

2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

American Academy of Family Physicians, American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, R. Scott Wright, Jeffrey L. Anderson, Cynthia D. Adams, Charles R. Bridges, Donald E. Casey, Jr, Steven M. Ettinger, Francis M. Fesmire, Theodore G. Ganiats, Hani Jneid, A. Michael Lincoff, Eric D. Peterson, George J. Philippides, Pierre Theroux, Nanette K. Wenger, and James Patrick Zidar

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ACCF/AHA FOCUSED UPDATE

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

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

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

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A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data on which recommendations are based. In an effort to respond promptly to new evidence, the American College of Cardiology Foundation/American Heart Association (ACCF/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. Before the initiation of this focused approach, periodic updates and revisions of existing guidelines required

up to 3 years to complete. Now, however, new evidence will be 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 will be reviewed at least twice a year, and updates will be 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 updated guideline recommendations reflect a consensus of expert opinion after a thorough review, primarily of late-breaking clinical trials identified through a broad-based vetting process as being important to the relevant patient population, as well as other new data deemed to have an impact on patient care (see Section 1.1, Methodology and Evidence Review, for details). This focused update is not intended to represent an update based on a full literature review from the date of the previous guideline publication. 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
- 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 relationships with industry or other potential bias
- Number of previous trials showing consistent results
- Need for consistency with a new guideline or guideline revisions

In analyzing the data and developing the recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the Task Force that are described elsewhere (1).

The committee reviewed and ranked evidence supporting current recommendations, with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported

by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for classification of recommendations and level of evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or 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 Class I and IIa, Level A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the writing group. Specifically, all members of the writing group, as well as peer reviewers of the document, are asked to disclose all current relationships and those existing 12 months before initiation of the writing effort. In response to implementation of a newly revised RWI policy approved by the ACC and AHA, it is also required that the writing group chair plus a majority of the writing group (50%) have no *relevant* RWI. All guideline recommendations require a confidential vote by the writing group and must be approved by a consensus of the members voting. Members who were recused from voting are noted on the title page of this document and in Appendix 1. Members must recuse themselves from voting on any recommendation to which their RWI apply. Any writing group member who develops a new RWI during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing group and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual (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 online as a supplement to this document. Disclosure information for the Task Force is also available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing group was supported exclusively by the ACCF and AHA without commercial support. Writing group members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of

Table 1. Applying Classification of Recommendation and Level of Evidence

		SIZE OF TREATMENT EFFECT													
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/ administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i> <table><tr><th></th><th>Procedure/ Test</th><th>Treatment</th></tr><tr><td>COR III: No benefit</td><td>Not Helpful</td><td>No Proven Benefit</td></tr><tr><td>COR III: Harm</td><td>Excess Cost w/o Benefit or Harmful</td><td>Harmful to Patients</td></tr></table>		Procedure/ Test	Treatment	COR III: No benefit	Not Helpful	No Proven Benefit	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients	
		Procedure/ Test	Treatment												
	COR III: No benefit	Not Helpful	No Proven Benefit												
	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients												
	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none">■ Recommendation that procedure or treatment is useful/effective■ Sufficient evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">■ Recommendation in favor of treatment or procedure being useful/effective■ Some conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">■ Recommendation's usefulness/efficacy less well established■ Greater conflicting evidence from multiple randomized trials or meta-analyses	<ul style="list-style-type: none">■ 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	<ul style="list-style-type: none">■ Recommendation that procedure or treatment is useful/effective■ Evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">■ Recommendation in favor of treatment or procedure being useful/effective■ Some conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">■ Recommendation's usefulness/efficacy less well established■ Greater conflicting evidence from single randomized trial or nonrandomized studies	<ul style="list-style-type: none">■ 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	<ul style="list-style-type: none">■ Recommendation that procedure or treatment is useful/effective■ Only expert opinion, case studies, or standard of care	<ul style="list-style-type: none">■ Recommendation in favor of treatment or procedure being useful/effective■ Only diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">■ Recommendation's usefulness/efficacy less well established■ Only diverging expert opinion, case studies, or standard of care	<ul style="list-style-type: none">■ 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	<table><tr><th>COR III: No Benefit</th><th>COR III: Harm</th></tr><tr><td>is not recommended</td><td>potentially harmful</td></tr><tr><td>is not indicated</td><td>causes harm</td></tr><tr><td>should not be done</td><td>associated with excess morbidity/mortality</td></tr><tr><td>is not useful/ beneficial/ effective</td><td>should not be done</td></tr></table>	COR III: No Benefit	COR III: Harm	is not recommended	potentially harmful	is not indicated	causes harm	should not be done	associated with excess morbidity/mortality	is not useful/ beneficial/ effective	should not be done
COR III: No Benefit	COR III: Harm														
is not recommended	potentially harmful														
is not indicated	causes harm														
should not be done	associated with excess morbidity/mortality														
is not useful/ beneficial/ effective	should not be done														
Comparative effectiveness phrases ¹		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												

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

subjects outside of North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and the 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 for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available current scientific evidence and are intended to improve patient care. 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. Thus, there are circumstances 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 better inform patient care; 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.

The recommendations in this focused update will be considered current until they are superseded by another focused update or the full-text guidelines are revised. This focused update is published in the *Journal of the American College of Cardiology* and *Circulation* as an update to the full-text guideline (2), and it is also posted on the ACC (www.cardiosource.org) and AHA (my.americanheart.org) World Wide Web sites. A revised version of the full-text guideline with links to the focused update is e-published in the May 3, 2011, issues of the *Journal of the American College of Cardiology* and *Circulation*. For easy reference, this online-only version denotes sections that have been updated.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

Late-breaking clinical trials presented at the 2008 and 2009 annual scientific meetings of the ACC, AHA, and European Society of Cardiology, as well as selected other data through April 2010, were reviewed by the standing guideline writing committee along with the parent Task Force and other experts to identify those trials and other key data that may impact guideline recommendations. On the basis of the criteria/considerations noted above, recent trial data and other clinical information were considered important enough to prompt a focused update of the 2007 ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) (2).

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 will be provided in the guideline, along with the confidence interval (CI) and data related to the relative treatment effects such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or 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 (2) for policy on clinical areas not covered by the focused update. 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 Committee

For this focused update, all eligible members of the 2007 UA/NSTEMI writing committee were invited to participate; those who agreed (referred to as the 2011 focused update writing group) were required to disclose all RWI relevant to

the data under consideration. The committee comprised representatives from 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 Academy of Family Physicians, American College of Emergency Physicians, American College of Physicians, Society for Coronary Angiography and Interventions, and Society of Thoracic Surgeons, and 25 individual content reviewers, including members of the ACCF Interventional Scientific Council and ACCF Surgeon's 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 American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

3. Early Hospital Care

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

3.2.1. Recommendations for Antiplatelet Therapy
(See Table 2, and Appendixes 3, 4, 5, 6, 7, and 8 for supplemental information.)

3.2.3. Recommendations for Additional Management of Antiplatelet and Anticoagulant Therapy
(See Table 3, and Appendixes 3, 4, 5, 6, 7, and 8 for supplemental information.)

3.2.3.1. ANTIPLATELET/ANTICOAGULANT THERAPY IN PATIENTS FOR WHOM DIAGNOSIS OF UA/NSTEMI IS LIKELY OR DEFINITE

3.2.3.1.1. Thienopyridines. Thienopyridine 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 guidelines recommended the use of clopidogrel in patients with UA/NSTEMI because it was the only US Food and Drug Administration (FDA)-approved thienopyridine agent at that time. Since the publication of the last guidelines (2), the FDA has approved a second thienopyridine agent for use in patients with UA/NSTEMI. The FDA approved the use of prasugrel based on data from a head-to-head comparison with clopidogrel, in which prasugrel was superior in reductions in clinical events but at the expense of an increased risk of bleeding.

Table 2. Recommendations for Antiplatelet Therapy

2007 Recommendations	2011 Focused Update Recommendations	Comments
<p>Class I</p> <p>ASA should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. (<i>Level of Evidence: A</i>) (Figs. 7 and 8; Box A)</p> <p>Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (<i>Level of Evidence: A</i>) (Figs. 7 and 8; Box A)</p> <p>In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., PPI), should be prescribed concomitantly. (<i>Level of Evidence: B</i>)</p> <p>For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to ASA should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose) or an IV GP IIb/IIIa inhibitor. (<i>Level of Evidence: A</i>) Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. (<i>Level of Evidence: B</i>)</p> <p>For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected (see Section 3.3), clopidogrel (loading dose followed by daily maintenance dose) should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (<i>Level of Evidence: A</i>) and ideally up to 1 year. (<i>Level of Evidence: B</i>) (Fig. 8; Box C2)</p> <p>For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. (<i>Level of Evidence: A</i>) (Fig. 8; Box D) Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; <i>Level of Evidence: A</i>) or clopidogrel (loading dose followed by daily maintenance dose; <i>Level of Evidence: A</i>) should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). (<i>Level of Evidence: C</i>)</p>	<ol style="list-style-type: none"> 1. ASA* should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (3–10). (<i>Level of Evidence: A</i>) 2. Clopidogrel (loading dose followed by daily maintenance dose) should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance (11–13). (<i>Level of Evidence: B</i>) 3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation (13,15–17). (<i>Level of Evidence: A</i>) ASA should be initiated on presentation (3–8,10). (<i>Level of Evidence: A</i>) The choice of a second antiplatelet therapy to be added to ASA on presentation includes 1 of the following: Before PCI: <ul style="list-style-type: none"> • Clopidogrel (13,17) (<i>Level of Evidence: B</i>); or • An IV GP IIb/IIIa inhibitor (18–21). (<i>Level of Evidence: A</i>) IV eptifibatide or tirofiban are the preferred GP IIb/IIIa inhibitors. At the time of PCI: <ul style="list-style-type: none"> • Clopidogrel if not started before PCI (13,17) (<i>Level of Evidence: A</i>); or • Prasugrel† (22) (<i>Level of Evidence: B</i>); or • An IV GP IIb/IIIa inhibitor (18,21,23,24). (<i>Level of Evidence: A</i>) 4. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected (see Section 3.3), clopidogrel (loading dose followed by daily maintenance dose) should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (13) and ideally up to 1 year (11,13). (<i>Level of Evidence: B</i>) 5. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed (13,25,26). (<i>Level of Evidence: A</i>). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban (19–21) [<i>Level of Evidence: A</i>]) or clopidogrel (loading dose followed by daily maintenance dose (13,15) [<i>Level of Evidence: B</i>]) should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). (<i>Level of Evidence: C</i>) 6. A loading dose of thienopyridine is recommended for UA/NSTEMI patients for whom PCI is planned. Regimens should be 1 of the following: <ol style="list-style-type: none"> a. Clopidogrel 300 to 600 mg should be given as early as possible before or at the time of PCI (13,27–31) (<i>Level of Evidence: A</i>) 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 (22). (<i>Level of Evidence: B</i>) 7. The duration and maintenance dose of thienopyridine therapy should be as follows: <ol style="list-style-type: none"> a. In UA/NSTEMI patients undergoing PCI, clopidogrel 75 mg daily (17) or prasugrel† 10 mg daily (22) should be given for at least 12 months (13,17). (<i>Level of Evidence: B</i>) b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. (<i>Level of Evidence: C</i>) 	<p>Modified recommendation (changed wording for clarity).</p> <p>Modified recommendation (level of evidence changed from A to B because trials do not address the specific subgroups in this recommendation).</p> <p>Deleted recommendation (see ACCF/ACG/AHA PPI expert consensus document [14]).</p> <p>Modified recommendation (modified to include prasugrel and define therapy more clearly).</p> <p>Modified recommendation (changed level of evidence from A to B for 1-month clopidogrel administration).</p> <p>Modified recommendation (changed level of evidence from A to B for clopidogrel addition).</p> <p>New recommendation (included to be concordant with 2009 STEMI and PCI Focused Update (32), modified for the UA/NSTEMI patient group).</p> <p>New recommendation (included to be concordant with 2009 STEMI and PCI Focused Update [32]).</p>

(Continued)

Table 2. Continued

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class IIa		
For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography. (<i>Level of Evidence: C</i>)	1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography. (<i>Level of Evidence: C</i>)	2007 recommendation remains current.
For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an IV GP IIb/IIIa antagonist before diagnostic angiography 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. (<i>Level of Evidence: B</i>)	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 (16,33,34). (<i>Level of Evidence: B</i>)	Modified recommendation (removed language about diagnostic angiography).
Class IIb		
For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. (<i>Level of Evidence: B</i>) (Fig. 8; Box C2)	1. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy (19,20). (<i>Level of Evidence: B</i>)	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 (22,35,36). (<i>Level of Evidence: C</i>)	New recommendation
	3. The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk UA/NSTEMI patients already receiving ASA and a thienopyridine 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 (19,20,25,27,37). (<i>Level of Evidence: B</i>)	New recommendation
	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 (28). (<i>Level of Evidence: B</i>)	New recommendation
Class III: No Benefit		
Abciximab should not be administered to patients in whom PCI is not planned. (<i>Level of Evidence: A</i>)	1. Abciximab should not be administered to patients in whom PCI is not planned (21,23). (<i>Level of Evidence: A</i>)	2007 recommendation remains current.
	2. In UA/NSTEMI patients who are at low risk for ischemic events (e.g., TIMI risk score ≤ 2) or at high risk of bleeding and who are already receiving ASA and clopidogrel, upstream GP IIb/IIIa inhibitors are not recommended (25,36–38). (<i>Level of Evidence: B</i>)	New recommendation
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 (22). (<i>Level of Evidence: B</i>)	New recommendation (included to be concordant with 2009 STEMI and PCI Focused Update [32]).

*Refer to the ACC/AHA/SCAI Guideline for Percutaneous Coronary Intervention for long-term dosing of ASA following stent placement.

†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 receiving a BMS or DES, a daily maintenance dose should be given for at least 12 months and for up to 15 months unless the risk of bleeding outweighs the anticipated net benefit afforded by a thienopyridine. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients ≥ 75 years of age, 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 days before any surgery (35). Additional risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs) (35).

The pivotal trial (22) for prasugrel, TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction), focused on patients with acute coronary syndrome (ACS) who were referred for percutaneous coronary intervention (PCI). TRITON-TIMI 38 randomly assigned 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 (ASA) 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.

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 myocar-

Table 3. Recommendations for Additional Management of Antiplatelet and Anticoagulant Therapy

2007 Recommendations	2011 Focused Update Recommendations	Comments
<p>Class I</p> <p>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, HF, or serious arrhythmias), a stress test should be performed. (<i>Level of Evidence: B</i>) (Fig. 8; Box O)</p> <p>a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed. (<i>Level of Evidence: A</i>) (Fig. 8; Box E1)</p> <p>b. If, after stress testing, the patient is classified as being at low risk (Fig. 8; Box E2), the instructions noted below should be followed in preparation for discharge (Fig. 8; Box K) (<i>Level of Evidence: A</i>):</p> <ol style="list-style-type: none"> 1. Continue ASA indefinitely. (<i>Level of Evidence: A</i>) 2. Continue clopidogrel for at least 1 month (<i>Level of Evidence: A</i>) and ideally up to 1 year. (<i>Level of Evidence: B</i>) 3. Discontinue IV GP IIb/IIIa inhibitor if started previously. (<i>Level of Evidence: A</i>) 4. Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy. (<i>Level of Evidence: A</i>) <p>For UA/NSTEMI patients in whom CABG is selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 9; Box G).</p> <p>a. Continue ASA. (<i>Level of Evidence: A</i>)</p> <p>b. Discontinue clopidogrel 5 to 7 days before elective CABG. (<i>Level of Evidence: B</i>) More urgent surgery, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable. (<i>Level of Evidence: C</i>)</p> <p>c. Discontinue IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 hours before CABG. (<i>Level of Evidence: B</i>)</p> <p>d. Anticoagulant therapy should be managed as follows:</p> <ol style="list-style-type: none"> 1. Continue UFH. (<i>Level of Evidence: B</i>) 2. Discontinue enoxaparin* 12 to 24 hours before CABG and dose with UFH per institutional practice. (<i>Level of Evidence: B</i>) 3. Discontinue fondaparinux 24 hours before CABG and dose with UFH per institutional practice. (<i>Level of Evidence: B</i>) 4. Discontinue bivalirudin 3 hours before CABG and dose with UFH per institutional practice. (<i>Level of Evidence: B</i>) <p>For UA/NSTEMI patients in whom CABG is selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 9; Box G).</p> <p>b. Discontinue clopidogrel 5 to 7 days before elective CABG. (<i>Level of Evidence: B</i>) More urgent surgery, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable. (<i>Level of Evidence: C</i>)</p> <p>For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 9; Box H):</p> <p>a. Continue ASA. (<i>Level of Evidence: A</i>)</p> <p>b. Administer a loading dose of clopidogrel if not started before diagnostic angiography. (<i>Level of Evidence: A</i>)</p> <p>c. Administer an IV GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography for troponin-positive and other high-risk patients (<i>Level of Evidence: A</i>). See Class IIa recommendation below if bivalirudin was selected as the anticoagulant.</p> <p>d. Discontinue anticoagulant therapy after PCI for uncomplicated cases. (<i>Level of Evidence: B</i>)</p> <p>For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom no significant obstructive CAD on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician (<i>Level of Evidence: C</i>). For patients in whom evidence of coronary atherosclerosis is present (e.g., luminal irregularities or intravascular ultrasound-demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with ASA and other secondary prevention measures should be prescribed. (Fig. 9; Box I) (<i>Level of Evidence: C</i>)</p>	<ol style="list-style-type: none"> 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, HF, or serious arrhythmias), a stress test should be performed (26). (<i>Level of Evidence: B</i>) <ol style="list-style-type: none"> a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed (25,26). (<i>Level of Evidence: A</i>) 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 (25,26): <ol style="list-style-type: none"> 1. Continue ASA indefinitely (4,6,10). (<i>Level of Evidence: A</i>) 2. Continue clopidogrel for at least 1 month (13) and ideally up to 1 year (11,13). (<i>Level of Evidence: B</i>) 3. Discontinue IV GP IIb/IIIa inhibitor if started previously (19,20). (<i>Level of Evidence: A</i>) 4. Continue UFH for 48 hours (8,39) (<i>Level of Evidence: A</i>) or administer enoxaparin (40–42) (<i>Level of Evidence: A</i>) or fondaparinux (43) (<i>Level of Evidence: B</i>) 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. <ol style="list-style-type: none"> a. Continue ASA (44–48). (<i>Level of Evidence: A</i>) b. See Class I, #3, in this section. c. Discontinue IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 hours before CABG (49–51). (<i>Level of Evidence: B</i>) d. Anticoagulant therapy should be managed as follows: <ol style="list-style-type: none"> 1. Continue UFH (40,52–54). (<i>Level of Evidence: B</i>) 2. Discontinue enoxaparin 12 to 24 hours before CABG and dose with UFH per institutional practice (40,52–54). (<i>Level of Evidence: B</i>) 3. Discontinue fondaparinux 24 hours before CABG and dose with UFH per institutional practice (55,56). (<i>Level of Evidence: B</i>) 4. Discontinue bivalirudin 3 hours before CABG and dose with UFH per institutional practice (57,58). (<i>Level of Evidence: B</i>) 3. In patients taking a thienopyridine 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) (<i>Level of Evidence: B</i>) The period of withdrawal should be at least 5 days in patients receiving clopidogrel (13,18,59) (<i>Level of Evidence: B</i>) and at least 7 days in patients receiving prasugrel* (35) (<i>Level of Evidence: C</i>) unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding (60). (<i>Level of Evidence: C</i>) 4. For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed: <ol style="list-style-type: none"> a. Continue ASA (4,6,10). (<i>Level of Evidence: A</i>) b. Administer a loading dose of a thienopyridine if not started before diagnostic angiography (12,29,31,61,62). (<i>Level of Evidence: A</i>) c. See Class IIa, #1, in this section. d. Discontinue anticoagulant therapy after PCI for uncomplicated cases (40,41,63–65). (<i>Level of Evidence: B</i>) 5. For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom no significant obstructive CAD on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician (<i>Level of Evidence: C</i>). For patients in whom evidence of coronary atherosclerosis is present (e.g., luminal irregularities or intravascular ultrasound-demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with ASA and other secondary prevention measures should be prescribed. (<i>Level of Evidence: C</i>) 	<p>Modified recommendation (changed level of evidence from A to B for 1-month clopidogrel administration; clarified levels of evidence for UFH, enoxaparin, and fondaparinux).</p> <p>Modified recommendation (changed item “b” to include prasugrel and be a stand-alone recommendation; see Class I, #3, in this section).</p> <p>Modified recommendation (changed to include prasugrel and update length of withdrawal period; from Class I, #2, in this section).</p> <p>Modified recommendation (included language to allow for prasugrel as choice of thienopyridine; class of item “c” changed from I to IIa).</p> <p>2007 recommendation remains current.</p>

(Continued)

Table 3. Continued

2007 Recommendations	2011 Focused Update Recommendations	Comments
<p>For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom CAD was found on angiography, the following approach is recommended (Fig. 9; Box J):</p> <ol style="list-style-type: none"> Continue ASA. (Level of Evidence: A) Administer a loading dose of clopidogrel if not given before diagnostic angiography. (Level of Evidence: A) Discontinue IV GP IIb/IIIa inhibitor if started previously. (Level of Evidence: B) Anticoagulant therapy should be managed as follows: <ol style="list-style-type: none"> Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography. (Level of Evidence: A) Continue enoxaparin for duration of hospitalization, up to 8 days, if given before diagnostic angiography. (Level of Evidence: A) Continue fondaparinux for duration of hospitalization, up to 8 days, if given before diagnostic angiography. (Level of Evidence: B) 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. (Level of Evidence: B) <p>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 (Fig. 8; Box K):</p> <ol style="list-style-type: none"> Continue ASA indefinitely. (Level of Evidence: A) Continue clopidogrel for at least 1 month (Level of Evidence: A) and ideally up to 1 year. (Level of Evidence: B) Discontinue IV GP IIb/IIIa inhibitor if started previously. (Level of Evidence: A) Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy. (Level of Evidence: A) <p>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, HF, or serious arrhythmias), LVEF should be measured. (Level of Evidence: B) (Fig. 8; Box L)</p>	<ol style="list-style-type: none"> For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom CAD was found on angiography, the following approach is recommended: <ol style="list-style-type: none"> Continue ASA (4,6,10). (Level of Evidence: A) Administer a loading dose of clopidogrel if not given before diagnostic angiography (13). (Level of Evidence: B) Discontinue IV GP IIb/IIIa inhibitor if started previously (16,19,20,38). (Level of Evidence: B) Anticoagulant therapy should be managed as follows: <ol style="list-style-type: none"> Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography (8,39,40). (Level of Evidence: A) Continue enoxaparin for duration of hospitalization, up to 8 days, if given before diagnostic angiography (40–42,56). (Level of Evidence: A) Continue fondaparinux for duration of hospitalization, up to 8 days, if given before diagnostic angiography (43). (Level of Evidence: B) 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 (34,67,68). (Level of Evidence: B) 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: <ol style="list-style-type: none"> Continue ASA indefinitely (4,6,10). (Level of Evidence: A) Continue clopidogrel for at least 1 month (13) and ideally up to 1 year (11,13,121). (Level of Evidence: B) Discontinue IV GP IIb/IIIa inhibitor if started previously (19,20). (Level of Evidence: A) Continue UFH for 48 hours (8,39) (Level of Evidence: A) or administer enoxaparin (40–42) (Level of Evidence: A) or fondaparinux (Level of Evidence: B) for the duration of hospitalization, up to 8 days (43), and then discontinue anticoagulant therapy. 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, HF, or serious arrhythmias), LVEF should be measured (25,69–72). (Level of Evidence: B) 	<p>Modified recommendation (changed level of evidence from A to B for clopidogrel loading dose).</p> <p>Modified recommendation (changed level of evidence from A to B for 1-month clopidogrel administration).</p> <p>2007 recommendation remains current.</p>
<p>Class IIa</p> <p>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 antagonist if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier. (Level of Evidence: B) (Fig. 9)</p> <p>If LVEF is ≤ 0.40, it is reasonable to perform diagnostic angiography. (Level of Evidence: B) (Fig. 8; Box M)</p> <p>If LVEF is greater than 0.40, it is reasonable to perform a stress test. (Level of Evidence: B) (Fig. 8; Box N)</p>	<ol style="list-style-type: none"> 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 (25,27). (Level of Evidence: A) 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 (16,25). (Level of Evidence: B) If LVEF is ≤ 0.40, it is reasonable to perform diagnostic angiography (69–72). (Level of Evidence: B) If LVEF is greater than 0.40, it is reasonable to perform a stress test (69). (Level of Evidence: B) 	<p>Modified recommendation (see Class I, #4, in this section).</p> <p>2007 recommendation remains current.</p> <p>2007 recommendation remains current.</p> <p>2007 recommendation remains current.</p>
<p>Class IIb</p> <p>For UA/NSTEMI patients in whom PCI is selected as a management strategy, it may be reasonable to omit an IV GP IIb/IIIa inhibitor if not started before diagnostic angiography for troponin-negative patients without other clinical or angiographic high-risk features. (Level of Evidence: C)</p>	<ol style="list-style-type: none"> Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management (73–77). (Level of Evidence: B) Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management (78–84). (Level of Evidence: C) 	<p>Deleted recommendation</p> <p>New recommendation</p> <p>New recommendation</p>
<p>Class III: No Benefit</p> <p>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. (Level of Evidence: A)</p>	<ol style="list-style-type: none"> 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 (85). (Level of Evidence: A) 	<p>2007 recommendation remains current.</p>

*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 receiving a bare-metal stent (BMS) or drug-eluting stent (DES), a daily maintenance dose should be given for at least 12 months and for up to 15 months unless the risk of bleeding outweighs the anticipated net benefit afforded by a thienopyridine. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients ≥ 75 years of age, 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 days before any surgery (35). Additional risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs) (35).

dial infarction (MI), or nonfatal stroke during the follow-up period. 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; $p < 0.001$) (22). 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; $p = 0.03$). The increased RR of major bleeding was 32%. Prasugrel was associated with a significant increase in fatal bleeding (0.4%) compared with clopidogrel (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) (22). 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; $p < 0.001$) (22). 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 ≥ 75 years of age 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 (22).

The FDA cited a contraindication against use of prasugrel in patients with a history of transient ischemic attack or stroke or with active pathological bleeding (35). The FDA labeling information includes a general warning against the use of prasugrel in patients ≥ 75 years of age 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 (35). 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; $p = 0.002$) (22).

The writing group cautions that data on the use of prasugrel come solely from the TRITON-TIMI 38 trial, and its use in clinical practice should carefully follow how it was tested in that study (22). Prasugrel was administered only after a decision to proceed to PCI was made. It is not our recommendation that prasugrel be administered routinely before angiography, such as in an emergency department, or be used in patients 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 (35). The writing group acknowledges this flexibility, but it is not our intention to make specific recommendations about which subgroups of patients might benefit from prasugrel instead of clopidogrel. We do wish to caution clinicians about the potential bleeding risks from prasugrel compared with clopidogrel, especially among the subgroups identified in the package insert (22,35).

3.2.3.1.2. Choice of Thienopyridine for PCI in UA/NSTEMI. These guidelines do not explicitly endorse one of the thienopyridines over the other. There were several reasons for this decision. Although the composite efficacy endpoint favored prasugrel, driven predominantly by a difference in nonfatal MIs, with deaths and nonfatal strokes being similar, bleeding was increased in the prasugrel group (22). In addition, the comparison of the 2 drugs is based on a single large trial. Also, the loading dose of clopidogrel in TRITON-TIMI 38 was lower than is currently recommended in these guidelines (22). 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 prasugrel. 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 thienopyridine for individual patients (86).

There may be other options for oral antiplatelet efficacy in the not too distant future. Ticagrelor is a reversible nonthienopyridine P2Y₁₂ receptor antagonist that has been tested in a head-to-head comparison with clopidogrel in PLATO (Study of Platelet Inhibition and Patient Outcomes) (87). It is not a prodrug like clopidogrel and prasugrel and thus does not require bioactivation (87,88). Ticagrelor reduced the risks of death and MI but at the expense of an increase in nonprocedural bleeding (87). Ticagrelor was not FDA approved or marketed at the time of writing of this update; hence, we could not recommend it for use in patients with UA/NSTEMI, although it may have a future role in patients with UA/NSTEMI.

3.2.3.1.2.1. Timing of Discontinuation of Thienopyridine Therapy for Surgical Procedures. The writing group weighed the current data on the use of thienopyridine therapy in patients who remain

hospitalized after UA/NSTEMI and are candidates for CABG and retained the 2007 recommendation (2) 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 for its discontinuation before planned CABG (35). Ultimately, the patient's clinical status will determine the risk-to-benefit ratio of CABG compared with awaiting restoration of platelet function.

3.2.3.1.3. Interindividual Variability in Responsiveness to Clopidogrel. Although clopidogrel in combination with ASA has been shown to reduce recurrent coronary events in the posthospitalized ACS population (13,17), the response to clopidogrel varies among patients, and diminished responsiveness to clopidogrel has been observed (89,90). 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 (81); of these, the CYP2C19 isoenzyme is responsible for almost half of the first step formation (78). At least 3 major genetic polymorphisms of the CYP2C19 isoenzyme are associated with loss of function: CYP2C19*1, *2, and *3 (78–80). The CYP2C19*2 and *3 variants account for 85% and 99% of the loss-of-function alleles in Caucasians and Asians, respectively (78). There are 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 (79,81,83,84,89–93) and are well delineated in the ACCF/AHA Clopidogrel Clinical Alert (78).

Prasugrel, the second FDA-approved thienopyridine 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 (94,95).

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 (86), 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 (78).

The FDA label revision does not mandate testing for CYP2C19 genotypes or overall platelet function (86). 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. At least 11 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 (78), 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 (78). The Class IIb classification 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 (78). 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 (28,96). The CURRENT-OASIS 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 ASA (300 to 325 mg daily) with low-dose ASA (75 to 100 mg daily). All patients received ≥300 mg of ASA 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 (96) failed to demonstrate a significant difference in the primary endpoint between the clopidogrel and ASA groups (4.2% versus 4.4%), the PCI subset (n=17,263) did show significant differences in the clopidogrel arm (28). 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 drug-eluting stent versus non-drug-eluting stent 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 (96).

As noted in the Dosing Table (Appendix 4), 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 Acute Coronary Syndrome. 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 complications such as ulceration and related bleeding (97) due to dual-antiplatelet therapy, in particular ASA and clopidogrel (90). Coupled with concern about the gastrointestinal precautions, there has been increased emphasis on the prevention of premature discontinuation of dual-antiplatelet therapy, particularly in patients who have received a drug-eluting stent for whom 12 months of antiplatelet therapy is recommended (98).

There have been retrospective reports of adverse cardiovascular outcomes (e.g., readmission for ACS) when the antiplatelet regimen of clopidogrel and ASA is accompanied by PPIs assessed as a group compared with use of this regimen without a PPI (90,99,101). 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 (90). Other post hoc study analyses (83,102) and a retrospective data analysis from the National Heart, Lung, and Blood Institute Dynamic Registry (103), in which PPIs were assessed as a class in combination with a clopidogrel and an ASA 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 (83,103).

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 (104,105). 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 (99).

Other studies have examined the thienopyridine agent 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 (106).

Another study (101) 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 (107) and the TRITON-TIMI 38 trial (22). 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 a preliminary report of a randomized study (the COSENT [Clopidogrel and the Optimization of Gastrointestinal Events] study (108); see Appendix 7), omeprazole was compared with placebo in 3627 patients starting dual-antiplatelet therapy with ASA and clopidogrel. No difference was found in the primary composite cardiovascular endpoint between clopidogrel plus omeprazole and clopidogrel plus placebo (HR:

*PPIs include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole (which are all available by prescription). Omeprazole is also sold over the counter for frequent heartburn.

1.02), but gastrointestinal bleeding complications were reduced (108). Clearly, 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 (86) 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 (86). Most recently, the ACC 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 (14).

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 (18–21,109–115). 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 ASA 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 (19,20,25,110,111,113). These studies did not directly test in a randomized fashion the selection of an oral thienopyridine versus an intravenous 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 ASA and a thienopyridine.

The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome) trial (37) 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 (creatinine kinase–MB 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 (i.e., at or before randomization) (37).

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 ACUTY (Acute Catheterization and Urgent Intervention Triage strategY) trial (16), 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: unfrac-

tionated 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; $p=0.044$), 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 (27,37,112,114,115), these 2 most recent studies more strongly support a strategy of selective rather than provisional use of GP IIb/IIIa inhibitor therapy as part of triple-antiplatelet therapy. Data from EARLY ACS (37) 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 ≥ 75 years of age, in whom the potential benefit may be significantly offset by the potential risk of bleeding.

3.3. Recommendations for Initial Conservative Versus Initial Invasive Strategies

(See Table 4, and Appendixes 3 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 recommendation in this guideline.

The ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling-Off) trial (119) 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 (119). Patients with “large MI,” defined by ST-segment elevation or creatine kinase-MB isoenzyme activity >3 times normal, were excluded. Underlying medical therapy in both treatment arms included ASA, 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-MB 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 (38), which compared early versus delayed angiography and intervention in patients with non-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 ASA, 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 4,000 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 (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

Table 4. Recommendations for Initial Invasive Versus Initial Conservative Strategies

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
An early invasive strategy (i.e., 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). (Level of Evidence: B)	1. An early invasive strategy (i.e., 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) (116,117). (Level of Evidence: B)	2007 recommendation remains current.
An early invasive strategy (i.e., 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 Table 11 and Sections 2.2.6 and 3.4.3). (Level of Evidence: A)	2. An early invasive strategy (i.e., 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 (2) Table 11 and 2007 Sections 2.2.6 and 3.4.3) (25,26,69). (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 <i>high-risk</i> patients with UA/NSTEMI.* For patients <i>not at high risk</i> , a delayed invasive approach is also reasonable (38). (Level of Evidence: B)	New recommendation (modified from 2009 STEMI and PCI Focused Update) (32).
Class IIb		
In initially stabilized patients, an initially conservative (i.e., 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 Table 11 and Sections 2.2.6 and 3.4.3), including those who are troponin positive. (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) An invasive strategy may be reasonable in patients with chronic renal insufficiency. (Level of Evidence: C)	1. In initially stabilized patients, an initially conservative (i.e., 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 (2) Table 11 and Sections 2.2.6 and 3.4.3), including those who are troponin positive (69,118). (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.
		Recommendation moved to Section 6.5, class changed to IIa, level of evidence changed to B.
Class III: No Benefit		
An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (e.g., 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)	1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (e.g., 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.
An early invasive strategy (i.e., 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)	2. An early invasive strategy (i.e., 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.
An early invasive strategy (i.e., 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)	3. An early invasive strategy (i.e., 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.

risk according to the Global Registry of Acute Coronary Events (GRACE) 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 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) (38).

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 (38).

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 (120) 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 ASA, 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; $p=0.31$) (120).

These 3 trials, 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.

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

5.2. Long-Term Medical Therapy and Secondary Prevention

5.2.1. Recommendations for Antiplatelet Therapy

(See Table 5, and Appendixes 3 and 4 for supplemental information.)

5.2.6. Recommendations for Warfarin Therapy

(See Table 6 and Appendix 3.)

6. Special Groups

6.2. Recommendations for Diabetes Mellitus

(See Table 7 and Appendix 3.)

6.2.1.1. INTENSIVE GLUCOSE CONTROL

As detailed in the 2004 STEMI guideline (147), 2007 UA/NSTEMI guideline revision (2), and 2009 STEMI and PCI focused update (32), 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) (143). 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 (143,144). 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 (143) 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 (148,149) suggest that glucose control may reduce inflammation and improve left ventricular ejection fraction (LVEF) 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 (150) 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 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 (150–152), 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, Level of Evidence: B) (32) and recommend treatment for hyperglycemia >180 mg/dL while avoiding hypoglycemia. The writing group believed that the 2007 recommendation(2) 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.

Table 5. Recommendations for Antiplatelet Therapy

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
For UA/NSTEMI patients treated medically without stenting, ASA* (75 to 162 mg per day) should be prescribed indefinitely (<i>Level of Evidence: A</i>); clopidogrel† (75 mg per day) should be prescribed for at least 1 month (<i>Level of Evidence: A</i>) and ideally for up to 1 year. (<i>Level of Evidence: B</i>)	1. For UA/NSTEMI patients treated medically without stenting, ASA* (75 to 162 mg per day) should be prescribed indefinitely (4,6,9,10) (<i>Level of Evidence: A</i>); clopidogrel† (75 mg per day) should be prescribed for at least 1 month (13) and ideally up to 1 year (13,121). (<i>Level of Evidence: B</i>)	Modified recommendation (level of evidence changed from A to B for 1-month duration of clopidogrel).
For UA/NSTEMI patients treated with a BMS, ASA* 162 to 325 mg per day should be prescribed for at least 1 month (<i>Level of Evidence: B</i>), then continued indefinitely at a dose of 75 to 162 mg per day (<i>Level of Evidence: A</i>); clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). (<i>Level of Evidence: B</i>)		Deleted recommendation (see Table 2, Class I, #1 and #7).
For UA/NSTEMI patients treated with a DES, ASA* 162 to 325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation, then continued indefinitely at a dose of 75 to 162 mg per day. (<i>Level of Evidence: B</i>) Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES. (<i>Level of Evidence: B</i>)		Deleted recommendation (see Table 2, Class I, #1 and #7).
Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when ASA is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as PPIs). (<i>Level of Evidence: A</i>)	2. Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when ASA is contraindicated or not tolerated because of hypersensitivity or GI intolerance (despite use of gastroprotective agents such as PPIs) (11,61,108). (<i>Level of Evidence: A</i>)	Modified recommendation (changed wording for clarity).
Class IIa		
For UA/NSTEMI patients in whom the physician is concerned about the risk of bleeding, a lower initial ASA dose after PCI of 75 to 162 mg per day is reasonable. (<i>Level of Evidence: C</i>)	1. For UA/NSTEMI patients in whom the physician is concerned about the risk of bleeding, a lower initial ASA dose (75 to 162 mg/day) after PCI is reasonable. (<i>Level of Evidence: C</i>)	2007 recommendation remains current.
Class IIb		
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.§ (<i>Level of Evidence: B</i>)	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.§ (122–131) (<i>Level of Evidence: B</i>)	2007 recommendation remains current.
	2. Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients following DES placement. (<i>Level of Evidence: C</i>)	New recommendation
Class III: No Benefit		
Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective. (<i>Level of Evidence: A</i>)	1. Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective (44,132,133). (<i>Level of Evidence: B</i>)	Modified recommendation (level of evidence changed from A to B).

*For ASA-allergic patients, use clopidogrel alone (indefinitely) or try ASA desensitization.

†For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily.

‡Continue ASA 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 ASA and clopidogrel, 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).

Diabetes is another characteristic associated with high risk for adverse outcomes after UA/NSTEMI. The 2007 UA/NSTEMI guidelines (2) 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 2011 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 (153). 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 (26). 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 [0.36 to 1.04]) compared with patients who did not have diabetes randomized to an invasive strategy (OR: 0.72 [0.54 to 0.95]). The risk of death was also

Table 6. Recommendations for Warfarin Therapy

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I Use of warfarin in conjunction with ASA and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. (<i>Level of Evidence: A</i>)	1. Use of warfarin in conjunction with ASA and/or a thienopyridine agent is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal, and seek medical evaluation for evidence of bleeding (13,22,86,134–137). (<i>Level of Evidence: A</i>)	Modified recommendation (updated to include a choice of thienopyridine).
Class IIb Warfarin either without (INR 2.5 to 3.5) or with low-dose ASA (75 to 81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel. (<i>Level of Evidence: B</i>)	1. Warfarin either without (INR 2.5 to 3.5) or with low-dose ASA (75 to 81 mg per day; INR 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel (138,139). (<i>Level of Evidence: B</i>)	2007 recommendation remains current.

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 (154). Thus, diabetes, as well as the often concurrent comorbidity of CKD (Section 6.5, “Recommendations for Chronic Kidney Disease”), 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 8).

Table 7. Recommendations for Diabetes Mellitus

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I 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. (<i>Level of Evidence: A</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 (25,26,42,140). (<i>Level of Evidence: A</i>)	2007 recommendation remains current.
In all patients with diabetes mellitus and UA/NSTEMI, attention should be directed toward aggressive glycemic management in accordance with current standards of diabetes care endorsed by the American Diabetes Association and the American College of Endocrinology. Goals of therapy should include a preprandial glucose target of <110 mg per dL and a maximum daily target of <180 mg per dL. The postdischarge goal of therapy should be HbA1C <7%, which should be addressed by primary care and cardiac caregivers at every visit. (<i>Level of Evidence: B</i>)		Deleted recommendation (defer to American Diabetes Association Guidelines [141]).
An IV GP IIb/IIIa inhibitor should be administered for patients with diabetes mellitus as recommended for all UA/NSTEMI patients (Section 3.2). (<i>Level of Evidence: A</i>) The benefit may be enhanced in patients with diabetes mellitus. (<i>Level of Evidence: B</i>)		Deleted recommendation (deleted to avoid redundancy; refer to Tables 2 and 3).
Class IIa 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. (<i>Level of Evidence: B</i>)	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 (142). (<i>Level of Evidence: B</i>)	2007 recommendation remains current.
PCI is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia. (<i>Level of Evidence: B</i>)	2. PCI is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia (25,142). (<i>Level of Evidence: B</i>)	2007 recommendation remains current.
In patients with UA/NSTEMI and diabetes mellitus, it is reasonable to administer aggressive insulin therapy to achieve a glucose <150 mg per dL during the first 3 hospital (intensive care unit) days and between 80 and 110 mg per dL thereafter whenever possible. (<i>Level of Evidence: B</i>)	3. It is reasonable to use an insulin-based regimen to achieve and maintain glucose levels < 180 mg/dL while avoiding hypoglycemia* for hospitalized patients with UA/NSTEMI with either a complicated or uncomplicated course (143–146). (<i>Level of Evidence: B</i>)	Modified recommendation (language changed to be concordant with 2009 STEMI and PCI Focused Update [32]).

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

Table 8. Recommendations for Chronic Kidney Disease

2007 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
CrCl should be estimated in UA/NSTEMI patients, and the doses of renally cleared drugs should be adjusted appropriately. (<i>Level of Evidence: B</i>)	1. CrCl 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 (155,156). (<i>Level of Evidence: B</i>)	Modified recommendation (changed wording for clarity).
In CKD patients undergoing angiography, isosmolar contrast agents are indicated and are preferred. (<i>Level of Evidence: A</i>)		Deleted recommendation.
	2. Patients undergoing cardiac catheterization with receipt of contrast media should receive adequate preparatory hydration (157,158). (<i>Level of Evidence: B</i>)	New recommendation
	3. Calculation of the contrast volume to CrCl ratio is useful to predict the maximum volume of contrast media that can be given without significantly increasing the risk of contrast-associated nephropathy (159,160). (<i>Level of Evidence: B</i>)	New recommendation
Class IIa		
	1. An invasive strategy is reasonable in patients with mild (stage II) and moderate (stage III) CKD (155,156,161,162). (<i>Level of Evidence: B</i>) (There are insufficient data on benefit/risk of invasive strategy in UA/NSTEMI patients with advanced CKD [stages IV, V].)	Modified recommendation (class changed from IIb to IIa, level of evidence changed from C to B, and moved from Section 3.3).

6.5. Recommendations for Chronic Kidney Disease

(See Table 8, and Appendixes 3 and 7 for supplemental information.)

6.5.1. Angiography in Patients With Chronic Kidney Disease

Since the 2007 UA/NSTEMI Guidelines were published (2), 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) (163–166). 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 (167) and 25 trials in 3260 patients (168), 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; $p=0.29$ (167); summary RR: 0.80; 95% CI: 0.61 to 1.04; $p=0.10$ (168), 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; $p=0.022$ [167]), and to iohexol, a nonionic LOCM (RR: 0.19; 95% CI: 0.07 to 0.56; $p<0.0002$ [167]), but no difference was noted in comparisons of iodixanol with iopamidol, iopromide, or ioversol (167), and a single trial favored iomeprol (166). 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; $p=0.86$ [168]). Results were consistent regardless of ancillary preventive therapies (hydration, acetylcysteine), route of administration (intravenous or intra-arterial), age, sex, dose, or preexisting CKD or diabetes. Of further interest, findings

were similar in the 8 studies ($n=1,793$ patients) performed in the setting of coronary angiography (167). These results have been incorporated into the 2009 STEMI/PCI Focused Update recommendations (32). A more recent study comparing iodixanol versus iopamidol provides additional supportive evidence (169). 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 (e.g., for iohexol versus other low-osmolar comparators) (170–173). Further, 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 (174) 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 (2,32), 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 (157,158,175–177). More recently, sodium bicarbonate has been tested as the hydrating solution. Some trials have reported superiority of sodium bicarbonate over saline in preventing CIN (178–181). Similarly, some have reported a benefit of N-acetylcysteine administration as adjunctive therapy to hydration (178,182), whereas others have not (183,184). 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 (160). In an earlier trial, administration of a contrast volume of 5 mL \times 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 (159).

Patients with CKD are consistently underrepresented in randomized controlled trials of cardiovascular disease (185). 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 ≥ 80 years of age (161). 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 <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; $p<0.001$) (161). The magnitude of the difference in 1-year mortality was similar in patients with normal estimated glomerular filtration rate (early revascularization versus medically treated: 1.9% versus 10%; HR: 0.58; 95% CI: 0.42 to 0.80; $p=0.001$), mild CKD (2.4% versus 10%; HR: 0.64; 95% CI: 0.52 to 0.80; $p<0.001$), and moderate CKD (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 IV

(22% versus 41%; HR: 0.91; 95% CI: 0.51 to 1.61; $p=0.780$) or in those with CKD stage V kidney failure or receiving dialysis (44% versus 53%; HR: 1.61; 95% CI: 0.84 to 3.09; $p=0.150$). Early revascularization was associated with 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 (161).

The findings from SWEDEHEART are limited by their nonrandomized nature and the potential for selection bias despite the intricate multivariable adjustment (161). 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 (162). 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 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; $p=0.24$) (162).

Our recommendation is that an early invasive strategy (i.e., 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 (155,156,162,186). Indeed, the risks of short- and long-term mortality are increased as the gradient of renal dysfunction worsens (156,162,186). 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. Recommendation for Quality of Care and Outcomes for Acute Coronary Syndromes (NEW SECTION)

(See Table 9 and Appendix 3.)

7.1.1. Quality Care and Outcomes

The development of regional systems of ACS care is a matter of utmost importance (187–189). This includes encouraging the participation of key stakeholders in collaborative efforts to

Table 9. Recommendation for Quality Care and Outcomes for Acute Coronary Syndromes (New Section)

2007 Recommendation	2011 Focused Update Recommendation	Comments
Class IIa	<ol style="list-style-type: none"> 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 (187–197). (<i>Level of Evidence: B</i>) 	New recommendation

evaluate care using standardized performance and quality-improvement measures, such as those endorsed by the ACC and the AHA for ACS (189). Standardized quality-of-care data registries designed to track and measure outcomes, complications, and adherence to evidence-based processes of care for ACS 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 (190–193). 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 (190). The evaluation of ACS 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 (194–197). The quality improvement data coming from registries like the ACTION-GTGW 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.

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

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This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee 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% or more of the voting stock or share of the business entity, or ownership of \$10,000 or more 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 in this table are modest unless otherwise noted.

*Significant relationship.

†Recused from voting on Section 3.2. Recommendations for Antiplatelet and Anticoagulant Therapy, and Section 5.2.1. Recommendations for Antiplatelet Therapy.

‡Relationship began after writing effort was complete but before final approval.

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

Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Joseph C. Cleveland	Organizational Reviewer—STS	<ul style="list-style-type: none"> Baxter Biosurgery Essential Pharmaceuticals 	None	None	None	<ul style="list-style-type: none"> Heartware Thoratec 	None
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Appendix 2. Continued

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Appendix 2. Continued

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*Significant relationship.

AAFP indicates American Academy of Family Physicians; ACCF, American College of Cardiology Foundation; ACEP, American College of Emergency Physicians; ACP, American College of Physicians; AHA, American Heart Association; DSMB, data safety monitoring board; NIH, National Institutes of Health; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; Sub-I, subinvestigator; and TIMI, Thrombolysis in Myocardial Infarction.

Appendix 3. Abbreviation List

ACS=acute coronary syndrome

ACT=activated clotting time

ASA=aspirin

BMS=bare-metal stent

CABG=coronary artery bypass graft

CAD=coronary artery disease

CIN=contrast-induced nephropathy

CKD=chronic kidney disease

CK-MB=creatinine kinase-myocardial band

CrCl=creatinine clearance

DES=drug-eluting stent

FDA=Food and Drug Administration

GP=glycoprotein

HF=heart failure

INR=international normalized ratio

IV=intravenous

LOCM=low-osmolar contrast media

LV=left ventricular

LVEF=left ventricular ejection fraction

MI=myocardial infarction

NSTEMI=non-ST-segment elevation myocardial infarction

PCI=percutaneous coronary intervention

PPI=proton-pump inhibitor

STEMI=ST-elevation myocardial infarction

TIA=transient ischemic attack

TIMI=Thrombolysis In Myocardial Infarction

TnI=troponin I

TnT=troponin T

UA=unstable angina

UA/NSTEMI=unstable angina/non-ST-elevation myocardial infarction

UFH=unfractionated heparin

Appendix 4. Dosing Table for Antiplatelet and Anticoagulant Therapy Discussed in This Focused Update to Support PCI in NSTEMI

During PCI			
Drug*	Patient Received Initial Medical Treatment (With a Thienopyridine)	Patient Did Not Receive Initial Medical Treatment (With a Thienopyridine)	Comments ► All Patients to Receive ASA (162–325 mg)
GP 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 (198,199).
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)	► An LD of eptifibatide is FDA approved when the medication is initiated in UA/NSTEMI patients who are started on medical therapy and when there is an appreciable delay to angiography/PCI: LD of 180 mcg/kg IV bolus followed by MD of 2.0 mcg/kg per min started after bolus; reduce infusion by 50% in patients with estimated creatinine clearance <30 mL/min (Class I, LOE:B). ► Infusion should be continued for 12 to 18 h at the discretion of the physician (198).
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 (199,202). ► Continue for up to 18 h at the discretion of the physician (202). ► 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 (e.g., 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 (19).
Thienopyridines			
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) An 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. ► 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 MD of 10 mg orally per d (Class I, LOE: B)	► There is no clear need for treatment with prasugrel before PCI. ► MD of 5 mg orally per d in special circumstances. ► Special dosing for patients <60 kg. ► There is a recommended duration of therapy for all post-PCI patients receiving a DES. ► Prasugrel is generally not recommended for patients ≥75 y of age because of increased bleeding risk and uncertain benefit compared with clopidogrel. ► Contraindicated for use in patients with prior history of TIA or stroke. (For full explanations, see footnote.)
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 (198). ► In UA/NSTEMI patients undergoing PCI who are at high risk of bleeding, bivalirudin anticoagulation is reasonable (198).
UFH	IV GP IIb/IIIa planned: target ACT 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)	IV GP IIb/IIIa planned: 50–70 units/kg bolus to achieve an ACT of 200–250 s. 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)	

ACT indicates activated clotting time; ASA, aspirin; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; FDA, Food and Drug Administration; GP, glycoprotein; IV, intravenous; LD, loading dose; LOE, level of evidence; MACE, major adverse cardiac events; MD, maintenance dose; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; 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.

*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 dosage if a drug is chosen for a given situation.

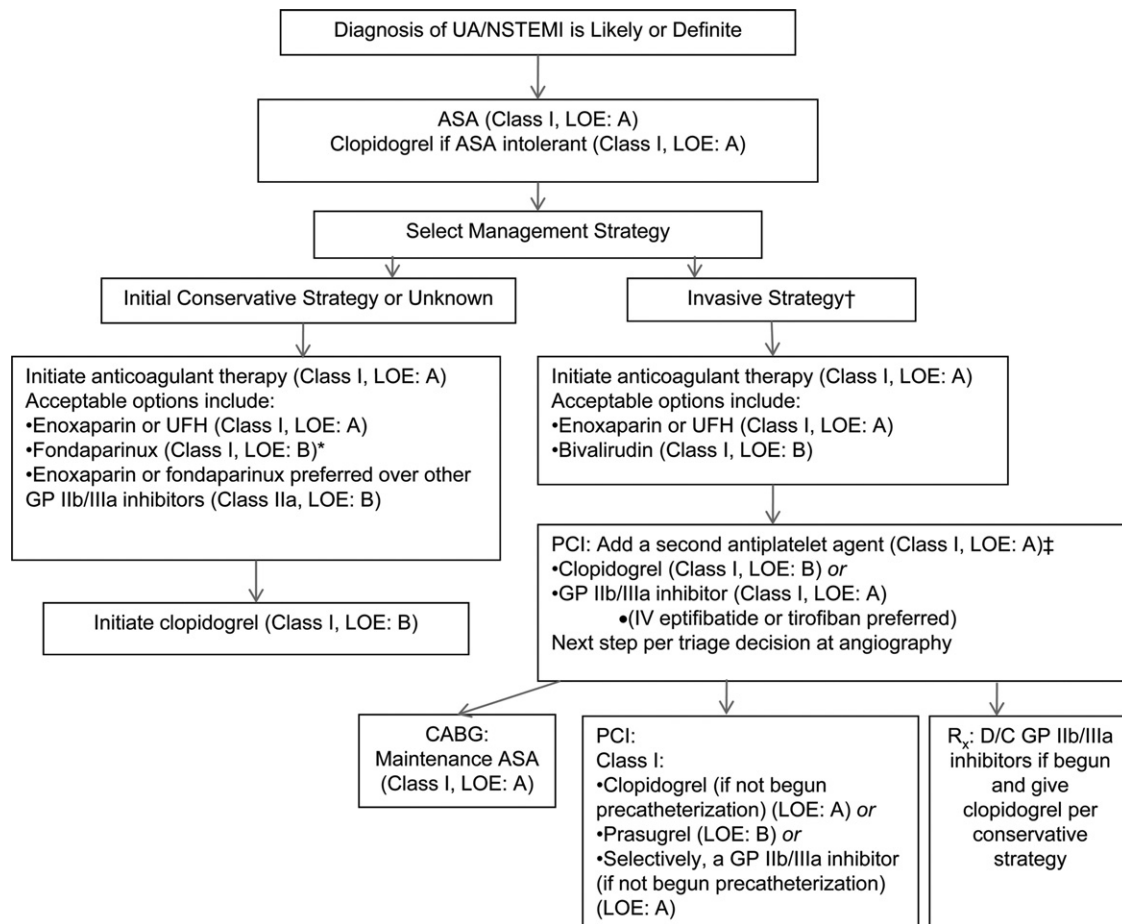
†The optimum LD of clopidogrel has not been established. Randomized trials establishing its efficacy and providing data on bleeding risks used an LD of 300 mg orally followed by a daily oral dose of 75 mg (22,203). Higher oral LDs such as 600 mg or >900 mg (204) of clopidogrel more rapidly inhibit platelet 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 thienopyridine. For post-PCI patients receiving a BMS, an MD should be given for a minimum of 1 mo (98) and ideally up to 12 mo (unless the risk of bleeding outweighs the anticipated net benefit afforded by a thienopyridine; then it should be given for a minimum of 2 wks). 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 (81). In 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 (59).

‡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 receiving a BMS or DES, a daily maintenance dose should be given for at least 12 mo and for up to 15 mo unless the risk of bleeding outweighs the anticipated net benefit afforded by a thienopyridine. Do not use prasugrel in patients with active pathological bleeding or a history of TIA or stroke. In patients ≥75 y of age, 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 (35). Additional risk factors for bleeding include body weight <60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, or chronic use of nonsteroidal anti-inflammatory drugs) (35).

Appendix 5. Comparisons Among Orally Effective P2Y12 Inhibitors

	Clopidogrel		Prasugrel	
Pharmacology	Prodrug—requires conversion to active metabolite that irreversibly blocks P2Y12 receptor.		Prodrug—requires conversion to active metabolite that irreversibly blocks P2Y12 receptor. Conversion to active metabolite occurs more rapidly and to a greater degree than with clopidogrel.	
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.	
Management strategy	<i>Conservative</i>	<i>Invasive</i>	<i>Conservative</i>	<i>Invasive</i>
Loading dose	300 mg	300–600 mg*	Generally not recommended	60 mg
Comment	*Optimal dose not established for invasive strategy although 600 mg generally preferred.		for preatherization use in UA/NSTEMI	
Timing	Initiate on presentation.	Give 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
Maintenance dose	75 mg	75 mg		10 mg
Comment	Optimal approach to dosing in individual patients based on genotype and individual antiplatelet effects not rigorously established.	Optimal individual dose not rigorously established (see comment to left). (150 mg for first 6 d is an alternative.)		Consider reduction to 5 mg in patients weighing <60 kg. The efficacy (or benefit) of prasugrel in those age ≥75 y is uncertain. Contraindicated in patients with a history of stroke or TIA.
Duration	At least 1 mo and ideally up to 1 y	At least 1 y for DES		At least 1 y for DES
Additional considerations				
Variability of Response	Greater compared with prasugrel. Factors impacting response in some patients may include genetic predisposition to convert parent compound to active metabolite and drug interactions (e.g., PPIs).		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.	
Genotyping	Identifies patients with a diminished (CYP2C19 *2,*3 alleles) or enhanced (CYP2C17 allele) ability 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.	
Risk of bleeding	Standard dosing with clopidogrel is associated with less bleeding than with prasugrel. 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.	
Transition to elective or nonurgent surgery	Wait at least 5 d after last dose.		Wait at least 7 d after last dose.	

DES indicates drug-eluting stent; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TIA, transient ischemic attack; and UA/NSTEMI, unstable angina/non-ST–elevation myocardial infarction.

Appendix 6. Flowchart for Class I and Class IIa Recommendations for Initial Management of UA/NSTEMI

*If fondaparinux is used (Class I, LOE: B), it must be coadministered with another anticoagulant with Factor IIa activity, for example, unfractionated heparin.

†Timing of invasive strategy generally is assumed to be 4 to 48 h. If immediate angiography is selected, see STEMI guidelines (147).

‡Precatheterization triple-antiplatelet therapy (ASA, clopidogrel, glycoprotein inhibitors) is a Class IIb, LOE: B recommendation for selected high-risk patients.

ASA indicates aspirin; CABG, coronary artery bypass graft; D/C, discontinue; 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.

Appendix 7. Summary Table

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	p Value (95% CI)	OR/HR/RR	Conclusion
CURRENT-OASIS 7 (96); Mehta et al	To evaluate whether doubling the dose of loading and initial maintenance doses of clopidogrel is superior to the standard-dose clopidogrel regimen and to investigate if higher-dose ASA is superior to lower-dose ASA. Patients were assigned in a 2×2 factorial design to 600 mg of clopidogrel loading on Day 1, followed by 150 mg/d for 6 d, then 75 mg thereafter versus 300 mg clopidogrel loading on Day 1, followed by 75 mg/d thereafter and either ASA 300–325 mg/d versus lower-dose ASA 75–100 mg/d.	25,086	Inclusion criteria: Age ≥18 y with non-ST-segment ACS or STEMI. Requirements included ECG changes compatible with ischemia or elevated cardiac biomarkers and coronary angiographic assessment, with plan to perform PCI as early as possible but no later than 72 h after randomization. Exclusion criteria: Increased risk of or known bleeding and allergy to clopidogrel or ASA.	Primary outcome was CV death, MI, or stroke, whichever occurred first, at 30 d. Prespecified secondary endpoint was definite or probable stent thrombosis (by ARC definition) in patients who underwent PCI. Main safety outcome was major bleeding according to trial criteria.	Primary outcome for clopidogrel dose comparison: 4.2% in double-dose clopidogrel group versus 4.4% in standard-dose clopidogrel group.	0.030 (0.83 to 1.06)	HR: 0.94	This analysis of the overall trial in 25,086 patients failed to demonstrate a significant difference in the primary endpoint of CV death, MI, or stroke at 30 d between the double-dose clopidogrel for 7 d versus standard-dose clopidogrel and between the higher-dose versus lower-dose aspirin subgroups. The secondary endpoint of definite stent thrombosis in those undergoing PCI was reduced in the clopidogrel higher-dose group for both DES versus non-DES subtypes, but this benefit was offset by increased major bleeding in the higher-dose clopidogrel group.
					Major bleeding for clopidogrel dose comparison: 2.5% in double-dose clopidogrel group versus 2.0% in standard-dose clopidogrel group.	0.01 (1.05 to 1.46)	HR: 1.24	
					Primary outcome for ASA dose comparison: 4.2% in higher-dose ASA group versus 4.4% in lower-dose ASA group.	0.47 (0.86 to 1.09)	HR: 0.97	
					Major bleeding for ASA comparison: 2.3% in higher-dose ASA group versus 2.3% in lower-dose ASA group.	0.90 (0.84 to 1.17)	HR: 0.99	
					Clopidogrel and ASA dose interaction—primary outcome for patients on higher-dose ASA: 3.8% in double-dose clopidogrel versus 4.6% in standard-dose clopidogrel.	0.03 (0.69 to 0.98)	HR: 0.82	
					Clopidogrel and ASA dose interaction—primary outcome for patients on lower-dose ASA: 4.5% in double-dose clopidogrel versus 4.2% in standard-dose clopidogrel.	0.46 (0.90 to 1.26)	HR: 1.07	
CURRENT-OASIS 7 (28); Mehta et al	The goal of this prespecified subgroup analysis of CURRENT-OASIS 7 (96) was to examine efficacy and safety outcomes in patients who underwent PCI.	17,263	Inclusion criteria: Patients with ACS (with or without ST-segment elevation) and either ECG evidence of ischemia or elevated biomarkers. Patients were required to have coronary angioplasty with intent to undergo PCI as early as possible but not later than 72 h after randomization. Exclusion criteria: Increased risk of bleeding or active bleeding. Additional information on study eligibility criteria in study Web appendix.	Primary outcome was composite of CV death, MI, or stroke from randomization to Day 30. Secondary outcomes included primary outcome plus recurrent ischemia, individual components of composite outcomes, and stent thrombosis per ARC criteria.	Stent thrombosis in patients who underwent PCI: 1.6% with double-dose clopidogrel versus 2.3% with standard-dose clopidogrel.	0.001 (0.55 to 0.85)	HR: 0.68	This substudy of CURRENT-OASIS-7 analyzed the 69% of patients (n=17,263) who underwent PCI, a prespecified analysis in a postrandomization subset. In this PCI subgroup, the primary outcome of CV death, MI, or stroke at 30 d was reduced in those randomized to higher-dose clopidogrel, and this was largely driven by a reduction in myocardial (re)infarction. Definite stent thrombosis also was reduced in the higher clopidogrel dose group with consistent results across DES versus non-DES subtypes. Outcomes were not significantly different by ASA dose. Major bleeding was more common with higher-dose clopidogrel but not with higher-dose ASA.
					Primary outcome in clopidogrel dose comparison reduced with double-dose clopidogrel: 3.9% in double-dose clopidogrel group versus 4.5% in standard-dose clopidogrel group.	0.039 (0.74 to 0.99)	Adjusted HR: 0.86	
					Secondary outcome (CV death, MI, stroke, or recurrent ischemia) in clopidogrel dose comparison was reduced with double-dose clopidogrel: 4.2% in double-dose clopidogrel versus 5.0% in standard-dose clopidogrel.	0.025 (0.74 to 0.98)	HR: 0.85	
					Rates of definite stent thrombosis were lower with double-dose clopidogrel (0.7%) versus standard-dose clopidogrel (1.3%).	0.0001 (0.39 to 0.74)	HR: 0.54	
					CURRENT-defined major bleed was more common with double-dose (0.1%) than standard-dose clopidogrel (0.04%); however, no difference in TIMI-defined severe or major bleeding.	0.16 (0.71 to 7.49)	HR: 2.31	

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Appendix 7. Continued

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	p Value (95% CI)	OR/HR/RR	Conclusion
TIMACS (38); Mehta et al	To study efficacy of an early invasive strategy (within 24 h of presentation) compared with delayed invasive strategy (any time >36 h after presentation).	3,031	Inclusion criteria: Presentation to a hospital with UA or MI without ST-segment elevation within 24 h after onset of symptoms and if 2 of the following 3 criteria for increased risk are present: age ≥ 60 y, cardiac biomarkers above ULN, or results on ECG compatible with ischemia (i.e., ST-segment depression ≥ 1 mm or transient ST-segment elevation or T-wave inversion >3 mm). Exclusion criteria: Patient who is not a suitable candidate for revascularization.	Composite of death, MI, or stroke at 6 mo.	At 6 mo, the primary outcome occurred in 9.6% of patients in early intervention group versus 11.3% of delayed-intervention group.	0.15 (0.68 to 1.06)	HR: 0.85	TIMACS initially targeted enrollment of 4000 patients but terminated enrollment at 3031 patients due to recruitment challenges, limiting its power. For the overall trial population, there was only a nonsignificant trend to a reduction in the primary ischemic endpoint in the early compared with delayed intervention groups. The prospectively defined secondary endpoint of death, MI, or refractory ischemia was reduced by early intervention, mainly because of a reduction in refractory ischemia. Heterogeneity was observed in the primary ischemic endpoint by a prespecified estimate of baseline risk according to the GRACE score, with patients in the highest tertile experiencing a sizeable risk reduction and suggesting a potential advantage of early revascularization in this high-risk subgroup.
					28% risk reduction in secondary outcome of death, MI, or refractory ischemia in early intervention group (9.5%) versus delayed-intervention group (12.9%).	0.003 (0.58 to 0.89)	HR: 0.72	
					Prespecified analyses indicated early intervention improved the primary outcome in the third of patients at highest risk.	0.06 (0.48 to 0.89)	HR: 0.65	
					Prespecified analyses did not show that early intervention improved primary outcome in the two thirds at low to intermediate risk.	0.48 (0.81 to 1.56)	HR: 1.12	
CARE (165); Solomon et al	To compare iopamidol and iodixanol in patients with CKD (eGFR 20–59 mL/min) who underwent cardiac angiography or PCI.	482	Inclusion criteria: Men and women (≥ 18 y) with moderate to severe CKD scheduled for diagnostic cardiac angiography or PCI. Exclusion criteria: Pregnancy, lactation, administration of any investigational drug within the previous 30 d, intra-arterial or IV administration of iodinated CM from 7d before to 72 h after administration of the study agents, medical conditions or circumstances that would have substantially decreased chance to obtain reliable data (NYHA class IV CHF, hypersensitivity to iodine-containing compounds, hyperthyroidism or thyroid malignancies, uncontrolled DM, unstable renal drug dependence, psychiatric disorders, dementia), administration of any medication to prevent CIN other than N-acetylcysteine, or intake of nephrotoxic medications from 24 h before to 24 h after administration of the study agent.	Primary endpoint was postdose SCr increase of 0.5 mg/dL (44.2 mol/L) over baseline. Secondary outcome was postdose SCr increase $\geq 25\%$, a postdose estimated GFR decrease $\geq 25\%$, and mean peak change in SCr.	In 414 patients, contrast volume, presence of DM, use of N-acetylcysteine, mean baseline SCr, and eGFR were comparable in the 2 groups. SCr increases of ≥ 0.5 mg/dL occurred in 4.4% (9 of 204 patients) after use of iopamidol and 6.7% (14 of 210 patients) after iodixanol.	0.39 (–6.7 to 2.1)		In this randomized trial of moderate size, the rate of CIN in higher-risk patients with moderate CKD was not significantly different between the low-osmolar contrast medium iopamidol and the iso-osmolar contrast medium iodixanol.
					Rates of SCr increases $\geq 25\%$ were 9.8% with iopamidol and 12.4% with iodixanol.	0.44 (–8.6 to 3.5)		
					In patients with DM, SCr increases to ≥ 0.5 mg/dL were 5.1% (4 of 78 patients) with iopamidol and 13% (12 of 92 patients) with iodixanol.	0.11		
					In patients with DM, SCr increases $\geq 25\%$ were 10.3% with iopamidol and 15.2% with iodixanol.	0.37		
					Mean post-SCr increases were significantly less with iopamidol (all patients: 0.07 mg/dL with iopamidol versus 0.12 mg/dL with iodixanol).	0.03		
					In patients with DM, SCr change from baseline was 0.07 mg/dL with iopamidol versus 0.16 mg/dL with iodixanol.	0.013		
					Decreases in eGFR $\geq 25\%$ were recorded in 5.9% (12 patients) with iopamidol and 10% (21 patients) with iodixanol.	0.15 (–9.3 to 1.1)		

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Appendix 7. Continued

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	p Value (95% CI)	OR/HR/RR	Conclusion
Relative renal safety of iodixanol compared with LOCM (167); Reed et al	Meta-analysis to compare nephrotoxicity of the iso-osmolar contrast medium iodixanol with LOCM.	16 trials (2763 subjects)	Patients enrolled in RCTs that compared incidence of CI-AKI with either iodixanol or LOCM.	Primary endpoint was incidence of CI-AKI. Secondary endpoints were need for renal replacement therapy and mortality.	No significant difference in incidence of CI-AKI in iodixanol group than in LOCM group (overall summary). CI-AKI was reduced when iodixanol was compared with ioxaglate and when iodixanol was compared with iohexol, but no difference was noted when iodixanol was compared with iopamidol, iodixanol was compared with iopromide, or iodixanol was compared with ioversol. No significant difference between iodixanol and LOCM noted in rates of postprocedure hemodialysis. No significant difference between iodixanol and LOCM in rates of death.	0.19 (0.56 to 1.12) 0.022 (0.37 to 0.92) (0.07 to 0.56) 0.55 (0.66 to 2.18) 0.84 (0.47 to 1.85) 0.68 (0.60 to 1.39) 0.20 (0.08 to 1.68) 0.663 (0.33 to 5.79)	Summary RR: 0.79 RR: 0.58 RR: 0.19 RR: 1.20 RR: 0.93 RR: 0.92 RR: 0.37 RR: 1.38	In this updated meta-analysis of 16 CIN trials, data supporting a reduction in CIN favoring the iso-osmolar medium iodixanol compared with LOCM were no longer significant. Subanalyses suggested potential variations in relative renal safety by specific LOCM with reductions in CIN for iodixanol compared with the ionic LOCM ioxaglate and with iohexol, a nonionic LOCM, but not with 4 other LOCM.
Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast (168); Heinrich et al	Meta-analysis of RCTs to compare nephrotoxicity of iso-osmolar iodixanol with nonionic LOCM.	25 trials (3270 subjects)	Inclusion criteria: RCTs analyzing SCr levels before and after intravascular application of iodixanol or LOCM.	Incidence of CIN and change in SCr levels.	Iodixanol did not significantly reduce risk of CIN (or risk of SCr increase) compared with LOCM overall. However, risk of intra-arterial iohexol was greater than that of iodixanol. No significant risk reduction after IV administration of CM. In patients with intra-arterial administration and renal insufficiency, risk of CIN was greater for iohexol than for iodixanol. No difference between iodixanol and the other (noniohexol) LOCM.	0.10 (0.61 to 1.04) 0.79 (0.62 to 1.89) <0.01 (0.21 to 0.68) 0.86 (0.50 to 1.78)	RR: 0.80 RR: 1.08 RR: 0.38 RR: 0.95	In this contemporary meta-analysis of 25 trials, the incidence of CIN was similar for a pooled comparison of all nonionic LOCM other than iohexol and for the iso-osmolar medium iodixanol, indicating equivalent safety for these 2 classes of CM.
EARLY-ACS (37); Giugliano et al	To evaluate upstream use of GP IIb/IIIa inhibitor eptifibatide versus provisional eptifibatide administration in the catheterization lab in high-risk patients with NSTEMI ACS.	9,492	Inclusion criteria: Patients at least 18 y of age were randomized within 8–12 h after presentation and assigned to an invasive treatment strategy no sooner than the next calendar day. To qualify as having a high-risk UA/NSTEMI, patients were required to have at least 2 of the following: ST-segment depression or transient ST elevation, elevated biomarker levels (CK-MB or troponin), and age ≥ 60 y. The study protocol was later amended to permit enrollment of patients 50–59 y of age with elevated cardiac biomarker levels and documented vascular disease and clarified the timing of angiography as ≥ 12 h after randomization. Exclusion criteria: Increased risk of bleeding, allergy to heparin or eptifibatide, pregnancy, renal dialysis within previous 30 d, intention of investigator to use a nonheparin anticoagulant, recent use of a GP IIb/IIIa inhibitor, and any other condition that posed increased risk.	The primary efficacy composite endpoint was death of any cause, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 h. The secondary efficacy endpoint was composite of death of any cause or MI within the first 30 d. Safety endpoints included rates of hemorrhage, transfusion, surgical reexploration, stroke, thrombocytopenia, and serious adverse events at 120 h after randomization.	The primary endpoint was less in the early-eptifibatide group (9.3%) versus the delayed-eptifibatide group (10%). At 30 days, the rate of death or MI was 11.2% in the early-eptifibatide group versus 12.3% in the delayed-eptifibatide group. Patients in the early-eptifibatide group experienced higher TIMI major hemorrhage compared with the delayed-eptifibatide group (2.6% versus 1.8%, respectively), higher rates of moderate GUSTO bleeding (6.8% in the early-eptifibatide group versus 4.3% in the delayed-eptifibatide group; $p < 0.001$), less severe GUSTO bleeding (0.8% early-eptifibatide group versus 0.9% in delayed-eptifibatide group; $p = 0.97$), and need for red-cell transfusion was increased in the early-eptifibatide group compared with the delayed-eptifibatide group (8.6% versus 6.7%, respectively; $p = 0.001$).	0.23 (0.80 to 1.06) 0.08 (0.79 to 1.01) 0.02	OR: 0.92 OR: 0.89 OR: 1.42; 95% CI: 1.07 to 1.89	In the setting of frequent early (precatheterization) use of clopidogrel, the administration of early, routine eptifibatide (double-bolus and infusion) did not achieve statistically significant reductions in ischemic events at 96 h (i.e., 8%, primary endpoint) and 30 d (i.e., 11%, secondary endpoint) compared with provisional administration of eptifibatide, given after angiography but before PCI. Early, routine eptifibatide was associated with a greater risk of bleeding. No significant interactions were noted between efficacy endpoints and prespecified baseline characteristics.

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Appendix 7. Continued

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	p Value (95% CI)	OR/HR/RR	Conclusion
ABOARD (120); Montalescot et al	To determine if immediate intervention on admission can result in reduction of MI versus delayed intervention.	252	Inclusion criteria: Presence of at least 2 of the following: ischemic symptoms, ECG abnormalities in at least 2 contiguous leads, or positive troponin, TIMI risk score ≥ 3 . Exclusion criteria: Hemodynamic or arrhythmic instability requiring urgent catheterization, chronic oral anticoagulation, or thrombolytic therapy in the preceding 24 h.	Primary endpoint was peak troponin value during hospitalization. Secondary endpoints were composite of death, MI, or urgent revascularization at 1-mo follow-up.	No difference was found in peak troponin-I between groups (median 2.1 versus 1.7 mg/mL in immediate- and delayed-intervention groups, respectively). Secondary endpoint was seen in 13.7% (95% CI: 8.6% to 18.8%) of immediate-intervention group and 10.2% (95% CI: 5.7% to 14.6%) of delayed-intervention group. The other endpoints did not differ between the 2 strategies.	0.79 0.31		Immediate (at a median of 70 min) versus delayed (at a median of 21 h) angiography and revascularization in UA/NSTEMI patients conferred no advantage with regard to the primary endpoint (myocardial necrosis by TnI), nor did it result in even a trend toward improved outcome in the clinical secondary endpoint of death, MI, or urgent revascularization by 1 mo.
TRITON-TIMI 38 (22); Wiviott et al	To evaluate treatment with prasugrel compared with clopidogrel among patients undergoing planned PCI for ACS.	13,608	Inclusion criteria: Scheduled PCI for ACS. For UA/NSTEMI patients, ischemic symptoms ≥ 10 min within 72 h of randomization, TIMI risk score ≥ 3 , and either ST-segment deviation ≥ 1 mm or elevated cardiac biomarker of necrosis. For STEMI patients, symptom onset within 12 h of randomization if primary PCI was scheduled or within 14 d if medically treated for STEMI. Exclusion criteria: Included increased bleeding risk, anemia, thrombocytopenia, intracranial pathology, or use of any thienopyridine within 5 d.	Primary endpoints were death of CV causes, nonfatal MI, or nonfatal stroke. Key safety endpoint was major bleeding.	Primary endpoint was significantly lower in prasugrel group compared with clopidogrel group (9.9% versus 12.1%, respectively). Primary endpoint was similar in UA/NSTEMI cohort (9.9% with prasugrel versus 12.1% with clopidogrel; 18% RR). Primary endpoint in STEMI cohort (10% in prasugrel versus 12.4% in clopidogrel; 21% RR). Efficacy benefit evident by 3 d (4.7% in prasugrel group versus 5.6% in clopidogrel group). Efficacy benefit from Day 3 to end of follow-up (5.6% in patients receiving prasugrel versus 6.9% of patients receiving clopidogrel). Definite or probable stent thrombosis occurred less frequently in prasugrel group than in clopidogrel group (1.1% versus 2.4%, respectively). Safety endpoint of TIMI major non-CABG bleeding was higher with prasugrel compared with clopidogrel (2.4% versus 1.8%, respectively). Increase in bleeding consistent for different categories of TIMI major bleeding, including life-threatening bleeding (1.4% in prasugrel versus 0.9% in clopidogrel; HR: 1.52; 95% CI: 1.08 to 2.13; $p=0.01$), fatal bleeding (0.4% in prasugrel versus 0.1% in clopidogrel; HR: 4.19; 95% CI: 1.58 to 11.11; $p=0.002$), and nonfatal bleeding (1.1% in prasugrel versus 0.9% in clopidogrel; HR: 1.25; 95% CI: 0.87 to 1.81; $p=0.23$). CABG-related TIMI major bleeding increased with prasugrel compared with clopidogrel (13.4% versus 3.2%, respectively). No difference in mortality (death of any cause) between groups (3.0% in prasugrel group versus 3.2% in clopidogrel group). Net clinical benefit endpoint (composite of death, MI, stroke or TIMI major bleeding) favored prasugrel over clopidogrel (12.2% versus 13.9%, respectively).	<0.001 (0.73 to 0.90) 0.002 (0.73 to 0.93) 0.02 (0.65 to 0.97) 0.01 (0.71 to 0.96) 0.003 (0.70 to 0.93) <0.001 (0.36 to 0.64) 0.03 (1.03 to 1.68) <0.001 (1.90 to 11.82) 0.64 (0.78 to 1.16) 0.004 (0.79 to 0.95)	HR: 0.81 HR: 0.82 HR: 0.79 HR: 0.82 HR: 0.80 HR: 0.48 HR: 1.32 HR: 4.73 HR: 0.95 HR: 0.87	TRITON-TIMI-38 compared the new thienopyridine prasugrel to clopidogrel in 13,608 moderate- to high-risk STEMI and NSTEMI patients scheduled to undergo PCI. Prasugrel was associated with a reduction in the composite ischemic event rate over 15 mo of follow-up, including stent thrombosis, but it was associated with a significantly increased rate of bleeding. In subgroup analyses, those with prior stroke/TIA fared worse on prasugrel, and no advantage was seen in those ≥ 75 y of age or < 60 kg in weight.

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Appendix 7. Continued

Study	Aim of Study	Study Size	Patient Population Inclusion and Exclusion Criteria	Endpoints	Statistical Analysis Reported	p Value (95% CI)	OR/HR/RR	Conclusion
SWEDHEART (161); Szummer et al	To describe distribution of CKD and use of early revascularization, as well as to determine if an invasive approach is associated with lower mortality at every level of renal function.	23,262	Inclusion criteria: NSTEMI patients ≤ 80 y of age from nationwide CCU register (2003 and 2006).	Description of 1-y survival according to renal function stage.	Patients treated with early revascularization had overall improved survival rate at 1 y. 1-y mortality for patients with eGFR ≥ 90 : 1.9% for invasive treatment versus 10% for medical treatment. 1-y mortality for patients with eGFR 60 to 89: 2.4% for invasive treatment versus 10% for medical treatment. 1-y mortality for patients with eGFR 30 to 59: 7% for invasive treatment versus 22% for medical treatment. 1-y mortality for patients with eGFR 15 to 29: 22% for invasive treatment versus 41% for medical treatment. 1-y mortality for patients with eGFR <15 /dialysis: 44% for invasive treatment versus 53% for medical treatment.	<0.001 (0.56 to 0.73) 0.001 (0.42 to 0.80) <0.001 (0.52 to 0.80) 0.001 (0.51 to 1.61) 0.940 (0.51 to 1.61) 0.150 (0.84 to 3.09)	HR: 0.64 HR: 0.58 HR: 0.64 HR: 0.91 HR: 0.91 HR: 1.61	A contemporary nationwide Swedish registry, evaluated the use of early revascularization after NSTEMI across all stages of CKD, and stratified outcomes by stage of CKD. Early revascularization was associated with improved adjusted 1-y survival in UA/NSTEMI patients with mild-to-moderate CKD, but no association was observed in those with severe and end-stage disease. SWEDHEART is limited by its observational nature, but by capturing unselected patients, it may be quite reflective of real-world experience.
COGENT (108); Bhatt et al	To investigate efficacy and safety of concomitant clopidogrel and PPI administration in patients with CAD receiving clopidogrel and ASA.	3,761	Inclusion criteria: Age ≥ 21 y, clopidogrel therapy with concomitant ASA anticipated for at least next 12 mo, including patients with ACS or coronary stent placement. Exclusion criteria: Hospitalized patients for whom discharge not anticipated within 48 h of randomization; need for current/long-term use of PPI, H ₂ -receptor antagonist, sucralfate, or misoprostol; erosive esophagitis or esophageal or gastric variceal disease or previous nonendoscopic gastric surgery; clopidogrel or other thienopyridine >21 d before randomization; receipt of oral anticoagulant unable to be discontinued safely; recent fibrinolytic therapy.	Primary GI safety endpoint: composite of GI overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstructions, or perforation. Primary CV safety endpoint: composite of death of CV causes, nonfatal MI, coronary revascularization, or ischemic stroke.	Total GI event rate: 1.1% with omeprazole versus 2.9% with placebo. Overt upper GI bleeding rate: 0.1% with omeprazole versus 0.6% with placebo. Total CV event rate: 4.9% with omeprazole versus 5.7% with placebo.	<0.001 (0.18 to 0.63) 0.001 (0.03 to 0.56) 0.96 (0.68 to 1.44)	HR: 0.34 HR: 0.13 HR: 0.99	In this randomized, placebo controlled comparison in 3873 patients with an indication for dual-antiplatelet therapy, no difference was found in the primary composite CV endpoint between clopidogrel plus omeprazole and clopidogrel plus placebo at 180 d. The rate of GI bleeding and associated complications were reduced with omeprazole. Study limitations include premature termination of planned enrollment, limited power to discern small to moderate differences between therapies, and the use of a single-pill formulation, which might differ in release kinetics for its 2 components.

ACS indicates acute coronary syndrome; ARC, academic research consortium; ASA, aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCU, coronary care unit; CHF, congestive heart failure; CI-AKI, contrast-induced acute kidney injury; CI, confidence interval; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; CM, contrast media; CURRENT, Clopidogrel optimal loading dose Usage to Reduce Recurrent Events; CV, cardiovascular; DES, drug-eluting stent; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; HR, hazard ratio; IV, intravenous; LD, loading dose; LOCM, low-osmolar contrast media; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTE, non-ST-elevation; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, relative risk; Scr, serum creatinine; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I; UA, unstable angina; and ULN, upper limit of normal.

Appendix 8. Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy (2) Reprinted from Anderson et al (2).

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

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

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