

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

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

An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

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PREAMBLE

Incorporation of new study results, medications, or devices that merit modification of existing clinical practice guideline recommendations, or the addition of new recommendations, is critical to ensuring that guidelines reflect current knowledge, available treatment options, and optimum medical care. To keep pace with evolving evidence, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines (“Task Force”) has issued this focused update to revise existing guideline recommendations on the basis of recently published study data. This update has been subject to rigorous, multilevel review and approval, similar to the full guidelines. For specific focused update criteria and additional methodological details, please see the ACC/AHA guideline methodology manual.¹

Modernization

Processes have evolved over time in response to published reports from the Institute of Medicine^{2,3} and ACC/AHA mandates,^{4–7} leading to adoption of a “knowledge byte” format. This process entails delineation of a recommendation addressing a specific clinical question, followed by concise text (ideally <250 words per recommendation) and hyperlinked to supportive evidence. This approach better accommodates time constraints on busy clinicians, facilitates easier access to recommendations via electronic search engines and other evolving technology, and supports the evolution of guidelines as “living documents” that can be dynamically updated as needed.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) and Level of Evidence (LOE) are derived independently of each other according to established criteria. The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit of a clinical action in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1). Recommendations in this focused update reflect the new 2015 COR/LOE system, in which LOE B and C are subcategorized for the purpose of increased granularity.^{1,7,8}

Relationships With Industry and Other Entities

The ACC and AHA exclusively sponsor the work of guideline writing committees (GWCs) without commercial support, and members volunteer time for this activity. Selected organizations and professional societies with related interests and expertise are invited to par-

ticipate as partners or collaborators. 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, beginning 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 RWI apply. Members of the GWC who recused themselves from voting are indicated and specific section recusals are noted in Appendixes 1 and 2. In addition, for transparency, GWC members' comprehensive disclosure information is available as an Online Supplement (<http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.000000000000404/-/DC1>). Comprehensive disclosure information for the Task Force is also available at <http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces>. The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, genders, ethnicities, intellectual perspectives, and scopes of clinical activities.

Intended Use

Guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a broader target. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. The guidelines are reviewed annually by the Task Force and are official policy of the ACC and AHA. Each guideline is considered current unless and until it is updated, revised, or superseded by a published addendum.

Related Issues

For additional information pertaining to the methodology for grading evidence, assessment of benefit and harm, shared decision making between the patient and clinician, structure of evidence tables and summaries, standardized terminology for articulating recommendations, organizational involvement, peer review, and policies regarding periodic assessment and updating of guideline documents, we encourage readers to consult the ACC/AHA guideline methodology manual.¹

Jonathan L. Halperin, MD, FACC, FAHA
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1. INTRODUCTION

The scope of this focused update is limited to addressing recommendations on duration of dual antiplatelet therapy (DAPT) (aspirin plus a P2Y₁₂ inhibitor) in patients with coronary artery disease (CAD). Recommendations considered are those in 6 guidelines: “2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention”,⁹ “2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery”,¹⁰ “2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease”,^{11,12} “2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction”,¹³ “2014 ACC/AHA Guideline for Non-ST-Elevation Acute Coronary Syndromes”,¹⁴ and “2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery”.¹⁵

The impetus for this focused update review is 11 studies^{16–27} of patients treated with coronary stent implantation (predominantly with drug-eluting stents [DES]) assessing shorter-duration or longer-duration DAPT, as well as a large, randomized controlled trial (RCT) of patients 1 to 3 years after myocardial infarction (MI) assessing the efficacy of DAPT compared with aspirin monotherapy.²⁸ These studies were published after the formulation of recommendations for duration of DAPT in prior guidelines. The specific mandate of the present writing group is to evaluate, update, harmonize, and, when possible, simplify recommendations on duration of DAPT.

Although there are several potential combinations of antiplatelet therapy, the term and acronym DAPT has been used to specifically refer to combination antiplatelet therapy with aspirin and a P2Y₁₂ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) and will be used similarly in this focused update. Recommendations in this focused update on duration of DAPT, aspirin dosing in patients treated with DAPT, and timing of elective noncardiac surgery in patients treated with percutaneous coronary intervention (PCI) and DAPT supersede prior corresponding recommendations in the 6 relevant guidelines. These recommendations for duration of DAPT apply to newer-generation stents and, in general, only to those not treated with oral anticoagulant therapy. For the purposes of this focused update, patients with a history of acute coronary syndrome (ACS) >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to stable ischemic heart disease (SIHD) and are addressed in the section on SIHD. Issues and recommendations with regard to P2Y₁₂ inhibitor “pretreatment,” “preloading,” and loading are beyond the scope of this document but are addressed in other guidelines.^{9,14,29}

This focused update is designed to function both as a standalone document and to serve as an update to the relevant sections on duration of DAPT in the 6

Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS I (STRONG) Benefit >>> Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> ■ Is recommended ■ Is indicated/useful/effective/beneficial ■ Should be performed/administered/other ■ Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> ○ Treatment/strategy A is recommended/indicated in preference to treatment B ○ Treatment A should be chosen over treatment B 	LEVEL A <ul style="list-style-type: none"> ■ High-quality evidence‡ from more than 1 RCT ■ Meta-analyses of high-quality RCTs ■ One or more RCTs corroborated by high-quality registry studies
CLASS IIa (MODERATE) Benefit >> Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> ■ Is reasonable ■ Can be useful/effective/beneficial ■ Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> ○ Treatment/strategy A is probably recommended/indicated in preference to treatment B ○ It is reasonable to choose treatment A over treatment B 	LEVEL B-R (Randomized) <ul style="list-style-type: none"> ■ Moderate-quality evidence‡ from 1 or more RCTs ■ Meta-analyses of moderate-quality RCTs
CLASS IIb (WEAK) Benefit ≥ Risk Suggested phrases for writing recommendations: <ul style="list-style-type: none"> ■ May/might be reasonable ■ May/might be considered ■ Usefulness/effectiveness is unknown/unclear/uncertain or not well established 	LEVEL B-NR (Nonrandomized) <ul style="list-style-type: none"> ■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies ■ Meta-analyses of such studies
CLASS III: No Benefit (MODERATE) Benefit = Risk <i>(Generally, LOE A or B use only)</i> Suggested phrases for writing recommendations: <ul style="list-style-type: none"> ■ Is not recommended ■ Is not indicated/useful/effective/beneficial ■ Should not be performed/administered/other 	LEVEL C-LD (Limited Data) <ul style="list-style-type: none"> ■ Randomized or nonrandomized observational or registry studies with limitations of design or execution ■ Meta-analyses of such studies ■ Physiological or mechanistic studies in human subjects
CLASS III: Harm (STRONG) Risk > Benefit Suggested phrases for writing recommendations: <ul style="list-style-type: none"> ■ Potentially harmful ■ Causes harm ■ Associated with excess morbidity/mortality ■ Should not be performed/administered/other 	LEVEL C-E0 (Expert Opinion) Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).
 A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
 * The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
 † For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
 ‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.
 COR indicates Class of Recommendation; E0, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

clinical practice guidelines, replacing relevant text, figures, and recommendations. Thus, by necessity, there is some redundancy in different sections of this document. When possible, the “knowledge byte” format was used for recommendations. In some cases, the complexity of this document required a modification of the knowledge byte format, with several interrelated recommendations grouped together, followed by concise associated text (<250 words of text per recommendation).

1.1. Methodology and Evidence Review

Clinical trials published since the 2011 PCI guideline⁹ and the 2011 coronary artery bypass graft (CABG) guideline,¹⁰ published in a peer-reviewed format through December 2015, were reviewed by the Task Force to identify trials and other key data that might affect guideline recommendations. The information considered important enough to prompt updated recommendations is included in evidence tables in the Data Supplement.

In accord with recommendations by the Institute of Medicine^{2,3} and the ACC/AHA Task Force Methodology Summit,^{1,6} 3 critical (PICOTS-formatted; population, intervention, comparison, outcome, timing, setting) questions were developed to address the critical questions related to duration of DAPT. These 3 critical questions were the basis of a formal systematic review and evaluation of the relevant study data by an Evidence Review Committee (ERC).³⁰ Concurrent with this process, writing group members evaluated study data relevant to the numerous current recommendations in the 6 guidelines, including topics not covered in the 3 critical questions (eg, DAPT after CABG). The findings of the ERC and the writing group members were formally presented and discussed, and then modifications to existing recommendations were considered. Recommendations that are based on a body of evidence that includes a systematic review conducted by the ERC are denoted by the superscript SR (eg, LOE B-R^{SR}). See the ERC systematic review report, "Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease," for the complete evidence review report.³⁰

1.2. Organization of the Writing Group

Recommendations on duration of DAPT are currently included in 6 clinical practice guidelines, which are interrelated and overlapping because they address the management of patients with CAD. Therefore, the writing group consisted of the chairs/vice chairs and/or members of all 6 guidelines, representing the fields of cardiovascular medicine, interventional cardiology, cardiac surgery, internal medicine, and cardiovascular anesthesia, as well as expertise in trial design and statistical analysis.

1.3. Review and Approval

This focused update was reviewed by the writing committee members from the 6 guidelines; by 5 official reviewers from the ACC and AHA; 2 reviewers each from the American Association for Thoracic Surgery, American College of Emergency Physicians, American Society of Anesthesiologists, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and the Society of Thoracic Surgeons; and by 23 additional content reviewers. Reviewers' RWI information is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the American Association for Thoracic Surgery, American Society of Anesthesiologists, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, Society of

Cardiovascular Anesthesiologists, Society of Thoracic Surgeons, and Society for Vascular Surgery.

2. CRITICAL QUESTIONS AND SYSTEMATIC REVIEW FINDINGS

2.1. Critical Questions on Duration of DAPT

The 3 critical (PICOTS-formatted) questions on DAPT duration are listed in Table 2. Most contemporary studies of DAPT have compared either shorter (3 to 6 months)^{17–21} or longer (18 to 48 months)^{16,22–26} duration of therapy with 12 months of DAPT, which is the recommended or minimal duration of therapy for most patients in ACC/AHA^{9,13,14} and European Society of Cardiology^{31–33} guidelines published between 2011 and 2014. Recommendations based on the findings from the critical question–focused systemic reviews are provided in Sections 4 to 8 of the present document.

2.2. Studies of Shorter-Duration DAPT After Stent Implantation

Five RCTs of patients treated with elective DES implantation have compared shorter-duration (3 to 6 months) DAPT with 12 months of DAPT^{17–21} (Data Supplement 1). The trials primarily enrolled low-risk (non-ACS) patients, with only a small proportion having had a recent MI. The main endpoints of these noninferiority trials were composite ischemic events (or net composite events) and stent thrombosis. These studies, as well as several meta-analyses^{34–37} and an analysis by the ERC,³⁰ did not find any increased risk of stent thrombosis with shorter-duration DAPT. A shorter duration of DAPT results in fewer bleeding complications.^{30,34–36} Shorter-duration DAPT may be most reasonable in patients currently being treated with

Table 2. Critical (PICOTS-Formatted) Questions on DAPT Duration

Q1: In patients treated with newer (non-first) generation DES for (1) SIHD or (2) ACS, compared with 12 months of DAPT, is 3–6 months of DAPT as effective in preventing stent thrombosis, preventing MACE and/or reducing bleeding complications?
Q2: In patients treated with newer (non-first) generation DES, compared with 12 months of DAPT, does >12 (18–48) months of DAPT result in differences in mortality rate, decreased MACE, decreased stent thrombosis, and/or increased bleeding?
Q3: In post-MI (NSTEMI or STEMI) patients who are clinically stable and >12 months past their event, does continued DAPT, compared with aspirin monotherapy, result in differences in mortality rate, decreased nonfatal MI, decreased MACE, and/or increased bleeding?

ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; PICOTS, population, intervention, comparison, outcome, timing, and setting; SIHD, stable ischemic heart disease; and STEMI, ST-elevation myocardial infarction.

“newer-generation” (eg, everolimus- or zotarolimus-eluting) DES, which are associated with lower stent thrombosis and MI rates than those of “first-generation” (eg, sirolimus- and paclitaxel-eluting) DES, which are rarely, if ever, used in current clinical practice.^{16,36,38}

2.3. Studies of Longer-Duration DAPT After Stent Implantation

Six RCTs, consisting predominantly of patients treated with elective DES implantation, compared prolonged DAPT (total therapy duration: 18 to 48 months) with 6 to 12 months of DAPT to determine whether extended therapy reduces late and very late stent thrombosis and prevents ischemic events associated with disease progression and plaque rupture at other nonstented sites^{16,22–27} (Data Supplement 2). In the Dual Antiplatelet Therapy study—the largest of these trials—patients who had undergone DES implantation, had been treated with DAPT for 12 months, and were without ischemic or bleeding events during this period were randomized to an additional 18 months of DAPT or to aspirin monotherapy.¹⁶ Extended DAPT resulted in a 0.7% absolute reduction in very late stent thrombosis, a 2.0% absolute reduction in MI, a 1.6% absolute reduction in major adverse cardiac events (MACE), and a 0.9% absolute increase in moderate or severe bleeding. In the subgroup of patients treated with everolimus-eluting stents—currently the most commonly used stent—extended DAPT resulted in a 0.4% absolute reduction in stent thrombosis, a 1.1% absolute reduction in MI, and a 1.2% absolute increase in moderate/severe bleeding.³⁹

Taken as a whole, studies of longer-duration (“prolonged” or “extended”) DAPT^{16,22–27} for an additional 18 to 36 months after DES found an absolute decrease in late stent thrombosis and ischemic complications of ≈1% to 2% and an absolute increase in bleeding complications of ≈1% (Data Supplements 2 and 3). A weighted risk-benefit analysis by the ERC of studies of patients treated with DES found 6 fewer MIs and 3 fewer stent thromboses but 5 additional major bleeds per 1000 patients treated with prolonged DAPT per year.³⁰

2.4. Other Studies Relevant to DAPT >1 Year After MI

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial randomized patients with established atherosclerosis or at high risk of clinical atherosclerotic disease to either DAPT (with clopidogrel) or aspirin monotherapy; with DAPT, no significant reduction was found in ischemic effects at a median follow-up of 28 months, but there was a 0.4% absolute increase in severe bleeding.⁴⁰ A post hoc analysis of patients enrolled in the study with prior MI found a 1.7% absolute decrease in the composite endpoint of

cardiovascular death, MI, or stroke events with DAPT, with no benefit in those with CAD without prior MI.^{40,41}

Patients in the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis In Myocardial Infarction 54) trial were randomized 1 to 3 years after MI with additional high-risk features to either DAPT (with ticagrelor 60 mg or 90 mg twice daily) or continued aspirin monotherapy.²⁸ After a mean of 33 months of therapy, DAPT, when compared with aspirin monotherapy, resulted in a 1.2% to 1.3% absolute reduction in the primary composite endpoint of cardiovascular death, MI, or stroke and a 1.2% to 1.5% absolute increase in major bleeding, with no excess in fatal bleeding or intracranial hemorrhage. In subgroup analysis, the greatest reduction in ischemic events with prolonged DAPT was in patients in whom P2Y₁₂ inhibitor therapy either had not been discontinued or had been discontinued for ≤30 days (absolute reduction in MACE: 1.9% to 2.5%). No benefit was seen in patients in whom P2Y₁₂ inhibitor therapy had been discontinued >1 year before enrollment in the study.⁴²

In the Dual Antiplatelet Therapy study, the benefit/risk ratio for prolonged DAPT was more favorable for those presenting with MI than those with SIHD.⁴³ In an analysis of patients with a history of prior MI enrolled in 6 RCTs of extended/prolonged DAPT, extended DAPT significantly decreased the absolute risk of MACE by 1.1% and significantly increased the absolute risk of major bleeding by 0.8%.⁴⁴

Taken as a whole, trials of prolonged or extended DAPT suggest that the benefit/risk ratio of prolonged DAPT may be more favorable for those with prior MI, with an absolute decrease in ischemic events of ≈1% to 3% at the cost of an absolute increase in bleeding events of ≈1% over the course of several years of prolonged or extended therapy (median durations of therapy: 18 to 33 months) (Data Supplements 3 and 4). This appears biologically plausible because patients with prior MI (usually mediated by plaque rupture) may be at greater risk for future plaque rupture than those without prior MI.^{37,40,41}

2.5. Prolonged/Extended DAPT and Mortality Rate

An unexpected finding in the Dual Antiplatelet Therapy study¹⁶ was a borderline-significant increase in overall mortality rate (0.5% absolute increase) with 30 months of DAPT versus 12 months of DAPT in DES-treated patients, which was due to significantly increased deaths from noncardiovascular causes (most commonly cancer), with no increase in cardiovascular deaths, and no significant increase in fatal bleeding.⁴⁵ Five subsequent meta-analyses^{35–37,46,47} restricted to RCTs of studies enrolling patients treated with predominantly newer generation DES, published prior to the presentation of the OPTIDUAL (Optimal Dual Antiplatelet Therapy) trial, found numerical-

ly^{36,47} or statistically^{35,37,46} significant increased risk of all-cause (though not cardiovascular) death associated with prolonged duration of DAPT (Data Supplements 3 and 4).

In contrast, a meta-analysis that combined studies of DAPT duration after stent implantation with studies of DAPT duration for other indications⁴⁸ and an analysis of 6 trials restricted to post-MI patients treated with DAPT⁴⁴ found no increase in cardiovascular or noncardiovascular mortality rate associated with prolonged DAPT (Data Supplement 3). A US Food and Drug Administration drug safety communication, based on an evaluation of long-term clinical trials of patients with cardiovascular disease or stroke treated with clopidogrel, concluded that long-term clopidogrel treatment did not increase the risk of all-cause death or cancer-related death.⁴⁹ The primary analysis by the ERC of 11 RCTs (including OPTIDUAL) compared use of DAPT for 18 to 48 months with use of DAPT for 6 to 12 months in patients who had received predominantly newer-generation DES and found no statistically significant difference in all-cause mortality rate.³⁰

A majority of writing group members believe the data as a whole do not seem to suggest prolonged DAPT results in increased mortality.

3. OVERRIDING CONCEPTS AND RECOMMENDATIONS FOR DAPT AND DURATION OF THERAPY

3.1. General Overriding Concepts

Overriding concepts and relevant recommendations for DAPT and duration of therapy are summarized in Table 3. Intensification of antiplatelet therapy, with the addition of a P2Y₁₂ inhibitor to aspirin monotherapy, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk.^{40,41,50–52} Similarly, longer compared with shorter duration of DAPT generally results in decreased ischemic risk at the expense of increased bleeding risk.^{16,24,28,30,46} Use of more potent P2Y₁₂ inhibitors (ticagrelor or prasugrel) in place of clopidogrel also results in decreased ischemic risk and increased bleeding risk.^{53–55}

In general, recommendations for duration of DAPT in the present focused update consist of a Class I recommendation (“should be given”) for a minimum period of time (in most cases 6 to 12 months) and a Class IIb recommendation (“may be considered”) for continuation of DAPT beyond that period of time. Shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk. These recommendations do not generally apply to patients treated with oral anticoagulant therapy, who were excluded from almost all studies of DAPT duration and who are at significantly increased bleeding risk (as discussed in Section

Table 3. Overriding Concepts and Updated Recommendations for DAPT and Duration

Intensification of antiplatelet therapy, with the addition of a P2Y ₁₂ inhibitor to aspirin monotherapy, as well as prolongation of DAPT, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk. Decisions about treatment with and duration of DAPT require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.
In general, shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk.
Prior recommendations for duration of DAPT for patients treated with DES were based on data from “first-generation” DES, which are rarely if ever used in current clinical practice. Compared with first-generation stents, newer-generation stents have an improved safety profile and lower risk of stent thrombosis. Recommendations in this focused update apply to newer-generation stents.
Updated recommendations for duration of DAPT are now similar for patients with NSTEMI-ACS and STEMI, as both are part of the spectrum of acute coronary syndrome.
A Class I recommendation (“should be given”) in most clinical settings is made for at least 6–12 months of DAPT (depending on the setting), and a Class IIb recommendation (“may be reasonable”) is made for prolonged DAPT beyond this initial 6- to 12-month period.
In studies of prolonged DAPT after DES implantation or after MI, duration of therapy was limited to several years (akin to many other studied therapies). Thus, in patients for whom the benefit/risk ratio seemingly favors prolonged therapy, the true optimal duration of therapy is unknown.
Recommendations in the document apply specifically to duration of P2Y ₁₂ inhibitor therapy in patients with CAD treated with DAPT. Aspirin therapy should almost always be continued indefinitely in patients with CAD.
Lower daily doses of aspirin, including in patients treated with DAPT, are associated with lower bleeding complications and comparable ischemic protection ^{56–60} than are higher doses of aspirin. The recommended daily dose of aspirin in patients treated with DAPT is 81 mg (range, 75 mg to 100 mg).

CAD indicates coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; and STEMI, ST-elevation myocardial infarction.

3.4). Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference. Aspirin therapy is almost always continued indefinitely in patients with CAD, and recommendations on duration of DAPT should be taken to mean the recommended duration of P2Y₁₂ inhibitor therapy (in addition to aspirin therapy). Figure 1 summarizes recommendations for duration of DAPT according to clinical status.

3.2. Factors Associated With Increased Ischemic and Bleeding Risk

Factors that have been associated with increased ischemic risk (including increased risk of stent thrombosis)

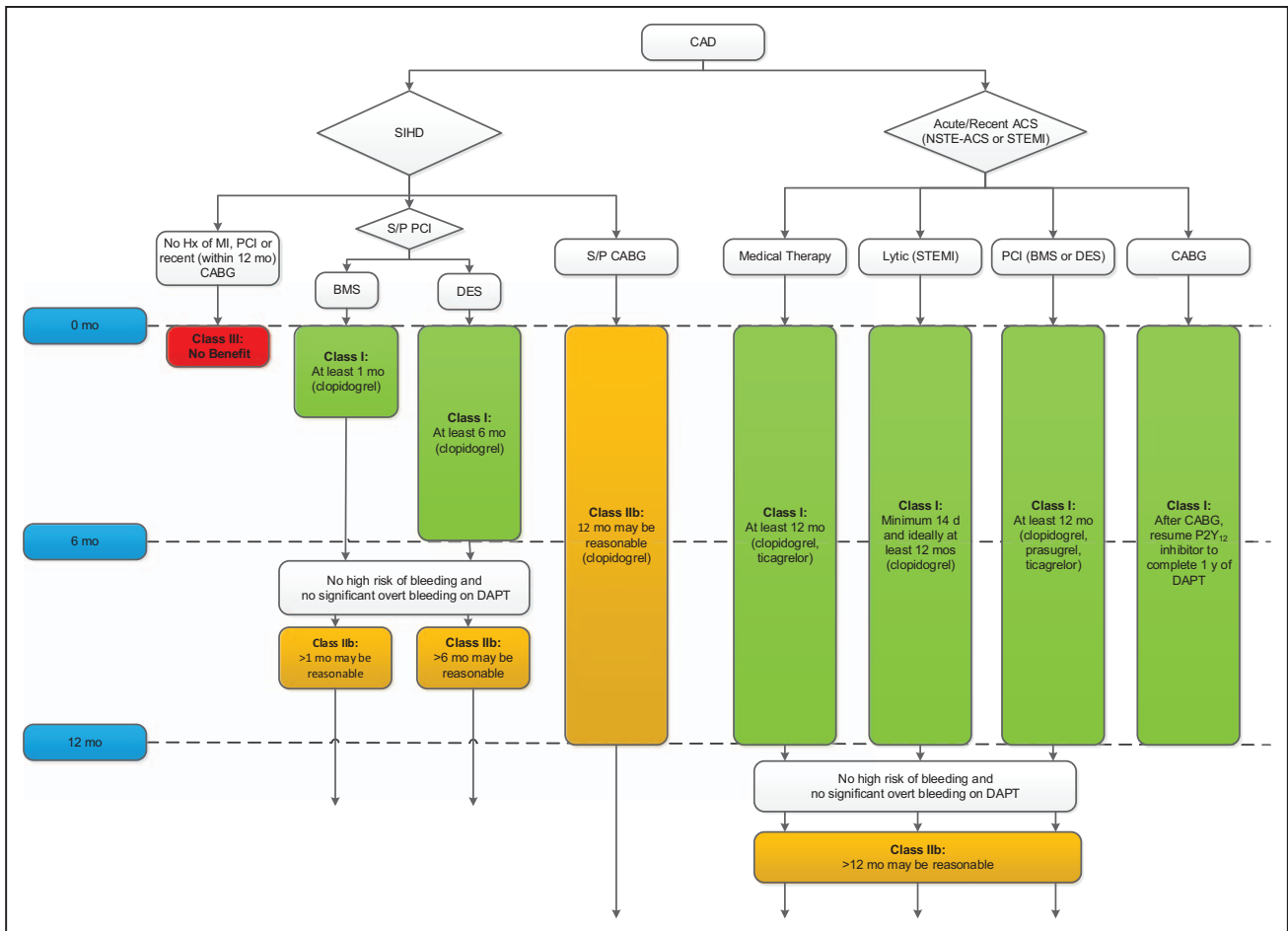


Figure 1. Master treatment algorithm for duration of P2Y₁₂ inhibitor therapy in patients with CAD treated with DAPT.

Colors correspond to Class of Recommendation in Table 1. Clopidogrel is the only currently used P2Y₁₂ inhibitor studied in patients with SIHD undergoing PCI. Aspirin therapy is almost always continued indefinitely in patients with CAD. Patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to SIHD. In patients treated with DAPT after DES implantation who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y₁₂ inhibitor therapy after 3 months for SIHD or after 6 months for ACS may be reasonable. Arrows at the bottom of the figure denote that the optimal duration of prolonged DAPT is not established. ACS indicates acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Hx, history; lytic, fibrinolytic therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; S/P, status post; and STEMI, ST-elevation myocardial infarction.

and increased bleeding risk are listed in Table 4. Individual patients may have factors for both increased ischemic and bleeding risk, and some factors are associated with both increased ischemic and bleeding risk, making it difficult in many patients to assess the benefit/risk ratio of prolonged DAPT.

A new risk score (the “DAPT score”), derived from the Dual Antiplatelet Therapy study, may be useful for decisions about whether to continue (prolong or extend) DAPT in patients treated with coronary stent implantation. Analysis of study data suggests that in patients treated for 1 year with DAPT without significant bleeding or ischemic events, the benefit/risk ratio with prolonged DAPT may be

favorable for those with a high DAPT score (≥2) because prolonged DAPT reduces net (ischemic plus bleeding) events when compared with nonprolonged DAPT.⁶¹ Conversely, in those with a low DAPT score (<2), the benefit/risk ratio with prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events). Factors that contribute to a high DAPT score include diabetes mellitus, current cigarette use, prior PCI or prior MI, congestive heart failure or left ventricular ejection fraction <30%, MI at presentation, vein graft PCI, and stent diameter <3 mm; older age contributes to a low (less favorable) DAPT score. Factors and their weighting used to calculate a DAPT score are provided in Table 5.

3.3. Specific P2Y₁₂ Inhibitors: Recommendations

See [Data Supplement 5](#) for evidence supporting these recommendations.

Recommendations for Specific P2Y ₁₂ Inhibitors		
COR	LOE	Recommendations
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTEMI-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{53,71,72}
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{54,55}
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA. ⁵⁴

In the PLATO (Platelet Inhibition and Patient Outcomes) trial,⁵³ patients with ACS were treated with either medical therapy alone or medical therapy plus PCI. Treatment with ticagrelor 90 mg twice daily, compared with clopidogrel 75 mg once daily, resulted in fewer ischemic complications and stent thromboses but more frequent non-CABG-related bleeding ([Data Supplement 5](#)). In the TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis In Myocardial Infarction 38)⁵⁴ study, patients with ACS undergoing planned PCI were treated with prasugrel 10 mg daily, compared with clopidogrel 75 mg daily. Prasugrel treatment resulted in fewer ischemic complications and stent thromboses but more frequent bleeding, including life-threatening and fatal bleeding. Because of increased rates of major bleeding with prasugrel (compared with clopidogrel), there was no net benefit of prasugrel therapy in those ≥75 years of age and those <60 kg, and there was net harm (including increased risk of intracranial hemorrhage) in those with prior stroke or transient ischemic attack (TIA). The Class IIa preferential recommendations for ticagrelor 90 mg twice daily and for prasugrel 10 mg once daily (compared with clopidogrel) in the 2014 Non-ST-Elevation Acute Coronary Syndromes (NSTEMI-ACS) guideline are continued in this focused update and are now included in relevant PCI and ST-Elevation Myocardial Infarction (STEMI) recommendations, as well.

In the PEGASUS-TIMI 54 study of post-MI patients, both 60-mg and 90-mg twice-daily doses of ticagrelor were evaluated.²⁸ The benefit/risk ratio appears to be numerically more favorable for the 60-mg dose, although no formal statistical comparison was made

Table 4. Clinical and Procedural Factors Associated With Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk^{62–70}

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)	Increased Bleeding Risk (may favor shorter-duration DAPT)
Increased ischemic risk	History of prior bleeding
Advanced age	Oral anticoagulant therapy
ACS presentation	Female sex
Multiple prior MIs	Advanced age
Extensive CAD	Low body weight
Diabetes mellitus	CKD
CKD	Diabetes mellitus
Increased risk of stent thrombosis	Anemia
ACS presentation	Chronic steroid or NSAID therapy
Diabetes mellitus	
Left ventricular ejection fraction <40%	
First-generation drug-eluting stent	
Stent undersizing	
Stent underdeployment	
Small stent diameter	
Greater stent length	
Bifurcation stents	
In-stent restenosis	

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; and NSAID, nonsteroidal anti-inflammatory drug.

between results of the 2 dosing regimens. The 60-mg twice-daily dose has now been approved by the US Food and Drug Administration for reduction in ischemic events in patients with ACS or a history of MI.⁷³

3.4. Platelet Function Testing, Genetic Testing, and Switching of P2Y₁₂ Inhibitors

The role of platelet function testing and genetic testing in patients treated with DAPT is addressed in the 2011 ACCF/AHA/SCAI PCI guideline and the 2014 ACC/AHA NSTEMI-ACS guideline.^{9,14} To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide P2Y₁₂ inhibitor therapy improves outcome; thus, the routine use of platelet function and genetic testing is not recommended (Class III: No Benefit).

No randomized data are available on the long-term safety or efficacy of “switching” patients treated for weeks or months with a P2Y₁₂ inhibitor to a different P2Y₁₂ inhibitor.

Table 5. Factors Used to Calculate a “DAPT Score”

Variable	Points
Age ≥75 y	-2
Age 65 to <75 y	-1
Age <65 y	0
Current cigarette smoker	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter <3 mm	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Saphenous vein graft PCI	2

A score of ≥2 is associated with a favorable benefit/risk ratio for prolonged DAPT while a score of <2 is associated with an unfavorable benefit/risk ratio.

CHF indicates congestive heart failure; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Adapted with permission from Yeh et al.⁶¹

3.5. Proton Pump Inhibitors and DAPT

The use of proton pump inhibitors (PPIs) in patients treated with DAPT is discussed in a 2010 ACCF/ACG/AHA expert consensus document.⁷⁴ Recommendations on the use of PPIs are given in the 2011 ACCF/AHA/SCAI PCI guideline.⁹ PPIs should be used in patients with a history of prior gastrointestinal bleeding treated with DAPT (Class I). In patients with increased risk of gastrointestinal bleeding, including those with advanced age and those with concomitant use of warfarin, steroids, or nonsteroidal anti-inflammatory drugs, use of PPIs is reasonable (Class IIa). Routine use of PPIs is not recommended for patients at low risk of gastrointestinal bleeding (Class III: No Benefit).

3.6. Aspirin Dosing in Patients Treated With DAPT: Recommendation

See [Data Supplement 6](#) for evidence supporting this recommendation.

Recommendation for Aspirin Dosing in Patients Treated With DAPT		
COR	LOE	Recommendation
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56–60,75–78}

Because aspirin dosing recommendations across ACC/AHA clinical practice guidelines are not consistent with regard to dose or class of recommendation, and

because aspirin is a component of DAPT, a comprehensive review of these issues was undertaken. Large overviews, including studies of nearly 200 000 persons, have consistently shown that lower aspirin doses (≤100 mg daily) are associated with less major and total bleeding than are higher doses, either when used as monotherapy or when combined with the P2Y₁₂ inhibitor clopidogrel.^{56,58,75,76,78} Daily aspirin doses as low as 30 mg to 50 mg inactivate the platelet cyclo-oxygenase-1 enzyme and inhibit thromboxane production.^{79–81} Studies comparing lower (75 mg to 150 mg) with higher aspirin doses have consistently found comparable ischemic event rates with either dose when used as monotherapy or when combined with the P2Y₁₂ inhibitor clopidogrel.^{56–60,78} The efficacy of ticagrelor seems to be decreased in patients treated with higher aspirin doses (≥300 mg daily) versus lower aspirin doses (≤100 mg daily).⁸² On the basis of available data, the optimal range of aspirin dose in patients treated with DAPT that provides maximal protection from ischemic events and minimizes bleeding risk appears to be 75 mg to 100 mg ([Data Supplement 6](#)). For practical purposes, because the relevant aspirin dose available in the United States is 81 mg, this maintenance dose is recommended in patients with CAD treated with DAPT. The ongoing ADAPT-ABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial, which the present writing group endorses, is expected to yield additional information on optimal aspirin dosing in patients with atherosclerotic cardiovascular disease.⁸³

3.7. Triple Therapy (Aspirin, P2Y₁₂ Inhibitor, and Oral Anticoagulant)

The recommended management of patients on “triple therapy” (aspirin, P2Y₁₂ inhibitor, and oral anticoagulant) is beyond the scope of this focused update. However, a brief discussion of the topic is included for the purposes of completeness and end-user education.

Compared with oral anticoagulation therapy alone, the addition of DAPT to oral anticoagulant therapy results in at least a 2- to 3-fold increase in bleeding complications.^{84–87} Discussion and recommendations on triple therapy are provided in the 2014 ACC/AHA NSTEMI-ACS guideline,¹⁴ a 2014 European joint consensus document,⁸⁸ a North American consensus document,⁸⁵ and several comprehensive state-of-the-art papers and reviews. A partial summary and synthesis of these recommendations are given in [Table 6](#).

One trial comparing “double therapy” (oral anticoagulant plus clopidogrel) with triple therapy (oral anticoagulant plus aspirin and clopidogrel)⁸⁹ and 1 trial comparing differing durations of triple therapy have been published.⁹⁰ Several more similar trials comparing oral anticoagulant therapy plus P2Y₁₂ inhibitor with triple therapy are ongoing.

Table 6. Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy^{14,88,91–93}

Assess ischemic and bleeding risks using validated risk predictors (eg, CHA ₂ DS ₂ -VASc, HAS-BLED)
Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
Consider a target INR of 2.0–2.5 when warfarin is used
Clopidogrel is the P2Y ₁₂ inhibitor of choice
Use low-dose (≤100 mg daily) aspirin
PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding

CHA₂DS₂-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly; INR, international normalized ratio; and PPIs, proton pump inhibitors.

4. PERCUTANEOUS CORONARY INTERVENTION

4.1. Duration of DAPT in Patients With SIHD Treated With PCI: Recommendations

See *Data Supplements 1 to 3 and 6 to 9* for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With SIHD Treated With PCI		
COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month. ^{94,95}
I	B-R ^{SR}	In patients with SIHD treated with DAPT after DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months. ^{17,18,21,30,96,97}
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56–60,75–78}
IIb	A ^{SR}	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable. ^{16,22,24–26,30,50}

Recommendations for Duration of DAPT in Patients With SIHD Treated With PCI (Continued)

COR	LOE	Recommendations
IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 3 months may be reasonable. ^{19,20,34,36,37}

SR indicates systematic review.

4.2. Duration of DAPT in Patients With ACS Treated With PCI: Recommendations

See *Data Supplements 1 to 9* for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With ACS Treated With PCI

COR	LOE	Recommendations
I	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months. ^{16,50–55,72,96–98}
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56–60,75–78}
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{53,72}
IIa	B-R	In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{54,55}
IIb	A ^{SR}	In patients with ACS (NSTEMI-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable. ^{16,22–26,28,30,40,41,43,53,54,72}
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 6 months may be reasonable. ^{17–21,34,36,37}
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA. ⁵⁴

SR indicates systematic review.

4.3. Duration of DAPT in Patients With SIHD and ACS Treated with PCI

DAPT in patients treated with coronary stent implantation reduces the risk of stent thrombosis and ischemic events^{50,51,94,95,99} (Data Supplement 7). The risk of stent thrombosis in patients treated with a bare metal stent (BMS) is greatest in the first days to weeks after implantation.^{99,100} Cessation of DAPT during this period, particularly in cases of patients undergoing surgery, is associated with an unacceptable rate of often catastrophic stent thrombosis.^{101–103} Thus, a minimum duration of DAPT of 1 month is generally recommended for patients treated with BMS. In current practice, BMS are generally reserved for patients who cannot receive DAPT for more than ≈1 month for reasons of active bleeding, nonadherence to medical therapy, or planned surgery.

The recommended minimum duration of DAPT in patients treated with first-generation DES, based primarily on observational data and one subgroup analysis, has been 12 months.^{9,51,97,104,105} Compared with first-generation DES, currently used newer-generation DES have a lower risk of stent thrombosis and appear to require a shorter minimum duration of DAPT.^{17,18,21,38,96,97} Five RCTs^{17–21} of primarily low-risk (non-ACS) patients treated with DES comparing shorter-duration (3 to 6 months) DAPT with 12 months of DAPT, as well as several meta-analyses^{34–37} and an analysis by the ERC,³⁰ did not find an increased risk of stent thrombosis with shorter-duration DAPT, although the individual trials were underpowered to detect such a difference (Data Supplements 1 and 3). Therefore, in patients with SIHD treated with DES, the minimum recommended duration of DAPT has been decreased from 12 to 6 months.

The PCI-CURE analysis⁵¹ of patients in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial⁵² demonstrated that treatment with DAPT for up to 12 months in patients with NSTEMI-ACS treated with BMS reduced ischemic events compared with aspirin monotherapy (Data Supplement 4). Based primarily on the CURE trial and PCI-CURE analyses, the prior recommendation that patients with NSTEMI-ACS treated with coronary stent implantation be treated with DAPT for at least 12 months is continued in this update and has been extrapolated to patients with STEMI treated with PCI as well, on the basis of the consideration that NSTEMI-ACS and STEMI are part of the spectrum of ACS.

As detailed in Section 2, treatment with prolonged (or “extended”) DAPT beyond a minimum recommended duration of therapy necessitates a fundamental tradeoff between decreasing ischemic risk (eg, MI and stent thrombosis) and increasing bleeding risk.^{16,30,34,36,37,46} Prolonged or extended DAPT for an additional 18 to 36 months (after an initial 6 to 12 months of DAPT) in patients treated with DES implantation results in an absolute decrease in stent thrombosis and ischemic complications of ≈1% to 2% and an absolute increase in bleeding complications of ≈1% (Data Supplements 1, 2, and 3).^{16,22–27,30,35–37,46} Newer-generation stents, par-

ticularly everolimus-eluting stents, are associated with lower rates of stent thrombosis, and the absolute reduction in the rate of stent thrombosis with prolonged DAPT in patients treated with everolimus-eluting stents is modest.^{39,106–109}

The benefit/risk ratio of prolonged DAPT in patients treated with PCI may be more favorable for those with prior MI (or ACS) than for those with SIHD.^{28,41,43} Preliminary data suggest that in patients with a high DAPT score the benefit/risk ratio with prolonged DAPT may be favorable and that in those with a low DAPT score the benefit/risk ratio with prolonged DAPT is not favorable.⁶¹ In patients treated with coronary stent implantation who have increased bleeding risk (eg, oral anticoagulation), increased risk of severe bleeding complications (eg, major intracranial surgery), or significant overt bleeding, the benefit/risk ratio may favor shorter-than-recommended duration of DAPT.^{17–21,34,36} Decisions about treatment with and duration of DAPT require a thoughtful assessment of the benefit/risk ratio, integration of current and future study data, and consideration of patient preference.

In studies of drug-eluting bioabsorbable polymer stents and bioabsorbable stents (third- and fourth-generation stents), by study protocol, DAPT was continued for at least 6 to 12 months.^{110–116} In a study of a novel polymer-free and carrier-free drug-coated stent in patients at high risk of bleeding complications, by study protocol, DAPT was continued for only 1 month.¹¹⁷ These stents have not been included in the studies of shorter- or longer-duration (prolonged/extended) DAPT discussed in this focused update. Because none of these stents (except one biodegradable polymer DES) was approved by the US Food and Drug Administration at the time this focused update was written, recommendations for duration of DAPT for such stents are not included.

Recommendations for duration of DAPT in patients treated with PCI are summarized in Figure 2.

5. RECOMMENDATIONS FOR DURATION OF DAPT IN PATIENTS UNDERGOING CABG

See Data Supplements 4, 6, 10, and 11 for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients Undergoing CABG

COR	LOE	Recommendations
I	C-EO	In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y ₁₂ inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed.
I	C-LD	In patients with ACS (NSTEMI-ACS or STEMI) being treated with DAPT who undergo CABG, P2Y ₁₂ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS. ^{52–54,118–120}

Recommendations for Duration of DAPT in Patients Undergoing CABG (Continued)		
COR	LOE	Recommendations
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56-60,75-78}
IIb	B-NR	In patients with SIHD, DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency. ¹²¹⁻¹²⁵

Aspirin therapy after CABG improves vein graft patency, particularly during the first postoperative year, and reduces MACE.¹²⁶⁻¹³⁰ In the CURE study,⁵² the reduction in ischemic events in patients treated with aspirin plus clopidogrel who underwent CABG was consistent with the study population as a whole, although benefit was primarily observed mainly before the procedure.¹¹⁸ A propensity score analysis of a Danish administrative database¹²⁰ demonstrated during a mean follow-up of 466±144 days significantly fewer deaths in patients treated with aspirin plus clopidogrel than in those treated with aspirin alone, although there was no reduction in the incidence of recurrent MI.

The impact of clopidogrel on graft occlusion after on-pump CABG has been evaluated in 5 studies (Data Supplement 10). Several randomized and nonrandomized trials and a post hoc substudy analysis of patients predominantly undergoing on-pump CABG did not demonstrate any differences in graft patency between antiplatelet monotherapy and DAPT when assessed at follow-up ranging from 1 month to 1 year after CABG.¹³¹⁻¹³⁴ In the only RCT to demonstrate a benefit of DAPT, vein graft patency 3 months after CABG was significantly higher in patients treated with clopidogrel and aspirin (100 mg) than in those receiving aspirin monotherapy.¹²¹

Two meta-analyses and 1 systematic overview assessed the potential benefits of DAPT after CABG and reported mixed results^{122,123,135} (Data Supplement 10). In the largest meta-analysis of patients pooled from 5 RCTs and 6 observational studies,¹²² DAPT was associated with reduced vein graft occlusion and 30-day mortality rate as compared with aspirin monotherapy. A meta-analysis of only the 5 RCTs¹²³ showed that DAPT was associated with a significantly lower vein graft occlusion at 1 year versus antiplatelet monotherapy but with no improvement in arterial graft patency. Major bleeding after surgery was more frequent with DAPT.^{122,123,135}

The benefits of DAPT in off-pump CABG patients were noted in terms of improved graft patency^{124,125} and clinical outcome¹³⁶ in single-center observational studies^{124,136} and an RCT¹²⁵ (Data Supplement 10).

Only data from post hoc analyses are available on the utility of newer P2Y₁₂ inhibitors in patients with ACS who undergo CABG. In a retrospective analysis of patients in the TRITON-TIMI 38 study⁵⁴ who underwent CABG,¹³⁷ prasugrel

treatment was associated with a significantly lower 30-day mortality rate than that of clopidogrel and more postoperative blood loss. A post hoc analysis of patients who underwent CABG in the PLATO study⁵³ showed that the primary endpoint at 1 year was similar for both treatments, but a significant reduction in cardiovascular mortality was noted with ticagrelor compared with clopidogrel.^{138,139}

Issues related to the timing of discontinuation of DAPT before CABG are beyond the scope of this update but are addressed in the 2011 CABG guideline.¹⁰ Figure 3 summarizes recommendations for the management and duration of P2Y₁₂ inhibitor therapy in patients undergoing CABG.

6. RECOMMENDATIONS FOR DURATION OF DAPT IN PATIENTS WITH SIHD

See *Data Supplements 1 to 4 and 6 to 11* for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With SIHD		
COR	LOE	Recommendations
I	A	In patients with SIHD treated with DAPT after BMS implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month. ^{94,95}
I	B-R ^{SR}	In patients with SIHD treated with DAPT after DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months. ^{17,18,21,30,96,97}
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56-60,75-78}
IIb	A ^{SR}	In patients with SIHD being treated with DAPT for an MI that occurred 1 to 3 years earlier who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), further continuation of DAPT may be reasonable. ^{28,30,40,41,44}
IIb	A ^{SR}	In patients with SIHD treated with BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable. ^{16,22,24-26,30,50}
IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 3 months may be reasonable. ^{19,20,34,36,37}

CLINICAL STATEMENTS AND GUIDELINES

Recommendations for Duration of DAPT in Patients With SIHD (Continued)		
COR	LOE	Recommendations
IIb	B-NR	In patients with SIHD, treatment with DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency. ¹²¹⁻¹²⁵
III: No Benefit	B-R	In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG, treatment with DAPT is not beneficial. ^{28,40-42}

SR indicates systematic review.

For the purposes of this update, patients with a history of ACS >1 year prior who have remained free of recurrent ACS are considered to have transitioned to SIHD.

In the CHARISMA trial, which randomized patients with established atherosclerosis or at high risk of clinical atherosclerotic disease to either DAPT (with clopidogrel) or aspirin monotherapy, no significant reduction was found in ischemic effects at a median follow-up of 28 months with DAPT, but a 0.4% absolute increase was seen in severe bleeding.⁴⁰ In a post hoc analysis of patients enrolled in the study with prior MI, a 1.7% absolute decrease in the composite endpoint of cardiovascular death, MI, or stroke events was observed with DAPT, but no benefit was seen in

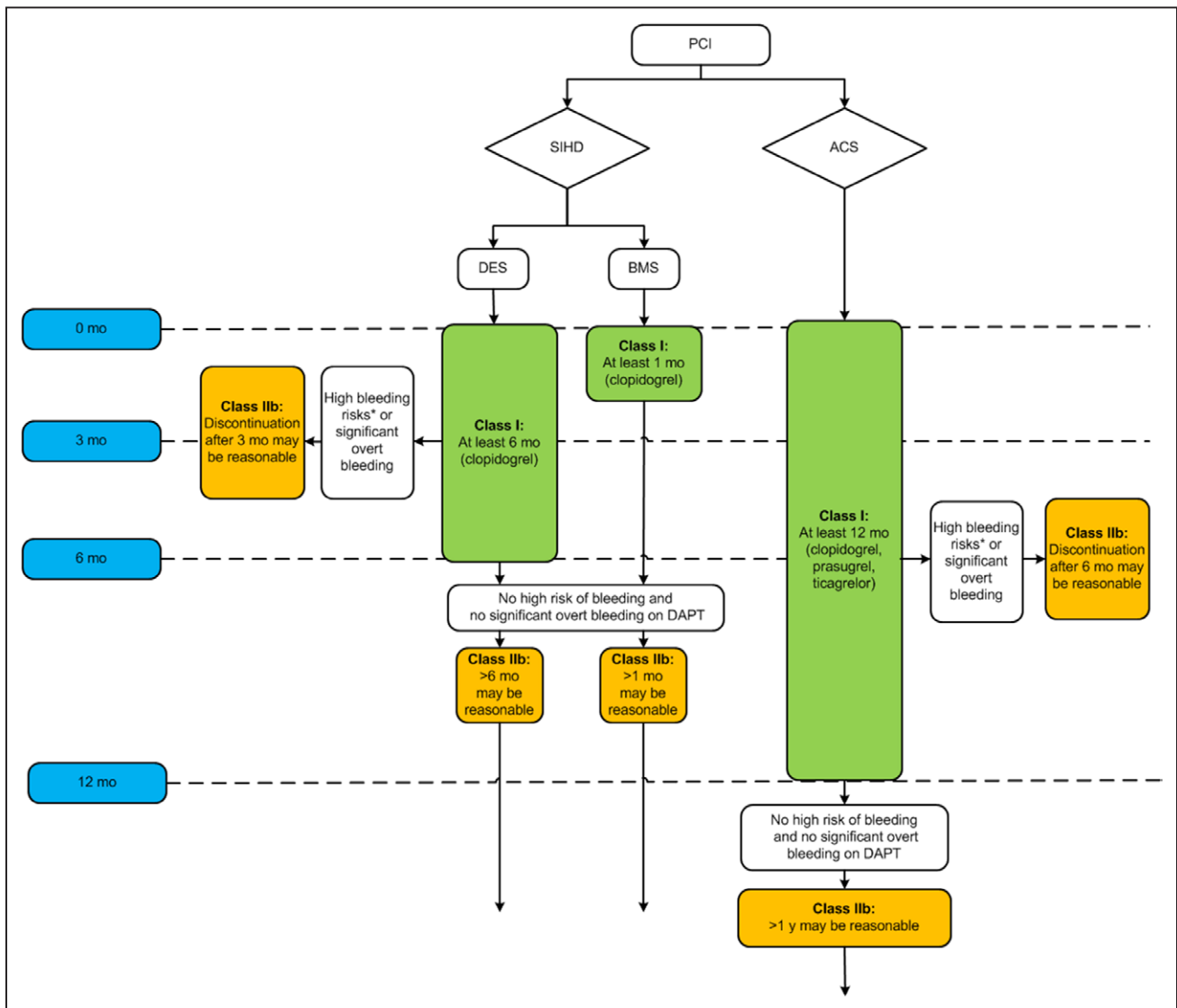


Figure 2. Treatment algorithm for duration of P2Y₁₂ inhibitor therapy in patients treated with PCI. Colors correspond to Class of Recommendation in Table 1.¹² Arrows at the bottom of the figure denote that the optimal duration of prolonged DAPT is not established. Clopidogrel is the only currently used P2Y₁₂ inhibitor studied in patients with SIHD undergoing PCI. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. *High bleeding risk denotes those who have or develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (eg, major intracranial surgery). ACS indicates acute coronary syndrome; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention; and SIHD, stable ischemic heart disease.

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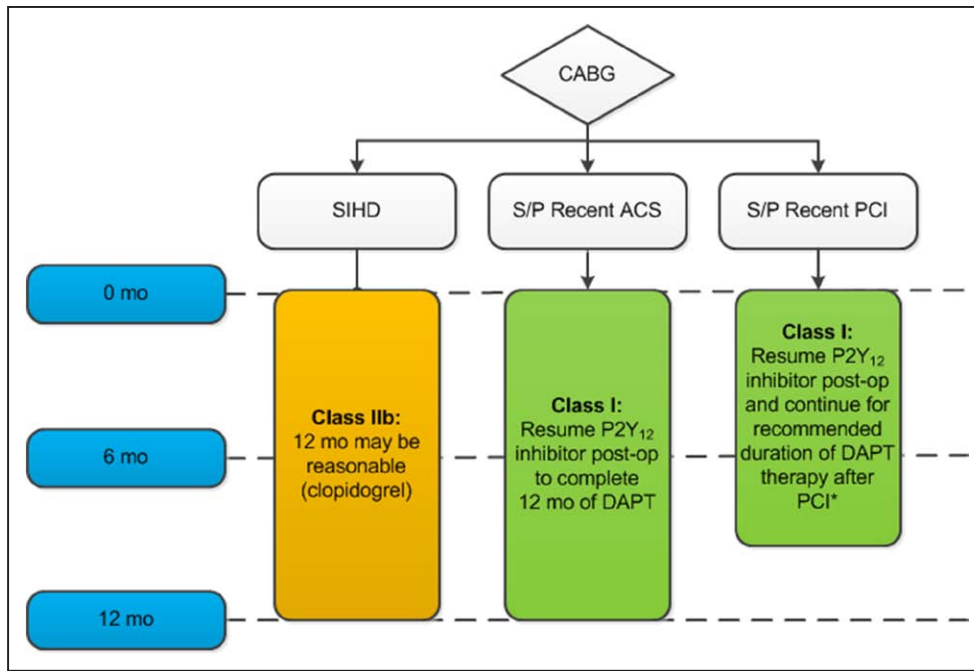


Figure 3. Treatment algorithm for management and duration of P2Y₁₂ inhibitor therapy in patients undergoing CABG.

Colors correspond to Class of Recommendation in Table 1. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. *Duration of DAPT therapy can vary from as little as 4 weeks to >12 months, depending on the clinical setting and bleeding risk. ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; NSTEMI-ACS, non-ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; post-op, postoperatively; SIHD, stable ischemic heart disease; and S/P, status post.

those with CAD without prior MI (Data Supplement 4).^{40,41} In the PEGASUS-TIMI 54 trial, in which stable patients 1 to 3 years after MI with additional high-risk features were randomized to either DAPT (with ticagrelor 60 mg or 90 mg twice daily) or continued aspirin monotherapy, a mean of 33 months of DAPT led to a 1.2% to 1.3% absolute reduction in ischemic events and a 1.2% to 1.5% increase in major bleeding.²⁸ In subgroup analysis, the greatest reduction in ischemic events was in patients in whom P2Y₁₂ inhibitor therapy either had not been discontinued or had been discontinued ≤30 days before enrollment in the study (absolute reduction in MACE: 1.9% to 2.5%), and no benefit was seen in patients in whom P2Y₁₂ inhibitor therapy had been discontinued >1 year before enrollment in the study.⁴² On the basis of all studies of DAPT in post-MI patients, extended DAPT for approximately 18 to 36 months leads to an absolute decrease in ischemic complications of ≈1% to 3% and an absolute increase in bleeding complications of ≈1% (Data Supplement 4).^{28,40,41,43,44}

DAPT is not recommended in patients with SIHD without prior stent implantation and no history of ACS or MI. Decisions about treatment with and duration of DAPT in patients with SIHD with a history of MI or coronary stent implantation require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.

Figure 4 summarizes recommendations on duration of P2Y₁₂ inhibitor therapy in patients with SIHD.

7. ACUTE CORONARY SYNDROME (NSTEMI-ACS AND STEMI)

7.1. Duration of DAPT in Patients With ACS Treated With Medical Therapy Alone (Without Revascularization or Fibrinolytic Therapy): Recommendations

See Data Supplements 4 to 6 for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With ACS Treated with Medical Therapy Alone

COR	LOE	Recommendations
I	B-R	In patients with ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, P2Y ₁₂ inhibitor therapy (clopidogrel or ticagrelor) should be continued for at least 12 months. ^{52,71,140,141}
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56-60,75-78}
IIa	B-R	In patients with NSTEMI-ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{53,71}

Recommendations for Duration of DAPT in Patients With ACS Treated with Medical Therapy Alone (Continued)		
COR	LOE	Recommendations
IIb	A ^{SR}	In patients with ACS treated with medical therapy alone (without revascularization or fibrinolytic therapy) who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 12 months may be reasonable. ^{28,30,40,41,43,53,71,141}

SR indicates systematic review.

7.2. Duration of DAPT in Patients With STEMI Treated With Fibrinolytic Therapy: Recommendations

See *Data Supplements 4 and 6* for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With STEMI Treated With Fibrinolytic Therapy		
COR	LOE	Recommendations
I	A	In patients with STEMI treated with DAPT in conjunction with fibrinolytic therapy, P2Y ₁₂ inhibitor therapy (clopidogrel) should be continued for a minimum of 14 days (<i>Level of Evidence: A</i>) ^{140,142} and ideally at least 12 months (<i>Level of Evidence: C-EO</i>).
	C-EO	
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56–60,75–78}
IIb	A ^{SR}	In patients with STEMI treated with fibrinolytic therapy who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 12 months may be reasonable. ^{16,22–26,28,30,40,41,43,53,54,71,72,141}

SR indicates systematic review.

7.3. Duration of DAPT in Patients With ACS Treated With PCI: Recommendations

See *Data Supplements 1 to 9* for evidence supporting these recommendations.

Recommendations for Duration of DAPT in Patients With ACS Treated With PCI		
COR	LOE	Recommendations
I	B-R	In patients with ACS treated with DAPT after BMS or DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months. ^{16,50–55,72,96–98}
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. ^{56–60,75–78}

Recommendations for Duration of DAPT in Patients With ACS Treated With PCI (Continued)		
COR	LOE	Recommendations
IIa	B-R	In patients with ACS treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{53,72}
IIa	B-R	In patients with ACS treated with DAPT after coronary stent implantation, who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy. ^{54,55}
IIb	A ^{SR}	In patients with ACS treated with coronary stent implantation who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use) continuation of DAPT for longer than 12 months may be reasonable. ^{16,22–26,28,30,40,41,43,53,54,72}
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ therapy after 6 months may be reasonable. ^{17–21,34,36,37}
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA. ⁵⁴

SR indicates systematic review.

7.4. Duration of DAPT in Patients With ACS Treated With CABG: Recommendation

See *Data Supplement 4 and 11* for evidence supporting this recommendation.

Recommendation for Duration of DAPT in Patients With ACS Treated With CABG		
COR	LOE	Recommendation
I	C-LD	In patients with ACS being treated with DAPT who undergo CABG, P2Y ₁₂ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS. ^{52–54,118–120}

7.5. Duration of DAPT in Patients With ACS

Aspirin remains the cornerstone of antiplatelet therapy in patients with ACS. Further platelet inhibition,

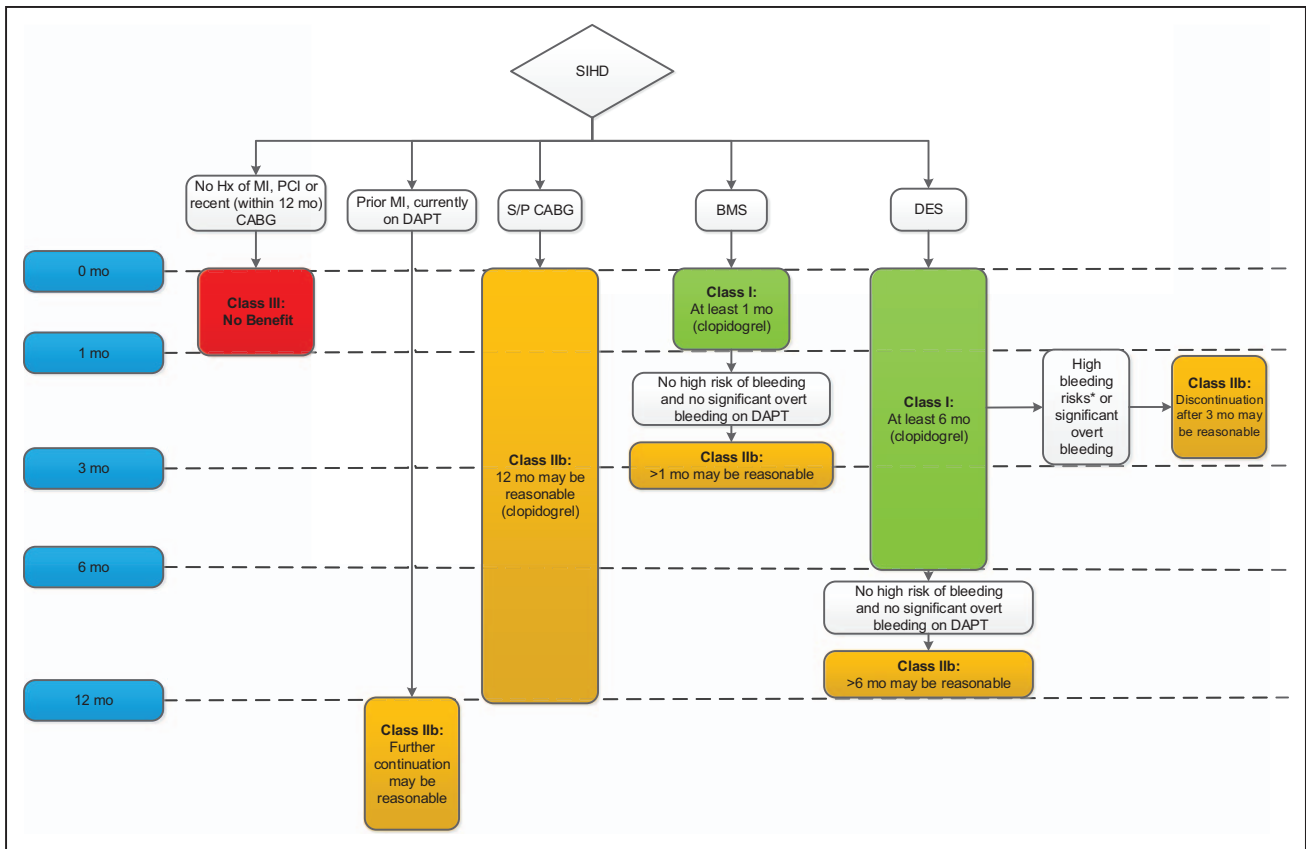


Figure 4. Treatment algorithm for duration of P2Y₁₂ inhibitor therapy in patients with SIHD (without ACS within the past several years).

Colors correspond to Class of Recommendation in Table 1. Patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to SIHD. Arrows at the bottom of the figure denote that the optimal duration of prolonged DAPT is not established. Clopidogrel is the only currently used P2Y₁₂ inhibitor studied in patients with SIHD undergoing PCI. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease.

*High bleeding risk denotes those who have or develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (eg, major intracranial surgery). ACS indicates acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Hx, history; MI, myocardial infarction; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; and S/P, status post.

with an associated reduction in ischemic risk, can be achieved by blocking the P2Y₁₂ receptor. In the CURE trial of patients with NSTEMI-ACS, the addition of clopidogrel (for up to 1 year) to aspirin monotherapy resulted in a 2.1% absolute reduction in subsequent ischemic events but also a 1.0% absolute increase in major bleeding.⁵² The majority of patients in this study were treated without revascularization, though benefit was observed both in those treated with revascularization (PCI or CABG) and in those treated with medical therapy alone.^{51,52} Available evidence from this trial, as well as from PLATO^{53,71,72} and TRITON-TIMI 38,^{54,55} supports DAPT duration of at least 12 months for patients with NSTEMI-ACS.

The results of the CURE trial⁵² and PCI-CURE analyses of the CURE trial⁵¹ (Data Supplement 4) have been

extrapolated to patients with STEMI on the basis of the consideration that NSTEMI-ACS and STEMI are both part of the spectrum of ACS and usually caused by coronary plaque rupture. Based on this consideration, as well as the results from the PLATO and TRITON-TIMI 38 trials, it is recommended that patients with STEMI treated with coronary stent implantation or medical therapy alone (without revascularization or reperfusion therapy) be treated with DAPT for at least 12 months.^{53–55,71,72} Ticagrelor is considered a P2Y₁₂ treatment option in patients with STEMI not treated with revascularization (or reperfusion therapy) on the basis of a similar extrapolation of the results of the “medically managed” patients with ACS in the PLATO trial.⁷¹ On the basis of CURE, PCI-CURE, PLATO, and TRITON-TIMI 38, clopidogrel, prasugrel, and ticagrelor

are all P2Y₁₂ treatment options in patients with ACS treated with PCI.

In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis In Myocardial Infarction 28) trial, short-term treatment (up to 8 days) with clopidogrel (in addition to aspirin) in patients with STEMI undergoing fibrinolytic therapy improved TIMI flow grade in the culprit artery and decreased the composite endpoint of cardiovascular death, reinfarction, or the need for urgent revascularization.¹⁴² In COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (93% with STEMI not managed with primary PCI), treatment for ≈2 weeks with clopidogrel (in addition to aspirin 162 mg) resulted in a 0.9% absolute reduction of the 28-day composite endpoint of death, reinfarction, or stroke and a 0.6% absolute reduction in death.¹⁴⁰ A 1.1% absolute risk reduction in the composite endpoint was seen in the subgroup of patients who received fibrinolytic therapy. On the basis of these trials and extrapolation of the results of CURE, DAPT with aspirin and clopidogrel is recommended for a minimum of 14 days and ideally at least 12 months in patients with STEMI treated with fibrinolytic therapy (Data Supplement 4).

As discussed in Section 3, treatment with prolonged (extended) DAPT beyond a minimum recommended duration necessitates a fundamental tradeoff between decreasing ischemic risk (eg, MI and stent thrombosis) and increasing bleeding risk.^{16,24,28,30,34,36,37,46} In post-MI patients, extended DAPT for approximately 18 to 36 months leads to an absolute decrease in ischemic complications of ≈1% to 3% and an absolute increase in bleeding complications of ≈1% (Data Supplement 4).^{28,40,41,43,44} An analysis from the PEGASUS-TIMI 54 trial found that the greatest reduction in ischemic events with prolonged DAPT in post-MI patients was in patients in whom P2Y₁₂ inhibitor therapy either had not been discontinued or had been discontinued for ≤30 days (absolute reduction in MACE: 1.9% to 2.5%). No benefit was seen in patients in whom P2Y₁₂ inhibitor therapy had been discontinued >1 year before enrollment in the study.⁴² Decisions about treatment with and duration of DAPT in patients with ACS require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.

In patients treated with DAPT with high bleeding risk (eg, oral anticoagulation), increased risk of severe bleeding complications (eg, major intracranial surgery), or significant overt bleeding, the benefit/risk ratio may favor shorter-than-recommended duration of DAPT.^{17–21,34,36}

Recommendations for DAPT in patients with ACS treated with medical therapy alone, fibrinolytic therapy, PCI, and CABG are summarized in Figure 5.

8. PERIOPERATIVE MANAGEMENT—TIMING OF ELECTIVE NONCARDIAC SURGERY IN PATIENTS TREATED WITH PCI AND DAPT: RECOMMENDATIONS

See *Data Supplement 12* for evidence supporting these recommendations.

Recommendations for Perioperative Management—Timing of Elective Noncardiac Surgery in Patients Treated With PCI and DAPT

COR	LOE	Recommendations
I	B-NR	Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation. ^{101–103,143–146}
I	C-EO	In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of P2Y ₁₂ inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y ₁₂ platelet receptor inhibitor be restarted as soon as possible after surgery.
IIa	C-EO	When noncardiac surgery is required in patients currently taking a P2Y ₁₂ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.
IIb	C-EO	Elective noncardiac surgery after DES implantation in patients for whom P2Y ₁₂ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.
III: Harm	B-NR	Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively. ^{101–103,143–146}

The timing of noncardiac surgery in patients treated with coronary stent implantation involves consideration of: (1) the risk of stent thrombosis (particularly if DAPT needs to be interrupted); (2) the consequences of delaying the desired surgical procedure; and (3) increased the intra- and peri-procedural bleeding risk and the consequences of such bleeding if DAPT is continued^{15,147,148} (Data Supplement 12). DAPT significantly reduces the risk of stent thrombosis,^{50,51,94,95,99} and discontinuation of DAPT in the weeks after stent implantation is one of the strongest risk factors for stent thrombosis, with the magnitude of risk and impact on mortality rate inversely proportional to the timing of occurrence after the procedure.^{145,149,150} Older observational studies found that the risk of stent-related thrombotic complications is highest

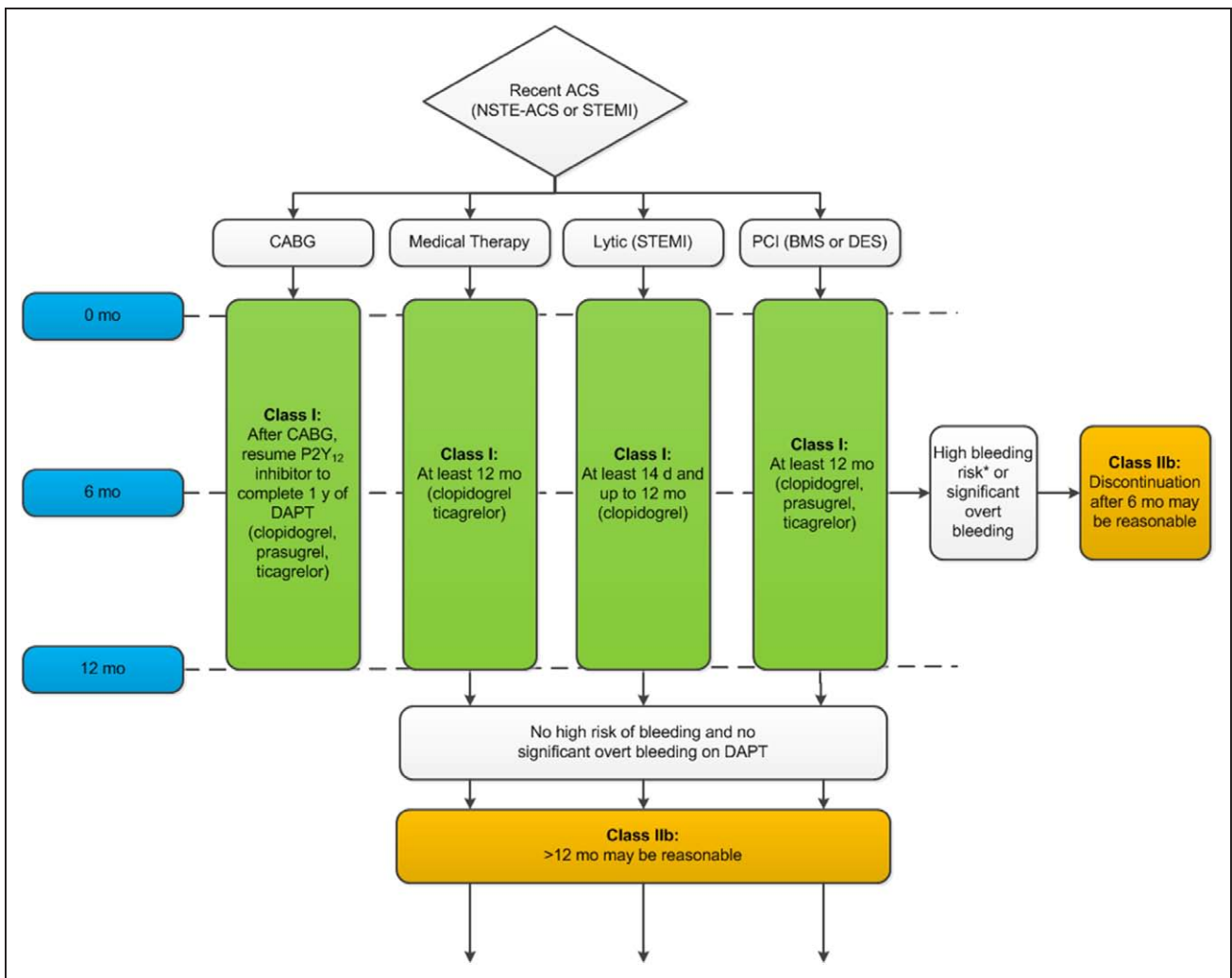


Figure 5. Treatment algorithm for duration of P2Y₁₂ inhibitor therapy in patients with recent ACS (NSTE-ACS or STEMI). Colors correspond to Class of Recommendation in Table 1. Arrows at the bottom of the figure denote that the optimal duration of prolonged DAPT is not established. Aspirin therapy is almost always continued indefinitely in patients with coronary artery disease. *High bleeding risk denotes those who have or develop a high risk of bleeding (eg, treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (eg, major intracranial surgery). ACS indicates acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; lytic, fibrinolytic therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

in the first 4 to 6 weeks after stent implantation but continues to be elevated at least 1 year after DES placement.^{101–103,149} Data from more recent large observational studies suggest that the time frame of increased risk of stent thrombosis is on the order of 6 months, irrespective of stent type (BMS or DES).^{151–153} In a large cohort of patients from the Veterans Health Administration hospitals, the increased risk of surgery for the 6 months after stent placement was most pronounced in those patients in whom the indication for PCI was an MI.¹⁴⁶ An additional consideration, irrespective of the timing of surgery, is that surgery is associated with proinflammatory and prothrombotic effects that may increase the risk of coronary thrombosis at the level of the stented vascular segment as well as throughout the coronary vasculature.^{154,155}

Prior recommendations with regard to duration of DAPT^{9,104} and the timing of noncardiac surgery^{15,156} in patients treated with DES were based on observations of those treated with first-generation DES. Compared with first-generation DES, currently used newer-generation DES are associated with a lower risk of stent thrombosis and appear to require a shorter minimum duration of DAPT^{17,18,21,38,96,97} Several studies of DAPT duration in patients treated with newer-generation DES did not detect any difference in the risk of stent thrombosis between patients treated with 3 to 6 months of DAPT or patients treated with longer durations of DAPT (although these studies were underpowered to detect such differences)^{17–21} (Data Supplement 1). Moreover, the safety of treating selected patients with newer-generation DES for shorter durations

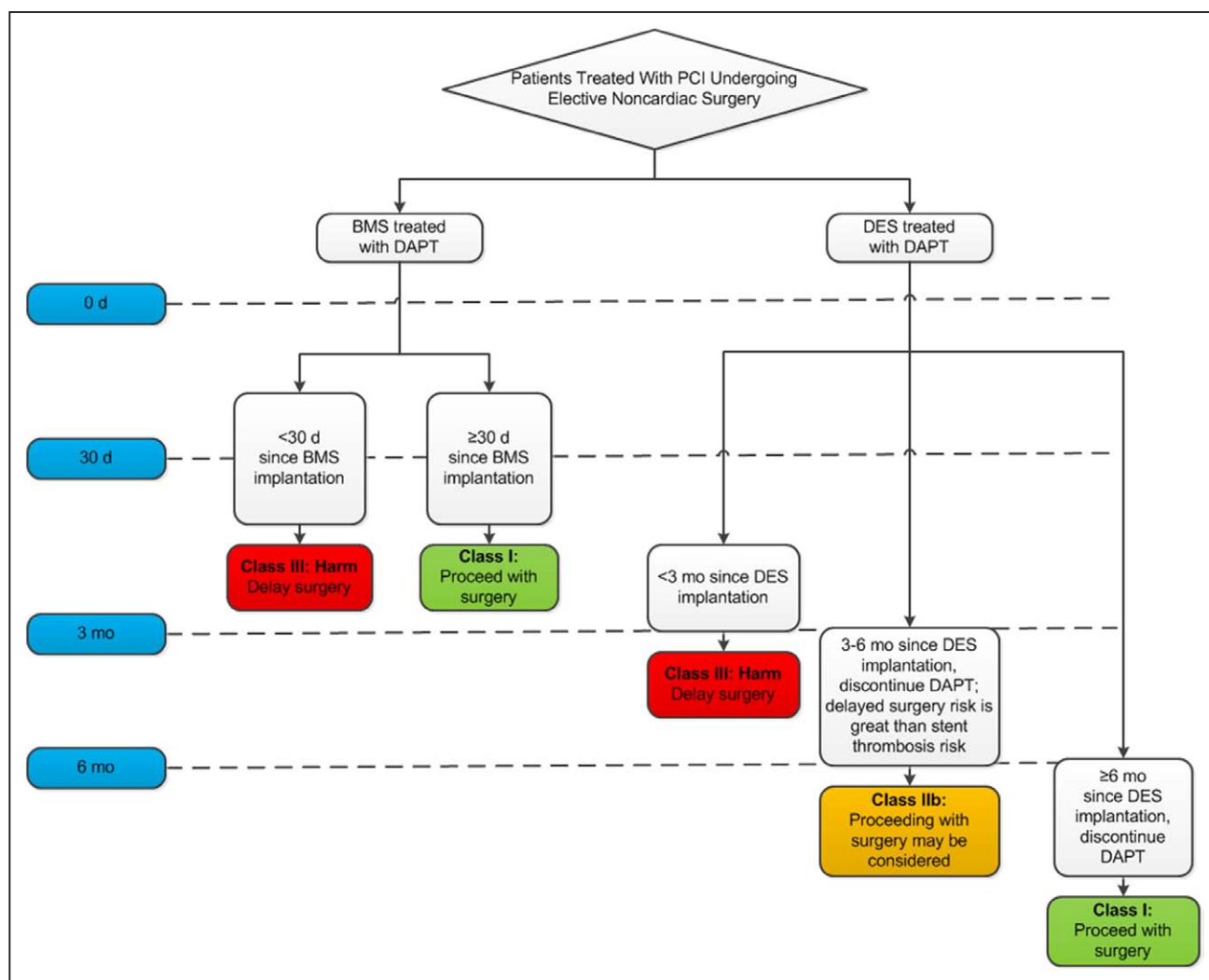


Figure 6. Treatment algorithm for the timing of elective noncardiac surgery in patients with coronary stents.

Colors correspond to Class of Recommendation in Table 1. BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

(3 or 6 months) of DAPT has been shown in a patient-level analysis pooling 4 trials evaluating DAPT durations.³⁴ Furthermore, in the PARIS (Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients) registry, interruption of DAPT according to physician judgment in patients undergoing surgery at any time point after PCI was not associated with an increased risk of MACE.¹⁴⁵ On the basis of these considerations, the prior Class I recommendation that elective noncardiac surgery in patients treated with DES be delayed 1 year¹⁵ has been modified to “optimally at least 6 months.” Similarly, the prior Class IIb recommendation that elective noncardiac surgery in patients treated with DES may be considered after 180 days¹⁵ has been modified to “after 3 months.” Figure 6 summarizes recommendations on timing of elective noncardiac surgery in patients with coronary stents.

The magnitude of incremental bleeding risk in patients treated with antiplatelet therapy who undergo surgery is

uncertain.^{157,158} If P2Y₁₂ inhibitor therapy needs to be held in patients being treated with DAPT after stent implantation, continuation of aspirin therapy if possible is recommended, though this is based primarily on expert opinion. If a P2Y₁₂ inhibitor has been held before a surgical procedure, therapy is restarted as soon as possible, given the substantial thrombotic hazard associated with lack of platelet inhibition early after surgery in patients with recent stent implantation. Although several small studies have used intravenous antiplatelet agents as a means of “bridging” in patients requiring temporary discontinuation of DAPT before surgery, there is no convincing clinical evidence demonstrating the efficacy of bridging with either parenteral antiplatelet or anticoagulant therapy.^{159–163}

Decisions about the timing of surgery and whether to discontinue DAPT after coronary stent implantation are best individualized. Such decisions involve weighing the particular surgical procedure and the risks of delaying

the procedure, the risks of ischemia and stent thrombosis, and the risk and consequences of bleeding. Given the complexity of these considerations, decisions are best determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patient.

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FOOTNOTES

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease (February 2015)

Committee Member	Employer/Title	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Glenn N. Levine, Chair	Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit	None	None	None	None	None	None	None
Eric R. Bates, Vice Chair, PCI	University of Michigan—Professor of Medicine	<ul style="list-style-type: none"> • AstraZeneca • Merck 	None	None	None	None	None	All sections
John A. Bittl	Munroe Regional Medical Center—Interventional Cardiologist	None	None	None	None	None	None	None
Ralph G. Brindis	University of California, San Francisco—Philip R. Lee Institute for Health Policy Studies—Clinical Professor of Medicine	None	None	None	None	None	None	None
Stephan D. Fihn, Chair, SIHD	Department of Veterans Affairs—Director, Office of Analytics and Business Intelligence	None	None	None	None	None	None	None
Lee A. Fleisher, Chair, Periop	University of Pennsylvania, Department of Anesthesiology—Professor of Anesthesiology	None	None	None	None	None	None	None
Christopher B. Granger	Duke Clinical Research Institute—Director, Cardiac Care Unit; Professor of Medicine	<ul style="list-style-type: none"> • AstraZeneca • Bayer • Bristol-Myers Squibb‡ • Daiichi-Sankyo • Janssen Pharmaceuticals • Sanofi-Aventis • Eli Lilly 	None	None	<ul style="list-style-type: none"> • AstraZeneca‡ • Bayer‡ • Bristol-Myers Squibb‡ • Daiichi-Sankyo‡ • Janssen Pharmaceuticals‡ • Merck‡ • Sanofi-Aventis‡ 	None	None	All sections
Richard A. Lange	Texas Tech University Health Sciences Center El Paso—President; Paul L. Foster School of Medicine—Dean	None	None	None	None	None	None	None
Michael J. Mack	The Heart Hospital Baylor—Director	None	None	None	• Abbott Vascular†	None	None	All sections
Laura Mauri	Brigham & Women's Hospital—Professor of Medicine, Harvard Medical School	None	None	None	<ul style="list-style-type: none"> • Abbott‡ • Bristol-Myers Squibb‡ • Daiichi-Sankyo‡ • Eli Lilly‡ • Sanofi-Aventis‡ 	None	None	All sections
Roxana Mehran	Mount Sinai Medical Center—Professor of Medicine	<ul style="list-style-type: none"> • Abbott • AstraZeneca • Merck 	None	None	<ul style="list-style-type: none"> • AstraZeneca‡ • Lilly/DSI† • STENTYS† 	None	None	All sections
Debabrata Mukherjee	Texas Tech University—Chief, Cardiovascular Medicine	None	None	None	None	None	None	None

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Committee Member	Employer/Title	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
L. Kristin Newby	Duke University Medical Center, Division of Cardiology—Professor of Medicine	<ul style="list-style-type: none"> • Janssen Pharmaceuticals‡ • Merck 	None	None	<ul style="list-style-type: none"> • Bristol-Myers Squibb‡ 	<ul style="list-style-type: none"> • AstraZeneca† 	None	All sections
Patrick T. O’Gara, Chair, STEMI	Harvard Medical School—Professor of Medicine	None	None	None	None	None	None	None
Marc S. Sabatine	Brigham and Women’s Hospital, Chairman—TIMI Study Group, Division of Cardiovascular Medicine; Harvard Medical School—Professor of Medicine	<ul style="list-style-type: none"> • AstraZeneca‡ • Merck • Sanofi-Aventis 	None	None	<ul style="list-style-type: none"> • Abbott‡ • AstraZeneca‡ • Daiichi-Sankyo‡ • Eisai‡ • Merck‡ • Sanofi-Aventis‡ 	<ul style="list-style-type: none"> • Abbott‡ • AstraZeneca‡ • Merck‡ 	None	All sections
Peter K. Smith, Vice Chair, CABG	Duke University Medical Center—Professor of Surgery; Chief, Thoracic Surgery	None	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$5000$ of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the 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 committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†No financial benefit.

‡Significant relationship.

ACC indicates American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft surgery; periop, perioperative noncardiac surgery; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; and TIMI, Thrombolysis In Myocardial Infarction.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease (December 2015)

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Joseph S. Alpert	Official Reviewer—AHA	University of Arizona Health Sciences Center—Clinical Professor of Medicine, Head of Department of Medicine	<ul style="list-style-type: none"> • AstraZeneca • Bayer • Daiichi-Sankyo • Sanofi-Aventis • Servier Pharmaceuticals • ZS Pharma 	None	None	<ul style="list-style-type: none"> • Bayer Pharma (DSMB)† • Janssen Pharmaceuticals (DSMB) • ZS Pharma* 	None	None
Joaquin E. Cigarroa	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health and Science University—Clinical Professor of Medicine	None	None	None	None	None	None
Ian C. Gilchrist	Official Reviewer—AHA	Hershey Medical Center—Physician, Professor of Medicine	<ul style="list-style-type: none"> • Terumo Interventional Systems 	None	None	<ul style="list-style-type: none"> • Angel Medical Systems† • Eli Lilly 	None	None
Dipti Itchhaporia	Official Reviewer—ACC Board of Trustees	Newport Coast Cardiology—Robert and Georgia Roth Chair of Cardiac Excellence; Hoag Heart and Vascular Institute—Medical Director, Disease Management	None	None	None	None	None	None
Mladen I. Vidovich	Official Reviewer—ACC Board of Governors	University of Illinois—Associate Professor of Medicine; Jesse Brown VA Medical Center—Chief of Cardiology	None	<ul style="list-style-type: none"> • Eli Lilly/ Daiichi-Sankyo* 	None	None	None	None
Dawn J. Abbott	Organizational Reviewer—SCAI	Brown University—Director of Interventional Cardiology Fellowship Training Program	None	None	None	None	<ul style="list-style-type: none"> • AstraZeneca† 	None
Dominick J. Angiolillo	Organizational Reviewer—SCAI	University of Florida College of Medicine—Cardiovascular Research Director	<ul style="list-style-type: none"> • Abbott Vascular • PLx Pharma • Sanofi-Aventis* • Eli Lilly* • Daiichi-Sankyo* • AstraZeneca* • Merck* 	None	None	<ul style="list-style-type: none"> • Eli Lilly* • Daiichi-Sankyo* • AstraZeneca • Janssen* Pharmaceuticals* • CSL Behring* • CeloNova (DSMB)* 	None	None
Herbert D. Aronow	Organizational Reviewer—SVM	Rhode Island Hospital—Director of Cardiac Catheterization Laboratory; The Warren Alpert School of Brown University—Clinical Professor of Cardiology; Lifespan Cardiovascular Institute—Director, Intervention Cardiology	None	None	None	<ul style="list-style-type: none"> • Endomax (Steering Committee) 	None	None

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Vinay Badhwar	Organizational Reviewer—STS	University of Pittsburgh Medical Center—Director, Center for Mitral Valve Disease	None	None	None	None	<ul style="list-style-type: none"> Abbott On-X Life Technologies 	None
Geoffrey D. Barnes	Organizational Reviewer—SVM	University of Michigan—Cardiologist, Vascular Medicine Specialist	<ul style="list-style-type: none"> Portola 	None	None	<ul style="list-style-type: none"> Blue Cross/Blue Shield of Michigan* 	None	None
Kathy Berra	Organizational Reviewer—PCNA	Stanford Prevention Research Center—Clinical Trial Director	<ul style="list-style-type: none"> Abor Pharmaceuticals 	None	None	None	None	None
Lola A. Coke	Organizational Reviewer—PCNA	Rush University Medical Center—Cardiovascular Clinical Nurse Specialist	None	None	None	None	None	None
Harold L. Lazar	Organizational Reviewer—AATS	Boston University Medical Center Department of Cardiology—Professor of Cardiothoracic Surgery	None	None	None	<ul style="list-style-type: none"> Paraxel International (DSMB) Eli Lilly 	None	None
David C. Mazer	Organizational Reviewer—SCA	St. Michael's Hospital, University of Toronto—Professor of Anesthesia	None	None	None	<ul style="list-style-type: none"> CSL Behring† 	None	None
John D. Puskas	Organizational Reviewer—AATS	Icahn School of Medicine at Mount Sinai, Emory Crawford Long Hospital—Chief of Cardiac Surgery	None	None	None	None	None	None
Joseph F. Sabik	Organizational Reviewer—STS	Cleveland Clinic, Department of Thoracic and Cardiovascular Surgery—Department Chair	<ul style="list-style-type: none"> Medistem 	None	None	<ul style="list-style-type: none"> Abbott† 	None	None
Linda Shore-Lesserson	Organizational Reviewer—ASA/SCA	Hofstra Northwell School of Medicine—Director, Cardiovascular Anesthesiology	<ul style="list-style-type: none"> Elcam Medical Grifols 	None	None	None	None	None
Scott M. Silvers	Organizational Reviewer—ACEP	Mayo Clinic College of Medicine, Emergency Medicine—Chair and Associate Professor	None	None	None	None	None	None
Christian A. Tomaszewski	Organizational Reviewer—ACEP	University of California San Diego Health—Emergency Medicine, Medical Toxicology Specialist	None	None	None	None	None	None

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Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sana M. Al-Khatib	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Duke University Medical Center— Associate Professor of Medicine	None	None	None	None	None	None
Saif Anwaruddin	Content Reviewer— ACC Interventional Scientific Council	University of Pennsylvania— Transcatheter Valve Program Co-Director, Assistant Professor of Medicine	None	None	None	None	None	None
Deepak L. Bhatt	Content Reviewer	Brigham and Women's Hospital— Executive Director of Interventional Cardiovascular Programs; Harvard Medical School— Professor of Medicine	None	None	None	<ul style="list-style-type: none"> • Amarin* • AstraZeneca* • Bristol-Myers Squibb* • Cardax† • Elsay* • Ethicon* • FlowCo† • Forest Laboratories* • Ischemix* • PLx Pharma† • Regado Biosciences† • Sanofi-Aventis* 	None	None
Kim K. Birtcher	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston College of Pharmacy—Clinical Professor	None	None	None	None	None	None
Biykem Bozkurt	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Michael E. DeBakey VA Medical Center—The Mary and Gordon Cain Chair and Professor of Medicine	None	None	None	None	None	None
Michael A. Borger	Content Reviewer— ACC Surgeons' Scientific Council	Columbia University Medical Center— Division of Cardiac, Vascular and Thoracic Surgery, Cardiothoracic Surgeon	None	None	None	None	None	None
Mauricio G. Cohen	Content Reviewer	University of Miami School of Medicine— Director of Cardiac Catheterization Laboratory	<ul style="list-style-type: none"> • Terumo Medical 	None	None	<ul style="list-style-type: none"> • AstraZeneca 	None	None
Frederico Gentile	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Centro Medico Diagnostico—Director, Cardiovascular Disease	None	None	None	None	None	None

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Samuel S. Gidding	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Nemours/Alfred I. DuPont Hospital for Children—Chief, Division of Pediatric Cardiology	None	None	None	None	None	None
Alan L. Hinderliter	Content Reviewer	University of North Carolina—Division of Cardiology	None	None	None	None	None	None
David R. Holmes	Content Reviewer—ACC Surgeons' Scientific Council	Mayo Clinic—Consultant, Cardiovascular Disease	None	None	None	None	None	None
José A. Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Texas Southwestern Medical Center—Professor of Internal Medicine	None	None	None	None	None	None
Ajay J. Kirtane	Content Reviewer	Columbia University Medical Center—Associate Professor of Medicine; Center for Interventional Vascular Therapy—Chief Academic Officer; NYC/Columbia Cardiac Catheterization Laboratories—Director	None	None	None	<ul style="list-style-type: none"> • Abbott Vascular* • Eli Lilly* 	<ul style="list-style-type: none"> • Abbott Vascular* • Eli Lilly* 	None
Lloyd W. Klein	Content Reviewer—ACC Interventional Scientific Council	Rush Medical College—Professor of Medicine	None	None	None	None	None	None
David J. Maron	Content Reviewer	Stanford University School of Medicine—Clinical Professor of Medicine and Emergency Medicine	None	None	None	None	None	None
Gilles Montalescot	Content Reviewer	Pitié-Salpêtrière University Hospital—Head of Institute of Cardiology	<ul style="list-style-type: none"> • Acuitude • AstraZeneca • Bayer • Bristol-Myers Squibb • Daiichi-Sankyo • Eli Lilly • Lead-up • Medcon International • Menarini • MSD • Sanofi-Aventis • Stentys 	None	None	<ul style="list-style-type: none"> • AstraZeneca* • Bristol-Myers Squibb* • Celladon • Daiichi-Sankyo* • Eli Lilly* • Janseen-Cilag Recor • Sanofi-Aventis • Stentys* 	None	None

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Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mark A. Munger	Content Reviewer	University of Utah— Professor of Pharmacy Practice	None	None	None	None	None	None
E. Magnus Ohman	Content Reviewer	Duke University— Professor of Medicine, Director of Program for Advanced Coronary Disease	<ul style="list-style-type: none"> • AstraZeneca • Janssen Pharmaceuticals* 	None	None	<ul style="list-style-type: none"> • Daiichi-Sankyo* • Eli Lilly * • Janssen Pharmaceuticals* 	None	None
Eric R. Powers	Content Reviewer	Medical University of South Carolina— Service Line Medical Director	None	None	None	None	None	None
Susan J. Pressler	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Indiana School of Nursing— Professor and Sally Reahard Chair; Center of Enhancing Quality of Life in Chronic Illness—Director	None	None	None	None	None	None
Sunil V. Rao	Content Reviewer	Duke University Medical Center— Associate Professor of Medicine	None	None	None	None	None	None
Philippe Gabriel Steg	Content Reviewer	Université Paris-Diderot—Professor	<ul style="list-style-type: none"> • AstraZeneca • Bristol-Myers Squibb* • Daiichi-Sankyo • Eli Lilly • Merck 	None	None	• AstraZeneca*	None	None
Tracy Y. Wang	Content Reviewer	Duke University Medical Center— Associate Professor of Medicine	<ul style="list-style-type: none"> • AstraZeneca* • Eli Lilly 	None	None	<ul style="list-style-type: none"> • AstraZeneca* • Bristol-Myers Squibb* • Eli Lilly/ Daiichi-Sankyo Alliance* 	None	None

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*Significant relationship.

†No financial benefit.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACEP, American College of Emergency Physicians; AHA, American Heart Association; CSL, Coordinated Science Laboratory; DSMB, data safety monitoring board; PCNA; Preventive Cardiovascular Nurses Association; SCA, Society of Cardiovascular Anesthesiologist; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and SVM, Society for Vascular Medicine