What's New in Antiplatelet and Anticoagulant Therapy Recommendations for Unstable Angina/Non-ST-Elevation Myocardial Infarction 2012 Focused Update From the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Nanette K Wenger, Emory University

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What’s New in Antiplatelet and Anticoagulant Therapy Recommendations for Unstable Angina/Non–ST-Elevation Myocardial Infarction

2012 Focused Update From the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Nanette K. Wenger, MD, MACC, MACP, FAHA
Division of Cardiology, Emory University School of Medicine; Consultant, Emory Heart and Vascular Center, Atlanta, Georgia

This focused update addresses the use of the newly approved oral antiplatelet agents, prasugrel and ticagrelor, for the management of patients with UA/NSTEMI.

Introduction
This 2012 focused update was designed to guide the clinician in incorporating newly approved oral antiplatelet agents into clinical practice for the management of patients with unstable angina/non–ST-elevation myocardial infarction (UA/NSTEMI). Specifically, it addresses the use of the P2Y12 receptor inhibitors prasugrel and ticagrelor. These were superior to clopidogrel in reducing clinical events but at the expense of an increased bleeding risk.

The pivotal trial for prasugrel, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), involved 13,608 acute coronary syndrome (ACS) patients referred for percutaneous coronary intervention (PCI) randomized to prasugrel or clopidogrel. Prasugrel was administered only after the coronary anatomy had been delineated. Prasugrel was associated with a 2.2% absolute and a 19% relative risk reduction in the composite end point of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. There was a significant increase in major hemorrhage ($P = 0.03$) and fatal bleeding ($P = 0.002$). However, the clopidogrel loading dose in TRITON-TIMI 38 was lower than that currently recommended. US Food and Drug Administration (FDA) approval of prasugrel cited a contraindication to its use in patients with a history of transient ischemic attack (TIA), stroke, or with active pathologic bleeding. It warned against use in patients $\geq 75$ years old owing to an increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk patients (those with diabetes or prior MI). Patients with a body weight of $< 60$ kg did not benefit from prasugrel.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) was the pivotal trial for ticagrelor in 18,624 ACS patients, 16.7% with UA and 42.7% with NSTEMI. Ticagrelor was compared with clopidogrel on a background of aspirin therapy. Of PLATO patients, 64.3% underwent PCI during the index hospitalization. Ticagrelor was associated with a 1.9% absolute and a 16% relative risk reduction in the composite end point of vascular death, MI, or stroke, largely driven by lower rates of MI. There were
no significant differences in major bleeding or coronary artery bypass graft (CABG) bleeding (clopidogrel and ticagrelor were discontinued for 5 days and 24–72 hours, respectively, preprocedure per protocol), but ticagrelor was associated with increased non–CABG-related major bleeding (P = 0.03). Benefit from ticagrelor was not evident in North American patients, potentially related to a ≥300 mg daily aspirin dose. FDA warnings indicate that aspirin >100 mg daily maintenance dose may decrease ticagrelor’s effectiveness.

### Class I Recommendations (Modified From Prior Guidelines)

The 2012 class I recommendations are summarized as follows (See Figure 1, Tables 1 and 2)

- In patients unable to take aspirin, clopidogrel (level of evidence [LOE] = B), prasugrel in PCI-treated patients (LOE = C), or ticagrelor (LOE = C) should be administered daily.
- Patients with definite UA/NSTEMI at medium or high risk in whom an initial invasive strategy is selected should receive dual antiplatelet therapy.

#### Before PCI:

- Clopidogrel (LOE = B) or
- Ticagrelor (LOE = B) or
- An intravenous [IV] glycoprotein [GP] IIb/IIIa inhibitor (LOE = A) IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors (LOE = B)

At the time of PCI:

- Clopidogrel if not started before PCI (LOE = A) or
- Prasugrel (LOE = B) or
- Ticagrelor (LOE = B) or
- An IV GP IIb/IIIa inhibitor (LOE = A)

For UA/NSTEMI patients in whom an initial conservative strategy is selected, clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to 12 months (LOE = B).

For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, diagnostic angiography should be performed (LOE = A). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban [LOE = A]), clopidogrel (loading dose followed by daily maintenance dose [LOE = B]), or ticagrelor (loading dose followed by daily maintenance dose [LOE = B]) should be added to aspirin and anticoagulant therapy before diagnostic angiography (LOE = C).

A loading dose of P2Y<sub>12</sub> Receptor inhibitor therapy is recommended for UA/NSTEMI patients for whom PCI is planned, with one of the following regimens used:

- Clopidogrel 600 mg should be given as early as possible before or at the time of PCI (LOE = B) or
- Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and decision is made to proceed with PCI (LOE = B) or
- Ticagrelor 180 mg should be given as early as possible before or at the time of PCI (LOE = B)

The duration and maintenance dose of P2Y<sub>12</sub> receptor inhibitor therapy should be as follows:

- In UA/NSTEMI patients undergoing PCI, either clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months (LOE = B).
- If the risk of bleeding morbidity outweighs the anticipated benefits of P2Y<sub>12</sub> receptor inhibitor therapy, earlier discontinuation should be considered (LOE = C).

### Table 2. Dose and Duration: Maintenance Therapy

<table>
<thead>
<tr>
<th>Aspirin, 81 mg daily</th>
<th>Indefinite</th>
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</thead>
<tbody>
<tr>
<td>Clopidogrel, 75 mg daily</td>
<td>Initial conservative strategy – up to 12 months</td>
</tr>
<tr>
<td>Ticagrelor, 90 mg BID</td>
<td>After PCI — at least 12 months</td>
</tr>
<tr>
<td>Ticagrelor, 75 mg daily</td>
<td>Prasugrel, 10 mg daily</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily.
Timing of Discontinuation of P2Y12 Receptor Inhibitor Therapy for Surgical Procedures

In hospitalized UA/NSTEMI patients who are candidates for CABG, empirical discontinuation of clopidogrel therapy is recommended for at least 5 days,5 of prasugrel for at least 7 days,6 and ticagrelor for at least 5 days7 prior to planned CABG.

Elective noncardiac procedures should probably be deferred until the patient finishes the appropriate course of P2Y12 receptor inhibition therapy, essentially up to 12 months of treatment after the deployment of a drug-eluting stent.

Interindividual Variability in Responsiveness to Clopidogrel and Genotype and Platelet Function Testing

In 2010, the FDA warned about the diminished effectiveness of clopidogrel in patients with an impaired ability to convert the drug into its active form,8 raising the question about routine testing for genetic variants of the CYP2C19 allele and/or for overall effectiveness for inhibition of platelet activity. These issues are summarized in the American College of Cardiology Foundation/American Heart Association Clopidogrel Clinical Alert Expert Consensus Document.9 Although either testing strategy may have some benefit, there is a class IIb recommendation for these strategies, suggesting that a selective limited approach to platelet genotype assessment and platelet function testing is prudent until better clinical evidence exists for a more scientifically derived recommendation.

Proton Pump Inhibitors and Dual Antiplatelet Therapy for ACS

When clopidogrel is started, proton pump inhibitors (PPIs) are often prescribed to prevent gastrointestinal bleeding.

Figure 1. Applying the classification of recommendation and level of evidence.* 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. † For comparative effectiveness recommendations (class I and IIa, level of evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated. Source: Wright RS, Anderson JL, Adams CD, et al. J Am Coll Cardiol. 2011;57:1920–1959. Reprinted by permission.
related to dual antiplatelet therapy. An FDA communication based on an ongoing safety review of clopidogrel advises that health care providers should reevaluate the need for starting or continuing treatment with a PPI, including omeprazole, in patients taking clopidogrel. The concern was that use of a PPI that inhibits CYP450 2C19 might decrease the inhibitory effect of clopidogrel on platelet aggregation. The FDA noted no evidence that other drugs that reduce stomach acid, such as H2 blockers or antacids, interfere with the antiplatelet activity of clopidogrel. The American College of Cardiology Foundation Expert Consensus Statement10 does not prohibit the use of PPI agents in appropriate clinical settings, but highlights the potential risks and benefits from the use of PPI agents in combination with clopidogrel.

Recommendations for Warfarin Therapy
The 2012 modification of the 2011 recommendations replaced the term thienopyridines with the term P2Y12 receptor inhibitors. A new recommendation is that oral anticoagulant therapy should be targeted to a lower International Normalized Ratio (2.0–2.5) in patients with UA/NSTEMI managed with aspirin and P2Y12 receptor inhibitor therapy (class IIb, LOE = C).

References