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Contemporary NSTEMI management: the role of the hospitalist.

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Contemporary NSTEMI management: the role of the hospitalist

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ABSTRACT

Non-ST-segment elevation myocardial infarction (NSTEMI) is defined as elevated cardiac biomarkers of necrosis in the absence of persistent ST-segment elevation in the setting of anginal symptoms or other acute event. It carries a poorer prognosis than most ST-segment elevation events, owing to the typical comorbidity burden of the older NSTEMI patients as well as diverse etiologies that add complexity to therapeutic decision-making. It may result from an acute atherothrombotic event ('Type 1') or as the result of other causes of mismatch of myocardial oxygen supply and demand ('Type 2'). Regardless of type and other clinical factors, the hospital medicine specialist is increasingly responsible for managing or coordinating the care of these patients. Following published guidelines for risk stratification and basing anti-anginal, anticoagulant, antiplatelet, other pharmacologic therapies, and overall management approach on that individualized patient risk assessment can be expected to result in better short- and long-term clinical outcomes, including near-term readmission and recurrent events. We present here a review of the evidence basis and expert commentary to assist the hospitalist in achieving those improved outcomes in NSTEMI. Given that the Society for Hospital Medicine cites care of patients with acute coronary syndrome as a core competency for hospitalists, it is essential that those specialists stay current on optimal NSTEMI care.

Abbreviations: ACC: American college of cardiology; ACCOAST: comparison of prasugrel at the time of diagnosis in patients with non-ST elevation myocardial infarction; ACS: acute coronary syndrome; ADP: adenosine diphosphate; AHA: American heart association; ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; cTn: cardiac troponin; CRUSADE: can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines; CURE: clopidogrel in unstable angina to prevent recurrent events; CURRENT: OASIS-7 clopidogrel and aspirin optimal dose usage to reduce recurrent events—seventh organization to assess strategies in ischemic syndromes; ECG: electrocardiogram; ED: emergency department; ESRD: endstage renal disease; ESC: European society of cardiology; FDA: food and drug administration; GRACE: global registry of acute coronary events; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; MI: myocardial infarction; MVO₂: myocardial oxygen demand; NSTEMI: non-ST-segment-elevation myocardial infarction; NTG: Nitroglycerin; PCI: percutaneous coronary intervention; plato: platelet inhibition and patient outcomes; PPI: proton pump inhibitor; PURSUIT: platelet glycoprotein IIb/IIIa in unstable angina: Receptor Suppression Using Integrilin Therapy; RAAS: Renin-Angiotensin-Aldosterone System; SHM: society of hospital medicine; STEMI: ST-segment-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; TRITON-TIMI: trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel—thrombolysis in myocardial infarction

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Introduction

This review and commentary are intended to distill information from evidence-based society guidelines, recent studies, and best practices held among specialists in hospital medicine, emergency medicine, and cardiology, to guide the hospitalist in managing non-ST-segment-elevation myocardial infarction (NSTEMI). In both tertiary care and community hospitals, hospitalists are increasingly responsible for some if not all of the medical management of

NSTEMI in a number of different clinical scenarios. Regardless of setting, their goal is to support, advocate for and provide data-driven risk stratification, and offer risk-driven treatment and evidence-based continuity of care from the hospital admission to discharge and follow up. We provide guidance to inform the hospitalist's evidence-based care in both the medical and interventional hospital cardiac care settings, and in both the upstream (prior to diagnostic coronary angiography and evaluation of the

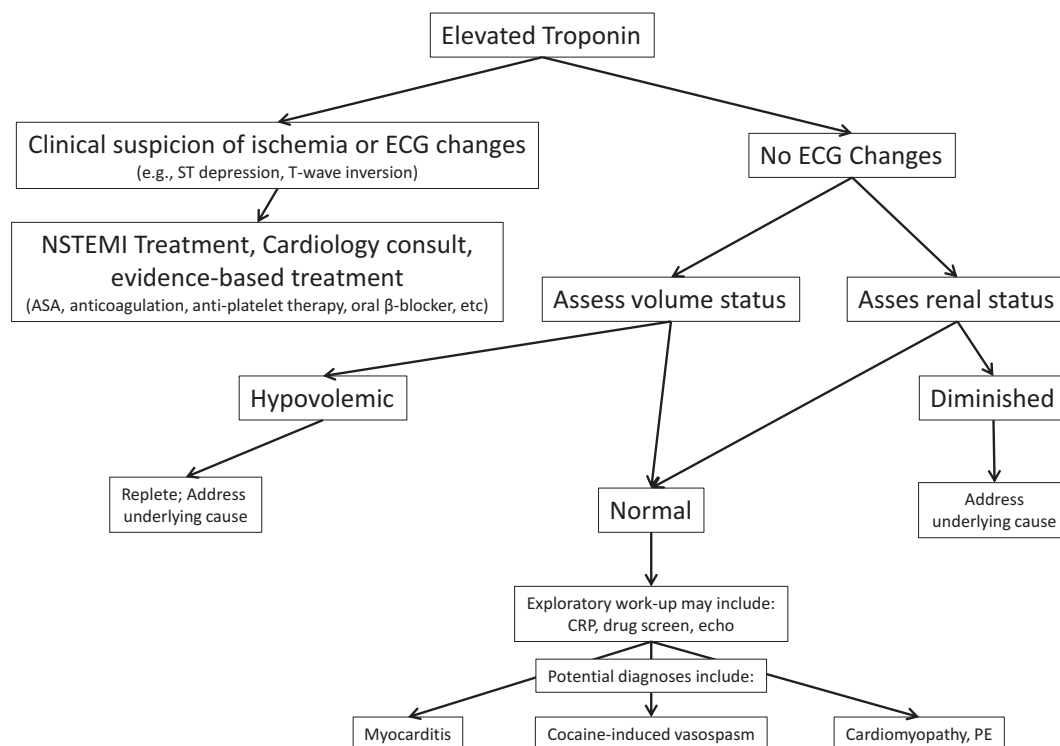


Figure 1. Initial evaluation pathway for elevated troponin.

coronary anatomy, if performed) and downstream (post-angiographic) timeframes. Recommendations from current guidelines, pivotal clinical trials and recent observational studies, along with expert consensus among the authors is offered.

Three hospital medicine specialists, two emergency medicine specialists, one noninvasive cardiologist, one interventional cardiologist, and one hospital pharmacist specializing in thrombosis care collaborated on this article. A panel was held to discuss individual perspectives on NSTEMI management and create a cohesive set of recommendations to disseminate for hospitalists' use in varying practice environments. The panel's deliberations and the writing of this paper were facilitated by the Hospital Quality Foundation (www.hospitalqualityfoundation.org) and supported by an unrestricted educational grant from AstraZeneca, whose representatives were not involved in the discussions or the editorial process.

Definition of NSTEMI

The term 'NSTEMI' is defined as elevated cardiac biomarkers of necrosis with the absence of persistent ST-segment elevation (with the exception of posterior myocardial infarction) in the setting of anginal symptoms or other acute event. It is distinguished from unstable angina, which has similar symptoms, by laboratory criteria (i.e., elevation of cardiac troponin). There are no diagnostic electrocardiographic criteria for NSTEMI. The term 'acute coronary syndrome' (ACS) encompasses STEMI, NSTEMI, and unstable angina, and is characterized in the Fourth Universal Definition of Myocardial Infarction as 'the sudden imbalance between myocardial oxygen consumption (MVO_2) and demand' [1]. This imbalance is typically rooted coronary atherosclerosis. The primary risk factors for the development of atherosclerotic disease include hypertension, dyslipidemia, diabetes mellitus, tobacco

use, and family history. While STEMI typically results from the rupture or erosion of an atherosclerotic plaque that triggers local inflammatory and prothrombotic activity *in situ*, resulting in occlusion by platelet aggregation, thrombus formation, and infarction of the muscle subtended by the affected vessel, NSTEMI results from an imbalance in oxygen supply and demand by and delivery to the myocardium, which can be caused by numerous pathologies including acute coronary thrombosis.

In the United States, the median age of NSTEMI is 68 years and occurs in an approximately 3:2 male:female ratio, though some of the gender imbalance may be due to diagnostic bias [2]. Myocardial infarction (MI) refers to the death of myocardial cells due to ischemia. In order to fit laboratory requirements for myocardial injury, regardless of etiology, cardiac troponin (cTn) levels must be elevated above the 99th percentile of normal [1]. When MI is due to atherothrombotic coronary artery disease, with or without demonstrable atherosclerotic plaque disruption, the designation of 'Type 1 MI' is used. Type 2 MI refers to myocardial injury resulting from a disparity between myocardial demand and available oxygen supply that is not directly due to acute thrombosis. There are multiple possible causes of this imbalance, including states of diminished myocardial perfusion (reduced supply) such as hypotension or severe anemia, increased myocardial oxygen demand such as severe hypertension or sustained tachyarrhythmia, cardiac conditions such as heart failure and Takotsubo syndrome, and systemic conditions such as chronic kidney disease, hyperthyroidism, pulmonary embolism, sepsis, and stroke (Table 1) [2]. The 'Type 2' designation distinguishes an infarct from, for example, a stable low-grade myocardial injury that occurs when an end stage renal disease (ESRD) patient on dialysis has a chronically elevated troponin.

Table 1. Non-ACS causes of elevated cardiac troponin.

CORONARY	
	Fixed severe coronary atherosclerosis
	Coronary artery spasm
	Coronary artery embolism
	Coronary artery dissection
CARDIAC	
	Myocarditis/pericarditis
	Sustained tachy- or bradyarrhythmia
	Takotsubo syndrome
	Drug toxicity (licit, such as neomycin, and illicit, such as cocaine)
	Instrumentation/ablation
	Defibrillation
	Trauma (cardiac contusion)
	Heart failure
	Cardiomyopathy
VASCULAR	
	Severe hypertension
	Acute ischemic stroke
	Acute aortic dissection
PULMONARY	
	Acute respiratory failure
	Acute pulmonary embolism
	Severe pulmonary hypertension
SYSTEMIC	
	Advanced age
	Sepsis
	CKD
	Burns
	Severe exertion
	Amyloid
	Cirrhosis
	Rhabdomyolysis
	Hypotension/shock
	Severe anemia
	Post-operative status
	Strenuous exercise
	Stroke

In part because of these co-morbidities and the insidious nature of their effect on global physiology, patients with Type 2 MI as a whole have higher short-and long-term mortality rates than Type 1 patients [1,3]. The former are less likely to undergo interventional procedures or to be placed on evidence-based anti-platelet therapy. Of note, women are more likely to have a Type 2 versus a Type 1 MI [4]. Care is often focused on stabilizing the presenting illness that cardiac sequelae and their management may be deprioritized, or their underlying illness presents contraindications to usual cardiac management.

The patient experiencing an NSTEMI most often presents to the emergency department (ED) for initial care, but there is also a significant proportion of these patients that will emerge from inpatient floors as a Type 1 event or as Type 2 resulting from comorbidities that lead to increased MVO₂. Hospitalists encounter these patients in a variety of settings. Presenting symptoms in Type 1 NSTEMI may include chest pain, pressure or tightness, nausea and/or vomiting, and lightheadedness or palpitations; however, a patient may not experience any 'typical' symptoms, especially in the setting of certain comorbidities, such as diabetes and advanced age [5]. The patient may even present with another, potentially misleading chief complaint, such as altered mental status or hyperglycemia, without any overt or atypical ACS symptoms, and NSTEMI is discovered only incidentally as part of the initial workup. A high index of

suspicion and proactive evaluation are important for the practicing hospitalist in at-risk patients presenting with atypical symptoms, in order to not miss an NSTEMI.

The hospitalist

Hospital medicine specialists comprise the fastest growing physician specialty in US healthcare. There are currently more than 60,000 hospitalists practicing in the US [6], and there are multiple fellowships [7] available throughout the country through internal medicine, family practice, and pediatrics that focus on further enhancing the safety, quality, and effectiveness of care for hospitalists [8]. The hospitalist 'model' of an inpatient practice covered in timed shifts has led to the development of other 'ist'-suffixed practices, such as those of 'nocturnists,' who are hospitalists working only night shifts, 'extensivists,' hospitalists who also maintain a limited (usually post-hospitalization follow-up) outpatient clinic practice, and hospitalists that primarily or solely support one specialty, such as cardiology, neurology, or orthopedic surgery. This diversity of practice patterns for hospitalists is reflected in the various settings in which a patient with NSTEMI might be encountered and managed or comanaged.

Hospitalists may provide care to patients with NSTEMI as:

- An initial consultant to the ED, whether as the primary inpatient admitting physician, as facilitator of inter-facility transfer (which may bypass the ED), or as a 'bridge' to care by a cardiologist;
- As the 'overseer' of patients being dynamically risk-stratified in a dedicated chest pain or observation unit;
- As a consultant to another inpatient service in a patient who develops NSTEMI on the non-medical or post-operative service;
- As a manager of 'upstream' care, overseeing risk stratification and facilitating evidence-based, risk-driven medical therapy including antithrombotic care, analgesia, blood pressure and glycemic control, and overall stabilization; and/or
- As a manager of 'downstream' care, caring for the NSTEMI patient after angiography and/or intervention, maintaining evidence-based care; and/or
- As the director of the discharge and follow-up process, ensuring that evidence-based therapies are provided and that the NSTEMI patient has adequate follow-up arranged. This function enhances continuity of care and, if done well, can have a positive impact on overall care quality and 30-day readmission rates [9].

The hospitalist's practice vis-à-vis NSTEMI care can also vary dramatically based on the hospital setting (small vs large, urban vs rural, teaching vs nonteaching), the extent of cardiology back-up (especially the availability of diagnostic angiography and percutaneous coronary intervention (PCI)), and the existence (or lack thereof) of protocols for care. In each of these scenarios, the hospitalist can play a key role in timely, high-quality, interdisciplinary care of the NSTEMI patient. In fact, the Society for Hospital Medicine (SHM) denotes management of ACS as a core competency for hospitalists [10,11].

Evaluation of suspected type I MI

A 66-year-old male with history of hypertension and obesity presents to the ED complaining of substernal pain that began while he was shoveling snow. He has had this sensation before with vigorous activity, but not with this extent of persistence. He reports mild dyspnea, but no diaphoresis, nausea, or vomiting. He had a 'normal' treadmill stress test 7 years ago. On arrival, he reports waxing and waning substernal discomfort. His pulse rate is 96 bpm, blood pressure is 176/112 mm Hg, and respiratory rate is 20 bpm.

Evaluation and risk stratification

This patient is suspected of having a Type 1 MI, given his presentation and his cardiac risk profile. Initial evaluation must include a 12-lead electrocardiogram (ECG); the initial ECG allows rapid exclusion of STEMI. An ECG without STEMI but with new ST-segment depression or T-wave inversion identifies a patient who is at higher risk of poorer outcomes. The most common presenting ECG findings in NSTEMI, however, are sinus tachycardia and nonspecific ST-T wave changes.

Low-flow supplemental oxygen should be administered to maintain the pulse oximetry at at least 90%. Laboratory tests for electrolytes, glucose, renal function, and cardiac biomarkers should be promptly sent. This particular patient is not in need of any immediate resuscitative measures, but his cardiac rhythm and blood pressure trends should be monitored. In the absence of any contraindications (allergy or active bleeding), the patient should be given 324 mg of chewable aspirin (ASA). Sublingual nitroglycerin (NTG) may provide both pain relief and antihypertensive effect, but analgesic response to NTG does not confirm angina, nor does the lack of a response refute the presence of ACS [12]. Further pain relief can be provided with small, incremental doses of morphine sulfate (ACC/AHA Guidelines Level of Evidence IIb-B); larger doses should be avoided [2].

It is now common for hospital laboratories to offer high-sensitivity troponin assays, with the result that more subtle elevations in troponin are detected, leading to a significant increase in positive results. The challenge to the clinician is to determine which of these abnormal markers is due to acute myocardial ischemia, and which can be attributed to chronic conditions or acute stress that secondarily impact the myocardium. In fact, the majority of patients with an elevation in troponin are from causes other than ACS [13].

Repeat troponin assays are vital in distinguishing ACS from non-ACS causes of troponinemia, as there will be little to no change in non-ACS elevated troponin between measurements.

If the patient with elevated troponin does not present with typical or atypical ACS symptoms and has a reassuring ECG, it is important to investigate other possible etiologies such as sepsis, pulmonary embolism, hypertensive crisis, etc. Troponin levels must also be evaluated in the context of the patient's renal function, as even minute quantities of troponin in the bloodstream resulting from normal myocardial cell turnover will accumulate if the kidneys are not clearing them.

The patient in Case 1 has nonspecific ST-T wave changes on his initial ECG, an estimated creatinine clearance of 78 ml/min, and an elevated level of troponin. A diagnosis of a Type 1 NSTEMI is made.

Risk stratification = treatment stratification

In NSTEMI, the defining elevation of cardiac troponin by itself identifies a high-risk patient. In ACS management, high risk substantiates the use of high-intensity therapy, so the troponin-positive patient is more likely to benefit from advanced antithrombotic therapy and an invasive approach than from conservative therapy [2]. Early stress testing is not a sound option for the troponin-positive patient. Absent any contraindications to coronary angiography, if it is available, an invasive diagnostic study would be recommended within 48 h by both the current American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) guidelines for NSTEMI care [2,14]. In many smaller institutions in which hospitalists may provide care for patients such as this, that would mandate a choice between medical management only and transfer to another facility. It is important to note that 'upstream' management of this patient when destined for angiography is the same overall medical management – whether the goal is preparing the patient for angiography or bridging the patient to a safe hospital discharge and later risk stratification during the post-MI period.

While the elevation in troponin in a patient with anginal symptoms identifies high risk, there are additional validated means of assessing short- and long-term risk in NSTEMI. Such risk assessment models can be used to substantiate the intensity of medical therapy given in the early hours of NSTEMI care. While never a substitute for sound clinical judgment, such models objectively apply the relative impact of different risk factors on clinical decision-making. For example, the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial provided evidence for early (<24 h) versus delayed (>36 h) coronary angiography intervention in ACS in high-risk patients, with a substantial reduction in the secondary outcome of the study of death, MI, or refractory ischemia at 6 months in patients with a Global Registry of Acute Coronary Events (GRACE) Risk Score >140 who underwent an early invasive strategy [13,15]. The three most commonly used tools for ischemic risk stratification are Thrombolysis in Myocardial Infarction (TIMI) [16], GRACE [17], and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) [18] (Table 2). These scores vary in ease of use and the outcomes being predicted, but evaluate many overlapping parameters, and generally can be used bedside (for example, see https://www.outcomes-umassmed.org/grace/acs_risk2/index.html, accessed 10/14/19).

As antithrombotic agents and doses are selected, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) study provides the clinician with a tool to evaluate post-NSTEMI patients for bleeding risk [19]. The therapies that have the potential to benefit NSTEMI patients in terms of ischemic outcomes – anticoagulants,

Table 2. Parameters included in GRACE [34], TIMI [33], and PURSUIT [18] risk scores, and CRUSADE bleeding risk score [30].

	GRACE	TIMI	PURSUIT	CRUSADE Bleeding
Age	Y	Y	Y	
Heart rate	Y			Y
Systolic BP	Y			Y
Cardiac Arrest	Y			
ST Change on ECG	Y	Y	Y	
Elevated Troponin	Y	Y		
Killip Class	Y			
Cardiac Risk Factors		Y		
Known CAD		Y		Y
ASA use in 7 days		Y		
Severe Angina		Y		
Sex			Y	Y
Worst CCS-class in 6w			Y	
Signs of heart failure			Y	Y
Hematocrit				Y
Renal Function	Y			Y
History of Diabetes				Y
Risk levels as initially validated	Low: 0–133 Intermed: 134–200 High: > 200	Low: 0–2 Intermed: 3–4 High: 5–7	Linear 0–18	Very low: < 20 Low: 21–30 Moderate: 31–40 High: 41–50 Very high: > 50
Predicts	Death or (re) MI in hospital and at 6 months	Death, (re) MI, revasc within 30 days	Death or (re)MI in 30 days	Major bleeding

BP = blood pressure; ST = ST-segment; ECG = electrocardiogram; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society Angina Grade

anti-platelet medications, and angiography – all are associated with an increase in bleeding risk, so these should be employed with an eye toward improved benefit:risk balance in each case. The CRUSADE Bleeding Risk Score can be used to guide medication selection (e.g., with a higher score, one might choose to delay P2Y₁₂ inhibition until after the coronary anatomy is defined) or to guide interventional management once selected (e.g., using a radial instead of femoral approach for vascular access). Using validated ischemic and bleeding risk calculations together, especially in conjunction with an echocardiogram, can provide hospitalists with valuable guidance in managing NSTEMI patients [20–22].

Initiation of treatment

The goals of pharmacological therapy of NSTEMI are to facilitate a decreased myocardial oxygen demand and/or increased a myocardial oxygen supply and prevent further thrombosis. Initial medical treatment comprises a multitarget approach consisting of oxygen, antithrombotics, antianginal drugs, and statins.

After administering full-dose ASA (ACC/AHA Guidelines Level of Evidence I-A), sublingual NTG (I-C) if warranted, anti-hypertensives as needed, the focus is on dynamic risk stratification evaluating trending of cardiac enzymes, serial ECGs, and serial physical examination for deterioration of cardiac function. Acute management of hypertension, which in the early setting may be provided by intravenous NTG given for angina (I-B), should be followed per guidelines with oral beta-

adrenergic blockers (I-A) with or with angiotensin-converting enzyme (ACE) inhibitors (I-B) [2]. The latter is particularly useful in patients with diabetes or a history of heart failure (Class I-B) [2]. Current guidelines recommend against intravenous beta blockade in ACS patients, as they are potentially harmful when risk for shock is present (Class III-B) [2].

If no resuscitation is needed, then upstream/medical care is built upon that foundation. Antithrombotic therapy (comprising anticoagulation and antiplatelet medications) form the primary line of defense against further ischemic damage to the heart. Anticoagulation in the upstream setting is usually effectuated with unfractionated heparin. In the patient either not destined for angiography or whose upstream interval may be prolonged, enoxaparin and fondaparinux are reasonable alternatives to heparin.

Advanced antiplatelet therapy – that is, beyond ASA – targets the P2Y₁₂ (or adenosine diphosphate (ADP) – receptor on the platelet membrane. These drugs are potentially effective because ADP is a very potent activator of platelets. There are three oral and one parenteral P2Y₁₂ blockers approved by the United States Food and Drug Administration (FDA): the oral agents clopidogrel, prasugrel, and ticagrelor, and intravenous cangrelor. Cangrelor is an intravenous P2Y₁₂ inhibitor that is unlikely to be in the hospitalist's arsenal for NSTEMI management with the potential exception of the patient with poor gastrointestinal absorption intended for an early invasive treatment [23]. Prasugrel is not indicated in the upstream setting, due to excessive bleeding not offset by reduction in major adverse cardiac events (MACE) among patients not known to be going to coronary intervention [24–26]

The historical data for clopidogrel in upstream or medical management derive from CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), in which a 300 mg loading dose of clopidogrel (followed then by 75 mg once daily) plus ASA was superior to ASA alone in reducing MACE [27]. The management strategy studied in CURE is now largely outdated, as it preceded wide use of PCI and even troponin measurement. In addition, most cardiologists now administer an off-label loading dose of 600 mg clopidogrel. A formal study of both higher doses of clopidogrel and ASA in CURRENT-OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes) failed to demonstrate superiority of the higher doses of clopidogrel and clearly demonstrated excess bleeding risk attributable to higher doses of ASA [28].

The current ACC/AHA NSTEMI Guidelines gives preference to ticagrelor over clopidogrel [2]. Ticagrelor was studied vs clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) study with all patients receiving upstream dosing [29]. Ticagrelor has a more rapid and consistent onset and offset of action compared with clopidogrel. In the NSTEMI-ACS cohort of PLATO, the primary efficacy endpoint of MACE showed a mortality advantage for ticagrelor without significant differences in major bleeding between the two arms. A dedicated secondary analysis showed that the ischemic benefit was not impacted by the duration of the upstream interval [30]. The benefits of ticagrelor were observed

regardless of revascularization performed during the first 10 days after randomization. These data notwithstanding, ticagrelor is a potent antiplatelet agent, and as with all antithrombotics, a patient-specific benefit:risk analysis should be conducted at the bedside, primarily to balance relative ischemic risk with bleeding risk. The key factors in assessing bleeding risk are age, prior bleeding history, and renal function; in a subanalysis of PLATO of ACS patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding [31]. Should bleeding risk preclude an early invasive approach, data suggest an advantage for ticagrelor over clopidogrel in the medically managed NSTEMI patient [32]. (the key factors to consider are prior bleeding history, renal function, and age). Concern for an angiographically determined need for coronary artery bypass grafting (CABG) surgery mitigates against upstream loading of advanced antiplatelet therapy, but in contemporary practice near-term CABG is increasingly rare and surgeons are generally more predisposed to proceed with surgery without overt delay in order to avoid prolonged hospitalization. Current guidelines suggest that clopidogrel and ticagrelor be held for 5 days prior to elective CABG, and for 24 h prior to urgent CABG [2]. The recent promise of a specific reversal agent for ticagrelor means that this concern may be substantially ameliorated in the future [33]. Particularly in the NSTEMI patient being managed medically, but also in the upstream care of patients being invasively managed, hospitalists should feel comfortable, in consultation with their cardiology colleagues, administering a loading dose of ticagrelor (180 mg, followed then by 90 mg twice daily) to most NSTEMI patients. Current observational data support this approach [34].

There are limited data to support the efficacy of high-dose statin therapy in the early management of NSTEMI, but its known anti-inflammatory activity, the lack of concern for adverse events in the acute setting, and the need to continue statin therapy after discharge all make this a reasonable option for upstream/medical care of NSTEMI as managed by the hospitalist.

Treatment team

While, as discussed above, the hospitalist may play either a leading or supporting role in the management of NSTEMI, a multidisciplinary approach is required to optimize and make more consistent the care provided. Likewise, implementation of an evidence-based NSTEMI treatment pathway improves the care provided by all NSTEMI stakeholders [35]. The team managing the NSTEMI patient may include emergency physicians, hospitalists, cardiologists, nurses, pharmacists, and case management. The hospitalist often has a crucial role to play as the conductor among these services, and hospitalists should therefore be well represented on pathway committees, quality improvement projects, and other multidisciplinary groups involved in NSTEMI management. Perhaps most importantly, it often falls to the hospitalist to manage discharge planning for the Type 1 NSTEMI, arranging outpatient medications,

cardiac rehabilitation, and follow-up, possibly in coordination with case management. This is a crucial step in the treatment process that involves not only knowledge of and compliance with evidence-based guidelines [24,36], but also an accurate assessment of the patient's health literacy [37].

Case: evaluation of suspected type 2 MI

A 77-year-old female is an inpatient on the general surgical floor, having been admitted for diverticulitis. She had been sent in from her assisted living facility for abdominal pain and fever. In the ED, she was mildly hypotensive, tachycardic, and febrile. She was started on intravenous fluids and empiric broad-spectrum antibiotics. A computed tomography scan demonstrated acute diverticulitis with concern for perforation. She was admitted and underwent resection of 22 inches of colon the same night. On postoperative day 2, she was noted to have continued hypotension and tachycardia. Laboratory abnormalities included troponin elevation from baseline, and the covering hospitalist was asked to evaluate her. She had no complaints of chest discomfort or shortness of breath, and clinically she had no overt signs of heart failure. She had no known prior diagnosis of, or evaluation for, coronary artery disease.

Evaluation and differential diagnosis

In this case, the task of the consulting hospitalist is substantially different from that in the first case. There is limited clinical concern for a Type 1 NSTEMI, but evaluation, risk stratification, differential diagnosis, and next therapeutic steps are nonetheless driven by the elevated troponin level. This patient has sustained myocardial damage, although probably not as the result of acute plaque rupture. Nonetheless, elevated troponin levels indicate a high risk of mortality even without ACS. The hospitalist is faced with these issues, in order of priority: (1) stabilize the patient and support the blood pressure, considering transfer to a critical care setting if the patient's condition does not rapidly improve; (2) evaluate the patient's baseline issue (concern for intra-abdominal sepsis or hemorrhage); and (3) evaluate the elevated cTn level, thereby developing a differential diagnosis and plotting next therapies (See Figure 1).

The finding of an elevated troponin level is an indicator of poor prognosis, independent of comorbidity or the specifics of the clinical situation [38–41]. It is therefore important for the hospitalist to be familiar with other diagnoses associated with an elevated troponin.

The abnormal laboratory value must first be interpreted in the clinical context: that is, is there reasonable clinical suspicion of ACS? If not, one must evaluate the patient for secondary explanations of an imbalance in oxygen supply and demand to the cardiac myocytes. A possible 'coronary but not ACS' explanation of an elevated troponin is, in fact, supply:demand mismatch due to flow across a fixed coronary stenosis. The most common causes of elevated troponin outside the ACS setting are listed in Table 1 [1,42–44].

It is advisable for the managing or consulting hospitalist to seek input from the cardiology service on patients with

presumed non-ACS troponin elevation. A proper diagnosis for such patients is Type 2 NSTEMI [3], but coronary angiography is often not indicated. An optimal strategy for rapid evaluation of these patients includes close-interval (e.g. every 2 h) trending of troponin values and bedside transthoracic echocardiography. Absence of regional wall motion abnormalities in a patient such as the elderly post-operative female in the second case makes it unlikely that angiography or aggressive cardiology intervention will be helpful. This reinforces for the hospitalist the need to obtain an echocardiogram, even when logistically challenging, in such patients [45].

A careful history and physical examination must guide the hospitalist in further diagnostic endeavors. In evaluating for coronary disease, which of course can co-exist with other diverse diagnoses, there may be a role for computed tomographic coronary angiography (CCTA), especially if that study is available and echocardiography is not [46]. CCTA can provide evidence for or against critical CAD, with a high negative predictive value [13]. In the unstable patient in the Type 2 case, however, CCTA would not be a reasonable option, and urgent echocardiography should be pursued. In general, advanced anticoagulation and antiplatelet therapy should not be empirically initiated in these patients unless there is a strong suspicion of an active ACS diagnosis [3]. It is worth noting, however, that this distinction can be quite difficult; many patients with NSTEMI have only nonspecific ST-T wave changes, particularly if they have a history of left ventricular hypertrophy and hypertensive heart disease and are tachycardic, or if they have superimposed electrolyte abnormalities. While some other diagnoses, such as sepsis or arrhythmias, may be readily apparent, others may not, and therapy should be guided by the progress of the diagnostic and risk-stratification process. A BNP (or NT-pro-BNP) assay may be helpful in identifying heart failure- and pulmonary-related diagnoses; D-dimer, with its high sensitivity and low specificity, may have limited utility in supporting or refuting suspicion for pulmonary embolism in the Type 2 MI patient. Other diagnostic testing, including possible coronary angiography, is driven by the patient's co-morbidities and physical examination.

Downstream treatment and transition of care for NSTEMI patients

For patients who have diagnosed with NSTEMI, whether subjected to invasive management or not, both Joint Commission Core Measures and society guidelines recommend a broad range of treatments aimed at reducing the risk of another ACS event. Prior to hospital discharge, the hospitalist should be focused on restoring the patient to normal activities to the extent possible and to use the new NSTEMI diagnosis to formulate a plan of care, focusing particularly on lifestyle and risk factor modification. This patient education by the hospitalist is imperative to reduce readmission, ensure long-term adherence, and improve outcomes. Patients with NSTEMI represent a high-risk cohort in whom secondary cardiovascular disease prevention is likely to be particularly effective, and this should be initiated prior to index hospital discharge. Hospitalists in these cases are presented with an opportunity to provide evidence-based care to manage both

existing disease and future risk with pharmacologic treatments and lifestyle modification. Discharge medications should generally include an anti-ischemic medical regimen (nitrates, beta-blockers, calcium channel blockers) and antithrombotic medications applicable to the inpatient therapy. In most cases, this includes dual antiplatelet therapy. Prognostic benefits have also been shown for continued therapy with statins and, especially for diabetics and those with a left ventricular ejection fraction (LVEF) of 40% or less, an inhibitor of the renin-angiotensin-aldosterone system. Lifestyle modification guidance such as smoking cessation support, increased activity as tolerated, and nutritional counseling are helpful as well, and should be initiated at discharge. In addition, a pre-discharge echocardiogram and fasting lipid panel should be obtained.

A secondary goal for the hospitalist managing these discharges is to reduce the likelihood of 30-day readmissions. A 2018 study of such readmissions using the National Readmission Database 2014 identifying patients with a primary diagnosis of NSTEMI-ACS using ICD9 coding found that of 300,269 patients admitted with NSTEMI-ACS; 13.4% were readmitted within 30 days [47]. The most common cause of readmission was heart failure (15.6%), followed by a recurrent MI (10%). Predictors of increased readmissions included age ≥ 75 years, female gender, kidney disease, length of stay ≥ 5 days, and complications during the index admission such as acute kidney injury and major bleeding. Factors associated with a lower risk of readmission included care in a teaching hospital and performance of PCI on the index admission.

The hospitalist should liaise with all available resources, including the cardiology service. Involvement of case management for the entire hospital stay can help with increased compliance as it allows more time for insurance approval of various post-discharge recommendations, and addresses individual barriers to care.

In planning for hospital discharge, guidelines recommend assignment to cardiac rehab, which is followed by the inpatient team 75.9% of the time post NSTEMI, but only 50% of those patients referred for cardiac rehab actually enroll and participate [48]. Lack of insurance coverage may be a limiting factor. The quality and performance measures for cardiac rehab are available online [48–52]. Smoking cessation counseling and a clinical nutrition evaluation, when appropriate, should be arranged prior to discharge. Such behavioral interventions are much more likely to be successful when patient education techniques that account for the patient's and family's health literacy are considered [37]. The hospital setting after NSTEMI offers an ideal 'teachable moment' in which to educate patients and families and reinforce the education daily under the care of the hospitalist. Time is usually not an issue for either the hospitalist or the patient while in inpatient status. Patient education should also focus on the symptoms of potential recurrent ACS and the appropriate use of nitroglycerin should such symptoms occur. A pneumococcal vaccine and an influenza vaccine (if seasonally appropriate) should also be administered, if needed, prior to discharge.

Follow-up after discharge is essential for good short- and long-term outcomes. We recommend a follow-up phone call (perhaps from either the hospitalist or a hospital pharmacist) within 72 h of discharge, and an in-person follow-up

visit with cardiology or the patient's PCP within 7 days. Delays in follow-up are associated with poorer outcomes and poorer patient medication adherence [24]. Communication between the hospitalist and the follow-up physician (cardiologist or PCP) is imperative to establish and maintain continuity of care.

Initiation of evidence-based post-discharge pharmaceutical therapy provides optimal secondary prevention and reduces the likelihood of early readmission of the NSTEMI patient. In many facilities, the hospitalist plays a primary role in assuring these guidelines are followed. Per ACC/AHA Guidelines, the following therapies should be instituted at discharge unless specifically contraindicated [2]:

- Antithrombotic therapy is a mainstay of secondary prevention for ACS, and, if applicable, is a first line of defense against in-stent thrombosis.
 - ASA should be continued indefinitely at a dose of 81 mg per day (I-A).
 - Ticagrelor or clopidogrel should be continued for 12 months after an NSTEMI, even if PCI was not performed. If a stent was placed and the patient has a low bleeding risk, prasugrel can be used as a P2Y₁₂ inhibitor at the time of discharge (I-B). The ACC/AHA Guidelines give preference to ticagrelor or prasugrel for those patients treated invasively [2] (IIa-B).
 - So-called 'triple' oral antithrombotic therapy (ASA + P2Y₁₂ + oral anticoagulant) can be considered in those who have been treated for NSTEMI but also have atrial fibrillation. The most informative recent trial addressing this issue is AUGUSTUS (Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) [51], which showed that in patients with atrial fibrillation and a recent ACS or PCI treated with a P2Y₁₂ inhibitor, an antithrombotic regimen of apixaban plus a P2Y₁₂ agent, without aspirin, resulted in similar rates of secondary ischemic events with less bleeding than regimens that included a vitamin K antagonist, a P2Y₁₂ antiplatelet agents, and aspirin) [51].
- Lipid management
 - There is no demonstrable benefit to niacin or fish oil in secondary prevention started acutely after NSTEMI.
 - Statins are effective in reducing lipid levels and have a presumed intravascular anti-inflammatory effect that reduces the likelihood of recurrent ACS [52] (I-A). The intensity of statin therapy should be individualized based on desired effect and tolerance. Ezetimibe may be a useful additional therapy [53]. The role of PCSK9 therapy is still being evaluated clinically and for cost-effectiveness, but holds promise [54].
- Beta-adrenergic blockers
 - Beta blockers decrease heart rate, contractility, and blood pressure, resulting in decreased myocardial oxygen demand, and should be provided as part of a secondary prevention strategy after NSTEMI. Beta blockers increase

long-term survival after NSTEMI and should be initiated during the ACS hospitalization and continued at discharge (I-A). In patients with LVEF <0.40, beta blockers are even more strongly recommended at the time of discharge (I-A).

- Beta blockers should be used carefully with ACE inhibitors or angiotensin-receptor blockers (ARBs) in patients with heart failure, and renin-angiotensin-aldosterone system (RAAS) blocking agents should be cautiously added in patients with decompensated HF.
- The preferred agents in the NSTEMI setting are those beta-blockers with no intrinsic sympathomimetic activity, particularly sustained-release β_1 blockers such as metoprolol succinate, bisoprolol, or carvedilol.
- ACE inhibitors and ARBs
 - ACE inhibitors reduce mortality in patients with recent MI, especially those with LV dysfunction (LVEF <0.40), and in diabetic patients with normal LV function (including patients with diabetes mellitus). Unless there are specific contraindications, an agent in this class should be prescribed at hospital discharge (I-A).
- Aldosterone inhibition
 - Spironolactone should be added to the NSTEMI discharge regimen in patients with a LVEF < 45% (I-A).
- Prophylaxis with proton pump inhibitors
 - Proton pump inhibitors (PPIs) need not be routinely used in patients on dual antiplatelet therapy. Those with a history of gastrointestinal bleeding, those taking triple antithrombotic therapy, and those on high-dose corticosteroid therapy are most likely to benefit from prophylaxis with PPIs (IIa-C).
- SGLT-2 agents in type 2 diabetics
 - There may be a role for these agents in the future specifically in secondary prevention of ACS [55], but they cannot be routinely recommended as yet. Nonetheless, this is an active area of research and the potential benefit of starting an SGLT-2 inhibitor in Type 2 diabetic patients (and perhaps even those who are *not* diabetic) may soon become evident [56,57].

The problem of adherence

In spite of coordinated efforts on the part of the treatment team aimed at ensuring optimal post-discharge care for the NSTEMI patient, there may still be challenges that continue after discharge. Adherence to DAPT and other therapies is often suboptimal [24], and hospitalists must be both attuned to anticipated adherence issues at the time of discharge. Hospitalists and case managers must stay abreast of available voucher programs, pill packs, smartphone alarms, and the strategy of filling the first month (or, optimally, 90 days) of pills at discharge ('meds to beds' program) [58]. More liberal dispensing at discharge is often, unfortunately, prohibited by insurers [59]. It is not clear that use of generic drugs, when available, results in improved adherence [60]. Adherence among post-NSTEMI

patients continues to be a challenge, and even the most innovative programs and devices do not necessarily lead to improvements for patients [3,24,48,61,62].

Summary of recommendations

The hospital medicine specialist is ideally situated to ensure evidence-based, risk-driven, timely care in acute NSTEMI and in follow-up secondary prevention. Whether primarily or co-managing the patient, the hospitalist has the time, expertise, and experience to apply optimal care in this challenging cohort of patients, many of whom have extensive comorbidities and will benefit from consistent care and targeted education. Aside from performing the procedural aspects of diagnostic angiography and catheterization laboratory or operating room-based therapy, protocols and systems of NSTEMI care should be centered on the hospitalist for managing the patient and as a resource for other clinicians on the hospital care team and in the follow-up environment.

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