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Dual Antiplatelet Therapy: Unlocking the Future of Cardiovascular Disease Management

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Abstract: ***Dual Antiplatelet Therapy (DAPT) is a cornerstone in managing thrombotic cardiovascular conditions, particularly in patients undergoing percutaneous coronary intervention (PCI), those with acute coronary syndrome (ACS), and individuals at risk of cerebrovascular and peripheral arterial events. This review explores the mechanisms of various antiplatelet agents, their clinical indications, and the optimal duration of DAPT across different patient populations. While DAPT effectively reduces ischemic complications, prolonged therapy is associated with an increased risk of bleeding, necessitating a tailored approach based on individual risk assessments. Recent advancements, including novel antiplatelet agents and evolving guidelines, emphasize balancing ischemic protection with bleeding risk. This review provides an in-depth analysis of the latest clinical evidence, emerging therapies, and guideline recommendations for optimizing DAPT in various cardiovascular conditions.***

Keywords: Dual Antiplatelet Therapy (DAPT), Antiplatelet Agents, Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), Ischemic Stroke, Peripheral Artery Disease (PAD), Thrombosis, Bleeding Risk, Antiplatelet Therapy Duration, Novel Antiplatelet Agents, Cardiovascular Disease, Risk Stratification, Clopidogrel, Aspirin, Ticagrelor, Prasugrel, Glycoprotein IIb/IIIa Inhibitors, P2Y12 Receptor Antagonists, Antithrombotic Therapy, Clinical Guidelines.

I. INTRODUCTION

cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, with thrombotic events playing a critical role in disease progression. Antiplatelet therapy, particularly DAPT, has revolutionized the management of conditions such as ACS, ischemic stroke, and peripheral arterial disease (PAD), reducing the risk of recurrent thrombotic events.[1-2] The choice of antiplatelet agents and the duration of therapy depend on patient-specific factors, including the nature of the underlying condition, risk of ischemic recurrence, and bleeding susceptibility. Over time, research has provided new insights into the safety and efficacy of different DAPT regimens, leading to updated clinical guidelines[1-2]. This review examines the mechanisms of action of various antiplatelet agents, indications for DAPT, and the challenges in determining the optimal treatment duration. Additionally, we discuss emerging antiplatelet therapies and their potential to refine current treatment strategies.[3]

II. MECHANISM OF ACTION ANTIPLATELET AGENTS

1) The following categories of antiplatelets can be made according to their mode of action: Aspirin and related cyclooxygenase inhibitors are examples of platelet aggregation inhibitors. Oral thienopyridines, including ticagrelor, prasugrel, and clopidogrel
2) Glycoprotein inhibitors of platelets (such as tirofiban, eptifibatide, and abciximab)
3) Antagonists of the protease-activated receptor-1 (such as vorapaxar)
4) Examples include phosphodiesterase type 3 (PDE3) and nucleoside transport inhibitors, (such as dipyridamole and cilostazol.)[1-4]

The most widely used oral antiplatelet medication, aspirin, irreversibly inhibits the cyclooxygenase enzyme (COX) activity in the prostaglandin synthesis pathway (PGH2), which is a precursor to thromboxane A2 (TXA2) and PGI2. Thromboxane A2 works by causing platelet aggregation and vasoconstriction, and COX-1 mediates its production, whereas PGI2 works by preventing platelet aggregation, causing vasodilation, and is mediated by COX-2. Complete or nearly complete inhibition of COX-1 can be produced by low doses of aspirin (75 mg to 150 mg), which inhibits the production of TXA2, whereas COX-2 requires higher doses.[3-4]
Adenosine diphosphate-induced (ADP-induced) platelet aggregation is specifically inhibited by oral thienopyridines. These medications are transformed into active ones by the hepatic CYP450 system, which has the ability to permanently block the platelet P2Y12 receptor. Prasugrel is the most potent of the 3 medicines, has a rapid beginning of action, and is superior to clopidogrel in patients having coronary stenting. A novel intravenous reversible P2Y12 receptor antagonist with a quick onset of action is called cangrelor. In comparison to clopidogrel, it achieves a notable level of platelet inhibition.[4]

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Glycoprotein platelet inhibitors reduce platelet aggregation by blocking glycoprotein IIb/IIIa (GpIIb-IIIa) receptors on platelets. ACS is where they are most frequently utilized. [2] Since these medications may only be administered intravenously, they are only utilized as temporary treatments.

Dipyridamole inhibits platelet cyclic nucleotide phosphodiesterase and has antiplatelet and vasodilating effects. Adenosine monophosphate (AMP) is broken down by this enzyme to 5'AMP, which promotes intra-platelet cyclic AMP buildup and prevents platelet aggregation. Additionally, it prevents the platelets from absorbing adenosine, which raises cyclic AMP[5].

Cilostazol is also said to have antiproliferative, antiplatelet, and vasodilatory actions. Additionally, it lessens intimal hyperplasia and smooth muscle cell proliferation following endothelium damage.[6-8]

III. CLINICAL INDICATION FOR DAPT

The patient's clinical characteristics, medical history, and bleeding risk should all be taken into account while determining duration and combination. The ideal moment varies depending on the process and circumstances.

Cardiovascular events in ACS are decreased when DAPT is used for less than a year. Long-term DAPT raises the risk of bleeding but may lower cardiovascular events. The ideal time frame in AF and after PCI is still up for debate.[5-6] In order to increase graft patency and decrease thrombotic events, ASA is advised for CABG patients after surgery. Although DAPT with ticagrelor or clopidogrel and ASA has also demonstrated advantages, there is a greater chance of bleeding. It's still unclear how long DAPT should last after TAVI. Compared to individuals with asymptomatic PAD, those with symptoms benefit somewhat with antiplatelet monotherapy. For secondary prevention, vorapaxar might offer a favorable benefit-risk profile. Antiplatelet therapy can reduce the risk of revascularization in PAD and increase pain-free walking distance. In patients with cerebral symptomatic stenosis, ASA and clopidogrel together reduce microembolization signals. For individuals undergoing CAS, DAPT is advised above aspirin alone.

Unfavorable clinical outcomes are predicted by clopidogrel non-responsiveness and ASA resistance.[7-10]

1) Acute Coronary Syndrome (ACS)
- ST-Elevation Myocardial Infarction (STEMI)
- Non-ST Elevation Myocardial Infarction (NSTEMI)
- Unstable Angina (UA)
- Post-percutaneous coronary intervention (PCI) with stenting

2) Post-Percutaneous Coronary Intervention (PCI) with Stent Placement
- Drug-eluting stents (DES): Minimum 6–12 months of DAPT
- Bare-metal stents (BMS): Minimum 1 month of DAPT

3) Post-Coronary Artery Bypass Grafting (CABG)
- Recommended for 1 year in patients with ACS post-CABG

4) Ischemic Stroke or Transient Ischemic Attack (TIA)
- Short-term DAPT (21–30 days) for minor ischemic stroke or high-risk TIA

5) Peripheral Artery Disease (PAD)
- Reduces limb-related and cardiovascular events
- Recommended for post-peripheral artery revascularization

6) Prevention of Stent Thrombosis and In-Stent Restenosis
- Essential post-PCI to prevent early and late stent thrombosis

IV. DURATION OF DAPT

A. Duration Of DAPT In ACS

Since DAPT was first used for a 12-month period to treat ACS and prevent drug-eluting stent thrombosis, short-term DAPT usually refers to a shorter therapy duration, typically 3-6 months, and some more recent studies recommend only 1 month in patients with high bleeding risk [8, 9]. Prior studies have evaluated the short-term safety and effectiveness of DAPT in individuals with ACS (Figure 2). In ACS patients with NSTEMI, the CURE study shown that using clopidogrel and aspirin together for three to twelve months reduced myocardial infarction episodes, ischemic recurrence, stroke, and cardiovascular death with elevated bleeding risk.[10-12]

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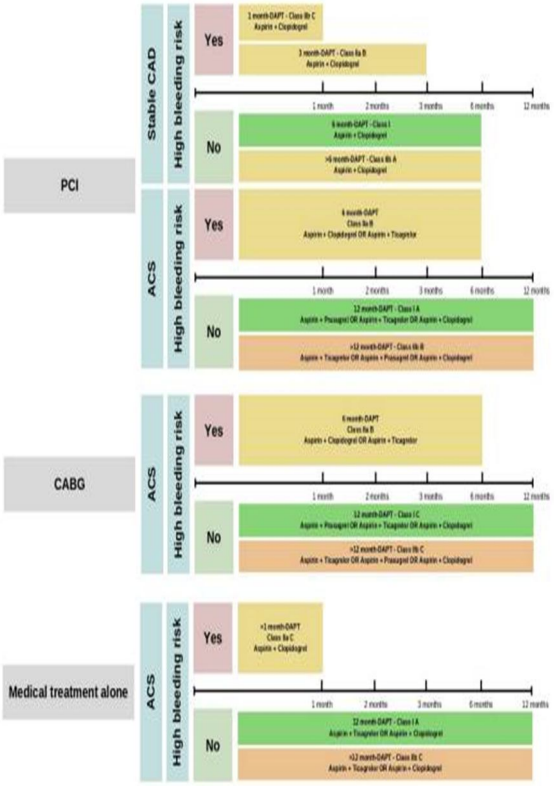


Figure 1 [7]

DAPT guidelines based on bleeding risk and therapeutic strategy. For patients with stable CAD receiving CABG or medical therapy alone, DAPT is not recommended. Acute Coronary Syndrome (ACS), Coronary Artery Bypass Graft (CABG), Dual Antiplatelet Therapy (DAPT), Percutaneous Coronary Intervention (PCI), and Stable Coronary Artery Disease (SCAD) are some examples of abbreviations.[13-16]

Short-term DAPT is recommended in the context of the newer generation drug-eluting stents (DES), particularly in older patients and non-east Asians, according to meta-analyses that looked into the ideal length of DAPT among patients undergoing PCI[11-12]. According to one meta-analysis, short-term DAPT (less than six months) after PCI for ACS treatment did not increase the risk of stent thrombosis more than long-term DAPT[13]. At one-year and two-year follow-ups, the REDUCE study observed no difference in mortality, MI, stroke, stent thrombosis incidence, revascularization, and bleeding rates between 3- and 12-month DAPT in either gender[14].

In the SMART-CHOICE trial, patients undergoing PCI were given DAPT for three months before being split into two groups: those who continued DATP or those who took a PY12 inhibitor as a stand-alone treatment for a further nine months. Major adverse events were comparable at 12 months, while the P2Y12 inhibitor group saw less bleeding [15].

Clopidogrel, prasugrel, or ticagrelor are recommended as initial "up-front" therapy for non-ST elevation ACS, regardless of planned treatment, according to the 2020 European Society of Cardiology (ESC) guidelines and the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Although ticagrelor and prasugrel are preferred over clopidogrel, prasugrel is mainly advised for patients scheduled for PCI who do not have an elevated risk of bleeding.[17-18]

B. Duration of DAPT in CAD

People with several risk factors or clinically obvious cardiovascular disease were randomly assigned to one of two groups in the CHARISMA experiment. Low-dose aspirin (75–162 mg daily) and clopidogrel (75 mg daily) were given to one group, whereas a placebo and low-dose aspirin were given to the other group. With a median duration of 28 months, this trial found no appreciable benefits of extended DAPT in terms of lowering the incidence of stroke, MI, or cardiovascular deaths. Additionally, the study pointed up certain drawbacks for patients who had several risk factors, including bleeding [18].

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The THEMIS trial studied ticagrelor plus ASA versus placebo plus ASA in 19,220 patients with type 2 diabetes and stable coronary artery disease. There was no prior history of MI or stroke. The median follow-up was 39.9 months. The ticagrelor group (7.7%) had a lower composite endpoint (CV death, MI, or stroke) compared to the placebo group (8.5%) with a hazard ratio of 0.90 (95% CI 0.81–0.99, p = 0.04). Fatal bleeding did not significantly differ[1.9] More importantly, the THEMIS PCI trial focused on patients with prior PCI. With a hazard ratio of 0.85 (CI 0.74–0.97, p = 0.013), the ticagrelor group experienced a lower primary endpoint rate (7.3%), which was a combination of CV mortality, MI, or stroke, than the placebo group (8.6%). With a hazard ratio of 2.03 (CI 1.48–2.76, p < 0.0001), ticagrelor was associated with a greater incidence of TIMI significant bleeding (2% vs. 1.1%) [20].

In the GLOBAL-LEADERS trial, patients with CAD or ACS receiving PCI were managed for two years using a single antiplatelet strategy. Initially, patients were given DAPT for a month together with ticagrelor and aspirin. Patients were given the option of continuing DAPT with aspirin and ticagrelor, taking ticagrelor by itself, or receiving conventional treatment with aspirin and clopidogrel for the next 23 months. Ticagrelor did not provide an advantage over conventional treatment in terms of preventing new Q-wave MI or all-cause mortality. Both groups experienced comparable rates of bleeding.[21-25]

In patients with stable CAD, the COMPASS study found that rivaroxaban with aspirin reduced mortality, stroke, and myocardial infarction by 24% more effectively than aspirin alone. Nevertheless, this method was found to significantly enhance the bleeding rate.[22]

C. Duration Of DAPT In post-PCI With Atrial Fibrilation In Addition To Anticoagulation

A number of guidelines suggest how long antiplatelet medication should be administered to patients with atrial fibrillation (AF) following PCI. Regardless of the stent used in the PCI, triple therapy (aspirin, clopidogrel, and an oral anticoagulant) should be considered for one month in accordance with the 2018 ESC guidelines on DAPT duration in patients taking oral anticoagulation, such as those with AF. Since the advantages of this strategy outweigh the danger of bleeding, it is advised to extend triple therapy for up to six months in patients with elevated ischemia risk. In the first month following PCI, patients may be treated with a combination of clopidogrel and an oral anticoagulant if bleeding is likely to occur. Depending on the patient's needs, these guidelines recommend stopping antiplatelet medication after a year and continuing oral anticoagulant.[23-28]

According to the 2021 AHA/ACC/SCAI Revascularization Guidelines, ASA therapy should be stopped by AF patients who have had PCI no later than four weeks following PCI. To lower the risk of bleeding, these patients should thereafter continue taking the P2Y12 inhibitor along with an oral anticoagulant that isn't vitamin K (apixaban, rivaroxaban, edoxaban, or dabigatran).[24]

To assist in identifying AF patients who are more likely to experience adverse events after PCI and to inform decisions about the length of antiplatelet medication, risk stratification methods such the CHA2DS2-VASc and HAS-BLED scores have been developed.[25]

D. Duration OF DAPT in CABG

According to current standards, patients having coronary artery bypass surgery (CABG) should begin taking ASA as soon as possible, ideally within six hours of the procedure's conclusion, at a dose of 100–325 mg. In order to reduce the risk of unfavorable cardiovascular events and saphenous vein graft closure, ASA should then be maintained forever. Additionally, compared to ASA monotherapy, the advantages of DAPT therapy in CABG patients—either ticagrelor or ASA + clopidogrel—for a year are linked to improved graft patency [24].

E. Duration Of DAPT In Post TAVI

For high-risk patients or those who are not candidates for surgery, transcatheter aortic valve implantation (TAVI) offers a viable alternative to surgery[58]. However, TAVI has its own risks and possible side effects, such as bleeding and stroke, just like any other medical operation.

The optimal length of antiplatelet therapy following TAVI is still being worked out. Patients who require anticoagulation during the periprocedural phase should only take ASA or clopidogrel. Depending on the risk of bleeding, anticoagulation treatment should be administered for three to six months either in conjunction with or without a single antiplatelet treatment. After then, switching to oral anticoagulation monotherapy is advised. For individuals not in need of anticoagulation, ASA or clopidogrel is recommended during the periprocedural phase. The bleeding risk should be taken into consideration when choosing between monotherapy and the DAPT method during the first three to six months. It is advised to continue monotherapy after this time.[26-28]

When compared to DAPT with either a 3- or 6-month treatment period, ASA monotherapy reduced bleeding rates without raising the risk of stroke or death, according to one meta-analysis that examined the use of antiplatelet medication following TAVI[27].

It's interesting to note that, even in the absence of anticoagulant use, clopidogrel is superior to aspirin in avoiding cardiovascular death after 24 months of treatment[27-28].

F. Duration Of DAPT In PAD

Millions of people throughout the world suffer with PAD, a prevalent vascular disease. According to one meta-analysis, antiplatelet monotherapy had a lower clinical benefit in silent PAD and only a marginally positive effect in symptomatic situations. Nonetheless, there appears to be a risk of significant bleeding when PAD is present.

Notably, vorapaxar reduced the ischemic limb event by 42% and the need for peripheral revascularization by 16% in patients with intermittent claudication who had previously experienced MI and PAD but had no prior history of stroke or TIA. However, compared to a placebo, vorapaxar caused 62% more bleeding incidents[30].

Cilostazol is useful in treating stable moderate-to-severe claudication, according to several meta-analyses[30-31]. Moreover, four studies demonstrated that antiplatelet therapy (ticlopidine for 6–21 months and piconamide for 18 months) reduced the incidence of revascularization in comparison to a placebo[32].

In the THEMIS study, ticagrelor/aspirin caused fewer significant adverse limb events (1.3%) compared to placebo/aspirin (1.6%). The ticagrelor/aspirin group also showed reduced rates of acute limb ischemia and peripheral revascularization. Compared to placebo/aspirin (11.0%), ticagrelor/aspirin had a decreased primary result of irreversible injury, such as death, MI, stroke, bleeding, or cerebral hemorrhage (9.3%)[29].

G. Duration Of DAPT In PAD Post-Peripheral Stent

The ideal time in the setting of PAD post-peripheral stent remains unclear, despite the fact that the length of DAPT following coronary stenting has been thoroughly investigated and standardized. Because of the peripheral arterial structure, comorbidities, and inherent bleeding risks associated with PAD, this patient population presents a unique difficulty in balancing the risk of stent thrombosis against the possibility for bleeding consequences[33-36].

Regardless of whether a drug-eluting or bare metal stent is utilized, the ESC guidelines indicate that DAPT be administered for at least one month after endovascular revascularization [34]. According to one trial, within the first six months of treatment, revascularized PAD patients receiving clopidogrel and aspirin had fewer revascularization episodes than those receiving aspirin and a placebo[35]. Compared to participants in the aspirin + placebo group, PAD patients receiving DAPT in the MIRROR trial exhibited lower platelet activation upon revascularization and fewer reinterventions. Furthermore, DAPT did not worsen bleeding in these patients[36].

H. Duration of Antiplatlet Therepy in carotid Artary Disease

In individuals with carotid disease, aspirin or clopidogrel are frequently administered to reduce the risk of cerebrovascular disease[37]. The idea that antiplatelet medication can prevent strokes in people who do not exhibit symptoms is not well-supported by evidence[38-39]. However, evidence indicates that ASA plus clopidogrel for seven days is more effective than ASA alone in reducing microembolization signals on day two in individuals with symptomatic intracranial stenosis (ISS) in patients with carotid disease[39].

When carotid artery disease is asymptomatic, the ESC guidelines suggest a single

The ESC guidelines advise a single antiplatelet medication for a minimum of one year in patients with asymptomatic carotid artery disease[34]. In individuals with ischemic stroke or transient ischemic attack (TIA), aspirin with dipyridamole is more effective than aspirin alone at avoiding recurrent cerebrovascular events. Within 24 hours of the onset of symptoms, this therapy can begin. For verified TIAs with neuroimaging or ischemic stroke, long-term aspirin + dipyridamole is not superior to clopidogrel alone.

I. Duration of Antiplatelet Therapy IN carotid Artery Disease Post carotid stent

According to ESC guidelines, DAPT should be used for carotid artery stenting (CAS). Two trials comparing aspirin alone and DAPT for CAS were discontinued early due to the high rate of neurological complications and stent thrombosis in the aspirin monotherapy group[43-45] which happened within 30 days of the procedure and were associated with the procedure.

There is ongoing discussion over the ideal length of DAPT following CAS. One month after CAS, tardily brain lesions were seen on magnetic resonance imaging, raising concerns about the necessity of continued DAPT after this time. However, there is a chance that these lesions will hemorrhagically convert with extended DAPT, resulting in cerebral bleeding. Prolonged DAPT beyond one month after CAS may be beneficial for patients with minimal bleeding risk and recent MI (<12 months)[34].

J. Duration of Antiplatelet Therepy in Myocardial Infraction With Non Obstructive Coronary Arteries

Myocardial infarction with non-obstructive coronary arteries, or MINOCA, is a term that encompasses a number of disorders with different underlying causes. While angiography shows normal or almost normal coronary arteries with stenosis of less than 50%, MINOCA is recognized by clinical indications that indicate a MI [43]. In comparison to people with MI and obstructive CAD, those with MINOCA are less likely to have recurrent cardiovascular events[44]. In terms of MACE and mortality reduction in patients with MINOCA in the first year, most trials that used DAPT revealed no advantages[45-47]. To ascertain the length of DAPT for patients with MINOCA, more research will be required.

K. Duration of Antiplatlet Therapy in Spontaneous Coronary Artery Dissection

Internal bleeding, with or without an inner lining tear, causes the layers inside the arterial wall of the epicardial coronary artery to separate, a condition known as spontaneous coronary artery dissection (SCAD). The majority of conservatively treated SCAD patients have acute DAPT before being released with a SAPT to lower MACE[47-52]. Nonetheless, patients who have stenting are recommended to get dual antiplatelet therapy for a year, after which they should continue taking a single medication for a long time or for the rest of their lives, usually aspirin[49]. Some people stop using DAPT altogether or take it for a brief time (1–3 months) before switching to longer-term aspirin therapy[51].

DAPT score[54]		PRECISE-DAPT score [53]		PARIS score[52]	
Age		Hemoglobin, g/dL		Bleeding risk	
≥75 Y	–2	≥12.0	0	Age, years	
65 to <75 Y	–1	11.5	4	<50	0
<65 Y	0	11.0	7	50-59	1
Cigarette smoking	1	10.5	11	60-69	2
Diabetes mellitus	1	≤10.0	15	70-79	3
MI at presentation	1	White blood cell count, cells/μL		≥80	4
Prior PCI or MI	1	$\leq 5 \times 10^3$	0	BMI, kg/m^2	
Paclitaxel-eluting stent	1	8×10^3	3	<25	2
Stent diameter <3 mm	1	10×10^3	5	25-34.9	0
CHF or LVEF <30%	2	12×10^3	7	≥35	2
Vein graft stent	2	14×10^3	9	Current smoking	2
Total	–2 to 10	16×10^3	11	Anemia present	3
		18×10^3	13	CrCl <60 mL/Min	2
		$\geq 20 \times 10^3$	15	Triple therapy at discharge	2
		Age*, years		Total	
		≤50	0	Low risk	0-3
		60	5	Intermediate risk	4-7
		70	9	High risk	≥8
		80	14	Ischemic risk	
		≥90	19	Diabetes present	
		Renal function*, mL/Min		NIDDM	1
		CrCl ≥100	0	IDDM	3
		CrCl 80	5	ACS	
		CrCl 60	10	Troponin negative	1
		CrCl 40	15	Troponin positive	2
		CrCl 20	20	Current smoking	1
		CrCl 0	25	CrCl <60 mL/Min	2
		Previous bleed	26	Prior PCI	2
		Total		Prior CABG	2
		Very low risk	0-11	Total	
		Low risk	12-18	Low risk	0-2
		Moderate risk	19-25	Intermediate risk	3-4
		High risk	≥26	High risk	≥5

V. RISKS AND CHALLENGES OF DAPT

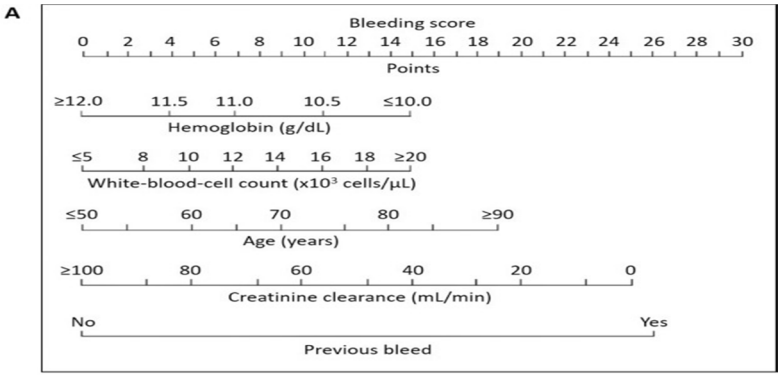
The most recent versions of the Canadian (2018) and European (2017, 2020) guidelines advise doctors to use one of the DAPT, PRECISE-DAPT, and PARIS scores, which are specific tools for predicting post-discharge events in patients with AC[52-55]. These scores are also used to determine how long patients should receive DAPT.[56-59]To determine whether patients may benefit net from DAPT for more than 12 months, all three risk ratings evaluate bleeding risk (Table VI; Figure 1A to C).[52-54] The DAPT score is the only assessment tool that generates a single risk score for both bleeding and ischemic risk, with a high score (≥2) indicating a greater risk of ischemic events. In contrast, PRECISE-DAPT evaluates only the bleeding risk, and the PARIS score computes the ischemic risk independently from the bleeding risk,45.

Furthermore, because it was based on data from the DAPT study, which randomized participants at 12 months after PCI to either continue DAPT or stop the P2Y12 inhibitor and receive aspirin monotherapy for an additional 18 months, the DAPT score might be the most pertinent factor in deciding which patients should continue DAPT after 12 months.[54]

Given that the majority of elderly patients (those aged and above) will have a PRECISE-DAPT score of ≥25 (high risk), PRECISE-DAPT may not be able to distinguish between bleeding risk in these patients.[58] Furthermore, there are worries that the PRECISE-DAPT score would not be appropriate for evaluating patients at subsequent times because it is based on the evaluation of patients at the time of DAPT beginning. An examination of the SMART-DATE trial's data, however, showed that the tool's ability to predict bleeding (and ischemic) occurrences at 18 months following the index procedure was only moderately successful.[59]

Acute coronary syndrome (ACS); coronary artery bypass grafting (CABG); congestive heart failure (CHF); creatinine clearance (CrCl); dual antiplatelet therapy (DAPT); insulin-dependent diabetes mellitus (IDDM); left ventricular ejection fraction (LVEF); myocardial infarction (MI); non-insulin-dependent diabetes mellitus (NIDDM); and percutaneous coronary intervention (PCI).

Intermediate scores can be given for values between these categories.



B

Integer Risk Score for Major Bleeding	
Parameter	**Score**
Age, years	
<50	0
50–59	+1
60–69	+2
70–79	+3
≥80	+4
BMI, kg/m²	
<25	+2
25–34.9	0
≥35	+2
Current smoking	
Yes	+2
No	0
Anemia	
Present	+3
Absent	0
CrCl <60 mL/min	
Present	+2
Absent	0
Triple therapy on discharge	
Yes	+2
No	0

C

Integer Risk Score for Coronary Thrombotic Events	
Parameter	**Score**
Diabetes mellitus	
None	0
Non-insulin-dependent	+1
Insulin-dependent	+3
Acute coronary syndrome	
No	0
Yes, Tn-negative	+1
Yes, Tn-negative	+2
Current smoking	
Yes	+1
No	0
CrCl <60 mL/min	
Present	+2
Absent	0
Prior PCI	
Yes	+2
No	0
Prior CABG	
Yes	+2
No	0

Figure 1.

Figure 2. Tools for predicting bleeding and thrombotic risk assessment. A PRECISE-DAPT score nomogram for coronary stenting patients to predict out-of-hospital bleeding. High bleeding risk is indicated by a score of ≥25, while non-high bleeding risk is indicated by a score of <25. 73 Reprinted from Costa F, James S, van Klaveren D, et al. with permission. A pooled analysis of individual-patient datasets from clinical trials was used to develop and validate the PRECISE-DAPT score, which predicts bleeding problems in patients undergoing stent implantation and subsequent dual antiplatelet medication.

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Reprinted with permission from Baber U, Mehran R, Giustino G, et al Coronary thrombosis and major bleeding after PCI with drug-eluting stents: Risk scores from PARIS. *J Am Coll* Cardiol 2016;67:2224-2234. doi: 10.1016/j.jacc.2016.02.064 ©Elsevier.
The ability of the PARIS and DAPT scores to identify individuals at high risk of ischemia or bleeding episodes from 12 months after ACS onward has been evaluated, with varying degrees of success.[60-64]. The DAPT score is a useful measure for detecting individuals who are at risk of significant bleeding or ischemic episodes, according to certain research.[60-63] According to a post hoc analysis of the DAPT study, patients who stopped taking P2Y12 inhibitor therapy at 12 months had a higher incidence of MI over the next 12 to 15 months than those who continued, regardless of whether their DAPT score was less than 2 or greater than 2. However, the effect was more pronounced in patients with a higher risk score (≥2).

VI. COMPARISON OF DIFFERENT DAPT REGIMENS.

A. Minor Stroke: Recurrent Stroke

In X of Y simulations, aspirin plus ticagrelor were consistently rated as the best treatment (94%; SUCRA, 0.94; Table 1). At 90 days, the protection of recurrent ischemic stroke was better with aspirin and ticagrelor (hazard ratio [HR], 0.70; 95% credibility interval [CrI], 0.61-0.81) and aspirin and clopidogrel (HR, 0.79; 95% CrI, 0.69-0.91) than with aspirin alone. The two combination therapies did not differ statistically significantly (HR, 1.13; 95% CrI, 0.97-1.31).

Table 1. Network Meta-Analysis Measures for Efficacy and Safety Up to 90 Days for Minor Stroke and for High-Risk TIA.

Outcome measure[a]	Minor stroke (NIHSS ≤5)				High-risk TIA ($ABCD^2$ >4)			
	Ischemic stroke	Hemorrhagic stroke	Mortality	Major hemorrhage	Ischemic stroke	Hemorrhagic stroke	Mortality	Major hemorrhage
SUCRA								
Aspirin and ticagrelor	0.94	0.15	0.75	0.00	0.60	0.08	0.03	0.00
Aspirin and clopidogrel	0.06	0.37	0.05	0.01	0.40	0.01	0.07	0.05
Aspirin alone	0.00	0.48	0.20	0.98	0.00	0.91	0.90	0.95
HR (95% CrI)								
Aspirin and ticagrelor vs aspirin alone	0.70 (0.61-0.81)	1.36 (0.54-3.53)	0.79 (0.45-1.41)	2.21 (1.20-4.19)	0.65 (0.43-0.98)	9.37 (0.44-848.72)	1.95 (0.98-3.99)	150.17 (4.66-214 774.80)
Aspirin and clopidogrel vs aspirin alone	0.79 (0.69-0.91)	1.06 (0.47-2.41)	1.18 (0.68-2.05)	2.04 (1.10-3.91)	0.68 (0.53-0.88)	7.37 (1.23-111.59)	2.06 (0.77-6.18)	2.20 (0.87-6.20)
Aspirin and ticagrelor vs aspirin and clopidogrel	0.89 (0.76-1.03)	1.28 (0.54-3.12)	0.68 (0.38-1.19)	1.08 (0.57-2.0				

Abbreviations: HR, hazard ratio; CrI, credibility interval; ABCD2, age, blood pressure, clinical characteristics, duration of transient ischemic attack, and diabetes; SUCRA, or surface under the cumulative rank curve; NIHSS, or National Institutes of Health Stroke Scale; transient ischemia attack, or TIA. Acetylsalicylic acid is what they call aspirin.[70-73]

B. Minor Stroke: Hemorrhagic Stroke

Aspirin and ticagrelor (HR, 1.36; 95% CrI, 0.54-3.53) and aspirin and clopidogrel (HR, 1.06; 95% CrI, 0.47-2.41) did not significantly enhance the risk of hemorrhagic stroke. The lowest risk of hemorrhagic stroke was linked to aspirin alone (SUCRA, 0.48), aspirin and clopidogrel (SUCRA, 0.37), and aspirin and ticagrelor (SUCRA, 0.15), according to SUCRA values (Table 1).

C. Stroke: Mortality

Aspirin plus ticagrelor (HR, 0.79; 95% CrI, 0.45-1.41) and aspirin and clopidogrel (HR, 1.18, 95% CrI, 0.68-2.05) did not significantly increase mortality when compared to aspirin alone. The lowest risk of death was linked to aspirin and ticagrelor (SUCRA, 0.75), aspirin alone (SUCRA, 0.20), and aspirin plus clopidogrel (SUCRA, 0.05) (Table 1).

D. Minor Stroke: Major Hemorrhage

Major hemorrhage rates were higher with aspirin and ticagrelor (HR, 2.20; 95% CrI, 1.21-4.19) and aspirin and clopidogrel (HR, 2.03; 95% CrI, 1.10-3.88) than with aspirin alone. The lowest risk of bleeding was linked to aspirin alone (SUCRA, 0.98), aspirin and ticagrelor (SUCRA, 0.00), and aspirin and clopidogrel (SUCRA, 0.01) (Table 1).

E. High-Risk TIA

Only high-risk TIAs—that is, those patients who were not included in the primary study—were subjected to secondary analysis. Both regimens were deemed unfavorable; according to Table 2, aspirin and ticagrelor had a 60% chance of being the best course of action (SUCRA, 0.60) while aspirin and clopidogrel had a 40% chance (SUCRA, 0.40). 3-96 777.94) raised the chance of a significant hemorrhage.[68-69]

Both ASA plus ticagrelor (HR, 0.65; 95% CrI, 0.43-0.98) and aspirin and clopidogrel (HR, 0.68; 95% CrI, 0.53-0.88) were superior to aspirin alone in the prevention of recurrent ischemic stroke at 90 days. The two combinations did not vary in any way that was statistically significant. Aspirin and clopidogrel appeared to increase risk of hemorrhagic stroke (HR, 7.37; 95% CrI, 1.23-111.59), and both aspirin and ticagrelor (HR, 150.17; 95% CrI, 4.66-214 774.80) and aspiring and clopidogrel (HR, 66.52; 95% CrI, 2.13-96 777.94) increased the risk of severe hemorrhage.

F. Combined Minor Stroke and High-Risk TIA

Using the trials that were part of our investigation, an analysis was also done on mild stroke and TIA combined. 4, 5, 6, 10, and 11 There was no clinically meaningful change in our small stroke group of 22,203 individuals when the additional 5945 TIA patients were added. Both aspirin and ticagrelor (HR, 0.70; 95% CrI, 0.61-0.79) and aspirin and clopidogrel (HR, 0.77; 95% CrI, 0.68-0.87) were better than aspirin alone for the primary outcome, and aspirin and ticagrelor was still the preferable regimen (SUCRA 0.92) as compared to aspirin and clopidogrel (SUCRA 0.08). When compared to aspirin alone, severe hemorrhage was linked to both aspirin and ticagrelor (HR, 2.89; 95% CrI, 1.62-5.42) and aspirin and clopidogrel (HR, 2.38, 95% CrI, 1.37-4.26) (eTable 1 in Supplement 1).

The same studies included in a previously published meta-analysis were used in a second study on mild stroke and TIA combined.[65]This differed from our study in that the 2021 Wang et al.[66] trial (i.e., CHANCE-2) was not included, and the Fast Assessment Of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial by Kennedy et al.[67] was added. Aspirin plus ticagrelor (HR, 0.76; 95% CrI, 0.65-0.89; SUCRA, 0.26) and aspirin and clopidogrel (HR, 0.71; 95% CrI, 0.62-0.82; SUCRA, 0.74) both outperformed aspirin alone for the primary outcome using this combination of trials.

When compared to aspirin alone, there was an increased risk of significant bleeding for both aspirin and ticagrelor (HR, 3.62; 95% CrI, 1.84-7.67) and aspirin and clopidogrel (HR, 2.13; 95% CrI, 1.26-3.72) (eTable 1 in Supplement 1).[74-76]

VII. EMERGING THERAPIES DAPT

Historically, ASA has been the most commonly prescribed antiplatelet therapy as monotherapy or combination therapy for decades[6]. However, the development of other oral antiplatelet medications, such as indobufen, clopidogrel, prasugrel, ticagrelor, dipyridamole, cilostazol, and vorapaxar, has broadened the treatment options for patients with cardiovascular diseases (Figure 2, Table 1).

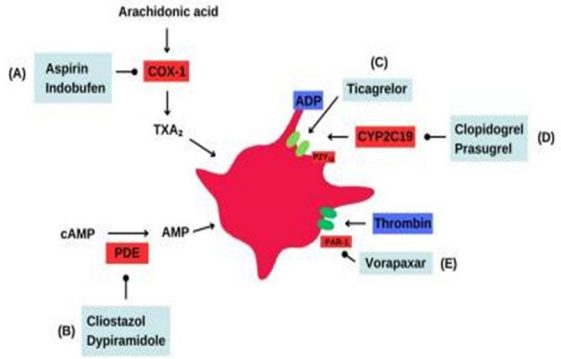


Figure 2.

antiplatelet medication. mechanisms of action. (A) By permanently blocking the cyclooxygenase-1 (COX-1) enzyme, aspirin lowers the production of thromboxane A2 and successfully prevents platelet aggregation. Although it is a reversible inhibitor, indobufen also inhibits COX-1. (B) By blocking phosphodiesterase type 3 (PDE3), clostazol causes platelets and vascular smooth muscle cells to produce higher amounts of intracellular cyclic adenosine 3′,5′-monophosphate (cAMP). As a result, peripheral arterial vasodilation and platelet aggregation are inhibited.[78-80]

Conversely, dipyridamole functions as a phosphodiesterase inhibitor, raising cAMP levels and causing vasodilatory and antiplatelet effects; it also prevents platelets and other tissues from absorbing adenosine, which raises the concentration of extracellular adenosine. (C) Ticagrelor acts as a reversible inhibitor directly on the P2Y12 receptor, preventing both receptor-mediated activation and platelet aggregation.

(D) Clopidogrel inhibits platelet aggregation and P2Y12-mediated activation by blocking the P2Y12 receptor on the platelet surface. Prasugrel efficiently prevents platelet aggregation and lowers the risk of blood clots by specifically inhibiting the P2Y12 receptor on platelets. (E) Vorapaxar reduces platelet responsiveness to thrombin and, as a result, blood clot formation by acting as an inhibitor of the protease-activated receptor-1 (PAR-1).

Table 1.
Pharmacological profile of common antiplatelet medications.

Medication	Properties	Dose	Adverse Effects	Contraindications
Inhibitor of the enzyme cyclooxygenase-1 (COX-1)				
Aspirin	Antiplatelet, analgesic, antipyretic	75–325 mg/day	Bleeding, gastrointestinal ulcers, tinnitus, Reye's syndrome	Hypersensitivity, active bleeding, history of bleeding disorders, recent surgery
Indobufen	Antiplatelet	200–300 mg/day	Bleeding, gastrointestinal ulcers, dyspepsia	Hypersensitivity, active bleeding, history of bleeding disorders
$P2Y_{12}$ receptor inhibitors				
Clopidogrel	Antiplatelet	75 mg/day	Bleeding, gastrointestinal ulcers, thrombotic thrombocytopenic purpura	Hypersensitivity, active bleeding, history of bleeding disorders
Prasugrel	Antiplatelet	10 mg/day	Bleeding, gastrointestinal ulcers	Hypersensitivity, active bleeding, history of bleeding disorders, previous stroke or transient ischemic attack
Ticagrelor	Antiplatelet	90 mg/twice daily	Bleeding, gastrointestinal ulcers, dyspnea	Hypersensitivity, active bleeding, history of bleeding disorders
Phosphodiesterase inhibitors				
Dipyridamole	Antiplatelet, vasodilator	200–400 mg/day	Headache, gastrointestinal upset, hypotension	Hypersensitivity, active bleeding, history of bleeding disorders
Cilostazol	Antiplatelet, vasodilator	100 mg/twice daily	Headache, gastrointestinal upset, hypotension	Heart failure, bleeding disorders, recent myocardial infarction
Protease-activated receptor-1 antagonists				
Vorapaxar	Antiplatelet	2.08 mg/day	Bleeding, gastrointestinal ulcers, intracranial hemorrhage	History of stroke, transient ischemic attack, bleeding disorders

1) Aspirin

2.1. Patients with a history of myocardial infarction (MI), stroke, or PAD have been shown to benefit from aspirin ASA in a number of ways, including a reduction in the cardiovascular event rate [69]. ASA works by permanently blocking the cyclooxygenase (COX) 1 and 2 enzymes, which are involved in the synthesis of thromboxane A2, a powerful platelet aggregator[70-72].

2) Indobufen

Indobufen is a reversible inhibitor of COX that has comparable effects to aspirin[72] and has been used as an antiplatelet medication in Europe to effectively lower the risk of recurrent strokes[73]. In patients with coronary stents, the OPTION study, a non-inferiority trial, contrasted traditional DAPT with indobufen-based DAPT. The purpose of this research was to ascertain whether the therapy groups' composite of stroke, stent thrombosis, nonfatal myocardial infarction, cardiovascular death, or bleeding events within a year differed significantly. The major endpoint event in the indobufen-based DAPT was 4.47%, while in the conventional DAPT group it was 6.11%[74]. Additionally, the DAPT group based on indobufen experienced a decreased incidence of bleeding. Although it is not yet authorized for usage in the US, indobufen is already approved in China and Europe to treat atherosclerotic cardiovascular disease.

3) P2Y12 Receptor Inhibitors

Platelet P2Y12 receptor inhibitors, such as ticagrelor, prasugrel, and clopidogrel, differ in their potency and rate of action; ticagrelor and prasugrel exhibit more consistent platelet inhibition, higher potency, and a quicker commencement of action than clopidogrel.

4) Clopidogrel

Clopidogrel, a prodrug with variable activation based on genetic loss-of-function alleles, is frequently used in conjunction with aspirin in patients following elective percutaneous coronary intervention (PCI)[75]. It effectively lowers the risk of cardiovascular events and recurrent stroke when compared to aspirin, albeit at an increased risk of bleeding.[76-78]

5) Prasugrel

Another prodrug that needs to be activated before it can bind to the platelet P2Y12 receptor and prevent platelet aggregation is prazosugrel. Prasugrel is more potent, acts more quickly, and activates metabolites more effectively than clopidogrel. Although prasugrel has a higher risk of serious bleeding than clopidogrel, it has considerably decreased cardiovascular events, including stent thrombosis. However, prasugrel and clopidogrel do not significantly vary in terms of overall mortality.

6) Ticagrelor

A non-prodrug called ticagrelor inhibits platelets without requiring metabolic activation by binding reversibly to the adenosine diphosphate (ADP) P2Y12 receptor [80]. It must be taken twice a day and has a shorter half-life. Ticagrelor inhibits platelets more quickly than clopidogrel[78]. Both during acute MI and during long-term treatment, ticagrelor guards against ischemia-reperfusion damage (IRI). Additionally, it improves stem cell recruitment, inhibits detrimental cardiac remodeling and atherosclerosis, and lowers damaging inflammation. The capacity of ticagrelor to raise adenosine levels and activate protective molecules in the damaged area of the heart is thought to be responsible for these beneficial effects [81-85].

Compared to clopidogrel, ticagrelor-treated ACS patients experienced fewer MIs, strokes, and cardiovascular mortality during a 12-month period, according to the PLATO research. Compared to clopidogrel, ticagrelor caused greater ventricular pauses and dyspnea but had a comparable risk of bleeding[82]. The ATLANTIC research found that, in contrast to in-hospital ticagrelor administration, the use of ticagrelor prior to hospital arrival did not improve coronary reperfusion prior to PCI in patients with ACS. In contrast, ticagrelor was safe both before and during hospitalization. Current data indicates that ticagrelor is a useful alternative for preventing thrombotic cardiovascular events in ACS patients, regardless of whether they get invasive or noninvasive therapy, even if further research is required to compare it with other antiplatelet medications.[84-86]

7) Prasugrel vs. Ticagrelor

The ISAR-REACT 5 research, a multicenter, randomized, open-label trial, revealed an unexpected finding. According to this investigation, in individuals with ACS, prasugrel was associated with a reduced incidence of cardiovascular mortality, MI, or stroke than ticagrelor[84]. Furthermore, ticagrelor was associated with a significantly higher risk of recurrent MI than prasugrel, according to the study [85].

In ACS patients after PCI, prasugrel was found to have a lower risk of bleeding than ticagrelor [86]. However, in terms of safety and effectiveness, the SWEDEHEART registry found no statistically significant differences between ticagrelor and prasugrel in ACS patients after PCI [87].

8) Dipyridamole

Dipyridamole decreases platelet aggregation and raises cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP) levels via blocking platelet phosphodiesterase. Higher interstitial adenosine levels result from its inhibition of adenosine reuptake. Activation of adenosine receptors raises cAMP levels[88]. Vasodilation is another side effect of dipyridamole[89-90]. When compared to ASA alone, ASA plus dipyridamole significantly decreased the risk of stroke (RR 0.77, 95% CI 0.67–0.89), according to a meta-analysis . According to a different meta-analysis, ASA by alone or in combination with dipyridamole decreased the risk of nonfatal stroke (RR 0.66; 95% CI 0.47–0.94) but had no discernible impact on the incidence of a composite outcome of nonfatal stroke, nonfatal MI, and cardiovascular mortality.

9) Cilostazol

Cilostazol, a 2-oxy quinolone byproduct, raises cAMP levels by interfering with phosphodiesterase III activity [92]. Cilostazol prolongs exercise duration and avoids cerebral infarction in claudication patients.[93-97]

10) Vorapaxar

A drug called vorapaxar blocks platelet activation brought on by thrombin by acting as an antagonist for protease-activated receptor-1 (PAR-1). According to clinical research, Vorapaxar, either by itself or in conjunction with conventional antiplatelet therapy, may reduce the risk of cardiovascular events in those who have previously experienced PAD or MI. It's crucial to remember that Vorapaxar carries a significant risk of bleeding, particularly in people who have already experienced a transient ischemic attack or stroke [97-99]. Despite being approved by the Food and Drug Administration, vorapaxar is not widely used in clinical practice[99-100]. The TRACER trial, however, shows that adding vorapaxar to the standard therapy in ACS patients did not reduce the primary combined end-point of death from stroke, MI, or cardiovascular etiologies[100].

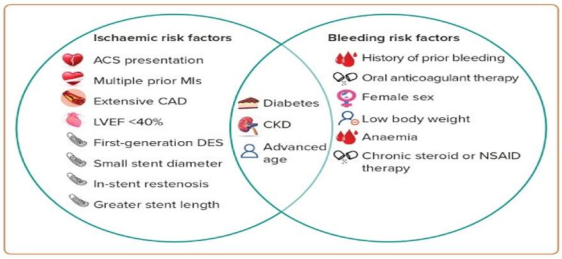
VIII. CURRENT GUIDELINES

AHA/ACC 2016 Focused Update on Coronary Artery Disease Patients' DAPT Duration

The ACC/AHA released a targeted update to the previous PCI, CABG, and ACS management guidelines in March 2016. The update explicitly addressed itervalevidenceregarding the best length of DAPT for different patient categories. The new advice to consider shorter-duration DAPT for patients with higher bleeding risk but lower ischemic risk was at the heart of this update. [101] Additionally, the targeted update was the first time official American recommendations cited research analyzing the effectiveness of second-generation DES, which have essentially replaced first-generation DES in contemporary practice due to their intrinsically lower risk of ST.[101-102]

Determining the ideal DAPT time requires evaluating a patient's ischemic and bleeding risk factors. Advanced age, ACS presentation, extensive CAD history, diabetes, and LVEF <40% are factors that may increase the risk of ISR or ischemic events; on the other hand, a history of bleeding events, current anticoagulation therapy, female sex, or chronic steroid/nonsteroidal anti-inflammatory drug therapy are factors that may increase the risk of bleeding. Figure 2 shows a comprehensive list of bleeding and ischemic risk variables that were modified from the 2016 ACC/AHA targeted update.

Factors Associated with Increased Risk of Stent Thrombosis/ischaemic Events or Increased Risk of Bleeding



ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug. Source: Levine et al. 2016.[23]

Figure 3.

A. ACC/AHA 2016 Focused Update on Duration of DAPT in Patients with Coronary Artery Disease

Longer than one year of DAPT may be recommended for some patients who have a low risk of bleeding events but a high risk of ischemic events. In order to stratify the benefit/risk ratio for patients according to the previously mentioned risk factors, the authors of the Dual Antiplatelet Therapy Study created a "DAPT score." events exceeded the absolute risk reduction in MI or ST by more than two times. To assess bleeding risk and direct DAPT duration in patients with ACS after PCI, the PRECISE-DAPT score is an iterative update that has been further validated by many trials.

Even for high-risk ACS patients, however, prolonged DAPT is still a class 2b recommendation according to ACC/AHA guidelines, and it requires a careful evaluation of the risks and benefits. Research indicates that extended DAPT for 18 to 36 months after MI may reduce the rate of ischemic complications by 1-3 percent, but it also increases the absolute rate of bleeding complications by about 1%.[105-108]

The suggested length of DAPT for patients receiving PCI with DES placement would mostly rely on the patient's presentation (stable CAD versus ACS) and bleeding risk. For stable CAD and ACS, respectively, the ACC/AHA continues to strongly urge class 1 treatment for at least 6 and 12 months of DAPT. However, class 2b recommends halving the DAPT length for each presentation to 3 and 6 months, respectively, in cases of significant bleeding risk (e.g., recent major surgery or being on anticoagulant treatment).[101] This stood in sharp contrast to the previous recommendations' 12-month minimum recommended for all PCI patients receiving first-generation DES treatment. Numerous large randomized controlled studies and meta-analyses that found no higher incidence of ST or ischemic events in shorter DAPT durations (3–6 months) compared to the prior 12-month norm helped to inform this trend towards more conservative therapy.[109]

B. ESC 2017 Focused Update on DAPT in Coronary Artery Disease

The ESC published a targeted update on DAPT length in August 2017 to take into account fresh data that had emerged in interval years, in accordance with the ACC/AHA.

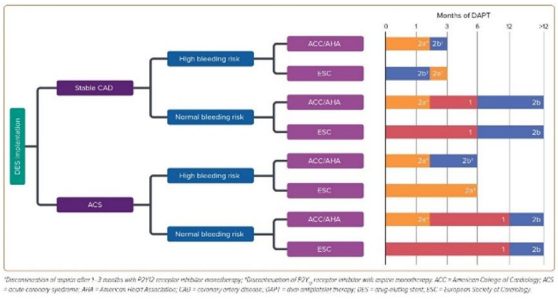


Figure 4.

The ESC framework stratifies recommendations according to bleeding risk and patient presentation (stable CAD versus ACS), just like the ACC/AHA guidelines do. Similar to the ACC/AHA, individuals with stable CAD and ACS who do not have a significant risk of bleeding are recommended to undergo 6- and 12-month DAPT, respectively, according to class 1. For patients with a history of MI, the ESC guidelines continue to propose a class 2b extended DAPT of more than 12 months.[110]

This was based on a meta-analysis that included patients who had experienced MI in the past from several big studies. The meta-analysis found that there was a significant decrease in cardiovascular death, MI, and stroke, as well as a significant rise in the risk of serious bleeding. Nonetheless, it was seen that the two groups' all-cause mortality was equal, and the absolute risk decrease in cardiovascular mortality was just 0.3%.

In contrast to the class 2b guidelines made by the ACC/AHA, there is a class 2a recommendation for a 3-month DAPT duration for patients with elevated bleeding risk, and a 6-month DAPT length for patients with ACS. Although the ESC update included the RESET and OPTIMIZE trials, which both found that a 3-month DAPT length did not significantly enhance MACE compared with a 12-month DAPT duration, a large portion of the evidence base was shared by the two societies standards.[112]

Interestingly, the ESC guidelines deviated from the norm by incorporating a class 2b consideration for a 1-month DAPT duration in patients with stable CAD who had an unacceptable risk of bleeding (Figure 3). 42 Two studies that looked at 1-month DAPT and found lower risks of re-intervention, MI, and ST after implantation of the Endeavor Sprint stent (Medtronic) or BioFreedom drug-coated stent (Biosensors) when compared to similar duration therapy for BMS implantation served as the basis for this recommendation. The external validity of these studies was questioned, nevertheless, because they only included zotarolimus-eluting stents and did not evaluate results for 1-month versus longer DAPT duration among second-generation [110-111]

C. ACC/AHA/SCAI 2021 Guideline for Coronary Artery Revascularisation

The 2016 focused update to DAPT duration was applied to the 2013 ST-elevation MI (STEMI) and 2014 non-STEMI-ACS guidelines, as well as the 2011 PCI and CABG guidelines, which were all partially or completely replaced by the updated coronary artery revascularization guideline published by the ACC/AHA/SCAI in late 2021.[114-116]

Additional interval trials supporting short-term 1- to 3-month DAPT were included in this update, along with a revised class IIa recommendation to stop DAPT 1-3 months after stent installation and then start P2Y12 receptor inhibitor monotherapy (Figure 3). Interestingly, despite the fact that patients with STEMI were rarely included in the trials included in the 2021 guidelines, the same class IIa recommendation was given to PCI in both stable CAD and for ACS. The authors observed a persistent lack of research comparing the results of short-term DAPT followed by P2Y12 receptor inhibitor monotherapy to aspirin alone, and thus upheld the previous IIb recommendation for three months of DAPT followed by aspirin monotherapy in patients at high bleeding risk.

D. Overall Evidence and Recommendations

The overall recommendations for the duration of DAPT after DES implantation in different demographics will be outlined in this section and summarized from the most recent ACC/AHA/SCAI and ESC guidelines. Figure 3 illustrates these recommendations. Each suggestion in the guidelines is accompanied by primary supporting evidence. Aspirin monotherapy is advised indefinitely after DAPT for one year in ACS and six months in stable CAD in patients without an elevated risk of bleeding. Patients at high risk of recurrent adverse cardiovascular events (such as those with a history of prior MI) may be eligible to continue DAPT for more than a year if they finish the approved DAPT treatment without experiencing significant bleeding episodes. Two groundbreaking trials from the early 2010s provided evidence for a shortened DAPT duration of six months for patients undergoing PCI for stable CAD.[118-121]

Following PCI with DES implantation for stable CAD, 1,443 patients were randomly assigned to either a 6-month or 1-year DAPT (aspirin + clopidogrel) treatment arm in the EXCELLENT study. In the abbreviated DAPT group, the composite of cardiac mortality, MI, or ischaemia-driven target vessel revascularization at 12 months was 4.8%, while in the conventional DAPT group, it was 4.3% (p=0.001 for noninferiority).[117]

In the PRODIGY trial, 2,013 patients were randomly assigned to groups that received DAPT (aspirin + clopidogrel) for 6 months as opposed to 24 months. The primary composite outcome included all-cause death, MI, stroke, or cerebrovascular accident. Short DAPT was linked to a decreased risk of major Bleeding Academic Research Consortium (BARC) bleeding events (1.9 versus 3.4%; HR 0.56; 95% CI [0.32–0.98]; p=0.037), but there was no significant difference in the incidence of the primary composite outcome at 24-month follow-up (10.1 versus 10.0%, p=0.91).

Notably, subjects exhibited heterogeneity in clinical presentation, with approximately 75% of patients presenting with ACS while 25% had stable CAD. Analysis of net adverse clinical events (NACE) demonstrated increased incidence with extended DAPT in stable CAD (13.3 versus 5.6%; HR 2.5; 95% CI [1.35–4.69]; p=0.004) but not in ACS patients (16.1 versus 14.1%; HR 1.15; 95% CI [0.88–1.50]; p=0.29).[118]

Since 2014, the superiority of reduced DAPT has been further supported by a number of other studies. The greatest of these was ISAR-SAFE, a double-blind, randomized research that included 4,005 patients, 60% of whom had stable CAD and 40% with ACS. In both ACS and stable CAD patients, the incidence of the primary composite outcome of mortality, MI, ST, stroke, and severe hemorrhage did not differ between 6-month and 12-month DAPT (aspirin + clopidogrel) (1.5 versus 1.6%; p<0.001 for noninferiority). [119] When comparing the results of the ITALIC and SECURITY trials with those of the 12-month or 24-month DAPT, the results were comparable.[120-121]

Aspirin monotherapy should be administered after three months of DAPT for individuals with stable CAD who have an elevated risk of bleeding. However, starting at one month, those with an intolerably high risk of bleeding might be given consideration for switching to aspirin monotherapy. After six months of DAPT, aspirin monotherapy should be administered to high-bleeding-risk patients who present with ACS. As an alternative, individuals with either presentation and significant bleeding risk may be evaluated for DAPT for one to three months, followed by indefinite P2Y12 receptor inhibitor monotherapy.

The RESET and OPTIMIZE trials were the first to offer compelling evidence in favor of a shortened 3-month DAPT duration. In the 3- and 12-month DAPT (aspirin + clopidogrel) trials, RESET randomly assigned 2,117 participants. The key composite endpoints of all-cause mortality, MI, and ST did not differ (0.8 versus 1.3%; p=0.48).[122]

28% of the included individuals had ACS upon presentation. Patients randomly assigned to the short DAPT group had a trend toward a higher incidence of the primary composite endpoint, according to a subgroup analysis of ACS-presenting patients, however this trend fell short of statistical significance (p=0.158).

Similar results were obtained by OPTIMIZE, which randomly assigned 3,119 patients to 3- and 12-month DAPT with aspirin + clopidogrel. The primary endpoint of NACE occurred in 6.0% of the short DAPT group and 5.8% of the long DAPT group (p=0.002 for noninferiority). [123] Interestingly, patients with high-risk MI and ACS were not included in the analysis.

In recent years, additional data has surfaced supporting the safety and effectiveness of a 3-month DAPT duration followed by P2Y12 receptor inhibitor monotherapy. In the TICO study and Mehran et al.[, 3-month and 12-month DAPT with aspirin and ticagrelor, followed by ticagrelor monotherapy, were compared.[112]

While the TICO trial found that brief DAPT reduced the incidence of NACE (3.9 versus 5.9%; HR 0.66; 95% CI [0.48–0.92]; p=0.01), Mehran et al. showed no significant difference in NACE (3.9 against 3.9%; HR 0.99; 95% CI [0.78–1.25]; p<0.001 for noninferiority). In the brief DAPT group, both demonstrated a significant decrease in major BARC bleeding (TICO, 1.7 versus 3.0%; HR 0.66; 95% CI [0.48–0.92]; p=0.01 and Mehran et al., 4.0 versus 7.1%; HR 0.56; 95% CI [0.45–0.68]; p<0.001).

2,994 patients were randomly assigned to 3- and 12-month DAPT with aspirin and a P2Y12 receptor inhibitor, followed by aspirin discontinuation and P2Y12 receptor inhibitor monotherapy. The results of the SMART-CHOICE trial were similar, indicating a significant decrease in major bleeding events (2.0 versus 3.4%; HR 0.58; 95% CI [0.36–0.92]; p=0.02) and no significant difference in NACE (4.5 versus 5.6%; HR 0.81; 95% CI [0.58–1.12]; p=0.20).[125]

According to current ACC/AHA and ESC guidelines, patients with AF who are on anticoagulation should stop taking aspirin after a brief period of triple therapy with DAPT and a non-vitamin K antagonist oral anticoagulant (NOAC) [ACC/AHA recommends 1-4 weeks, while ESC recommends up to 1 week or up to 1 month with high ischemic risk].[126]

Additionally, the ESC permits patients who are considered to be at high bleeding risk to stop using the P2Y12 receptor inhibitor after 6 months of NOAC monotherapy. The AUGUSTUS trial, which randomly assigned AF patients who presented with ACS and underwent PCI with DES implantation to receive a P2Y12 receptor inhibitor together with either apixaban or warfarin, aspirin (triple treatment), or a placebo, is included in these guidelines.

According to the trial's findings, NOAC was linked to a considerably lower risk of severe bleeding episodes (10.5 versus 14.7%; HR 0.69; 95% CI [0.58–0.81]; p<0.001) and a lower incidence of hospitalization or death (23.5 versus 27.4%; HR 0.83; 95% CI [0.74–0.93]; p=0.002) when compared to warfarin. While there was no difference in the rates of hospitalization or death, triple therapy with aspirin as opposed to a placebo was linked to a higher incidence of bleeding (16.1 versus 9.0%; HR 1.89; 95% CI [1.59–2.24]; p<0.001). [127]

IX. CONCLUSION

DAPT remains a cornerstone in preventing thrombotic complications in patients with cardiovascular diseases, yet its use requires careful consideration of both ischemic and bleeding risks. While standard therapy durations have been established for conditions such as ACS, PCI, and stroke, recent studies suggest that individualized approaches, guided by patient-specific risk factors, may enhance treatment outcomes. The emergence of novel antiplatelet agents and evolving guideline recommendations highlight the need for continuous re-evaluation of DAPT strategies. Future research should focus on refining risk stratification models and exploring alternative therapies to optimize cardiovascular protection while minimizing adverse events. A patient-centered approach, integrating clinical judgment with the latest evidence, is essential for achieving the best outcomes in antiplatelet therapy.

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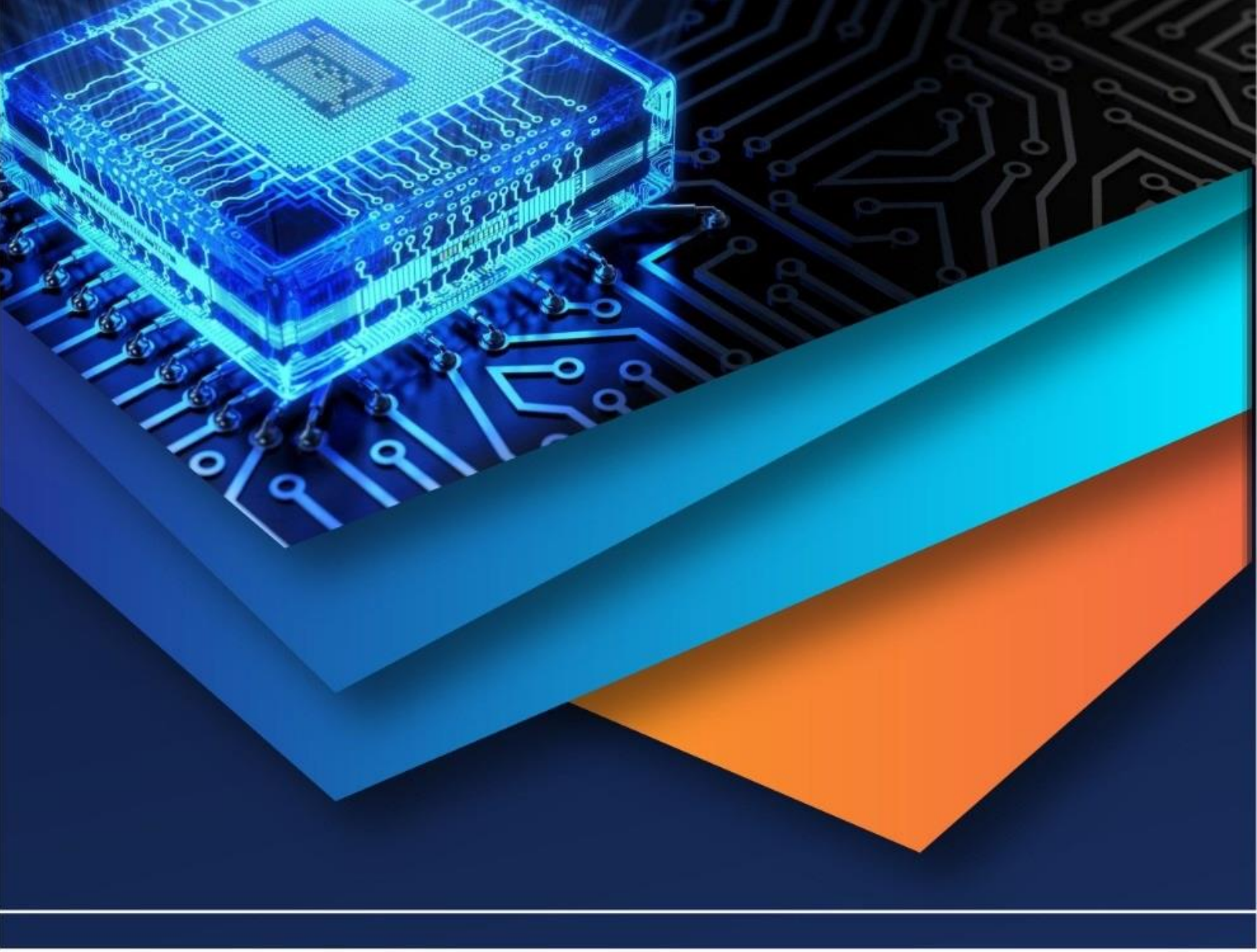
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