JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 23, 2018

PUBLISHED BY ELSEVIER

JACC GUIDELINE COMPARISON

ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy

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ABSTRACT

Dual antiplatelet therapy (DAPT) is the cornerstone of pharmacological treatment aimed at preventing the atherothrombotic complications in patients with a variety of coronary artery disease (CAD) manifestations. Prescribers of DAPT are confronted with a number of challenges that include selecting the appropriate $P2Y_{12}$ inhibitor and determining the optimal duration of DAPT with the scope of minimizing the risk of ischemic and bleeding complications in light of each patient's clinical characteristic and circumstance. Recently, a guideline writing committee from the American College of Cardiology/American Heart Association (ACC/AHA) and a task force from the European Society of Cardiology (ESC) released their respective focused update recommendations on "Duration of DAPT in Patients with CAD" (ACC/AHA) and "DAPT in CAD" (ESC). This paper aims to review the ACC/AHA and ESC updates for DAPT to delineate common domains, consistent messages, and differences in recommended management strategies across the Atlantic.
(J Am Coll Cardiol 2018;72:2915–31) © 2018 by the American College of Cardiology Foundation.

Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and a platelet $P2Y_{12}$ inhibitor, is the cornerstone of pharmacological treatment aimed at preventing atherothrombotic complications in patients with a variety of coronary artery disease (CAD) manifestations (1). A patient with CAD may require DAPT in the context of myocardial revascularization (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG], after an acute coronary syndrome [ACS]) (e.g., non-ST-segment elevation acute coronary syndrome [NSTE-ACS] or ST-segment elevation myocardial infarction [STEMI]), or for secondary prevention in high-risk clinical presentations (e.g., stable CAD in a patient with a history of myocardial infarction [MI]) (2–4). In each of these intersecting scenarios, decision-making of DAPT prescribers is confronted with a number of challenges that essentially include, but are not limited to, selecting the $P2Y_{12}$ inhibitor and determining the optimal duration

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Manuscript received May 9, 2018; revised manuscript received September 5, 2018, accepted September 8, 2018.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.09.057

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

CAD = coronary artery disease

COR = Class of Recommendation

DAPT = dual antiplatelet therapy

ESC = European Society of Cardiology

LOE = Level of Evidence

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

of DAPT with the scope of minimizing the risk of ischemic and bleeding complications in light of each patient's clinical characteristic and circumstance (5).

Clinical practice guidelines are written under the auspices of national or international societies, such as the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC), to provide physicians with practical recommendations for the best management strategies of patients with given conditions. In both the United States and Europe, DAPT has for years been a subchapter or a brief mention in the guidelines for the management of patients presenting with NSTE-ACS, STEMI, or stable CAD, and those undergoing myocardial revascularization or noncardiac surgery. More recently, a guideline writing committee from the ACC/AHA and a task force from the ESC released their respective focused update recommendations on "Duration of DAPT in Patients with CAD" (ACC/AHA), published in 2016, and "DAPT in CAD" (ESC, in collaboration with the European Association for Cardio-Thoracic Surgery), published in 2017 (6,7).

The need for dedicated DAPT updates is well justified by the large amount of data and new information generated in the field over the past few years. As expected, the ACC/AHA and ESC updates contain large areas of overlap as well as some differences. Differences were largely explained by the different times of publication of the 2 documents rather than a different interpretation of the evidence available at that time. Indeed, the 2017 ESC update was published 1.5 years after the 2016 ACC/AHA update, thus allowing for more chance to incorporate the newest data, and also to put into perspective data that were new when the 2016 ACC/AHA document was published. With respect to antiplatelet therapy, the ESC/European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization, released in 2018, essentially reflect the recommendations provided in the 2017 ESC update on DAPT with few notable exceptions mentioned in the following text (8).

From a methodological standpoint, the 2016 ACC/AHA update was built around 3 critical questions related to the duration of DAPT, which served as the basis for a formal systematic review and evaluation of the available data (6). The writing group consisted of the chairs, vice-chairs, and members of previous guidelines tackling the topic of DAPT. Conversely, the 2017 ESC update was built in keeping with recommendations for formulating and issuing ESC guidelines by a selection of experts in the field, based on a comprehensive review of the published evidence (7). This paper aims to review and compare the ACC/AHA and ESC updates for DAPT to delineate common domains, consistent messages, and differences in recommended management strategies across the Atlantic. Meanings and suggested phrasings of Class of Recommendation (COR) and Level of Evidence (LOE) for each update are summarized in **Tables 1 and 2**. While the interpretation of the COR I and III is straightforward, the COR IIa and IIb imply conflicting evidence or divergence of opinion regarding the relative benefit and risk of a given treatment or procedure. In general, when the COR is IIa, the weight of the evidence or opinion is in favor of the treatment or procedure, whereas a COR IIb implies that there is not enough data to make a more definitive recommendation, the data may be somewhat contradictory, or the benefit may be extremely modest. Notably, despite some subtle differences that exist in criteria for and phrasing of COR and LOE in the ACC/AHA and ESC updates, the general meaning is essentially consistent. Common themes in both the ACC/AHA and ESC focused updates include risk stratification, the type and initial timing of $P2Y_{12}$ inhibitor administration, the duration of DAPT in different patient scenarios, the use of proton pump inhibitors, and the management of antiplatelet therapy in patients on oral anticoagulation (6,7). Some areas of controversy (e.g., drug-to-drug interactions, platelet function and genetic testing, bridging of antiplatelet agents in the perioperative period, and dual-pathway inhibition therapy with both antiplatelet and anticoagulant agents) are either not addressed or only briefly discussed due to lack of conclusive data supporting specific recommendations.

GENERAL CONCEPTS

RISK STRATIFICATION FOR ISCHEMIC AND BLEEDING EVENTS. Risk characterization for ischemic or bleeding complications is an overriding concept in both the ACC/AHA and ESC updates, although it is recognized that many patients are at high risk for both types of event (6,7). In both documents, the DAPT score, derived from the DAPT trial (9), is discussed as a way to assess the risk/benefit of prolonging DAPT beyond 12 months from PCI, based on the contribution of a number of risk factors (10). The prediction rule assigns positive integer values to diabetes mellitus, current cigarette use, prior PCI or prior MI, congestive heart failure or left ventricular

TABLE 1 Comparative Meaning and Suggested Phrasing of Classes of Recommendation in the ACC/AHA and ESC Guidelines

		ACC/AHA	ESC
COR I	Meaning	Benefit >>> risk	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
	Suggested phrasing	• Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • A is recommended/indicated in preference to B • A should be chosen over B	• Is recommended • Is indicated
COR IIa	Meaning	Benefit >> risk ("routine practice")	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure: weight of evidence/opinion is in favor of usefulness/efficacy
	Suggested phrasing	• Is reasonable • Can be useful, effective, beneficial • A is probably recommended/indicated in preference to B • It is reasonable to choose A over B	• Should be considered
COR IIb	Meaning	Benefit ≥ risk ("case by case decision")	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure: usefulness/efficacy is less well established by evidence/opinion
	Suggested phrasing	• May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well established	• May be considered
COR III	Meaning	No benefit (benefit = risk) Harm (risk > benefit)	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful
	Suggested phrasing	Moderate • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other Strong • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	• Is not recommended

ACC = American College of Cardiology; AHA = American Heart Association; COR = Class of Recommendation; ESC = European Society of Cardiology.

ejection fraction <30%, MI at presentation, vein graft PCI, and stent diameter <3 mm. Conversely, it assigns negative integer values to older age categories. Based on the DAPT score, continued $P2Y_{12}$ inhibitor use is expected to decrease ischemic events (without a substantial increase in bleeding) or to increase bleeding (without a substantial reduction in ischemic events) in patients with ≥2 or <2 points, respectively. With respect to specific bleeding risk prediction, the approach of the 2016 ACC/AHA update to risk stratification is essentially qualitative, with a focus on bleeding risk factors rather than an emphasis on predictive models. After the publication of the 2016 ACC/AHA document, the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score has become available. The 2017 ESC update suggests using this 5-item bleeding risk score (age, creatinine clearance, hemoglobin, white blood cell count, and prior spontaneous bleeding) for the prediction of out-of-hospital bleeding hazard as a complementary tool to the DAPT score (11). In particular, the ESC guideline suggests the use of risk scores designed to evaluate the benefits and risks of different DAPT duration (i.e., PRECISE-DAPT and DAPT scores) with a COR IIb, LOE A.

TYPE OF $P2Y_{12}$ INHIBITOR AND TIME OF INITIATION. Recommendations on $P2Y_{12}$ inhibitor selection and timing are largely consistent between the ACC/AHA and ESC updates, and depend on the clinical scenario (**Figures 1 to 3**) (6,7). Both documents recommend that in patients with NSTE-ACS or STEMI with no contraindications, aspirin therapy should be combined with ticagrelor or prasugrel in preference to clopidogrel. However, with the same LOE B (based on data from 2 large randomized trials) (12,13), in the 2017 ESC update, prasugrel or ticagrelor are given

TABLE 2 Comparative Meaning and Suggested Phrasing of Levels of Evidence in the ACC/AHA and ESC Guidelines

	ACC/AHA	ESC
LOE A	• High-quality evidence from >1 RCT • Meta-analyses of high-quality RCTs • ≥1 RCTs corroborated by high-quality registry studies	• Data derived from multiple randomized clinical trials or meta-analyses
LOE B	Randomized (R) • Moderate-quality evidence from ≥1 RCTs • Meta-analyses of moderate-quality RCTs Nonrandomized (NR) • Moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	• Data derived from a single randomized clinical trial or large nonrandomized study
LOE C	Limited data (LD) • Randomized or nonrandomized observational or registry studies with limitation of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects Expert opinion (EO) • Consensus of expert opinion based on clinical experience	• Consensus of opinion of the experts and/or small studies, retrospective studies, registries

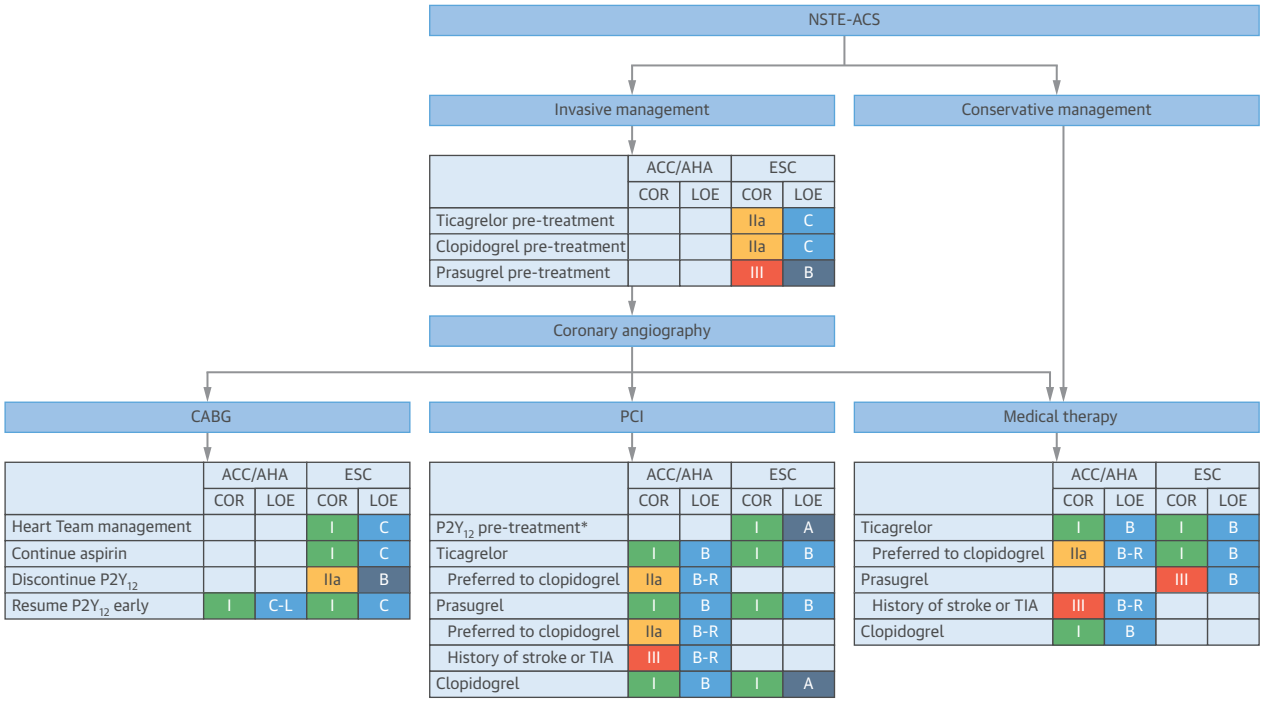
LOE = Level of Evidence; RCT = randomized clinical trial; other abbreviations as in Table 1.

COR I, with clopidogrel reserved for those who cannot receive prasugrel or ticagrelor, whereas in the 2016 ACC/AHA update, there is a preferential COR IIa in favor of prasugrel or ticagrelor over clopidogrel (6,7). With respect to the issue of pre-treatment with $P2Y_{12}$ inhibitors, the 2016 ACC/AHA update refers to previous guidelines, where a loading dose was recommended (COR I, LOE A) "before the procedure" in NSTE-ACS patients undergoing PCI with stenting (14) and "as early as possible" or at the time of primary PCI in STEMI patients (COR I, LOE B) (15). The topic is covered in greater detail by the 2017 ESC update, where the indication for pre-treatment is specific to the $P2Y_{12}$ inhibitor and the clinical setting. Accordingly, in NSTE-ACS, ticagrelor and clopidogrel (where applicable) should be considered early (COR IIa, LOE C) regardless of the initial management strategy (e.g., invasive or conservative), whereas prasugrel is recommended only for patients undergoing PCI where the coronary anatomy is known (otherwise the COR is III, LOE B, based on trial data [16]). Notably, in previous ESC guidelines for NSTE-ACS, no recommendation for or against pre-treatment with ticagrelor or clopidogrel was formulated due to lack of adequate investigations on the subject (17,18). Still, in the absence of clear data and acknowledging the limitations of this approach, the ESC 2017 task force aimed to provide practical guidance to physicians on the matter by leveraging the timing by which ticagrelor, prasugrel, and clopidogrel were administered across trials. Recommendations for STEMI patients in the 2017 ESC update are similar to those previously mentioned for NSTE-ACS patients, with the exception that prasugrel can be given before coronary angiography if the indication to primary PCI is established, because this strategy was permitted in the regulatory trial of prasugrel and not shown to be harmful (13). Patients undergoing thrombolysis were excluded from the regulatory trials of ticagrelor and prasugrel and therefore are currently recommended to receive clopidogrel by the ESC (COR I, LOE A). The ESC guidelines for STEMI, published simultaneously with the 2017 DAPT focused update, provide consistent messages and recommendations (19). The 2017 ESC focused update also provide indications regarding DAPT for patients with stable CAD undergoing PCI, where clopidogrel is the drug of choice (COR I, LOE A), with pre-treatment applicable if the probability of PCI is high (COR IIb, LOE C). Prasugrel and ticagrelor may be considered in selected patients who are at high ischemic risk and low bleeding risk (COR IIb, LOE C).

PLATELET FUNCTION TESTING AND GENETIC TESTING. Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended by the ACC/AHA or ESC due to the neutral results of multiple randomized trials (20–23). A reduced platelet inhibition of clopidogrel was reported in subjects who are poor metabolizers of the drug (e.g., due to 2 loss-of-function alleles of the *CYP2C19* gene), and a consistent drug safety "boxed warning" was issued by the Food and Drug Administration (24,25). However, according to the new 2018 ESC guidelines for myocardial revascularization, de-escalation of $P2Y_{12}$ inhibitors (e.g., from prasugrel to clopidogrel in patients with normal clopidogrel platelet inhibition response) guided by platelet function testing may be considered, particularly in ACS unsuitable for 12-month DAPT (COR IIb, LOE B) (8). This recommendation follows the result of the TROPICAL ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial, published after the release of the 2017 ESC focused update on DAPT, where genetic testing is not currently recommended to guide DAPT. A new study reported after publication of the ACC/AHA and ESC updates may suggest a need to update this topic, as described in the following text.

SWITCHING OF $P2Y_{12}$ INHIBITORS. The issue of switching is simply referred to but not addressed by the 2016 ACC/AHA update by acknowledging the lack

FIGURE 1 **Decision-Making for the Selection of the $P2Y_{12}$ Inhibitors in DAPT Combination With Aspirin for Patients With NSTE-ACS According to the ACC/AHA and ESC Guidelines**



	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Ticagrelor pre-treatment			IIa	C
Clopidogrel pre-treatment			IIa	C
Prasugrel pre-treatment			III	B

	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Heart Team management			I	C
Continue aspirin			I	C
Discontinue $P2Y_{12}$			IIa	B
Resume $P2Y_{12}$ early	I	C-L	I	C

	ACC/AHA		ESC	
	COR	LOE	COR	LOE
$P2Y_{12}$ pre-treatment*			I	A
Ticagrelor	I	B	I	B
Preferred to clopidogrel	IIa	B-R		
Prasugrel	I	B	I	B
Preferred to clopidogrel	IIa	B-R		
History of stroke or TIA	III	B-R		
Clopidogrel	I	B	I	A

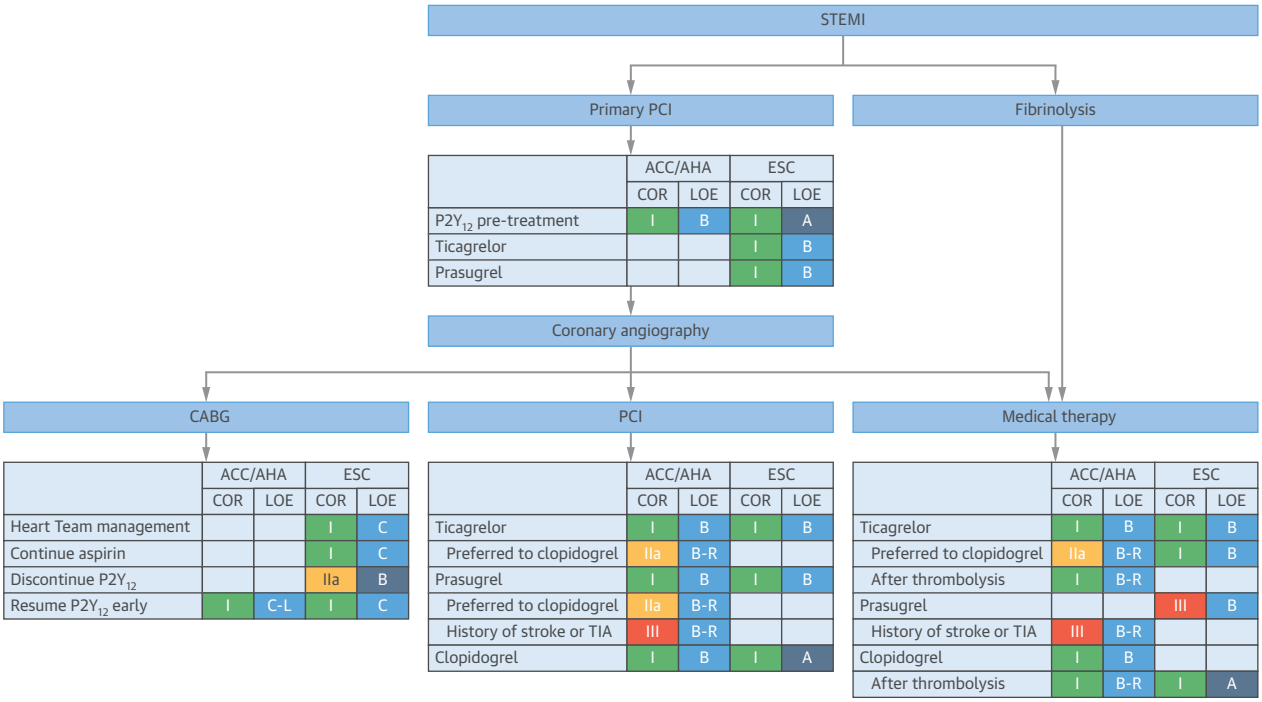
	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Ticagrelor	I	B	I	B
Preferred to clopidogrel	IIa	B-R	I	B
Prasugrel			III	B
History of stroke or TIA	III	B-R		
Clopidogrel	I	B		

*According to the 2017 ESC focused update, pre-treatment with a $P2Y_{12}$ inhibitor is "generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made." A COR IIa is given in patients with NSTE-ACS undergoing invasive management, where ticagrelor administration, or clopidogrel if ticagrelor is not an option, should be considered "as soon as the diagnosis is established." ACC = American College of Cardiology; AHA = American Heart Association; COR = Class of Recommendation; DAPT = dual antiplatelet therapy; ESC = European Society of Cardiology; LOE = Level of Evidence; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; TIA = transient ischemic attack.

of randomized studies on the long-term safety and efficacy of transitioning from one $P2Y_{12}$ inhibitor to another (6). In the 2017 ESC update the topic is covered in greater detail, and 2 CORs are issued: 1 for the early upgrading from clopidogrel to ticagrelor in ACS (COR I, LOE B), as permitted in the PLATO (Platelet inhibition and patient outcomes) trial of ticagrelor (26); and 1 for switching between $P2Y_{12}$ inhibitors if side-effects or drug intolerance occur (COR IIb, LOE C) (7). A practical algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute and chronic setting is also provided in the 2017 ESC update, which depicts 2 scenarios. In the first scenario (switching in the acute setting), a reload is always recommended to avoid gaps in the inhibitory effects of any of the $P2Y_{12}$ inhibitors. Switching to prasugrel or ticagrelor can occur irrespective of prior clopidogrel dosing and timing, whereas downgrades to clopidogrel should occur at 24 h from the last prasugrel or ticagrelor dose. Transitions between prasugrel and ticagrelor should also occur at 24 h from the last prasugrel or ticagrelor dose. In the second scenario (switch in the chronic setting) a reload is not always necessary, depending on the switched drugs (e.g., a loading dose is recommended when transitioning from ticagrelor to prasugrel or from ticagrelor to clopidogrel to avoid drug-to-drug interactions limiting the antiplatelet effect of ticagrelor, as noted in pharmacodynamic investigations in the field). All of these practices are in line with recently available expert consensus recommendations, as noted in the following text (27,28).

PROTON PUMP INHIBITORS AND DAPT. In 2009, the U.S. Food and Drug Administration issued a warning that omeprazole reduces the antithrombotic effect of clopidogrel when taken concomitantly (29,30). The writing committee of the 2016 ACC/AHA update felt that although a pharmacokinetic interaction exists between omeprazole and clopidogrel, there is no evidence of diminished clinical efficacy (31). Therefore, among measures to minimize bleeding while on DAPT, the 2016 ACC/AHA update recommends the use

FIGURE 2 Decision-Making for the Selection of the $P2Y_{12}$ Inhibitors in DAPT Combination With Aspirin for Patients With STEMI According to the ACC/AHA and ESC Guidelines



	ACC/AHA		ESC	
	COR	LOE	COR	LOE
$P2Y_{12}$ pre-treatment	I	B	I	A
Ticagrelor			I	B
Prasugrel			I	B

	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Heart Team management			I	C
Continue aspirin			I	C
Discontinue $P2Y_{12}$			IIa	B
Resume $P2Y_{12}$ early	I	C-L	I	C

	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Ticagrelor	I	B	I	B
Preferred to clopidogrel	IIa	B-R		
Prasugrel	I	B	I	B
Preferred to clopidogrel	IIa	B-R		
History of stroke or TIA	III	B-R		
Clopidogrel	I	B	I	A

	ACC/AHA		ESC	
	COR	LOE	COR	LOE
Ticagrelor	I	B	I	B
Preferred to clopidogrel	IIa	B-R	I	B
After thrombolysis	I	B-R		
Prasugrel			III	B
History of stroke or TIA	III	B-R		
Clopidogrel	I	B		
After thrombolysis	I	B-R	I	A

STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.

of proton pump inhibitors in patients with a history of gastrointestinal bleeding (COR I) and those at increased risk of gastrointestinal bleeding, including the elderly and patients with concomitant use of warfarin, steroids, or nonsteroidal anti-inflammatory drugs (COR IIa); however, the routine use of proton pump inhibitors for patients at low risk of gastrointestinal bleeding is not recommended (COR III) (6). The 2016 ACC/AHA update does not mention LOE for these recommendations, which were "C" in previous guideline for PCI (32). Conversely, in the ESC document, the use of a proton pump inhibitor while on DAPT is COR I, LOE B, with no further distinctions (7) based on an in-depth assessment of patient selection criteria and results of a large trial (31).

RECOMMENDATIONS ON DAPT DURATION

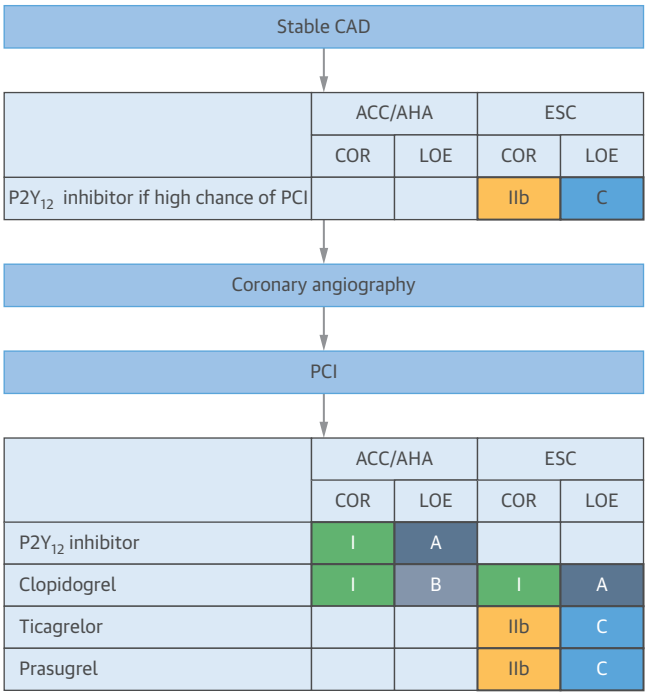
Recommendations on DAPT duration play a major part in the ACC/AHA and ESC focused updates and are discussed in the following paragraphs (6,7). For each clinical scenario, an evidence summary is provided, followed by a description of specific recommendations (**Central Illustration, Figure 4**).

PATIENTS UNDERGOING PCI FOR STABLE CAD. The current evidence base on DAPT duration for PCI patients (mostly with stable CAD or low-risk ACS) is currently made of 8 studies of shorter (3 to 6 months) versus 12-month DAPT duration (33–40), 3 studies of shorter (6 months) versus 24-month DAPT duration (41–43), and 4 studies of prolonged/extended (>12 months) DAPT duration versus 12-month DAPT duration (9,44–46) (**Table 3**). Of these 15 trials, 10 were designed around the hypothesis of shorter DAPT being noninferior to longer DAPT and 5 were designed around the hypothesis of one strategy being superior to the other. Of the noninferiority trials, all but one used an open-label design, most had lower-than-anticipated observed ischemic event rates determining a bias toward noninferiority, and 4 were stopped prematurely. Of the superiority trials, one was stopped prematurely and only the DAPT (Dual Antiplatelet Therapy Study) (9) was adequately powered for relatively rare endpoints (i.e., stent thrombosis), showing a reduction in stent thrombosis and spontaneous myocardial infarction, at the expense of increased bleeding with extended DAPT compared with shortened DAPT duration. Notably,

the ACC/AHA and ESC focused updates base their recommendation on most of the previously mentioned evidence, with the exception of a few trials unavailable at the time of publication (6,7). In the systematic review for the 2016 ACC/AHA update, which encompassed the 11 trials available at the time of publication and 33,051 patients treated with predominantly newer-generation drug-eluting stents, the use of DAPT for 12 months, compared with use for 3 to 6 months, resulted in no significant differences in the incidence of death (odds ratio [OR]: 1.17; 95% confidence interval [CI]: 0.85 to 1.63), major hemorrhage (OR: 1.65; 95% CI: 0.97 to 2.82), MI (OR: 0.87; 95% CI: 0.65 to 1.18), or stent thrombosis (OR: 0.87; 95% CI: 0.49 to 1.55) (47). Conversely, the use of DAPT for 18 to 48 months, compared with use for 6 to 12 months, was associated with no difference in all-cause death (OR: 1.14; 95% CI: 0.92 to 1.42) but was associated with increased major hemorrhage (OR: 1.58; 95% CI: 1.20 to 2.09), decreased MI (OR: 0.67; 95% CI: 0.47 to 0.95), and decreased stent thrombosis (OR: 0.45; 95% CI: 0.24 to 0.74). Three overlapping meta-analyses encompassing 10 randomized trials of DAPT duration showed similar results and were referenced to substantiate the 2017 ESC update, which does not include a systematic review like the 2016 ACC/AHA update (48–50).

With regard to specific recommendations, in patients with stable CAD undergoing PCI the 2016 ACC/AHA update recommends aspirin indefinitely (COR I, LOE B) and clopidogrel for 1 month after implantation of a bare-metal stent (COR I, LOE A) or 6 months after implantation of a drug-eluting stent (COR I, LOE B) (6). Patients who tolerate DAPT during this mandatory course without a bleeding complication and who are not at high risk of bleeding are candidates for an undefined period of prolonged DAPT (COR IIb, LOE A). Conversely, patients treated with drug-eluting stents who are at high risk of bleeding or develop significant overt bleeding may discontinue DAPT at 3 months (COR IIb, LOE C). In the 2017 ESC update, DAPT is recommended for 6 months irrespective of the stent type (COR I, LOE A), with drug-eluting stents representing the preferred treatment option (COR I, LOE A) (7). Similarly, patients who receive treatment with drug-coated balloons should receive DAPT for 6 months (COR IIa, LOE B). In all PCI patients with stable CAD, DAPT prolongation beyond 6 months and up to 30 months may be considered in patients who have tolerated DAPT and are at low bleeding risk but high thrombotic risk (COR IIb, LOE A), whereas patients who are at high bleeding risk are candidates for a shorter 3-month (COR IIa, LOE B) or even 1-month (COR IIb, LOE C) term of DAPT.

FIGURE 3 **Decision-Making for the Selection of the $P2Y_{12}$ Inhibitors in DAPT Combination With Aspirin for Patients With Stable Coronary Artery Disease Undergoing PCI According to the ACC/AHA and ESC Guidelines**

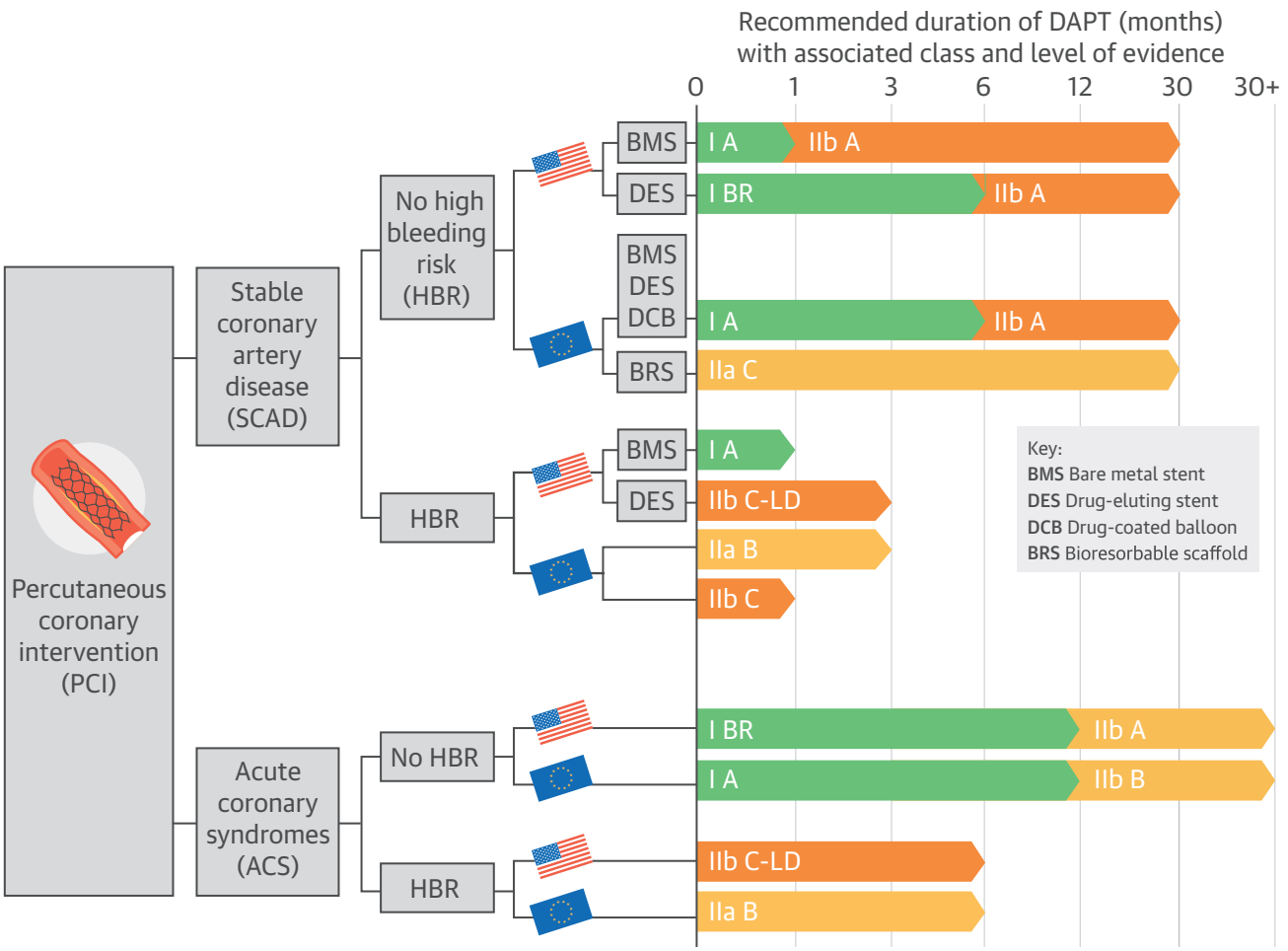


Abbreviations as in Figure 1.

In aggregate, a consistent message of both guidelines is a shift toward a shorter standard post-PCI DAPT regimen than previously recommended (e.g., 6 months) (**Central Illustration**) (6,7). This default duration is flexible and may be adapted (e.g., prolonged or shortened) according to patient-specific risks of ischemia and bleeding (51). Patients who are at high bleeding risk, in particular, represent an emerging class of individuals who are more prone to hemorrhagic consequences with long-term DAPT (e.g., due to age, concomitant use of oral anticoagulants, thrombocytopenia, active cancer, and so on). In these patients, 1 to 3 months of DAPT may ensure sufficient protection from stent thrombosis reducing the risk of bleeding. As noted in the previous text, this practice is optional in the 2016 ACC/AHA update (COR IIb for 3-month DAPT) and more encouraged in the 2017 ESC update (COR IIa for 3-month DAPT and COR IIb for 1 month DAPT) (6,7).

PATIENTS UNDERGOING PCI FOR ACS. The recommendation for keeping ACS patients on a 12-month term of DAPT is historically based on the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (52) and its PCI-CURE substudy (53).

CENTRAL ILLUSTRATION **Recommendations for Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention**



Capodanno, D. et al. J Am Coll Cardiol. 2018;72(23):2915–31.

ACS = acute coronary syndromes; BMS = bare metal stent; B-R = Level of Evidence B based on randomized evidence; BRS = bioresorbable scaffold; CAD = coronary artery disease; C-LD = Level of Evidence C based on limited data; DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; DES = drug-eluting stent; HBR = high bleeding risk; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease.

At the time of publication of the ACC/AHA and ESC updates, no available trials of DAPT duration included only patients with ACS, and recommendations were based on subgroup analyses from trials of DAPT duration including a proportion of ACS patients (6,7). In patients with ACS undergoing PCI, the recommendation of the 2016 ACC/AHA update for $P2Y_{12}$ inhibitor therapy, in combination with aspirin (COR I, LOE B), is "at least 12 months" regardless of the type of stent implanted (COR I, LOE B). Ticagrelor or prasugrel, if no contraindications exist, should be used in preference to clopidogrel for maintenance therapy (COR IIa, LOE B). DAPT prolongation beyond 12 months may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (COR IIb, LOE A) (6). Conversely, patients who are at high risk of bleeding or develop significant overt bleeding may discontinue DAPT at 6 months (COR IIb, LOE C). Similarly, in the 2017 ESC update, the default duration of DAPT for ACS patients undergoing PCI is also 12 months (COR I, LOE A) and DAPT prolongation for longer than 12 months may be considered in patients who have tolerated DAPT without a bleeding complication

(COR IIb, LOE A), whereas discontinuation at 6 months should be considered in patients who are at high bleeding risk (COR IIa, LOE B) (7). As noted in the following text, the 2017 ESC update is more specific on the drug to be preferentially used in combination with aspirin beyond 1 year of therapy in patients with prior MI. Based on the results of 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, ticagrelor may be preferred over clopidogrel or prasugrel (COR IIb, LOE B).

PATIENTS UNDERGOING CABG. No dedicated randomized study exists to guide the duration of DAPT after CABG. Based on the 2016 ACC/AHA update, DAPT must be reinstituted as soon as possible after CABG in patients with ACS or recent stent implantation (COR I, LOE C) and maintained to complete the recommended 12-month period (6). Twelve-month DAPT may also be considered in patients with stable CAD to improve vein graft patency (COR IIb, LOE B). Similar to previous PCI guidelines (32), no recommendation is given with respect to the timing of discontinuation. However, the topic was previously covered in great details in guidelines for NSTE-ACS (14) and for CABG (54), where patients referred for elective CABG are recommended discontinuation of clopidogrel and ticagrelor for at least 5 days before surgery (COR I, LOE B) and prasugrel discontinuation for at least 7 days before surgery (COR I, LOE C). In case of urgent CABG, it may be reasonable to perform surgery <5 days after clopidogrel or ticagrelor has been discontinued and <7 days after prasugrel has been discontinued (COR IIb, LOE C), but no sooner than 24 h (COR I, LOE B). On the other hand, the 2017 ESC update defines a role for the heart team in determining the individual bleeding and ischemic risks, and guiding the timing of CABG as well as the appropriate antithrombotic management (COR I, LOE C) (7). Before CABG, the $P2Y_{12}$ inhibitor should be discontinued to decrease the risk of perioperative bleeding (at least 3 days for ticagrelor, 5 days for clopidogrel, and 7 days for prasugrel; COR IIa, LOE B). Aspirin is recommended throughout the perioperative period (COR I, LOE C), while the $P2Y_{12}$ inhibitor must be resumed as soon as possible in patients with ACS and those who recently received a stent (COR I, LOE C). In patients with prior MI at high risk of bleeding, 6-month DAPT should be considered as a sufficient timeframe (COR IIa, LOE C), but those with prior MI and low risk of bleeding may be considered for a >12- and up to 36-month term of DAPT (COR IIb, LOE C). Finally, a COR IIb, LOE B is given for platelet function testing to guide decisions on timing of CABG in patients who have recently received $P2Y_{12}$ inhibitors.

TABLE 3 Studies of Dual Antiplatelet Therapy Duration

ACC/AHA*	ESC*	Trial	Comparison (Months)	Design
PCI				
Yes	Yes	RESET (N = 2,217)	3 vs. 12	Noninferiority
Yes	Yes	OPTIMIZE (N = 2,199)	3 vs. 12	Noninferiority
Yes	Yes	EXCELLENT (N = 1,443)	6 vs. 12	Noninferiority
Yes	Yes	SECURITY (N = 1,399)	6 vs. 12	Noninferiority (halted)
Yes	Yes	ISAR-SAFE (N = 4,000)	6 vs. 12	Noninferiority (halted)
No	No	I-LOVE-IT-2 (N = 1,829)	6 vs. 12	Noninferiority
No	No	IVUS-XPL (N = 1,400)	6 vs. 12	Noninferiority
No	No	OPTIMA-C (N = 1,368)	6 vs. 12	Noninferiority
No	No	NIPPON (N = 2,772)	6 vs. 24	Noninferiority (halted)
Yes	Yes	PRODIGY (N = 1,970)	6 vs. 24	Superiority
Yes	Yes	ITALIC (N = 1,822)	6 vs. 24	Noninferiority (halted)
Yes	Yes	ARCTIC (N = 1,259)	12 vs. 18	Superiority
Yes	Yes	DAPT (N = 9,961)	12 vs. 30	Superiority
Yes	Yes	DES-LATE (N = 5,045)	12 vs. 36	Superiority
Yes	No	OPTIDUAL (N = 1,385)	12 vs. 48	Superiority (halted)
ACS-PCI				
No	No	DAPT-STEMI (N = 870)	6 vs. 12	Noninferiority
No	No	REDUCE (N = 1,496)	3 vs. 12	Noninferiority
No	No	SMART-DATE (N = 2,172)	6 vs. 12	Noninferiority

*The availability status at the time of the ACC/AHA and ESC guidelines publication is indicated.
Abbreviations as in Table 1.

PATIENTS WITH PRIOR MI. In the PEGASUS-TIMI 54 trial, 2 doses of ticagrelor (60 and 90 mg twice daily) were studied, and both decreased the incidence of ischemic events in 21,162 patients with a history of prior MI from 1 to 3 years earlier, but also both increased the incidence of major bleeding (55). The 60-mg twice daily dose was subsequently approved by regulatory authorities in both the United States and Europe. In the 2016 ACC/AHA update, continued DAPT is given a COR IIb, LOE B for patients with an MI that occurred 1 to 3 years earlier and who have tolerated DAPT without bleeding or who are not at high bleeding risk (6). In the 2017 ESC update, the same COR IIb, LOE B is given for DAPT continuation with ticagrelor in patients with MI and high ischemic risk who have tolerated DAPT without a bleeding complication, in preference to prasugrel or clopidogrel (7).

PATIENTS WITH ACS MEDICALLY MANAGED. Patients with ACS who were medically managed were included in the CURE trial for clopidogrel (56), the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial for prasugrel (57), and the

PLATO trial for ticagrelor (12). Among these studies, TRILOGY ACS included only ACS patients with no invasive management, and they were not found to derive a significant ischemic benefit from prasugrel compared with clopidogrel (57). In the studies of clopidogrel and ticagrelor, the treatment effects of the drugs were consistent regardless of whether the ACS was managed invasively or not. Based on this data, in the 2016 ACC/AHA update, 12-month DAPT with aspirin and clopidogrel or ticagrelor is given a COR I, LOE B for patients with ACS who are managed with medical therapy alone, with preference to ticagrelor (COR IIa, LOE B) and an option for extending DAPT beyond 12 months in patients who are at low risk of bleeding (COR IIb, LOE A) (6). The 2017 ESC update provide similar recommendations but also additional statements, with slightly different COR and/or LOE for key recommendations (7). In particular, 12-month DAPT with aspirin and clopidogrel or ticagrelor is given a COR I, LOE A, with ticagrelor recommended over clopidogrel if the bleeding risk is acceptable (COR I, LOE B). The duration of DAPT should be shortened to 1 month for patients at high bleeding risk (COR IIa, LOE C). Patients with prior MI with "PEGASUS-TIMI 54-like" characteristics are candidate to DAPT with ticagrelor (COR IIb, LOE B) or clopidogrel (COR IIb, LOE C) for longer than 12 months if the bleeding risk is acceptable. Prasugrel is not recommended in this context (COR III, LOE B).

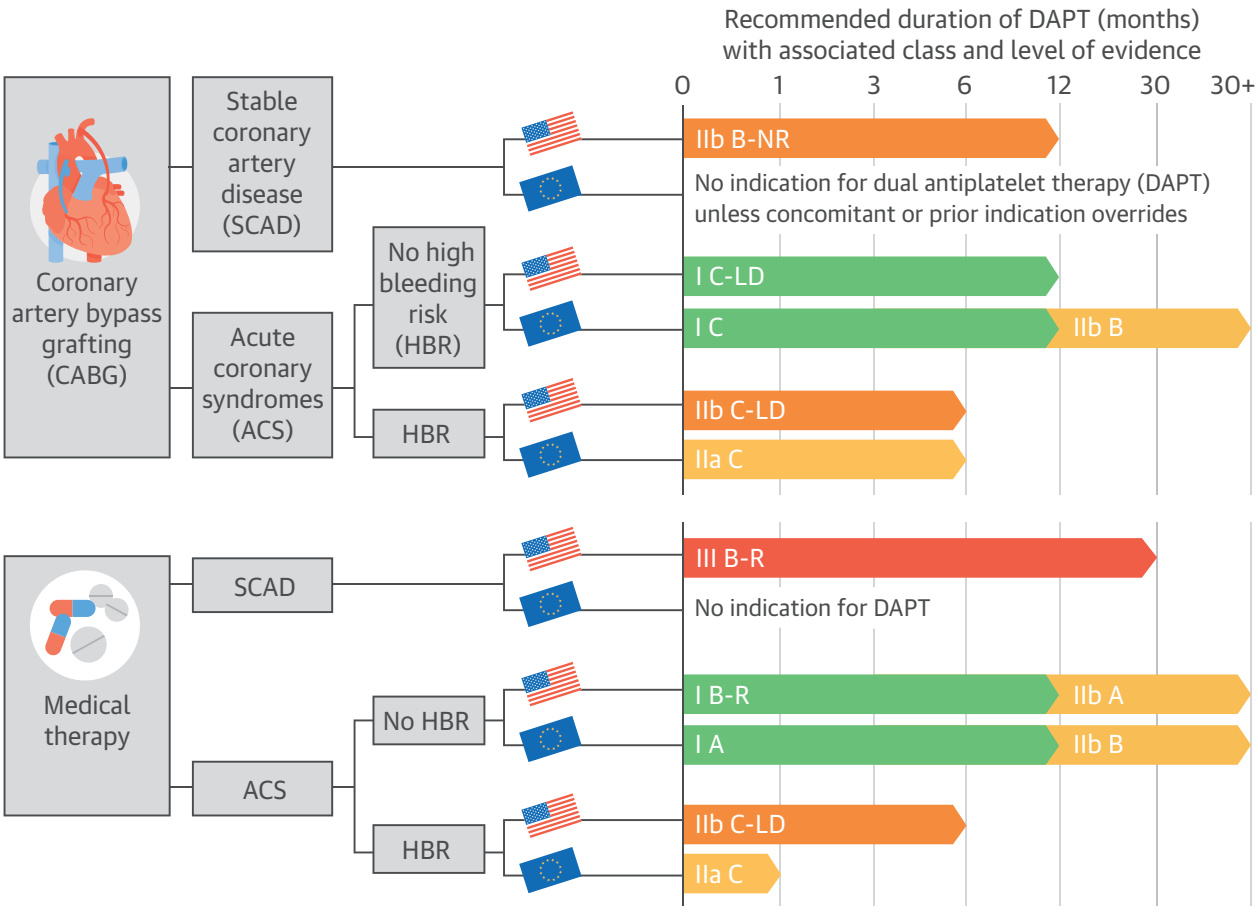
DAPT IN PATIENTS UNDERGOING NONCARDIAC SURGERY. Both the ACC/AHA and ESC updates recommend the use of a multidisciplinary approach to antithrombotic management in the perioperative period (COR IIa, LOE C) (6,7). The 2016 ACC/AHA update recommends delaying noncardiac surgery 1 month after implantation of bare-metal stents and 6 months after implantation of drug-eluting stents (COR I, LOE B), although a shorter period of 3 months may be considered if the risk of further delaying surgery is greater than the expected risks of stent thrombosis (COR IIb, LOE C). Aspirin should be continued throughout the perioperative period and the $P2Y_{12}$ inhibitor must be resumed as soon as possible postoperatively (COR I, LOE C), which is also recommended by the 2017 ESC update with the same COR but LOE B. No recommendation is given for bridging $P2Y_{12}$ inhibitors in patients requiring temporary perioperative discontinuation of DAPT before surgery. Based on the 2017 ESC update, after PCI, surgery should occur no sooner than 1 month irrespective of the stent type (COR IIa, LOE B) and may occur no sooner than 6 months in case of recent MI or other high ischemic-risk features (COR IIb, LOE C). Perioperative discontinuation of $P2Y_{12}$ inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel, and at least 7 days for prasugrel (COR IIa, LOE B). If both oral antiplatelet agents have to be discontinued due to high risk of bleeding, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation (COR IIb, LOE C).

ANTIPLATELET THERAPY IN PATIENTS ON ORAL ANTICOAGULATION

The 2016 ACC/AHA update does not provide specific recommendations for patients who require concomitant antiplatelet and anticoagulant therapy (6), which is a topic covered by a North American consensus document to which they refer to and which has been recently updated after the release of the guidelines (58,59); however, the update gives general guidance on the approach to such patients. Moreover, none of the trials using the non-vitamin K oral antagonists were available at the time these recommendations were written. In contrast, the 2017 ESC update covers the topic based essentially on 3 randomized trials that investigated antithrombotic strategies to improve the safety of triple antithrombotic therapy with oral anticoagulation and DAPT (60–62). Importantly, none of these studies were adequately powered for detecting differences in ischemic endpoints. The results of an additional trial of PCI patients with atrial fibrillation, showing that dual therapy with dabigatran at the doses of 150 or 110 mg reduces bleeding as compared with triple antithrombotic therapy, were not available at the time of publication of both the ACC/AHA and ESC updates (63). Further guidance on the topic in the context of similar recommendations is given by a recent European expert consensus document (64).

The 2017 ESC update emphasizes the need for implementing strategies to minimize PCI-related complications, including risk stratification for ischemia and bleeding, keeping triple antithrombotic therapy to the shortest possible duration with dual antithrombotic therapy as an alternative, using non-vitamin K antagonist oral anticoagulants whenever possible instead of vitamin K antagonists (at the lowest approved dose effective for stroke prevention tested in atrial fibrillation trials when combined with antiplatelet drugs [COR IIa, LOE C]), considering an INR in the lowest part of the therapeutic range in case of warfarin use (COR IIa, LOE C), and using proton pump inhibitors routinely (7). For patients in whom concerns about the risk of ischemic complications

FIGURE 4 Summary of Recommendations for DAPT in Patients Undergoing CABG or Referred to Medical Therapy After Coronary Angiography



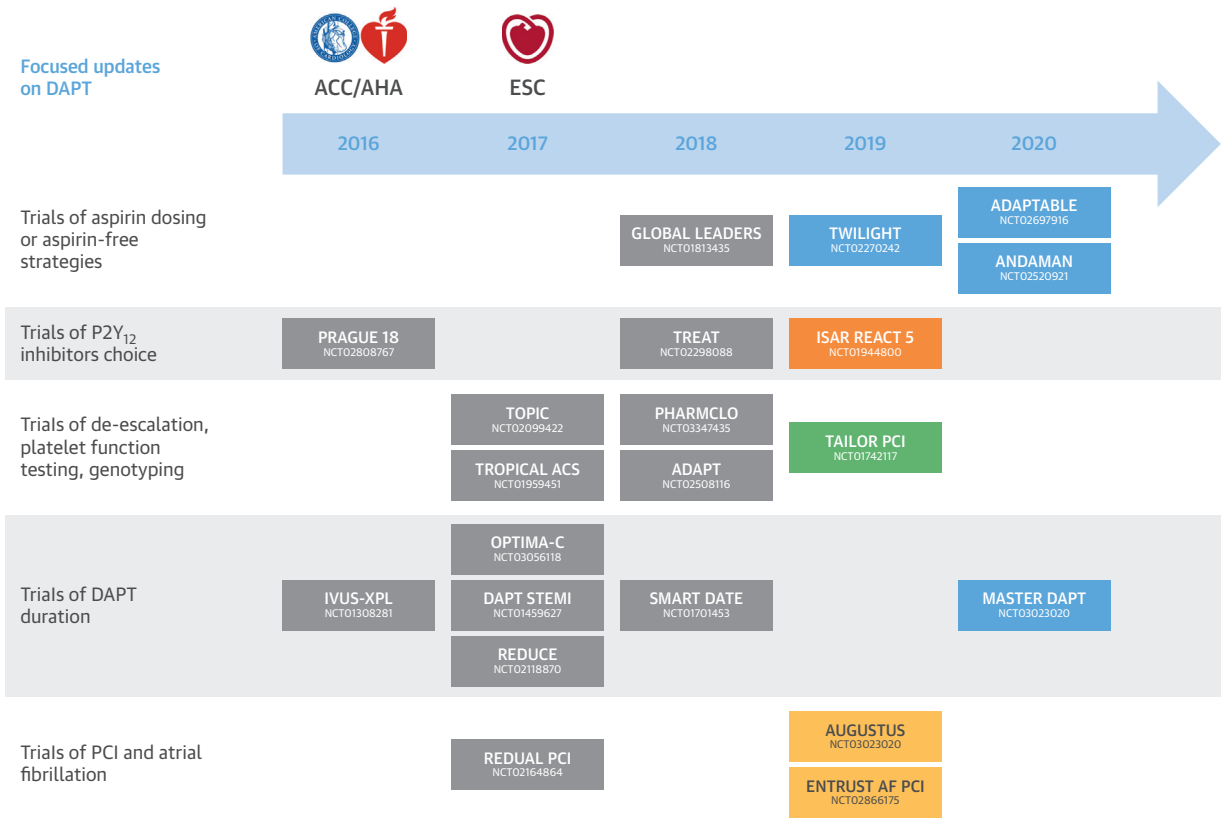
ACS = acute coronary syndromes; BMS = bare metal stent; B-R = Level of Evidence B based on randomized evidence; CAD = coronary artery disease; CABG = coronary artery bypass grafting; C-LD = Level of Evidence C based on limited data; DAPT = dual antiplatelet therapy; HBR = high bleeding risk; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease.

prevail, 1 month of triple antithrombotic therapy with OAC, aspirin, and clopidogrel should be recommended irrespective of the type of stent used (COR IIa, LOE B), but may be considered up to 6 months in patients who are at high ischemic risk due to ACS or other anatomical/procedural characteristics that outweigh the risk of bleeding (COR IIa, LOE B). When the period of triple antithrombotic therapy is concluded, a dual antithrombotic regimen with OAC and aspirin or clopidogrel should be recommended up to 12 months (COR IIa, LOE A), followed by OAC alone (COR IIa, LOE B). In patients where concerns about the risk of bleeding complications prevail, triple antithrombotic therapy should not be prolonged beyond 1 month (COR IIa, LOE B) and should be even avoided using double antithrombotic therapy with OAC and clopidogrel as an alternative (COR IIa, LOE A). When rivaroxaban is used in combination with aspirin and/or clopidogrel, the 15-mg once-daily dose of rivaroxaban may be used instead of the conventional 20-mg once-daily dose (COR IIb, LOE B). The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy (COR III, LOE C).

NEW EVIDENCE AND ONGOING STUDIES

Several randomized clinical trials have been published after the release of the ACC/AHA and ESC updates on DAPT, which have the potential to influence or inform the COR and/or reinforce the relative LOE, and other trials are ongoing (Figure 5). A description of trials looking at alternative antithrombotic strategies, such as the adjunctive use of oral anticoagulant

FIGURE 5 New Evidence and Ongoing Studies in the Field of DAPT



Published studies that are not currently referenced in the 2016 ACC/AHA or 2017 ESC DAPT focused updates are displayed with a **gray** background. Ongoing studies according to expected completion dates are shown with **colored** backgrounds. Abbreviations as in Figures 1 and 4.

therapy, goes beyond the scope of this section and is described elsewhere (65,66).

ASPIRIN DOSING. The optimal dose of aspirin in patients treated with DAPT, which is currently 81 mg (acceptable range between 75 and 100 mg) according to the 2016 ACC/AHA update and 75 to 100 mg according to the 2017 ESC update, is under further investigation. The ongoing ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness) trial is randomly assigning 20,000 subjects with established coronary artery disease to either low-dose (81 mg) or high-dose (325 mg) aspirin (67). Results of investigations suggesting more favorable pharmacodynamics results with twice-daily administration of low-dose aspirin in patients with diabetes mellitus (68,69) have also prompted clinical investigations in the field such as in the ongoing ANDAMAND (Aspirin Twice a Day in Patients With Diabetes and Acute Coronary Syndrome) trial (NCT02520921). In addition, several trials of aspirin-free strategies (e.g., NCT02270242, NCT03023020) are ongoing that will clarify the net benefit of using a single potent $P2Y_{12}$ inhibitor (e.g., ticagrelor) for maintenance therapy after PCI (70,71). The first trial in this series, named GLOBAL LEADERS, failed to show a difference in 2-year death or Q-wave myocardial infarction with the use of ticagrelor monotherapy (after 1 month of DAPT) compared with standard DAPT for 12 months followed by aspirin monotherapy for an additional 12 months (72).

CHOICE OF $P2Y_{12}$ INHIBITOR. No differences in clinical efficacy and safety of prasugrel and ticagrelor were noted in a STEMI head-to-head comparison terminated early for futility (73). Therefore, both options remain valid with the same COR, while another head-to-head comparison between the 2 drugs in ACS is underway (74). Most recently, the results of the TREAT (Ticagrelor in Patients With ST-Elevation

TABLE 4 Major Differences Between the ACC/AHA and ESC Updates on DAPT

Topic	2016 ACC/AHA Update	2017 ESC Update
Risk stratification	DAPT score to assess the risk/benefit of prolonging DAPT.	Use of both DAPT and PRECISE-DAPT scores recommended.
Type of $P2Y_{12}$ inhibitor in ACS	Class IIa recommendation for ticagrelor or prasugrel preferred to clopidogrel.	Class I recommendation for ticagrelor or prasugrel preferred to clopidogrel.
Timing of $P2Y_{12}$ inhibitor	Does not include updated recommendations or revision of existing recommendations from previous guidelines.	Focused update with recommendations on early use of ticagrelor or clopidogrel for non-ST-segment elevation ACS undergoing invasive management and option to pre-treat with ticagrelor or prasugrel in patients at high ischemic risk and low bleeding risk undergoing elective PCI.
Switching of $P2Y_{12}$ inhibitors	Does not include updated recommendations or revision of existing recommendations from previous guidelines.	Covered in detail with recommendations on early upgrading from clopidogrel to ticagrelor in ACS and switching between $P2Y_{12}$ inhibitors once side effects or drug intolerance occurs.
Proton pump inhibitors	Class I in patients on DAPT with a history of gastrointestinal bleeding and those at increased risk of gastrointestinal bleeding.	Class I in patients on DAPT.
DAPT duration after PCI for stable coronary artery disease	Default DAPT duration is 6 months after drug-eluting stent and 1 month after bare-metal stent implantation.	Default DAPT duration is 6 months regardless of stent type. A 1-month course of DAPT may be considered in selected patients treated with drug-eluting stents and at high bleeding risk.
DAPT duration after PCI for ACS	Extended therapy recommended as Class IIb for selected patients at low bleeding risk.	Extended therapy, preferentially with ticagrelor, recommended as Class IIb for selected patients with prior myocardial infarction.
DAPT duration in patients undergoing CABG	Does not include updated recommendations or revision of existing recommendations from previous guidelines.	Includes an updated dedicated section.
DAPT duration in patients with ACS medically managed	Class IIa for ticagrelor in preference to clopidogrel for 12 months.	Class I for ticagrelor in preference to clopidogrel for 12 months.
DAPT in patients undergoing noncardiac surgery	Surgery must be delayed 1 month after implantation of bare-metal stents and 6 months after implantation of DES (Class I).	Surgery should occur no sooner than 1 month irrespective of the stent type (Class IIa) and no sooner than 6 months in case of recent MI or other high ischemic risk features (Class IIb). Option for bridging strategy with intravenous antiplatelet agents in selected patients (Class IIb).
Antiplatelet therapy in patients on oral anticoagulation	Does not include updated recommendations or revision of existing recommendations from previous guidelines.	Includes an updated dedicated section.
Companion document with clinical vignettes illustrating DAPT scenarios in the real-life setting	No.	Yes.

ACS = acute coronary syndromes; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

Myocardial Infarction Treated With Pharmacological Thrombolysis) trial showed that, in patients younger than age 75 years presenting with STEMI, administration of ticagrelor after fibrinolytic therapy was noninferior to clopidogrel on 30-day major bleeding events, with no differences in ischemic events (75). However, a critical aspect that remains unanswered and not addressed in this trial is the effect of ticagrelor administration concomitant to fibrinolytic therapy given that timing of administration of oral $P2Y_{12}$ inhibiting therapy typically occurred within 11.5 h post-fibrinolysis.

SWITCHING, DE-ESCALATION, PLATELET FUNCTION TESTING, AND GENOTYPING. With respect to switching, a recent international document from American and European experts covering the topic in detail has been recently released, with practical recommendations mostly based on consensus and pharmacodynamic investigations (27). A number of studies have investigated the clinical impact of switching therapies. In the TOPIC (Timing Of Platelet Inhibition after acute Coronary Syndrome) trial, bleeds were reduced by de-escalating from the more potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor to clopidogrel at 30 days after PCI for an ACS (76). However, the study was of limited sample size and not powered for efficacy. Building on the same principle of "de-escalation," the TROPICAL ACS trial suggested that de-escalation of antiplatelet treatment (e.g., from prasugrel to clopidogrel in patients with normal clopidogrel platelet inhibition response) guided by platelet function testing is noninferior to standard treatment

with prasugrel at 1 year (77). Recently, in the PHARMCLO (Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Acute Coronary Syndromes) trial, genotyping to inform selection of antiplatelet therapy improved outcomes in patients with NSTE-ACS or STEMI compared with the standard of care (78). However, the results of this trial need to be interpreted with caution as it was terminated prematurely, potentially overestimating the effect size (79). A number of ongoing randomized studies using genetic testing are currently ongoing (80). The results of these studies may have an effect on future guideline recommendations on the use of genetic testing.

DAPT DURATION. A number of PCI trials of DAPT duration were unpublished at the time when meta-analyses informing current documents were conducted (39,40) (**Table 3**). Their contribution to the overall evidence is likely minimal or confirmatory. A patient-level meta-analysis of 6 DAPT duration trials identified PCI complexity as a potential treatment modifier when comparing longer and shorter DAPT regimens (81). This issue was not covered by both the ACC/AHA and ESC updates. In addition, 2 ACS trials of DAPT duration were presented at the Transcatheter Cardiovascular Therapeutics meeting in 2017, which are unpublished at the time of drafting this article. The DAPT-STEMI (Randomized, Open Label Trial of 6 Months Versus 12 Months DAPT After Drug-Eluting Stent in STEMI) trial met the primary hypothesis of 6-month DAPT being noninferior to 12-month DAPT with respect to a composite of ischemic and bleeding outcomes, but the observed rate of events was lower than anticipated. A power issue was even more pronounced in the REDUCE (Short-term Dual Anti Platelet Therapy in Patients With ACS Treated With the COMBO Dual-therapy Stent) trial, where the investigators compared 3-month DAPT versus 12-month DAPT in patients with ACS. Again, the noninferiority hypothesis was met, but the margin of noninferiority was large, and the direction of the estimates for some important ischemic endpoints disfavored the 3-month DAPT group. A third published trial, named SMART-DATE (Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes) (N = 2,172), also recently met the hypothesis of shorter DAPT (6 months) being noninferior to 12-month DAPT in ACS, but also showed an increased risk of MI with shorter duration, concluding that prolonged DAPT should remain the standard of care in patients with ACS undergoing PCI (82).

Overall, the newly available data seem to support current recommendations. Following the results of the ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) (83,84), LEADERS-FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) (85), and SENIOR (Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization) (86) trials, showing that drug-eluting stents outperform bare-metal stents in high bleeding risk candidates on a 1-month term of DAPT, a number of additional trials of very short DAPT for patients at high risk of bleeding are ongoing (NCT03023020; NCT03344653; NCT03218787; NCT02594501). Risk stratification tools, such as the DAPT score and the PRECISE-DAPT score, are useful companions in daily practice but more research in this field is necessary, because prospective validation is lacking and the discrimination ability in retrospective validation studies is at best moderate-to-good (87).

ANTIPLATELET THERAPY IN PATIENTS ON ORAL ANTICOAGULANTS. In patients with atrial fibrillation who had undergone PCI, the RE-DUAL PCI trial showed that at a mean of 14 months the risk of major or clinically relevant nonmajor bleeding was lower using a dual-therapy regimen with dabigatran (110 or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) compared with those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin for 1 or 3 months according to stent type (63). Overall, dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. Other ongoing studies testing antithrombotic strategies in atrial fibrillation patients undergoing PCI, including strategies with the use of apixaban (88) and edoxaban (89), are currently ongoing.

ANTIPLATELET THERAPY IN PATIENTS UNDERGOING CARDIAC AND NON-CARDIAC SURGERY. A number of national societies have developed algorithms based on multidisciplinary collaborative efforts providing guidance on how to manage antiplatelet therapy in patients undergoing surgery (90–92). Even so, several other questions remain on DAPT in cardiac surgery, including whether and for how long DAPT should be restarted in CABG patients with stable CAD, and the timing for reinitiation in ACS patients. Other unsolved issues in the CABG setting regard the timing of discontinuation for different $P2Y_{12}$ inhibitors, the optimal use of platelet function testing while awaiting surgery, and how to manage perioperative bleeding complications caused by DAPT.

CONCLUSIONS

The rapid evolution of the field of antithrombotic pharmacotherapy, in an ever-changing landscape of safer stents, bleeding avoidance strategies, and newer drugs for secondary prevention, requires regular updates of recommendations for DAPT. Indeed, the risk-benefit of DAPT depends on many individual circumstances, including the clinical scenario and the susceptibility to ischemia, bleeding, or both. The current ACC/AHA and ESC updates for DAPT are substantially similar with respect to key recommendations on $P2Y_{12}$ inhibitor selection and DAPT duration. However, whereas the 2016 ACC/AHA update is essentially centered around the topic of DAPT duration, the ESC document has a broader focus on antiplatelet therapy in general and relative to specific clinical scenarios (**Table 4**). Nevertheless, a common and important theme in both updates is the shift from a population-based treatment approach to one that is more "patient-centered." Indeed, this is a step toward an emerging approach for disease treatment and prevention called "precision medicine," which takes into account individual variability in genes, environment, and lifestyle for each person. Although the evidence generated since the publication of the ACC/AHA and ESC updates seems unlikely to provoke breakthrough changes with respect to existing recommendations, ongoing studies will define new areas of interest and possibly lead to modifications in future recommendations to better personalize patient care.

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KEY WORDS antiplatelet, bleeding, stent, thrombosis