The 2011 Update to the Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) Guideline is based on evolving data or expert opinion and incorporates information from late-breaking clinical trials presented at the 2008–2009 Scientific Sessions of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, among others, as well as selected data through April 2010.

The 5 key issues highlighted in this summary are: (1) the timing of acute interventional therapy in non–ST-elevation myocardial infarction; (2) emphasis on the timing, duration, and application of dual and triple antiplatelet therapy; (3) specific recommendations for patients with diabetes mellitus; (4) the role and potential benefit of invasive therapy in patients with advanced renal dysfunction; and (5) issues of quality improvement for acute coronary syndromes.

Timing of Acute Interventional Therapy in Non–ST-Elevation Myocardial Infarction

In all but the highest-risk patients, immediate cardiac catheterization/interventional therapy does not offer benefit over initial medical stabilization and subsequent early cardiac catheterization and intervention when appropriate. Three trials comparing different strategies of intervention formed the basis for this updated recommendation.

The Intracoronary Stenting With Antithrombotic Regimen Cooling Off (ISAR-COOL) trial compared intervention within 6 hours of presentation to a “cooling-off” period of 3 to 5 days prior to angiography, with the latter failing to improve outcome. However, ISAR-COOL was a small trial, and the delay prior to angiography was more prolonged than in current practice.

Much more relevant to contemporary clinical practice is the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial comparing angiography as rapidly as possible to a median delay of 50 hours. Although in the overall trial population there was a nonsignificant trend toward a reduced incidence of the primary endpoint of death, new myocardial infarction (MI), or stroke at 6 months, patients in the highest tertile of the Global Registry of Acute Coronary Events (GRACE) risk score (>140) had a sizeable significant reduction in the primary ischemic endpoint, whereas no difference was observed among patients in the lower tertiles.

Dr. Wenger is a consultant at Emory Heart and Vascular Center, Atlanta, Georgia. The author has no other funding, financial relationships, or conflicts of interest to disclose.
Table 1. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>SIZE OF TREATMENT EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I</strong> Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
</tr>
<tr>
<td><strong>CLASS IIA</strong> Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Additional studies with focused objectives needed</td>
</tr>
<tr>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
</tr>
<tr>
<td><strong>CLASS IIb</strong> Benefit ≥ Risk</td>
</tr>
<tr>
<td>Additional studies with broad objectives needed; additional registry data would be helpful</td>
</tr>
<tr>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td><strong>CLASS III No Benefit or CLASS III Harm</strong></td>
</tr>
<tr>
<td>Procedure/Treatment is not useful/effective and may be harmful</td>
</tr>
<tr>
<td><strong>COR II:</strong> No Benefit</td>
</tr>
<tr>
<td><strong>COR II:</strong> Helpful</td>
</tr>
<tr>
<td><strong>COR II:</strong> Harm</td>
</tr>
<tr>
<td><strong>COR II:</strong> Potentially harmful</td>
</tr>
<tr>
<td><strong>COR III:</strong> No Benefit</td>
</tr>
<tr>
<td><strong>COR III:</strong> Helpful</td>
</tr>
<tr>
<td><strong>COR III:</strong> Harm</td>
</tr>
<tr>
<td><strong>COR III:</strong> Potentially harmful</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association. In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation. Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. ”

In the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes (ABOARD) study; immediate angiography was compared with intervention on the next working day; immediate intervention conferred no advantage for the primary endpoint, median troponin I value during the hospitalization. Nor was there benefit in the prespecified clinical secondary outcomes of death, MI, or urgent revascularization at 1 month.

Thus, in the setting of intensive background antithrombotic therapy, benefit of early angiography and intervention to reduce ischemic complications was evident only among high-risk patients (defined by a GRACE score > 140), with a
Timing, Duration, and Application of Dual and Triple Antiplatelet Therapy

The highlight of this section is that further evidence supports the role of triple antiplatelet therapy in high-risk patients, with dual antiplatelet therapy appropriate in all others (class I; LOE: A). New information is that at least 2 thienopyridine drugs can be used as 1 of the 2 agents in dual antiplatelet therapy.

Thienopyridines

A second thienopyridine agent, prasugrel, was approved by the US Food and Drug Administration (FDA) for patients with UA/NSTEMI, based on a head-to-head comparison with clopidogrel in which prasugrel was superior in the reduction of clinical events, but at the expense of an increased risk of bleeding (class I; LOE: B). The pivotal trial for prasugrel, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38)5 was conducted in ACS patients referred for percutaneous coronary intervention (PCI). Among the patients undergoing PCI, a loading dose of prasugrel was administered before, during, or within 1 hour after PCI, but only after the coronary anatomy had been defined, so as to exclude patients who would be referred for coronary artery bypass graft surgery and the decision made to proceed to PCI. A loading dose of 60 mg of prasugrel and a 10-mg daily maintenance dose was compared with a 300-mg loading dose of clopidogrel and a 75-mg daily maintenance dose for a median follow-up of 14.5 months. As noted, prasugrel significantly reduced by 2.2% the absolute risk and by 19% the relative risk in the primary endpoint of death due to cardiovascular causes, nonfatal MI, and nonfatal stroke, with the benefit primary related to the difference in the rates of nonfatal MI. Stent thrombosis was significantly reduced by prasugrel.

However, prasugrel was associated with a significant increase in the rate of bleeding, including life-threatening bleeding, so that the net clinical benefit of the TRITON-TIMI 38 study showed a primary efficacy and safety endpoint rate of 13.9% for clopidogrel, vs 12.2% for prasugrel, P = 0.004. A post-hoc analysis defined 3 subgroups of patients where the update, its use in patients with UA/NSTEMI could not be recommended.

Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients following drug-eluting stent placement (class IIb; LOE: C).

Interindividual Variability and Responsiveness to Clopidogrel

Because clopidogrel is a prodrug requiring conversion to its active metabolite, several major genetic polymorphisms may be operative in diminished responsiveness to clopidogrel. These are well delineated in the American College of Cardiology Foundation/American Heart Association Clopidogrel Clinical Alert.9 By contrast, prasugrel, also a prodrug that requires conversion to its active metabolite, has not been shown to have significant decrease in plasma concentration or platelet-inhibition activity based on isoenzyme alleles.10,11 Because no prospective studies demonstrate that routine use of genotype testing, coupled with modification of antiplatelet therapy, improves clinical outcomes or reduces subsequent clinical events, the Guideline does not recommend such an approach routinely to guide changes in clinical management. Platelet-function testing to determine platelet-inhibitory response in patients with UA/NSTEMI on thienopyridine therapy may be considered if the results of testing may alter management (class IIb; LOE: B). Genotyping in patients with UA/NSTEMI on clopidogrel therapy might be considered if the results of testing may alter management (class IIb; LOE: C).

Proton Pump Inhibitors and Dual Antiplatelet Therapy in Acute Coronary Syndrome

There has been a challenge as to the role of proton pump inhibitor (PPI) medications interfering with clopidogrel metabolism, with conflicting results from observational studies. In a preliminary report of a randomized study, Clopidogrel in the Optimization of Gastrointestinal Events (COGENT),12 no difference was found in the primary composite cardiovascular endpoint between clopidogrel + omeprazole and clopidogrel + placebo. The recent American College of Cardiology statement on the use of PPI agents in combination with clopidogrel does not prohibit the use of PPI medications in appropriate clinical settings, but highlights the potential risks and benefits from a combination of PPI agents and clopidogrel.13
Glycoprotein IIb/IIIa Receptor Antagonists

The early evidence supporting the use of glycoprotein (GP) IIb/IIIa inhibitor therapy during PCI procedures antedated the established benefits of clopidogrel, early invasive therapy, and contemporary medical treatments in patients with UA/NSTEMI, particularly in high-risk subsets. However, these studies did not directly test the selection of an oral thienopyridine vs an intravenous GP IIb/IIIa inhibitor as the second antiplatelet agent in UA/NSTEMI. Contemporary clinical trials have clarified the relative benefit and risk of GP IIb/IIIa inhibitor therapy as the third antiplatelet agent combined with aspirin and a thienopyridine.

The Early Glycoprotein IIb/IIIa Inhibition in Patients with Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial14 compared early routine eptifibatide infused for 18–24 hours with delayed provisional eptifibatide at the time of PCI. Early routine eptifibatide was associated with a greater risk of major hemorrhage; but in a subgroup analysis, early eptifibatide was associated with numerically fewer ischemic events in patients who underwent PCI.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial15 examined an optimal strategy for GP IIb/IIIa inhibitors in moderate- and high-risk ACS patients undergoing invasive therapy: unfractionated heparin or enoxaparin + GP IIb/IIIa inhibitor therapy; bivalirudin + GP IIb/IIIa inhibitor therapy; or bivalirudin alone. The composite ischemic endpoint occurred in 7.1% of patients assigned to upstream GP IIb/IIIa administration, and in 7.9% of patients to deferred selective GP IIb/IIIa administration; thus, the noninferiority hypothesis was not achieved.

These studies support the strategy of selective rather than the provisional use of GP IIb/IIIa inhibitor therapy as part of triple antiplatelet therapy (class IIb; LOE: B), with data from the EARLY ACS14 highlighting the potential bleeding risks of upstream use of GP IIb/IIIa inhibitor therapy. There was concern for increased bleeding risk with GP IIb/IIIa therapy, and particularly in non–high-risk subsets of patients such as those with a normal baseline troponin level, without DM, and those age >75 years, among whom potential benefit may be offset by potential bleeding risk.

Summary

Aspirin should be administered to UA/NSTEMI patients as soon as possible after presentation and continued indefinitely (class I; LOE: A). The choice of a second antiplatelet therapy includes1 before PCI, clopidogrel (class I; LOE: B) or an intravenous GP IIb/IIIa inhibitor, with eptifibatide or tirofiban preferred (class I; LOE: A);2 at the time of PCI, clopidogrel (class I; LOE: A) or prasugrel (class I; LOE: B) or an IV GP IIb/IIIa inhibitor (class I; LOE: A). If an initial conservative strategy is chosen, a loading dose of clopidogrel followed by daily maintenance should be added to aspirin and administered for at least a month, and ideally up to a year (class I; LOE: B). Clopidogrel should be given in a loading dose of 300–600 mg and prasugrel 60 mg, with clopidogrel 75 mg daily, or prasugrel 10 mg daily for patients undergoing PCI for at least 12 months (class I; LOE: B), with earlier discontinuation because of bleeding risk (class I; LOE: C).

Abciximab should not be administered to patients for whom PCI is not planned (class III; LOE: A). In UA/NSTEMI patients at low risk for ischemic events, upstream use of GP IIb/IIIa inhibitors is not recommended (class III; LOE: B). In patients with a prior history of stroke and/or transient ischemic attack for whom PCI is planned, prasugrel is potentially harmful as part of a dual antiplatelet therapy regimen.

Recommendations for Diabetes Mellitus

Although it is unclear “whether hyperglycemia is a marker of underlying health status or a mediator of complications after acute MI, noniatrogenic hypoglycemia has also been associated with adverse outcomes and is a predictor of higher mortality.”16

In keeping with the recent 2009 STEMI and PCI Focused Update,17 the recommendation for the use of insulin to control blood glucose in UA/NSTEMI is changed from a more stringent to a more moderate target range (class IIa; LOE: B). The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study18 showed more episodes of treatment-related hypoglycemia in the intensely managed group, and excess deaths in the intensive-management group, predominantly of cardiovascular causes. Because the trial enrolled critically ill medical and surgical patients, it is unclear the extent to which extrapolation is appropriate to the management of all patients with UA/NSTEMI.

It is reasonable to use an insulin-based regimen to achieve and maintain glucose levels <180 mg/dL while avoiding hypoglycemia for hospitalized patients with UA/NSTEMI with either a complicated or an uncomplicated course (class IIa; LOE: B).18–21

The Writing Group also noted that DM was not listed as a high-risk feature for which an invasive strategy was specifically preferred. However, subgroup analysis of the TACTICS-TIMI 18 trial22 (effects of renal insufficiency on early invasive management in patients with ACS) was consistent with this finding in that DM, as well as the often concurrent comorbidity of chronic kidney disease (CKD), is not only a high-risk factor, but also benefits from an invasive approach. Accordingly, DM has been added to the list of characteristics for which an early invasive strategy is generally preferred.

Role and Potential Benefit of Invasive Therapies in Patients With Advanced Renal Dysfunction

An early invasive strategy is reasonable in patients with mild (stage II) and moderate (stage III) CKD (class IIa; LOE: B). The risks of short- and long-term mortality are increased as renal dysfunction worsens.23–25

Patients with CKD undergoing cardiac catheterization using contrast media should receive adequate preparatory hydration26,27 (class I; LOE: B), with adjustment of the maximal dose to each patient’s renal function and clinical characteristics. Calculation of the contrast volume to creatinine clearance ratio is useful to predict the maximum volume of contrast media that can be given without

N.K. Wenger: 2011 guidelines for management of patients with UA/NSTEMI
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20964 © 2011 Wiley Periodicals, Inc.
significantly increasing the risk of contrast-associated nephropathy\(^28,29\) (class I; LOE: B). The strength and consistency of the relationships between specific isomolar or low-osmolar agents and contrast-induced nephropathy or renal failure are not sufficient to enable a guideline statement on selection among the commonly used contrast media. Instead, the focus should be on proper patient preparation with hydration and adjustment of maximal contrast to each patient’s renal function and other clinical characteristics. There was insufficient evidence to recommend a specific regimen for hydration preparatory to angiography.

In Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDHEART),\(^30\) the benefit of invasive therapy was not evident in patients with stage IV or stage V CKD or those receiving dialysis, but these data are limited by the nonrandomized design of the study. A recent collaborative meta-analysis of randomized controlled trials to estimate the effectiveness of early angiography in patients with CKD\(^24\) demonstrated that an invasive strategy was associated with a significant reduction in rehospitalization (\(P < 0.001\)).

Quality Improvement for Acute Coronary Syndromes

Participation in a quality-of-care data registry designed to track and measure outcomes, complications, and adherence to evidence-based processes of care and quality improvement for UA/NSTEMI can drive quality improvement for ACS,\(^31–35\) with the goal of elimination of healthcare disparities and to enable the conduct of comparative effectiveness research (class IIa; LOE: B).

Post–Guideline-Update Relevant Acute Coronary Syndrome Trials

For ACS patients receiving anticoagulation, fondaparinux reduced major bleeding risk and was associated with a mortality reduction at 30 days in the Organization to Assess Strategies for Ischemic Syndrome 5 (OASIS 5) trial. However, fondaparinux was associated with an excess of catheter-related thrombosis. The Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA/OASIS 8) trial\(^36\) in patients initially treated with fondaparinux compared low-dose and standard-dose unfractionated heparin, adjusted by activated clotting time. Low-dose had no advantage over standard-dose unfractionated heparin, but, importantly, neither dose increased major bleeding compared with a historical control group with fondaparinux alone. Thus, the authors concluded that the problem of catheter thrombosis could be reduced by activated clotting time–guided unfractionated heparin without increasing major bleeding.

US Food and Drug Administration Drug Approval Subsequent to the Guideline Update

Ticagrelor

The PLATO trial\(^8\) demonstrated significant reduction in the combined endpoint of cardiovascular death, stroke, and MI in patients treated with ticagrelor compared with those treated with clopidogrel. However, benefit was not evident in patients recruited from North America. A question was raised whether this geographic disparity is related to the higher dose of aspirin typically used in the United States vs Europe, in that patients on high-dose aspirin tended to do better with clopidogrel. The FDA approval for ticagrelor warned that its use was not recommended in patients taking more than 100 mg/day of aspirin.\(^37\) The label further recommends that clinicians should ideally discontinue ticagrelor 5 days prior to surgery.

Dabigatran

Dabigatran, a direct thrombin inhibitor and the first new oral anticoagulant in 50 years, was approved by the FDA for stroke prevention in patients with nonvalvular atrial fibrillation. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,\(^38\) dabigatran 150 mg was associated with lower rates of stroke and systemic embolism than conventional warfarin with comparable bleeding risk. The drug is contraindicated in patients with severe heart valve disease, stroke within 14 days or severe stroke in the past 6 months, conditions increasing the risk of hemorrhage, a creatinine clearance <30 mL/minute, active liver disease, or pregnancy. This drug, administered in fixed dose twice daily, does not require international normalized ratio measurement. Patients with atrial fibrillation taking dabigatran may present with an ACS, but the drug has not been studied in that setting. It has a serum half-life of 12–17 hours.

References


