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The art of delivering evidence-based dual antiplatelet therapy

This review, which details 2 DAPT risk scoring systems and includes a treatment guide, can help ensure that you deliver the right treatment to the right patients.

PRACTICE RECOMMENDATIONS

❯ *Use a dual antiplatelet therapy (DAPT) risk calculator to encourage patient-centric decisions when presenting information to the health care team and the patient.* **B**

❯ *Consider the potential benefit of a shorter duration of DAPT for patients who 1) have prior bleeding complications or 2) are taking an oral anticoagulant, chronic corticosteroid, or nonsteroidal anti-inflammatory drug.* **B**

❯ *Continue aspirin use upon completion of DAPT or if a P2Y12 inhibitor is being held for surgery.* **A**

❯ *Reduce the risk of recurrent stroke in patients who have had a mild ischemic stroke or transient ischemic attack by providing DAPT for 21 to 28 days, followed by aspirin indefinitely—so long as treatment can begin within 24 hours of the event.* **B**

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence

B Inconsistent or limited-quality patient-oriented evidence

C Consensus, usual practice, opinion, disease-oriented evidence, case series

In landmark clinical research published in 1996, aspirin (ASA) and the P2Y12 inhibitor ticlopidine used after coronary artery stent implantation was compared to intravenous anticoagulation—at the time, the postprocedure standard of care for preventing thrombosis. What investigators found was a marked reduction in cardiac and hemorrhagic events in patients who were treated with this novel dual antiplatelet therapy (DAPT).[1] Since publication of the results of that trial, the use of ASA plus a P2Y12 inhibitor has expanded to treating acute coronary syndrome (ACS) and stroke.

Over the past 2 decades, much research has been devoted to 1) determining the effectiveness of more potent P2Y12 inhibitors—which block chemoreceptors for adenosine diphosphate—to prevent stent thrombosis and 2) safer regimens to reduce hemorrhagic complications.

When does stent thrombosis occur?

The timing of stent thrombosis is defined as:
- acute (within 24 hours of placement),
- subacute (within 30 days),
- late (within 1 year), or
- very late (after 1 year).

Acute stent thrombosis is almost always related to technical issues surrounding stent implantation. Subacute thrombosis is almost always platelet activation within the stent with thrombus formation—the reason why antiplatelet therapy is beneficial and anticoagulation pathway inhibition is *not* beneficial.

Late stent complications can be caused by thrombosis, but also might be related to restenosis by 4 to 6 months—ie, tissue overgrowth as the stent becomes part of the body, not clot formation. In several studies, restenosis was a significant issue with balloon dilation alone, occurring in 33% of patients.[2] Bare-metal stents (BMS) have been shown to reduce the rate

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> The delay in healing caused by drug-eluting stents makes it necessary to administer dual antiplatelet therapy for a longer duration—an increase not needed with bare-metal stents.

of restenosis to approximately 20%; drug-eluting stents (DES) have further decreased restenosis to approximately 5%, in various reports, by impairing endothelial healing, thus limiting tissue overgrowth that leads to restenosis.[3] This delay in healing caused by DES makes it necessary to administer DAPT for a longer duration—an increase that is not needed with BMS.

DAPT has well-defined benefits

As drug-eluting stents were introduced and improved, trials studying optimal duration of DAPT showed that longer duration of treatment reduced stroke incidence and the long-term risk of myocardial infarction (MI) unrelated to stent thrombosis.[4] Nuances in the treatment of ischemic coronary artery disease (CAD) and secondary prevention of stroke can be perplexing, as can be P2Y12 inhibitor selection. Here, we review DAPT agents and discuss current evidence and evidence-based guidelines, thus providing a framework to better understand treatment options and recommendations.

What constitutes DAPT?

Many combinations of antiplatelet therapy are possible but, in the United States, DAPT denotes ASA 81 mg/d plus any of the 3 P2Y12 inhibitors: clopidogrel, prasugrel, and ticagrelor. Stimulation of the platelet P2Y12 receptor causes stimulation of the platelet glycoprotein IIb/IIIa receptor, which, in turn, enhances platelet degranulation, thromboxane production, and prolonged platelet aggregation. Blocking P2Y12 receptors thus impairs the thrombotic processes.[5]

▮ **ASA**, as a component of DAPT, is recommended at a dosage of 81 mg/d. In trials of ASA plus clopidogrel, lower ASA dosages had comparable ischemic event rates compared to higher ASA dosages.[6,7] Patients given higher ASA dosages with ticagrelor had poorer outcomes when compared with low-dosage ASA.[8] Higher dosages of ASA, alone or with DAPT, increase the risk of bleeding complications.[9,10]

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❚ **Clopidogrel** is the only P2Y12 inhibitor available as a generic medication in the United States. As a pro-drug, clopidogrel requires 2 metabolic transformations to its active metabolite after being hydrolyzed in the gut, which delays onset of platelet inhibition for several hours after ingestion.[11] Furthermore, individual genetic variation in cytochrome P450 (CYP) 2C19 (CYP2C19), one of the hepatic enzymes in this metabolic process, may lead to less alteration of clinical platelet aggregation response, and increased drug interactions.[12] Methods to assess platelet function have shown decreased inhibition of platelet aggregation for some CYP2C19 polymorphisms, although consistent clinical effects of this inhibition have not been identified to date; genetic testing for these polymorphisms is, therefore, not recommended routinely.[13]

Indications for DAPT treatment with clopidogrel are unstable angina or non-ST-segment elevation acute coronary syndrome (NSTE-ACS), whether planned treatment is medical or coronary revascularization. Other indications include acute ST-segment elevation MI (STEMI) with planned medical treatment, and recent MI, stroke, or established peripheral arterial disease.[13,14]

❚ **Prasugrel** has faster onset of action and greater and more consistent P2Y12 inhibition than clopidogrel. After prasugrel is hydrolyzed in the gut, an intermediary metabolite is activated in the liver. Peak serum concentration is reached within 30 minutes.[12] Unlike the case with clopidogrel, genetic variation in the CYP gene does not impart significant impact on forming the active metabolite.[15]

Indication for the use of prasugrel is ACS that is managed with percutaneous coronary intervention (PCI). Dual antiplatelet therapy with prasugrel results in reduced risk of cardiovascular death, nonfatal MI, and stroke, compared with ASA plus clopidogrel, with an increase in bleeding events.[16] Thrombolysis patients and those who have a history of stroke had a greater risk of hemorrhage complications with prasugrel treatment, compared with clopidogrel. Prasugrel offered no benefit to patients older than 75 years or those who weigh <60 kg. If used in patients who weigh <60 kg, however, dosage reduction is recommended.[16]

> **Longer duration of DAPT reduces stroke incidence and the long-term risk of myocardial infarction—unrelated to stent thrombosis.**

❚ **Ticagrelor.** Unlike clopidogrel and prasugrel, ticagrelor is a direct oral, reversible-binding P2Y12 inhibitor. Peak serum concentration is reached within 2 to 3 hours.[17] Indications are ACS or a history of MI, and those with ACS undergoing stent implantation. Ticagrelor was superior to clopidogrel in reducing the risk of death from vascular causes, MI, and stroke, and superior to clopidogrel in reducing the risk of stent thrombosis. There was no increase in the overall major bleeding rate and a decrease in fatal bleeding events compared to clopidogrel. Adverse effects unique to ticagrelor include dyspnea and, in patients with bradydysrhythmias, asymptomatic ventricular pauses. Both effects tend to resolve with continued treatment. This P2Y12 inhibitor should be avoided in patients with severe liver disease.

Loading and maintenance doses of the 3 P2Y12 inhibitors are provided in **TABLE 1**.[13,14]

When—and when not—to initiate DAPT

Treatment recommendations for DAPT originated in the 2016 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease[14] and in the 2017 European Society of Cardiology (ESC) focused update on dual antiplatelet therapy in coronary artery disease.[13] Although these guidelines differ slightly, the overall approach they present is similar, with an emphasis on limiting bleeding while preventing stent thrombosis.

Stable ischemic heart disease (SIHD) is defined as confirmed obstructive CAD without either ACS or a history of PCI in the past year.[18] Patients with SIHD but without a history of PCI or recent coronary artery bypass grafting (CABG) receive no benefit from DAPT (*Strength of recommendation [SOR]: A*).[19] (See **TABLE 2** for definitions of SOR and corresponding levels of evidence.)

❚ **For patients who have undergone BMS placement**, minimum DAPT with clopidogrel is 1 month (*SOR: A*) and, if there is no significant bleeding on DAPT and no high risk of bleeding (ie, no prior bleeding while

TABLE 1

DAPT: Regimens and dosing[13,14]

Drug	Indication		Comment
	Acute coronary syndrome	Prevention of thrombotic event	
Clopidogrel	600 mg initial dose; then, 75 mg/d plus ASA, 81 mg/d	75 mg/d	No renal adjustment
Prasugrel	60 mg initial dose; then, 10 mg/d plus ASA, 81 mg/d	Not indicated	No renal adjustment
Ticagrelor	180 mg initial dose; then, 90 mg/d plus ASA, 81 mg/d	60 mg plus 81 mg ASA twice daily	No renal adjustment; take caution in the presence of hepatic disease, bradydysrhythmias

ASA, aspirin; DAPT, dual antiplatelet therapy.

taking DAPT, coagulopathy, or oral anticoagulant use), continuation of ASA and clopidogrel beyond 1 month might be reasonable (*SOR: B*).

❚ **With a drug-eluting stent**, the minimum time for DAPT (using clopidogrel) is 6 months (*SOR: A*), with a longer duration being reasonable if the patient is not at high risk of bleeding and has had no bleeding complications (*SOR: B*). For DES patients who have developed a high risk of bleeding, have had significant bleeding, or require a procedure that will place them at high risk of bleeding, DAPT discontinuation can be considered at 3 months (*SOR: B*).

❚ **Updated guidelines allow longer therapy for patients who tolerate DAPT**; for them, 12 months of therapy is preferred. In comparing longer and shorter therapy, it has been determined that longer DAPT treatment is superior for reducing the risk of MI and stent thrombosis without increasing the risk of stroke or bleeding complications.[20] With increased bleeding, or where there is a need for elective surgery, shortened DAPT is an option.

❚ **When treating patients with ACS**, including NSTE-ACS or STEMI, DAPT for 1 year is recommended (*SOR: A*). When medical therapy alone is planned, DAPT is provided with clopidogrel or ticagrelor.

❚ **When a patient has been treated with PCI (BMS or DES)**, DAPT with any of the P2Y12 inhibitors is recommended (*SOR: A*) unless there is history of stroke or transient ischemic attack (TIA) or the patient is

TABLE 2

Strength-of-recommendation taxonomy and corresponding levels of evidence

Strength of recommendation	Levels of evidence
A Recommendation is based on good-quality, patient-oriented evidence	**1** High-quality systematic reviews; randomized controlled trials
B Recommendation is based on inconsistent or limited-quality, patient-oriented evidence	**2** High-quality cohort study; validated clinical decision tool
C Recommendation is based on consensus, usual practice, opinion, disease-oriented evidence, or case series evidence	**3** Consensus guideline, opinion, usual practice, or clinical experience

Source: Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *Am Fam Physician*. 2004;69:548-556 (www.aafp.org/afp/2004/0201/p548.html. Accessed November 14, 2018).

≥75 years of age, in which case prasugrel is contraindicated (*SOR: A: Harm*).

❚ **When lytic interventions are employed in STEMI**, DAPT with clopidogrel—for a minimum of 14 days and, ideally, for 12 months—should be considered. Without high risk of bleeding, or significant bleeding on DAPT, continuing DAPT for >12 months might be reasonable (*SOR: A*).

TABLE 3,[13,14] adapted from 2016 ACC/AHA[14] and 2017 ESC[13] guidelines, provides recommendations about agents and duration of therapy in the management of patients with CAD.

How long should you give DAPT?

Balancing the hemorrhagic complications of DAPT against its benefits is challenging. The use of risk scores to guide duration of DAPT may be considered (*SOR: B*).

▮ **The PRECISE-DAPT score**[21] is used at the time of coronary artery stenting to guide treatment duration. The scoring algorithm incorporates hemoglobin level, leukocyte count, age, creatinine clearance and prior bleeding to create a composite score on a 100-point scale.[22] (The algorithm can be found at www.precisedaptscore.com/predapt/webcalculator.html.) If the composite is <25 points, the number needed to treat to prevent an ischemic event is 65, and standard or long-term DAPT (12 to 24 months) is recommended. When the PRECISE-DAPT score is ≥25, the number needed to harm with a hemorrhagic event is 38, and a shorter duration of therapy (3 to 6 months) is recommended.

▮ **The DAPT score**,[23] available from the American College of Cardiology[24] (http://tools.acc.org/DAPTriskapp/#!/content/calculator) is a risk calculator for use after 12 months of DAPT in the absence of complications. Age, cigarette use, diabetes, current or previous MI, presence of congestive heart disease, and type and location of stent all factor into calculating the risk score. DAPT scores range from -2 to 10. A score ≥2 suggests less bleeding risk, with a recommendation to consider longer treatment (≤30 months); a score <2 leads to a recommendation to adhere to standard treatment duration of 12 months.

Patients with CAD should continue ASA treatment when DAPT is discontinued or completed, unless contraindicated.[13,14]

Triple therapy: DAPT + anticoagulant

Given that the US population is aging, there are an increasing number of patients with CAD and atrial fibrillation. Stroke is prevented in patients with atrial fibrillation with anticoagulant therapy; when these patients have stent placement for coronary, carotid, vertebral, or intracranial arterial disease, they need DAPT to prevent stent thrombosis. In the immediate post-stenting period, therefore, patients are often placed on an oral anticoagulant as well as DAPT. Vitamin K antagonists (VKAs) should be discontinued after acute stroke, with individualized resumption of a VKA when clinically appropriate.

As we emphasize throughout this article, there is a balance between bleeding risk and the potential benefits of therapy of the selected anticoagulant/DAPT regimen. These complex patients are best managed in close consultation with Cardiology and Neurology because of their potential risk of 3-fold bleeding.[25] The findings of a recent study addressing post-stent placement therapy in patients with nonvalvular atrial fibrillation suggests that the direct oral anticoagulant dabigatran may be preferable to warfarin in this setting, because of the lower risk of bleeding with dabigatran without increased thrombotic risk.[26] In this study, 3-drug therapy was used for 1 month, followed by discontinuation of ASA and continuation of 2-drug therapy with the direct oral anticoagulant and the P2Y12 inhibitor for the 6- to 12-month time frame post-stenting (*SOR: B*).

Consider a PPI to reduce the risk of a GI bleed

Proton-pump inhibitors (PPIs) should be considered for patients treated with DAPT if there is a history of gastrointestinal (GI) bleeding (*SOR: A*). Although a potential interaction between PPIs and P2Y12 inhibition has been identified in laboratory studies, this has not been supported in clinical studies. Therefore, although warnings exist for concomitant use of clopidogrel and PPIs, a PPI is reasonable for patients who are at increased risk of GI hemorrhage, including those taking warfarin, a corticosteroid, or a nonsteroidal anti-inflammatory drug and those of advanced age (*SOR: B*). Risks and benefits of clopidogrel and PPIs should be discussed with patients. There is no benefit in using PPIs for low-risk patients. (*SOR: A: No benefit*).[27,28]

Perioperative management with DAPT can be thorny

Perioperative management of DAPT patients

> **Ticagrelor should be avoided in patients with severe liver disease.**

TABLE 3

Evidence-based recommendations for DAPT[13,14]

Recommendation	Strength of recommendation	Level of evidence
ASA, 81 mg/d, is recommended for patients treated with a P2Y12 inhibitor	A	2
Stable ischemic heart disease with BMS		
Treat for at least 1 month of DAPT with clopidogrel	A	1
Consider DAPT with clopidogrel for >1 month if the patient has not had a bleeding complication and is not at high risk of bleeding*	B	1
Stable ischemic heart disease with DES		
Treat for at least 6 months of DAPT with clopidogrel	A	1
Consider continuing DAPT with clopidogrel for >6 months if the patient has not had a bleeding complication and is not at high risk of bleeding*	B	1
For patients who have developed a high risk of bleeding,* are at high risk of serious bleeding complications (eg, neurosurgical intervention), or have had significant bleeding, discontinuing a P2Y12 inhibitor after 3 months might be reasonable	B	2
ACS (NSTE-ACS or STEMI)		
DAPT with ticagrelor (preferred) or clopidogrel for 12 months is recommended for patients with medically managed ACS	A	1
A patient with ACS treated with BMS or DES should receive ≥12 months of DAPT with clopidogrel, prasugrel, or ticagrelor	A	1
Consider continuing DAPT for >12 months in a patient with ACS treated with stent implantation who is not on oral anticoagulants, has not had a bleeding complication, and is not at high risk of bleeding*	B	1
Ticagrelor is a reasonable P2Y12 inhibitor over clopidogrel for an ACS patient treated with DAPT after stent placement who is not at high risk of bleeding* complications and who has not had a stroke or TIA	B	1
Prasugrel is a reasonable P2Y12 inhibitor over clopidogrel for an ACS patient <75 years of age treated with DAPT after stent placement who is not at high risk of bleeding* complications and who has not had a stroke or TIA	B	1
If a patient requires subsequent CABG after stent placement, DAPT should be resumed and continued to complete the recommended therapy duration, based on stent type	A	2
In an ACS patient being treated with DAPT who undergoes CABG, DAPT should be resumed postoperatively to complete 12 months of therapy after the ACS event	A	2
If a patient with ACS treated with DAPT after DES implantation has a high risk of severe bleeding*, is at high risk for severe bleeding complications (major bleed with intracranial surgery), or develops bleeding, a P2Y12 inhibitor might reasonably be discontinued at 3 to 6 months	B	2
Contraindications and cautions		
Prasugrel should *not* be used in patients with a history of stroke or TIA	A: HARM	1
Prasugrel is *not* recommended for patients with ACS who are being medically managed	A: HARM	1
Prasugrel should *not* be used in NSTE-ACS patients in whom coronary anatomy is unknown	A: HARM	1
Once DAPT is initiated, it is *not* recommended to discontinue the regimen during the first month if the patient is undergoing noncardiac surgery	A: HARM	1
Platelet function testing and genetic testing are *not* recommended to guide selection of a P2Y12 inhibitor	A: No benefit	1

ACS, acute coronary syndrome; ASA, aspirin; BMS, bare metal stent; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

*"High risk of bleeding" is defined as a history of bleeding while taking DAPT, coagulopathy, or oral anticoagulant use.

Adapted from: Valgimigli M et al. 2017[13] and Levine GN et al. 2016.[14]

who have an indwelling coronary stent and require noncardiac surgery is complicated. Stent thrombosis is a calamity, with ≥50% risk of death. Delaying surgery for at least 4 weeks after placement of a BMS and 6 months after placement of a DES reduces the risk of thrombosis.[29]

For emergent surgery, when severe bleeding is not seen or expected, interruption of DAPT can be minimized. After cessation of DAPT components, normal platelet function will return in[12]:

- 7 to 10 days for ASA,
- 5 to 7 days for prasugrel,
- 5 days for clopidogrel, and
- 3 to 5 days for ticagrelor.

> **Consider giving a proton-pump inhibitor to a patient receiving DAPT who has a history of gastrointestinal bleeding.**

If significant bleeding occurs perioperatively, or is expected, platelet transfusion can be helpful, and might need to be repeated because each P2Y12 inhibitor has a half-life of between 8 and 12 hours.

For urgent or time-sensitive surgery, discontinuing a P2Y12 inhibitor can be considered—while continuing ASA, if possible. DAPT should be restarted as soon as safely possible. If enteral administration is not feasible, ASA can be administered rectally. In this setting, cardiology consultation is strongly encouraged.

Last, elective surgery should be delayed until DAPT is completed, but without discontinuing ASA, if feasible. Spinal, intracranial, prostate, middle-ear, and ophthalmologic surgery while taking ASA can lead to catastrophic complications; consider discontinuing ASA. Cardiology consultation can provide an estimate of thrombosis risk to guide clinical decision-making.[30]

Can DAPT prevent secondary stroke?

DAPT has brought improvements in the treatment of patients with cardiovascular disease; it has been hypothesized that similar benefits can be seen in patients with ischemic stroke. Knowing the cause of stroke is key to developing a secondary prevention plan; patients with stroke secondary to atherosclerotic disease are most likely to benefit from DAPT.[31] Conversely, secondary prevention in patients with small-vessel disease and in studies of unselected stroke type has been shown to be harmful.[32,33]

Clopidogrel and ASA initiated within 24 hours of a minor stroke (ie, National Institutes of Health Stroke Score/Scale <4 [www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale_Booklet.pdf][34]) or TIA and continued for a total of 21 days of DAPT, followed by clopidogrel alone to complete 90 days of treatment, have been demonstrated to reduce the risk of recurrent ischemic stroke compared to ASA alone without increasing the risk of bleeding (*SOR: B*).[35]

In a multinational trial of DAPT, stroke risk was reduced at 90 days after TIA or mild stroke but bleeding risk was higher, compared to ASA alone; continuing DAPT for 90 days might explain the higher risk of bleeding.[36]

For secondary prevention of stroke in patients with aspirin allergy, monotherapy with clopidogrel is an option, but use of clopidogrel or ticagrelor is not superior to ASA.[37,38] Therefore, there may be benefit, in patients with TIA or minor stroke, to continue DAPT beyond 21 days but at the risk of bleeding complications. (*SOR: A: Harm*).[33,34]

Based on these data, the best duration of DAPT after TIA or mild stroke is likely 21 to 28 days.

When a patient requires VKA therapy, the benefit of using DAPT to further reduce ischemic cerebrovascular or cardiovascular events is unknown (*SOR: C*). In the setting of atrial fibrillation with unstable angina or CAD stent implantation, however, therapy with DAPT plus a VKA can be considered—but with increased risk of nonfatal and fatal bleeding.[39]

Summing up: Key guidance

DAPT has benefits for patients with SIHD and ACS in the setting of medical management or implantation of a coronary artery stent. Balancing the reduction in risk of ongoing ischemic events with hemorrhagic complications presents challenges, as does deciding on duration of therapy. Using a DAPT risk calculator can be helpful to present informa-

tion to the health care team and the patient, thus encouraging patient-centered treatment decisions.

Patients at increased risk of ischemia, such those with an ACS presentation, multiple myocardial infarcts, extensive CAD, left-ventricular ejection fraction <40%, chronic kidney disease, or diabetes mellitus might benefit from longer DAPT. Conversely, patients with prior bleeding complications, taking oral anticoagulation, with body weight <60 kg, or on chronic steroids or nonsteroidal medications might benefit from shorter duration of DAPT.

Earlier recommendations about the duration of DAPT continue to be refined by ongoing clinical research. Current-generation DESs have improved over first-generation stents; updated guidelines from the AHA and ESC presented in this review are based on new, improved stents.

ASA should almost always be continued upon completion of DAPT or if P2Y12 inhibitors are held for surgery.

Last, in patients with mild ischemic stroke or TIA, DAPT therapy, begun within 24 hours and continued for 21 to 28 days, followed by ASA, 81 mg/d, alone indefinitely, can reduce the risk of recurrent stroke. **JFP**

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> **Unless there is a contraindication, patients with coronary artery disease should continue taking aspirin after DAPT.**

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