2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary

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2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary

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

Developed in Collaboration With the Society of Thoracic Surgeons

Endorsed by the American Association for Clinical Chemistry

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information. †ACC/AHA Representative. ‡ACC/AHA Task Force on Practice Guidelines Liaison. §American College of Physicians Representative. ‖American Academy of Family Physicians Representative. ¶Society of Thoracic Surgeons Representative. #ACC/AHA Task Force on Performance Measures Liaison. **Society for Cardiovascular Angiography and Interventions Representative. ††Former Task Force member; current member during the writing effort.

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Preamble

The American College of Cardiology (ACC) and the American Heart Association (AHA) are committed to the prevention and management of cardiovascular diseases through professional education and research for clinicians, providers, and patients. Since 1980, the ACC and AHA have shared a responsibility to translate scientific evidence into clinical practice guidelines (CPGs) with recommendations to standardize and improve cardiovascular health. These CPGs, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care.

In response to published reports from the Institute of Medicine (1, 2) and the ACC/AHA's mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Practice Guidelines (Task Force) began modifying its methodology. This modernization effort is published in the 2012 Methodology Summit Report (3) and 2014 perspective article (4). The latter recounts the history of the collaboration, changes over time, current policies, and planned initiatives to meet the needs of an evolving healthcare environment. Recommendations on value in proportion to resource utilization will be incorporated as high-quality comparative-effectiveness data become available (5). The relationships between CPGs and data standards, appropriate use criteria, and performance measures are addressed elsewhere (4).

Intended Use—CPGs provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but CPGs developed in collaboration with other organizations may have a broader target. Although CPGs may be used to inform regulatory or payer decisions, the intent is to improve the quality of care and be aligned with the patient's best interest.

Evidence Review—Guideline writing committee (GWC) members are charged with reviewing the literature; weighing the strength and quality of evidence for or against particular tests, treatments, or procedures; and estimating expected health outcomes when data exist. In analyzing the data and developing CPGs, the GWC uses evidence-based methodologies developed by the Task Force (6). A key component of the ACC/AHA CPG methodology is the development of recommendations on the basis of all available evidence. Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only selected references are cited in the CPG. To ensure that CPGs remain current, new data are reviewed biannually by the GWCs and the Task Force to determine if recommendations should be updated or modified. In general, a target cycle of 5 years is planned for full revisions (1).

Guideline-Directed Medical Therapy—Recognizing advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force designated the term "guideline-directed medical therapy" (GDMT) to represent recommended medical therapy as defined mainly by Class I measures, generally a combination of lifestyle modification and drug- and device-based therapeutics. As medical science advances, GDMT evolves, and hence GDMT is preferred to "optimal medical therapy." For GDMT and all other recommended drug treatment regimens, the reader should confirm the dosage with product insert material and carefully evaluate for contraindications and possible drug interactions. Recommendations are limited to treatments, drugs, and devices approved for clinical use in the United States.

Class of Recommendation and Level of Evidence—Once recommendations are written, the Class of Recommendation (COR; i.e., the strength the GWC assigns to the recommendation, which encompasses the anticipated magnitude and judged certainty of benefit in proportion to risk) is assigned by the GWC. Concurrently, the Level of Evidence (LOE) rates the scientific evidence supporting the effect of the intervention on the basis on the type, quality, quantity, and consistency of data from clinical trials and other reports (Table 1) (4). Unless otherwise stated, recommendations are presented in order by the COR and then the LOE. Where comparative data exist, preferred strategies take precedence. When more than 1 drug, strategy, or therapy exists within the same COR and LOE and there are no comparative data, options are listed alphabetically.

Relationships With Industry and Other Entities—The ACC and AHA exclusively sponsor the work of GWCs without commercial support, and members volunteer their time for this activity. The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All GWC members and reviewers are required to fully disclose current industry relationships or personal interests from 12 months before initiation of the writing effort. Management of RWI involves selecting a balanced GWC and requires that both the chair and a majority of GWC members have no relevant RWI (see Appendix 1 for the definition of relevance). GWC members are restricted with regard to writing or voting on sections to which their RWI apply. In addition, for transparency, GWC members' comprehensive disclosure information is available as an online supplement (http://jaccjacc.cardiosource.com/acc_documents/2014_NSTE-ACS_Comprehensive_RWI.pdf). Comprehensive disclosure information for the Task Force is also available at (http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx). The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. Selected organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

Individualizing Care in Patients With Associated Conditions and Comorbidities—The ACC and AHA recognize the complexity of managing patients with multiple conditions, compared with managing patients with a single disease, and the challenge is compounded when CPGs for evaluation or treatment of several coexisting illnesses are discordant or interacting (7). CPGs attempt to define practices that meet the needs of patients in most, but not all, circumstances and do not replace clinical judgment.

Clinical Implementation—Management in accordance with CPG recommendations is effective only when followed; therefore, to enhance their commitment to treatment and compliance with lifestyle adjustment, clinicians should engage the patient to participate in selecting interventions on the basis of the patient's individual values and preferences, taking associated conditions and comorbidities into consideration (e.g., shared decision making). Consequently, there are circumstances in which deviations from these guidelines are appropriate.

The recommendations in this CPG are the official policy of the ACC and AHA until they are superseded by a published addendum, focused update, or revised full-text CPG. The reader is encouraged to consult the full-text CPG (8) for additional guidance and details about the management of patients with non–ST-elevation acute coronary syndrome (NSTE-ACS) because the executive summary contains mainly the recommendations.

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

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT

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

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the clinical practice guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this CPG are, whenever possible, evidence based. An extensive evidence review was conducted through October 2012, and other selected references published through April 2014 were reviewed by the GWC. Literature included was derived from research involving human subjects, published in

English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this CPG. The relevant data are included in evidence tables in the Data Supplement available online at (http://jaccjacc.cardiosource.com/acc_documents/2014_NSTE-ACS_Data_Supplement_Tables.pdf). Key search words included but were not limited to the following: *acute coronary syndrome, anticoagulant therapy, antihypertensives, anti-ischemic therapy, antiplatelet therapy, antithrombotic therapy, beta blockers, biomarkers, calcium channel blockers, cardiac rehabilitation, conservative management, diabetes mellitus, glycoprotein IIb/IIIa inhibitors, heart failure, invasive strategy, lifestyle modification, myocardial infarction, nitrates, non-ST elevation, $P2Y_{12}$ receptor inhibitor, percutaneous coronary intervention, renin-angiotensin-aldosterone inhibitors, secondary prevention, smoking cessation, statins, stent, thienopyridines, troponins, unstable angina,* and *weight management.* Additionally, the GWC reviewed documents related to NSTE-ACS previously published by the ACC and AHA. References selected and published in this document are representative and not all-inclusive.

1.2. Organization of the GWC

The GWC was composed of clinicians, cardiologists, internists, interventionists, surgeons, emergency medicine specialists, family practitioners, and geriatricians. The GWC included representatives from the ACC and AHA, American Academy of Family Physicians, American College of Emergency Physicians, American College of Physicians, Society for Cardiovascular Angiography and Interventions (SCAI), and Society of Thoracic Surgeons.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA; 1 reviewer each from the American Academy of Family Physicians, American College of Emergency Physicians, SCAI, and STS; and 37 individual content reviewers (including members of the American Association of Clinical Chemistry, ACC Heart Failure and Transplant Section Leadership Council, ACC Cardiovascular Imaging Section Leadership Council, ACC Interventional Section Leadership Council, ACC Prevention of Cardiovascular Disease Committee, ACC Surgeons' Council, Association of International Governors, and Department of Health and Human Services). Reviewers' RWI information was distributed to the GWC and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and endorsed by the American Association for Clinical Chemistry and the Society of Thoracic Surgeons.

1.4. Scope of the CPG

The 2014 NSTE-ACS CPG is a full revision of the 2007 ACCF/AHA CPG for the management of patients with unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI) and the 2012 focused update (9).

The new title, "Non–ST-Elevation Acute Coronary Syndromes," emphasizes the continuum between UA and NSTEMI. At presentation, patients with UA and NSTEMI can be indistinguishable and are therefore considered together in this CPG.

In the United States, NSTE-ACS affects >625,000 patients annually,* or almost three fourths of all patients with acute coronary syndrome (ACS) (10). In selecting the initial approach to care, the term "ischemia-guided strategy" has replaced the previous descriptor, "initial conservative management," to more clearly convey the physiological rationale of this approach.

The task of the 2014 GWC was to establish a contemporary CPG for the optimal management of patients with NSTE-ACS. It incorporates both established and new evidence from published clinical trials, as well as information from basic science and comprehensive review articles. These recommendations were developed to guide the clinician in improving outcomes for patients with NSTE-ACS. Table 2 lists documents deemed pertinent to this effort and is intended for use as a resource, thus obviating the need to repeat extant CPG recommendations.

The GWC abbreviated the discussion sections to include an explanation of salient information related to the recommendations. In contrast to textbook declaratory presentations, explanations were supplemented with evidence tables. The GWC also provided a brief summary of the relevant recommendations and references related to secondary prevention rather than detailed reiteration. Throughout, the goal was to provide the clinician with concise, evidence-based contemporary recommendations and the supporting documentation to encourage their application.

Table 2. Associated CPGs and Statements

Title	Organization	Publication Year (Reference)
CPGs		
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/ SCAI/STS	2014 (11)* 2012 (12)
Atrial fibrillation	AHA/ACC/HRS	2014 (13)
Assessment of cardiovascular risk	ACC/AHA	2013 (14)
Heart failure	ACC/AHA	2013 (15)
Lifestyle management to reduce cardiovascular risk	AHA/ACC	2013 (16)
Management of overweight and obesity in adults	AHA/ACC/TOS	2013 (17)
ST-elevation myocardial infarction	ACC/AHA	2013 (18)
Treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults	ACC/AHA	2013 (19)
Acute myocardial infarction in patients presenting with ST-segment elevation	ESC	2012 (20)
Device-based therapy	ACC/AHA/HRS	2013 (21)
Third universal definition of myocardial infarction	ESC/ACC/AHA/WHF	2012 (22)
Acute coronary syndromes in patients presenting without persistent ST-segment elevation	ESC	2011 (23)
Coronary artery bypass graft surgery	ACC/AHA	2011 (24)
Hypertrophic cardiomyopathy	ACC/AHA	2011 (25)

*Estimate includes secondary discharge diagnoses.

Effectiveness-based guidelines for the prevention of cardiovascular disease in women	AHA/ACC	2011 (26)
Percutaneous coronary intervention	ACC/AHA/SCAI	2011 (27)
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 (28)
Assessment of cardiovascular risk in asymptomatic adults	ACC/AHA	2010 (29)
Myocardial revascularization	ESC	2010 (30)
Unstable angina and non–ST-elevation myocardial infarction	NICE	2010† (31)
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care—Part 9: postcardiac arrest care	AHA	2010 (32)
Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure	NHLBI	2003 (33)
Statements		
Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease	ACC/AHA	2013 (34)
Practical clinical considerations in the interpretation of troponin elevations	ACC	2012 (35)
Testing of low-risk patients presenting to the emergency department with chest pain	AHA	2010 (36)
Primary prevention of cardiovascular diseases in people with diabetes mellitus	AHA/ADA	2007 (37)
Prevention and control of influenza	CDC	2005 (38)

*The full-text SIHD CPG is from 2012 (12). A focused update was published in 2014 (11).
†Minor modifications were made in 2013. For a full explanation of the changes, see http://publications.nice.org.uk/unstable-angina-and-nstemi-cg94/changes-after-publication.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; CDC, Centers for Disease Control and Prevention; CPG, clinical practice guideline; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Clinical Excellence; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; SIHD, stable ischemic heart disease; STS, Society of Thoracic Surgeons; TOS, The Obesity Society; and WHF, World Heart Federation.

2. Overview of ACS

ACS has evolved as a useful operational term that refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction due to an abrupt reduction in coronary blood flow (Figure 1).

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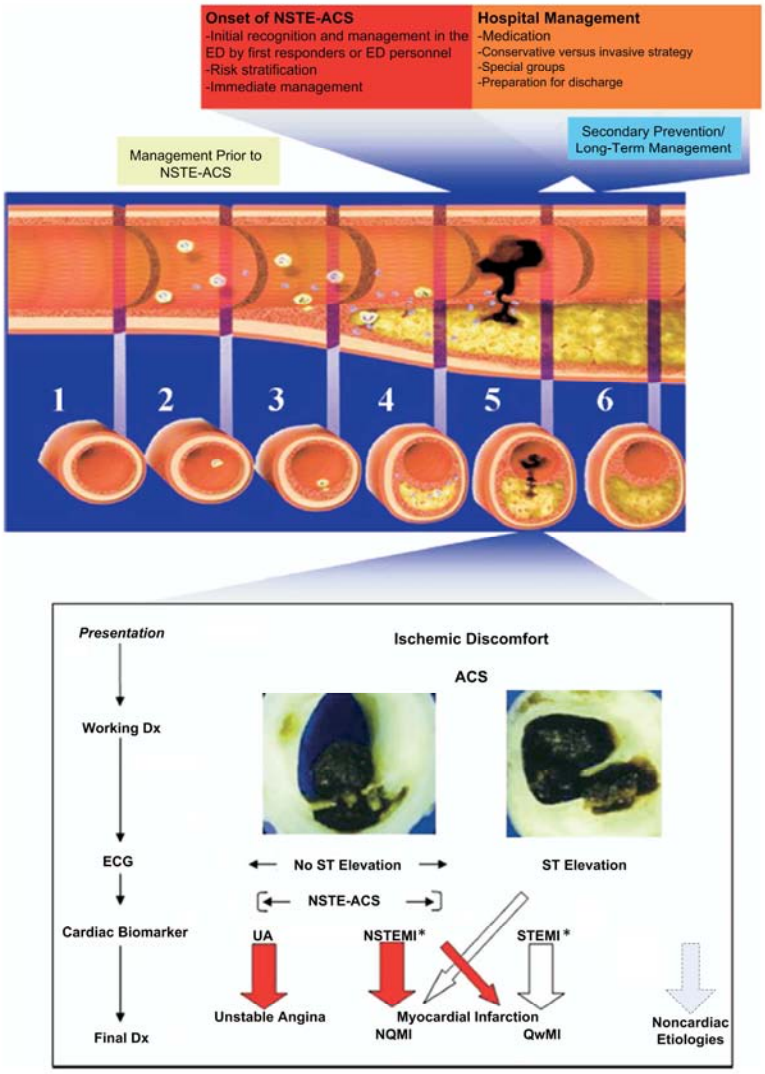
Figure 1. Acute Coronary Syndromes



The top half of the figure illustrates the progression of plaque formation and onset and complications of NSTE-ACS, with management at each stage. The numbered section of an artery depicts the process of atherogenesis from 1) normal artery to 2) extracellular lipid in the subintima to 3) fibrofatty stage to 4) procoagulant expression and weakening of the fibrous cap. ACS develops with 5) disruption of the fibrous cap, which is the stimulus for thrombogenesis. 6) Thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth. Thrombus formation and possible coronary vasospasm reduce blood flow in the affected coronary artery and cause ischemic chest pain.

The bottom half of the figure illustrates the clinical, pathological, electrocardiographic, and biomarker correlates in ACS and the general approach to management. Flow reduction may be related to a completely occlusive thrombus (bottom half, right side) or subtotally occlusive thrombus (bottom half, left side). Most patients with ST elevation (thick white arrow in bottom panel) develop QwMI, and a few (thin white arrow) develop NQMI. Those without ST elevation have either UA or NSTEMI (thick red arrows), a distinction based on cardiac biomarkers. Most patients presenting with NSTEMI develop NQMI; a few may develop QwMI. The spectrum of clinical presentations including UA, NSTEMI, and STEMI is referred

to as ACS. This NSTE-ACS CPG includes sections on initial management before NSTE-ACS, at the onset of NSTE-ACS, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase. Patients with noncardiac etiologies make up the largest group presenting to the ED with chest pain (dashed arrow).

*Elevated cardiac biomarker (e.g., troponin), Section 3.4.
ACS indicates acute coronary syndrome; CPG, clinical practice guideline; Dx, diagnosis; ECG, electrocardiogram; ED, emergency department; MI, myocardial infarction; NQMI, non–Q-wave myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndromes; NSTEMI, non–ST-elevation myocardial infarction; QwMI, Q-wave myocardial infarction; STEMI, ST-elevation myocardial infarction; and UA, unstable angina.
Modified with permission from Libby et al (39).

3. Initial Evaluation and Management: Recommendations

3.1. Clinical Assessment and Initial Evaluation

Class I

1. **Patients with suspected ACS should be risk stratified based on the likelihood of ACS and adverse outcome(s) to decide on the need for hospitalization and assist in the selection of treatment options (40-42).** ***(Level of Evidence: B)***

3.2. Emergency Department or Outpatient Facility Presentation

Class I

1. **Patients with suspected ACS and high-risk features such as continuing chest pain, severe dyspnea, syncope/presyncope, or palpitations should be referred immediately to the emergency department (ED) and transported by emergency medical services when available.** ***(Level of Evidence: C)***

Class IIb

1. **Patients with less severe symptoms may be considered for referral to the ED, a chest pain unit, or a facility capable of performing adequate evaluation depending on clinical circumstances.** ***(Level of Evidence: C)***

3.3. Prognosis—Early Risk Stratification

See Table 4 for a summary of recommendations from this section.

Class I

1. **In patients with chest pain or other symptoms suggestive of ACS, a 12-lead electrocardiogram (ECG) should be performed and evaluated for ischemic changes within 10 minutes of the patient's arrival at an emergency facility (22).** ***(Level of Evidence: C)***
2. **If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, serial ECGs (e.g., 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes.** ***(Level of Evidence: C)***
3. **Serial cardiac troponin I or T levels (when a contemporary assay is used) should be obtained at presentation and 3 to 6 hours after symptom onset (see Section 3.4.1, Class I, #3 recommendation if time of symptom onset is unclear) in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern of values (22, 43-48).** ***(Level of Evidence: A)***
4. **Additional troponin levels should be obtained beyond 6 hours after symptom onset (see Section 3.4.1, Class I, #3 recommendation if time of symptom onset is unclear) in patients with normal**

troponin levels on serial examination when changes on ECG and/or clinical presentation confer an intermediate or high index of suspicion for ACS (22, 49-51). ***(Level of Evidence: A)***

5. **Risk scores should be used to assess prognosis in patients with NSTE-ACS (40-42, 52-57).** ***(Level of Evidence: A)***

Class IIa

1. **Risk-stratification models can be useful in management (40-42, 52-58).** ***(Level of Evidence: B)***
2. **It is reasonable to obtain supplemental electrocardiographic leads V_7 to V_9 in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS (59-61).** ***(Level of Evidence: B)***

Class IIb

1. **Continuous monitoring with 12-lead ECG may be a reasonable alternative in patients whose initial ECG is nondiagnostic and who are at intermediate/high risk of ACS (62, 63).** ***(Level of Evidence: B)***
2. **Measurement of B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide may be considered to assess risk in patients with suspected ACS (64-68). (*Level of Evidence: B)***

Table 3. TIMI Risk Score* for NSTE-ACS

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0–1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6–7	40.9

*The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: ≥65 y of age; ≥3 risk factors for CAD; prior coronary stenosis ≥50%; ST deviation on ECG; ≥2 anginal events in prior 24 h; use of aspirin in prior 7 d; and elevated cardiac biomarkers.

CAD indicates coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndromes; and TIMI, Thrombolysis In Myocardial Infarction.
Modified with permission from Antman et al. (40).

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Figure 2. Global Registry of Acute Coronary Events Risk Calculator for In-Hospital Mortality for Acute Coronary Syndrome

A. GRACE Risk Model Nomogram

1. Find Points for Each Predictive Factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0-0.39	1
II	20	80-99	53	50-69	3	30-39	8	0.40-0.79	4
III	39	100-119	43	70-89	9	40-49	25	0.80-1.19	7
IV	59	120-139	34	90-109	15	50-59	41	1.20-1.59	10
		140-159	24	110-149	24	60-69	58	1.60-1.99	13
		160-199	10	150-199	38	70-79	75	2.00-3.99	21
		≥200	0	≥200	46	80-89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum Points for All Predictive Factors:

Killip Class + SBP + Heart Rate + Age + Creatinine Level + Cardiac Arrest at Admission + ST-Segment Deviation + Elevated Cardiac Enzyme Levels = Total Points

3. Look Up Risk Corresponding to Total Points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.

His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196

This person would have about a 16% risk of having an in-hospital death.

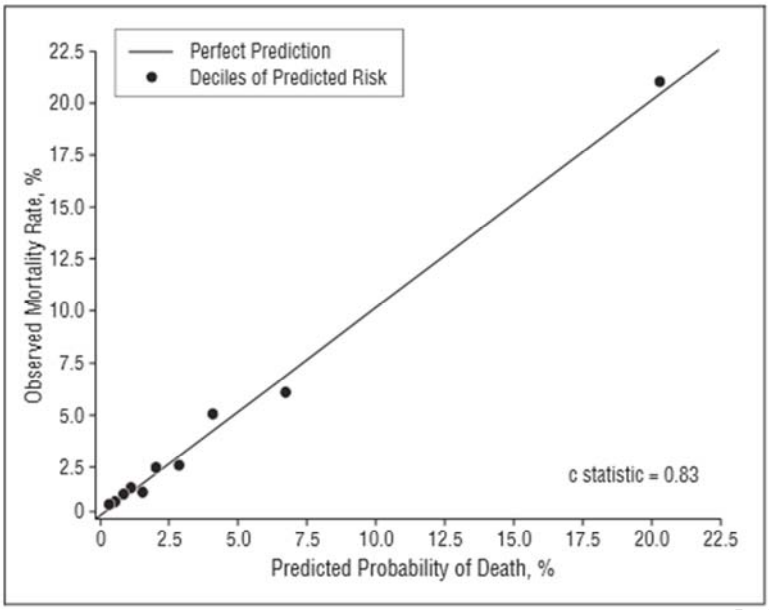
Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4, and no risk factors would have the following score:

0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

To convert serum creatine level to micromoles per liter, multiply by 88.4.

SBP indicates systolic blood pressure.
Reprinted with permission from Granger et al. (69).

B. Calibration of Simplified Global Registry of ACS Mortality Model



ACS indicates acute coronary syndrome.
Reprinted with permission from Granger et al. (69).

Table 4. Summary of Recommendations for Prognosis: Early Risk Stratification

Recommendations	COR	LOE	References
Perform rapid determination of likelihood of ACS, including a 12-lead ECG within 10 min of arrival at an emergency facility, in patients whose symptoms suggest ACS	I	C	(22)
Perform serial ECGs at 15- to 30-min intervals during the first hour in symptomatic patients with initial nondiagnostic ECG	I	C	N/A
Measure cardiac troponin (cTnI or cTnT) in all patients with symptoms consistent with ACS*	I	A	(22, 43-48)
Measure serial cardiac troponin I or T at presentation and 3–6 h after symptom onset* in all patients with symptoms consistent with ACS	I	A	(22, 49-51)
Use risk scores to assess prognosis in patients with NSTE-ACS	I	A	(40-42, 52-57)
Risk-stratification models can be useful in management	IIa	B	(40-42, 52-58)
Obtain supplemental electrocardiographic leads V_7 to V_9 in patients with initial nondiagnostic ECG at intermediate/high risk for ACS	IIa	B	(59-61)
Continuous monitoring with 12-lead ECG may be a reasonable alternative with initial nondiagnostic ECG in patients at intermediate/high risk for ACS	IIb	B	(62, 63)
BNP or NT–pro-BNP may be considered to assess risk in patients with suspected ACS	IIb	B	(64-68)

*See Section 3.4.1, Class I, #3 recommendation if time of symptom onset is unclear.

ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; COR, Class of Recommendation; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ECG, electrocardiogram; LOE, Level of Evidence; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndromes; and NT–pro-BNP, N-terminal pro–B-type natriuretic peptide.

3.4. Cardiac Biomarkers and the Universal Definition of Myocardial Infarction

See Table 5 for a summary of recommendations from this section.

3.4.1. Biomarkers: Diagnosis

Class I

1. **Cardiac-specific troponin (troponin I or T when a contemporary assay is used) levels should be measured at presentation and 3 to 6 hours after symptom onset in all patients who present with symptoms consistent with ACS to identify a rising and/or falling pattern (22, 43-48, 70-74). *(Level of Evidence: A)***
2. **Additional troponin levels should be obtained beyond 6 hours after symptom onset in patients with normal troponins on serial examination when electrocardiographic changes and/or clinical presentation confer an intermediate or high index of suspicion for ACS (22, 49-51, 75). *(Level of Evidence: A)***
3. **If the time of symptom onset is ambiguous, the time of presentation should be considered the time of onset for assessing troponin values (44, 45, 49). *(Level of Evidence: A)***

Class III: No Benefit

1. **With contemporary troponin assays, creatine kinase myocardial isoenzyme (CK-MB) and myoglobin are not useful for diagnosis of ACS (76-82). *(Level of Evidence: A)***

3.4.2. Biomarkers: Prognosis

Class I

1. **The presence and magnitude of troponin elevations are useful for short- and long-term prognosis (48, 50, 83, 84). *(Level of Evidence: B)***

Class IIb

1. **It may be reasonable to remeasure troponin once on day 3 or day 4 in patients with a myocardial infarction (MI) as an index of infarct size and dynamics of necrosis (82, 83). *(Level of Evidence: B)***
2. **Use of selected newer biomarkers, especially B-type natriuretic peptide, may be reasonable to provide additional prognostic information (64, 65, 85-89). *(Level of Evidence: B)***

Table 5. Summary of Recommendations for Cardiac Biomarkers and the Universal Definition of MI

Recommendations	COR	LOE	References
Diagnosis			
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values	I	A	(22, 43-48, 70-74)
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A	(22, 49-51, 75)
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A	(44, 45, 49)
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A	(76-82)
Prognosis			
Troponin elevations are useful for short- and long-term prognosis	I	B	(48, 50, 83, 84)
Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis	IIb	B	(82, 83)
BNP may be reasonable for additional prognostic information	IIb	B	(64, 65, 85-89)

ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; CK-MB, creatine kinase myocardial isoenzyme; COR, Class of Recommendation; LOE, Level of Evidence; and MI, myocardial infarction.

3.5. Discharge From the ED or Chest Pain Unit

Class IIa

1. **It is reasonable to observe patients with symptoms consistent with ACS without objective evidence of myocardial ischemia (nonischemic initial ECG and normal cardiac troponin) in a chest pain unit or telemetry unit with serial ECGs and cardiac troponin at 3- to 6-hour intervals (90-94). *(Level of Evidence: B)***
2. **It is reasonable for patients with possible ACS who have normal serial ECGs and cardiac troponins to have a treadmill ECG (93-95) (*Level of Evidence: A*), stress myocardial perfusion imaging (93), or stress echocardiography (96, 97) before discharge or within 72 hours after discharge. *(Level of Evidence: B)***
3. **In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of coronary artery disease (CAD), it is reasonable to initially perform (without serial ECGs and troponins) coronary computed tomography angiography to assess coronary artery anatomy (98-100) *(Level of Evidence: A)* or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia (101, 102). *(Level of Evidence: B)***
4. **It is reasonable to give low-risk patients who are referred for outpatient testing daily aspirin, short-acting nitroglycerin, and other medication if appropriate (e.g., beta blockers), with instructions about activity level and clinician follow-up. *(Level of Evidence: C)***

4. Early Hospital Care: Recommendations

See Table 6 for a summary of recommendations from this section.

4.1. Standard Medical Therapies

4.1.1. Oxygen

Class I

1. **Supplemental oxygen should be administered to patients with NSTE-ACS with arterial oxygen saturation less than 90%, respiratory distress, or other high-risk features of hypoxemia. *(Level of Evidence: C)***

4.1.2. Nitrates

Class I

1. **Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 mg–0.4 mg) every 5 minutes for up to 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin if not contraindicated (103-105). *(Level of Evidence: C)***
2. **Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure (HF), or hypertension (106-111). *(Level of Evidence: B)***

Class III: Harm

1. **Nitrates should not be administered to patients with NSTE-ACS who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil (112-114). *(Level of Evidence: B)***

4.1.3. Analgesic Therapy

Class IIb

1. **In the absence of contraindications, it may be reasonable to administer morphine sulfate intravenously to patients with NSTE-ACS if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications (115, 116).** ***(Level of Evidence: B)***

Class III: Harm

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use (117, 118).** ***(Level of Evidence: B)***

4.1.4. Beta-Adrenergic Blockers

Class I

1. **Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) (119-121).** ***(Level of Evidence: A)***
2. **In patients with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function, it is recommended to continue beta-blocker therapy with 1 of the 3 drugs proven to reduce mortality in patients with HF: sustained-release metoprolol succinate, carvedilol, or bisoprolol.** ***(Level of Evidence: C)***
3. **Patients with documented contraindications to beta blockers in the first 24 hours of NSTE-ACS should be reevaluated to determine their subsequent eligibility.** ***(Level of Evidence: C)***

Class IIa

1. **It is reasonable to continue beta-blocker therapy in patients with normal left ventricular (LV) function with NSTE-ACS (120, 122).** ***(Level of Evidence: C)***

Class III: Harm

1. **Administration of intravenous beta blockers is potentially harmful in patients with NSTE-ACS who have risk factors for shock (123).** ***(Level of Evidence: B)***

4.1.5. Calcium Channel Blockers

Class I

1. **In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta blockers, a nondihydropyridine calcium channel blocker (CCB) (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval greater than 0.24 second, or second- or third-degree atrioventricular block without a cardiac pacemaker (124-126).** ***(Level of Evidence: B)***
2. **Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta blockers and nitrates.** ***(Level of Evidence: C)***
3. **CCBs[†] are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects.** ***(Level of Evidence: C)***
4. **Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm.** ***(Level of Evidence: C)***

[†]Short-acting dihydropyridine calcium channel antagonists should be avoided.

Class III: Harm

1. **Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy (127, 128). *(Level of Evidence: B)***

4.1.6. Cholesterol Management

Class I

1. **High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use (129-133). (*Level of Evidence: A*)**

Class IIa

1. **It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. (*Level of Evidence: C*)**

Table 6. Summary of Recommendations for Early Hospital Care

Recommendations	COR	LOE	References
Oxygen			
Administer supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxemia	I	C	N/A
Nitrates			
Administer sublingual NTG every 5 min × 3 for continuing ischemic pain and then assess need for IV NTG	I	C	(103-105)
Administer IV NTG for persistent ischemia, HF, or hypertension	I	B	(106-111)
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III: Harm	B	(112-114)
Analgesic therapy			
IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications	IIb	B	(115, 116)
NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use	III: Harm	B	(117, 118)
Beta-adrenergic blockers			
Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade	I	A	(119-121)
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function	I	C	N/A
Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers	I	C	N/A
It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS	IIa	C	(120, 122)
IV beta blockers are potentially harmful when risk factors for shock are present	III: Harm	B	(123)
CCBs			
Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker	I	B	(124-126)
Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications	I	C	N/A
CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*	I	C	N/A
Long-acting CCBs and nitrates are recommended for patients with coronary	I	C	N/A

artery spasm			
Immediate-release nifedipine is contraindicated in the absence of a beta blocker	III: Harm	B	(127, 128)
Cholesterol management			
Initiate or continue high-intensity statin therapy in patients with no contraindications	I	A	(129-133)
Obtain a fasting lipid profile, preferably within 24 h	IIa	C	N/A

*Short-acting dihydropyridine calcium channel antagonists should be avoided.

CCB indicates calcium channel blocker; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; MACE, major adverse cardiac event; N/A, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-elevation acute coronary syndromes; and NTG, nitroglycerin.

4.2. Inhibitors of Renin-Angiotensin-Aldosterone System

Class I

1. **Angiotensin-converting enzyme (ACE) inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction (LVEF) less than 0.40 and in those with hypertension, diabetes mellitus, or stable chronic kidney disease (CKD) (Section 7.6), unless contraindicated (134, 135). (*Level of Evidence: A*)**
2. **Angiotensin receptor blockers are recommended in patients with HF or MI with LVEF less than 0.40 who are ACE inhibitor intolerant (136, 137). (*Level of Evidence: A*)**
3. **Aldosterone blockade is recommended in post–MI patients who are without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta blocker and have a LVEF 0.40 or less, diabetes mellitus, or HF (138). *(Level of Evidence: A)***

Class IIa

1. **Angiotensin receptor blockers are reasonable in other patients with cardiac or other vascular disease who are ACE inhibitor intolerant (139). (*Level of Evidence: B*)**

Class IIb

1. **ACE inhibitors may be reasonable in all other patients with cardiac or other vascular disease (140, 141). (*Level of Evidence: B*)**

4.3. Initial Antiplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS

4.3.1. Initial Oral and Intravenous Antiplatelet Therapy in Patients With Definite or Likely NSTE-ACS Treated With an Initial Invasive or Ischemia-Guided Strategy

See Table 7 for a summary of recommendations from this section.

Class I[‡]

1. **Non–enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to *all* patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg/d to 162 mg/d) should be continued indefinitely (142-144). *(Level of Evidence: A)***
2. **In patients with NSTE-ACS who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered (145). (*Level of Evidence: B*)**

[‡]See Section 5.1 for recommendations at the time of PCI.

3. **A $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with either an early invasive[§] or ischemia-guided strategy. Options include:**
    - **Clopidogrel: 300-mg or 600-mg loading dose, then 75 mg daily (143, 146) *(Level of Evidence: B)***
    - **Ticagrelor[‖]: 180-mg loading dose, then 90 mg twice daily (147, 148) *(Level of Evidence: B)***

Class IIa

1. **It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy (147, 148). *(Level of Evidence: B)***

Class IIb

1. **In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a glycoprotein (GP) IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban (41, 149, 150). *(Level of Evidence: B)***

4.3.2. Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS

See Table 7 for a summary of recommendations from this section.

Class I[‡]

1. **In patients with NSTE-ACS, anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:**
    - **Enoxaparin: 1 mg/kg subcutaneous (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until percutaneous coronary intervention (PCI) is performed. An initial intravenous loading dose is 30 mg (151-153). *(Level of Evidence: A)***
    - **Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor, provided the patient is also treated with DAPT (146, 147, 154, 155). *(Level of Evidence: B)***
    - **Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed (156-158). *(Level of Evidence: B)***
    - **If PCI is performed while the patient is on fondaparinux, an additional anticoagulant with anti-IIa activity (either UFH or bivalirudin) should be administered because of the risk of catheter thrombosis (157-159). *(Level of Evidence: B)***
    - **UFH IV: initial loading dose of 60 IU/kg (maximum 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time to maintain therapeutic anticoagulation according to the specific hospital protocol, continued for 48 hours or until PCI is performed (160-166). *(Level of Evidence: B)***

Class III: Harm

1. **In patients with NSTE-ACS (i.e., without ST elevation, true posterior MI, or left bundle-branch block not known to be old), intravenous fibrinolytic therapy should not be used (167, 168). *(Level of Evidence: A)***

[§]See Section 4.3.1.2 in the full-text CPG for prasugrel indications in either an early invasive or ischemia-guided strategy.
[‖]The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (144).
[‡]See Section 5.1 for recommendations at the time of PCI.

Table 7. Summary of Recommendations for Initial Antiplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS and PCI

See Section 5.1 for recommendations on antiplatelet/anticoagulant therapy at the time of PCI and Sections 6.2 and 6.3 for recommendations on posthospital therapy.

Recommendations	Dosing and Special Considerations	COR	LOE	References
Aspirin				
• Non–enteric-coated aspirin to *all* patients promptly after presentation	162 mg–325 mg	I	A	(142-144)
• Aspirin maintenance dose continued indefinitely	81 mg/d–162 mg/d	I	A	(142-144)
$P2Y_{12}$ inhibitors				
• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B	(145)
• $P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy:		I	B	
– Clopidogrel	300-mg or 600-mg loading dose, then 75 mg/d			(143, 146)
– Ticagrelor*	180-mg loading dose, then 90 mg BID			(147, 148)
• $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post–PCI patients treated with coronary stents	N/A	I	B	(147, 169-172)
• Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B	(147, 148)
GP IIb/IIIa inhibitors				
• GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	• Preferred options are eptifibatide or tirofiban	IIb	B	(41, 149, 150)
Parenteral anticoagulant and fibrinolytic therapy				
• SC enoxaparin for duration of hospitalization or until PCI is performed	• 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min) • Initial IV loading dose 30 mg	I	A	(151-153)
• Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	• Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h • Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I	B	(146, 147, 154, 155)
• SC fondaparinux for the duration of hospitalization or until PCI is performed	• 2.5 mg SC daily	I	B	(156-158)
• Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B	(157-159)
• IV UFH for 48 h or until PCI is performed	• Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000	I	B	(160-166)

	IU/h) • Adjusted to therapeutic aPTT range			
• IV fibrinolytic treatment not recommended in patients with NSTE-ACS	N/A	III: Harm	A	(167, 168)

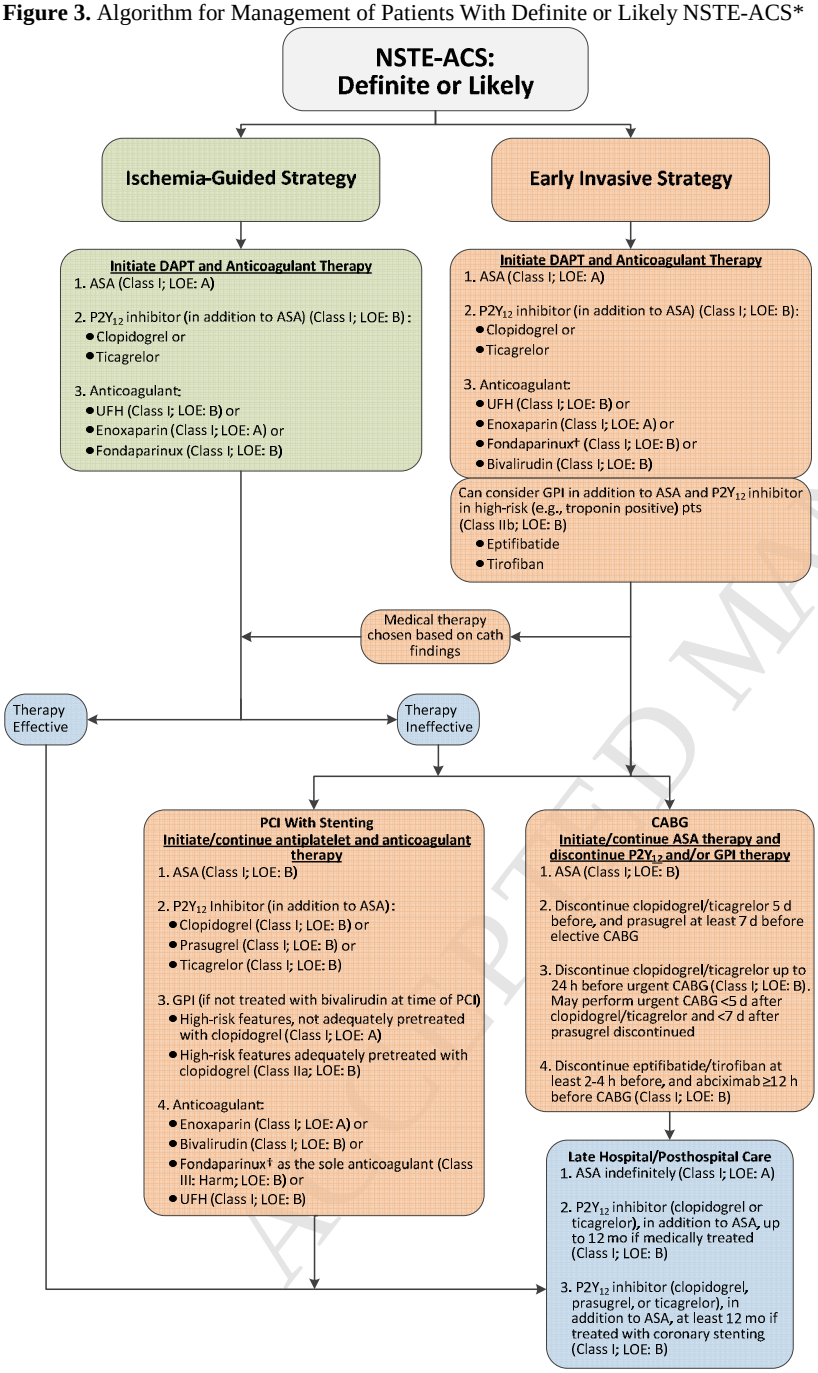
*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (144).

aPTT indicates activated partial thromboplastin time; BID, twice daily; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; GP, glycoprotein; IV, intravenous; LOE, Level of Evidence; max, maximum; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin.

4.4. Ischemia-Guided Strategy Versus Early Invasive Strategies

See Figure 3 for the management algorithm for ischemia-guided versus early invasive strategy.

Figure 3. Algorithm for Management of Patients With Definite or Likely NSTE-ACS*



*See corresponding full-sentence recommendations and their explanatory footnotes.

†In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis.

ASA indicates aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual-antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; and UFH, unfractionated heparin.

4.4.1. Early Invasive and Ischemia-Guided Strategies

For definitions of invasive and ischemia-guided strategies, see Table 8.

Class I

1. **An urgent/immediate invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in patients (men and women[¶]) with NSTE-ACS who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures) (40, 42, 173, 174).** ***(Level of Evidence: A)***
2. **An early invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in initially stabilized patients with NSTE-ACS (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (Table 8) (40, 42, 173-177).** ***(Level of Evidence: B)***

Class IIa

1. **It is reasonable to choose an early invasive strategy (within 24 hours of admission) over a delayed invasive strategy (within 24 to 72 hours) for initially stabilized high-risk patients with NSTE-ACS. For those not at high/intermediate risk, a delayed invasive approach is reasonable (173).** ***(Level of Evidence: B)***

Class IIb

1. **In initially stabilized patients, an ischemia-guided strategy may be considered for patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events (174, 175, 177).** ***(Level of Evidence: B)***
2. **The decision to implement an ischemia-guided strategy in initially stabilized patients (without serious comorbidities or contraindications to this approach) may be reasonable after considering clinician and patient preference.** ***(Level of Evidence: C)***

Class III: No Benefit

1. **An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with:**
    a. **Extensive comorbidities (e.g., hepatic, renal, pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization.** ***(Level of Evidence: C)***
    b. **Acute chest pain and a low likelihood of ACS** ***(Level of Evidence: C)*** **who are troponin-negative, especially women (178).** ***(Level of Evidence: B)***

Table 8. Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTE-ACS

Immediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Hemodynamic instability
	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy

[¶]See Section 7.7 for additional information on women.

	Sustained VT or VF
Ischemia-guided strategy	Low-risk score (e.g., TIMI [0 or 1], GRACE [<109])
	Low-risk Tn-negative female patients
	Patient or clinician preference in the absence of high-risk features
Early invasive (within 24 h)	None of the above, but GRACE risk score >140
	Temporal change in Tn (Section 3.4)
	New or presumably new ST depression
Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus
	Renal insufficiency (GFR <60 mL/min/1.73 m²)
	Reduced LV systolic function (EF <0.40)
	Early postinfarction angina
	PCI within 6 mo
	Prior CABG
	GRACE risk score 109–140; TIMI score ≥2

CABG indicates coronary artery bypass graft; EF, ejection fraction; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; Tn, troponin; VF, ventricular fibrillation; and VT, ventricular tachycardia.

4.5. Risk Stratification Before Discharge for Patients With an Ischemia-Guided Strategy of NSTE-ACS

Class I

1. **Noninvasive stress testing is recommended in low- and intermediate-risk patients who have been free of ischemia at rest or with low-level activity for a minimum of 12 to 24 hours (179-183).** ***(Level of Evidence: B)***
2. **Treadmill exercise testing is useful in patients able to exercise in whom the ECG is free of resting ST changes that may interfere with interpretation (179-182).** ***(Level of Evidence: C)***
3. **Stress testing with an imaging modality should be used in patients who are able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information (179-182).** ***(Level of Evidence: B)***
4. **Pharmacological stress testing with imaging is recommended when physical limitations preclude adequate exercise stress.** ***(Level of Evidence: C)***
5. **A noninvasive imaging test is recommended to evaluate LV function in patients with definite ACS (179-182).** ***(Level of Evidence: C)***

5. Myocardial Revascularization: Recommendations

5.1. PCI—General Considerations

Class IIb

1. **A strategy of multivessel PCI, in contrast to culprit lesion–only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTE-ACS (169, 184-189).** ***(Level of Evidence: B)***

5.1.1. PCI—Oral and Intravenous Antiplatelet Agents

Class I

1. **Patients already taking daily aspirin before PCI should take 81 mg to 325 mg non–enteric-coated aspirin before PCI (27, 190-192).** ***(Level of Evidence: B)***

2. **Patients not on aspirin therapy should be given non–enteric-coated aspirin 325 mg as soon as possible before PCI (27, 190-192).** ***(Level of Evidence: B)***
3. **After PCI, aspirin should be continued indefinitely at a dose of 81 mg to 325 mg daily (28, 142, 193).** ***(Level of Evidence: B)***
4. **A loading dose of a $P2Y_{12}$ receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting (27, 147, 170, 172, 194-197).** ***(Level of Evidence: A)*** **Options include:**
    a. **Clopidogrel: 600 mg (170, 194-196, 198-200)** ***(Level of Evidence: B)*** **or**
    b. **Prasugrel[#]: 60 mg (172)** ***(Level of Evidence: B)*** **or**
    c. **Ticagrelor[‖]: 180 mg (147)** ***(Level of Evidence: B)***
5. **In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (201-204).** ***(Level of Evidence: A)***
6. **In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months (169). Options include:**
    a. **Clopidogrel: 75 mg daily (170, 171)** ***(Level of Evidence: B)*** **or**
    b. **Prasugrel[#]: 10 mg daily (172)** ***(Level of Evidence: B)*** **or**
    c. **Ticagrelor[‖]: 90 mg twice daily (147)** ***(Level of Evidence: B)***

Class IIa

1. **It is reasonable to choose ticagrelor over clopidogrel for $P2Y_{12}$ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting (147, 148).** ***(Level of Evidence: B)***
2. **It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications (172, 205).** ***(Level of Evidence: B)***
3. **In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI (206-208).** ***(Level of Evidence: B)***
4. **After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses (170, 190, 209-212).** ***(Level of Evidence: B)***
5. **If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable (169).** ***(Level of Evidence: C)***

Class IIb

1. **Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation.** ***(Level of Evidence: C)***

Class III: Harm

1. **Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack (172).** ***(Level of Evidence: B)***

5.1.1.1. PCI—GP IIb/IIIa Inhibitors

[#]Patients should receive a loading dose of prasugrel provided that they were not pretreated with another $P2Y_{12}$ receptor inhibitor.
[‖]The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (144).

Class I

1. **In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) and not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (201-204).** ***(Level of Evidence: A)***

Class IIa

1. **In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI (206, 207). (*Level of Evidence: B)***

5.1.2. Anticoagulant Therapy in Patients Undergoing PCI

See Table 9 for dosing information on dosing of parenteral anticoagulants during PCI.

Class I

1. **An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation.** ***(Level of Evidence: C)***
2. **Intravenous UFH is useful in patients with NSTE-ACS undergoing PCI.** ***(Level of Evidence: C)***
3. **Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH in patients with NSTE-ACS undergoing PCI (154, 213-217).** ***(Level of Evidence: B)***
4. **An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than 2 therapeutic subcutaneous doses (e.g., 1 mg/kg SC) or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI (152, 218-222).** ***(Level of Evidence: B)***
5. **If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time) (27, 157-159, 223).** ***(Level of Evidence: B)***
6. **In patients with NSTE-ACS, anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue such therapy.** ***(Level of Evidence: C)***

Class IIa

1. **In patients with NSTE-ACS undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (154, 215).** ***(Level of Evidence: B)***

Class IIb

1. **Performance of PCI with enoxaparin may be reasonable in patients treated with upstream subcutaneous enoxaparin for NSTE-ACS (27, 152, 218-221, 224, 225).** ***(Level of Evidence: B)***

Class III: Harm

1. **Fondaparinux should not be used as the sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis (27, 157-159).** ***(Level of Evidence: B)***

Table 9. Dosing of Parenteral Anticoagulants During PCI

Drug*	In Patients Who Have Received Prior Anticoagulant Therapy	In Patients Who Have Not Received Prior Anticoagulant Therapy
Enoxaparin	• For prior treatment with enoxaparin, if last SC dose was administered 8–12 h earlier or if <2 therapeutic SC doses of enoxaparin have been administered, an IV dose of enoxaparin 0.3 mg/kg should be given	• 0.5 mg/kg–0.75 mg/kg IV loading dose

	• If the last SC dose was administered within prior 8 h, no additional enoxaparin should be given	
Bivalirudin	• For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV loading dose, then 1.75 mg/kg/h IV infusion • For patients already receiving bivalirudin infusion, give additional loading dose 0.5 mg/kg and increase infusion to 1.75 mg/kg/h during PCI	• 0.75 mg/kg loading dose, 1.75 mg/kg/h IV infusion
Fondaparinux	• For prior treatment with fondaparinux, administer additional IV treatment with anticoagulant possessing anti-IIa activity, considering whether GPI receptor antagonists have been administered	N/A
UFH	• IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 200–250 s • No IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve ACT of 250–300 s for HemoTec, 300–350 s for Hemochron	• IV GPI planned: 50–70 U/kg loading dose to achieve ACT of 200–250 s • No IV GPI planned: 70–100 U/kg loading dose to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron

*Drugs presented in order by the COR and then the LOE as noted in the Preamble. When more than 1 drug exists within the same LOE, and there are no comparative data, then the drugs are listed alphabetically.

ACT indicates activated clotting time; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; N/A, not applicable; PCI, percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin.
Modified from Levine et al. (27).

5.2. Timing of Urgent Coronary Artery Bypass Graft in Patients With NSTE-ACS in Relation to Use of Antiplatelet Agents

Class I

1. **Non–enteric-coated aspirin (81 mg to 325 mg daily) should be administered preoperatively to patients undergoing coronary artery bypass graft (CABG) (226-228).** ***(Level of Evidence: B)***
2. **In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (24, 229-231)** ***(Level of Evidence: B)*** **and prasugrel for at least 7 days before surgery (9, 232).** ***(Level of Evidence: C)***
3. **In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (9, 230, 233-235).** ***(Level of Evidence: B)***
4. **In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery (236, 237) and abciximab for at least 12 hours before to limit blood loss and transfusion (238).** ***(Level of Evidence: B)***

Class IIb

1. **In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued.** ***(Level of Evidence: C)***

6. Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care: Recommendations

6.1. Medical Regimen and Use of Medications at Discharge

Class I

1. **Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required (239, 240).** ***(Level of Evidence: C)***
2. **All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use (241).** ***(Level of Evidence: C)***
3. **Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms (241).** ***(Level of Evidence: C)***
4. **Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use (241).** ***(Level of Evidence: C)***
5. **For patients who are post–NSTE-ACS and have initial angina lasting more than 1 minute, nitroglycerin (1 dose sublingual or spray) is recommended if angina does not subside within 3 to 5 minutes; call 9-1-1 immediately to access emergency medical services (241).** ***(Level of Evidence: C)***
6. **If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing (241).** ***(Level of Evidence: C)***
7. **Before discharge, patients should be educated about modification of cardiovascular risk factors (240).** ***(Level of Evidence: C)***

6.2. Late Hospital and Posthospital Oral Antiplatelet Therapy

Class I

1. **Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients (142-144).** ***(Level of Evidence: A)***
2. **In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. Options include:**
    - **Clopidogrel: 75 mg daily (143, 171)** ***(Level of Evidence: B)*** **or**
    - **Ticagrelor‖: 90 mg twice daily (147, 148)** ***(Level of Evidence: B)***
3. **In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months (169). Options include:**
    - **Clopidogrel: 75 mg daily (170, 171)** ***(Level of Evidence: B)*** **or**
    - **Prasugrel#: 10 mg daily (172)** ***(Level of Evidence: B)*** **or**
    - **Ticagrelor‖: 90 mg twice daily (147)** ***(Level of Evidence: B)***

Class IIa

1. **It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation (27, 170, 190, 209-212).** ***(Level of Evidence: B)***
2. **It is reasonable to choose ticagrelor over clopidogrel for maintenance $P2Y_{12}$ treatment in patients with NSTE-ACS treated with an early invasive strategy and/or PCI (147, 148).** ***(Level of Evidence: B)***

#Patients should receive a loading dose of prasugrel provided that they were not pretreated with another $P2Y_{12}$ receptor inhibitor.

‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily (144).

3. **It is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk for bleeding complications (172, 205). *(Level of Evidence: B)***
4. **If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable (169). (*Level of Evidence: C)***

Class IIb

1. **Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation. *(Level of Evidence: C)***

6.3. Combined Oral Anticoagulant Therapy and Antiplatelet Therapy in Patients With NSTE-ACS

Class I

1. **The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. *(Level of Evidence: C)***
2. **Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor (27, 242, 243). *(Level of Evidence: C)***

Class IIa

1. **Proton pump inhibitor use is reasonable in patients with NSTE-ACS *without* a known history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor (27, 242, 243). *(Level of Evidence: C)***

Class IIb

1. **Targeting oral anticoagulant therapy to a lower international normalized ratio (e.g., 2.0 to 2.5) may be reasonable in patients with NSTE-ACS managed with aspirin and a $P2Y_{12}$ inhibitor. *(Level of Evidence: C)***

6.4. Risk Reduction Strategies for Secondary Prevention

Class I

1. **All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either before hospital discharge or during the first outpatient visit (244-247). *(Level of Evidence: B)***
2. **The pneumococcal vaccine is recommended for patients 65 years of age and older and in high-risk patients with cardiovascular disease (248-250). *(Level of Evidence: B)***
3. **Patients should be educated about appropriate cholesterol management, blood pressure (BP), smoking cessation, and lifestyle management (16, 17, 19). (*Level of Evidence: C)***
4. **Patients who have undergone PCI or CABG derive benefit from risk factor modification and should receive counseling that revascularization does not obviate the need for lifestyle changes (251). (*Level of Evidence: C)***
5. **Before hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach should be used for selection of treatments. Pain treatment before consideration of NSAIDs should begin with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics if these medications are not adequate (18, 252). *(Level of Evidence: C)***

Class IIa

1. **It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics is insufficient (252).** ***(Level of Evidence: C)***

Class IIb

1. **NSAIDs with increasing degrees of relative cyclooxygenase-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs. In all cases, use of the lowest effective doses for the shortest possible time is encouraged (117, 118, 252, 253).** ***(Level of Evidence: C)***

Class III: No Benefit

1. **Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in patients with NSTE-ACS (254, 255).** ***(Level of Evidence: A)***
2. **Folic acid, with or without vitamins B_6 and B_{12}, should not be used for secondary prevention in patients with NSTE-ACS (256, 257).** ***(Level of Evidence: A)***

Class III: Harm

1. **Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention of coronary events to postmenopausal women after NSTE-ACS and should not be continued in previous users unless the benefits outweigh the estimated risks (18, 258-260).** ***(Level of Evidence: A)***
2. **NSAIDs with increasing degrees of relative cyclooxygenase-2 selectivity should not be administered to patients with NSTE-ACS and chronic musculoskeletal discomfort when therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs provide acceptable pain relief (117, 118, 252, 253).** ***(Level of Evidence: B)***

6.5. Plan of Care for Patients With NSTE-ACS

Class I

1. **Posthospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care for all patients with NSTE-ACS (261-265).** ***(Level of Evidence: B)***
2. **An evidence-based plan of care (e.g., GDMT) that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with NSTE-ACS.** ***(Level of Evidence: C)***
3. **In addition to detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., lifting, climbing stairs, yard work, and household activities) that are permissible and those to avoid. Specific mention should be made of resumption of driving, return to work, and sexual activity (247, 266, 267).** ***(Level of Evidence: B)***
4. **An annual influenza vaccination is recommended for patients with cardiovascular disease (28, 268).** ***(Level of Evidence: C)***

7. Special Patient Groups: Recommendations

See Table 10 for summary of recommendations for this section.

7.1. NSTE-ACS in Older Patients

Class I

1. **Older patients[**] with NSTE-ACS should be treated with GDMT, an early invasive strategy, and revascularization as appropriate (269-273). (*Level of Evidence: A)***
2. **Pharmacotherapy in older patients with NSTE-ACS should be individualized and dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity (269, 274-276). *(Level of Evidence: A)***
3. **Management decisions for older patients with NSTE-ACS should be patient centered, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy (269, 277-279). *(Level of Evidence: B)***

Class IIa

1. **Bivalirudin, rather than a GP IIb/IIIa inhibitor plus UFH, is reasonable in older patients with NSTE-ACS, both initially and at PCI, given similar efficacy but less bleeding risk (215, 280-282). (*Level of Evidence: B)***
2. **It is reasonable to choose CABG over PCI in older patients[**] with NSTE-ACS who are appropriate candidates, particularly those with diabetes mellitus or complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal left anterior descending artery, to reduce cardiovascular disease events and readmission and to improve survival (283-288). *(Level of Evidence: B)***

7.2. Heart Failure and Cardiogenic Shock

Class I

1. **Patients with a history of HF and NSTE-ACS should be treated according to the same risk stratification guidelines and recommendations for patients without HF (15, 40-42, 52-58). *(Level of Evidence: B)***
2. **Selection of a specific revascularization strategy should be based on the degree, severity, and extent of CAD; associated cardiac lesions; the extent of LV dysfunction; and the history of prior revascularization procedures (15, 173, 175, 177, 178, 289-292). *(Level of Evidence: B)***
3. **Early revascularization is recommended in suitable patients with cardiogenic shock due to cardiac pump failure after NSTE-ACS (291, 293, 294). *(Level of Evidence: B)***

7.3. Diabetes Mellitus

Class I

1. **Medical treatment in the acute phase of NSTE-ACS and decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus (173, 176, 295). *(Level of Evidence: A)***

7.4. Post–CABG

Class I

1. **Patients with prior CABG and NSTE-ACS should receive antiplatelet and anticoagulant therapy according to GDMT and should be strongly considered for early invasive strategy because of their increased risk (44, 45, 178, 290, 296, 297). *(Level of Evidence: B)***

[**]Those ≥75 years of age (see Section 7.1 in the full-text CPG).

7.5. Perioperative NSTE-ACS Related to Noncardiac Surgery

Class I

1. **Patients who develop NSTE-ACS following noncardiac surgery should receive GDMT as recommended for patients in the general population but with the modifications imposed by the specific noncardiac surgical procedure and the severity of NSTE-ACS (298, 299).** ***(Level of Evidence: C)***
2. **In patients who develop NSTE-ACS after noncardiac surgery, management should be directed at the underlying cause (22, 298-306).** ***(Level of Evidence: C)***

7.6. Chronic Kidney Disease

Class I

1. **CrCl should be estimated in patients with NSTE-ACS, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications (307, 308).** ***(Level of Evidence: B)***
2. **Patients undergoing coronary and LV angiography should receive adequate hydration.** ***(Level of Evidence: C)***

Class IIa

1. **An invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD (307-310).** ***(Level of Evidence: B)***

7.7. Women

Class I

1. **Women with NSTE-ACS should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention, with attention to weight and/or renally-calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk (311-315).** ***(Level of Evidence: B)***
2. **Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy (178, 292, 316, 317).** ***(Level of Evidence: A)***

Class IIa

1. **Myocardial revascularization is reasonable in pregnant women with NSTE-ACS if an ischemia-guided strategy is ineffective for management of life-threatening complications (318).** ***(Level of Evidence: C)***

Class III: No Benefit

1. **Women with NSTE-ACS and low-risk features (see Section 3.3.1 in the full-text CPG) should not undergo early invasive treatment because of the lack of benefit (178, 316, 317) and the possibility of harm (178).** ***(Level of Evidence: B)***

7.8. Anemia, Bleeding, and Transfusion

Class I

1. **All patients with NSTE-ACS should be evaluated for the risk of bleeding.** ***(Level of Evidence: C)***
2. **Anticoagulant and antiplatelet therapy should be weight-based where appropriate and should be adjusted when necessary for CKD to decrease the risk of bleeding in patients with NSTE-ACS (276, 319, 320).** ***(Level of Evidence: B)***

Class III: No Benefit

1. **A strategy of routine blood transfusion in hemodynamically stable patients with NSTE-ACS and hemoglobin levels greater than 8 g/dL is not recommended (321-325).** ***(Level of Evidence: B)***

7.9. Cocaine and Methamphetamine Users

Class I

1. **Patients with NSTE-ACS and a recent history of cocaine or methamphetamine use should be treated in the same manner as patients without cocaine- or methamphetamine-related NSTE-ACS. The only exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and/or hypertension) and beta-blocker use, unless patients are receiving coronary vasodilator therapy.** ***(Level of Evidence: C)***

Class IIa

1. **Benzodiazepines alone or in combination with nitroglycerin are reasonable for management of hypertension and tachycardia in patients with NSTE-ACS and signs of acute cocaine or methamphetamine intoxication (326-329).** ***(Level of Evidence: C)***

Class III: Harm

1. **Beta blockers should not be administered to patients with ACS with a recent history of cocaine or methamphetamine use who demonstrate signs of acute intoxication due to the risk of potentiating coronary spasm.** ***(Level of Evidence: C)***

7.10. Vasospastic (Prinzmetal) Angina

Class I

1. **CCBs alone (330-334) or in combination with long-acting nitrates (332, 335) are useful to treat and reduce the frequency of vasospastic angina.** ***(Level of Evidence: B)***
2. **Treatment with HMG-CoA reductase inhibitor (336, 337), cessation of tobacco use (338, 339), and additional atherosclerosis risk factor modification (339, 340) are useful in patients with vasospastic angina.** ***(Level of Evidence: B)***
3. **Coronary angiography (invasive or noninvasive) is recommended in patients with episodic chest pain accompanied by transient ST elevation to rule out severe obstructive CAD.** ***(Level of Evidence: C)***

Class IIb

1. **Provocative testing during invasive coronary angiography[††] may be considered in patients with suspected vasospastic angina when clinical criteria and noninvasive testing fail to establish the diagnosis (341-344).** ***(Level of Evidence: B)***

7.11. ACS With Angiographically Normal Coronary Arteries

[††]Provocative testing during invasive coronary angiography (e.g., using ergonovine, acetylcholine, methylergonovine) is relatively safe, especially when performed in a controlled manner by experienced operators. However, sustained spasm, serious arrhythmias, and even death can also occur very infrequently. Therefore, provocative testing should be avoided in patients with significant left main disease, advanced 3-vessel disease, presence of high-grade obstructive lesions, significant valvular stenosis, significant LV systolic dysfunction, and advanced HF.

Class IIb

1. **If coronary angiography reveals normal coronary arteries and endothelial dysfunction is suspected, invasive physiological assessment such as coronary flow reserve measurement may be considered (301, 345-348).** ***(Level of Evidence: B)***

7.12. Stress (Takotsubo) Cardiomyopathy

Class I

1. **Stress (Takotsubo) cardiomyopathy should be considered in patients who present with apparent ACS and nonobstructive CAD at angiography.** ***(Level of Evidence: C)***
2. **Imaging with ventriculography, echocardiography, or magnetic resonance imaging should be performed to confirm or exclude the diagnosis of stress (Takotsubo) cardiomyopathy (349-352).** ***(Level of Evidence: B)***
3. **Patients should be treated with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) as otherwise indicated if hemodynamically stable.** ***(Level of Evidence: C)***
4. **Anticoagulation should be administered in patients who develop LV thrombi.** ***(Level of Evidence: C)***

Class IIa

1. **It is reasonable to use catecholamines for patients with symptomatic hypotension if outflow tract obstruction is not present.** ***(Level of Evidence: C)***
2. **The use of an intra-aortic balloon pump is reasonable for patients with refractory shock.** ***(Level of Evidence: C)***
3. **It is reasonable to use beta blockers and alpha-adrenergic agents in patients with outflow tract obstruction.** ***(Level of Evidence: C)***

Class IIb

1. **Prophylactic anticoagulation may be considered to inhibit the development of LV thrombi.** ***(Level of Evidence: C)***

Table 10. Summary of Recommendations for Special Patient Groups

Recommendations	COR	LOE	References
NSTE-ACS in older patients			
Treat older patients (≥75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate	I	A	(269-273)
Individualize pharmacotherapy in older patients, with dose adjusted by weight and/or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics/dynamics, volume of distribution, comorbidity, drug interactions, and increased drug sensitivity	I	A	(269, 274-276)
Undertake patient-centered management for older patients, considering patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy	I	B	(269, 277-279)
Bivalirudin rather than GP IIb/IIIa inhibitor plus UFH is reasonable for older patients (≥75 y of age), given similar efficacy but less bleeding risk	IIa	B	(215, 280-282)
It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events	IIa	B	(283-288)
HF and cardiogenic shock			
Treat patients with a history of HF according to the same risk stratification guidelines and recommendations for patients without HF	I	B	(15, 40-42, 52-58)
Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization	I	B	(15, 173, 175, 177, 178, 289-292)
Recommend early revascularization for cardiogenic shock due to cardiac pump	I	B	(291, 293,

failure			294)
DM			
Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM	I	A	(173, 176, 295)
Post–CABG			
Recommend GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG	I	B	(44, 45, 178, 290, 296, 297)
Perioperative NSTE-ACS			
Administer GDMT to perioperative patients with limitations imposed by noncardiac surgery	I	C	(298, 299)
Direct management at underlying cause of perioperative NSTE-ACS	I	C	(22, 298-306)
CKD			
Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data	I	B	(307, 308)
Administer adequate hydration to patients undergoing coronary and LV angiography	I	C	N/A
Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD	IIa	B	(307-310)
Women			
Manage women with the same pharmacological therapy as that for men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk	I	B	(311-315)
Early invasive strategy is recommended in women with NSTE-ACS and high-risk features (troponin positive)	I	A	(178, 292, 316, 317)
Myocardial revascularization is reasonable for pregnant women if ischemia-guided strategy is ineffective for management of life-threatening complications	IIa	C	(318)
Women with low-risk features (Section 3.3.1 in the full-text CPG) should not undergo early invasive treatment because of lack of benefit and the possibility of harm	III: No Benefit	B	(178, 316, 317)
Anemia, bleeding, and transfusion			
Evaluate all patients for risk of bleeding	I	C	N/A
Recommend that anticoagulant and antiplatelet therapy be weight-based where appropriate and adjusted for CKD to decrease the risk of bleeding	I	B	(276, 319, 320)
There is no benefit of routine blood transfusion in hemodynamically stable patients with hemoglobin levels >8 g/dL	III: No Benefit	B	(321-325)
Cocaine and methamphetamine users			
Manage patients with recent cocaine or methamphetamine use similarly to those without cocaine- or methamphetamine-related NSTE-ACS. The exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and hypertension) and beta-blocker use unless patients are receiving coronary vasodilator therapy.	I	C	N/A
It is reasonable to use benzodiazepines alone or in combination with NTG to manage hypertension and tachycardia and signs of acute cocaine or methamphetamine intoxication.	IIa	C	(326-329)
Do not administer beta blockers to patients with recent cocaine or methamphetamine use who have signs of acute intoxication due to risk of potentiating coronary spasm	III: Harm	C	N/A
Vasospastic (Prinzmetal) angina			
Recommend CCBs alone or in combination with nitrates	I	B	(330-335)
Recommend HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification	I	B	(336-340)
Recommend coronary angiography (invasive or noninvasive) for episodic chest pain with transient ST elevation to detect severe CAD	I	C	N/A
Provocative testing during invasive coronary angiography* may be considered for	IIb	B	(341-344)

suspected vasospastic angina when clinical criteria and noninvasive assessment fail to determine diagnosis			
ACS with angiographically normal coronary arteries			
Invasive physiological assessment (coronary flow reserve measurement) may be considered with normal coronary arteries if endothelial dysfunction is suspected	IIb	B	(301, 345-348)
Stress (Takotsubo) cardiomyopathy			
Consider stress-induced cardiomyopathy in patients with apparent ACS and nonobstructive CAD	I	C	N/A
Perform ventriculography, echocardiography, or MRI to confirm or exclude diagnosis	I	B	(349-352)
Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if hemodynamically stable	I	C	N/A
Administer anticoagulant therapy for LV thrombi	I	C	N/A
It is reasonable to administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction	IIa	C	N/A
It is reasonable to use IABP for refractory shock	IIa	C	N/A
It is reasonable to use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction	IIa	C	N/A
Prophylactic anticoagulation may be considered to prevent LV thrombi	IIb	C	N/A

*Provocative testing during invasive coronary angiography (e.g., using ergonovine, acetylcholine, methylergonovine) is relatively safe, especially when performed in a controlled manner by experienced operators. However, sustained spasm, serious arrhythmias, and even death can also occur but very infrequently. Therefore, provocative tests should be avoided in patients with significant left main disease, advanced 3-vessel disease, presence of high-grade obstructive lesions, significant valvular stenosis, significant LV systolic dysfunction, and advanced HF.

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; COR, Class of Recommendation; CPG, clinical practice guideline; CrCl, creatinine clearance; CVD, cardiovascular disease; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; GP, glycoprotein; HF, heart failure; IABP, intra-aortic balloon pump; LOE, Level of Evidence; LV, left ventricular; MRI, magnetic resonance imaging; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; NTG, nitroglycerin; PCI, percutaneous coronary intervention; and UFH, unfractionated heparin.

8. Quality of Care and Outcomes for ACS—Use of Performance Measures and Registries: Recommendation

Class IIa

1. **Participation in a standardized quality-of-care data registry designed to track and measure outcomes, complications, and performance measures can be beneficial in improving the quality of NSTE-ACS care (353-361).** ***(Level of Evidence: B)***

9. Summary and Evidence Gaps

Despite landmark advances in the care of patients with NSTE-ACS since the publication of the 2007 UA/NSTEMI CPG (362), many emerging diagnostic and therapeutic strategies have posed new challenges. There is general acceptance of an early invasive strategy for patients with NSTE-ACS in whom significant coronary vascular obstruction has been precisely quantified. Low-risk patients with NSTE-ACS are documented to benefit substantially from GDMT, but this is often suboptimally used. Advances in noninvasive testing have the potential to identify patients with NSTE-ACS who are at intermediate risk and are candidates for invasive versus medical therapy.

Newer, more potent antiplatelet agents in addition to anticoagulant therapy are indicated irrespective of initial treatment strategy. Evidence-based decisions will require comparative-effectiveness studies of available and novel agents. The paradox of newer and more potent antithrombotic and anticoagulant drugs that reduce major adverse cardiac outcomes but increase bleeding risk occurs with greater frequency in patients with atrial fibrillation. Patients with atrial fibrillation who develop NSTE-ACS and receive a coronary stent are the population at risk from triple anticoagulant/antiplatelet therapy. This regimen has been reported to be safely modified by elimination of aspirin, a finding that requires confirmation.

Among the most rapidly evolving areas in NSTE-ACS diagnosis is the use of cardiac troponin, the preferred biomarker of myocardial necrosis. Although a truly high-sensitivity cardiac troponin is not available in the United States at the time this CPG was prepared, the sensitivity of contemporary assays continues to increase. This change is accompanied by higher rates of elevated cardiac troponin unrelated to coronary plaque rupture. The diagnostic quandary posed by these findings necessitates investigation to elucidate the optimal utility of this advanced biomarker. A promising approach to improve the diagnostic accuracy for detecting myocardial necrosis is measurement of absolute cardiac troponin change, which may be more accurate than the traditional analysis of relative alterations.

Special populations are addressed in this CPG, the most numerous of which are older persons and women. More than half of the mortality in NSTE-ACS occurs in older patients, and this high-risk cohort will increase as our population ages. An unmet need is to more clearly distinguish which older patients are candidates for an ischemia-guided strategy compared with an early invasive management strategy. An appreciable number of patients with NSTE-ACS have angiographically normal or nonobstructive CAD, a group in which women predominate. Their prognosis is not benign and the multiple mechanisms of ACS postulated for these patients remain largely speculative. Clinical advances are predicated on clarification of the pathophysiology of this challenging syndrome.

A fundamental aspect of all CPGs is that these carefully developed, evidence-based documents cannot encompass all clinical circumstances, nor can they replace the judgment of individual physicians in management of each patient. The science of medicine is rooted in evidence, and the art of medicine is based on the application of this evidence to the individual patient. This CPG has adhered to these principles for optimal management of patients with NSTE-ACS.

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2014 AHA/ACC NSTE-ACS Executive Summary

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Key Words: ACC/AHA Clinical Practice Guidelines ▪ acute coronary syndrome ▪ angina, unstable ▪ antiplatelet agents ▪ coronary artery bypass graft ▪ electrocardiography ▪ ischemia ▪ myocardial infarction ▪ percutaneous coronary intervention ▪ troponin.

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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					Diagnostics† • Daiichi-Sankyo† • Genzyme† • GlaxoSmithKline† • Nanosphere† • Roche Diagnostics† • Sanofi-aventis† • Takeda†	• Singulex†		
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According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

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

†Significant relationship.
‡No financial benefit.

ACC indicates American College of Cardiology, AHA, American Heart Association, BMS, Bristol-Myers Squibb; CPG, clinical practice guideline; DCRI, Duke Clinical Research Institute; NIH, National Institutes of Health; NYU, New York University; RWI, relationships with industry and other entities; TIMI, Thrombolysis In Myocardial Infarction; and VA, Veterans Affairs.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

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significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

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

*Significant relationship.
†No financial benefit.

AAAHC indicates Accreditation Association for Ambulatory Health Care; AACC, American Association for Clinical Chemistry; AAFP, American Academy of Family Physicians; AHA, American Heart Association; AIG, Association of International Governors; BMS, Bristol-Myers Squibb; DCRI, Duke Clinical Research Institute; DSMB, data safety monitoring board; HHS, Health and Human Services; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; TIMI, Thrombolysis In Myocardial Infarction; and VA, Veterans Affairs.

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