2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

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Preamble

Keeping pace with the stream of new data and evolving evidence on which guideline recommendations are based is an ongoing challenge to timely development of clinical practice guidelines. In an effort to respond promptly to new evidence, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines (Task Force) has created a "focused update" process to revise the existing guideline recommendations that are affected by the evolving data or opinion. New evidence is reviewed in an ongoing fashion to more efficiently respond to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence is reviewed at least twice a year, and updates are initiated on an as-needed basis and completed as quickly as possible while maintaining the rigorous methodology that the ACCF and AHA have developed during their partnership of more than 20 years.

These focused updates are prompted following a thorough review of late-breaking clinical trials presented at national and international meetings in addition to other new published

data deemed to have an impact on patient care (Section 1.1, Methodology and Evidence Review). Through a broad-based vetting process, the studies included are identified as being important to the relevant patient population. The focused update is not intended to be based on a complete literature review from the date of the previous guideline publication but rather to include pivotal new evidence that may affect changes to current recommendations. Specific criteria/considerations for inclusion of new data include the following:

- publication in a peer-reviewed journal;
- large, randomized, placebo-controlled trial(s);
- nonrandomized data deemed important on the basis of results affecting current safety and efficacy assumptions, including observational studies and meta-analyses;
- strength/weakness of research methodology and findings;
- likelihood of additional studies influencing current findings;
- impact on current and/or likelihood of need to develop new performance measure(s);
- request(s) and requirement(s) for review and update from the practice community, key stakeholders, and other sources free of industry relationships or other potential bias;
- number of previous trials showing consistent results; and
- need for consistency with a new guideline or guideline updates or revisions.

In analyzing the data and developing recommendations and supporting text, the writing group uses evidence-based methodologies developed by the Task Force.[1] The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective and in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing group reviews and ranks evidence supporting each recommendation with the weight of evidence ranked as LOE A, B, or C using specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinicians on the writing group is the basis for LOE C recommendations, and no references are cited. The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR. A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy (GDMT)* to represent optimal medical therapy as defined by ACCF/AHA guideline (primarily Class I) recommended therapies. This new term, *GDMT*, will be used herein and throughout all future guidelines.

Because the ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to inform patient care more effectively; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the writing group. All writing group members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. In December 2009, the ACCF and AHA implemented a new policy for relationships with industry and other entities (RWI) that requires the writing group chair plus a minimum of 50% of the writing group to have no *relevant* RWI (Appendix 1 for the ACCF/AHA definition of relevance). These statements are reviewed by the Task Force and all members during each

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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.

†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.

conference call and/or meeting of the writing group and are updated as changes occur. All guideline recommendations require a confidential vote by the writing group and must be approved by a consensus of the voting members. Members are not permitted to draft or vote on any text or recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing group members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, writing group members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement. Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing group is supported exclusively by the ACCF and AHA without commercial support. Writing group members volunteered their time for this activity.

In an effort to maintain relevance at the point of care for practicing physicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on

summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Clinical Practice Guidelines We Can Trust* and *Finding What Works in Health Care: Standards for Systematic Reviews*.[2,3] It is noteworthy that the ACCF/AHA practice guidelines were cited as being compliant with many of the standards that were proposed. A thorough review of these reports and our current methodology is under way, with further enhancements anticipated.

The recommendations in this focused update are considered current until they are superseded in another focused update or the full-text guideline is revised. Guidelines are official policy of both the ACCF and AHA.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The standing guideline writing committee along with the parent Task Force identified trials and other key data through October 2011 that may impact guideline recommendations. On the basis of the criteria/considerations noted in the Preamble and the approval of new oral antiplatelets, a focused update was initiated to provide guidance on how to incorporate these agents into daily practice. Now that multiple agents are available, a comparison of their use in various settings within clinical practice is provided. This iteration replaces the sections in the 2007 ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction[4] that were updated by the 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction.[5,6]

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline, along with confidence intervals (CI) and data related to the relative treatment effects such as odds ratio (OR), relative risk (RR), hazard ratio (HR), and incidence rate ratio.

Consult the full-text version of the 2007 ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction[4] for policy on clinical areas not covered by the current document. Individual recommendations updated in this focused update will be incorporated into future revisions and/or updates of the full-text guidelines.

1.2. Organization of the Writing Group

For this focused update, members of the 2011 Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) focused update writing group were invited and all agreed to participate (referred to as the 2012 focused update writing group). Members were required to disclose all RWI relevant to the data under consideration. The writing group included representatives from the ACCF, AHA, American Academy of Family Physicians, American College of Emergency Physicians, American College of Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACCF and the AHA, as well as 1 or 2 reviewers each from the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, and 29 individual content reviewers, including members of the ACCF Interventional Scientific Council. The information on reviewers' RWI was distributed to the writing group and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and the AHA and endorsed by the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

3. Early Hospital Care

3.2. Antiplatelet/Anticoagulant Therapy in Patients for Whom Diagnosis of UA/NSTEMI Is Likely or Definite: Recommendations

3.2.1. Antiplatelet Therapy: Recommendations

(See Table 2, Appendixes 3, 4, 5, 6, and the Online Data Supplement.)

3.2.3. Additional Management of Antiplatelet and Anticoagulant Therapy: Recommendations

(See Table 3, Appendixes 3, 4, 5, 6, and the Online Data Supplement.)

3.2.3.1. Antiplatelet/Anticoagulant Therapy in Patients for Whom Diagnosis of UA/NSTEMI Is Likely or Definite

3.2.3.1.1. $P2Y_{12}$ Receptor Inhibitors. $P2Y_{12}$ receptor inhibitor therapy is an important component of antiplatelet therapy in patients with UA/NSTEMI and has been tested in several large trial populations with UA/NSTEMI. The last version of the guideline recommended the use of clopidogrel in patients with UA/NSTEMI because it was the only US Food and Drug Administration (FDA)–approved $P2Y_{12}$ receptor inhibitor in this patient population at that time.[6] Since the publication of the last guideline,[6] the FDA has approved 2 additional $P2Y_{12}$ receptor inhibitors for use in patients with UA/NSTEMI. The FDA approved the use of prasugrel and ticagrelor based on data from head-to-head comparison trials with clopidogrel, in which prasugrel and ticagrelor were respectively superior to clopidogrel in reducing clinical events but at the expense of an increased risk of bleeding.

The pivotal trial for prasugrel, TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction),[7] focused on patients with acute coronary syndrome (ACS) who were referred for percutaneous coronary intervention (PCI). TRITON–TIMI 38 randomly as-

signed 13 608 patients with moderate- to high-risk ACS, of whom 10 074 (74%) had UA/NSTEMI, to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for a median follow-up of 14.5 months. Acetylsalicylic acid (aspirin) was prescribed within 24 hours of PCI. Clinical endpoints were assessed at 30 and 90 days and then at 3-month intervals for 6 to 15 months. Among patients with UA/NSTEMI undergoing PCI, a prasugrel loading dose was administered before, during, or within 1 hour after PCI but only after coronary anatomy had been defined. Patients taking any thienopyridine within 5 days of randomization were excluded.

Prasugrel was associated with a significant 2.2% absolute reduction and a 19% relative reduction in the primary efficacy endpoint, a composite of the rate of death due to cardiovascular causes (including arrhythmia, congestive heart failure, shock, and sudden or unwitnessed death), nonfatal myocardial infarction (MI), or nonfatal stroke during the follow-up period (see Online Data Supplement). The primary efficacy endpoint occurred in 9.9% of patients receiving prasugrel and 12.1% of patients receiving clopidogrel (HR for prasugrel versus clopidogrel: 0.81; 95% CI: 0.73 to 0.90; $P<0.001$).[7] Prasugrel decreased cardiovascular death, MI, and stroke by 138 events (number needed to treat=46). The difference in the primary endpoint was largely related to the difference in rates of nonfatal MI (7.3% for prasugrel versus 9.5% for clopidogrel; HR: 0.76; 95% CI: 0.67 to 0.85; $P<0.001$). Rates of cardiovascular death (2.1% versus 2.4%; $P=0.31$) and nonfatal stroke (1.0% versus 1.0%; $P=0.93$) were not reduced by prasugrel relative to clopidogrel. Rates of stent thrombosis were significantly reduced from 2.4% to 1.1% ($P<0.001$) by prasugrel.

Prasugrel was associated with a significant increase in the rate of bleeding, notably TIMI (Thrombolysis In Myocardial Infarction) major hemorrhage, which was observed in 2.4% of patients taking prasugrel and in 1.8% of patients taking clopidogrel (HR for prasugrel versus clopidogrel: 1.32; 95% CI: 1.03 to 1.68; $P=0.03$). Prasugrel was associated with a significant increase in fatal bleeding compared with clopidogrel (0.4% versus 0.1%; $P=0.002$). From the standpoint of safety, prasugrel was associated with an increase of 35 TIMI major and non–coronary artery graft bypass (CABG) bleeds (number needed to harm=167).[7] Also, greater rates of life-threatening bleeding were evident in the prasugrel group than in the clopidogrel group: 1.4% versus 0.9%, respectively (HR for prasugrel: 1.52; 95% CI: 1.08 to 2.13; $P=0.01$). In the few patients who underwent CABG, TIMI major bleeding through 15 months was also greater with prasugrel than with clopidogrel (13.4% versus 3.2%, respectively; HR for prasugrel: 4.73; 95% CI: 1.90 to 11.82; $P<0.001$).[7] The net clinical benefit in the TRITON–TIMI 38 study demonstrated a primary efficacy and safety endpoint rate of 13.9% in the clopidogrel group versus 12.2% in the prasugrel group (HR: 0.87; 95% CI: 0.79 to 0.95; $P=0.004$).

A post hoc analysis suggested there were 3 subgroups of ACS patients who did not have a favorable net clinical benefit (defined as the rate of death due to any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding) from the use of prasugrel or who had net harm: Patients with a history of stroke or transient ischemic attack before enrollment had net harm from prasugrel (HR: 1.54; 95% CI: 1.02 to 2.32; $P=0.04$); patients age ≥75 years had no net benefit from prasugrel (HR: 0.99; 95% CI: 0.81 to 1.21; $P=0.92$); and patients with a body weight of <60 kg had no net benefit from prasugrel (HR: 1.03; 95% CI: 0.69 to 1.53; $P=0.89$). In both treatment groups, patients with at least 1 of these risk factors had higher rates of bleeding than those without them.[7]

The FDA approved prasugrel on July 10, 2009, and cited a contraindication against its use in patients with a history of transient ischemic attack or stroke or with active pathological bleeding.[8] The FDA labeling information includes a general warning against the use of prasugrel in patients age ≥75 years because of concerns of an increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk situations (patients with diabetes or a history of prior MI), in which case the net benefit appears to be greater and its use may be considered.[8] In focusing specifically on patients with UA/NSTEMI, the rate of the primary efficacy endpoint was significantly reduced in favor of prasugrel (9.9% versus 12.1%; adjusted HR: 0.82; 95% CI: 0.73 to 0.93; $P=0.002$).[7]

The pivotal trial for ticagrelor, PLATO (Study of Platelet Inhibition and Patient Outcomes),[9] was a multicenter, international, randomized controlled trial comparing ticagrelor with clopidogrel (on a background of aspirin therapy) to determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in a broad population of patients with ACS (see Online Data Supplement). A total of 18 624 patients hospitalized with an ACS were randomized at 862 centers (from 2006 through 2008). Of those, 11 598 patients had UA/NSTEMI (patients with UA and NSTEMI made up 16.7% and 42.7% of the overall population, respectively), whereas 7026 patients had STEMI.

The primary efficacy endpoint was the time to first occurrence of the composite of vascular death, MI, or stroke. The primary safety endpoint was the first occurrence of any major bleeding event. The randomized treatment was scheduled to continue for 12 months; however, patients were allowed to leave the trial at 6 to 9 months if the event-driven study achieved its targeted number of primary events. Overall, the median duration of study drug administration was 277 days. Using a double-blind, double-dummy design, ticagrelor (180-mg loading dose followed by 90 mg twice daily) was compared with clopidogrel (300- to 600-mg loading dose followed by 75 mg daily).[9] At 24 hours after randomization, 79% of patients treated with clopidogrel received at least 300 mg, and nearly 20% received at least 600 mg. Overall, 64.3% of patients underwent PCI during the index hospitalization and 60.6% had stent implantation. Median times from the start of hospitalization to initiation of study treatment were 4.9 and 5.3 hours for ticagrelor and clopidogrel, respectively.

At 12 months, ticagrelor was associated with a 1.9% absolute reduction and 16% relative reduction in the primary composite outcome compared with clopidogrel (9.8% versus 11.7%; HR: 0.84; 95% CI: 0.77 to 0.92), which was driven by lower rates of MI (5.8% versus 6.9%; HR: 0.84; 95% CI: 0.75 to 0.95) and vascular death (4.0% versus 5.1%; HR: 0.79; 95% CI: 0.69 to 0.91).[9] The benefits of ticagrelor appeared consistent across most subgroups studied, with no significant interaction being

observed between the treatment effect and type of ACS. In focusing specifically on patients with UA/NSTEMI, ticagrelor was associated with a significant reduction in the primary efficacy endpoint among NSTEMI patients (n=7955 patients; 11.4% versus 13.9%; HR: 0.83; 95% CI: 0.73 to 0.94) but not among UA patients (n=3112 patients; 8.6% versus 9.1%; HR: 0.96; 95% CI: 0.75 to 1.22), although caution is urged against overinterpreting subgroup analyses. The benefits of ticagrelor in PLATO appeared within the first 30 days, persisted for up to 360 days, and were evident irrespective of clopidogrel pretreatment and whether patients had invasive or medical management planned. Notably, ticagrelor was associated with a 1.4% absolute reduction in all-cause mortality (4.5% versus 5.9%; HR: 0.78; 95% CI: 0.69 to 0.89) and with lower rates of definite stent thrombosis (1.3% versus 1.90%; HR: 0.67; 95% CI: 0.50 to 0.91).

There were no significant differences between the ticagrelor and clopidogrel groups in rates of major bleeding (the primary safety endpoint: composite of major life-threatening and other major bleeding events, PLATO study criteria; 11.6% versus 11.2%; HR: 1.04; 95% CI: 0.95 to 1.13), TIMI major bleeding (7.9% versus 7.7%; HR: 1.03; 95% CI: 0.93 to 1.15), or fatal bleeding (0.3% versus 0.3%; HR: 0.87; 95% CI: 0.48 to 1.59).[9] There were also no differences in major bleeding in patients undergoing CABG, in whom clopidogrel and ticagrelor were discontinued before the procedure for 5 days and 24 to 72 hours, respectively, per study protocol. Ticagrelor, however, was associated with a higher rate of non–CABG-related major bleeding (4.5% versus 3.8%, $P=0.03$). In addition, ticagrelor caused a higher incidence of dyspnea (13.8% versus 7.8%; HR: 1.84; 95% CI: 1.68 to 2.02; although not necessitating drug discontinuation except in a few cases), mild increases in creatinine and uric acid levels, and a higher rate of ventricular pauses ≥3 seconds in the first week (5.8% versus 3.6%, $P=0.01$; but without causing differences in syncope or pacemaker implantation). Overall, discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (7.4% versus 6.0%; $P<0.001$). Patients with a history of bleeding were excluded in PLATO, and <4% of patients had a prior history of nonhemorrhagic stroke.[9] The efficacy and safety of ticagrelor in patients with prior transient ischemic attack or stroke were not reported in PLATO,[9] and the balance of risks and benefits of ticagrelor in this patient population remains unclear.

A separate analysis was performed for the 5216 patients in PLATO admitted with ACS and prespecified as planned for noninvasive management (constituting 28% of the overall PLATO study population).[10] Compared with clopidogrel, ticagrelor was associated with a lower incidence of the primary endpoint (12.0% versus 14.3%; HR: 0.85; 95% CI: 0.73 to 1.00; $P=0.04$) and overall mortality without increasing major bleeding. These results indicate the benefits of intensified $P2Y_{12}$ inhibition with ticagrelor applied broadly for patients regardless of the intended or actualized management strategy.[10]

The benefits of ticagrelor in PLATO appeared to be attenuated in patients weighing less than the median weight for their sex and those not taking lipid-lowering therapies at randomization.[9] There was a significant interaction between treatment and geographic region, with patients enrolled in North America having no statistically significant differences between ticagrelor and clopidogrel with respect to the primary efficacy endpoint.[9] Extensive additional analyses were conducted to explore potential explanations for this interaction between treatment effect in PLATO and geographic region and whether this could be explained by specific patient characteristics or concomitant therapies.[11] Mahaffey and colleagues[11] noted that a significantly higher proportion of patients in the United States received a median aspirin dose of ≥300 mg daily compared with the rest of the world (53.6% versus 1.7%). Indeed, of all 37 baseline and postrandomization variables explored, only aspirin maintenance dose appeared to explain a substantial fraction of the regional interaction. Of note, subgroup analysis consistently showed the same aspirin-dose effect outside the United States. Without being able to fully rule out the play of chance or other factors related to clinical care in North America as explanations for the regional interaction, PLATO concluded that a low aspirin maintenance dose (≤100 mg daily) is likely to be associated with the most favorable outcomes when using the potent $P2Y_{12}$ inhibitor ticagrelor in patients with ACS.[11]

Because of its reversible inhibition of the $P2Y_{12}$ receptor, ticagrelor is associated with more rapid functional recovery of circulating platelets and, consequently, a faster offset of effect than clopidogrel. Although this may represent a potential advantage for patients with ACS undergoing early CABG, it may theoretically pose a problem for noncompliant patients (especially given its twice-daily dosing regimen).

The FDA approved ticagrelor on July 20, 2011.[12] The FDA also issued a "Boxed Warning" indicating that aspirin daily maintenance doses of >100 mg decrease the effectiveness of ticagrelor, cautioned against its use in patients with active bleeding or a history of intracranial hemorrhage, and advocated a Risk Evaluation and Mitigation Strategy, a plan to help ensure that the benefits of ticagrelor outweigh its risks. As part of that plan, the manufacturer is mandated to conduct educational outreach programs to alert physicians about the risk of using higher doses of aspirin.

Dual antiplatelet therapy with aspirin and either clopidogrel or prasugrel has increased the risk of intracranial hemorrhage in several clinical trials and patient populations (especially in those with prior stroke).[7,13a,13b,13c] In PLATO, the number of patients with prior stroke was small, limiting the power to detect treatment differences in intracranial bleeding in this subgroup.[13d] Patients with prior stroke or TIA have been excluded from PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin),[13e] an ongoing trial of ticagrelor versus placebo in addition to aspirin in patients with stable coronary artery disease. Until further data become available, it seems prudent to weigh the possible increased risk of intracranial bleeding when considering the addition of ticagrelor to aspirin in patients with prior stroke or TIA.[13f]

3.2.3.1.2. Choice of $P2Y_{12}$ Receptor Inhibitors for PCI in UA/NSTEMI. The writing group cautions that data on the use of prasugrel and ticagrelor come solely from the TRITON–TIMI 38 and PLATO trials, respectively, and their use in clinical practice should carefully follow how they were tested in these studies.[7,9] Prasugrel was administered only after a decision to proceed to PCI was made, whereas ticagrelor was studied in "all-comer" patients with UA/NSTEMI, including invasively and medically managed patients. The writing group does not recommend that prasugrel be administered routinely to patients with UA/NSTEMI before angiography,

such as in an emergency department, or used in patients with UA/NSTEMI who have not undergone PCI. The FDA package label suggests that it is reasonable to consider selective use of prasugrel before catheterization in subgroups of patients for whom a decision to proceed to angiography and PCI has already been established for any reason.[8] The writing group acknowledges this flexibility, but it is not its intention to make more specific recommendations about which subgroups of patients might benefit from prasugrel or ticagrelor instead of clopidogrel. The writing group does wish to caution clinicians about the potential increased bleeding risks associated with prasugrel and ticagrelor compared with clopidogrel in specific settings and especially among the subgroups identified in the package insert and clinical trials.[7–9,12] This guideline explicitly does not endorse one of the $P2Y_{12}$ receptor inhibitors over the other. There were several reasons for this decision. Although the composite efficacy endpoint in TRITON–TIMI 38 favored prasugrel, driven predominantly by a difference in nonfatal MIs (mostly asymptomatic), with deaths and nonfatal strokes being similar, bleeding was increased in the prasugrel group.[7] On the other hand, the composite efficacy endpoint in PLATO favoring ticagrelor over clopidogrel was driven by differences in both vascular death and nonfatal MIs, with stroke rates being similar. Ticagrelor was also associated with a notable reduction in all-cause mortality in PLATO. Compared with clopidogrel, ticagrelor was associated with a higher rate of non–CABG-related major bleeding and slightly more frequent discontinuation of the study drug due to adverse events.[9] On the other hand, prasugrel was associated with a significant increase in the rate of TIMI major hemorrhage, TIMI major and non-CABG bleeding, as well as higher fatal and life-threatening bleeding. There was a significant interaction between the treatment effect in PLATO and the geographic region, with lack of benefit in the United States for ticagrelor versus clopidogrel (with the explanation depending on a post hoc analysis of aspirin maintenance dose, as noted in the preceding text)[11] (see Online Data Supplement).

It must be recognized, however, that the 2 newer $P2Y_{12}$ receptor inhibitors were studied in different patient populations and that there is no head-to-head comparative trial of these agents. Also, the loading dose of clopidogrel in TRITON–TIMI 38 was lower than is currently recommended in this guideline.[7] Furthermore, some emerging studies suggest there may be some patients who are resistant to clopidogrel, but there is little information about the use of strategies to select patients who might do better with newer $P2Y_{12}$ receptor inhibitors. Considerations of efficacy in the prevention of thrombosis and risk of an adverse effect related to bleeding and experience with a given medication may best guide decisions about the choice of $P2Y_{12}$ receptor inhibitor for individual patients[14] (Appendix 4).

3.2.3.1.2.1. Timing of Discontinuation of $P2Y_{12}$ Receptor Inhibitor Therapy for Surgical Procedures. The writing group weighed the current data on the use of $P2Y_{12}$ receptor inhibitor therapy in patients who remain hospitalized after UA/NSTEMI and are candidates for CABG and retained the 2007 recommendation[4] of empirical discontinuation of clopidogrel therapy for at least 5 days[13] and advocated a period of at least 7 days in patients receiving prasugrel and a period of at least 5 days in patients receiving ticagrelor for their respective discontinuation before planned CABG.[8,12] Ultimately, the patient's clinical status will determine the risk-to-benefit ratio of CABG compared with awaiting restoration of platelet function.

It is the opinion of the writing group that physicians and patients should be cautioned against early discontinuation of $P2Y_{12}$ receptor inhibitors for elective noncardiac procedures. Given the increased hazard of recurrent cardiovascular events from premature discontinuation of $P2Y_{12}$ inhibitors and the increased bleeding risk in patients undergoing procedures on therapy (eg, colonoscopy with biopsy, dental procedures), it is advisable to consult a cardiologist and preferably defer elective noncardiac procedures until the patient finishes the appropriate course of $P2Y_{12}$ receptor inhibition therapy, especially in UA/NSTEMI patients who received <12 months of treatment with dual antiplatelet therapy after deployment of a drug-eluting stent (DES).[15]

3.2.3.1.3. Interindividual Variability in Responsiveness to Clopidogrel. Although clopidogrel in combination with aspirin has been shown to reduce recurrent coronary events in the posthospitalized ACS population,[13,16] the response to clopidogrel varies among patients, and diminished responsiveness to clopidogrel has been observed.[17,18] Clopidogrel is a prodrug and requires conversion to R130964, its active metabolite, through a 2-step process in the liver that involves several *CYP450* isoenzymes[19]; of these, the *CYP2C19* isoenzyme is responsible for almost half of the first step formation.[20] At least 3 major genetic polymorphisms of the *CYP2C19* isoenzyme are associated with loss of function: *CYP2C19**1, *2, and *3.[20–22] The *CYP2C19**2 and *3 variants account for 85% and 99% of the loss-of-function alleles in Caucasians and Asians, respectively.[20] There are racial and ethnic differences in the prevalence of these loss-of-function alleles among Caucasians, African Americans, Asians, and Latinos, but all of these groups have some expression of them.

Data from a number of observational studies have demonstrated an association between an increased risk of adverse cardiovascular events and the presence of ≥ 1 of the nonfunctioning alleles[17,18,20,21,23–27] and are well delineated in the ACCF/AHA Clopidogrel Clinical Alert.[20]

Prasugrel, the second FDA-approved $P2Y_{12}$ receptor inhibitor for use in ACS, is also a prodrug that requires conversion to its active metabolite. Prasugrel requires a single CYP-dependent step for its oxidation to the active metabolite, and at least 2 observational studies have demonstrated no significant decrease in plasma concentrations or platelet inhibition activity in carriers of at least 1 loss-of-function allele of the *CYP2C19* isoenzyme.[28,29] On the other hand, ticagrelor, the latest FDA-approved $P2Y_{12}$ receptor inhibitor, is a nonthienopyridine, reversible, direct-acting oral antagonist of the $P2Y_{12}$ receptor that does not require transformation to an active metabolite.[30]

Since the FDA announced a "Boxed Warning" on March 12, 2010, about the diminished effectiveness of clopidogrel in patients with an impaired ability to convert the drug into its active form,[14] there has been much interest in whether clinicians should perform routine testing in patients being treated with clopidogrel. The routine testing could be for genetic variants of the *CYP2C19* allele and/or for overall effectiveness for inhibition of platelet activity. The ACCF/AHA Clopidogrel Clinical Alert expertly summarizes the issues surrounding clopidogrel and the use of genotype testing, as well as the potential for routine platelet function testing.[20]

The FDA label revision does not mandate testing for *CYP2C19* genotypes or overall platelet function.[14] The revision serves to warn clinicians that certain patient subgroups may exhibit reduced clopidogrel-mediated platelet inhibition and emphasizes that clinicians should be aware of alternative treatment strategies to tailor alternative therapies when appropriate.

A number of commercially available genetic test kits will identify the presence of ≥1 of the loss-of-function *CYP2C19* alleles, but these tests are expensive and not routinely covered by most insurance policies. Additionally, there are no prospective studies that demonstrate that the routine use of these tests coupled with modification of antiplatelet therapy improves clinical outcomes or reduces subsequent clinical events. A recent meta-analysis demonstrated an association between the *CYP2C19* genotype and clopidogrel responsiveness but no significant association of genotype with cardiovascular events.[31] Several ongoing studies are examining whether genotype assessment with attendant alteration in antiplatelet therapy for those with loss-of-function alleles can improve clinical outcomes. On the basis of the current evidence, it is difficult to strongly recommend genotype testing routinely in patients with ACS, but it might be considered on a case-by-case basis, especially in patients who experience recurrent ACS events despite ongoing therapy with clopidogrel.

Some argue that clinicians should consider routine testing of platelet function, especially in patients undergoing high-risk PCI,[20] to maximize efficacy while maintaining safety. Again, no completed prospective studies have examined such an approach to guide such a sweeping change in clinical management. At least 4 randomized clinical evaluation studies being conducted now are testing the hypothesis that routine platelet function testing should be used to tailor antiplatelet therapy, and any strong recommendation regarding more widespread use of such testing must await the results of these trials. The lack of evidence does not mean lack of efficacy or potential benefit, but the prudent physician should maintain an open yet critical mind-set about the concept until data are available from ≥1 of the ongoing randomized clinical trials examining this strategy.

Our recommendations for the use of genotype testing and platelet function testing seek to strike a balance between not imposing an undue burden on clinicians, insurers, and society to implement these strategies in patients with UA or NSTEMI and that of acknowledging the importance of these issues to patients with UA/NSTEMI. Our recommendations that the use of either strategy may have some benefit should be taken in the context of the remarks in this update, as well as the more comprehensive analysis in the ACCF/AHA Clopidogrel Clinical Alert.[20] The Class IIb recommendation of these strategies suggests that a selective, limited approach to platelet genotype assessment and platelet function testing is the more prudent course until better clinical evidence exists for us to provide a more scientifically derived recommendation.

3.2.3.1.4. Optimal Loading and Maintenance Dosages of Clopidogrel. Some have suggested that the loading and maintenance doses of clopidogrel should be altered to account for potential reduced responsiveness to clopidogrel therapy or that some subgroups of high-risk patients should be treated preferentially with prasugrel.[20] Accordingly, the optimal loading and short-term maintenance dosing for clopidogrel in patients with UA/NSTEMI undergoing PCI is uncertain.

Loading and short-term maintenance doses of clopidogrel were studied in CURRENT–OASIS 7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes), with published data demonstrating a potential benefit of higher-dose clopidogrel in patients with definite UA/NSTEMI undergoing an invasive management strategy.[32,33] The CURRENT–OASIS 7 trial randomized 25 086 patients with ACS who were intended for PCI and who were not considered to be at high risk for bleeding to receive higher-dose clopidogrel (600 mg loading, 150 mg daily for 6 days, 75 mg daily thereafter) versus standard-dose clopidogrel (300 mg loading, 75 mg daily) as part of a 2×2 design that also compared maintenance higher-dose aspirin (300 to 325 mg daily) with low-dose aspirin (75 to 100 mg daily). All patients received ≥300 mg of aspirin on Day 1 regardless of randomization after Day 1. The primary endpoint of the trial was the combination of cardiovascular death, myocardial (re)infarction, or stroke at 30 days. Although the overall trial[33] failed to demonstrate a significant difference in the primary endpoint between the clopidogrel and aspirin groups (4.2% versus 4.4%), the PCI subset (n=17 263) did show significant differences in the clopidogrel arm.[32] The primary outcome was reduced in the PCI subgroup randomized to higher-dose clopidogrel (3.9% versus 4.5%; $P=0.035$), and this was largely driven by a reduction in myocardial (re)infarction (2.0% versus 2.6%; $P=0.017$). Definite stent thrombosis was reduced in the higher-dose clopidogrel group (0.7% versus 1.3%; $P=0.0001$), with consistent results across DES versus non-DES subtypes. Higher-dose clopidogrel therapy increased major bleeding in the entire group (2.5% versus 2.0%; $P=0.012$) and the PCI subgroup (1.1% versus 0.7%; $P=0.008$). The benefit of higher-dose clopidogrel loading was offset by an increase in major bleeding.[32] The findings from the prespecified PCI subgroup analysis[32] should be interpreted with caution and considered hypothesis generating, because the primary endpoint of the CURRENT–OASIS 7 trial was not met and given that the P value for interaction ($P=0.026$) between treatment effect and PCI was of borderline statistical significance.

As noted in the dosing table (Appendix 3), the current recommended loading dose for clopidogrel is uncertain. In addition, several hours are required to metabolize clopidogrel to its active metabolite, leaving a window of time where there is a reduced level of effectiveness even in patients who respond to clopidogrel.

3.2.3.1.5. Proton Pump Inhibitors and Dual Antiplatelet Therapy for ACS. Proton pump inhibitor (PPI) medications have been found to interfere with the metabolism of clopidogrel. When clopidogrel is started, PPIs are often prescribed prophylactically to prevent gastrointestinal (GI) complications such as ulceration and related bleeding[34] due to dual antiplatelet therapy, in particular aspirin and clopidogrel.[17] Coupled with concern about the GI precautions, there has been increased emphasis on the prevention of premature discontinuation of dual antiplatelet therapy, particularly in patients who have received a DES for whom 12 months of antiplatelet therapy is recommended.[15]

There have been retrospective reports of adverse cardiovascular outcomes (eg, readmission for ACS) when the antiplatelet regimen of clopidogrel and aspirin is accompanied by PPIs assessed as a group compared with use of this regimen without a PPI.[17,35,36] In a retrospective cohort study

from the Veterans Affairs' medical records and pharmacy database, concomitant clopidogrel and PPI therapy (with omeprazole, rabeprazole, lansoprazole, or pantoprazole) at any time during follow-up of 8205 patients discharged for ACS was associated with an increased risk of death or rehospitalization for ACS.[17] Other post hoc study analyses[25] and a retrospective data analysis from the National Heart, Lung, and Blood Institute Dynamic Registry, in which PPIs were assessed as a class in combination with a clopidogrel and an aspirin regimen, have not found an effect of PPI therapy on the clinical effect of clopidogrel in ACS patients, post-ACS patients, and a general post-PCI population, respectively.[25]

Some studies have suggested that adverse cardiovascular outcomes with the combination of clopidogrel and a PPI are explained by the individual PPI, in particular, the use of a PPI that inhibits *CYP450 2C19*, including omeprazole, lansoprazole, or rabeprazole. Notably, the PPI omeprazole has been reported to significantly decrease the inhibitory effect of clopidogrel on platelet aggregation.[38,39] One study reported that the PPI pantoprazole was not associated with recurrent MI among patients receiving clopidogrel, possibly due to pantoprazole's lack of inhibition of *CYP450 2C19*.[35]

Other studies have examined the $P2Y_{12}$ receptor inhibitor prescribed with the PPI. One open-label drug study evaluated the effects of the PPI lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel in healthy subjects given single doses of prasugrel 60 mg and clopidogrel 300 mg with and without concurrent lansoprazole 30 mg per day. The data suggest that inhibition of platelet aggregation was reduced in patients who took the combination of clopidogrel and lansoprazole, whereas platelet aggregation was unaffected after a prasugrel dose.[40]

Another study[36] assessed the association of PPIs with the pharmacodynamics and clinical efficacy of clopidogrel and prasugrel, based on populations from 2 randomized trials, the PRINCIPLE (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) TIMI-44 trial[41] and the TRITON–TIMI 38 trial.[7] The findings indicated that first, PPI treatment attenuated the pharmacodynamic effects of clopidogrel and, to a lesser extent, those of prasugrel. Second, PPI treatment did not affect the clinical outcome of patients given clopidogrel or prasugrel. This finding was true for all PPIs that were studied, including omeprazole and pantoprazole.

Observational trials may be confounded by selection bias. In the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) study,[42] omeprazole was compared with placebo in 3627 patients starting dual antiplatelet therapy with aspirin and clopidogrel. No difference was found in the primary composite cardiovascular endpoint between clopidogrel plus omeprazole and clopidogrel plus placebo (HR: 1.02), but GI bleeding complications were reduced.[42] COGENT had several shortcomings (see Online Data Supplement), and more controlled, randomized clinical trial data are needed to address the clinical impact of conjunctive therapy with clopidogrel and PPIs.

The FDA communication on an ongoing safety review of clopidogrel bisulfate[14] advises that healthcare providers should reevaluate the need for starting or continuing treatment with a PPI, including omeprazole, in patients taking clopidogrel. The FDA notes there is no evidence that other drugs that reduce stomach acid, such as H2 blockers or antacids, interfere with the antiplatelet activity of clopidogrel. Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke. Healthcare providers should reevaluate the need for starting or continuing treatment with a PPI, including omeprazole (over the counter), in patients taking clopidogrel. Patients taking clopidogrel should consult their healthcare provider if they are currently taking or considering taking a PPI, including omeprazole.[14] The ACCF has released a statement on the use of PPI agents in combination with clopidogrel. The expert consensus statement does not prohibit the use of PPI agents in appropriate clinical settings, yet highlights the potential risks and benefits from use of PPI agents in combination with clopidogrel.[43]

3.2.3.1.6. Glycoprotein IIb/IIIa Receptor Antagonists. The efficacy of glycoprotein (GP) IIb/IIIa inhibitor therapy has been well established during PCI procedures and in patients with UA/NSTEMI, particularly among high-risk patients such as those with elevated troponin biomarkers, those with diabetes, and those undergoing revascularization.[44–54] The preponderance of the evidence supporting the use of GP IIb/IIIa inhibitor therapy predated the trials that established the benefits of clopidogrel, early invasive therapy, and contemporary medical treatments in patients with UA/NSTEMI. These studies supported the upstream use of a GP IIb/IIIa inhibitor as a second agent in combination with aspirin for dual antiplatelet therapy in patients with UA/NSTEMI, especially in high-risk subsets such as those with an initial elevation in cardiac troponins, those with diabetes, and in those undergoing revascularization.[47,48,50–52,55] These studies did not directly test in a randomized fashion the selection of an oral thienopyridine versus an intravenous (IV) GP IIb/IIIa inhibitor as the second antiplatelet agent in UA/NSTEMI.

Contemporary clinical trials have therefore been needed to define the optimal timing of initiation of GP IIb/IIIa inhibitor therapy in patients with UA/NSTEMI, whether "upstream" (at presentation and before angiography) or "deferred" (at the time of angiography/PCI), and its optimal application (whether routine, selective, or provisional) and to clarify the relative benefit and risk of GP IIb/IIIa inhibitor therapy as a third antiplatelet agent in combination with aspirin and a thienopyridine.

The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome) trial[56] tested the hypothesis that a strategy of early routine administration of the GP IIb/IIIa inhibitor eptifibatide would be superior to delayed provisional administration in reducing ischemic complications among high-risk patients with UA/NSTEMI. The study investigators enrolled 9492 patients who presented within 24 hours of an episode of ischemic rest discomfort of at least 10 minutes' duration. The study subjects were randomized within 8 to 12 hours after presentation and assigned to an invasive treatment strategy no sooner than the next calendar day. To qualify as having high-risk UA/NSTEMI, the subjects were required to have at least 2 of the following: ST-segment depression or transient ST-segment elevation, elevated biomarker levels (creatine kinase–myocardial band or troponin), or age ≥60 years. The study subjects were randomized in a double-blind design to receive either early routine administration of eptifibatide (double bolus followed by standard infusion) or delayed provisional eptifibatide at the time of PCI. Eptifibatide infusion was given for 18 to 24 hours after PCI in both groups. For patients who underwent PCI, the total duration of the infusion

was ≤96 hours. For patients who did not receive PCI for whatever reason, the duration of infusion was ≤96 hours. The study infusion was stopped 2 hours before surgery for those undergoing CABG. Early clopidogrel was allowed at the investigators' discretion (75% intended early use), and if used, a loading dose of 300 mg was recommended. For patients beginning clopidogrel during PCI (intended in 25% of study subjects, but actually implemented in 11%), a dose of 600 mg was permitted. Randomization to 1 of 3 antithrombotic regimens was stratified according to the intention of the investigator to administer early clopidogrel (ie, at or before randomization).[56]

The primary endpoint (a 30-day composite of all-cause death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours) occurred in 9.3% of patients in the early therapy arm versus 10.0% of patients in the provisional GP IIb/IIIa inhibitor therapy arm (OR: 0.92; 95% CI: 0.80 to 1.06; $P=0.23$). Secondary endpoint (all-cause death or MI within 30 days) event rates were 11.2% versus 12.3% (OR: 0.89; 95% CI: 0.79 to 1.01; $P=0.08$). Early routine eptifibatide administration was associated with a greater risk of TIMI major hemorrhage (2.6% versus 1.8%; $P=0.02$). Severe or moderate bleeding, as defined by the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) criteria, also occurred more commonly in the early eptifibatide group (7.6% versus 5.1%; $P<0.001$). Rates of red blood cell transfusion were 8.6% and 6.7% in the early-eptifibatide and delayed-eptifibatide groups, respectively ($P=0.001$). There were no significant interactions with respect to prespecified baseline characteristics, including early clopidogrel administration, and the primary or secondary efficacy endpoints. In a subgroup analysis, early administration of eptifibatide in patients who underwent PCI was associated with numerically fewer ischemic events.

A second contemporary study, the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial,[57] examined in part the optimal strategy for the use of GP IIb/IIIa inhibitors in moderate- and high-risk ACS patients undergoing early invasive therapy. A total of 9207 patients were randomized to 1 of 3 antithrombin regimens: unfractionated heparin (UFH) or enoxaparin plus GP IIb/IIIa inhibitor therapy; bivalirudin plus GP IIb/IIIa inhibitor therapy; or bivalirudin alone. Patients assigned to the heparin (UFH or enoxaparin) plus GP IIb/IIIa inhibitor therapy or to the bivalirudin plus GP IIb/IIIa inhibitor therapy were also randomized to immediate upstream routine GP IIb/IIIa inhibitor therapy or deferred selective use of GP IIb/IIIa inhibitor therapy at the time of PCI. A clopidogrel loading dose of ≥300 mg was required in all cases no later than 2 hours after PCI, and provisional GP IIb/IIIa inhibitor use was permitted before angiography in the deferred group for severe breakthrough ischemia. The composite ischemic endpoint occurred in 7.1% of the patients assigned to upstream administration and in 7.9% of patients assigned to deferred selective administration (RR: 1.12; 95% CI: 0.97 to 1.29; $P=0.13$),[57] and thus the noninferiority hypothesis was not achieved. Major bleeding was lower in the deferred-use group versus the upstream group (4.9% to 6.1%; $P<0.001$ for noninferiority and $P=0.009$ for superiority).

Although early GP IIb/IIIa inhibitor therapy as dual antiplatelet therapy also reduced complications after PCI, supporting its continued role in patients undergoing PCI,[49,53,54,56,58] these 2 most recent studies[56,57] more strongly support a strategy of selective rather than routine upstream use of GP IIb/IIIa inhibitor therapy as part of triple antiplatelet therapy. Data from EARLY ACS[56] highlight the potential bleeding risks of upstream use of a GP IIb/IIIa inhibitor as part of triple antiplatelet therapy. The use of a GP IIb/IIIa inhibitor should be undertaken when the risk-benefit ratio suggests a potential benefit for the patient. The use of these agents as part of triple antiplatelet therapy may therefore not be supported when there is a concern for increased bleeding risk or in non–high-risk subsets such as those with a normal baseline troponin level, those without diabetes, and those aged ≥75 years, in whom the potential benefit may be significantly offset by the potential risk of bleeding (Tables 2 and 3).

3.3. Initial Invasive Versus Initial Conservative Strategies: Recommendations

(See Table 4, and Appendixes 5 and 6 for supplemental information.)

3.3.3.1. Timing of Invasive Therapy

Among initially stabilized patients with UA/NSTEMI for whom an early invasive strategy of coronary angiography is chosen, optimal timing of angiography has not been well defined. Early or immediate catheterization with revascularization of unstable coronary lesions may prevent ischemic events that would otherwise occur during medical therapy. Conversely, pretreatment with intensive antithrombotic therapy may diminish thrombus burden and "passivate" unstable plaques, improving the safety of percutaneous revascularization and reducing the risk of periprocedural ischemic complications. Three trials have compared different strategies of "early" versus "delayed" intervention in patients with UA/NSTEMI and form the basis of the updated recommendations in this guideline.

The ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling-Off) trial[122] carried out at 2 hospitals between 2000 and 2002 randomized 410 patients with unstable chest pain and either electrocardiographic ST-segment depression or elevated troponin levels to undergo coronary angiography within 6 hours of presentation (median 2.4 hours) or after 3 to 5 days (median 86 hours) of antithrombotic pretreatment.[122] Patients with "large MI," defined by ST-segment elevation or creatine kinase–myocardial band isoenzyme activity >3 times normal, were excluded. Underlying medical therapy in both treatment arms included aspirin, clopidogrel, UFH, and tirofiban. By 30 days' follow-up, the primary endpoint of death or large MI (defined by new electrocardiographic Q waves, left bundle-branch block, or creatine kinase–myocardial band elevation >5 times normal) occurred in 11.6% of patients randomized to delayed catheterization versus 5.9% of those in the early angiography group ($P=0.04$). Differences between treatment groups were observed exclusively in the period before catheterization, with identical event rates in the 2 arms after angiography. Although providing evidence that a strategy of "cooling-off" for 3 to 5 days before angiography does not improve outcome in this setting, the findings of this trial were limited because of the small sample size and the prolonged delay before angiography in the medical pretreatment arm.

Information more relevant to contemporary practice patterns was provided in the 2009 publication of the large-scale multicenter TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial,[107] which compared early versus delayed angiography and intervention in patients with non–

Table 2. Recommendations for Antiplatelet Therapy

2012 Focused Update Recommendations	2012 Comments
Class I	
1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.[59–66] *(Level of Evidence: A)*	2011 recommendation remains current.
2. A loading dose followed by daily maintenance dose of either clopidogrel[13,67,68] *(Level of Evidence: B)*, prasugrel* (in PCI-treated patients)[7] *(Level of Evidence: C)*, or ticagrelor†[9] *(Level of Evidence: C)* should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major GI intolerance.	2011 recommendation modified (included prasugrel and ticagrelor).
3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected (Appendix 6) should receive dual antiplatelet therapy on presentation.[13,16,45,69] *(Level of Evidence: A)* Aspirin should be initiated on presentation.[59,61–66] *(Level of Evidence: A)* The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy): *Before PCI*: • Clopidogrel[13,16] *(Level of Evidence: B)*; or • Ticagrelor†[9] *(Level of Evidence: B)*; or • An IV GP IIb/IIIa inhibitor.[45,50,51,70,71] *(Level of Evidence: A)* IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors.[50,51] *(Level of Evidence: B)* *At the time of PCI*: • Clopidogrel if not started before PCI[13,16] *(Level of Evidence: A)*; or • Prasugrel*[7] *(Level of Evidence: B)*; or • Ticagrelor†[9] *(Level of Evidence: B)*; or • An IV GP IIb/IIIa inhibitor.[46,50,51] *(Level of Evidence: A)*	2011 recommendation modified (included ticagrelor).
4. For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) 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.[9,10,13] *(Level of Evidence: B)*	2011 recommendation modified (included ticagrelor and changed duration of therapy to "up to 12 months").
5. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed.[55,72] *(Level of Evidence: A)* Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban[46,50,51] [*Level of Evidence: A*]), clopidogrel (loading dose followed by daily maintenance dose[13] [*Level of Evidence: B*]), or ticagrelor† (loading dose followed by daily maintenance dose[9] [*Level of Evidence: B*]) should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). *(Level of Evidence: C)*	2011 recommendation modified (included ticagrelor).
6. A loading dose of $P2Y_{12}$ receptor inhibitor therapy is recommended for UA/NSTEMI patients for whom PCI is planned.‡ One of the following regimens should be used: a. Clopidogrel 600 mg should be given as early as possible before or at the time of PCI[32,73,74] *(Level of Evidence: B)* or b. Prasugrel* 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI[7] *(Level of Evidence: B)* or c. Ticagrelor† 180 mg should be given as early as possible before or at the time of PCI.[9] *(Level of Evidence: B)*	2011 recommendation modified (included ticagrelor and changed loading dose of clopidogrel and associated level of evidence to be concordant with 2011 PCI guideline[75]).
7. The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows: a. In UA/NSTEMI patients undergoing PCI, either clopidogrel 75 mg daily,[13,16] prasugrel* 10 mg daily,[7] or ticagrelor† 90 mg twice daily[9] should be given for at least 12 months. *(Level of Evidence: B)* b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. *(Level of Evidence: C)*	2011 recommendation modified (included ticagrelor; a footnote added pertaining to recommended aspirin maintenance dose).
Class IIa	
1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with aspirin, a $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor), and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography. *(Level of Evidence: C)*	2007 recommendation modified ("clopidogrel" replaced with "$P2Y_{12}$" receptor inhibitor [clopidogrel or ticagrelor]).
2. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier than planned catheterization or PCI.[57,76,77] *(Level of Evidence: B)*	2011 recommendation remains current.

(*Continued*)

Table 2. Continued

2012 Focused Update Recommendations	2012 Comments
Class IIb	
1. For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy.[50,51] *(Level of Evidence: B)*	2007 recommendation remains current.
2. Prasugrel* 60 mg may be considered for administration promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely.[7,8,78] *(Level of Evidence: C)*	2011 recommendation remains current.
3. The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk UA/NSTEMI patients already receiving aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) who are selected for an invasive strategy, such as those with elevated troponin levels, diabetes, or significant ST-segment depression, and who are not otherwise at high risk for bleeding.[50,51,55,56,58] *(Level of Evidence: B)*	2011 recommendation modified ("clopidogrel" replaced with "$P2Y_{12}$" receptor inhibitor [clopidogrel or ticagrelor]).
4. In patients with definite UA/NSTEMI undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel of 600 mg, followed by a higher maintenance dose of 150 mg daily for 6 days, then 75 mg daily may be reasonable in patients not considered at high risk for bleeding.[32] *(Level of Evidence: B)*	2011 recommendation remains current.
Class III: No Benefit	
1. Abciximab should not be administered to patients in whom PCI is not planned.[46,71] *(Level of Evidence: A)*	2007 recommendation remains current.
2. In UA/NSTEMI patients who are at low risk for ischemic events (eg, TIMI risk score ≤2) or at high risk of bleeding and who are already receiving aspirin and a $P2Y_{12}$ receptor inhibitor, upstream GP IIb/IIIa inhibitors are not recommended.[56,57,78] *(Level of Evidence: B)*	2011 recommendation modified ("clopidogrel" replaced with "$P2Y_{12}$ receptor inhibitor").
Class III: Harm	
1. In UA/NSTEMI patients with a prior history of stroke and/or TIA for whom PCI is planned, prasugrel* is potentially harmful as part of a dual antiplatelet therapy regimen.[7] *(Level of Evidence: B)*	2011 recommendation remains current.

*Patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10-mg once-daily maintenance dose. Consideration should be given to lowering the maintenance dose to 5 mg in patients who weigh <60 kg, although the effectiveness and safety of the 5-mg dose have not been studied prospectively. For post-PCI patients, a daily maintenance dose should be given for at least 12 months for patients receiving DES and up to 12 months for patients receiving BMS unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients age ≥75 years, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk situations (patients with diabetes or a history of prior myocardial infarction), in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent CABG. When possible, discontinue prasugrel at least 7 days before any surgery.[8] Additional risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs).[8]

†The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.[11] Ticagrelor's benefits were observed irrespective of prior therapy with clopidogrel. [9] When possible, discontinue ticagrelor at least 5 days before any surgery.[12] Issues of patient compliance may be especially important. Consideration should be given to the potential and as yet undetermined risk of intracranial hemorrhage in patients with prior stroke or TIA.

‡Applies to patients who were not treated chronically with these medications.

BMS indicates bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; GI, gastrointestinal; GP, glycoprotein; IV, intravenous; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

ST-segment elevation ACS. Patients were included if they presented within 24 hours of onset of unstable ischemic symptoms with advanced age (≥60 years), elevated cardiac biomarkers, or ischemic electrocardiographic changes, and were randomized to undergo angiography as rapidly as possible and within 24 hours of randomization (median 14 hours) versus after a minimum delay of 36 hours (median 50 hours). Anticoagulation included aspirin, clopidogrel in >80% of patients, heparin or fondaparinux, and GP IIb/IIIa inhibitors in 23% of patients. Although the trial was initially powered for enrollment of 4000 patients to detect a 25% reduction in the primary endpoint of death, new MI, or stroke at 6 months, the steering committee chose to terminate enrollment at 3031 patients because of recruitment challenges. Among the overall trial population, there was only a nonsignificant trend toward a reduced incidence of the primary clinical endpoint, from 11.3% in the delayed intervention group to 9.6% in the early intervention arm (HR for early intervention: 0.85; 95% CI: 0.68 to 1.06; $P=0.15$). However, a prospectively defined secondary endpoint of death, MI, or refractory ischemia was significantly reduced by early intervention from 12.9% to 9.5% (HR: 0.72; 95% CI: 0.58 to 0.89; $P=0.003$), mainly because of a difference in the incidence of refractory ischemia (3.3% versus 1.0% in the delayed versus early intervention arms, respectively; $P<0.001$). The occurrence of refractory ischemia was associated with a >4-fold increase in risk of subsequent MI. Moreover, significant heterogeneity was observed in the primary endpoint when stratified according to a prespecified estimation of baseline risk according to the GRACE (Global Registry of Acute Coronary Events) score. Patients in the highest tertile of the GRACE risk score (>140) experienced a sizeable and significant reduction in the incidence of the primary ischemic endpoint, from 21.0% to 13.9% (HR: 0.65; 95% CI: 0.48 to

Table 3. Recommendations for Additional Management of Antiplatelets and Anticoagulants

2012 Focused Update Recommendations	2012 Comments
Class I	
1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, heart failure, or serious arrhythmias), a stress test should be performed.[72] *(Level of Evidence: B)*	2011 recommendation modified (included ticagrelor, and duration of antiplatelet therapy changed to "up to 12 months").
a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed.[55,72] *(Level of Evidence: A)*	
b. If, after stress testing, the patient is classified as being at low risk, the instructions noted below should be followed in preparation for discharge[55,72]:	
1. Continue aspirin indefinitely.[61,63,64] *(Level of Evidence: A)*	
2. Continue clopidogrel or ticagrelor* for up to 12 months.[9,10,13] *(Level of Evidence: B)*	
3. Discontinue IV GP IIb/IIIa inhibitor if started previously.[50,51] *(Level of Evidence: A)*	
4. Continue UFH for 48 hours[66,79] *(Level of Evidence: A)* or administer enoxaparin[80–82] *(Level of Evidence: A)* or fondaparinux[83] *(Level of Evidence: B)* for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy.	
2. For UA/NSTEMI patients in whom CABG is selected as a postangiography management strategy, the instructions noted below should be followed.	2011 recommendation remains current.
a. Continue aspirin.[84–90] *(Level of Evidence: A)*	
b. *See Class I, #3, in this section.*	
c. Discontinue IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 hours before CABG.[84,88,91] *(Level of Evidence: B)*	
d. Anticoagulant therapy should be managed as follows:	
1. Continue UFH.[80,92–94] *(Level of Evidence: B)*	
2. Discontinue enoxaparin 12 to 24 hours before CABG and dose with UFH per institutional practice.[80,92–94] *(Level of Evidence: B)*	
3. Discontinue fondaparinux 24 hours before CABG and dose with UFH per institutional practice.[95,96] *(Level of Evidence: B)*	
4. Discontinue bivalirudin 3 hours before CABG and dose with UFH per institutional practice.[97,98] *(Level of Evidence: B)*	
3. In patients taking a $P2Y_{12}$ receptor inhibitor in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect[13] *(Level of Evidence: B).* The period of withdrawal should be at least 5 days in patients receiving clopidogrel[13,45,99] *(Level of Evidence: B)* or ticagrelor*[12] *(Level of Evidence: C)* and at least 7 days in patients receiving prasugrel†[8] *(Level of Evidence: C)* unless the need for revascularization and/or the net benefit of the $P2Y_{12}$ receptor inhibitor therapy outweighs the potential risks of excess bleeding.[100] *(Level of Evidence: C)*	2011 recommendation modified (included ticagrelor).
4. For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed:	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
a. Continue aspirin.[61,63,64] *(Level of Evidence: A)*	
b. Administer a loading dose of a $P2Y_{12}$ receptor inhibitor if not started before diagnostic angiography.[9,68,74,101–103] *(Level of Evidence: A)*	
c. Discontinue anticoagulant therapy after PCI for uncomplicated cases.[80,82,104–106] *(Level of Evidence: B)*	
5. For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom no significant obstructive coronary artery disease on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician *(Level of Evidence: C).* For patients in whom evidence of coronary atherosclerosis is present (eg, luminal irregularities or intravascular ultrasound-demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with aspirin and other secondary prevention measures should be prescribed. *(Level of Evidence: C)*	2007 recommendation remains current.
6. For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom coronary artery disease was found on angiography, the following approach is recommended:	2011 recommendation modified (included ticagrelor).
a. Continue aspirin.[61,63,64] *(Level of Evidence: A)*	
b. Administer a loading dose of clopidogrel or ticagrelor* if not given before diagnostic angiography.[9,13] *(Level of Evidence: B)*	
c. Discontinue IV GP IIb/IIIa inhibitor if started previously.[50,51,57,107] *(Level of Evidence: B)*	

(*Continued*)

Table 3. Continued

2012 Focused Update Recommendations	2012 Comments
d. Anticoagulant therapy should be managed as follows:	
1. Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography[66,79,80] *(Level of Evidence: A)*	
2. Continue enoxaparin for duration of hospitalization, up to 8 days, if given before diagnostic angiography.[80–82,96] *(Level of Evidence: A)*	
3. Continue fondaparinux for duration of hospitalization, up to 8 days, if given before diagnostic angiography.[83] *(Level of Evidence: B)*	
4. Either discontinue bivalirudin or continue at a dose of 0.25 mg/kg per hour for up to 72 hours at the physician's discretion if given before diagnostic angiography.[77,108,109] *(Level of Evidence: B)*	
7. For UA/NSTEMI patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, the instructions noted below should be followed:	2011 recommendation modified (included ticagrelor; duration of antiplatelet therapy changed to "up to 12 months").
a. Continue aspirin indefinitely.[61,63,64] *(Level of Evidence: A)*	
b. Continue clopidogrel or ticagrelor* for up to 12 months.[9,13,67,110] *(Level of Evidence: B)*	
c. Discontinue IV GP IIb/IIIa inhibitor if started previously.[50,51] *(Level of Evidence: A)*	
d. Continue UFH for 48 hours[66,79] *(Level of Evidence: A)* or administer enoxaparin[80–82] *(Level of Evidence: A)* or fondaparinux[83] *(Level of Evidence: B)* for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy.	
8. For UA/NSTEMI patients in whom an initial conservative strategy is selected and in whom no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, heart failure, or serious arrhythmias), LVEF should be measured.[55,111–114] *(Level of Evidence: B)*	2007 recommendation remains current.
Class IIa	
1. For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, it is reasonable to administer an IV GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography, particularly for troponin-positive and/or other high-risk patients.[55,58] *(Level of Evidence: A)*	2011 recommendation remains current.
2. For UA/NSTEMI patients in whom PCI is selected as a management strategy, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier.[55,57] *(Level of Evidence: B)*	2007 recommendation remains current.
3. If LVEF is less than or equal to 0.40, it is reasonable to perform diagnostic angiography.[111–114] *(Level of Evidence: B)*	2007 recommendation remains current.
4. If LVEF is greater than 0.40, it is reasonable to perform a stress test.[111] *(Level of Evidence: B)*	2007 recommendation remains current.
Class IIb	
1. Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on $P2Y_{12}$ receptor inhibitor therapy may be considered if results of testing may alter management.[115–119] *(Level of Evidence: B)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
2. Genotyping for a *CYP2C19* loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on $P2Y_{12}$ receptor inhibitor therapy might be considered if results of testing may alter management.[19–22,25,27,120] *(Level of Evidence: C)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
Class III: No Benefit	
1. IV fibrinolytic therapy is not indicated in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block.[121] *(Level of Evidence: A)*	2007 recommendation remains current.

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.[11] The benefits of ticagrelor were observed irrespective of prior therapy with clopidogrel.[9] When possible, discontinue ticagrelor at least 5 d before any surgery.[12] Issues of patient compliance may be especially important. Consideration should be given to the potential and as yet undetermined risk of intracranial hemorrhage in patients with prior stroke or TIA.

†Patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10-mg once-daily maintenance dose. Consideration should be given to lowering the maintenance dose to 5 mg in patients who weigh <60 kg, although the effectiveness and safety of the 5-mg dose have not been studied prospectively. For post-PCI patients, a daily maintenance dose should be given for at least 12 mo for patients receiving DES and up to 12 months for patients receiving BMS unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients age ≥75 y, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk situations (patients with diabetes or a history of prior MI), in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent CABG. When possible, discontinue prasugrel at least 7 d before any surgery.[8] Additional risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs).[8]

ACS indicates acute coronary syndrome; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; GP, glycoprotein; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and UFH, unfractionated heparin.

0.89; $P=0.006$), whereas no difference in outcome (6.7% versus 7.6% in the delayed and early groups, respectively; HR: 1.12; 95% CI: 0.81 to 1.56; $P=0.48$) was observed among patients in the lower 2 risk tertiles (GRACE score ≤140).[107]

Results of the TIMACS trial suggested superior outcome among patients managed by early rather than delayed intervention in the setting of UA/NSTEMI, although the reduction in the primary endpoint did not reach statistical significance for the overall trial population. Nevertheless, refractory ischemia was reduced by an early approach, as were the risks of death, MI, and stroke among patients at the highest tertile of ischemic risk as defined by the GRACE risk score.[107]

To assess whether a more aggressive strategy of very early intervention, analogous to the standard of primary PCI for STEMI, would lead to improved outcomes in patients with non–ST-elevation ACS, the ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes) study investigators[123] compared angiography and intervention performed immediately on presentation with intervention carried out on the next working day. A total of 352 patients with unstable ischemic symptoms, ECG changes, or troponin elevation were randomized at 13 hospitals to immediate (at a median 70 minutes after enrollment) versus delayed (at a median 21 hours) angiography and revascularization. Background antithrombotic therapy consisted of aspirin, clopidogrel with a loading dose of ≥300 mg, abciximab during PCI, and the anticoagulant of the investigator's choice. The primary trial endpoint was peak troponin I value during the hospitalization period. Immediate intervention conferred no advantage with regard to the primary endpoint (median troponin I value 2.1 versus 1.7 ng/mL in the immediate and delayed intervention groups, respectively), nor was there even a trend toward improved outcome in the prespecified clinical secondary endpoint of death, MI, or urgent revascularization by 1 month (13.7% versus 10.2% in the immediate and delayed intervention groups, respectively; $P=0.31$).[123]

These 3 trials,[107,122,123] taken together with earlier studies, do provide support for a strategy of early angiography and intervention to reduce ischemic complications in patients who have been selected for an initial invasive strategy, particularly among those at high risk (defined by a GRACE score >140), whereas a more delayed approach is reasonable in low- to intermediate-risk patients. The "early" time period in this context is considered to be within the first 24 hours after hospital presentation, although there is no evidence that incremental benefit is derived by angiography and intervention performed within the first few hours of hospital admission. The advantage of early intervention was achieved in the context of intensive background antithrombotic therapy (Table 4).

5. Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care

5.2. Long-Term Medical Therapy and Secondary Prevention

5.2.1. Convalescent and Long-Term Antiplatelet Therapy: Recommendations

(See Table 5 and Appendix 3 for supplemental information.)

Table 4. Recommendations for Initial Invasive Versus Initial Conservative Strategies

2012 Focused Update Recommendations	2012 Comments
Class I	
1. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures).[124,125] *(Level of Evidence: B)*	2007 recommendation remains current.
2. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is indicated in initially stabilized UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see 2007[4] Table 11 and 2007 Sections 2.2.6 and 3.4.3).[55,72,111] *(Level of Evidence: A)*	2007 recommendation remains current.
Class IIa	
1. It is reasonable to choose an early invasive strategy (within 12 to 24 hours of admission) over a delayed invasive strategy for initially stabilized high-risk patients with UA/NSTEMI.* For patients not at high risk, a delayed invasive approach is also reasonable.[107] *(Level of Evidence: B)*	2011 recommendation remains current.
Class IIb	
1. In initially stabilized patients, an initially conservative (ie, a selectively invasive) strategy may be considered as a treatment strategy for UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see 2007[4] Table 11 and Sections 2.2.6 and 3.4.3), including those who are troponin positive.[111,126] *(Level of Evidence: B)* The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made by considering physician and patient preference. *(Level of Evidence: C)*	2007 recommendation remains current.
Class III: No Benefit	
1. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (eg, liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. *(Level of Evidence: C)*	2007 recommendation remains current.
2. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is not recommended in patients with acute chest pain and a low likelihood of ACS. *(Level of Evidence: C)*	2007 recommendation remains current.
3. An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) should not be performed in patients who will not consent to revascularization regardless of the findings. *(Level of Evidence: C)*	2007 recommendation remains current.

*Immediate catheterization/angiography is recommended for unstable patients.

ACS indicates acute coronary syndrome; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Table 5. Recommendations for Convalescent and Long-Term Antiplatelet Therapy

2012 Focused Update Recommendations	2012 Comments
Class I	
1. For UA/NSTEMI patients treated medically without stenting, aspirin* should be prescribed indefinitely[60,61,63,64] *(Level of Evidence: A)*; clopidogrel (75 mg per day) or ticagrelor† (90 mg twice daily) should be prescribed for up to 12 months.[9,10,14] *(Level of Evidence: B)*	2011 recommendation modified (included ticagrelor and footnote added pertaining to recommended aspirin maintenance dose).
2. For UA/NSTEMI patients treated with a stent (BMS or DES), aspirin should be continued indefinitely. *(Level of Evidence: A)* The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows:	2011 recommendation modified (included the term "$P2Y_{12}$ receptor inhibitor" and altered aspirin dosing and duration of therapy after stent deployment).
a. Clopidogrel 75 mg daily,[16] prasugrel‡ 10 mg daily,[7] or ticagrelor† 90 mg twice daily[9] should be given for at least 12 months in patients receiving DES and up to 12 months for patients receiving BMS.[9,13,16] *(Level of Evidence: B)*	
b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. *(Level of Evidence: C)*	
3. Clopidogrel 75 mg daily[13,67] *(Level of Evidence: B),* prasugrel‡ 10 mg daily (in PCI-treated patients)[7] *(Level of Evidence: C)*, or ticagrelor† 90 mg twice daily[9] *(Level of Evidence: C)* should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or GI intolerance (despite use of gastroprotective agents such as PPIs).[42,68]	2011 recommendation modified (included prasugrel and ticagrelor; deleted ticlopidine).
Class IIa	
1. After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.[32,33,90,127,128] *(Level of Evidence: B)*	2011 recommendation modified (changed wording and aspirin dose to be concordant with the 2011 PCI guideline[75]).
Class IIb	
1. For UA/NSTEMI patients who have an indication for anticoagulation, the addition of warfarin§ may be reasonable to maintain an INR of 2.0 to 3.0.‖[129–138] *(Level of Evidence: B)*	2007 recommendation remains current.
2. Continuation of a $P2Y_{12}$ receptor inhibitor beyond 12 months may be considered in patients following DES placement. *(Level of Evidence: C)*	2011 recommendation modified (changed time period to be concordant with 2011 PCI guideline[75] and replaced "clopidogrel and prasugrel" with "$P2Y_{12}$ receptor inhibitor").
Class III: No Benefit	
1. Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective.[90,139,140] *(Level of Evidence: B)*	2011 recommendation remains current.

*For aspirin-allergic patients, use either clopidogrel or ticagrelor alone (indefinitely) or try aspirin desensitization. Note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy.

†The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.[11] Ticagrelor's benefits were observed irrespective of prior therapy with clopidogrel.[9] When possible, discontinue ticagrelor at least 5 d before any surgery.[12] Issues of patient compliance may be especially important. Consideration should be given to the potential and as yet undetermined risk of intracranial hemorrhage in patients with prior stroke or TIA.

‡Patients weighing $<$60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10-mg once-daily maintenance dose. Consideration should be given to lowering the maintenance dose to 5 mg in patients who weigh $<$60 kg, although the effectiveness and safety of the 5-mg dose have not been studied prospectively. For post-PCI patients, a daily maintenance dose should be given for at least 12 mo for patients receiving DES and up to 12 mo for patients receiving BMS unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients age $\geq$75 y, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk situations (patients with diabetes or a history of prior myocardial infarction), in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent CABG. When possible, discontinue prasugrel at least 7 d before any surgery.[8] Additional risk factors for bleeding include body weight $<$60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs).[8]

§Continue aspirin indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; or cerebral, venous, or pulmonary emboli.

‖An INR of 2.0 to 2.5 is preferable while given with aspirin and a $P2Y_{12}$ receptor inhibitor, especially in older patients and those with other risk factors for bleeding. For UA/NSTEMI patients who have mechanical heart valves, the INR should be at least 2.5 (based on type of prosthesis).

BMS indicates bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; GI, gastrointestinal; INR, international normalized ratio; LV, left ventricular; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TIA, transient ischemic attack; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Table 6. Recommendations for Warfarin Therapy

2012 Focused Update Recommendations	2012 Comments
Class I	
1. Use of warfarin in conjunction with aspirin and/or $P2Y_{12}$ receptor inhibitor therapy is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially GI, and seek medical evaluation for evidence of bleeding.[7,9,13,14,141–144] *(Level of Evidence: A)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
Class IIb	
1. Warfarin either without (INR 2.5 to 3.5) or with low-dose aspirin (81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high coronary artery disease risk and low bleeding risk who do not require or are intolerant of $P2Y_{12}$ receptor inhibitor therapy.[145,146] *(Level of Evidence: B)*	2011 recommendation modified ("thienopyridine" replaced with "$P2Y_{12}$ receptor inhibitor").
2. Targeting oral anticoagulant therapy to a lower INR (eg, 2.0 to 2.5) might be reasonable in patients with UA/NSTEMI managed with aspirin and a $P2Y_{12}$ inhibitor. *(Level of Evidence: C)*	New recommendation

GI indicates gastrointestinal; INR, international normalized ratio; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

5.2.6. Warfarin Therapy: Recommendations

(See Table 6.)

6. Special Groups

6.2. Diabetes Mellitus: Recommendations

(See Table 7.)

6.2.1.1. Intensive Glucose Control

As detailed in the 2004 STEMI guideline,[153] 2007 UA/NSTEMI guideline revision,[4] and 2009 STEMI and PCI focused update,[154] randomized trial evidence supported use of insulin infusion to control hyperglycemia. A clinical trial of intensive versus conventional glucose control in critically ill patients raised uncertainty about the optimal level to target when achieving glucose control. NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation), a large international randomized trial (n=6104) of adults admitted to the intensive care unit with either medical or surgical conditions, compared intensive glucose control (target glucose range, 81 to 108 mg/dL) with conventional glucose control (to achieve a glucose level of <180 mg/dL, with reduction and discontinuation of insulin if the blood glucose level dropped below 144 mg/dL).[149] Time-weighted glucose levels achieved were 115±18 mg/dL in the intensive group versus 144±23 mg/dL in the conventional group. The risk of death was increased at 90 days in the intensive group by 2.6% (27.5% versus 24.9%; OR: 1.14; 95% CI: 1.02 to 1.08; $P=0.02$; number needed to harm=38). The result remained the same after adjusting for potential confounders. There were significantly more episodes of treatment-related hypoglycemia in the intensely managed group (6.8% versus 0.5%; $P=0.001$), although the contribution of hypoglycemia to excess mortality is uncertain.[149,150] Overall, the hospital course and proximate causes of death were similar in the 2 groups. Excess deaths in the intensive management group were predominantly of cardiovascular causes (absolute difference: 5.8%; $P=0.02$). More patients in the intensive group than in the conventional group were treated with corticosteroids.

Because NICE-SUGAR[149] enrolled critically ill medical and surgical patients, the degree to which its results can be extrapolated to the management of patients with UA/NSTEMI is unclear. Although recent data from a small, mechanistic clinical trial[155] suggest that glucose control may reduce inflammation and improve left ventricular ejection fraction in patients with acute MI, it remains uncertain whether acute glucose control will improve patient outcomes.

A consensus statement by the American Association of Clinical Endocrinologists and the American Diabetes Association[157] summarized that "although hyperglycemia is associated with adverse outcomes after acute MI, reduction of glycemia per se and not necessarily the use of insulin is

Table 7. Recommendations for Diabetes Mellitus

2012 Focused Update Recommendations	2012 Comments
Class I	
1. Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus.[55,72,81,147] *(Level of Evidence: A)*	2007 recommendation remains current.
Class IIa	
1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes mellitus.[148] *(Level of Evidence: B)*	2007 recommendation remains current.
2. PCI is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia.[55] *(Level of Evidence: B)*	2007 recommendation remains current.
3. It is reasonable to use an insulin-based regimen to achieve and maintain glucose levels less than 180 mg/dL while avoiding hypoglycemia* for hospitalized patients with UA/NSTEMI with either a complicated or uncomplicated course.[149–152] *(Level of Evidence: B)*	2011 recommendation remains current.

*There is uncertainty about the ideal target range for glucose necessary to achieve an optimal risk-benefit ratio.

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Table 8. Recommendations for Chronic Kidney Disease

2012 Focused Update Recommendations	2012 Comments
Class I	
1. Creatinine clearance should be estimated in UA/NSTEMI patients and the doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications.[162,163] *(Level of Evidence: B)*	2011 recommendation remains current.
2. Patients undergoing cardiac catheterization with receipt of contrast media should receive adequate preparatory hydration.[164,165] *(Level of Evidence: B)*	2011 recommendation remains current.
3. Calculation of the contrast volume to creatinine clearance ratio is useful to predict the maximum volume of contrast media that can be given without significantly increasing the risk of contrast-associated nephropathy.[166,167] *(Level of Evidence: B)*	2011 recommendation remains current.
Class IIa	
1. An invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD.[162,163,168,169] *(Level of Evidence: B)* (There are insufficient data on benefit/risk of invasive strategy in UA/NSTEMI patients with advanced CKD [stages 4, 5].)	2011 recommendation remains current.

CKD indicates chronic kidney disease; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

associated with improved outcomes. It remains unclear, however, whether hyperglycemia is a marker of underlying health status or is a mediator of complications after acute MI. Noniatrogenic hypoglycemia has also been associated with adverse outcomes and is a predictor of higher mortality."

There is a clear need for a well-designed, definitive randomized trial of target-driven glucose control in UA/NSTEMI patients with meaningful clinical endpoints so that glucose treatment thresholds and glucose targets can be determined. Until such a trial is completed, and on the basis of the balance of current evidence,[157–159] the writing group concluded that it was prudent to change the recommendation for the use of insulin to control blood glucose in UA/NSTEMI from a more stringent to a more moderate target range in keeping with the recent 2009 STEMI and PCI focused update (Class IIa, LOE: B)[154] and recommend treatment for hyperglycemia >180 mg/dL while avoiding hypoglycemia. The writing group believed that the 2007 recommendation[4] regarding long-term glycemic control targets failed to reflect recent data casting doubt on a specific ideal goal for the management of diabetes in patients with UA/NSTEMI.

Diabetes is another characteristic associated with high risk for adverse outcomes after UA/NSTEMI. The 2007 UA/NSTEMI guidelines[4] state that patients with diabetes are at high risk and in general should be treated similarly to patients with other high-risk features. However, the 2012 writing group noted that diabetes was not listed as a high-risk feature for which an invasive strategy was specifically preferred, in contrast to the inclusion of chronic kidney disease (CKD) and diabetes mellitus as characteristics favoring an invasive approach in the 2007 European Society of Cardiology guidelines for management of UA/NSTEMI.[160] To revisit this question for diabetes, the writing group reviewed results of the published analysis of patients with diabetes in the FRISC-II (FRagmin and Fast Revascularization during InStability in Coronary artery disease) trial.[72] Overall, the FRISC-II trial demonstrated a benefit with invasive management compared with conservative management in patients with UA/NSTEMI. There were similar reductions in the risk of MI/death at 1 year in the diabetic subgroup randomized to an invasive strategy (OR: 0.61; 95% CI: 0.36 to 1.04) compared with patients who did not have diabetes randomized to an invasive strategy (OR: 0.72; 95% CI: 0.54 to 0.95). The risk of death was also reduced by randomization to an invasive strategy among patients with diabetes (OR: 0.59; 95% CI: 0.27 to 1.27) and without diabetes (OR: 0.50; 95% CI: 0.27 to 0.94). Subgroup analysis of the TACTICS-TIMI-18 (Treat Angina with aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18) study in patients with diabetes, available in abstract form, was consistent with this finding.[161] Thus, diabetes, as well as the often concurrent comorbidity of CKD (Section 6.5, Chronic Kidney Disease: Recommendations), is not only a high-risk factor but also benefits from an invasive approach. Accordingly, diabetes has been added to the list of characteristics for which an early invasive strategy is generally preferred (Appendix 6).

6.5. Chronic Kidney Disease: Recommendations

(See Table 8, and Online Data Supplement.)

6.5.1. Angiography in Patients With CKD

Since the 2007 UA/NSTEMI Guidelines were published,[4] several larger randomized trials have been published that reported no difference in contrast-induced nephropathy (CIN) when iodixanol was compared with various other low-osmolar contrast media (LOCM).[170–173] These and other randomized trials comparing isosmolar iodixanol with LOCM have been summarized in 2 mutually supportive and complementary meta-analyses involving 16 trials in 2763 patients[174] and 25 trials in 3260 patients,[175] respectively. When more recent trials were combined with the older studies, the data supporting a reduction in CIN favoring iodixanol were no longer significant (summary RR: 0.79; 95% CI: 0.56 to 1.12; $P=0.29$[174]; summary RR: 0.80; 95% CI: 0.61 to 1.04; $P=0.10$,[175] respectively). However, subanalyses showed variations in relative renal safety by specific LOCM: A reduction in CIN was observed when iodixanol was compared to ioxaglate, the only ionic LOCM (RR: 0.58; 95% CI: 0.37 to 0.92; $P=0.022$[174]), and to iohexol, a nonionic LOCM (RR: 0.19; 95% CI: 0.07 to 0.56; $P<0.0002$[174]), but no difference was noted in comparisons of iodixanol with iopamidol, iopromide, or ioversol,[174] and a single trial favored iomeprol.[170] A pooled comparison of iodixanol with all nonionic LOCM other than iohexol indicated equivalent

safety (RR: 0.97; 95% CI: 0.72 to 1.32; $P=0.86$[175]). Results were consistent regardless of ancillary preventive therapies (hydration, acetylcysteine), route of administration (IV or intra-arterial), age, sex, dose, or preexisting CKD or diabetes. Of further interest, findings were similar in the 8 studies (n=1793 patients) performed in the setting of coronary angiography.[174] A more recent study comparing iodixanol versus iopamidol provides additional supportive evidence.[176] However, even these clinical inferences must be tempered by the relative paucity of head-to-head trials comparing CIN rates among the various contrast media and the variability in results (eg, for iohexol versus other low-osmolar comparators).[177–180] Furthermore, the assumption that a transient rise in serum creatinine after 24 to 48 hours is a reliable predictor of the more serious but somewhat delayed development of renal failure requiring hospitalization or dialysis has been challenged. A nationwide Swedish survey[181] of hospitalizations for renal failure after coronary procedures in 57 925 patients found that this risk was paradoxically higher with iodixanol (1.7%) than ioxaglate (0.8%) or iohexol (0.9%; $P<0.001$). Although the result was observational, hence subject to selection bias, it persisted in analyses of high-risk patient subsets (patients with diabetes, prior history of renal failure), in multivariable analysis, and in hospitals crossing over from ioxaglate to iodixanol. Iodixanol's greater viscosity was speculated but not demonstrated to be a possible mechanism for the observed effect. Thus, an overall summary of the current database, updated since previous guideline recommendations,[4] is that strength and consistency of relationships between specific isosmolar or low-osmolar agents and CIN or renal failure are not sufficient to enable a guideline statement on selection among commonly used low-osmolar and isosmolar media. Instead, the writing group recommends focusing on operator conduct issues shown to be important to protect patients, that is, 1) proper patient preparation with hydration, and 2) adjustment of maximal contrast dose to each patient's renal function and other clinical characteristics.

With respect to patient preparation, the writing group reviewed several trials addressing the optimal preparatory regimen of hydration and pharmacotherapy. The basic principle of hydration follows from experimental studies and clinical experience, with isotonic or half-normal saline alone being the historical gold standards.[164,165,182–184] More recently, sodium bicarbonate has been tested as the hydrating solution. Some trials have reported superiority of sodium bicarbonate over saline in preventing CIN.[185–188] Similarly, some have reported a benefit of N-acetylcysteine administration as adjunctive therapy to hydration,[185,189] whereas others have not.[190,191] Thus, although the writing group found the evidence compelling for adequate hydration preparatory to angiography with contrast media, it found the evidence insufficient to recommend a specific regimen.

With respect to limitation of contrast dose by renal function, mounting evidence points to renal-function–specific limits on maximal contrast volumes that can be given without significantly increasing the baseline risk of provoking CIN. In a contemporary study, Laskey et al studied 3179 consecutive patients undergoing PCI and found that a contrast volume to creatinine clearance ratio >3.7 was a significant and independent predictor of an early and abnormal increase in serum creatinine.[166] In an earlier trial, administration of a contrast volume of 5 mL×body weight (kg)/serum creatinine (mg/dL), applied to 16 592 patients undergoing cardiac catheterization, was associated with a 6-fold increase in the likelihood of patients developing CIN requiring dialysis.[167]

Patients with CKD are consistently underrepresented in randomized controlled trials of cardiovascular disease.[192] The impact of an invasive strategy has been uncertain in this group. The SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) study included a cohort of 23 262 patients hospitalized for NSTEMI in Sweden between 2003 and 2006 who were age ≤80 years.[169] This contemporary nationwide registry of nearly all consecutive patients examined the distribution of CKD and the use of early revascularization after NSTEMI and evaluated whether early revascularization (by either PCI or CABG) within 14 days of admission for NSTEMI altered outcomes at all stages of kidney function.

In SWEDEHEART, all-cause mortality was assessed at 1 year and was available in >99% of patients. Moderate or more advanced CKD (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2) was present in 5689 patients (24.4%). After multivariable adjustment, the 1-year mortality in the overall cohort was 36% lower with early revascularization (HR: 0.64; 95% CI: 0.56 to 0.73; $P<0.001$).[169] The magnitude of the difference in 1-year mortality was similar in patients with normal eGFR (early revascularization versus medically treated: 1.9% versus 10%; HR: 0.58; 95% CI: 0.42 to 0.80; $P=0.001$), mild CKD [eGFR 60 to 89 mL/min per 1.73 m^2] (2.4% versus 10%; HR: 0.64; 95% CI: 0.52 to 0.80; $P<0.001$), and moderate CKD [eGFR 30 to 59 mL/min per 1.73 m^2] (7% versus 22%; HR: 0.68; 95% CI: 0.54 to 0.86; $P=0.001$). The benefit of an invasive therapy was not evident in patients with severe CKD stage 4 [eGFR 15 to 29 mL/min per 1.73 m^2] (22% versus 41%; HR: 0.91; 95% CI: 0.51 to 1.61; $P=0.780$) or in those with CKD stage 5 kidney failure [eGFR <15 mL/min per 1.73 m^2 or receiving dialysis] (44% versus 53%; HR: 1.61; 95% CI: 0.84 to 3.09; $P=0.150$). Early revascularization was associated with increased 1-year survival in UA/NSTEMI patients with mild to moderate CKD, but no association was observed in those with severe or end-stage kidney disease.[169]

The findings from SWEDEHEART are limited by their nonrandomized nature and the potential for selection bias despite the intricate multivariable adjustment.[169] On the other hand, SWEDEHEART captured unselected patients with more comorbidities and is therefore more reflective of real-world patients.

Recently, a collaborative meta-analysis of randomized controlled trials that compared invasive and conservative treatments in UA/NSTEMI was conducted to estimate the effectiveness of early angiography in patients with CKD.[168] The meta-analysis demonstrated that an invasive strategy was associated with a significant reduction in rehospitalization (RR: 0.76; 95% CI: 0.66 to 0.87; $P<0.001$) at 1 year compared with conservative strategy. The meta-analysis did not show any significant differences with regard to all-cause mortality (RR: 0.76; 95% CI: 0.49

Table 9. Recommendation for Quality Care and Outcomes for UA/NSTEMI

2012 Focused Update Recommendations	2012 Comments
Class IIa	
1. It is reasonable for clinicians and hospitals that provide care to patients with UA/NSTEMI to participate in a standardized 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.[194–204] *(Level of Evidence: B)*	2011 recommendation remains current.

UA/NSTEMI indicates unstable angina/non–ST-elevation myocardial infarction.

to 1.17; $P=0.21$), nonfatal MI (RR: 0.78; 95% CI: 0.52 to 1.16; $P=0.22$), and the composite of death/nonfatal MI (RR: 0.79; 95% CI: 0.53 to 1.18; $P=0.24$).[168]

Our recommendation is that an early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is a reasonable strategy in patients with mild and moderate CKD. Clinicians should exercise judgment in all populations with impaired kidney function when considering whether to implement an invasive strategy. Such implementation should be considered only after careful assessment of the risks, benefits, and alternatives for each individual patient.

The observational data with regard to patients with mild to severe CKD also support the recognition that CKD is an underappreciated high-risk characteristic in the UA/NSTEMI population. The increased risk of mortality associated with mild, moderate, and severe CKD remains evident across studies.[162,163,168,193] Indeed, the risks of short- and long-term mortality are increased as the gradient of renal dysfunction worsens.[162,168,193] The optimal role of early revascularization in this heterogeneous population of patients remains an important topic of research and investigation as discussed earlier in this update.

7. Conclusions and Future Directions

7.1. Quality of Care and Outcomes for UA/NSTEMI: Recommendation

(See Table 9.)

7.1.1. Quality Care and Outcomes

The development of regional systems of UA/NSTEMI care is a matter of utmost importance.[196,198,199] This includes encouraging the participation of key stakeholders in collaborative efforts to evaluate care using standardized performance and quality-improvement measures, such as those endorsed by the ACC and the AHA for UN/NSTEMI.[199] Standardized quality-of-care data registries designed to track and measure outcomes, complications, and adherence to evidence-based processes of care for UA/NSTEMI are also critical: programs such as the NCDR (National Cardiovascular Data Registry) ACTION Registry-GWTG, the AHA's Get With The Guidelines (GWTG) quality-improvement program, and those performance-measurement systems required by The Joint Commission and the Centers for Medicare and Medicaid Services.[194,201–203] More recently, the AHA has promoted its Mission: Lifeline initiative, which was developed to encourage closer cooperation and trust among prehospital emergency services personnel and cardiac care professionals.[194] The evaluation of UA/NSTEMI care delivery across traditional care-delivery boundaries with these tools and other resources is imperative to identify systems problems and enable the application of modern quality-improvement methods, such as Six Sigma, to make necessary improvements.[195,197,200,204] The quality-improvement data coming from registries like the ACTION-GTWG may prove pivotal in addressing opportunities for quality improvement at the local, regional, and national level, including the elimination of healthcare disparities and conduct of comparative effectiveness research.

President and Staff

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KEY WORDS: AHA Scientific Statements ■ antiplatelet therapy ■ focused update ■ glycoprotein IIb/IIIa inhibitors ■ myocardial infarction ■ non–ST elevation ■ percutaneous coronary intervention ■ thienopyridines ■ $P2Y_{12}$ receptor inhibitor ■ unstable angina

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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Jeffrey L. Anderson, Vice Chair	Intermountain Medical Center—Associate Chief of Cardiology	• AstraZeneca	None	None	None	None	None	3.2.1 3.2.3 5.2.1
R. Scott Wright, Vice Chair	Mayo Clinic—Professor of Medicine and Consultant in Cardiology	• Hoffman LaRoche†	None	None	None	None	None	None
Cynthia D. Adams	Community Health Network/The Indiana Heart Hospital—Supervisor	None	None	None	None	None	None	None
Charles R. Bridges	University of Pennsylvania Medical Center—Chief, Cardiothoracic Surgery, Pennsylvania Hospital; Associate Professor of Surgery	• AstraZeneca	• Bayer Pharmaceuticals	None	None	None	None	3.2.1 3.2.3 5.2.1
Donald E. Casey, Jr	Atlantic Health—Vice President of Quality and Chief Medical Officer	None	None	None	None	None	None	None
Steven M. Ettinger	Pennsylvania State University Penn State Heart and Vascular Institute	None	None	None	None	None	None	None
Francis M. Fesmire	Director, Heart-Stroke Center, Assistant Professor	None	None	None	None	None	None	None
Theodore G. Ganiats	University of California San Diego—Professor and Interim Chair	None	None	None	None	None	None	None
A. Michael Lincoff	Cleveland Clinic Foundation Cleveland Clinic Lerner College of Medicine—Professor of Medicine	• AstraZeneca • Merck	None	None	• AstraZeneca† • Bristol-Myers Squibb† • Eli Lilly† • Novartis† • Pfizer† • Roche† • Schering Plough† • Takeda†	None	None	3.2.1 3.2.3 5.2.1
Eric D. Peterson	Duke Clinical Research Institute Duke University Medical Center—Professor of Medicine, Director, Cardiovascular Outcomes	None	None	None	• Eli Lilly† • Johnson & Johnson†	None	None	3.2.1 3.2.3 5.2.1 5.2.6
George J. Philippides	Boston University School of Medicine—Associate Professor of Medicine; Associate Chair for Clinical Affairs and Chief Quality Officer, Cardiovascular Section	None	None	None	None	None	None	None
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Nanette K. Wenger	Emory University School of Medicine—Professor of Medicine (Cardiology)	• Abbott • AstraZeneca • Gilead Sciences (formerly CV Therapeutics)† • Merck • Pfizer	None	None	• Abbott† • Eli Lilly† • Gilead Sciences (formerly CV Therapeutics)† • Merck • Pfizer†	None	None	3.2.1 3.2.3 5.2.1

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing group during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household* has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing group members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.

†Significant relationship.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
John E. Brush	Official Reviewer—ACCF Board of Trustees	Cardiology Consultants	• Healthcare Incentives Improvement Institute—Board Member* • United Healthcare—Scientific Advisory Board	None	None	None	None	None
David P. Faxon	Official Reviewer—AHA	Brigham and Women's Hospital—Professor of Medicine	• Boston Scientific • Sanofi-aventis	None	• RIVA Medical	None	• *Circulation: Cardiovascular Interventions*—Editor†	None
Robert A. Harrington	Official Reviewer—AHA	Duke Clinical Research Institute—Professor of Medicine; Duke University Medical Center—Director	• Bristol-Myers Squibb • Genentech* • Gilead Sciences • Merck • Mitsubishi-Tanabe • Momenta Pharmaceutical • Pfizer* • Regado • Sanofi-aventis • WebMD†	None	None	• AstraZeneca† • Bristol-Myers Squibb† • GlaxoSmithKline† • Merck† • Portola† • Sanofi-aventis† • The Medicines Company	None	None
Judith S. Hochman	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	New York University School of Medicine—Harold Snyder Family Professor of Cardiology; NYU-HHC Clinical and Translational Science Institute—Co-Director; Leon Charney Division of Cardiology—Clinical Chief; Cardiovascular Clinical Research Center—Director	• Bristol-Myers Squibb • Eli Lilly • GlaxoSmithKline • Sanofi-aventis	None	None	• Bayer Healthcare AG—DSMB • Johnson & Johnson—DSMB • Merck, TIMI 50— DSMB • Schering-Plough, TIMI 50—DSMB	None	None
Rodney H. Zimmermann	Official Reviewer—ACCF Board of Governors	Regina General Hospital—Director of the Cardiac Catheterization Laboratory	• AstraZeneca • Boehringer Ingelheim • Hoffmann-La Roche	• AstraZeneca • Boehringer Ingelheim • Merck-Frost	None	• Eli Lilly • Schering-Plough	None	None
Joseph C. Cleveland	Organizational Reviewer—STS	University of Colorado Anschutz Medical Center—Associate Professor of Surgery; Surgical Director, Cardiac Transplantation and MCS	• Baxter Biosurgery • Sorin	None	None	• HeartWare Corporation • Thoratec Corporation	None	None
Joseph A. DeGregorio	Organizational Reviewer—SCAI	Englewood Hospital—Chief, Invasive Cardiology	None	None	None	None	None	None
Deborah B. Diercks	Organizational Reviewer—ACEP	UC Davis Medical Center	None	None	None	• Beckman Coulter*	• AHRQ, QUADRICS Trial—DSMB* • Emergencies in Medicine* • Society of Academic Emergency Medicine* • Society of Chest Pain Centers and Providers*	None
Benjamin Hatten	Organizational Reviewer—ACEP	Denver Health Medical Center	None	None	None	None	None	None
Loren F. Hiratzka	Organizational Reviewer—STS	Cardiac, Vascular and Thoracic Surgeons—Medical Director, Cardiac Surgery	None	None	None	None	None	None
Nancy M. Albert	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	Cleveland Clinic, Kaufman Center for Heart Failure, Nursing Research, Innovation and CNS—Senior Director	• Merck*	None	None	None	None	None

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Appendix 2. Continued

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ezra Amsterdam	Content Reviewer	UC Davis Medical Center, Division of Cardiology	None	None	None	None	None	None
Elliott M. Antman	Content Reviewer	Harvard Medical School—Associate Dean for Clinical/Translational Research	None	None	None	• AstraZeneca • Bayer Healthcare • Biosite • Bristol-Myers Squibb • CV Therapeutics • Daiichi Sankyo† • Eli Lilly† • GlaxoSmithKline • Integrated Therapeutics • Merck • Novartis • Nuvelo • Ortho-Clinical Diagnostics • Pharmaceutical Research Institute • Pfizer • Roche Diagnostics • Sanofi-aventis† • Sanofi-Synthelabo Recherche • Schering-Plough Research Institute	None	None
James C. Blankenship	Content Reviewer	Geisinger Medical Center—Staff Physician; Director, Cardiac Cath Lab	None	None	None	• Abiomed* • AstraZeneca* • Boston Scientific* • Novartis* • Schering-Plough* • The Medicines Company* • Volcano Corp*	None	None
James A. Burke	Content Reviewer—ACCF Interventional Scientific Council	Lehigh Valley Heart Specialists	None	None	None	None	None	None
William A. Chavey	Content Reviewer	University of Michigan Department of Family Medicine—Clinical Assistant Professor	None	None	None	None	None	None
John M. Field	Content Reviewer	Pennsylvania State University, College of Medicine—Professor of Medicine and Surgery	None	None	None	None	None	None
Christopher B. Granger	Content Reviewer	Duke Clinical Research Institute—Associate Professor of Medicine; Cardiac Care Unit—Director	• AstraZeneca • Boehringer Ingelheim† • Bristol-Myers Squibb • GlaxoSmithKline • Hoffmann-La Roche • Novartis • Otsuka Pharmaceuticals • Pfizer • Sanofi-aventis† • The Medicines Company	None	None	• Astellas† • AstraZeneca† • Boehringer Ingelheim† • Bristol-Myers Squibb† • GlaxoSmithKline† • Merck† • Sanofi-aventis† • The Medicines Company†	None	None
Mary Hand	Content Reviewer	Agency for Healthcare Research and Quality—Health Science Administrator	None	None	None	None	None	None
Allan S. Jaffe	Content Reviewer	Mayo Clinic Cardiovascular Division—Professor of Medicine	• Alere • Critical Diagnostics • Radiometer	None	None	None	None	None
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Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Harlan M. Krumholz	Content Reviewer	Yale University School of Medicine—Harold H. Hines, Jr, Professor of Medicine and Epidemiology and Public Health	• United Healthcare (Scientific Advisory Board)†	None	None	None	None	None
Frederick G. Kushner	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	Tulane University Medical Center—Clinical Professor; Heart Clinic of Louisiana—Medical Director	None	None	None	None	None	None
Shamir R. Mehta	Content Reviewer	Hamilton Health Sciences, General Division HGH McMaster Clinic—Director, Coronary Care Unit	• Astellas • AstraZeneca • Bristol-Myers Squibb • Eli Lilly • Sanofi-aventis	None	None	• Bristol-Myers Squibb† • Sanofi-aventis†	None	None
Douglass A. Morrison	Content Reviewer	Yakima Heart Center—Professor of Medicine, Radiology; Cardiac Cath Lab—Director	None	None	None	None	None	None
L. Kristin Newby	Content Reviewer	Duke University Medical Center—Associate Professor of Clinical Medicine	• AstraZeneca • Daiichi Sankyo • GlaxoSmithKline • Johnson & Johnson • Novartis	None	None	• Amylin • Bristol-Myers Squibb • Eli Lilly • GlaxoSmithKline† • Regado • Merck†	None	None
E. Magnus Ohman	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	Duke University Medical Center, Department of Medicine, Division of Cardiovascular Medicine—Professor of Medicine; Subspecialty Signature Care—Director Program for Advanced Coronary Disease—Director	• AstraZeneca • Bristol-Myers Squibb • Boehringer Ingelheim • Gilead Sciences† • LipoScience • Merck • Pozen • Hoffmann-La Roche • Sanofi-aventis • The Medicines Company • WebMD†	• Boehringer Ingelheim • Gilead Sciences†	None	• Daiichi Sankyo† • Eli Lilly†	None	None
William A. Tansey III	Content Reviewer	Summit Medical Group	None	None	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household* has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

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†Significant relationship.

ACCF indicates American College of Cardiology Foundation; ACEP, American College of Emergency Physicians; AHA, American Heart Association; AHRQ, Agency for Healthcare Quality and Research; DSMB, data safety monitoring board; SCAI, Society for Cardiovascular Interventions and Angiography; STS, Society of Thoracic Surgeons; and TIMI, Thrombolysis In Myocardial Infarction.

Appendix 3. Dosing Table for Antiplatelet and Anticoagulant Therapy Discussed in This Focused Update to Support PCI in UA/NSTEMI

Drug*	During PCI: Patient Received Initial Medical Treatment (With a $P2Y_{12}$ Receptor Inhibitor)	During PCI: Patient Did Not Receive Initial Medical Treatment (With a $P2Y_{12}$ Receptor Inhibitor)	Comments ▶ All Patients to Receive ASA
Glycoprotein IIb/IIIa Receptor Antagonists			
Abciximab	Of uncertain benefit	LD of 0.25 mg/kg IV bolus MD of 0.125 mcg/kg per min (maximum 10 mcg/min) (Class I, LOE: A)	▶ Continue for up to 12 h at the discretion of the physician.
Eptifibatide	Of uncertain benefit	LD of 180 mcg/kg IV bolus followed 10 min later by second IV bolus of 180 mcg/kg MD of 2.0 mcg/kg per min, started after first bolus; reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min (Class I, LOE: A)	▶ Double bolus is recommended to support PCI in STEMI as the recommended adult dosage of eptifibatide in patients with normal renal function. ▶ Infusion should be continued for 12 to 18 h at the discretion of the physician.
Tirofiban	Of uncertain benefit	LD of 25 mcg/kg IV bolus MD of IV infusion of 0.15 mcg/kg per min; reduce rate of infusion by 50% in patients with estimated creatinine clearance <30 mL/min (Class I, LOE: B)	▶ Increased dosing over previous recommendation. ▶ Continue for up to 18 h at the discretion of the physician. ▶ A lower-dose regimen for tirofiban is FDA approved and has been shown to be effective when used to treat UA/NSTEMI patients who are started on medical therapy and when there is a substantial delay to angiography/PCI (eg, 48 h): LD of 50 mcg/mL administered at an initial rate of 0.4 mcg/kg per min for 30 min MD of a continuous infusion of 0.1 mcg/kg per min. Continue the infusion through angiography and for 12 to 24 h after angioplasty or atherectomy.
$P2Y_{12}$ Receptor Inhibitors			
Clopidogrel†	If 600 mg given orally, then no additional treatment A second LD of 300 mg may be given orally to supplement a prior LD of 300 mg (Class I, LOE: C)	LD of 300–600 mg orally (Class I, LOE: A) MD of 75 mg orally per d (Class I, LOE: A) MD of 150 mg orally per d for initial 6 d may be considered (Class IIb, LOE: B)	▶ Optimum LD requires clinical consideration. ▶ Dose for patients ≥75 y of age has not been established. ▶ There is a recommended duration of therapy for all post-PCI patients receiving a BMS or DES. ▶ Caution should be exercised for use with a PPI. ▶ Period of withdrawal before surgery should be at least 5 d. (For full explanations, see footnote.)
Prasugrel‡	No data are available to guide decision making	LD of 60 mg orally (Class I, LOE: B) MD of 10 mg orally per d (Class I, LOE: B)	▶ There are no data for treatment with prasugrel before PCI. ▶ MD of 5 mg orally per d in special circumstances. ▶ Special dosing for patients <60 kg or ≥75 y of age. ▶ There is a recommended duration of therapy for all post-PCI patients receiving a DES. ▶ Contraindicated for use in patients with prior history of TIA or stroke. ▶ Period of withdrawal before surgery should be at least 7 d. (For full explanations, see footnote.)
Ticagrelor	Patients who are already receiving clopidogrel should receive a loading dose of ticagrelor	LD of 180 mg orally (Class I, LOE: B) MD of 90 mg orally twice daily (Class I, LOE: B)	▶ The recommended maintenance dose of ASA to be used with ticagrelor is 81 mg daily. ▶ Ticagrelor's benefits were observed irrespective of prior therapy with clopidogrel (47% of patients in PLATO received clopidogrel at the time of randomization). ▶ Period of withdrawal before surgery should be at least 5 d. ▶ Issues of patient compliance may be especially important with twice-daily dosing regimen. ▶ Ticagrelor increases the risk of fatal ICH compared with clopidogrel and should be avoided in those with a prior history of ICH. Until further data become available, it seems prudent to weigh the possible increased risk of intracranial bleeding when considering the addition of ticagrelor to aspirin in patients with prior stroke or TIA.

(*Continued*)

Appendix 3. Continued

Drug*	During PCI: Patient Received Initial Medical Treatment (With a $P2Y_{12}$ Receptor Inhibitor)	During PCI: Patient Did Not Receive Initial Medical Treatment (With a $P2Y_{12}$ Receptor Inhibitor)	Comments ▶ All Patients to Receive ASA
Parenteral Anticoagulants			
Bivalirudin	For patients who have received UFH, wait 30 min, then give 0.75 mg/kg bolus, then 1.75 mg/kg per h infusion (Class I, LOE: B)	0.75 mg/kg bolus, 1.75 mg/kg per h infusion	▶ Bivalirudin may be used to support PCI and UA/NSTEMI with or without previously administered UFH with the addition of 600 mg of clopidogrel. ▶ In UA/NSTEMI patients undergoing PCI who are at high risk of bleeding, bivalirudin anticoagulation is reasonable.
UFH	IV GP IIb/IIIa planned: target ACT 200–250 s	IV GP IIb/IIIa planned: 50–70 units/kg bolus to achieve an ACT of 200–250 s	
	No IV GP IIb/IIIa planned: target ACT 250–300 s for HemoTec, 300–350 s for Hemochron (Class I, LOE: B)	No IV GP IIb/IIIa planned: 70–100 units/kg bolus to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron (Class I, LOE: B)	

*This list is in alphabetical order and is not meant to indicate a particular therapy preference. This drug table does not make recommendations for combinations of listed drugs. It is only meant to indicate an approved or recommended dosage if a drug is chosen for a given situation.

†The optimum LD of clopidogrel has not been established. Randomized trials establishing its efficacy and providing data on bleeding risks used an LD of 300 mg orally followed by a daily oral dose of 75 mg. Higher oral LDs such as 600 mg or more than 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and safety of higher oral LD have not been rigorously established. For post-PCI patients receiving a DES, a daily MD should be given for at least 12 mo unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor. For post-PCI patients receiving a BMS, an MD should be given for up to 12 mo (unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor; then it should be given for a minimum of 2 wk). The necessity for giving an LD of clopidogrel before PCI is driven by the pharmacokinetics of clopidogrel, for which a period of several hours is required to achieve desired levels of platelet inhibition. Patients who have a reduced-function *CYP2C19* allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of MACE, including stent thrombosis. In UA/NSTEMI patients taking clopidogrel for whom CABG is planned and can be delayed, it is reasonable to discontinue the clopidogrel to allow for dissipation of the antiplatelet effect unless the urgency for revascularization and/or the net benefit of clopidogrel outweigh the potential risks of excess bleeding. The period of withdrawal should be at least 5 d in patients receiving clopidogrel.

‡Patients weighing $<$60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10-mg once-daily MD. Consider lowering the MD to 5 mg in patients who weigh $<$60 kg. The effectiveness and safety of the 5-mg dose have not been studied prospectively. For post-PCI patients receiving DES, a daily MD should be given for at least 12 mo unless the risk of bleeding outweighs the anticipated net benefit afforded by a $P2Y_{12}$ receptor inhibitor. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients age $\geq$75 y, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior myocardial infarction), for which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent CABG. When possible, discontinue prasugrel at least 7 d before any surgery. Additional risk factors for bleeding include body weight $<$60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, or long-term use of nonsteroidal anti-inflammatory drugs).

ACT indicates activated clotting time; ASA, aspirin; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; GP, glycoprotein; FDA, Food and Drug Administration; ICH, intracranial hemorrhage; IV, intravenous; LD, loading dose; LOE, level of evidence; MACE, major adverse cardiac events; MD, maintenance dose; PCI, percutaneous coronary intervention; PLATO, PLATelet inhibition and patient Outcomes trial; PPI, proton pump inhibitor; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and UFH, unfractionated heparin.

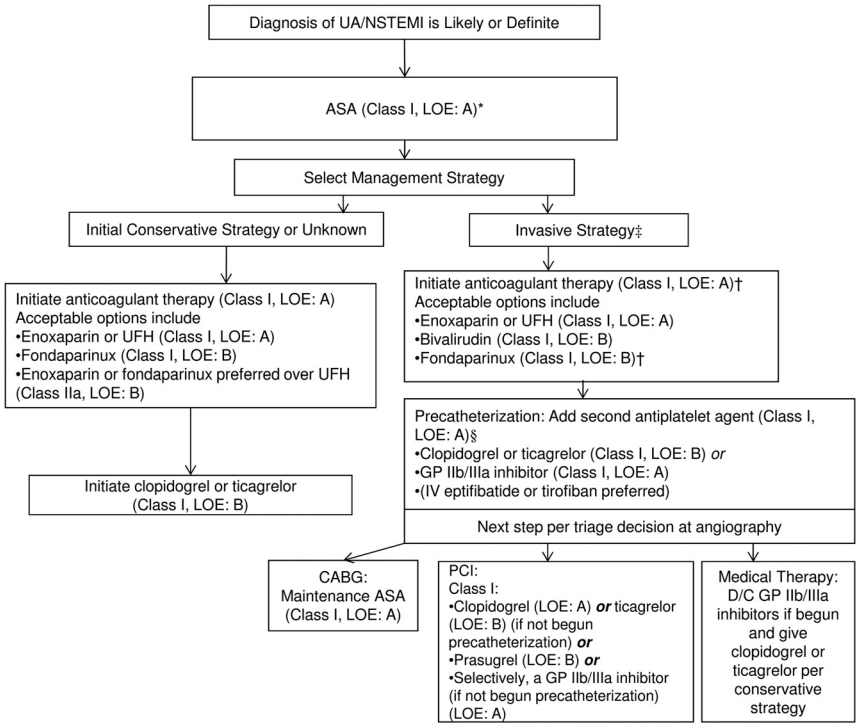
Modified from Wright et al.[6]

Appendix 4. Comparisons Among Orally Effective $P2Y_{12}$ Inhibitors

	Clopidogrel		Prasugrel		Ticagrelor	
Pharmacology	Prodrug—requires conversion to active metabolite that irreversibly blocks $P2Y_{12}$ receptor		Prodrug—requires conversion to active metabolite that irreversibly blocks $P2Y_{12}$ receptor. Conversion to active metabolite occurs more rapidly and to a greater degree than with clopidogrel		Parent compound is active and no biotransformation is required for reversible inhibition of $P2Y_{12}$ receptor	
Effect on platelet aggregation	There is a delay of several hours before maximal antiplatelet effect is seen		Onset of antiplatelet effect is faster and extent of inhibition of aggregation is greater than with clopidogrel (a significant antiplatelet effect was observed within 30 min of loading)		Onset of antiplatelet effect is faster and extent of inhibition of aggregation is greater than with clopidogrel (a significant antiplatelet effect was observed within 30 min of loading)	
Management strategy	*Conservative*	*Invasive*	*Conservative*	*Invasive*	*Conservative*	*Invasive*
Loading dose	300 mg	600 mg	Generally not recommended for precatheterization use in UA/NSTEMI	60 mg at time of PCI	180 mg	180 mg
Timing	Initiate on presentation	Initiate as soon as possible before or at the time of PCI		Initiate as soon as coronary anatomy is known and decision is made to proceed with PCI	Initiate on presentation	Initiate as soon as possible before or at the time of PCI
Maintenance dose	75 mg Optimal approach to dosing in individual patients based on genotype and individual antiplatelet effects not rigorously established	75 mg Optimal individual dose not rigorously established (see comment to left). (150 mg for first 6 d is an alternative)		10 mg Consider reduction to 5 mg in patients weighing $<$60 kg. The efficacy (or benefit) of prasugrel in those age $\geq$75 y is uncertain. Contraindicated in patients with a history of stroke or TIA.	90 mg twice daily (The recommended maintenance dose of ASA to be used with ticagrelor is 81 mg daily)	90 mg twice daily (The recommended maintenance dose of ASA to be used with ticagrelor is 81 mg daily)
Duration	Ideally up to 12 mo	At least 12 mo for patients receiving DES Up to 12 mo for patients receiving BMS		At least 12 mo for patients receiving DES Up to 12 mo for patients receiving BMS	Ideally up to 12 mo	At least 12 mo for patients receiving DES Up to 12 mo for patients receiving BMS
Additional considerations						
Variability of response	Greater than with prasugrel or ticagrelor. Factors impacting on response in some patients may include genetic predisposition to convert parent compound to active metabolite and drug interactions (eg, PPIs)		Less than with clopidogrel. Impact of genotype and concomitant medications appears less than with clopidogrel.		Less compared with clopidogrel. Impact of genotype and concomitant medications appears less than with clopidogrel.	
Platelet function testing	Clinical utility not rigorously established. May be useful in selected patients with ischemic/thrombotic events while compliant with a clopidogrel regimen		Clinical utility not rigorously established but less likely to be necessary given lesser degree of variation in response		Clinical utility not rigorously established but less likely to be necessary given lesser degree of variation in response	
Genotyping	Identifies patients with a diminished (*CYP2C19* *2, *3 alleles) or enhanced (*CYP2C17* allele) to form active metabolite. Role of genotyping in clinical management not rigorously established.		Clinical utility not rigorously established but less likely to be necessary given lesser degree of variation in response		Clinical utility not rigorously established but less likely to be necessary given lesser degree of variation in response	
Risk of bleeding	Standard dosing with clopidogrel is associated with less bleeding than with prasugrel and ticagrelor. Higher doses of clopidogrel are associated with greater risk of bleeding than standard dose clopidogrel.		Risk of spontaneous, instrumented, and fatal bleeds higher with prasugrel compared with standard dose clopidogrel		Risk of non-CABG bleeds higher with ticagrelor compared with standard dose clopidogrel	
Transition to surgery	Wait 5 d after last dose		Wait 7 d after last dose		Wait 5 d after last dose	

ASA indicates aspirin; BMS, bare-metal stent; DES, drug-eluting stent; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TIA, transient ischemic attack; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction.

Appendix 5. Flowchart for Class I and Class IIa Recommendations for Initial Management of UA/NSTEMI



*A loading dose followed by a daily maintenance dose of either clopidogrel (LOE: B), prasugrel (in PCI-treated patients), or ticagrelor (LOE: C) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major GI intolerance.

†If fondaparinux is used during PCI (Class I, LOE: B), it must be coadministered with another anticoagulant with Factor IIa activity (ie, UFH).

‡Timing of invasive strategy generally is assumed to be 4 to 48 h. If immediate angiography is selected, see STEMI guidelines.

§Precatheterization triple antiplatelet therapy (ASA, clopidogrel or ticagrelor, GP inhibitors) is a Class IIb, LOE: B recommendation for selected high-risk patients. Also, note that there are no data for therapy with 2 concurrent $P2Y_{12}$ receptor inhibitors, and this is not recommended in the case of aspirin allergy.

ASA indicates aspirin; CABG, coronary artery bypass graft; D/C, discontinue; GI, gastrointestinal; GP, glycoprotein; IV, intravenous; LOE, level of evidence; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and UFH, unfractionated heparin.

Modified from Wright et al.[6]

Appendix 6. Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

Generally Preferred Strategy	Patient Characteristics
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers (TnT or TnI)
	New or presumably new ST-segment depression
	Signs or symptoms of HF or new or worsening mitral regurgitation
	High-risk findings from noninvasive testing
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 mo
	Prior CABG
	High-risk score (eg, TIMI, GRACE)
	Mild to moderate renal dysfunction
	Diabetes mellitus
	Reduced LV function (LVEF $<$40%)
Conservative	Low-risk score (eg, TIMI, GRACE)
	Patient or physician preference in the absence of high-risk features

CABG indicates coronary artery bypass graft; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; TnI, troponin I; and TnT, troponin T.

Reprinted from Anderson et al.[4]