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


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Key Words: AHA Scientific Statements □ acute coronary syndrome □ aspirin □ coronary artery disease □ coronary stents □ dual antiplatelet therapy (DAPT) □ focused update □ P2Y₁₂ inhibitor □ stable ischemic heart disease

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TABLE OF CONTENTS

Preamble .................................................. e124
1. Introduction ........................................... e125
   1.1. Methodology and Evidence Review ............ e126
   1.2. Organization of the Writing Group ............ e127
   1.3. Review and Approval .......................... e127
2. Critical Questions and Systematic Review Findings .... e127
   2.1. Critical Questions on Duration of DAPT ...... e127
   2.2. Studies of Shorter-Duration DAPT
        After Stent Implantation ......................... e127
   2.3. Studies of Longer-Duration DAPT After
        Stent Implantation ............................... e128
   2.4. Other Studies Relevant to DAPT >1 Year
        After MI ........................................... e128
   2.5. Prolonged/Extended DAPT and Mortality Rate .. e128
3. Overriding Concepts and Recommendations
   for DAPT and Duration of Therapy .................. e129
   3.1. General Overriding Concepts .................. e129
   3.2. Factors Associated With Increased
        Ischemic and Bleeding Risk ...................... e129
   3.3. Specific P2Y12 Inhibitors: Recommendations .. e131
   3.4. Platelet Function Testing, Genetic Testing,
        and Switching of P2Y12 Inhibitors .............. e131
   3.5. Proton Pump Inhibitors and DAPT .............. e132
   3.6. Aspirin Dosing in Patients Treated With
        DAPT: Recommendation .......................... e132
   3.7. Triple Therapy (Aspirin, P2Y12 Inhibitor,
        and Oral Anticoagulant) ......................... e132
4. Percutaneous Coronary Intervention ................... e133
   4.1. Duration of DAPT in Patients With SIHD
        Treated With PCI: Recommendations .......... e133
   4.2. Duration of DAPT in Patients With ACS
        Treated With PCI: Recommendations .......... e133
   4.3. Duration of DAPT in Patients With SIHD
        and ACS Treated With PCI ....................... e134
   4.4. Recommendations for Duration of DAPT
        in Patients Undergoing CABG ................. e134
   4.5. Recommendations for Duration of DAPT
        in Patients With SIHD ......................... e135
7. Acute Coronary Syndrome (NSTE-ACS and STEMI) ...... e137
   7.1. Duration of DAPT in Patients With
        ACS Treated With Medical Therapy Alone
        (Without Revascularization or
        Fibrinolytic Therapy): Recommendations ...... e137
   7.2. Duration of DAPT in Patients With
        STEMI Treated With Fibrinolytic
        Therapy: Recommendations ...................... e138
   7.3. Duration of DAPT in Patients With ACS
        Treated With PCI: Recommendations .......... e138
   7.4. Duration of DAPT in Patients With ACS
        Treated With CABG: Recommendation .......... e138
   7.5. Duration of DAPT in Patients With ACS ........ e138
8. Perioperative Management—Timing of Elective
   Noncardiac Surgery in Patients Treated With
   PCI and DAPT: Recommendations .................. e140
References ................................................................ e143
Appendix 1. Author Relationships With Industry
       and Other Entities (Relevant) .................... e149
Appendix 2. Reviewer Relationships With Industry
       and Other Entities (Relevant) .................... e151

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 Medicine2,3 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-
participate 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 Appendices 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.0000000000000404/-/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
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

1. INTRODUCTION

The impetus for this focused update review is 11 studies16–27 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.3,14,29

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
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).

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

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong> Benefit &gt;&gt; Risk</td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>▪ Is recommended</td>
<td></td>
</tr>
<tr>
<td>▪ Is indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>▪ Should be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>
| ▪ Comparative-Effectiveness Phrases‡:
  - Treatment/strategy A is recommended/indicated in preference to treatment B |
| ▪ Treatment A should be chosen over treatment B |
| **CLASS IIa (MODERATE)** Benefit >> Risk | **LEVEL B-R** (Randomized) |
| Suggested phrases for writing recommendations: |
| ▪ Is reasonable |
| ▪ Can be useful/effective/beneficial |
| ▪ Comparative-Effectiveness Phrases‡:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B |
| ▪ It is reasonable to choose treatment A over treatment B |
| **CLASS IIb (WEAK)** Benefit ≥ Risk | **LEVEL B-NR** (Nonrandomized) |
| Suggested phrases for writing recommendations: |
| ▪ May/might be reasonable |
| ▪ May/might be considered |
| ▪ Usefulness/effectiveness is unknown/unclear/uncertain or not well established |
| **CLASS III: No Benefit (MODERATE)** Benefit = Risk | **LEVEL C-LD** (Limited Data) |
| Suggested phrases for writing recommendations: |
| ▪ Is not recommended |
| ▪ Is not indicated/useful/effective/beneficial |
| ▪ Should not be performed/administered/other |
| **CLASS III: Harm (STRONG)** Risk > Benefit | **LEVEL C-EO** (Expert Opinion) |
| Suggested phrases for writing recommendations: |
| ▪ Potentially harmful |
| ▪ Causes harm |
| ▪ Associated with excess morbidity/mortality |
| ▪ Should not be performed/administered/other |

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; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

### 1.1. Methodology and Evidence Review

Clinical trials published since the 2011 PCI guideline and the 2011 coronary artery bypass graft (CABG) guideline, 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.
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) or longer (18 to 48 months) duration of therapy with 12 months of DAPT, which is the recommended or minimal duration of therapy for most patients in ACC/AHA9,13,14 and European Society of Cardiology31–33 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 DAPT17–21 (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-analyses34–37 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 DES 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.

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td></td>
</tr>
<tr>
<td>Q2: In patients treated with newer (non-first) generation DES, compared with 12 months of DAPT, does &gt;12 (18–48) months of DAPT result in differences in mortality rate, decreased MACE, decreased stent thrombosis, and/or increased bleeding?</td>
<td></td>
</tr>
<tr>
<td>Q3: In post-MI (NSTEMI or STEMI) patients who are clinically stable and &gt;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?</td>
<td></td>
</tr>
</tbody>
</table>

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 sites16,22–27 (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”) DAPT16,22–27 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.40

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-analyses35–37,46,47 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 or statistically 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 indications and an analysis of 6 trials restricted to post-MI patients treated with DAPT 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. 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.

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

3. OVER RIDING 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 P2Y$_{12}$ inhibitor to aspirin monotherapy, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk. Similarly, longer compared with shorter duration of DAPT generally results in decreased ischemic risk at the expense of increased bleeding risk. Use of more potent P2Y$_{12}$ inhibitors (ticagrelor or prasugrel) in place of clopidogrel also results in decreased ischemic risk and increased bleeding risk.

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 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 P2Y$_{12}$ 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)
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. 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 P2Y_{12} 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 (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y_{12} inhibitor therapy.²⁴,²⁷,²² |
| IIa | B-R | In patients with ACS (NSTE-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.²⁴,²⁷,²² |
| III: Harm | B-R | Prasugrel should not be administered to patients with a prior history of stroke or TIA.²⁴ |

In the PLATO (Platelet Inhibition and Patient Outcomes) trial,²³ 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)²⁴ 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 (NSTE-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 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

### Table 4. Clinical and Procedural Factors Associated With Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk⁶²–⁷⁰

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

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.

3.4. Platelet Function Testing, Genetic Testing, and Switching of P2Y_{12} 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 NSTE-ACS guideline.⁹,¹⁴ To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide P2Y_{12} 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 P2Y_{12} inhibitor to a different P2Y_{12} inhibitor.
Table 5. Factors Used to Calculate a “DAPT Score”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 y</td>
<td>-2</td>
</tr>
<tr>
<td>Age 65 to &lt;75 y</td>
<td>-1</td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>0</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Saphenous vein graft PCI</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.56-60,75-78</td>
</tr>
</tbody>
</table>

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 ADAPTABLE (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 NSTE-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

<table>
<thead>
<tr>
<th>CoR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients with ACS (NSTE-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 P2Y₁₂ inhibitor therapy.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In patients with ACS (NSTE-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.</td>
</tr>
<tr>
<td>IIb</td>
<td>A</td>
<td>In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after DES implantation who develop a high risk of bleeding (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with prasugrel or ticagrelor for longer than 12 months may be reasonable.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), at high risk of severe bleeding complication (eg, major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y₁₂ inhibitor therapy after 6 months may be reasonable.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>Prasugrel should not be administered to patients with a prior history of stroke or TIA.</td>
</tr>
</tbody>
</table>

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.

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

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

Assess ischemic and bleeding risks using validated risk predictors (eg, CHA₂DS₂-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

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.
4.3. 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\(^5,51,94,95,99\) (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 \(\geq 1\) 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 analysis\(^51\) of patients in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial\(^62\) demonstrated that treatment with DAPT for up to 12 months in patients with NSTE-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 NSTE-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 NSTE-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 \(\approx 1\)% to 2% and an absolute increase in bleeding complications of \(\approx 1\)% (Data Supplements 1, 2, and 3).\(^16,22-27,30,35-37,46\) Newer-generation stents, particularly 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.\(^110-115\) 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-E0 | In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y\(_1\) 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 (NSTE-ACS or STEMI) being treated with DAPT who undergo CABG, P2Y\(_1\) inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS.\(^16,64,118-120\) |
Aspirin therapy after CABG improves vein graft patency, particularly during the first postoperative year, and reduces MACE. In the CURE study, 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. A propensity score analysis of a Danish administrative database 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.

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 treated with aspirin alone, although there was no reduction in the incidence of recurrent MI.

Two meta-analyses and 1 systematic overview assessed the potential benefits of DAPT after CABG and reported mixed results (Data Supplement 10). In the largest meta-analysis of patients pooled from 5 RCTs and 6 observational studies, 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 RCTs 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.

The benefits of DAPT in off-pump CABG patients were noted in terms of improved graft patency and clinical outcome in single-center observational studies and an RCT (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 study who underwent CABG, 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 study 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.

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. Figure 3 summarizes recommendations for the management and duration of P2Y₁₂ inhibitor therapy in patients undergoing CABG.

### Recommendations for Duration of DAPT in Patients Undergoing CABG (Continued)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>In patients with SIHD, DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency.</td>
</tr>
</tbody>
</table>

### 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.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>In patients with SIHD treated with DAPT after BMS implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month.</td>
</tr>
<tr>
<td>I</td>
<td>B-R ⁹⁶</td>
<td>In patients with SIHD treated with DAPT after DES implantation, P2Y₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months.</td>
</tr>
<tr>
<td>IIb</td>
<td>A ⁹⁶</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.</td>
</tr>
<tr>
<td>IIb</td>
<td>A ⁹⁶</td>
<td>In patients with SIHD 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.</td>
</tr>
<tr>
<td>IIb</td>
<td>A ⁹⁶</td>
<td>In patients with SIHD treated with DAPT after 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.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (eg, prior bleeding on 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 may be reasonable.</td>
</tr>
</tbody>
</table>
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. 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

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**Figure 2. Treatment algorithm for duration of P2Y<sub>12</sub> inhibitor therapy in patients treated with PCI.**

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. Clopidogrel is the only currently used P2Y<sub>12</sub> 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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**Recommendations for Duration of DAPT in Patients With SIHD (Continued)**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>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.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG, treatment with DAPT is not beneficial.</td>
</tr>
</tbody>
</table>
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.

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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; NSTE-ACS, non–ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; post-op, postoperatively; SIHD, stable ischemic heart disease; and S/P, status post.

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### 7. ACUTE CORONARY SYNDROME (NSTE-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.

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<td>In patients with ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, P2Y12 inhibitor therapy (clopidogrel or ticagrelor) should be continued for at least 12 months.52,71,140,141</td>
</tr>
<tr>
<td>I</td>
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<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.56–60,75–78</td>
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<tr>
<td>IIa</td>
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<td>In patients with NSTE–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 P2Y12 inhibitor therapy.53,71</td>
</tr>
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</table>
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.

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

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

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

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

7.5. Duration of DAPT in Patients With ACS

Aspirin remains the cornerstone of antiplatelet therapy in patients with ACS. Further platelet inhibition,
with an associated reduction in ischemic risk, can be achieved by blocking the P2Y$_{12}$ receptor. In the CURE trial of patients with NSTE-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 NSTE-ACS.

The results of the CURE trial$^{52}$ and PCI-CURE analyses of the CURE trial$^{51}$ (Data Supplement 4) have been extrapolated to patients with STEMI on the basis of the consideration that NSTE-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.$^{53-55}$ Ticagrelor is considered a P2Y$_{12}$ 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

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**Figure 4. Treatment algorithm for duration of P2Y$_{12}$ 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 P2Y$_{12}$ 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.
are all P2Y\textsubscript{12} 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.\textsuperscript{142} In COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (93% with STEMI not managed with primary PCI), treatment for \(\approx 2\) weeks with clopidogrel (in addition to aspirin \(162 \text{ mg}\)) 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.\textsuperscript{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 fibrinolitic 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.\textsuperscript{16,24,28,30,34,36,37,46} An analysis from the PEGASUS-TIMI 54 trial found that the greatest reduction in ischemic events with prolonged DAPT in post-MI patients, extended DAPT for approximately 18 to 36 months leads to an absolute decrease in ischemic complications of \(\approx 1\)% to 3% and an absolute increase in bleeding complications of \(\approx 1\)% (Data Supplement 4).\textsuperscript{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 P2Y\textsubscript{12} inhibitor therapy either had not been discontinued or had been discontinued for \(\approx 30\) days (absolute reduction in MACE: 1.9 % to 2.5%). No benefit was seen in patients in whom P2Y\textsubscript{12} inhibitor therapy had been discontinued \(>1\) year before enrollment in the study.\textsuperscript{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.\textsuperscript{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.

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<td>I</td>
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<td>Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation.\textsuperscript{101–103,143–146}</td>
</tr>
<tr>
<td>I</td>
<td>C-EO</td>
<td>In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of P2Y\textsubscript{12} inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y\textsubscript{12} platelet receptor inhibitor be restarted as soon as possible after surgery.</td>
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<td>IIa</td>
<td>C-EO</td>
<td>When noncardiac surgery is required in patients currently taking a P2Y\textsubscript{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.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-EO</td>
<td>Elective noncardiac surgery after DES implantation in patients for whom P2Y\textsubscript{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.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>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.\textsuperscript{101–103,143–146}</td>
</tr>
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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.\textsuperscript{115,147,148} (Data Supplement 12). DAPT significantly reduces the risk of stent thrombosis.\textsuperscript{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.\textsuperscript{145,149,150} Older observational studies found that the risk of stent-related thrombotic complications is highest.
in the first 4 to 6 weeks after stent implantation but continues to be elevated at least 1 year after DES placement.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{154,155}

Prior recommendations with regard to duration of DAPT\textsuperscript{104} and the timing of noncardiac surgery\textsuperscript{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\textsuperscript{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)\textsuperscript{17-21} (Data Supplement 1). Moreover, the safety of treating selected patients with newer-generation DES for shorter durations
(3 or 6 months) of DAPT has been shown in a patient-level analysis pooling 4 trials evaluating DAPT durations.\textsuperscript{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.\textsuperscript{145} On the basis of these considerations, the prior Class I recommendation that elective noncardiac surgery in patients treated with DES be delayed 1 year\textsuperscript{15} 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 days\textsuperscript{15} 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.\textsuperscript{157,158} If P2Y\textsubscript{12} 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 P2Y\textsubscript{12} 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.\textsuperscript{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**

This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in February 2016, and the American Heart Association Executive Committee in March 2016.

The Comprehensive RWI Data Supplement table is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000404/-/DC1.

The Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000404/-/DC2.

This article has been copublished in the *Journal of the American College of Cardiology*. It has been reprinted by the *Journal of Thoracic and Cardiovascular Surgery*.

**REFERENCES**


### 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)

<table>
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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, Thrombosis 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)

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