Bridging the Gap Between Scientific Evidence and Clinical Practice in the Management of Non-ST-segment Elevation Acute Coronary Syndromes

a report by
Sandeep Nathan, MD and Rajiv Swamy, MD

Section of Cardiology, University of Chicago Medical Center

The spectrum of acute coronary syndromes (ACS) encompasses a broad array of clinical characteristics and risk strata, ranging from unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI) and sudden cardiac death (SCD). In this article, UA and NSTEMI will be considered together as non-ST-segment elevation acute coronary syndromes (NSTE-ACS), reflecting the similarity in the pathogenesis and management of these entities.

Despite the significant advances that have been made in diagnostic technologies, the availability of newer therapeutic agents, and greater access to invasive therapies, as well as the burgeoning body of clinical trial and registry data linking specific treatment paradigms with improved clinical outcomes, many challenges remain in the management of NSTE-ACS. The dynamic nature of ACS presentation often confounds accurate risk stratification, with a resultant impact on early use of proven therapies. Hospital-specific resource limitations and uncertainties arising from the timing and use of invasive cardiac diagnostics and revascularization also often complicate management. The consistent observation that patients with NSTE-ACS, who make up the greatest proportion of ACS patients overall, suffer equal or higher rates of one-year mortality than STEMI patients underscores the need for further clarification and continued progress in this area of cardiovascular medicine.

Revised practice guidelines published by the American College of Cardiology and the American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) have helped to distill the enormous body of scientific data regarding ACS into organized recommendations suitable for implementation by the practicing clinician. Quality improvement initiatives have facilitated the benchmarking of ACS care at both institutional and national levels and these measures, along with a greater adoption of evidence-based strategies and increased clinician awareness, have vastly improved patient outcomes. The goal of this review is to provide the clinician with a succinct and up-to-date perspective on the evidence-based acute pharmacological treatment of NSTE-ACS, which has become a complex and often confusing endeavor.

Pathophysiology of Acute Coronary Syndromes

The contemporary model of ACS pathophysiology implicates several contributing factors, including acute and chronic vascular alterations, plaque growth, activation of the platelet and coagulation cascades, and inflammation (local and systemic). The term ‘atherothrombosis’ is often used to describe these and related systemic processes occurring in any of a number of diseased arterial beds, most often the coronary, cerebral, and peripheral vasculature. Rupture or erosion of a thin-capped coronary plaque serves as the initiating factor for most ACS events. Resultant exposure of thrombogenic plaque contents and bound tissue factor to the circulating blood pool activates the coagulation cascade. Activated platelets that adhere to the site of vascular injury occupy a central pathogenetic role in that they participate in both early and late thrombin generation, promote the efficient assembly of coagulation factors, and aggregate via interactions between activated platelet surface glycoprotein (GP) Ib/IIa receptors and soluble fibrinogen to form a platelet-rich thrombus. The binding of fibrin, trapping of cellular material, and formation of a mature, occlusive thrombus represent relatively late events in the atherothrombotic process. The presence of collateral coronary flow, the counterbalancing effects of endogenous thrombolytic mechanisms, and ultimately the degree of coronary luminal compromise largely determine the nature of the clinical presentation. Transient reductions in coronary blood flow often manifest as UA, whereas more prolonged flow reduction and macro- or microvascular embolization may result in myocardial necrosis and NSTEMI presentation. It is now recognized that simultaneous activation of multiple coronary plaques and/or polyvascular disease occurs in a significant proportion of
patients with atherothrombosis. Furthermore, manifest disease in one vascular territory significantly increases the cross-risk of future and recurrent vascular events in subclinically involved territories. Thus, the coagulation and platelet cascades serve in unique and complementary roles in the pathogenesis of ACS (see Figure 1). Accordingly, the available clinical evidence suggests that targeted co-administration of anticoagulant and antiplatelet agents, as detailed below, yields the greatest clinical benefit.

**Risk Stratification in Acute Coronary Syndromes**

Rapid, accurate risk stratification remains a critically important component of the ACS management paradigm. In addition to providing important prognostic information, risk stratification helps to ensure that patients manifesting the greatest presentation acuity receive the most intensive pharmacological and invasive therapies. Several risk stratification schema have been shown to provide independent value in this regard. The Thrombolysis in Myocardial Infarction (TIMI) risk score for UA/NSTEMI is perhaps the most widely used tool for the rapid bedside assessment of patient risk. Originally derived from the TIMI 11B and Enoxaparin Versus Heparin in Unstable Angina and Non-Q-wave Myocardial Infarction (ESSENCE) trial data sets, the TIMI risk score has since been validated in a variety of patient groups including contemporary registry-derived populations for the prognostication of short- and intermediate-term ischemic morbidity and mortality. Other scoring systems recognized in the 2007 ACC/AHA UANSTEMI practice guidelines include those derived from the Global Registry of Acute Coronary Events (GRACE) database and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. Along with the attendant benefits of pairing appropriate patient groups with targeted therapeutics, the routine use of bedside risk stratification also holds the potential for improving communication between the various groups of healthcare providers involved in the care of the ACS patient.

**Invasive versus Initial Conservative Management Strategies**

Invasive versus initial conservative (also referred to as ‘selective invasive’) management represents a point of divergence that the treating physician must negotiate early in the course of treatment. While there is no consensus regarding what timeframe constitutes ‘early’ invasive therapy, direct cardiac catheterization within 24–48 hours of presentation without the initial use of non-invasive testing or waiting for failure of medical therapy generally fulfills this designation. Potential benefits offered by this strategy include early identification and disposition of patients at both ends of the risk spectrum (i.e. those with non-obstructive disease warranting medical management alone and those with multivessel or left main coronary disease requiring surgical revascularization) and the use of percutaneous coronary intervention (PCI) in appropriately selected patients before recurrent ischemic events can occur.

Certain individual studies evaluating the merit of the routine use of early invasive strategies have reported conflicting results. In the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS TIMI-18) trial, patients with NSTE-ACS, elevated levels of cardiac markers, a history of coronary artery disease (CAD), or all three criteria were treated with aspirin, heparin, and the GPIIb/IIIa inhibitor tirofiban. Patients were randomized to an early invasive strategy (within 48 hours after presentation) or to a more conservative strategy, in which catheterization was performed only if patients had objective evidence of recurrent ischemia or abnormal stress testing. At six months, the early invasive strategy was associated with death, MI, or rehospitalization in 15.9% of patients compared with 19.4% of those in the conservative strategy group. The rate of death or non-fatal MI was also significantly reduced in the early invasive strategy group (7.3 versus 9.5%; p<0.05). The benefits of an invasive strategy were seen in both men and women. Furthermore, the benefits of the invasive strategy were achieved at no significant increase in the costs of care over the six-month follow-up period.

The Fragmin During Instability in Coronary Artery Disease II (FRISC-II) trial compared three months of the low-molecular-weight heparin (LMWH) dalteparin versus placebo, as well as the use of an early invasive strategy with a conservative strategy. At six months, the composite of death or MI was decreased in the early invasive strategy group from 12.1 to 9.4% (p=0.031) compared with those managed conservatively. At one-year follow-up, the greatest reduction in mortality was primarily seen in men.

In contrast to the results of the FRISC-II and TACTICS TIMI-18 trials, the recent Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) study demonstrated a favorable benefit for a selective invasive strategy. The study randomized patients to invasive or selective invasive management and followed them up for one year with respect to the composite primary end-point of death, MI, and rehospitalization due to angina. All patients in the study received aspirin and substituent LMWH (enoxaparin). Additionally, all patients undergoing PCI during the initial hospitalization were treated with abciximab, and early use of clopidogrel and high-dose atorvastatin was recommended. At one-year follow-up, no significant differences were observed between the invasive and conservative strategies.
observed between the groups with respect to the primary end-point. However, the incidence of MI was significantly higher in the early invasive group (15 versus 19%; p=0.005), although rehospitalization was less frequent in the invasive group (7.4 versus 10.9%; p=0.04). Possible reasons that have been proposed for the lack of benefit of the invasive strategy include the trial-specific criteria used to define myocardial infarction, the high rate of revascularization in the conservatively managed group (47%), and aggressive medical therapy in both groups.

Despite these conflicting data, several contemporary meta-analyses have largely put this issue to rest. In these pooled analyses, routine early invasive revascularization management, there was no increase in in-hospital death or MI, as might have been expected. It should be noted that in such registry-based experiences, the role of operator/selection bias cannot be discounted, and may indeed be the explanation for this seemingly disparate finding. Importantly, the use of routine or selective invasive therapies does not obviate the need to treat all ACS patients with intensive, risk-appropriate medical therapies and risk factor modification. Rather, intensive pharmacological therapies interact in a synergistic fashion with catheterization and coronary intervention, and should therefore be implemented even before the invasive management decision has been taken. In summary, early invasive management in conjunction with intensive pharmacotherapy remains the preferred approach in intermediate- to high-risk or clinically unstable patients in the absence of contraindications or patient preference to the contrary.

Acute Pharmacotherapies

Whereas only a subset of NSTE-ACS patients requires early invasive cardiac evaluation, virtually all patients benefit from and should ideally receive aggressive pharmacotherapies early and indefinitely. Despite the publication of the aforementioned practice guidelines and the wide availability of related educational initiatives, it remains a significant challenge for practicing physicians to keep pace with scientific discovery in this area. Acute pharmacotherapies for ACS can be broadly divided into three classes: anti-ischemic, anticoagulant, and antiplatelet agents. Anti-ischemic agents such as nitrates offer symptomatic relief of angina, while beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers and non-dihydropyridine calcium channel blockers may also yield reductions in ischemic morbidity and mortality in select populations.

Antiplatelet and anticoagulant therapies, perhaps to a greater extent than anti-ischemic therapies, are subject to both controversy and uncertainty. These classes of agents have consistently been underutilized in eligible NSTE-ACS patients enrolled in the CRUSADE registry, with significant differences noted in rates of use at leading versus lagging institutions (see Figure 2). Much of the uncertainty stems from the fact that the available data, abundant though they may be, have failed to yield one clearly superior anticoagulant or antiplatelet strategy. Additionally, there are concerns regarding bleeding risk and differences between procedural and non-procedural physicians with respect to choice and timing of various agents. However, the fact remains that these agents form the foundation of acute pharmacotherapy for NSTE-ACS and are essential for flow restoration in the ‘culprit’ coronary vessel(s) and resolution of intracoronary thrombus both before and after mechanical revascularization.

Anticoagulant Therapy

Indirect antithrombins (unfractionated heparins and LMWHs), direct thrombin inhibitors (bivalirudin), and factor Xa inhibitors (fonataparinux) currently comprise the anticoagulant class. Through binding with antithrombin, unfractionated heparin (UFH) indirectly inactivates thrombin (factor IIa) and factors IXa and Xa. Limitations of this compound include non-linear pharmacokinetics, inability to penetrate and resolve organized thrombus, and interaction with plasma proteins and platelets. Nevertheless, the value of UFH has been demonstrated in several placebo-controlled trials against the backdrop of aspirin therapy. A meta-analysis of these trials found a 33% relative risk reduction in the short-term incidence of death or MI. Weight-based administration is strongly preferred to the prior practice of fixed-dose therapy with a target activated partial thromboplastin time (aPTT) of 60–80 seconds.

Low-molecular-weight Heparins

LMWHs represent a more homogeneous population of molecules than UFH, and more effectively inactivate factor Xa than thrombin. They also offer more predictable anticoagulant response without the need for laboratory monitoring. Potential disadvantages of this class include the relative inability to monitor anticoagulant levels, long half-life, and
increase in bleeding and transfusion. Until these issues are clarified, it is
and antiplatelet agents were frequently overdosed, with a resultant
gained by a CRUSADE registry analysis, which found that anticoagulants
administration of pre-randomization anticoagulant therapies with 'cross-
IIb/IIIa Inhibitors (SYNERGY) trial, and may be linked in part to
of platelets. The bivalent DTIs hirudin and bivalirudin (a bio-engineered
form of hirudin) bind thrombin at the active site and exosite 1. The latter
agent is particularly attractive for use in ACS management and PCI as it
undergoes cleavage by bound thrombin, with return of active-site function
and a resultant short biological half-life. Use of bivalirudin
monotherapy in invasively managed intermediate- to high-risk NSTE-ACS
patients was evaluated in the Acute Catheterization and Urgent
Intervention Triage Strategy (ACUITY) trial. When viewed from the
perspective of net clinical benefit (inclusive of cardiovascular morbidty,
mortality, and protocol-specified bleeding end-points), the use of
bivalirudin with provisional use of GPIIb/IIIa inhibitors was non-inferior to
a strategy of heparin and mandatory GPIIb/IIIa inhibition. A modest
increase in ischemic events with bivalirudin monotherapy was
counterbalanced by decreases in major and minor bleeding. While this
data set in many ways mirrored contemporary, registry-derived patterns
of resource utilization in ACS, several important caveats should
be acknowledged when applying these data to clinical practice.
Pre-catheterization use of clopidogrel enhanced the efficacy of the
bivalirudin strategy to a greater degree than in the GP inhibitor groups.
Very early cardiac catheterization limited the duration of post-
randomization protocol-assigned therapies prior to PCI. Therefore, in
high-risk patients, those manifesting recurrent ischemic symptoms, or
when a delay to angiography is anticipated, the use of clopidogrel and/or
GPIIb/IIIa inhibition in conjunction with consistent anticoagulant therapy
may be more effective than DTI monotherapy. Fondaparinux is a synthetic
pentasaccharide that avidly binds antithrombin and rapidly inhibits factor
Xa. This compound was tested in NSTE-ACS patients against enoxaparin
in the Organisation to Assess Strategies in Acute Ischaemic Syndromes
(OASIS)-5 trial and was non-inferior with respect to death, MI, or
refractory ischemia at nine days. Interestingly, the mortality benefit of
fondaparinux over enoxaparin at 30 and 180 days was largely driven by
decreased major bleeding. Further evidence of the more modest
anticoagulant effect of fondaparinux was the excess of catheter
thrombosis seen in fondaparinux-treated patients undergoing coronary
angiography, necessitating additional peri-procedural dosing with UFH.
Thus, fondaparinux is also an anticoagulant option for NSTE-ACS
management, albeit a less attractive choice in patients undergoing early
invasive evaluation.

**Antiplatelet Therapy**

Activated platelets play a central role in the initiation and propagation of
vascular thrombosis. Circulating quiescent platelets adhere to the site
of vascular injury, triggering a variety of intracellular signaling
mechanisms that further strengthen the adhesive process and result in
platelet activation. Numerous endogenous agonists have been implicated
in the platelet activation sequence, with thrombin, adenosine
diphosphate (ADP), epinephrine, and thromboxane A2 (TXA2) playing
prominent roles. Upon activation, various soluble adhesive proteins,
growth factors, platelet agonists, and pro-coagulant substances are
either expressed on the platelet surface or released into circulation from
cytoplasmic granules. Importantly, the GPIIb/IIIa (αIIb/β3 integrin)
receptor found abundantly on the surface of the quiescent platelet
undergoes conformational activation and further upregulation. The
observed complexity of the activation sequence serves as the rationale
for the use of multiple complementary antiplatelet agents in the
management of coronary thrombosis. Three classes of agent play a major
role in the management of NSTE-ACS: aspirin, thienopyridines, and
platelet GPIIb/IIIa receptor inhibitors. Aspirin inhibits platelet aggregation
through irreversible inhibition of platelet cyclo-oxygenase-1-mediated
generation of thromboxane A2. Pooled data from 195 trials including
143,000 patients have demonstrated a 22% risk reduction in the odds of
MI, stroke, or vascular death with aspirin versus placebo when used in
the capacity of secondary prevention. In suspected or definite ACS,
aspirin should be administered immediately (162–325mg) and continued
indefinitely in the absence of contraindications or adverse reactions.

**Oral Platelet Antagonists**

Thienopyridines (ticlopidine, clopidogrel) exert their antiplatelet effect by
permanently binding with the ADP P2Y12 platelet surface receptor,
which in turn downregulates activity of the GPIIb/IIIa receptor complex.
Clopidogrel in conjunction with aspirin was shown in the Clopidogrel in
Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial to
reduce major adverse early and late cardiac events following admission
for NSTE-ACS versus aspirin alone. While the benefit of dual antiplatelet therapy (aspirin and clopidogrel) was noted across all risk strata, these findings were most pronounced in the highest-risk groups and in those patients undergoing PCI. The time to plateau platelet inhibition with clopidogrel is significantly shortened with initial administration of an oral loading dose; however, questions remain regarding the optimal dose. Several investigations have examined this issue in the context of ACS and PCI. The available data suggest that the non-US Food and Drug Administration (FDA)-approved 600mg loading dose is safe and more rapidly efficacious than FDA-approved regimens. However, despite broad demonstrations of efficacy, a persistent concern is that of clopidogrel hypo-response. This phenomenon appears to be multifactorial in etiology, is prevalent in up to one-third of ACS or PCI patients, remains difficult to predict, and is strongly associated with increased cardiac events in high-risk patient groups. Investigational antiplatelet agents such as the thienopyridine compound prasugrel offer greater potency than clopidogrel with a lower rate of non-response and faster onset of action. In the TRITON-TIMI 38 study, which compared prasugrel with clopidogrel in NSTE-ACS with planned PCI, prasugrel decreased ischemic events and stent thrombosis at the cost of increased bleeding rates. Current recommendations strongly support early (pre-angiography) initiation of dual antiplatelet therapy with aspirin plus either clopidogrel or a GPIIb/IIIa receptor inhibitor.

**Intravenous Platelet Inhibitors**

GPIIb/IIIa receptor inhibitors have demonstrated benefit in NSTE-ACS management independent of other pharmacological strategies and revascularization. Approved agents include the monoclonal antibody abciximab and the two small-molecule agents eptifibatide and tirofiban. GPIIb/IIIa receptor inhibitors bind to the conformationally active platelet GPIIb/IIIa receptor, thereby preventing cross-linking of activated platelets via binding with soluble fibrinogen. Vascular clot burden is reduced not only by the prevention of new thrombus formation, but also by disaggregation of the existing thrombus. Several large meta-analyses found that GPIIb/IIIa receptor inhibitors conferred a 9% reduction in 30-day odds of death or MI in all NSTE-ACS patients, 26% 30-day mortality reduction in diabetic ACS patients, and 27% 30-day mortality reduction in high-risk patients undergoing PCI. Contemporary registries also support these findings, and data continue to accrue linking the use of this drug class and other evidence-based pharmacotherapies with improved survival after hospital discharge (see Figure 3). Accordingly, early use of intravenous GPIIb/IIIa inhibitors in high-risk NSTE-ACS has been endorsed in the published practice guidelines, with specific recommendations for the use of small-molecule GPIIb/IIIa inhibitors (eptifibatide or tirofiban) pre-angiography (‘upstream’) and abciximab in patients proceeding immediately to catheterization with PCI. However, despite a substantial amount of supportive evidence, GPIIb/IIIa receptor inhibitors remain vastly underutilized in NSTE-ACS, as reflected in large-scale registry data, which note that fewer than 50% of eligible patients receive GPIIb/IIIa receptor inhibitors within the first 24 hours of admission. To some degree, underutilization may stem from uncertainties related to the combination and timing of antiplatelet therapies. Dual antiplatelet therapy early in the treatment course is recommended, but the specific combination is left to the clinician. Clopidogrel offers proven efficacy and ease of administration and may be appropriate for long-term continuation in the majority of ACS patients. Concerns of bleeding in the small proportion of ACS patients requiring in-hospital coronary artery bypass grafting temper its usage, however. The GPIIb/IIIa receptor inhibitors also show early ischemic benefit that is at least comparable to that seen with clopidogrel, although no direct large-scale comparison exists. Additionally, the small-molecule GPIIb/IIIa inhibitors eptifibatide and tirofiban are parenteral compounds with relatively short half-lives. Therefore, these agents rapidly achieve steady-state platelet inhibition and can be discontinued at short notice should clinical circumstances warrant.

With a staggering amount of complex and sometimes contradictory scientific data to navigate by, and a necessary degree of ambiguity in the practice guidelines, how is a clinician to decide on an appropriate care plan? While several antiplatelet/anticoagulant strategies are currently supported by the available evidence, one unifying principle that should guide therapy is that higher-risk patients should receive more intensive therapies earlier in their hospital course. Deferral of dual antiplatelet therapy until the time of angiography allows for the occurrence of many potentially preventable ischemic events within the first 24–48 hours. Triple antiplatelet therapy (aspirin plus clopidogrel and GPIIb/IIIa receptor inhibitors) may also be considered in selected high-risk patients undergoing an early invasive strategy with likely PCI. However, importantly, the ischemic benefits of antiplatelet therapy must be balanced with the attendant bleeding risks. Therapeutic choices must be tailored to specific clinical scenarios, assessed early and often for adequacy of treatment effect, and revised as warranted.
Non-ST-segment Elevation Acute Coronary Syndromes

Conclusion

In summary, the management of NSTE-ACS has progressed greatly in recent years but there is still considerable room for improvement. Current US estimates suggest that only 12% of NSTE-ACS patients receive all guideline-recommended therapies within the first 48 hours. Other investigators note that evidence-based therapies paradoxically target low-risk patients despite evidence suggesting their greatest benefit in higher-risk patients. The goals of ACS management are rapid identification of the condition, risk stratification, early implementation of optimal pharmacological therapies, and appropriate use of invasive diagnostics and therapeutics. Targeted pharmacotherapy and prompt mechanical revascularization generally yield the best clinical outcomes in high-risk patients.

Efforts to improve the process and quality of ACS care should continue on individual, institutional, and national levels. Adoption of structured, evidence-based treatment strategies is essential for insuring optimal patient outcomes in this rapidly evolving sector of cardiovascular medicine.