
Diabetes	
Normal renal function	

Table 8 Treatment recommendations

	High risk for ischemia (TIMI > 4, high GRACE score)	Low risk ischemia (TIMI < 4, low GRACE score)
High bleeding risk	Ticagrelor + ASA	ASA
Low bleeding risk	Clopidigrel	ASA
	Ticagrelor/prasugrel	LMWH
	Heparin/LMWH	
	ASA	

(LMWH), such as enoxaparin, would be appropriate because this patient will not go to the catheterization lab immediately, and the use of a GPIIb/IIIa is not indicated because he is not experiencing ongoing angina.

In our third case, we examine a patient with high ischemic risk and low bleeding risk. This patient is a 58-year-old Caucasian male who received a bare metal stent 13 months ago and now presents to the ED with angina, which he reports has been ongoing for the past two months. He is obese, smokes, and has hypertension, hyperlipidemia, and Killip class II heart failure. He also has type 2 diabetes and is remarkably noncompliant, as a chart review finds an extremely elevated HgbA1c. His CRUSADE bleeding risk is only 5.0 %, but his GRACE risk of MI/death is 10.0 %. For this patient, a suggested course of action would be to immediately administer 325 mg of aspirin and unfractionated heparin, but hold LMWH because of his known coronary artery disease while attempting to obtain the cardiac catheterization report from his stent procedure 13 months ago. This patient is unlikely to be a PCI candidate; rather he is more likely to undergo

CABG surgery after angiography as there is high likelihood of triple-vessel disease. These factors suggest that due to its shorter offset, ticagrelor is the preferred antiplatelet therapy at this time. The high likelihood of a CABG procedure also suggests that, even though he has a low risk score for bleeding, his prior stent and CAD history suggest he may not be an appropriate candidate for triple antiplatelet therapy with the GPIIb/IIIa. This example shows that although risk scores may be helpful in clinical decision making, they must be considered in the context of the individual patient. In this gentleman, his comorbidities complicate his situation and his diabetes control, renal function, obesity, hypertension, and cigarette smoking must all factor into his ongoing care.

Our final hypothetical patient case highlights a patient with low ischemia/high bleeding risk. A 66-year-old Hispanic woman presents to the ED with mild chest pain. She has atrial fibrillation (AF) and is already taking rivaroxaban. She is hypertensive; has type-2 DM that she controls by diet, and has mild chronic renal failure with a serum creatinine of 1.7 mg/dL (eGR 50 mL/min). Upon calculation, her CRUSADE bleeding risk is 12.8 % while her GRACE ischemic risk is 8.0 %. An appropriate course of action would be to put her on 325 mg of aspirin, but not an anticoagulant, because she is already taking rivaroxaban for her AF. An activated prothrombin time measurement could provide some guidance as to her anticoagulant exposure in consideration of her renal status as well as the timing of her last rivaroxaban dose. No antiplatelet treatment is recommended because her bleeding risk is high and a cardiology consult is strongly recommended as soon as possible (see Tables 7, 8).

Conclusion

Treatment of NSTEMI has customarily focused on the early prevention or reduction of ischemic complications with potent antiplatelet and antithrombotic medications. However, these reductions in recurrent ischemic events have come at a price: increased risk of major bleeding, which is associated with adverse clinical outcomes. In fact, bleeding has emerged as an important predictor of early and late mortality in patients with ACS. While it is important to appreciate the role of early antiplatelet agents and anticoagulation in the treatment of NSTEMI patients, appropriate therapy must balance the need for potent ischemic inhibition against the potential for bleeding.

There is, thus, a strong case for balancing ischemic risk, which is usually emergent, against bleeding risk at the time ED treatment is initiated rather than addressing bleeding risk later in a patient's clinical course. Often, however, balancing ischemic risk against risk of bleeding presents a clinical conundrum because of the subjective nature of clinical judgment. In this manner, applying empirical data by the use of ischemia and bleeding risk scores may assist the provider in early decision making. Unfortunately, although validated tools for estimating risks are available, these tools are seldom used in the initial environment. Finally, complicating the issue is the fact that many of the same risk factors appear in the bleeding risk calculators and the ischemic risk calculators.

The HEMI-ACS panel, thus, submits that dual risk stratification can be conducted at bedside in a semi-quantitative way from the moment a NSTEMI patient presents at the hospital. To this end, the HEMI-ACS panel suggests several steps on which emergency physicians and hospitalists could base decisions about a course of action in a given patient:

1. Clinical judgment—what is best for that patient
2. Specific patient characteristics—e.g., history of prior catheterization, overall physiologic state (frail patient vs stronger patient)
3. Logistics of subsequent care—e.g., does the patient need to be transferred; if PCI required, what is the wait time, time of day, weekend)
4. Collaboration with a cardiologist

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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