JAMA Cardiology Clinical Guidelines Synopsis

Focused Update on Duration of Dual Antiplatelet Therapy for Patients With Coronary Artery Disease

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

DEVELOPER: American College of Cardiology (ACC) and American Heart Association (AHA)

RELEASE DATE: March 23, 2016 (online)

PRIOR VERSIONS: November 7, 2011 (2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention); December 6, 2011 (2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery); December 18, 2012, and November 4, 2014 (2012 and 2014 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease); January 29, 2013 (2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction); December 23, 2014 (2014 ACC/AHA Guideline for Non–ST-Elevation Acute Coronary Syndromes); and December 9, 2014 (2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery)

FUNDING SOURCES: The ACC and AHA

TARGET POPULATION: Patients with coronary artery disease (CAD)

MAJOR RECOMMENDATIONS: This guideline-focused update on dual antiplatelet therapy (DAPT) for patients with CAD updates and replaces prior recommendations regarding duration of therapy. The following new recommendations were generated:

1. Patients with stable ischemic heart disease (SIHD) treated with DAPT should be given clopidogrel for at least 1 month after implantation of a bare-metal stent (class of recommendation, I; level of evidence, A [high-quality, randomized data]) and for at least 6 months after implantation of a drug-eluting stent (DES) (class of recommendation, I; level of evidence, B-R [moderate-quality randomized data]).
2. Continuation of DAPT with clopidogrel for longer than 1 month after implantation of a bare-metal stent and for longer than 6 months after implantation of a DES may be reasonable for patients with SIHD who are not at high risk of bleeding and who tolerated DAPT without a bleeding complication (class of recommendation, IIb; level of evidence, A [high-quality randomized data]).
3. Continuation of DAPT for longer than 12 months may be reasonable for patients with acute coronary syndrome (ACS) who are not at high risk of bleeding, who tolerated DAPT without a bleeding complication, and who have a coronary stent implanted, or are treated with medical therapy only (no revascularization or fibrinolytic agents), or have ST-elevation myocardial infarction (MI) and are treated with fibrinolytic therapy (class of recommendation, IIb; level of evidence, A [high-quality randomized data]).

Summary of the Clinical Problem

The combination of aspirin and platelet $P2Y_{12}$ receptor inhibitor therapy (ie, DAPT) reduces the risk of recurrent ischemia following ACS and reduces risk of stent thrombosis following coronary stenting regardless of clinical presentation, yet it increases the risk of bleeding. Until recently, there have been few randomized controlled trials (RCTs) assessing the duration of treatment.

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Characteristics of the Guideline Source

The ACC/AHA Task Force on Clinical Practice Guidelines issued this focused update[1] (summarized in the eFigure in the Supplement), which was subject to the same level of rigor as their full guidelines, and was approved for publication by the governing bodies of the ACC/AHA. It was developed in collaboration with the American Association for Thoracic Surgery (AATS), the American Society of Anesthesiologists, the Society for Cardiovascular Angiography and Interventions (SCAI), the Society of Cardiovascular Anesthesiologists, and the Society of Thoracic Surgeons (STS) and was endorsed by Preventive Cardiovascular Nurses Association (PCNA) and the Society for Vascular Surgery. All guideline writing committee members disclosed industry relationships and abstained from work on sections for which they had any relevant relationship with industry.

Evidence Base

Six previous guidelines addressed the duration of DAPT for patients with CAD. The most recent stated that aspirin should be continued indefinitely after ACS or after coronary stenting, and that $P2Y_{12}$ inhibitor therapy should be given for at least 12 months after ACS or after implantation of a DES in patients with SIHD (except for patients at high risk of bleeding). Continuation of $P2Y_{12}$ inhibitor therapy beyond 12 months after ACS or after implantation of a DES in

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patients with SIHD had a class IIb recommendation (level of evidence, B). The 2016 focused update is based on publications comparing the durations of DAPT; these publications were released after these guidelines, including 11 RCTs comparing durations of 3 to 6 months with a duration of 12 months,[2] 1 RCT assessing a duration of 30 months vs a duration of 12 months,[3] and 1 RCT comparing ticagrelor with placebo for patients 1 to 3 years after an MI.[4] These data pertain mainly to patients treated with current-generation stents who received aspirin but not an oral anticoagulant. A systematic review of these data was conducted by an evidence review committee.[2]

Benefits and Harms

Decisions regarding the duration of DAPT inherently involve balancing a reduction in the risk of ischemia with an increase in the risk of bleeding. Overall, continued DAPT is associated with lower risks of MI and stent thrombosis and a higher risk of nonfatal bleeding.[2-4] Continued DAPT beyond 1 year is associated with a larger absolute reduction in the risk of recurrent MI for patients presenting with MI compared with patients being treated for SIHD,[5] and for patients with a history of MI, continued DAPT may be associated with reduced risks of stroke[4] and cardiovascular death[6]; reductions in the risk of ischemia are largest for those patients who have not discontinued or who have recently discontinued therapy. With current coronary stents, in the absence of ACS or a high risk of recurrent ischemia, a shorter duration of DAPT can be considered for patients with a high risk of bleeding.[2] Patients at a high risk of bleeding include those with prior bleeding during DAPT, with a coagulopathy, or who are receiving oral anticoagulants. One study observed an unexpected increase in noncardiovascular mortality with longer treatment duration,[3] albeit not related to prior or recent bleeding. Overall, however, an analysis of 12 RCTs of clopidogrel performed by the US Food and Drug Administration did not identify an increase in mortality.[7]

Discussion

Individualization of therapy based on balancing the expected benefits and harms is central to deciding the duration of DAPT. The focused update included a a summary of factors associated with ischemic risk (eg, extensive coronary atherosclerosis, or treatment of bifurcations or stent restenosis) or bleeding risk (oral anticoagulant therapy, low body weight, or anemia), as well as a new decision tool, the DAPT Score, that may help predict the expected benefit or risk of continued DAPT.[8] For patients receiving DAPT for 1 year without significant bleeding or ischemic events, a score of 2 or higher indicates a favorable benefit to risk ratio for continuing DAPT beyond 1 year, and a score of less than 2 indicates an unfavorable benefit to risk ratio. The focused update does not recommend routine use of platelet function testing or genotyping to guide clinical decisions.

Areas in Need of Future Study or Ongoing Research

Additional methods for tailoring the duration of DAPT to individual patients based on their risk profile and specific presentation are needed. Comparison of treatment regimens combining an oral anticoagulant (using warfarin sodium or novel oral anticoagulants) with single or dual antiplatelet therapy for patients with atrial fibrillation and ACS or coronary stents is the subject of several ongoing trials. $P2Y_{12}$ monotherapy with novel $P2Y_{12}$ inhibitors is also under investigation.

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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

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

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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 <500 words) 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 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

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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.0000000000000404/-/DC1). Comprehensive disclosure information for the Task Force is also available at http://www.acc.org/about-acc/leadership/guidelines-and-documents-task-forces.aspx. The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, 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).

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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	
CLASS I (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: ■ Is recommended ■ Is indicated/useful/effective/beneficial ■ Should be performed/administered/other ■ Comparative-Effectiveness Phrases†: ○ Treatment/strategy A is recommended/indicated in preference to treatment B ○ Treatment A should be chosen over treatment B	
CLASS IIa (MODERATE)	**Benefit >> Risk**
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**
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) *(Generally, LOE A or B use only)*	**Benefit = Risk**
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**
Suggested phrases for writing recommendations: ■ Potentially harmful ■ Causes harm ■ Associated with excess morbidity/mortality ■ Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
■ High-quality evidence‡ from more than 1 RCT ■ Meta-analyses of high-quality RCTs ■ One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
■ Moderate-quality evidence‡ from 1 or more RCTs ■ Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies ■ Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
■ 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	
LEVEL C-EO	**(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; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor "pretreatment," "preloading," and loading are beyond the scope of this document but are addressed in other guidelines (9,14,29).

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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).

1.1. Methodology and Evidence Review

Clinical trials published since the 2011 PCI guideline (9) 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 Online 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 (e.g., 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 (e.g., LOE B-R ^{SR}). See the ERC systematic review report, "Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 Guideline Update," 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

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reviewers from the ACC and AHA; 2 reviewer 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, and the Society of Thoracic Surgeons.

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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.

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.

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

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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 1,000 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

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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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 study (16) 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 numerically (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 indications (48) and an analysis of 6 trials restricted to post-MI patients treated with DAPT (44) found no increase in cardiovascular or noncardiovascular mortality rate associated with prolonged DAPT (Data Supplement 3). A U.S. 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

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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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 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.

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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 NSTE-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; NSTE-ACS, non–ST-elevation acute coronary syndrome; and STEMI, ST-elevation myocardial infarction.

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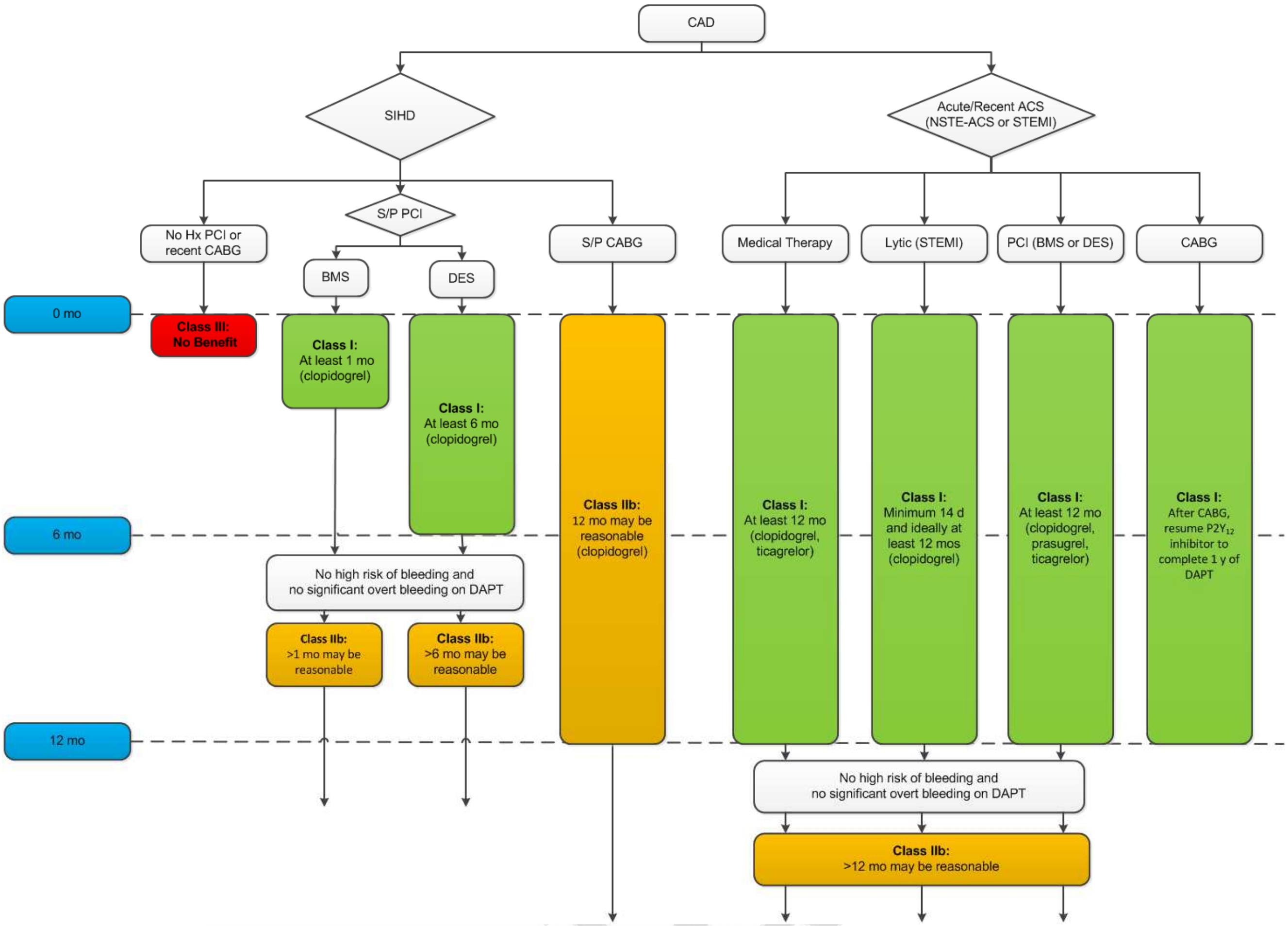

Figure 1. Master Treatment Algorithm for Duration of P2Y$_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT

Colors correspond to Class of Recommendation in Table 1. 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 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 (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y$_{12}$ 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.

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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) 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 suggest 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.

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 • Advanced age • ACS presentation • Multiple prior MIs • Extensive CAD • Diabetes mellitus • CKD Increased risk of stent thrombosis • ACS presentation • 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	• History of prior bleeding • Oral anticoagulant therapy • Female sex • Advanced age • Low body weight • CKD • Diabetes mellitus • Anemia • Chronic steroid or NSAID therapy

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.

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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).

3.3. Specific $P2Y_{12}$ Inhibitors: Recommendations

See *Online 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 (53,71,72).**
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 (54,55).**

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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 (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 U.S. 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 $P2Y_{12}$ 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.

3.5. Proton Pump Inhibitors and DAPT

The use of proton pump inhibitors (PPIs) in patients treated with DAPT is discussed in a 2010

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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 *Online 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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, $P2Y_{12}$ Inhibitor, and Oral Anticoagulant)

The recommended management of patients on "triple therapy" (aspirin, $P2Y_{12}$ 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.

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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 $P2Y_{12}$ 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 (e.g., CHA_2DS_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

CHA_2DS_2-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 *Online 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 with 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 with clopidogrel should be given for at least 6 months (17,18,21,30,96,97).**
I	B-NR	**In patients treated with DAPT, the recommended daily dose of aspirin is**

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		81 mg (range, 75 mg to 100 mg) (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 (e.g., 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 (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., 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.

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

See *Online 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 (NSTE-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, the recommended daily dose of aspirin is 81 mg (range, 75 mg to 100 mg) (56-60,75-78).
IIa	B-R	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 $P2Y_{12}$ inhibitor therapy (53,72).
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 (54,55).
IIb	A [SR]	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 (e.g., 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 (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., 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 analysis (51) of patients in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (52) 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 (e.g., 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

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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, 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 (e.g., oral anticoagulation), increased risk of severe bleeding complications (e.g., 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 U.S. 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.

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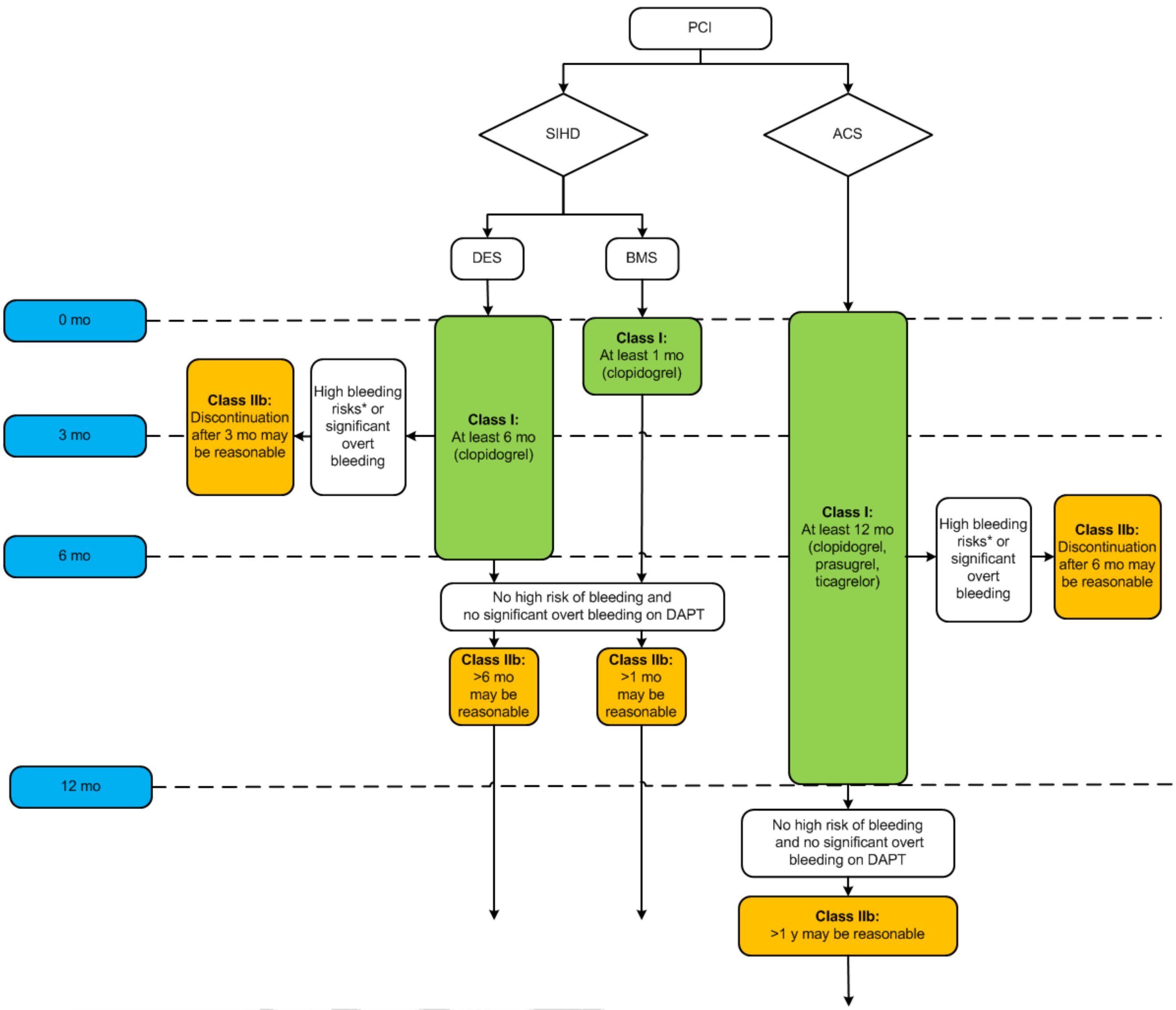

Figure 2. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI
Colors correspond to Class of Recommendation in Table 1. Arrows at the bottom of the figure denote that the optimal duration of prolonged DAPT is not established. Clopidogrel is the only currently used $P2Y_{12}$ 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 (e.g., treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (e.g., 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.

5. CABG: Recommendations

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

Recommendations for 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 (NSTE-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).**
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 database (120) 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 RCTs (123) showed that

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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 outcome (136) in single-center observational studies (124,136) and an RCT (125) (Data Supplement 10).

Only data from post hoc analyses are available on the utility of newer $P2Y_{12}$ inhibitors in patients with ACS who undergo CABG. In a retrospective analysis of patients in the TRITON-TIMI 38 study (54) 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 study (53) 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 $P2Y_{12}$ inhibitor therapy in patients undergoing CABG.

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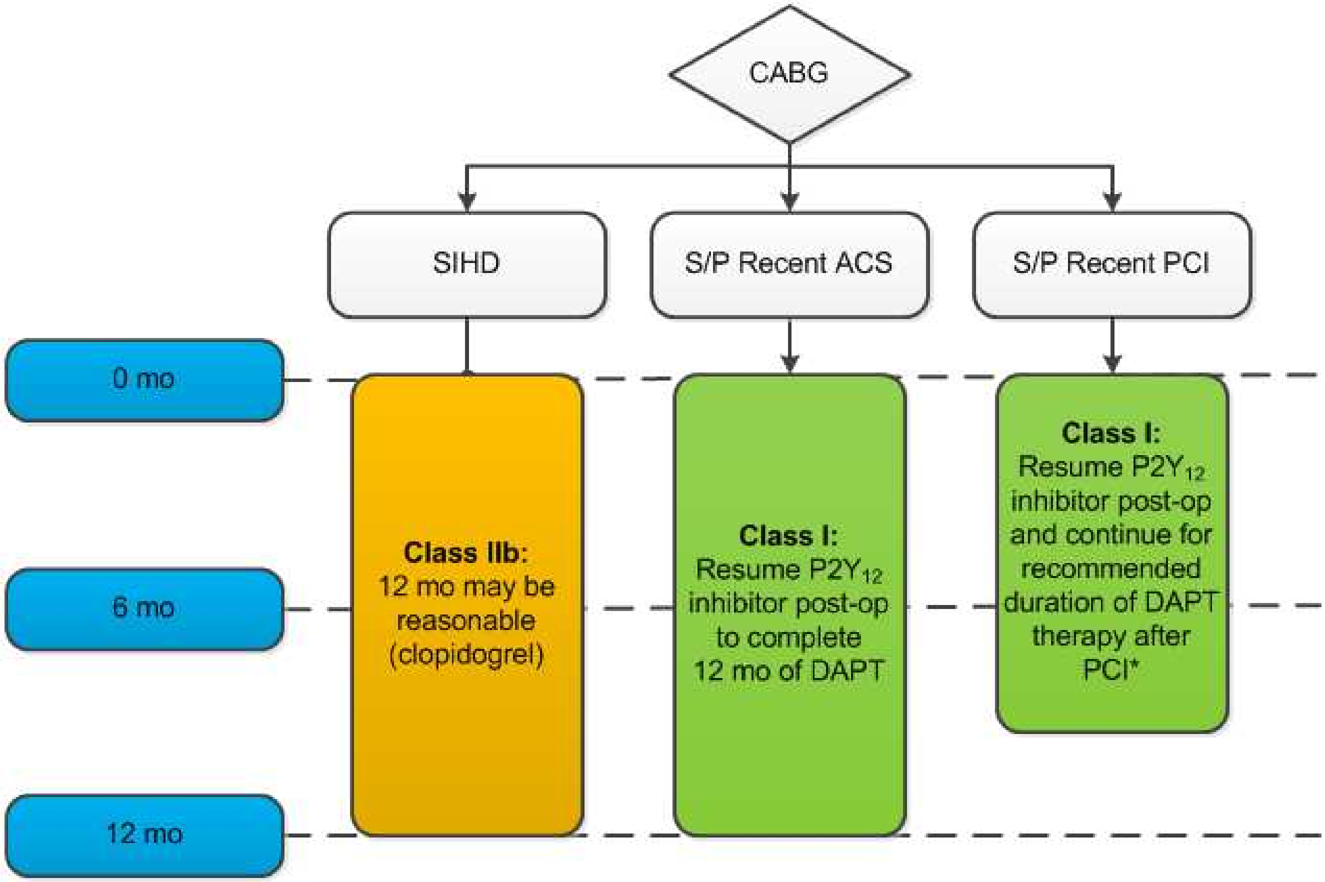

Figure 3. Treatment Algorithm for Management and Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Undergoing CABG

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

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6. SIHD: Recommendations

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

Recommendations for 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-NR** [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 (e.g., 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 (e.g., 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 (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., 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).**
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

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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 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor therapy in patients with SIHD.

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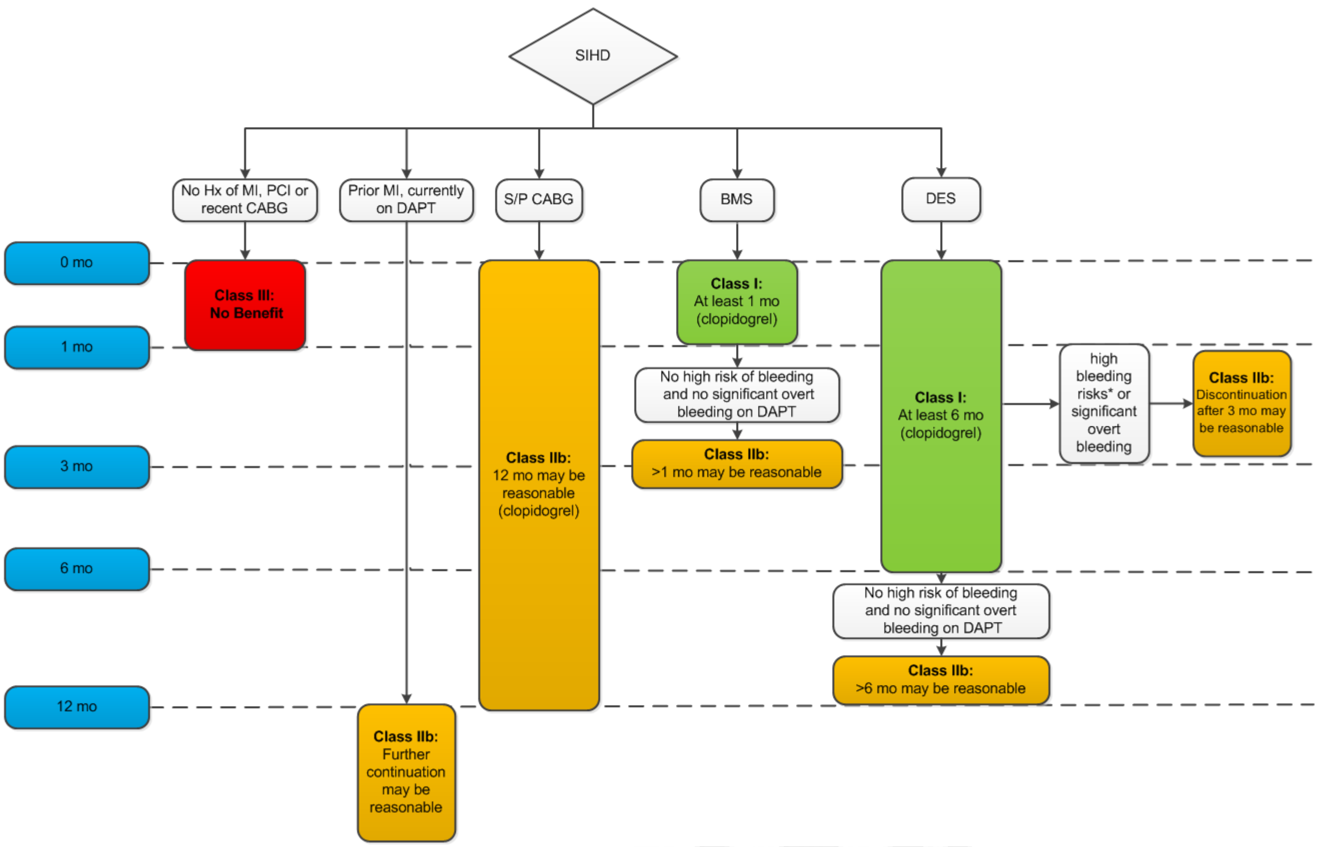

Figure 4. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With SIHD (Without ACS Within the Past Several Years)
Colors correspond to Class of Recommendation in Table 1. Patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered 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 (e.g., treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (e.g., 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.

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 *Online 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**

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		revascularization or fibrinolytic therapy) and treated with DAPT, $P2Y_{12}$ inhibitor therapy (either 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 NSTE–ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (53,71).
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 (e.g., 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 *Online 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 C-EO	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 (*Level of Evidence: A*) (140,142) and ideally at least 12 months (*Level of Evidence: 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 (e.g., 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 *Online 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

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		100 mg) is recommended (56-60,75-78).
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 (e.g., 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 (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., 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 *Online 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, 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.

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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 (53-55,55,71,72). 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 are all $P2Y_{12}$ 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 (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 (e.g., 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 (e.g., oral anticoagulation), increased risk of severe bleeding complications (e.g., major intracranial surgery), or significant overt bleeding, the benefit/risk

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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.

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Figure 5. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patient 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 (e.g., treatment with oral anticoagulant therapy) or are at increased risk of severe bleeding complication (e.g., 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.

8. Perioperative Management–Timing of Elective Noncardiac Surgery in Patients Treated With PCI and DAPT: Recommendations

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

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

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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 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).

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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 (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 year (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 (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 (157,158). If $P2Y_{12}$ 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 $P2Y_{12}$ 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 (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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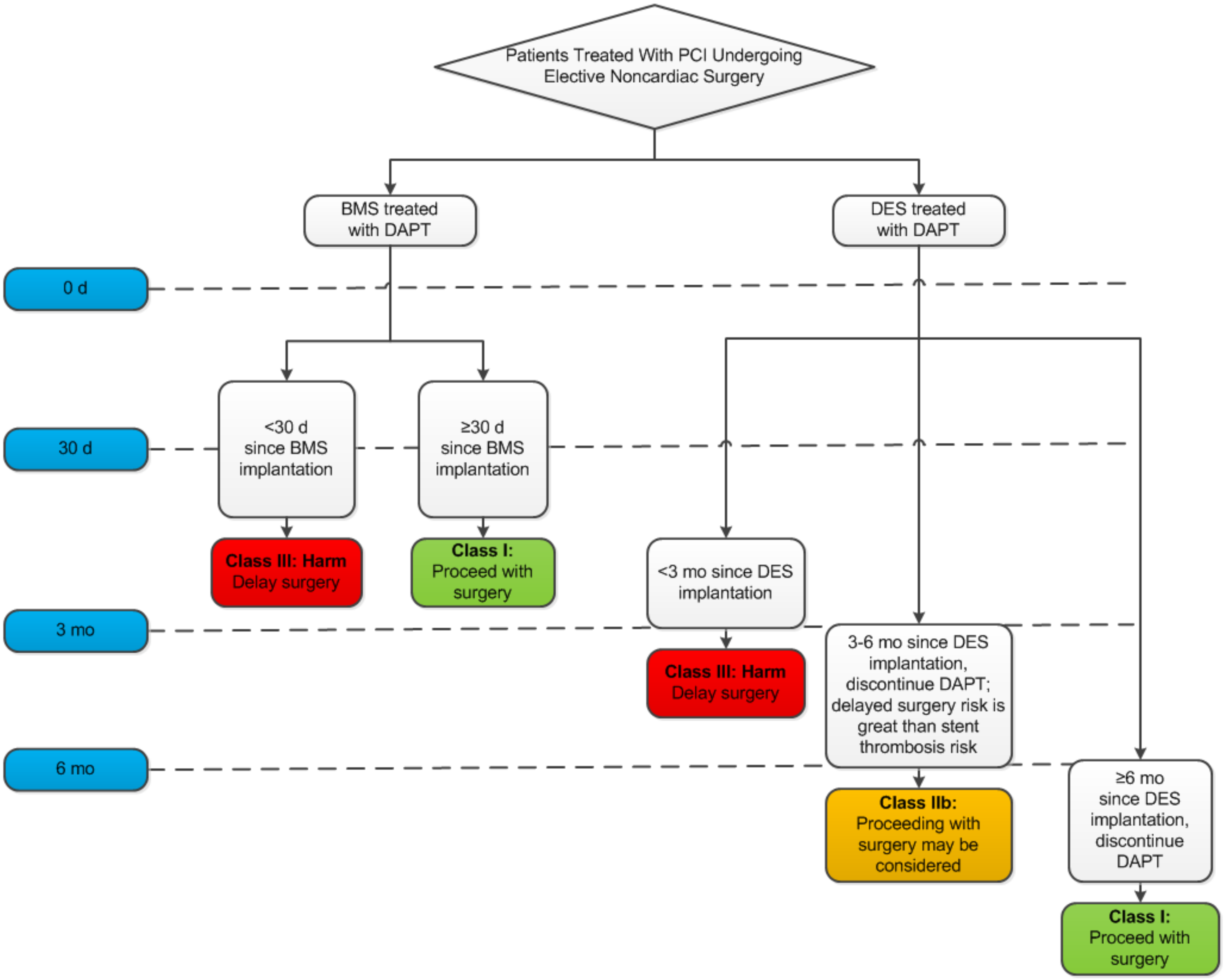

Figure 6. Treatment Algorithm for the Timing of Elective Noncardiac Surgery in Patients With Coronary Stents

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.

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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	• 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	• AstraZeneca • Bayer • Bristol-Myers Squibb‡ • Daiichi-Sankyo • Janssen	None	None	• AstraZeneca‡ • Bayer‡ • Bristol-Myers Squibb‡ • Daiichi-Sankyo‡	None	None	All sections

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		Pharmaceuticals • Sanofi-Aventis • Eli Lilly			• Janssen Pharmaceuticals‡ • Merck‡ • Sanofi-Aventis‡			
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	• Abbott‡ • Bristol-Myers Squibb‡ • Daiichi-Sankyo‡ • Eli Lilly‡ • Sanofi-Aventis‡	None	None	All sections
Roxana Mehran	Mount Sinai Medical Center—Professor of Medicine	• Abbott • AstraZeneca • Merck	None	None	• AstraZeneca‡ • Lilly/DSI† • STENTYS†	None	None	All sections
Debabrata Mukherjee	Texas Tech University—Chief, Cardiovascular Medicine	None	None	None	None	None	None	None
L. Kristin Newby	Duke University Medical Center, Division of Cardiology—Professor of Medicine	• Janssen Pharmaceuticals • Merck	None	None	• Bristol-Myers Squibb‡	• 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	• AstraZeneca‡ • Merck • Sanofi-Aventis	None	None	• Abbott‡ • AstraZeneca‡ • Daiichi-Sankyo‡ • Eisai‡ • Merck‡ • Sanofi-Aventis‡	• Abbott‡ • AstraZeneca‡ • Merck‡	None	All sections

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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 ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the 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, Thrombosis In Myocardial Infarction.

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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—Professor of Medicine, Head of Department of Medicine	• AstraZeneca • Bayer • Daiichi-Sankyo • Sanofi-Aventis • Servier Pharmaceuticals • ZS Pharma	None	None	• Bayer Pharma (DSMB)† • Janssen Pharmaceuticals (DSMB) • ZS Pharma*	None	None
Joaquin E. Cigarroa	Official Reviewer—ACC/AHA Task Force on 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	• Terumo Interventional Systems	None	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	• Eli Lilly/ Daiichi-Sankyo*	None	None	None	None

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Dawn J. Abbott	Organizational Reviewer—SCAI	Brown University—Director of Interventional Cardiology Fellowship Training Program	None	None	None	None	• AstraZeneca†	None
Dominick J. Angiolillo	Organizational Reviewer—SCAI	University of Florida College of Medicine—Cardiovascular Research Director	• Abbott Vascular • PLx Pharma • Sanofi-Aventis* • Eli Lilly* • Daiichi-Sankyo* • AstraZeneca* • Merck*	None	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	• Endomax (Steering Committee)	None	None
Vinay Badhwar	Organizational Reviewer—STS	University of Pittsburgh Medical Center—Director, Center for Mitral Valve Disease	None	None	None	None	• Abbott • On-X Life Technologies	None
Geoffrey D. Barnes	Organizational Reviewer—SVM	University of Michigan—Cardiologist, Vascular Medicine Specialist	• Portola	None	None	• Blue Cross/Blue Shield of Michigan*	None	None
Kathy Berra	Organizational Reviewer—PCNA	Stanford Prevention Research Center—Clinical Trial Director	• 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	• Paraxel International (DSMB) • Eli Lilly	None	None

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David C. Mazer	Organizational Reviewer—SCA	St. Michael's Hospital, University of Toronto — Professor of Anesthesia	None	None	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	• Medistem	None	None	• Abbott†	None	None
Linda Shore-Lesserson	Organizational Reviewer—ASA/SCA	Hofstra Northwell School of Medicine—Director, Cardiovascular Anesthesiology	• 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
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	• Amarin* • AstraZeneca* • Bristol-Myers Squibb* • Cardax†	None	None

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						• Elsai* • Ethicon* • FlowCo† • Forest Laboratories* • Ischemix* • PLx Pharma† • Regado Biosciences† • Sanofi-Aventis*		
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	• Terumo Medical	None	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
Samuel S. Gidding	Content Reviewer—	Nemours/Alfred I. DuPont Hospital for Children—	None	None	None	None	None	None

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	ACC/AHA Task Force on Clinical Practice Guidelines	Chief, Division of Pediatric Cardiology						
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	• Abbott Vascular* • Eli Lilly*	• 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
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ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Physicians; AHA, American Heart Association; AMA, American Medical Association; DAPT, dual antiplatelet therapy; DSMB, data safety monitoring board; ECG, electrocardiogram; JAHA, Journal of the American Heart Association; NCDR, National Cardiovascular Data Registry; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; SCAI, Society for Cardiovascular Angiography and Interventions; and TIMI, Thrombosis In Myocardial Infarction.

2016 Duration of Dual Antiplatelet Therapy Guideline Focused Update Data Supplement

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Data Supplement 1. RCTs of Shorter (3–6 Month) Duration of DAPT in Patients Treated With Stent Implantation

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Studies of shorter (3-6 mo) vs. 12 mo duration of DAPT					
ISAR-SAFE Schulz-Schupke S, et al., 2015 (1) 25616646	**Aim**: Test if 6 mo DAPT is noninferior to 12 mo DAPT **Study type**: RCT, noninferiority trial **Size**: 6,000 pts (4,005 pts actually enrolled, 4,000 pts analyzed)	**Inclusion criteria**: Pts being treated with DAPT 6 mo after DES **Exclusion criteria**: Left main PCI, MI in the initial 6 mo after stent, previous stent thrombosis	**Intervention**: 6 additional mo DAPT after initial 6 mo of DAPT (n=2,003) **Comparator**: No further clopidogrel after initial 6 mo (n=1,997)	**1° endpoint**: Composite endpoint of death, MI, stent thrombosis, CVA, or TIMI major bleeding 9 mo after randomization (15 mo after stent) • 1.5% with no additional DAPT (6 mo total) vs. 1.6% with 6 additional mo DAPT (12 mo total) (p<0.001 for noninferiority)	• Trial stopped early due to slow recruitment • Lower than expected event rates • Stent thrombosis and TIMI major bleeding rates low and not statistically different
SECURITY Colombo A, et al., 2014 (2) 25236346	**Aim**: Test noninferiority of 6 vs. 12 mo DAPT after 2nd generation DES **Study type**: RCT, noninferiority trial **Size**: 1,399 pts	**Inclusion criteria**: Pts with stable angina, unstable angina, or silent ischemia **Exclusion criteria**: Recent STEMI or NSTEMI, left main PCI , SVG PCI, CKD, active bleeding or significant bleeding risk	**Intervention**: 6 mo DAPT (n=682) **Comparator**: 12 mo DAPT (n=717)	**1° endpoint**: Cardiac death, MI, CVA, stent thrombosis or BARC type 3 or 5 bleeding • 4.5% with 6 mo DAPT vs. 3.7% with 12 mo DAPT (risk difference 0.8%; 95% CI: -2.4%–1.7%; p=0.469) • p<0.05 for noninferiority	• Stent thrombosis rates low and not significantly different • Relatively low-risk population enrolled
OPTIMIZE Feres, et al., 2013 (3) 24177257	**Aim**: Assess whether 3 mo of DAPT is clinically noninferior to 12 mo in pts undergoing PCI with ZES **Study type**: RCT, noninferiority trial **Size**: 3,211 pts	**Inclusion criteria**: Stable angina, low-risk ACS **Exclusion criteria**: STEMI for primary or rescue PCI, PCI with BMS in nontarget lesion <6 mo prior to index procedure, previous DES Rx., schedule elective surgery within 12 mo after index procedure, any contraindication to ASA and clopidogrel, SVG lesion, DES stenosis	**Intervention**: 3 mo DAPT (1,605) **Comparator:** 12 mo DAPT (1,606)	**1° endpoint**: NACCE. At 1 y follow-up • 93 pts with 3 mo Rx vs. 90 pts with 12 mo Rx (95% CI: 1.52–1.86) • p=0.002 for noninferiority **Safety endpoint**: GUSTO major bleeding • 0.2% with 3 mo Rx vs. 0.4% with long term Rx (HR: 0.50, 95% CI: 0.16–1.11)	• Stent thrombosis (5 pts in short term vs. 4 pts in long term) • Study not powered to detect small differences in ischemic and bleeding events after 90 d. • Overall event rate for NACCE was lower than anticipated.

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RESET Kim BK, et al., 2012 (4) 22999717	**Aim**: Evaluate noninferiority of shorter DAPT after DES **Study type**: RCT, open label, noninferiority trial **Size**: 2,117 pts	**Inclusion criteria**: Pts undergoing DES implantation **Exclusion criteria**: Contraindication to antiplatelet agents, bleeding, STEMI within 48 h or cardiogenic shock, left main PCI	**Intervention**: 3 mo DAPT with E-ZES (n=1059) **Comparator**: 12 mo DAPT with other DES (n=1058)	**1° endpoint**: CV death, MI, stent thrombosis, TVR, bleeding at 1 y. • 4.7% with 3 mo DAPT/E-ZES vs. 4.7% with 12 mo DAPT/other DES (difference 0.0%; 95% CI: -2.5–2.5; p=0.84) • p<0.001 for noninferiority	• No significant differences in rates of stent thrombosis, bleeding or TVR • Study underpowered due to low event rates • Same stents not used in the 2 randomization arms
EXCELLENT Gwon HC, et al., 2012 (5) 22179532	**Aim**: Evaluate whether 6 mo DAPT would be noninferior to 12 mo DAPT after DES **Study type**: RCT, open label, noninferiority trial **Size**: 1,443 pts	**Inclusion criteria**: >50% lesion with evidence of myocardial ischemia or >75% lesion (with or without documented ischemia) **Exclusion criteria**: MI within 72 h, LVEF<25% or cardiogenic shock, recent major bleeding or surgery	**Intervention**: 6 mo DAPT after DES (n=722) **Comparator**: 12 mo DAPT after DES (n=721)	**1° endpoint**: Target vessel failure (cardiac death, MI, ischemia-driven TVR) at 12 mo • 4.8% with 6 mo DAPT vs. 4.3% with 12 mo DAPT (p=0.001 for noninferiority)	• Stent thrombosis 0.9% with 6 mo DAPT vs. 0.1% with 12 mo DAPT (HR: 6.02; 95% CI: 0.72–49.96; p=0.10) • TIMI major bleeding 0.3% with 6 mo DAPT vs. 0.6% with 12 mo DAPT (HR: 0.50; 95% CI: 0.09–2.73; p=0.42) • Target vessel failure occurred more frequently with 6 mo DAPT in diabetic pts • Study underpowered for death or MI
Studies of shorter (6 mo) vs. 24 mo duration of DAPT					
ITALIC Gilard M, et al., 2015 (6) 25461690	**Aim**: Evaluate noninferiority of 6 mo DAPT vs. 24 mo DAPT with newer generation (Xience) DES **Study type**: RCT, open label, noninferiority trial **Size**: 2,031 pts (actual 1,850 pts)	**Inclusion criteria**: Pts undergoing PCI **Exclusion criteria**: Primary PCI for STEMI, left main PCI, ASA nonresponder	**Intervention**: 6 mo DAPT (n=926) **Comparator**: 24 mo DAPT (n=924)	**1° endpoint**: Death, MI, urgent TVR, CVA, major bleeding at 12 mo post-stenting • 1.6% with 6 mo vs. 1.5% with 24 mo (p=0.85) • p<0.00002 for noninferiority (absolute risk difference 0.11%; 95% CI: -1.04–1.26%)	• Study terminated early due to recruitment problems • No significant differences in stent thrombosis or bleeding complications • Low event rates (lower than expected)
PRODIGY Valgimigli M, et al., 2012 (7) 22438530	**Aim**: To evaluate the impact of up 6 or 24 mo DAPT after BMS or DES **Study type**: RCT **Size**: 2,013 pts (1970 eligible for	**Inclusion criteria**: SIHD or ACS pts undergoing PCI **Exclusion criteria**: Bleeding diathesis, bleeding or stroke within 6 mo, oral anticoagulant therapy	**Intervention**: 24 mo DAPT (n=987) **Comparator**: 6 mo DAPT (n=983)	**1° endpoint**: Death, MI or CVA at 2 y • 10.1% with 24 mo DAPT vs. 10.0% with 6 mo DAPT (HR: 0.98; 95% CI: 0.74–1.29; p=0.91) **1° Safety endpoint**: BARC type 2, 3 or 5 bleeding • 7.4% with 24 mo DAPT vs.	• Stent thrombosis rates low and not significantly different between treatment groups

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	randomization at 30 d)			3.5% with 6 mo DAPT (HR:0.46; 95% CI 0.31–0.69; p=0.00018)	

ACS indicates acute coronary syndrome; ASA, aspirin; BARC, Bleeding Academic Research Consortium; BMS, bare metal stent; CKD, chronic kidney disease; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NACCE, Net Adverse Clinical and Cerebral Events; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; Rx, prescription; STEMI, ST-elevation myocardial infarction; SIHD, stable ischemic heart disease; SVG, saphenous vein graft; TIMI, Thrombolysis In Myocardial Infarction; and TVR, target-vessel revascularization.

Data Supplement 2. RCTs of Prolonged/Extended (>12 Month) Duration of DAPT in Patients Treated With Stent Implantation

Study Acronym Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
OPTIDUAL Helft G, et al., 2015 (8) 26364288	**Aim**: Evaluate hypothesis that continuing clopidogrel would be superior to stopping clopidogrel at 12 mo following DES **Study type**: RCT, open label, superiority trial **Size**: 1,966 pts (1385 included in ITT analysis)	**Inclusion criteria**: Pts (SIHD or ACS) undergoing PCI with DES free of MACCE or major bleeding after 12 mo DAPT **Exclusion criteria**: Need for oral anticoagulation, unprotected left main PCI, life expectancy <2 y	**Intervention**: Additional 36 mo DAPT (n=695) **Comparator**: ASA therapy alone (n=690)	**1° endpoint**: Net adverse clinical events (death, MI, CVA or major bleeding) • 5.8% with additional 36 mo DAPT vs. 7.5% with ASA alone (HR: 0.75; 95% CI: 0.50–1.28; p=0.017)	• Study terminated early due to slow recruitment • Actual median follow-up 33.4 mo • Rates of death 2.3% with extended DAPT vs. 3.5% with ASA alone (HR: 0.65; 95% CI: 0.34–1.22; p=0.18) • Rates of major bleeding identical at 2.0% (p=0.95) • Post hoc analysis of MACCE (death, MI or CVA) found rates of 4.2% with extended DAPT vs. 6.4% with ASA alone (HR: 0.64; 95% CI: 0.40–1.02; p=0.06)
ITALIC Gilard M, et al., 2015 (6) 25461690	**Aim**: Evaluate noninferiority of 6 mo DAPT vs. 24 mo DAPT with newer generation (Xience) DES **Study type**: RCT, open label, noninferiority trial **Size**: 2,031 pts (actual 1850 pts)	**Inclusion criteria**: Pts undergoing PCI **Exclusion criteria**: Primary PCI for STEMI, left main PCI, ASA nonresponder	**Intervention**: 6 mo DAPT (n=926) **Comparator**: 24 mo DAPT (n=924)	**1° endpoint**: Death, MI, urgent TVR, CVA, major bleeding at 12 mo post-stenting •1.6% with 6 mo vs. 1.5% with 24 mo (p=0.85) • p<0.00002 for noninferiority (absolute risk difference 0.11%; 95% CI: -1.04–1.26%)	• Study terminated early due to recruitment problems • No significant differences in stent thrombosis or bleeding complications • Low event rates (lower than expected)

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DAPT Mauri L, et al., 2014 (9) 25399658	**Aim**: To assess benefits and risks of >12 mo DAPT after BMS or DES **Study type**: RCT, placebo-controlled **Size**: 9,961 pts	**Inclusion criteria**: Pts treated with BMS or DES, but only DES-treated pts included in this report **Exclusion criteria**: MI, CVA, repeat revascularization, stent thrombosis, or moderate-severe bleeding during the 1st 12 mo DAPT after DES (before randomization); oral anticoagulant use	**Intervention**: Additional 18 mo of DAPT after initial 12 mo **Comparator**: Placebo thienopyridine after initial 12 mo DAPT	**Co-1° endpoints (after additional 18 mo Rx)**: • Stent thrombosis: 0.4% with continued DAPT vs. 1.4% with placebo thienopyridine (HR: 0.29; 95% CI: 0.17–0.48; p=0.001) • MACCE (death, MI, CVA): 4.3% with continued DAPT vs. 5.9% with placebo thienopyridine (HR: 0.71; 95% CI: 0.59–0.85; p<0.001) **1° Safety endpoint**: GUSTO moderate or severe bleeding • 2.6% with continued DAPT vs. 1.6% with placebo thienopyridine (p=0.001)	• All-cause death 2.0% with continued DAPT vs. 1.5% with placebo thienopyridine (HR: 1.36; 95% CI:1.00–1.85; p=0.05) • Increased death due to more non–CV deaths • Only DES-treated pts included in this report • DES included 1st and 2nd generation stents
ARCTIC-Interruption Collet JP, et al., 2014 (10) 25037988	**Aim**: To demonstrate superiority of continued (>12 mo) vs. interrupted (12 mo) DAPT **Study type**: Planned extension of ARTIC-Monitoring trial. Pts treated with 1 y DAPT randomized to interrupt (stop) therapy or continue therapy. RCT, open label. **Size**: 1,259 pts	**Inclusion criteria**: Pts prior enrolled in ARCTIC-Monitoring trial without an event at 12 mo **Exclusion criteria**: Primary PCI, bleeding diathesis, chronic anticoagulation use	**Intervention**: Interruption (cessation) of DAPT after 12 mo Rx (n=624) **Comparator**: Continuation of DAPT after 12 mo Rx for an additional 6-18 mo (n=635)	**1° endpoint**: Death, MI, stent thrombosis, CVA or urgent TVR • 4% of interruption group vs. 4% of continuation group (HR: 1.17; 95% CI: 0.68–2.03; p=0.58) **1° Safety endpoint**: STEEPLE major bleeding • <0.5% of interruption group vs. 1% of continuation group (HR: 0.15; 95% CI: 0.02–1.20; p=0.073)	• High-risk pts not enrolled • No differences in secondary endpoints, including stent thrombosis
DES-LATE Lee CW, et al., 2014 (11) 24097439	**Aim**: To compare 12 mo DAPT to >12 mo DAPT after DES **Study type**: RCT, open label **Size**: 5,045 pts	**Inclusion criteria**: Pts treated with DES event-free after 12-18 mo of DAPT **Exclusion criteria**: Recent ACS, ischemic or bleeding event on DAPT before enrollment	**Intervention**: Continued DAPT after 12 mo of Rx (n=2514) **Comparator**: ASA monotherapy (n=2531)	**1° endpoint**: CV death, MI, CVA 24 mo after randomization • 2.4% in ASA alone vs 2.6% in continued DAPT (HR: 0.94; 95% CI: 0.66–1.35; p=0.75)	• Publications includes pts from ZEST-LATE and REAL-LATE (the results of which were first published by Park SJ in 2010) and an additional 2,344 pts TIMI major bleeding at 24 mo follow-up occurred in 1.1% of ASA alone vs. 1.4 of continued DAPT (HR: 0.71; 95% CI: 0.42–1.20; p=0.20); difference was statistically significant by the end of all follow-up

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					• No significant difference in stent thrombosis
PRODIGY Valgimigli M, et al., 2012 (7) 22438530	**Aim**: To evaluate the impact of up 6 or 24 mo DAPT after BMS or DES **Study type**: RCT **Size**: 2,013 pts (1,970 eligible for randomization at 30 d)	**Inclusion criteria**: SIHD or ACS pts undergoing PCI **Exclusion criteria**: Bleeding diathesis, bleeding or stroke within 6 mo, oral anticoagulant therapy	**Intervention**: 24 mo DAPT (n-987) **Comparator**: 6 mo DAPT (n=983)	**1° endpoint**: Death, MI or CVA at 2 y • 10.1% with 24 mo DAPT vs. 10.0% with 6 mo DAPT (HR: 0.98; 95% CI: 0.74–1.29; p=0.91) **1° Safety endpoint**: BARC type 2, 3 or 5 bleeding • 7.4% with 24 mo DAPT vs. 3.5% with 6 mo DAPT (HR: 0.46; 95% CI: 0.31–0.69; p=0.00018)	• Stent thrombosis rates low and not significantly different between treatment groups
Park SJ, et al., 2010 (12) 20231231	**Aim**: Compare ASA + clopidogrel to ASA alone in pts treated with DES who were event free for 12 mo **Study type**: RCT, open label **Size**: 2,701 pts	**Inclusion criteria**: Pts treated with DES who were event free for 12 mo **Exclusion criteria**: Ischemic or bleeding event during first 12 mo of DAPT after DES implantation	**Intervention**: ASA + clopiodogrel **Comparator**: ASA alone	**1° endpoint**: MI or cardiac death at 2 y •1.8% with DAPT vs. 1.2% with ASA (HR: 1.65; 95% CI: 0.80–3.36; p=0.17)	• Study combined pts from ZEST-LATE and REAL-LATE

ACS indicates acute coronary syndrome; ASA, aspirin; BMS, bare metal stent; CI, confidence interval; CV, cardiovascular; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; f/u, follow up; HR, hazard ratio; ITT, intent to treat; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; Rx, prescription; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.

Data Supplement 3. Meta-Analyses of Duration of DAPT

Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

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Udell JA, et al., 2015 (13) 26324537	**Aim**: Compare benefits and risks of more than one y of DAPT with ASA alone in high-risk pts with Hx of prior MI **Study type**: Meta-analysis **Size**: 33,435 pts	**Inclusion criteria**: RCTs of secondary prevention in pts with MI randomized to extended duration (>12 mo) DAPT compared with ASA alone **Exclusion criteria**: ≤12 mo of follow-up, trials of oral anticoagulant therapies, trials of pts with SIHD alone undergoing PCI	**Intervention**: >12 mo DAPT **Comparator**: ASA therapy alone	**1° endpoint: MACE (CV death, nonfatal MI, and nonfatal stroke)** • 6.4% with DAPT vs. 7.5% with ASA alone (RR: 0.78; 95% CI: 0.67–0.90; p=0.001)	• Studies included in analysis: CHARISMA, PRODIGY, ARCTIC-Interruption, DAPT, DES-LATE, and PEGASUS-TIMI 54 • For all studies except PEGASUS-TIMI 54, a subgroup of the study population was used for the meta-analysis • CV death 2.3% with DAPT vs. 2.6% with ASA alone (RR: 0.85; 95% CI: 0.74–0.98; p= 0.03), • No increase in non–CV death (RR: 1.03; CI: 0.86–1.23; p= 0.76). • Major bleeding 1.85% with DAPT vs. 1.09% with ASA (RR: 1.73; 95% CI: 1.19–2.50; p=0.004)
Elmariah S, et al., 2015 (14) 25467565	**Aim**: Assess the effect of extended duration DAPT on mortality **Study type**: Hierarchical Bayesian random effects model meta-analysis, trial level data **Size**: 14 RCT; total n=69,644 pts	**Patients**: Pts enrolled in RCTs of extended vs. short duration DAPT or DAPT vs. ASA alone. Clinical settings of studies included post-PCI, post-ACS, atrial fibrillation, lacunar stroke, and documented or high-risk of CV disease	**Intervention**: Longer duration DAPT **Comparators**: Shorter duration DAPT or ASA alone	**CV Mortality:** 4.2% with longer DAPT vs. 4.1% with shorter DAPT/ASA alone (HR:1.01; 95% credible interval: 0.93–1.12; p=0.81) **Non–CV Mortality:** 1.7% with longer DAPT vs. 1.7% with shorter DAPT/ASA alone (HR: 1.04; 95% credible interval: I: 0.90–1.26; p=0.66) **All-cause mortality**: 5.8% with longer DAPT vs. 5.7% with shorter DAPT/ASA alone (HR: 1.04; 95% credible interval: I: 0.96–1.18; p=0.17)	• Trial level data used • Authors concluded extended-duration APT not associated with differences in all-cause, CV, or non–CV death compared with ASA alone or short duration DAPT
Palmerini T, et al., 2015 (15) 25790880	**Aim**: To compare clinical outcomes between short- (≤6 mo) and long-term (1 y) DAPT in pts treated with DES **Study type**: Individual pts data pairwise and network meta-analysis of RCTs	**Inclusion criteria**: RCTs comparing short-duration (3 or 6 mo) with longer-duration DAPT (≥1 y).	**Intervention**: Short-term (≤6 mo) DAPT **Comparator**: Long-term (1 y) DAPT	**1° endpoint**: MACE (cardiac death, MI, stent thrombosis) •For short-term DAPT, HR: 1.11 (95% CI: 0.86–1.42; p=0.44) **Safety endpoint**: Bleeding •For short-term DAPT, HR: 0.66 (95% CI: 0.46–0.94; p=0.03)	• No significant differences in 1 y rates of MACE among 3 mo vs. 1 y DAPT, 6-mo vs. 1 y DAPT, or 3 mo vs. 6 mo DAPT

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	Size: 4 RCT; total n=8,180 pts				
Giustino G, et al., 2015 (16) [25681754](25681754)	**Aim**: Evaluate the efficacy and safety of DAPT after DES **Study type**: Meta-analysis of RCT, trial level data **Size**: 10 RCT; total n=32,135 pts	**Patients**: Pts treated with DES enrolled in RCTs of shorter vs. longer duration DAPT	**Comparators**: Shorter duration vs. Longer duration DAPT	**Stent thrombosis**: 0.9% with shorter vs. 0.5% with longer (OR: 1.71; 95% CI:1.26–2.32, p=0.001) **Clinically significant bleeding:** 1.2% with shorter vs. 1.9% with longer (OR: 0.63, 95% CI: 0.52–0.75; p<0.001	• Trial level data used • The effect of shorter DAPT on stent thrombosis was attenuated with the use of second-generation DES (OR: 1.54; 95% CI: 0.96–2.47) compared with the use of first-generation DES (OR: 3.94; 95% CI: 2.20–7.05); p for interaction=0.008. • All-cause mortality 2.0% with shorter vs. 2.2% with longer (OR: 0.87; 95% CI: 0.74–1.01; p=0.073)
Navarese, et al., 2015 (17) [25883067](25883067)	**Aim**: To assess the benefits and risks of short term (<12 mo) or extended (>12 mo) DAPT vs. 12 mo DAPT after DES. **Study type**: Meta-analysis of RCT, trial level data **Size**: 10 RCT; total n=32,287	**Patients**: Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT	**Comparator**: Shorter or longer duration DAPT compared to 12 mo DAPT	**MI:** • Short vs. 12 mo: 1.65% vs. 1.50% (OR: 1.11; 95% CI: 087–1.43; p=0.40) • Extended vs. 12 mo: 1.55% vs. 2.89% (OR: 0.53; 95% CI: 0.42–0.66; p<0.001) **Stent thrombosis:** • Short vs. 12 mo: 0.53% vs. 0.40% (OR: 1.32; 95% CI: 0.83–2.08; p=0.24) • Extended vs. 12 mo: 0.32% vs. 0.98% (OR: 0.33; 95% CI: 0.21–0.51; p<0.001) **Major bleeding:** • Short vs. 12 mo: 0.35% vs. 0.61% (OR:0.58; 95% CI: 0.36–0.92, p=0.02) • Extended vs. 12 mo: 1.95% vs. 1.21% (OR:1.62; 95% CI: 1.26–2.09; p<0.001) **CV mortality:** • Short vs. 12 mo: 1.13% vs. 1.20% (OR: 0.95; 95% CI: 0.68–1.33; p=0.76)	• Trial level data used • Authors concluded that compared with standard 12 mo DAPT, shorter duration reduced bleeding with no apparent increase in ischemic complications and could be considered for most pts. In selected pts with low bleeding risk and very high ischemic risk, extended DAPT could be considered

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				• Extended vs. 12 mo: 1.03% vs. 0.95% (OR:1.09; 95% CI: 0.79–1.50; p=0.62) **All-cause mortality:** • Short vs. 12 mo: 1.43% vs. 1.56% (OR: 0.91; 95% CI: 0.781–1.18; p=0.49) • Extended vs. 12 mo: 1.84% vs. 1.42% (OR: 1.30; 95% CI: 1.02–1.66; p=0.03)	
Palmerini T, et al., 2015 (18) 26065988	**Aim**: Investigate mortality and other clinical outcomes with different DAPT strategies **Study type**: Pair wise and Bayesian network meta-analysis of RCT, trial level data **Size**: 10 RCT; total n=31,666 pts	**Patients:** Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT	**Comparators**: Shorter duration vs. longer duration DAPT	**All-cause mortality:** Shorter vs. longer DAPT: HR: 0.82; 95% CI: 0.69–0.98; p=0.02; NNT=325	• Trial level data used • Reduced mortality with shorter compared to longer DAPT attributable to lower non–cardiac mortality (HR: 0.67; 95% CI: 0.51–0.89; p=0.006; NNT=347) with similar cardiac mortality (HR: 0.93; 95% CI: 0.73–1.17; p=0.52) • Shorter DAPT associated with lower risk of major bleeding, but a higher risk of MI and stent thrombosis
Spencer FA, et al., 2015 (19) 26005909	**Aim**: To summarize data on clinical outcome with longer vs. shorter duration DAPT after DES **Study type**: Meta-analysis of RCT, trial level data **Size**: 9 RCT; total n=28,808	**Patients:** Pts treated with DES enrolled in RCT of shorter vs. longer duration DAPT	**Comparators**: Shorter duration vs. longer duration DAPT	**MI:** 1.7% with longer vs. 2.6% with shorter (RR: 0.73; CI: 0.58–0.92) **Major Bleeding**: 1.4% with longer vs. 0.8% with shorter (RR: 1.66; 95% CI: 1.34–1.99) **Total Mortality:** 2.0% with longer vs. 1.7% with shorter (RR–1.19; 95% CI: 1.04–1.36)	• Trial level data used • Authors concluded moderate-quality evidence showed that longer-duration DAPT decreased risk for MI and increased mortality, and that high-quality evidence showed that DAPT increased risk for major bleeding • Authors calculated that extended DAPT associated with 8 fewer MI per 1000 treated per year but 6 more major bleeding events per year than shorter-duration DAPT

ACS indicates acute coronary syndrome; ASA, aspirin; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HR, hazard ratio; Hx, history; MACE, major adverse cardiac events; MI, myocardial infarction; NNT, number need to treat; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SIHD, stable ischemic heart disease; and TIMI, Thrombolysis In Myocardial Infarction.

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Data Supplement 4. RCTs, RCT Subgroup Analyses, and Meta-Analyses of RCTs of DAPT Post–MI or Post–ACS

Study Acronym Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Udell JA, et al., 2015 (13) 26324537	**Aim**: Compare benefits and risks of more than one y of DAPT with ASA alone in high-risk pts with Hx of prior MI **Study type**: Meta-analysis **Size**: 33,435 pts	**Inclusion criteria**: RCTs of secondary prevention in pts with MI randomized to extended duration (>12 mo) DAPT compared with ASA alone **Exclusion criteria**: ≤12 mo of follow-up, trials of oral anticoagulant therapies, trials of pts with SIHD alone undergoing PCI	**Intervention**: >12 mo DAPT **Comparator**: ASA therapy alone	**1° endpoint: MACE (CV death, nonfatal MI, and nonfatal stroke)** • 6.4% with DAPT vs. 7.5% with ASA alone (RR: 0.78; 95% CI: 0.67–0.90; p=0.001)	• Studies included in analysis: CHARISMA, PRODIGY, ARCTIC-Interruption, DAPT,-LATE, and PEGASUS-TIMI 54 • For all studies except PEGASUS-TIMI 54, a subgroup of the study population was used for the meta-analysis • CV death 2.3% with DAPT vs. 2.6% with ASA alone (RR: 0.85; 95% CI: 0.74–0.98; p=0.03), • No increase in non–CV death (RR: 1.03; 95% CI: 0.86–1.23; p=0.76). • Major bleeding 1.85% with DAPT vs 1.09% with ASA (RR: 1.73; 95% CI:1.19–2.50; p=0.004)
DAPT (MI subgroup analysis) Yeh RW, et al., 2015 (20) 25787199	**Aim**: Assess benefits and risks of extended DAPT in subgroups of pts in the DAPT study with MI and stable presentations **Study type**: Post-hoc analysis of the DAPT trial **Size**: 11,648 pts	**Inclusion criteria**: Pts enrolled in DAPT trial treated with either BMS or DES **Exclusion criteria**: N/A	**Intervention**: Additional 18 mo DAPT after initial 12 mo **Comparator**: Placebo thienopyridine after initial 12 mo DAPT **Subgroup analysis**: Pts with MI (n=3,576) and without MI (n=8,072)	**Co-1° endpoints (after additional 18 mo Rx)**: • Stent thrombosis in MI group: 0.5% with extended DAPT vs. 1.9% with placebo thienopyridine (HR: 0.27; CI: 0.13–0.57, p<0.001) • MACCE (death, MI, CVA) in MI group: 3.9% with continued DAPT vs. 6.8% with placebo thienopyridine (HR: 0.56; CI: 0.42–0.76; p<0.001) **1° Safety endpoint**: GUSTO moderate or severe bleeding • In pts with MI: 1.9% with continued DAPT vs. 0.8% with placebo thienopyridine (HR: 2.38; CI: 1.28–4.43, p=0.005)	• All cause death 1.4% with extended DAPT vs. 1.6% with placebo thienopyridine (HR: 0.87; CI: 0.50–1.50, p=0.61)

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PEGASUS-TIMI 54 Bonaca MP, et al., 2015 (21) 25773268	**Aim:** To investigate the efficacy and safety of ticagrelor beyond 1 y after a MI **Study type:** RCT, placebo controlled **Size:** 21,162 pts	**Inclusion criteria:** MI 1-3 y prior, age ≥50, and an additional high-risk feature **Exclusion criteria:** Bleeding disorder, Hx of ischemic stroke of ICH, CNS tumor, GI bleeding within 6 mo, major surgery within 30 d, oral anticoagulant use	**Intervention:** Ticagrelor 90 mg (n=7050) or ticagrelor 60 mg (n=7045) **Comparator:** Placebo (n=7067)	**1° endpoint:** CV death, MI or stroke at median 33 mo follow-up • 7.85% with 90 mg ticagrelor, 7.77% with 60 mg ticagrelor, and 9.04% with placebo •HR for 90 mg vs. placebo: 0.85; 95% CI: 0.75–0.96; p=0.008 • HR for 60 mg vs. placebo: 0.84; 95% CI: 0.74–0.95; p=0.004 **1° Safety endpoint:** TIMI major bleeding • 2.60 with 90 mg ticagrelor, 2.30 with 60 mg ticagrelor, and 1.06% with placebo (p<0.001 for each dose vs. placebo)	• All pts treated with ASA • No differences in death between the either dose of ticagrelor and placebo
TRILOGY Row MT, et al., 2012 (22) 22920930	**Aim:** To compare prasugrel with clopidogrel in pts with NSTE-ACS not undergoing revascularization **Study type:** RCT **Size:** 7,243 pts	**Inclusion criteria:** Pts with NSTE-ACS selected for medical management without revascularization **Exclusion criteria:** Hx CVA or TIA, PCI or CABG within prior 30 d, renal failure requiring dialysis, concomitant oral anticoagulation treatment	**Intervention:** Prasugrel **Comparator:** Clopidogrel	**1° endpoint:** MACE (CV death, MI or CVA) in pts <75 y at 30 mo • 13.9% with prasugrel vs. 16.0% with clopidogrel (HR: 0.91; 95% CI: 0.79–1.05; p=0.21) **Safety endpoint):** GUSTO severe or life-threatening bleeding • 0.9% with prasugrel vs. 0.6% with clopidogrel (HR: 0.94; 95% CI: 0.44–1.99; p=0.87)	• All pts treated with ASA
PLATO James SK, et al., 2011 (23) 21685437	**Aim:** To evaluate efficacy and safety outcomes in pts in PLATO who at randomization were planned for a noninvasive treatment strategy. **Study type:** Pre-specified subgroup analysis of the PLATO RCT **Size:** 5,216 pts	**Inclusion criteria:** Pts with ACS admitted to hospital with planned noninvasive management **Exclusion criteria:** Pts in PLATO with planned invasive management	**Intervention:** Ticagrelor (90 mg bid) **Comparator:** Clopidogrel (75 mg qD)	**1° endpoint:** Vascular death, MI or CVA • 12.0% with ticagrelor compared to 14.3% with clopidogrel (HR: 0.85; 95% CI: 0.73–1.00; p=0.04) **Safety endpoint:** • Total major bleeding: (11.9% with ticagrelor vs. 10.3% with clopidogrel (HR: 1.17; 95% CI: 0.98–1.39; p=0.08) • Non–CABG major bleeding: 4.0% with ticagrelor vs. 3.1% with clopidogrel (HR:	• N/A

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				1.30, 95% CI:0.95–1.77; p=0.10)	
PLATO Steg PG, et al., 2010 (24) 21060072	**Aim**: To examine the efficacy and safety of ticagrelor compared with clopidogrel in pts with STE-ACS intended for reperfusion with primary PCI. **Study type**: Pre specified subgroup analysis of PLATO; RCT **Size**: 7,544 pts	**Inclusion criteria**: Pts enrolled in PLATO with STEMI **Exclusion criteria**: Same as PLATO study	**Intervention**: Ticagrelor **Comparator**: Clopidogrel	**1° endpoint**: MACE (CV death, MI, CVA) • 9.4% with ticagrelor vs. 10.8% with clopdiogrel; (HR: 0.87; 95% CI: 0.75–1.01; p=0.07) **Safety endpoint**: major bleeding • No difference in major bleeding (HR: 0.98; p=0.76).	• 72% of pts with STEMI underwent primary PCI • Definite stent thrombosis lower with ticagrelor (HR: 0.66; p=0.03). • Risk of stroke higher with ticagrelor (1.7% vs. 1.0%; HR: 1.63; 95% CI: 1.07–2.48; p=0.02).
TRITON-TIMI 38 Montalescot, et al., 2009 (25) 19249633	**Aim**: To asses prasugrel vs. clopidogrel in pts undergoing PCI for STEMI enrolled in TRITON-TIMI 38 **Study type**: Double-blind RCT **Size**: 3,534 pts	**Inclusion criteria**: Pts undergoing PCI for STEMI **Exclusion criteria**: Increased risk of bleeding, anemia, recent fibrinolytic administration, need from chronic oral anticoagulants, cardiogenic shock, or thienopyridine treatment within 5 d of randomization.	**Intervention**: Prasugrel (n=1,769) **Comparator**: Clopidogrel (n=1,765)	**1° endpoint**: CV death, nonfatal MI, nonfatal stroke at 15 mo. • 10.0% with prasugrel vs. 12.4% with clopidogrel (HR: 0.79; 95% CI: 0.65-0.97; p=0.0221) **Safety endpoint:** • No significant different in non–CABG related TIMI major bleeding at 30 d or 15 mo	• Secondary endpoint of CV death, nonfatal MI or target vessel revascularization at 30 d 6.5% with prasugrel vs. 9.5% with clopidogrel (HR: 0.75; 95% CI: 0.59–0.96; p=0.0205)
TRITON Wiviott SD, et al., 2007 (26) 17982182	**Aim**: To compare prasugrel with clopidogrel in pts with ACS scheduled for PCI **Study type**: RCT, double-blind, double-dummy design **Size**: 13,608 pts	**Inclusion criteria**: ACS (NSTE-ACS or STEMI) pts undergoing planned PCI **Exclusion criteria**: Increased risk of bleeding, anemia, thrombocytopenia	**Intervention**: Prasugrel (10 mg qD) (n=6,813) **Comparator**: Clopidogrel (75 mg qD) (n=6,795)	**1° endpoint**: CV death, MI, CVA • 9.9% with prasugrel vs. 12.1% with clopidogrel (HR: 0.81; CI: 0.73–0.90; p<0.001) **1° Safety endpoint**: Non–CABG related TIMI major bleeding • 2.4% with prasugrel vs. 1.8% with clopidogrel (HR: 1.32; 95% CI: 1.03–1.68, p=0.03)	• Stent thrombosis rate lower with prasugrel (1.1% vs. 2.4%, p=0.001) • Life-threatening bleeding higher with prasugrel (1.4% vs. 0.9%, p=0.01) • Fatal bleeding higher with prasugrel (0.4% vs. 0.1%, p=0.002) • Increased rate of ICH in those treated with prasugrel with Hx of CVA or TIA • Increased risk of bleeding in those with Hx CVA or TIA, elderly (≥75 y) and body weight <60 kg

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CHARISMA Bhatt DL, et al., 2006, 2007 (27,28) 7498584 16531616	**Aim**: Assess effect of DAPT in a broad population of pts at high risk for atherothrombotic events **Study type**: RCT, placebo controlled **Size**: 15,603 pts	**Inclusion criteria**: Age ≥45 with multiple atherothrombotic risk factors and/or documented CAD, cerebrovascular disease, or PAD **Exclusion criteria**: Long-term use of oral antithrombotic medications of NSAID, recent ACS	**Intervention**: ASA + clopidogrel (n=7,802) **Comparator**: ASA + placebo (n=7,801)	**1° endpoint**: CV death, MI or CVA (median follow-up 28 mo) • 6.8% with ASA+clopidogrel vs. 7.4% with ASA+placebo (RR: 0.93; 95% CI: 0.83–1.05; p=0.22) **1° Safety endpoint**: GUSTO severe bleeding • 1.7% with ASA+clopidogrel vs. 1.3% with ASA+placebo (RR: 1.25; 95% CI: 0.97–1.61; p=0.09)	• In a post hoc subgroup analysis of those with Hx of prior MI, composite endpoint of CV death, MI and CVA occurred in 8.3% of placebo-treated pts and 6.6% of clopidogrel-treated pts (HR: 0.774; 95% CI: 0.613–0.978; p=0.031)
COMMIT-CCS 2 Chen ZM, et al., 2005 (29) 16271642	**Aim**: To compare ASA alone to ASA + clopidogrel in pts with STEMI **Study type**: RCT **Size**: 45,852 pts	**Inclusion criteria**: Pts with suspected MI within 24 H **Exclusion criteria**: Pts undergoing primary PCI, high-risk of adverse event with study treatments	**Intervention**: ASA + clopidogrel **Comparator**: ASA alone	**Co-1° endpoints (during scheduled treatment – discharge or d 28)**: • MACE (death, reinfarction, CVA): 9.2% with DAPT vs. 10.1% with ASA (RRR: 9%; 95% CI: 3%–14%; p=0.002) • Death: 7.5% with DAPT vs. 8.1% with ASA (RRR: 7%; 95% CI: 1%–13%; p=0.03) **Safety endpoint**: Life-threatening bleeding • 0.58% with DAPT vs. 0.55% with ASA (p=0.59)	• 87% with ST elevation; 6% with bundle branch block; and 7% with ST depression
PCI-CLARITY Sabatine MS, et al., 2005 (30) 16143698	**Aim**: Determine if clopidogrel pretreatment before PCI in pts with recent STEMI is superior to clopidogrel treatment initiated at the time of PCI in preventing MACE **Study type**: RCT; prespecified subgroup analysis of pts in CLARITY-TIMI 28 who underwent PCI **Size**: 1,863 pts	**Inclusion criteria**: Pts receiving fibrinolytics for STEMI undergoing subsequent angiography and PCI enrolled in CLARITY **Exclusion criteria**: Planned treatment with clopidogrel or a GPI before angiography, cardiogenic shock, prior CABG	**Intervention**: Clopidogrel pretreatment **Comparator**: Standard therapy (clopidogrel at the time of PCI)	**1° endpoint**: MACE at 30 d • 3.6% with pretreatment vs. 6.2% with standard Rx; (adjusted OR=0.54; 95% CI: 0.35–0.85; p=0.008) **Safety endpoint**: TIMI major or minor bleeding • 2.0% with pretreatment vs. 1.9% with standard Rx (p>0.99)	• Pretreatment with clopidogrel also reduced the incidence of MI or stroke prior to PCI (4.0% vs. 6.2%; OR: 0.62; 95% CI: 0.40–0.95; p=0.03)

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Sabatine MS, et al., 2005 (31) [15758000](15758000)	**Aim**: To assess benefit of addition of clopidogrel to ASA in pts with STEMI treated with fibrinolytic therapy **Study type**: RCT **Size**: 3,491 pts	**Inclusion criteria**: Pts with STEMI being treated with fibrinolytic therapy and ASA **Exclusion criteria**: recent clopidogrel treatment or GPI, planned performance of angiography within 48 h, prior CABG, cardiogenic shock	**Intervention**: Clopidogrel + ASA **Comparator**: Placebo + ASA	**1° endpoint**: Composite of occluded infarct-related artery (TIMI flow grade 0 or1) at angiography, or death or recurrent MI before angiography • 15.0% with DAPT vs. 21.7% with ASA (absolute reduction 6.7%; RRR: 36%; 95% CI: 24%–47%; p<0.001) **Safety endpoint: TIMI major bleeding** • 1.3% with DAPT vs. 1.1% with ASA (p=0.64)	• At 30 d, DAPT reduced composite endpoint of CV death, recurrent MI or recurrent ischemia leading to urgent TVR by 20% (from 14.1% – 11.6%; p=0.03) • Angiography performed 48-192 h after the start of the study
CURE Fox KA, et al., 2004 (32) [15313956](15313956)	**Aim**: To assess benefits and risks of ASA plus clopidogrel in pts undergoing CABG for NSTE-ACS **Study type**: Post hoc subgroup analysis of CURE; RCT **Size**: 12,562 pts entire study population; 1,061 pts underwent CABG	**Inclusion criteria**: NSTE-ACS within <24 h **Exclusion criteria**: NYHA class IV HF, PCI or CABG <3 mo, contraindication to antiplatelets and antithrombotics, hemorrhagic or IC stroke, severe thrombocytopenia	**Intervention**: Clopidogrel + ASA **Comparator**: Placebo + ASA	**1° endpoint**: **MACE** (CV death, MI or stroke) • 14.5% with DAPT vs. 16.2% with ASA (RR: 0.89; 95% CI: 0.71–1.11)	• Benefits of DAPT with CABG were deemed "consistent" (test for interaction among strata 0.53) with the benefits in pts undergoing PCI (9.6% with DAPT vs. 13.2% with ASA; RR: 0.72; 95% CI: 0.47–0.90) and in those treated with medical therapy alone (8.1% with DAPT vs. 10.0% with ASA; RR: 0.80; 95% CI: 0.69–0.92)
CURE CURE Investigators, 2001 (33) [11519503](11519503)	**Aim**: Compare efficacy and safety of DAPT in pts with NSTE-ACS treated 3-12 mo **Study type**: Randomized, double-blind, placebo controlled trial **Size**: 12,562 pts	**Inclusion criteria**: Pts with NSTE-ACS hospitalized within 24 h of symptom onset **Exclusion criteria**: STEMI, high bleeding risk, oral anticoagulant use	**Intervention**: ASA + clopidogrel (DAPT) (n=6,259) **Comparator**: ASA + placebo (n=6,303)	**1° endpoint**: CV death, MI or CVA • 9.3% with DAPT vs. 11.4% with ASA alone (RR: 0.80; 95% CI: 0.72–0.90; p<0.01) **1° Safety endpoint**: Major bleeding • 3.7% with DAPT vs. 2.7% with ASA alone (RR: 1.38; p=0.001)	• Mean duration of treatment was 9 mo • Results comparable in those with and without a Dx of "MI"

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PCI-CURE Mehta SR, et al., 2001 (34) 11520521	**Aim**: To assess whether pretreatment with clopidogrel followed by long-term Rx after PCI is superior to no pretreatment and 4 wk Rx **Study type**: Analysis of those pts in CURE who were treated with PCI **Size**: 2,658 pts	**Inclusion criteria:** Pts enrolled in CURE undergoing PCI **Exclusion criteria**: N/A	**Intervention**: ASA + clopidogrel (DAPT) (n=1,313) **Comparator**: ASA + placebo (n=1,345)	**1° endpoint**: CV death, MI or urgent TVR within 30 d of PCI • 4.5% with ASA+clopidogrel vs. 6.4% with ASA+placebo (RR: 0.70; 95% CI: 0.50–0.97; p=0.03)	• CV death or MI rate between PCI and end of follow-up: 6.0% with ASA+clopidogrel vs. 8.0% with ASA+placebo (RR: 0.75; 95% CI: 0.56–1.00; p=0.047)

ACS indicates acute coronary syndrome; ASA, aspirin; bid, two times per day; BMS, bare metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CNS, central nervous system; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; Dx, diagnosis; GI; gastrointestinal; GPI, glycoprotein inhibitor; HR, hazard ratio; Hx, history; ICH, intracerebral hemorrhage; MACE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; Rx, prescription; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; SIHD, stable ischemic heart disease; STE-ACS, ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.

Data Supplement 5. RCTs and RCT Subgroup Analyses Comparing Clopidogel With Prasugrel or Ticagrelor In Patients With ACS

Study Acronym Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
TRILOGY Row MT, et al., 2012 (22) 22920930	**Aim**: To compare prasugrel with clopidogrel in pts with NSTE-ACS not undergoing revascularization **Study type**: RCT **Size**: 7,243 pts	**Inclusion criteria**: Pts with NSTE-ACS selected for medical management without revascularization **Exclusion criteria**: Hx CVA or TIA, PCI or CABG within prior 30 d, renal failure requiring dialysis, concomitant oral anticoagulation treatment	**Intervention**: Prasugrel **Comparator**: Clopidogrel	**1° endpoint**: MACE (CV death, MI or CVA) in pts <75 y at 30 mo •13.9% with prasugrel vs. 16.0% with clopidogrel (HR: 0.91; 95% CI: 0.79–1.05; p=0.21) **Safety endpoint)**: GUSTO severe or life-threatening bleeding • 0.9% with prasugrel vs. 0.6% with clopidogrel (HR: 0.94; 95% CI: 0.44–1.99; p=0.87)	• All pts treated with ASA

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PLATO James SK, et al., 2011 (23) 21685437	**Aim:** To evaluate efficacy and safety outcomes in pts in PLATO who at randomization were planned for a noninvasive treatment strategy. **Study type:** Prespecified subgroup analysis of the PLATO RCT **Size:** 5,216 pts	**Inclusion criteria:** Pts with ACS admitted to hospital with planned noninvasive management **Exclusion criteria:** Pts in PLATO with planned invasive management	**Intervention:** Ticagrelor (90 mg bid) **Comparator:** Clopidogrel (75 mg qD)	**1° endpoint:** Vascular death, MI or CVA • 12.0% with ticagrelor compared to 14.3% with clopidogrel (HR: 0.85; 95% CI: 0.73–1.00; p=0.04) **Safety endpoint:** • Total major bleeding: (11.9% with ticagrelor vs. 10.3% with clopidogrel (HR: 1.17; 95% CI: 0.98–1.39; p=0.08) • Non–CABG major bleeding: 4.0% with ticagrelor vs. 3.1% with clopidogrel (HR: 1.30, 95% CI: 0.95–1.77; p=0.10)	• N/A
PLATO Steg PG, et al., 2010 (24) 21060072	**Aim:** To examine the efficacy and safety of ticagrelor compared with clopidogrel in pts with STE-ACS intended for reperfusion with primary PCI. **Study type:** Prespecified subgroup analysis of PLATO; RCT **Size:** 7,544 pts	**Inclusion criteria:** Pts enrolled in PLATO with STEMI **Exclusion criteria:** Same as PLATO study	**Intervention:** Ticagrelor **Comparator:** Clopidogrel	**1° endpoint:** MACE (CV death, MI, CVA) •9.4% with ticagrelor vs. 10.8% with clopdiogrel; HR: 0.87; 95% CI: 0.75–1.01; p=0.07 **Safety endpoint: major bleeding** • No difference in major bleeding (HR: 0.98; p=0.76).	• 72% of pts with STEMI underwent primary PCI • Definite stent thrombosis lower with ticagrelor (HR: 0.66; p=0.03). • Risk of stroke higher with ticagrelor (1.7% vs. 1.0%; HR: 1.63; 95% CI: 1.07–2.48; p=0.02).

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PLATO Wallentin L, et al., 2009 (35) 19717846	**Aim**: To compare ticagrelor and clopidogrel in pts with ACS **Study type**: RCT, double-blind, double-dummy design **Size**: 18,624 pts	**Inclusion criteria**: ACS with symptom onset within 24 h **Exclusion criteria**: Fibrinolytic therapy within 24 h, oral anticoagulant therapy, increased risk of bradycardia, concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer	**Intervention**: Ticagrelor (90 mg bid) (n=9,333) **Comparator**: Clopidogrel (75 mg qD) (n=9,291)	**1° endpoint**: Vascular death, MI or CVA • 9.8% with ticagrelor vs. 11.7% with clopidogrel (HR: 0.84; 95% CI: 0.77–0.92; p<0.001 **1° Safety endpoint**: Trial-defined major bleeding • 11.6% with ticagrelor vs. 11.2% with clopidogrel (p=0.43)	• All pts treated with ASA • Study included both NSTE-ACS and STEMI pts, with treatment either med Rx alone or med Rx plus revascularization • Ticagrelor associated with higher rate of non–CABG related bleeding (4.5% vs. 3.8%, p=0.03 • Stent thrombosis rate lower with ticagrelor (1.3% vs. 1.9%, HR: 0.67; 95% CI: 0.50–0.91; p=0.009)
TRITON-TIMI 38 Montalescot, et al., 2009 (25) 19249633	**Aim**: To asses prasugrel vs. clopidogrel in pts undergoing PCI for STEMI enrolled in TRITON-TIMI 38 **Study type**: Double-blind RCT **Size**: 3,534 pts	**Inclusion criteria**: Pts undergoing PCI for STEMI **Exclusion criteria**: Increased risk of bleeding, anemia, recent fibrinolytic administration, need from chronic oral anticoagulants, cardiogenic shock, or thienopyridine treatment within 5 d of randomization.	**Intervention**: Prasugrel (n=1,769) **Comparator**: Clopidogrel (n=1,765)	**1° endpoint**: CV death, nonfatal MI, nonfatal stroke at 15 mo. • 10.0% with prasugrel vs. 12.4% with clopidogrel (HR: 0.79; 95% CI: 0.65–0.97; p=0.0221) **Safety endpoint**: • No significant different in non–CABG related TIMI major bleeding at 30 d or 15 mo	• Secondary endpoint of CV death, nonfatal MI or TVR at 30 d 6.5% with prasugrel vs. 9.5% with clopidogrel (HR: 0.75; 95% CI: 0.59–0.96; p=0.0205)
TRITON Wiviott SD, et al., 2007 (26) 17982182	**Aim**: To compare prasugrel with clopidogrel in pts with ACS scheduled for PCI **Study type**: RCT, double-blind, double-dummy design **Size**: 13,608 pts	**Inclusion criteria**: ACS (NSTE-ACS or STEMI) pts undergoing planned PCI **Exclusion criteria**: Increased risk of bleeding, anemia, thrombocytopenia	**Intervention**: Prasugrel (10 mg qD) (n=6,813) **Comparator**: Clopidogrel (75 mg qD) (n=6,795)	**1° endpoint**: CV death, MI, CVA • 9.9% with prasugrel vs. 12.1% with clopidogrel (HR: 0.81; 95% CI: 0.73–0.90; p<0.001) **1° Safety endpoint**: Non–CABG related TIMI major bleeding • 2.4% with prasugrel vs. 1.8% with clopidogrel (HR: 1.32; CI: 1.03–1.68; p=0.03)	• Stent thrombosis rate lower with prasugrel (1.1% vs. 2.4%, p=0.001) • Life-threatening bleeding higher with prasugrel (1.4% vs. 0.9%, p=0.01) • Fatal bleeding higher with prasugrel (0.4% vs. 0.1%, p=0.002) • Increased rate of ICH in those treated with prasugrel with Hx of CVA or TIA • Increased risk of bleeding in those with Hx CVA or TIA, elderly (≥75 y) and body weight <60 kg

ACS indicates acute coronary syndrome; ASA, aspirin; bid, two times per day; CABG, coronary artery bypass graft; CI, confidence interval; CVA, cerebrovascular accident; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; Hx, history; MACE; major adverse cardiac events; MI, myocardial infarction; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST-

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elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; Rx, prescription; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; and TVR, target-vessel revascularization.

Data Supplement 6. Studies and Comparisons of Short-Term or Chronic Aspirin Dose in Patients With Coronary Artery Disease

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
TRANSLATE-ACS Xian Y, et al., 2015 (36) 25995313	**Aim**: Compare outcome of pts in TRANSLATE-ACS treated with high-dose (325 mg) or low-dose (81 mg) ASA **Study type**: Analysis of data in the TRANSLATE-ACS observational study **Size**: 10,213 pts	**Inclusion criteria**: Pts enrolled in TRANSLATE-ACS **Exclusion criteria**: Pts died in-hospital, were not discharged on ASA or were missing ASA dosing information, did not undergo stent implantation, or did not complete follow-up	**Intervention**: ASA dose (nonrandomized) **Comparator**: Higher or lower ASA dose	**1° endpoint**: MACE • MACE not statistically significantly different between treatment groups • 8.2% with high dose vs. 9.2% with low-dose (adjusted HR: 0.99; 95% CI: 0.85–1.17). **Safety endpoint**: bleeding (BARC) • BARC (1-5) bleeding higher with high-dose ASA (unadjusted 24.2% with high-dose vs. 22.7% with low-dose; adjusted HR: 1.19; 95% CI:1.06–1.33)	• High-dose ASA was 325 mg; low-dose ASA was 81 mg
CURRENT-OASIS 7 Mehta SR, et al., 2010 (37) 20817281	**Aim**: To assess the efficacy and safety of standard vs. double-dose clopidogrel and of high- vs. low-dose ASA in pts with ACS undergoing PCI **Study type**: Randomized factorial trial. Analysis of pts in CURRENT-OASIS 7 undergoing PCI **Size**: 17,260 pts	**Inclusion criteria**: Pts with ACS (STEMI or non–STEMI) undergoing PCI **Exclusion criteria**: Increased risk of bleeding or active bleeding	**Intervention 1**: High-dose ASA (300-325 mg) **Intervention 1**: Low-dose ASA (75-100 mg)	**1° endpoint**: CV death, MI, or stroke at 30 d • 4.1% with high-dose ASA vs. 4.2% with low-dose ASA (HR: 0.98; 95% CI: 0.84–1.13; p=0.76) **Safety endpoint**: Major bleeding • 1.5% with high-dose ASA vs. 1.3% with low-dose ASA (HR: 1.18; 95% CI: 0.92–1.53; p=0.20)	
PCI-CURE Jolly SS, et al., 2009 (38) 18819961	**Aim**: Evaluate the safety of different doses of ASA after PCI in PCI-CURE **Study type**: Post hoc	**Inclusion criteria**: NSTE-ACS pts in CURE who underwent PCI (PCI-CURE cohort)	**Intervention**: ASA dose (nonrandomized) **Comparator**: Higher or lower ASA dose	**1° endpoint**: N/A **Safety endpoint**: Major bleeding at 30 d and long term (mean 8 mo) • Major bleeding increased with high-dose ASA	• ASA doses were categorized as low-dose (≤100 mg), moderate dose (101–199 mg), and high-dose (≥200 mg • Net adverse clinical events

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	analysis of PCI-CURE **Size**: 2,658 pts	**Exclusion criteria**: N/A		• 1.9% with low-dose, 1.5% with moderate dose, and 3.9% with high-dose • For high vs. low-dose HR: 2.05 (95% CI: 1.20–3.50; p=0.009)	(death, MI, stroke, major bleeding) favored Low-dose over high-dose ASA (8.4% vs. 11.0%; HR: 1.31; 95% CI: 1.00–1.73; p=0.056).
CHARISMA Steinhubl, et al., 2009 (39) 19293071	**Aim**: Assess MACE based on ASA dose in CHARISMA **Study type**: Post hoc observational analyses **Size**: 15,595 pts	**Inclusion criteria**: Pts enrolled in CHARISMA **Exclusion criteria**: N/A	**Intervention**: ASA dose (nonrandomized) **Comparator**: Higher or lower ASA dose	**1° endpoint**: MACE MI, CVA or CV death) • The hazard the same regardless of dose • Adjusted HR: 0.95, 95% CI: 0.80–1.13, for 100 mg vs. <100 mg • Adjusted HR: 1.0; 95% CI: 0.85–1.18; for >100 mg vs. <100 mg. **Safety endpoint**: Severe or life-threatening bleeding • Hazard similar regardless of dose • Adjusted HR: 0.85; 95% CI: 0.57–1.26, for 100 mg vs. <100 mg • Adjusted HR: 1.05; 95% CI: 0.74–1.48, for > 100 mg vs. <100 mg.	• ASA doses were categorized as <100 mg (75 mg or 81 mg), 100 mg or>100 mg (150 mg or 162 mg) • In pts also receiving clopidogrel, daily ASA doses >100 mg seemed to be nonstatistically significantly associated with reduced efficacy (adjusted HR: 1.16; CI: 0.93–1.44]) and increased harm (adjusted HR: 1.30; CI: 0.83–2.04]).
Patrono C, et al., 2008 (40) 18574266	**Aim**: Comparison of OR in vascular events with different ASA doses **Study type**: Indirect comparison of ASA doses reducing vascular events in high-risk pts; data from prior studies and publications **Size**: 68 trials; >50,000 pts	**Inclusion criteria**: Studies of ASA in high-risk pts **Exclusion criteria**: N/A	**Intervention**: Different ASA dosing ranges	**1° endpoint**: Odds reduction in vascular events • 500–1,500 mg/d: OR: 19±3% • 160–325 mg/d: OR: 26±3% • 75–150 mg/d: OR: 32±6% • <75 mg/d: OR: 13±8%	• N/A
Serebruany, et al., 2005 (41) 15877994	**Aim**: To compare the risk of bleeding with low, moderate and high-doses of ASA **Study type**: Systematic overview of 31 trials	**Inclusion criteria**: Clinical trials with follow-up of ≥1 mo and contained a detailed description of hemorrhagic complications, pts characteristics, therapy	**Intervention**: ASA dose (nonrandomized) **Comparator**: Higher or lower ASA dose	**1° endpoint**: None specifically defined Major bleeding event rates (most commonly TIMI bleeding): • 1.56% with low-dose; 1.54% with moderate dose; 2.29% with high-dose; p=0.0001 for comparison of low-dose vs. high-dose	• Low-dose ASA defined as <100 mg; moderate-dose ASA 100–200 mg; high-dose ASA >200 mg

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	Size: 192,036 pts	duration and concomitant agents used. **Exclusion criteria**: Studies not meeting above criteria		Total bleeding event rates: • 3.72% with low-dose; 11.31% with moderate dose; 9.8% with high- dose; p=0.0001 for comparisons of low-dose with either moderate or high-dose	
CURE Peters, et al., 2003 (42) 14504182	**Aim**: To study the benefits and risks of adding clopidogrel to different doses of ASA in the treatment of pts with ACS **Study type**: Post hoc analysis of the CURE study **Size**: 12,562 pts	**Inclusion criteria**: Pts with NSTE-ACS enrolled in the CURE study	**Intervention**: ASA dose (nonrandomized) **Comparator**: Higher or lower ASA dose	**1° endpoint**: MACE • Impact of clopidogrel in preventing MACE was not significantly heterogeneous by ASA dose -high-dose group, 9.8% vs. 13.6%; RR: 0.71; 95% 95% CI: 0.59 -medium-dose group, 9.5% vs. 9.8%; RR: 0.97; 95% CI: 0.77–1.22 -low-dose group, 8.6% vs. 10.5%; RR: 0.81; 95% CI: 0.68–0.97 **Safety endpoint**: Major bleeding • The incidence of major bleeding complications increased significantly with increasing ASA dose both in the placebo (1.9%, 2.8%, 3.7%; p=0.0001) and the clopidogrel (3.0%, 3.4%, 4.9%; p=0.0009) groups	• Incidence of MACE not heterogeneous in pts receiving ASA alone when examined by dose (highest and medium ASA dose groups compared with the low-dose group: adjusted OR, 1.0 (95% CI: 0.82–1.23) and 1.2 (95% CI: 1.08–1.51), respectively
Antithrombotic Trialists' Collaboration, 2002 (43) 11786451	**Aim**: To determine the effects of antiplatelet therapy among pts at high-risk of occlusive vascular events. **Study type**: Collaborative meta-analyses **Size**: 135,000 pts for comparisons of antiplatelet therapy vs. control and 77,000 pts for comparisons of different antiplatelet regimens	**Inclusion criteria**: Randomized trials of an antiplatelet regimen vs. control or one regimen vs. another regimen	**Intervention**: ASA **Comparator**: Control or placebo	**1° endpoint**: Series vascular event (nonfatal MI, nonfatal stroke, vascular death) • The proportional reduction in vascular events was 19% (3%) with 500–1500 mg daily, 26% (3%) with 160–325 mg daily, and 32% (6%) with 75–150 mg daily; parentheses denote standard error.	• N/A

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Lorenz RL, et al., 1984 (44) 6144975	**Aim:** To study the effect of ASA in the prevention of aortocoronary bypass occlusion **Study type:** Prospective, double blind RCT **Size:** 60 pts	**Inclusion criteria:** Pts undergoing aortocoronary bypass **Exclusion criteria:** Peptic ulcer, anticoagulant therapy, acute MI	**Intervention:** 100 mg of ASA once daily (n=29) **Comparator:** Placebo (n=31)	**1° endpoint:** Grafts occluded at 4 mo angiographic follow-up • 4/40 (10%) with ASA vs. 17/53 (32%) with placebo (2p=0.012) **Safety endpoint:** N/A	• 100 mg/d dose of ASA found to effectively block platelet thromboxane formation and thromboxane-supported aggregation on collagen

ACS indicates acute coronary syndrome; ASA, aspirin; CI, confidence interval; CVA, cerebrovascular accident; CV, cardiovascular; HR, hazard ratio; MACE; major adverse cardiac events; MI, myocardial infarction; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; OR, odds ratio; RCT, randomized controlled trials; and RR, relative risk.

Data Supplement 7. RCTs Comparing Antiplatelet Therapy With Anticoagulant Therapy in Patients Undergoing Coronary Stenting

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
STARS Leon MB, et al., 1998 (45) 9834303	**Aim:** To compared the efficacy and safety of three antithrombotic-drug regimens — ASA alone, ASA and warfarin, and ASA and ticlopidine — after coronary stenting (BMS) **Study type:** RCT **Size:** 1,653 pts	**Inclusion criteria:** Pts undergoing successful coronary stent implantation **Exclusion criteria:** Left main or bifurcation stenting, AMI, bleeding diathesis	**Intervention 1:** ASA alone **Intervention 2:** ASA + warfarin **Intervention 3:** ASA + ticagrelor	**1° endpoint:** Death, TLR, Angiographically-evident thrombosis, or MI within 30 d • 3.6% with ASA alone; 2.7% with ASA + warfarin; 0.5% with ASA + ticagrelor (p=0.001 for the comparison of all 3 groups). **Safety endpoint:** bleeding complications • 1.8% with ASA alone; 6.2% with ASA + warfarin; 5.5% with ASA + ticlopidine (p<0.001 for the comparison of all 3 groups)	• Compared to ASA alone, ASA + ticlopidine reduced incidence of primary endpoint (RR: 0.15; CI: 0.05–0.43; p<0.001
Schomig A, et al., 1996 (46) 8598866	**Aim:** To compare antiplatelet therapy with conventional anticoagulant therapy with respect to clinical outcomes 30 d after coronary-artery stenting (BMS)	**Inclusion criteria:** Pts undergoing coronary stent implantation (BMS) **Exclusion criteria:** Stent placed as a bridge to CABG, cardiogenic shock, need for	**Intervention:** ASA + ticlopidine (antiplatelet therapy) **Comparator:** anticoagulant therapy (intravenous heparin,	**1° endpoint:** Primary cardiac endpoint a composite of CV death, MI, CABG or repeated angioplasty. • 1.6% with antiplatelet therapy vs. 6.2% with anticoagulation therapy (RR: 0.25; 95% CI: 0.06–0.77)	• N/A

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	Study type: RCT **Size**: 517 pts	mechanical ventilation	phenprocoumon, and ASA)	**Safety endpoint**: Bleeding events • 0% with antiplatelet therapy vs. 6.5% with anticoagulant therapy RR: 0.00; p<0.001)	

ASA indicates aspirin; BMS, bare metal stent; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; and TLR, target-lesion revascularization.

Data Supplement 8. Nonrandomized Studies of DAPT Duration After BMS or DES

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Brar SS, et al., 2008 (47) 18534267	**Aim**: To asses long term clinical outcomes with BMS or DES by duration of clopidogrel use in pts with DM **Study type**: Retrospective, observational **Size**: 749 pts	**Inclusion criteria**: Pts with DM who underwent stent implantation with either BMS or DES **Exclusion criteria**: Pts with CABG, pts who received both a BMS and DES, pts with valvular disease, nonhealth plan members	**Intervention**: Clopidogrel >6 mo **Comparator**: No clopidogrel >6 mo	**1° endpoint**: All-cause death and nonfatal MI • 3.2% with >9 mo clopidogrel; 9.4% with 6–9 mo clopidogrel; and 16.5% with <6 mo clopidogrel (p<0.001)	• For pts treated with DES adjusted HR: 0.48; 95% CI: 0.16–1.47; p=0.48) for >6 mo clopidogrel vs. no clopidogrel >6 mo
Eisenstein, et al., 2007 (48) 17148711	**Aim**: Assess the association between clopidogrel use and long-term clinical outcomes of pts receiving DES and BMS **Study type**: Observational study **Size**: 4,666 pts; 3,165 BMS and 1,501 DES	**Inclusion criteria**: Consecutive pts treated at 1 institution undergoing BMS or DES	**Comparators**: Duration of self-reported clopidogrel use	**1° endpoints in DES-treated pts at 24 mo follow-up**: • Death: 2.% with clopidogrel vs. 5.3% without clopidogrel (difference -3.3%; CI: -6.3% –-0.3%; p=0.03) • Death or MI: 3.1% with clopidogrel vs. 7.2% without clopidogrel (difference -4.1%; 95% CI: -7.6% – -0.6%; p=0.02)	• Results based on landmark analysis of those event-free at 6 or 12 mo follow-up (6 mo results included in this table)

ASA indicates aspirin; BMS, bare metal stent; CABG, coronary artery bypass graft; CI confidence interval; DES, drug-eluting stent; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.

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Data Supplement 9. Randomized Studies of 1 Versus 12 Months of DAPT After BMS

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Steinhubl SR, et al., 2002 (49) 12435254	**Aim:** To evaluate the benefit of long-term (12 mo) treatment with clopidogrel (in addition to ASA) after PCI in pts treated with BMS **Study type:** RCT **Size:** 2,116 pts	**Inclusion criteria:** Pts referred for planned PCI **Exclusion criteria:** Contraindications to antiplatelet or antithrombotic therapy, recent STEMI, recent use of GPI, clopidogrel, or thrombolytic therapy	**Intervention:** ASA + clopidogrel **Comparator:** ASA + placebo	**1° endpoint:** 1 y incidence of MACE (death, MI or stroke) • RRR: 26.9% (CI: 3.9%–44.4%; p=0.02) **Safety endpoint:** Major bleeding • 8.8% with DAPT vs. 6.7% with ASA (p=0.07)	• All study pts treated with DAPT for the first 28 d • Absolute risk reduction 3% with DAPT

ASA indicates aspirin; BMS, bare metal stent; CI, indicates confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; N/A, not available; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; and STEMI, ST-elevation myocardial infarction.

Data Supplement 10. Studies and Meta-Analyses Comparing Graft Patency Post–CABG in Patients Treated With Either Antiplatelet Monotherapy or DAPT

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Randomized Trials					
Mannacio VA, et al., 2012 (50) 22942294	**Aim:** To determine the individual variability in the response to ASA and/or clopidogrel and its impact on graft patency after off-pump CABG **Study type:** Single center RCT	**Inclusion criteria:** Consecutive pts undergoing off-pump CABG **Exclusion criteria:** Additional surgical procedures, emergency operations, active bleeding or bleeding diathesis	**Intervention:** ASA + clopidogrel **Comparator:** ASA	**1° endpoint:** Platelet resistance and inhibition • In the ASA group 32.6% were ASA resistant and, in the ASA-clopidogrel group, 12.6% were ASA and clopidogrel resistant. **Safety endpoint:** Major bleeding • 1.3% with DAPT vs. 1.3% with ASA	• Secondary endpoint of SVG graft occlusion at 12 mo as assessed by CTA: 7.4% with DAPT vs. 13.1% with ASA (p=0.04)

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	Size: 300 pts			(p=1.00)	
Sun JCJ, et al., 2010 (51) 21146675	**Aim**: Assess graft patency 1 mo after CABG in pts treated with ASA alone or ASA+clopidogrel **Study type**: RCT, pilot study **Size**: 100 pts (79 of whom underwent follow-up CTA)	**Inclusion criteria**: Pts undergoing on-pump CABG treated with ≥1 free bypass graft **Exclusion criteria**: Indication for anticoagulation, Hx of GI or intracranial bleeding	**Intervention**: ASA+clopidogrel **Comparator**: ASA+ placebo	**1° endpoint**: Proportion of pts with ≥ occluded grafts at 1 mo as assessed by CTA • 17.5% with ASA+clopidogrel vs. 23.1% with ASA+placebo (RR: 0.95; 95% CI: 0.80–1.14; p=0.54) **Safety endpoint**: Major bleeding complication • 6.1% with ASA+clopidogrel vs. 6.0% with ASA+placebo (p=1.00)	N/A
CASCADE Kulik A, et al., 2010 (52) 21135365	**Aim**: Assess if addition of clopidogrel to ASA after CABG inhibits SVG disease at 1 y as assessed by IVUS **Study type**: RCT **Size**: 113 pts (92 underwent follow-up IVUS)	**Inclusion criteria**: Pts undergoing 1st time CABG treated with at least 2 SVG with or without the use of cardiopulmonary bypass **Exclusion criteria**: Concomitant valve surgery, need for oral anticoagulation	**Intervention**: Clopidogrel (in addition to ASA) **Comparator**: Placebo (in addition to ASA)	**1° endpoint**: Mean SVG intimal area per pts at 1 y follow-up • 4.1 mm² with clopidogrel vs. 4.5 mm² with placebo (p=0.90) **Safety endpoint**: Major bleeding • 1.8% with clopidogrel vs. 0% with placebo (p=0.50)	• Overall 1 y graft patency 95.2% with clopidogrel vs. 95.5% with placebo (p=0.90) • 1 y SVG patency 94.3% with clopidogrel vs. 95.5% with placebo (p=0.90)
Gao G, et al., 2010 (53) 21050973	**Aim**: Assess 3 mo graft patency after CABG in those treated with or without clopidogrel (in addition to baseline ASA) **Study type**: Single center, RCT **Size**: 249 pts (244 underwent CTA)	**Inclusion criteria**: Pts referred for isolated CABG, with or without cardiopulmonary bypass **Exclusion criteria**: Thrombocytopenia, previous CABG, concomitant valve surgery or aneurysm resection	**Intervention**: Clopidogrel (n=113) **Comparator**: No clopiodogrel (n=111)	**1° endpoint**: SVG graft patency at 3 mo (assessed by CTA) • 91.6% with clopidogrel vs. 85.7% without clopidogrel (RR: 1.7; 95% CI: 1.0–2.9; p=0.043)	• In the multivariate analysis, combined antiplatelet therapy independently • Increased venous graft patency (RR: 1.996; CI: 1.015–3.922; p=0.045).
Gao C, et al 2009 (54) 19559191	**Aim**: Assess 1 and 12 mo SVG patency after CABG with either clopidogrel alone or clopidogrel+ASA	**Inclusion criteria**: Elective CABG **Exclusion criteria**: Thrombocytopenia,	**Intervention**: Clopidogrel + ASA (n=95) **Comparator**:	**1° endpoint**: SVG patency rates (as assessed by CTA) • 1 mo: 98.2% with clopdigrel+ASA vs. 98.1% with clopidogrel alone (p=0.73)	• All pts underwent CABG performed by one surgeon • Treatment assignment was alternated every wk in consecutively treated pts

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	Study type: RCT **Size**: 197 pts	concomitant valve surgery or aneurysm resection	Clopidogrel alone (n=102)	• 12 mo: 96.3% with clopiodgrel+ASA vs. 93.5% with clopidogrel alone (p=0.25)	• Report states no obvious bleeding events in any pts
Nonrandomized Studies					
ROOBY Ebrahimi R, et al., 2014 (55) 24206971	**Aim**: Evaluate the role of clopidogrel use post CABG to improve graft patency when added to ASA therapy. **Study type**: Post hoc substudy analysis of the ROOBY trial **Size**: 2,203 pts enrolled in trial; 953 pts included in analysis	**Inclusion criteria**: Pts who were enrolled in the ROOBY trial with complete data on clopidogrel use and with 1 y angiographic data **Exclusion criteria (for substudy):** No data on clopidogrel use, no 1 y angiographic follow-up	**Intervention**: Clopidogrel use at discharge (nonrandomized) (n=345) **Comparator**: No clopidogrel use at discharge (n=608)	**1° endpoint**: 1 y graft patency rates at angiography • 86.5% with clopiogrel vs. 85.3% without clopidogrel (p=0.43)	• No significant difference in graft patency found in those who underwent on-pump CABG nor in those who underwent off-pump CABG
Ibrahim K, et al., 2006 (56) 17060036	**Aim**: To evaluate the effect of clopidogrel on midterm graft patency following off-pump coronary revascularization surgery **Study type**: Single center study in which the first 36 pts were treated with ASA alone then the next 58 pts were treated with ASA + clopidogrel **Size**: 94 consecutively treated pts; 62 pts underwent angiographic follow-up	**Inclusion criteria**: Pts undergoing off-pump CABG	**Intervention**: ASA + clopidogrel **Comparator**: Antiplatelet monotherapy	**1° endpoint**: Overall graft patency at 6 mo angiographic follow-up • 42/45 (93%) with ASA + clopidogrel vs. 31/37 (84%) with ASA alone (p=NS)	• LIMA patency: 28/29 (96%) with DAPT vs. 23/35 (92%) with ASA (p=NS) • SVG patency: 14/16 (87%) with DAPT vs. 7/11 (66%) with ASA (p=NS)
Meta-Analyses and Systematic Overviews					
Deo SV, et al., 2013 (57) 23488578	**Aim**: Assess effects of clopidogrel (in addition to ASA) after CABG **Study type**: Meta-analysis	**Inclusion criteria**: Studies of isolated CABG, on-pump or off-pump	**Intervention**: Clopidogrel (in addition to ASA) **Comparator**: ASA	**1° endpoint**: SVG patency as assessed by coronary angiography or CT angiography in the 5 RCT • Early SVG occlusion rates reduced with DAPT (RR: 0.59; 95% CI: 0.43–	• Trend towards a higher incidence of major bleeding episodes with DAPT (RR: 1.17; CI: 1.00–1.37; p=0.05)

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	Size: 5 RCT and 6 observations studies; 25,728 pts		alone	0.82; p=0.02).	
Nocerino AG, et al., 2013 (58) 24035160	**Aim**: Assess whether DAPT is superior to antiplatelet monotherapy to improve graft patency early after CABG **Study type**: Meta-analysis of 5 RCT **Size**: 958 pts; 2,919 grafts	**Inclusion criteria**: RCT of single vs. dual antiplatelet therapy for ≥30 d **Exclusion criteria**: Nonrandomized studies	**Intervention**: DAPT **Comparator**: Antiplatelet monotherapy	**1° endpoint**: Overall graft patency • Early graft occlusion 5.0% with DAPT vs. 7.7% with monotherapy (p=0.005) • OR=1.59 for graft occlusion with monotherapy (95% CI: 1.16–2.1)	• Follow-up in studies ranged from 3 d to 12 mo • For SVG only, monotherapy, when compared to DAPT, associated with increased graft loss rate (10.8% vs. 6.6%; OR: 1.70; p=0.03) • No significant reduction in arterial graft occlusion with DAPT found
de Leon N, et al., 2012 (59) 22570427	**Aim**: Evaluate the evidence for DAPT post–CABG **Study type**: Systematic overview **Size**: 4 RCT evaluating surrogate endpoints and 9 studies evaluating clinical endpoints	**Inclusion criteria**: Peer-reviewed studies that evaluated DAPT after CABG	**Intervention**: DAPT after CABG **Comparator**: Antiplatelet monotherapy	**Primary relevant finding:** • 3 clinical trials assessing surrogate end points failed to demonstrate an improvement in graft patency with DAPT use, while 1 clinical trial found an increase in graft patency.	• N/A

ASA indicates aspirin; CABG, coronary artery bypass graft; CI, confidence interval; CTA, computed tomography angiography; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HR, hazard ratio; Hx, history; N/A, not available; LIMA, left internal mammary artery; OR, odds ratio; RCT, randomized controlled trials; RR, relative risk; and SVG, saphenous vein graft.

Data Supplement 11. Studies Comparing Outcome Post–CABG in Patients Treated With Either Aspirin or DAPT

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Sorenson, et al., 2001 (60) 21371637	**Aim**: To study efficacy of post–op clopidogrel treatment in pts with MI undergoing CABG	**Inclusion criteria**: Pts surviving ≥ 30 d after CABG, pts observed 18 mo. after CABG	**Intervention**: Clopidogrel (n=957) **Comparator**: No clopidogrel (n=2,588)	**1° endpoint**: Death or recurrent MI •4.1% with clopidogrel vs. 7.8% without clopidogrel (HR: 0.59; 95% CI: 0.42–0.85; p=0.0003) •By propensity score (total n=945)	• N/A

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	Study type: Registry study **Size:** 3,545 pts	**Exclusion criteria:** Those not meeting above inclusion criteria		4.0% with clopidogrel vs. 6.0% without clopidogrel (HR: 0.67; 95% CI: 0.44–1.00; p=0.05)	
Kim DH, et al., 2009 (61) 19931667	**Aim:** To determine benefit and risk of ASA + clopidogrel use (vs. ASA alone) postoperatively following on-pump or off-pump CABG. **Study type:** Observational **Size:** 15,067 pts	**Inclusion criteria:** Pts undergoing CABG treated in the early post–operative period with ASA or clopidogrel + ASA **Exclusion criteria:** Pre-op and late post–op clopidogrel use, prolonged hospitalization >1wk before surgery, valvular procedure, warfarin use	**Intervention:** ASA + clopidogrel (n=3,268) **Comparator:** ASA (n=11,799)	**1° endpoint:** In-hospital mortality • 0.95% with DAPT vs. 1.78% with ASA (adjusted OR: 0.50; 95% CI: 0.25–0.99) **Safety endpoint:** in-hospital bleeding events • 4.19% with DAPT vs. 5.17% with ASA (adjusted OR: 0.70; 95% CI: 0.51–0.97)	• Adjusted HR: 0.83 (CI: 0.61–1.12) for in-hospital mortality or 30 d readmission with DAPT compared to ASA
CURE Fox KA, et al., 2004 (32) 15313956	**Aim:** To assess benefits and risks of ASA plus clopidogrel in pts undergoing CABG for NSTE-ACS **Study type:** Post hoc subgroup analysis of CURE; RCT **Size:** 12,562 pts entire study population; 1,061 pts underwent CABG	**Inclusion criteria:** NSTE-ACS within <24 h **Exclusion criteria:** NYHA class IV HF, PCI or CABG <3 mo, contraindication to antiplatelets and antithrombotics, hemorrhagic or IC stroke, severe thrombocytopenia	**Intervention:** Clopidogrel + ASA **Comparator:** Placebo + ASA	**1° endpoint: MACE** (CV death, MI or stroke) • 14.5% with DAPT % vs. 16.2% with ASA (RR: 0.89; 95% CI: 0.71–1.11)	• Benefits of DAPT with CABG were deemed "consistent" (test for interaction among strata 0.53) with the benefits in pts undergoing PCI (9.6% with DAPT vs. 13.2% with ASA; RR: 0.72; CI: 0.47–0.90) and in those treated with medical therapy alone (8.1% with DAPT vs. 10.0% with ASA; RR: 0.80; CI: 0.69–0.92)

ASA indicates aspirin; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; N/A, not available; NSTE-ACS, non–ST-elevation acute coronary syndrome; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention and RR, relative risk.

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Data Supplement 12. Studies of Timing of Noncardiac Surgery After PCI

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Kaluza, et al., 2000 (62) 10758971	**Aim**: To assess the clinical course of pts who have undergone coronary stent placement >6 wk before noncardiac surgery. **Study type**: Retrospective cohort **Size**: 40 pts	**Inclusion criteria**: Consecutive pts who underwent coronary stent placement >6 wk before noncardiac surgery requiring a general anesthesia were included in the study **Exclusion criteria**: N/A	**Intervention**: N/A **Comparator**: N/A	**1° endpoint**: • MI: 7 pts Major Bleeds: 11pts Deaths: 8 • All deaths/MI and 8/11 bleeds occurred if surgery <14 d from stent placement	• DAPT not well described • Single center
Wilson, et al., 2003 (63) 12875757	**Aim**: To determine the frequency and timing of complications at our institution when surgery was performed within 2 mo of coronary stent placement. **Study type**: Retrospective cohort **Size**: 207 pts	**Inclusion criteria**: Analysis of the PCI database and the General Surgery database at Mayo Clinic for pts who underwent noncardiac surgery within 60 d of coronary stent placement. Surgical procedures included in this analysis were those that required a significant incision and had the potential for perioperative bleeding. **Exclusion criteria**: Procedures such as joint aspirations, endoscopy, and skin biopsies, among others, were not included in this analysis	**Intervention**: N/A **Comparator**: N/A	**1° endpoint**: • MACE: 8/207 **1° Safety endpoint:** • Excessive bleeding: 2/207	• Single center

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Nuttal, et al., 2008 (64) 18813036	**Aim:** To address the hypothesis that the risk of MACEs and bleeding events is related to the time interval between PCI with BMS and NCS **Study type:** Retrospective **Size:** 889 pts	**Inclusion criteria:** Analysis of pts who underwent NCS within 1 y after PCI with BMS at Mayo Clinic (Rochester, Minnesota) between January 1, 1990, and January 1, 2005. Pts were identified using the Mayo Clinic PCI registry and the Mayo Clinic Surgical database. **Exclusion criteria:** Pts on long-term warfarin therapy	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** • MACE- 47 (5.2%; 95% CI: 3.8–6.7%) • Frequency of MACEs was 10.5% (95% CI: 6.7–14.3%) when NCS was performed 30 or fewer d after PCI with BMS, 3.8% (95% CI: 1.5–6.2%) when NCS was 31–90 d after PCI with BMS, and 2.8% (95% CI: 1.2–4.5%) when NCS was 91 or more d after PCI with BMS	• DAPT not well described • Single center
Wijeysundera, et al., 2012 (65) 22893606	**Aim:** To evaluate the outcomes of pts who underwent elective intermediate- to high-risk noncardiac surgery in Ontario, Canada after stent implantation. **Study type:** A population-based cohort study **Size:** 8,116 pts	**Inclusion criteria:** All Ontario residents who were ≥40 y, underwent any 1 of 16 prespecified elective noncardiac surgeries between April 1, 2003 and March 31, 2009, and underwent coronary stent implantation within 10 y before their index surgery. The included surgeries were abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular bypass, total hip replacement, total knee replacement, large bowel resection, partial liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, total abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy. **Exclusion criteria:** • Individuals who underwent CABG surgery between the preoperative PCI and subsequent index noncardiac surgery were excluded. • Low-risk ambulatory surgeries	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** • Overall risk of 30 d MACE was relatively low at 2.1% (n=170), whereas the risk of 1 y MACE was 9.8% (n=798). • The rate of postoperative mortality was 1.2% (n=100) at 30 d and 5.2% (n=419) at 1 y. • BMS: 1-45 d OR: 2.35 (95% CI: 0.98–5.64); 46–180 d OR: 1.06 (95% CI: 0.58–1.92); 181–365 d OR 1.89 (1.08–3.32) • DES: 1-45 d OR: 11.58 (95% CI: 4.08-32.80); 46-180 d OR: 1.71 (95% CI: 0.73–4.01); 181-365 d OR: 0.64 (95% CI: 0.20–2.04)	• Administrative database

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EVENT Registry Berger, et al., 2010 (66) 20850090	**Aim**: To determine the frequency of noncardiac surgery and adverse postoperative events among pts who recently received a DES following noncardiac surgery **Study type**: Registry **Size**: 206 pts	**Inclusion criteria**: The EVENT registry, consecutive pts who underwent attempted stent placement at 42 hospitals between July 2004 and September 2005 were enrolled and followed for 1 y. Major noncardiac surgical procedures in which a significant surgical incision was required from which bleeding would result were included in this analysis. **Exclusion criteria**: Pts who underwent CABG or valve surgery (n=67), pacemaker and defibrillator placement (n=46), and pts who underwent surgery whose nature could not be determined (n=50) were prospectively excluded from this analysis. Pts who underwent minor surgical procedures (n=27), such as minor dermatological procedures, endoscopic procedures, joint aspirations, and cataract surgery	**Intervention**: Pts who underwent major surgery **Comparator**: Pts who did not undergo major surgery	**1° endpoint**: • In the 7 d after surgery, 4 pts had a cardiac death, myocardial infarction, or stent thrombosis (1.9%; 95% CI=0.5%–4.9%). • The risk of the composite outcome was increased 27-fold in the wk following noncardiac surgery compared with any other wk after stent implantation (HR: 27.3; 95% CI: 10.0–74.2; p <0.001).	• DAPT status and bleeding endpoint not well described
PARIS Mehran, et al., 2013 (67) 24004642	**Aim**: To determine the association between different modes of DAPT cessation and cardiovascular risk after PCI in the PARIS Registry **Study type**: Retrospective analysis of a prospective registry **Size**: 5,031 pts undergoing PCI	**Inclusion criteria**: Adult pts (≥18 y) undergoing successful stent implantation in ≥1native coronary artery and discharged on DAPT were eligible for enrolment. **Exclusion criteria**: Pts participating in an investigational device or drug study or with evidence of stent thrombosis at the index procedure were excluded.	**DAPT Cessation 1:** physician recommended discontinuation **DAPT Cessation 2:** brief interruption (for surgery) **DAPT Cessation 3:** disruption (noncompliance or because of bleeding	**1° Findings**: • Overall incidence DAPT cessation 57.3% (discontinuation 40.8%; interruption 10.5%; disruption 14.4% • Compared with those on DAPT, the adjusted HR for MACE due to discontinuation was 0.63 (95% CI: 0.46–0.86); for interruption was 1·41 (95% CI: 0.94–2.12; p=0·10) and for disruption was 1·50 (95% CI: 1.14–1.97; p=0.004). • Within 7 d, 8–30 d, and more than 30 d after disruption, adjusted HRs were 7·04 (95% CI: 3.31–14.95), 2.17 (95% CI: 0.97–4.88), and 1.3 (95% CI: 0.97–1.76), respectively.	• N/A

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Holcomb, et al., 2015 (68) 26720292	**Aim:** To better understand the factors contributing to cardiac risk in pts who have undergone recent PCI and require noncardiac surgery, we comparatively examined the postoperative MACE associated with 3 distinct subgroups of stent indication: (1) MI; (2) unstable angina; and (3) non–ACS revascularization. **Study type:** Retrospective cohort **Size:** 26,661 pts	**Inclusion criteria:** All pts with coronary stents implanted in the VA between January 1, 2000, and December 31, 2010 **Exclusion criteria:** Minor operations such as endoscopic procedures and minor musculoskeletal procedures such as application of a cast and joint aspiration. Operations performed under local or monitored anesthesia were excluded from analyses.	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** • Postoperative MACE rates were significantly higher in the MI group (7.5%) compared with the unstable angina (2.7%) and non–ACS (2.6%) groups (p<0.001). • When surgery was performed within 3 mo of PCI, adjusted odds of MACE were significantly higher in the MI group compared with the non–ACS group (OR: 5.25; 95% CI: 4.08–6.75). This risk decreased overtime, although it remained significantly higher at 12–24 mo from PCI (OR: 1.95; 95% CI: 1.58–2.40). •The adjusted odds of MACE for the unstable angina group were similar to those for the non–ACS group when surgery was performed within 3 mo (OR: 1.11; CI: 0.80–1.53) or between 12 and 24 mo (OR: 1.08; CI: 0.86–1.37) from stent placement.	• Primarily older white males • Unknown medication regimen • Stent type was not significantly associated with MACE regardless of indication.

ACS indicates acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; N/A, not available; NCS, noncardiac surgery; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trials; RR, relative risk; and VA, US Veterans Affairs Hospital.

ARCTIC indicates Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation 1 Year AfterS; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DES-LATE, Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events; EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC, Is There A Life for DES After Discontinuation of Clopidogrel; MACCE, major adverse cardiac and cerebrovascular events (death, MI, or stroke); MI, myocardial infarction; OPTIDUAL, Optimal Dual Antiplatelet Therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; NACCE, net adverse cardiac and cerebrovascular events (death, MI, stroke or major bleeding); PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; REAL-LATE, REAL-world patients treated with drug-eluting stent implantation and Late coronary Arterial Thrombotic Events; RESET, Real Safety and Efficacy of 3-month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; revasc, revascularization; SECURITY, Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; TVF, target-vessel failure; TVR, target-vessel revascularization; and ZEST-LATE, Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions-Late coronary Arterial Thrombotic Events.

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