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ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

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The disclosure forms of all experts involved in the development of this focused update are available on the ESC website http://www.escardio.org/guidelines.

The Addenda and Clinical Cases companion document of this focused update are available at: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2017-focused-update-on-dual-antiplatelet-therapy-dapt

Web addenda

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Abbreviations and acronyms

ABC	Age, Biomarkers (GDF-15, cTnT-hs, and haemoglobin), and Clinical history (previous bleeding)
ACCA	Acute Cardiovascular Care Association
ACCOAST	A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention Or as Pretreatment At the Time of Diagnosis in Patients with Non-ST-Elevation Myocardial Infarction
ACS	Acute coronary syndrome
ADP	Adenosine 5'-diphosphate
AF	Atrial fibrillation
ANTARCTIC	Platelet Function Monitoring to Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome
ARCTIC-Interruption	Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and, of Treatment Interruption Versus Continuation 1 Year After Stenting-Interruption
ART	Arterial Revascularisation Trial
ASA	Acetylsalicylic acid
ATACAS	Aspirin and Tranexamic Acid for Coronary Artery Surgery
ATLANTIC	Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery
BARC	Bleeding Academic Research Consortium
b.i.d	*Bis in die* (twice a day)
BMS	Bare-metal stent
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
$CHADS_2$	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CHA_2DS_2-VASc	Cardiac failure, Hypertension, Age $\geq$ 75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CI	Confidence interval
COGENT	Clopidogrel and the Optimization of Gastrointestinal Events Trial
CORONARY	CABG Off or On Pump Revascularization Study
CPG	Committee for Practice Guidelines
CrCl	Creatinine clearance
CREDO	Clopidogrel for the Reduction of Events During Observation
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
EACTS	European Association for Cardio-Thoracic Surgery
EAPC	European Association of Preventive Cardiology
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ESC	European Society of Cardiology
EXAMINATION	Clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION
EXCELLENT	Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting
FDA	Food and Drug Administration
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs and alcohol
HR	Hazard ratio
I-LOVE-IT 2	Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization
INR	International normalized ratio
ISAR	Intracoronary Stenting and Antithrombotic Regimen
ISAR-SAFE	Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting
ISAR-TRIPLE	Intracoronary Stenting and Antithrombotic Regimen–Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting
ITALIC	Is There a Life for DES After Discontinuation of Clopidogrel
IVUS XPL	Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions
LATE	Late coronary Arterial Thrombotic Events
LEAD	Lower-extremities artery disease
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
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular events
MACE	Major adverse cardiovascular events

MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
MI	Myocardial infarction
NACE	Net adverse clinical events
NCDR	National Cardiovascular Data Registry
NNT	Number needed to treat
NOAC	Non-vitamin K oral anticoagulant
NORSTENT	NORwegian coronary STENT trial
NSTE-ACS	Non-ST elevation acute coronary syndrome
NSTEMI	Non-ST-segment elevation myocardial infarction
OAC	Oral anticoagulant
o.d.	*Omni die* (once a day)
OPTIMIZE	Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice
OR	Odds ratio
PARIS	Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients
PCI	Percutaneous coronary intervention
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
PIONEER AF-PCI	Rivaroxaban and a dose- adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes
PPI	Proton pump inhibitor
PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy
PRODIGY	PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hYperplasia study
PROTECT	Patient-Related Outcomes With Endeavor vs Cypher Stenting
q.d.	*Quaque die* (one a day)
RCT	Randomized controlled trial
REDUAL-PCI	Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AFib That Undergo a PCI With Stenting
RESET	Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation
ROOBY	Veterans Affairs Randomized On/Off Bypass trial
RR	Relative risk
RRR	Relative risk reduction
SECURITY	Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy
STEMI	ST-segment elevation myocardial infarction
STREAM	STrategic Reperfusion Early After Myocardial Infarction
SYNTAX	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
TIA	Transient ischaemic attack
TIMI	Thrombolysis In Myocardial Infarction
TL-PAS	Taxus Liberté Post Approval Study
TRA 2°P-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
TRILOGY ACS	Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
TROPICAL-ACS	Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial
VA	Veterans' Administration
VKA	Vitamin K antagonist
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing
ZES	Zotarolimus-eluting stent
ZEUS	Zotarolimus-eluting Endeavor sprint stent in Uncertain DES Candidates
24/7	24 h a day, seven days a week

1. Preamble

Guidelines and Focused Updates written under the auspices of the European Society of Cardiology's (ESC) Committee for Practice Guidelines (CPG) summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. The CPG Guidelines' and Focused Updates' recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines and focused updates have been issued in recent years by the ESC and by the European Association for Cardio-Thoracic Surgery (EACTS) as well as by other societies and organizations. Because of the impact on

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC and EACTS to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the EACTS. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines and of its Focused Updates. The Committee is also responsible for the endorsement process of these documents. These CPG documents undergo extensive review by the CPG and external experts, and in this case by EACTS-appointed experts. After appropriate revisions the CPG documents are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal and in the European Journal of Cardio-Thoracic Surgery. These CPG documents were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing this CPG Focused Update in collaboration with EACTS also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, and an electronic version for digital applications (smartphones, etc.) as well as other educational tools depending on the topic. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines and official focused updates, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC CPG Guidelines and Focused Updates developed in collaboration with EACTS fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the CPG documents do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

The estimated number of patients requiring dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and an oral inhibitor of the platelet $P2Y_{12}$ receptor for adenosine 5'-diphosphate (ADP), is considerable and has increased over time in Europe. Based on population estimates from 2015, in the region of 1 400 000 and 2 200 000 patients per year may have an indication for DAPT after coronary intervention or myocardial infarction (MI), respectively.[1]

This year, 2017, is the 21st anniversary of the publication of the first randomized clinical trial to establish the superiority of DAPT over anticoagulant therapy among patients undergoing percutaneous coronary intervention (PCI) (*Figure 1*).[2] Based on over 35 randomized clinical trials, including more than 225 000 patients, DAPT is among the most intensively investigated treatment options in the field of cardiovascular medicine. Along with progressive refinement of $P2Y_{12}$ inhibition strategies—embracing firstly safer (from ticlopidine to clopidogrel) and then more potent and predictable (from clopidogrel to ticagrelor or prasugrel) drugs—research has concomitantly focused on optimal treatment duration. The need to investigate longer DAPT regimens firstly arose from concerns over late and very

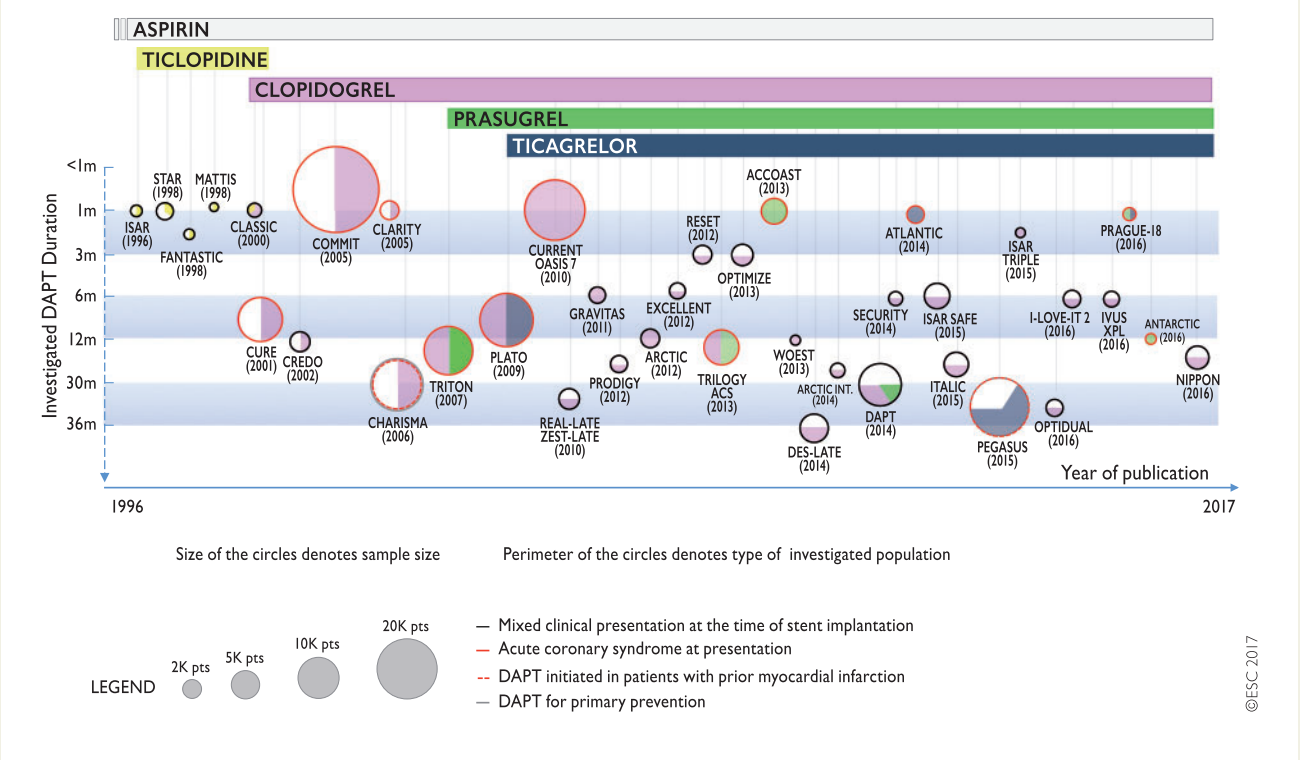


Figure 1 History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease. The size of the circles denotes sample size. The colours of perimeters identify the type of included patient populations within each study. The colours within each circle identify the antiplatelet agent(s) investigated. Head-to-head studies comparing similar durations of two different antiplatelet strategies are shown with a vertical line, whereas those investigating different treatment durations are shown with a horizontal line. Studies investigating different treatment strategies or regimens and not treatment durations or type (e.g. pre-treatment in ACCOAST, tailored therapy in GRAVITAS, double dose of clopidogrel in CURRENT OASIS 7, etc.) are represented with a single colour indicating the $P2Y_{12}$ inhibitor, which was tested on top of aspirin.
pts = patients.

late stent thrombosis occurring after first-generation drug-eluting stent (DES) implantation.[3] Yet, the advent of safer newer-generation DESs and the results of the most recent randomized controlled trials (RCTs) have established a major paradigm shift in the way DAPT should be conceived and used in clinical practice. DAPT remains a highly effective preventive treatment for stent thrombosis across the board; however, the risks of late and (even more) very late stent thrombosis have declined considerably since the advent of newer-generation DESs. Hence, the risk of bleeding associated with DAPT prolongation beyond 1 year does not seem to be justified by the small absolute benefit observed in terms of very late stent thrombosis prevention. On the other hand, there is emerging evidence that DAPT reduces the long-term risk of non-stent-related MI as well as stroke. Hence, after 21 years of research, DAPT has moved from a local (i.e. stent-related) to a systemic treatment strategy (i.e. capable of preventing thrombotic arterial vessel occlusion), conveying global patient protection (*Figure 1*).

There is, however, confusion in the community around the optimal type and duration of DAPT in patients with established coronary artery disease (CAD), undergoing coronary revascularization or not.[4] This derives from apparently conflicting results arising from the available studies and limited evidence on various patient subsets (e.g. elderly patients, with comorbidities or at greater bleeding risk) in whom the trade-off between the benefits and risks of DAPT may differ from those observed in more selected patient cohorts included in trials. Therefore, the scope of this focused update is to address recommendations on DAPT in patients with CAD.

2.1 Short- and long-term outcomes after percutaneous coronary intervention

See Web Addenda.

2.2 Risk of stent thrombosis in relation to stent type

See Web Addenda.

2.3 Short- and long-term outcomes after coronary artery bypass surgery

See Web Addenda.

2.4 Short- and long-term outcomes after medically managed acute coronary syndrome

See Web Addenda.

3. Efficacy and safety of dual antiplatelet therapy and risk stratification tools

Current evidence suggests that DAPT mitigates the risk of stent thrombosis across the whole spectrum, from acute to very late events. However, treatment with DAPT beyond 1 year after MI, or after PCI, exerts the majority of its benefit by reducing the rate of spontaneous MI, which is associated with mortality rates of 15%.[5] Nonetheless, because continued antiplatelet therapy is also associated with increased bleeding risk, it is necessary to weigh this risk against the potential benefit. Current evidence suggests that the risk of bleeding in patients on DAPT is proportionally related to its duration both within and beyond 1 year of treatment duration. Since the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on prior cardiovascular history [such as prior acute coronary syndrome (ACS)/MI vs. stable CAD], and prediction models to estimate on-DAPT bleeding risk have been developed, an individualized approach based on ischaemic vs. bleeding risk assessment is warranted.

3.1 Dual antiplatelet therapy for the prevention of stent thrombosis

See Web Addenda.

3.2 Dual antiplatelet therapy for the prevention of spontaneous myocardial infarction

See Web Addenda.

3.3 Dual antiplatelet therapy and mortality rate

See Web Addenda.

3.4 Safety of dual antiplatelet therapy

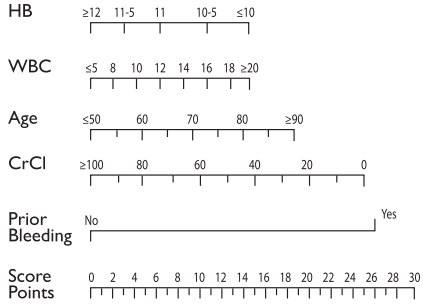
See Web Addenda.

3.5 Risk stratification tools for ischaemia and bleeding risks

Given the trade-off between ischaemic vs. bleeding risks for any given DAPT duration, the use of scores might prove useful to tailor DAPT duration in order to maximize ischaemic protection and minimize bleeding risks in the individual patient.[6] Most of the frequently used risk scores for assessing ischaemic events[7–9] and major bleeds[10–12] were originally developed and validated for the prediction of events occurring mainly during hospital stay or early on thereafter.[13,14] As a result, the application of these risk scores to decide upon DAPT duration remains problematic, as only limited data exist exploring their value to guide DAPT duration.[13] On the other hand, the use of risk scores that were specifically designed to guide and inform decision making on DAPT duration should be prioritized over other available risk scores (*Table 3*).

The DAPT score was developed from 11 648 patients enrolled in the DAPT trial and was initially validated in 8136 patients enrolled in the Patient-Related Outcomes With Endeavor vs. Cypher Stenting (PROTECT) trial.[15] This prediction rule identified nine factors [age, congestive heart failure/low left ventricular ejection fraction (LVEF), vein graft stenting, MI at presentation, prior MI or PCI, diabetes, stent diameter <3 mm, smoking, and paclitaxel-eluting stent] resulting in a score ranging from -2 to + 10. Within the DAPT trial, a high-risk score (i.e. a score ≥2) selected patients who showed a reduction in MI/stent thrombosis and cardiovascular or cerebrovascular events risk [number needed to treat (NNT) for benefit for ischaemic event reduction = 34] after a prolonged, 30-month DAPT, with only a modest increase in bleeding risk (NNT for harm = 272). In turn, a

Table 3 Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score[18]	DAPT score[15]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

CHF = congestive heart failure; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; Hb = haemoglobin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; WBC = white blood cell count.

[a]For the PRECISE-DAPT score use the score nomogram: mark patient's value for each of the five clinical variables of the score and draw a vertical line to the 'Point' axis to determine the number of points obtained for each clinical variable. Then summate the points obtained for each clinical variable to the total score. A practical case example for score calculation is provided in Web Figure 1 of the Web Addenda.

For the DAPT score summate positive points for each value and subtract values for age to the total score.

low-risk score (<2) selected patients recruited in the DAPT trial who did not derive any reduction of ischaemic events from prolonging DAPT, with a significant increase in moderate/major bleeding (NNT for harm = 64). As DAPT duration was not randomized in the PROTECT trial, the value of the DAPT score in guiding the duration of therapy has so far only been shown for patients recruited to the DAPT trial. Additional validation of the DAPT score to guide DAPT duration is needed, especially in the context of less well-selected patients as compared to those recruited in the DAPT trial and undergoing treatment with new-generation DES only.

Two independent predictive scores for bleeding [age, body mass index, smoking, anaemia, creatinine clearance (CrCl), and triple therapy at discharge] and MI or stent thrombosis [diabetes mellitus, ACS, smoking, CrCl, prior PCI, and prior coronary artery bypass graft surgery (CABG)] have also been developed from the Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients (PARIS) registry.[16] PARIS was a prospective, multicentre, observational study of patients undergoing PCI with stent implantation in the USA and Europe, which was designed to examine the different modes of DAPT cessation and to investigate the influence of these modes on subsequent clinical adverse events.[17] This registry study included patients with an indication for oral anticoagulation. The value of the PARIS bleeding and/or ischaemic risk scores to tailor DAPT duration remains unclear, since therapy duration was not randomized in the PARIS study and no study to date has applied the results of these scores for DAPT type or duration guidance. A high ischaemic risk status was observed in roughly 40% of high bleeding risk patients[16] and as many as 65.3% presented low ischaemic and bleeding risks.[16] Therefore, it remains unclear how DAPT duration should be guided by the simultaneous assessment of ischaemic and bleeding risk features according to PARIS.

The PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) collaborative study included a total of 14 963 patients with CAD who underwent elective, urgent, or emergent PCI and generated a five-item (age, CrCl, haemoglobin, white blood cell count, and prior spontaneous bleeding) prediction algorithm for out-of-hospital bleeding in patients treated with DAPT.[18]

The predictive performance of this novel score was assessed in the derivation cohort and validated in 8595 and 6172 patients treated with PCI from the PLATelet inhibition and patient Outcomes (PLATO) trial and the Bern PCI registry,[19,20] respectively. The PRECISE-DAPT score showed improved integrated discrimination and reclassification performance as compared to the PARIS bleeding score in both validation cohorts.[18] The usefulness of this score was also assessed within patients randomized to different DAPT durations (n = 10 081) to identify the effect on bleeding and ischaemia of a long (12–24 months) or short (3–6 months) treatment duration in relation to baseline bleeding risk. It was observed that among patients deemed at high bleeding risk based on PRECISE-DAPT (PRECISE-DAPT score ≥25), prolonged

DAPT was associated with no ischaemic benefit but a remarkable bleeding burden leading to an NNT for harm of 38.[18] On the other hand, longer treatment in patients without high bleeding risk (PRECISE-DAPT score <25) was associated with no increase in bleeding and a significant reduction in the composite ischaemic endpoint of MI, definite stent thrombosis, stroke, and target vessel revascularization, with an NNT for benefit of 65.[18] Selecting a shorter than 12-month treatment duration in patients deemed at high bleeding risk upfront may therefore prevent their exposure to an excessive bleeding hazard. In turn, patients at non-high bleeding risk might receive a standard (i.e. 12 months) or prolonged (i.e. >12 months) course of treatment if tolerated.

However, none of these risk prediction models have been prospectively tested in the setting of RCTs. Therefore, their value in improving patient outcomes remains unclear.

Use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.[15,18]	IIb	A

DAPT = dual antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]The DAPT and PRECISE-DAPT scores are those currently fulfilling these requirements.

3.6 Type of $P2Y_{12}$ inhibitor and timing of initiation

Clopidogrel: Clopidogrel is associated with a better safety profile than ticlopidine, mainly in terms of allergy, skin or gastrointestinal disorders, and neutropenia, while it has a similar degree and consistency of $P2Y_{12}$ inhibition and bleeding risk.[21,22] The wide variability in the pharmacodynamic response to ticlopidine and clopidogrel is linked to several factors, including genotype polymorphisms.[22] Clinical evidence with respect to the optimal duration of clopidogrel therapy after PCI is discussed elsewhere (Chapter 4).

Prasugrel: Prasugrel achieves a faster, greater, and more consistent degree of $P2Y_{12}$ inhibition as compared to clopidogrel. Prasugrel requires two metabolic steps for formation of its active metabolite, which is chemically similar to the active metabolite of clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) included $P2Y_{12}$ inhibitor-naïve ACS patients in whom coronary anatomy was deemed suitable for PCI, or patients with ST-segment elevation myocardial infarction (STEMI) referred for primary PCI.[23] Duration of DAPT was up to 15 months in both study arms. The composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) occurred in 9.3% of prasugrel-treated patients vs. 11.2% of clopidogrel-treated patients [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.73–0.93; P = 0.002], mostly driven by a significant risk reduction for MI [from 9.2% to 7.1%; relative risk reduction (RRR) 23.9%, 95% CI 12.7–33.7; P < 0.001).[23] There was no difference in the rates of either non-fatal stroke or cardiovascular death.

Prasugrel was associated with a significant increase in the rate of non-CABG-related TIMI major bleeding (2.4% vs. 1.8%; HR 1.32, 95% CI 1.03–1.68; P = 0.03). Life-threatening bleeding was significantly increased under prasugrel compared with clopidogrel (1.4% vs. 0.9%; HR 1.52, 95% CI 1.08–2.13; P = 0.01), as was fatal bleeding (0.4% vs. 0.1%, HR 4.19, 95% CI 1.58–11.11; P = 0.002). CABG-related bleeding was also higher in prasugrel-treated patients (13.4% vs. 3.2%; HR 4.72, 95% CI 1.90–11.82; P < 0.001). There was evidence of net harm with prasugrel in patients with a history of cerebrovascular events. In addition, there was no apparent net clinical benefit in patients ≥75 years of age and in patients with low body weight (<60 kg).[23] Prasugrel was not tested in medically managed ACS patients in the setting of the TRITON-TIMI 38 study. In the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study, which exclusively included medically managed ACS patients, the primary endpoint of death from cardiovascular causes, MI, or stroke among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (HR 0.91, 95% CI 0.79–1.05; P = 0.21), at a median follow-up of 17 months.[24] Similar results were observed in the overall population (i.e. also including elderly patients). Hence, prasugrel is not indicated in medically managed ACS patients.

The TRITON-TIMI 38 study mandated the use of prasugrel or clopidogrel after coronary angiography if an indication to proceed to PCI was established. Pre-treatment was allowed only in STEMI patients undergoing primary intervention (n = 2438).

For the comparison of prasugrel at the time of PCI, in the A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention Or as Pretreatment At the Time of Diagnosis in Patients with Non-ST-Elevation Myocardial Infarction (ACCOAST), 4033 patients with non-STEMI (NSTEMI) who were scheduled to undergo coronary angiography within 2–48 h after randomization were assigned to receive prasugrel (a 30 mg loading dose) before angiography (pre-treatment group) or placebo (control group).[25] When PCI was indicated, an additional 30 mg of prasugrel was given in the pre-treatment group at the time of PCI and 60 mg of prasugrel was given in the control group. The rate of the primary efficacy endpoint, a composite of death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7, did not differ significantly between the two groups (HR with pre-treatment 1.02, 95% CI 0.84–1.25; P = 0.81).[25] The rate of the key safety endpoint of all TIMI major bleeding episodes, whether related to CABG or not, through day 7 was increased with pre-treatment (HR 1.90, 95% CI 1.19–3.02; P = 0.006). The rates of TIMI major bleeding and life-threatening bleeding not related to CABG were increased by a factor of 3 and 6, respectively. Pre-treatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days.[25]

Hence, prasugrel is not indicated in patients with ACS in whom coronary anatomy is not known and an indication for PCI is not clearly established, with the exception of STEMI patients scheduled to undergo immediate coronary catheterization and PCI, if clinically indicated.

In the DAPT trial, 3461 patients (34.7% of the total trial population) who were treated with prasugrel within the first 12 months after

intervention were randomly allocated to stop or continue the treatment for an additional 18 months.[26] The type of $P2Y_{12}$ inhibitor or stent type were not randomized for. However, the largest cohort of prasugrel-treated patients (n = 2191) was provided by the TAXUS Liberté Post Approval Study (TL-PAS), which was a prospective, multicentre, open-label study developed to review the clinical performance of the Taxus Liberté paclitaxel-eluting stent in routine clinical practice in the USA.[27] Enrolled TL-PAS patients received open-label prasugrel plus aspirin for 12 months after stent placement; enrolment was not restricted to patients presenting with ACS (i.e. those with an approved indication for prasugrel). Rates of death and stroke were similar between groups, but MI was significantly reduced with prolonged prasugrel treatment (1.9% vs. 7.1%; HR 0.255; $P < 0.001$). The DAPT co-primary endpoint, stent thrombosis, was also lower with longer therapy (0.2% vs. 2.9%; HR 0.063; $P < 0.001$). The safety endpoint of GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) moderate or severe bleeding was numerically increased in the patients continuing prasugrel to 30 months, although the difference was not statistically significant (2.4% vs. 1.7%; HR 1.438; $P = 0.234$).[27] No subgroup data have been provided among patients treated with prasugrel with respect to indication for PCI (i.e. ACS vs. stable CAD) or type of implanted stent (i.e. paclitaxel-eluting stent vs. other stent types).

Ticagrelor: Ticagrelor belongs to a novel chemical class, cyclopentyl triazolopyrimidine, and is a direct oral, reversibly binding $P2Y_{12}$ inhibitor with a plasma half-life of ~12 h. In the PLATO trial, ticagrelor proved to be superior to clopidogrel in ACS patients, who were allowed to be pre-treated with clopidogrel at hospital admission, irrespective of the final revascularization strategy (i.e. planned or not planned invasive management).[20] Patients with either moderate- to high-risk non-ST elevation ACS (NSTE-ACS) (planned for either conservative or invasive management) or STEMI planned for primary PCI were randomized to either clopidogrel 75 mg daily, with a loading dose of 300 mg, or ticagrelor 180 mg loading dose followed by 90 mg twice daily.[20] Patients undergoing PCI were allowed to receive an additional blinded 300 mg loading dose of clopidogrel (total loading dose 600 mg) or its placebo, and were also recommended to receive an additional 90 mg of ticagrelor (or its placebo) if > 24 h after the initial loading dose. Treatment was continued for up to 12 months, with a minimum intended treatment duration of 6 months and a median duration of study drug exposure of 9 months.[20]

In the overall cohort, the primary composite efficacy endpoint (death from vascular causes, MI, or stroke) was observed in 9.8% of the patients in the ticagrelor group and in 11.7% of the patients in the clopidogrel group (HR 0.84, 95% CI 0.77–0.92; $P < 0.001$).[20] According to the pre-defined statistical analysis plan, death from vascular causes was significantly reduced from 5.1% to 4.0% (HR 0.79, 95% CI 0.69–0.91; $P = 0.001$), and from MI from 6.9% to 5.8% (HR 0.84, 95% CI 0.75–0.95; $P = 0.005$). There was no significant difference in the rates of stroke (1.3% vs. 1.5%; $P = 0.22$). The rate of definite stent thrombosis was reduced from 1.9% to 1.3% ($P < 0.01$) and total mortality from 5.9% to 4.5% ($P < 0.001$). Overall, there was no significant difference in PLATO-defined major bleeding rates between the clopidogrel and ticagrelor groups (11.2% vs. 11.6%, respectively; $P = 0.43$). Major bleeding unrelated to CABG was increased from 3.8% in the clopidogrel group to 4.5% in the ticagrelor group (HR 1.19, 95% CI 1.02–1.38; $P = 0.03$). Major bleeding related to CABG was similar with ticagrelor and clopidogrel (7.4% vs. 7.9%, respectively; $P = 0.32$). There was no difference in the overall rates of fatal haemorrhage between the groups (0.3% in both groups). The superiority of ticagrelor over clopidogrel with respect to the primary study endpoint as well as cardiovascular death or overall mortality was consistent across management strategies, i.e. patients undergoing PCI, those medically managed, and patients who underwent CABG.[20]

No dedicated study exists assessing the value of early (i.e. before coronary angiography) vs. delayed (i.e. after coronary angiography) ticagrelor administration in patients with NSTE-ACS. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study involved 1862 patients with STEMI <6-h duration and compared pre-hospital (in the ambulance) vs. in-hospital (in the catheterization laboratory) treatment with ticagrelor.[28] The co-primary endpoints were the proportion of patients who did not have ≥70% resolution of ST-segment elevation before PCI and the proportion of patients who did not have TIMI flow grade 3 in the infarct-related artery at initial angiography. Secondary endpoints included the rates of major adverse cardiovascular events (MACE) and definite stent thrombosis at 30 days. The median time difference between the two treatment strategies was 31 min. The two co-primary endpoints did not differ significantly between the pre-hospital and in-hospital groups. The rates of definite stent thrombosis were lower in the pre-hospital group than in the in-hospital group (0% vs. 0.8%, $P = 0.008$ in the first 24 h; 0.2% vs. 1.2%, $P = 0.02$ at 30 days). Rates of major bleeding events were low and virtually identical in the two groups, regardless of the bleeding definition used.[28]

The value of ticagrelor beyond 12 months of therapy in patients with prior ACS has been investigated in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction (PEGASUS) trial, which is described in Chapter 4.[29]

$P2Y_{12}$ inhibitors in STEMI patients treated with lysis: Clopidogrel is the only $P2Y_{12}$ inhibitor that has been properly investigated in patients with STEMI undergoing initial treatment with thrombolysis.[31,32] Clopidogrel 300 mg loading dose has been investigated only in patients ≤75 years of age.[31] While not specifically investigating the value of clopidogrel, in the STrategic Reperfusion Early After Myocardial Infarction (STREAM) study, patients aged 75 or more received clopidogrel treatment without loading dose (i.e. initiated at 75 mg *q.d.*) in association with half dose of lytic therapy.[30] Hence, the administration of a clopidogrel loading dose in elderly patients requires a patient-by-patient decision. While prasugrel[33] or ticagrelor[20] were allowed as per protocol in patients with prior treatment with lysis in $P2Y_{12}$ inhibitor-naïve patients or those with prior clopidogrel administration, respectively, there are insufficient safety data to recommend their concomitant use during or soon after thrombolysis.

Timing of initiation of $P2Y_{12}$ inhibitor: The evidence (and lack thereof) on optimal timing for the initiation of $P2Y_{12}$ inhibitors has been extensively discussed in previous guidelines[34] and reviewed elsewhere.[35,36] A reasonable approach is to start treatment with a $P2Y_{12}$ inhibitor based on the timing with which the drug was investigated in approval studies (i.e. start as soon as possible and deemed safe for clopidogrel and ticagrelor or after the indication for PCI is established based on coronary anatomy for prasugrel). The decision to withhold early administration of $P2Y_{12}$ inhibitors may also depend on planned

use of cangrelor in the catheterization laboratory, which ensures immediate inhibition of the target receptor in oral $P2Y_{12}$ inhibitor-naïve patients. Timing of administration of $P2Y_{12}$ inhibitors in patients receiving cangrelor infusion at the time of PCI should be drug-specific.[37] While ticagrelor can be given any time before, during or at the end of cangrelor infusion, it is recommended that clopidogrel or prasugrel is given at the time of cangrelor infusion discontinuation (or within 30 minutes before the end of infusion in the case of prasugrel administration).[37] However, the comparative efficacy and safety of routine early oral $P2Y_{12}$ inhibitor administration vs. the use of cangrelor in the catheterization laboratory in patients with ACS undergoing invasive management deserves further investigation. If coronary anatomy is known or the probability of PCI is high (such as for STEMI patients), there is evidence and general consensus that early administration of oral $P2Y_{12}$ inhibitors outweighs any potential risks. On the other hand, there are no convincing data that the benefits of early administration of a $P2Y_{12}$ inhibitor outweigh the possible risks in stable CAD patients undergoing diagnostic angiography.

3.7 Measures to minimize bleeding while on dual antiplatelet therapy

Bleeding events after successful PCI are independently associated with increased mortality and morbidity and this association is likely causal.[41,42] Therefore, every effort should be made to minimize bleeding. Individualization of therapy is a key measure and includes the identification of risk factors for bleeding, radial access site, dosing of therapies, use of proton pump inhibitors (PPIs), and appropriate selection of $P2Y_{12}$ inhibitors.

Vascular access site: The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX (MATRIX) trial is the most contemporary and largest trial on access site selection where 8404 ACS patients were randomly allocated to radial or femoral access.[43] The first co-primary outcome of 30-day MACE—defined as death, MI, or stroke—occurred in 8.8% of patients with radial access and 10.3% of patients with femoral access [relative risk (RR) 0.85, 95% CI 0.74–0.99; two-sided $P = 0.031$; formally non-significant at the pre-specified α of 0.025]. The second co-primary

Recommendations on $P2Y_{12}$ inhibitor selection and timing

Recommendations	Class[a]	Level[b]
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin[c] is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.[20]	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization[c] unless there is a high risk of life-threatening bleeding or other contraindications.[23]	I	B
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 as well as in patients with STEMI.[20,23,38]	I	A
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
In patients with stable CAD, pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.[20,23,39,40]	I	A
Clopidogrel (300 mg loading dose in patients aged ≤75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.[31,32]	I	A
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT score) risks.	IIb	C
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.[25]	III	B

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; NSTE-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds; prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.

outcome of 30-day net adverse clinical events (NACE) [MACE or non-CABG BARC (Bleeding Academic Research Consortium) major bleeding] was experienced in 9.8% and 11.7% of patients, respectively (RR 0.83, 95% CI 0.73–0.96; $P = 0.009$). Radial access was associated with a lower risk of all-cause mortality (1.6% vs. 2.2%; RR 0.72, 95% CI 0.53–0.99; $P = 0.045$). Major BARC 3 or 5 bleeding was significantly reduced in the radial group (1.6% vs. 2.3%; RR 0.67, 95% CI 0.49–0.92; $P = 0.013$). Radial access was associated with significantly lower rates of surgical access site repair or transfusion of blood products. An updated meta-analysis including MATRIX found a significant reduction in major bleeds; death, MI, or stroke; and in all-cause mortality associated with radial as compared to femoral access.[44]

Aspirin dosing in patients treated with DAPT: Lower aspirin doses (≤100 mg daily) have been consistently demonstrated to be associated with less major and total bleeding than higher doses, either when used as monotherapy or when combined with the $P2Y_{12}$ inhibitor clopidogrel.[45–52] This is because daily aspirin doses as low as 30–50 mg are able to completely inactivate the platelet cyclooxygenase-1 enzyme and inhibit thromboxane production.[53,54] In addition, the efficacy of ticagrelor may be decreased in patients treated with higher aspirin doses (≥300 mg daily) vs. lower aspirin doses (≤100 mg daily).[55] Although the molecular mechanism behind this finding is not entirely clear, it reinforces the use of low dose aspirin. The optimal range of aspirin dose in patients treated with DAPT that provides maximal protection from ischaemic events and minimizes bleeding risk appears to be 75–100 mg.

Platelet function testing, genetic testing, and switching of $P2Y_{12}$ inhibitors: High and low platelet reactivity on $P2Y_{12}$ antagonist treatment predicts ischaemic and bleeding risks, respectively.[56] These data have led to the rationale for individualized antiplatelet therapy based on platelet function monitoring to identify the patients out of the expected range of platelet inhibition.[57] All randomized trials have failed to demonstrate any benefit of platelet function monitoring to adjust therapy.[58–60] The low-risk level of the study populations, the exclusive use of clopidogrel, and the $P2Y_{12}$ reaction unit thresholds to define the optimal window of $P2Y_{12}$ inhibition have been recognized as the main limitations of these trials.[61–63]

The Platelet Function Monitoring to Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome (ANTARCTIC) trial has re-evaluated the concept of individualized antiplatelet therapy by selecting only ACS patients at high risk of both ischaemic and bleeding events (based on age ≥75 years) and more accurate thresholds in reflecting optimal $P2Y_{12}$ inhibition. Clopidogrel was replaced by prasugrel using the recommended daily dose of 5 mg for the elderly, with the possibility of adjustment up and down according to individual response. Platelet function monitoring performed 14 days after discharge and later if needed led to a change of treatment in 45% of patients who were identified as being overtreated or undertreated by measurement of the $P2Y_{12}$ inhibition level; however, this strategy did not improve ischaemic or safety outcomes.[64] The influence of genetic variants on the response to antiplatelet agents, especially clopidogrel, has been well-established in patients with ACS and planned PCI.[65] Rapidly-obtained genetic information on the 2C19 genotype can help in reaching the optimal window of $P2Y_{12}$ inhibition according to the cytochrome P450 (CYP) 2C19 profile,[66,67] but no randomized trial has ever demonstrated any clinical benefit of such an approach. Moreover, only 6–12% of the variability in on-clopidogrel platelet reactivity can be explained by the differences in genotype.[68,69]

For these reasons, neither platelet function testing nor genetic testing can be recommended for tailoring DAPT. It may be considered in specific situations (e.g. patients suffering from recurrent adverse events) if the results may change the treatment strategy. This is the case for patients undergoing CABG who are exposed to DAPT (see Chapter 5).

Proton pump inhibitors and DAPT: Gastrointestinal haemorrhage is the most common serious bleeding complication from the use of long-term antiplatelet therapy.[70] RCTs have shown that PPIs reduce the rate of recurrent gastrointestinal bleeding in high-risk patients receiving aspirin.[71] Similar data exist regarding the use of famotidine, a histamine H_2-receptor antagonist.[72]

Clopidogrel requires metabolic transformation in the liver by CYP isoenzymes (mainly CYP2C19) to elicit its antiplatelet effect. PPIs are also metabolized by CYP enzymes, leading to a potential inhibition of CYP2C19 (mainly omeprazole and esomeprazole) translating into reduced metabolic activation of clopidogrel when taken together. Pharmacodynamic studies demonstrated the reduction of clopidogrel-induced antiplatelet effects when a PPI, mainly omeprazole, was concomitantly administered.[73–76] Based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, lansoprazole an intermediate probability, while pantoprazole and rabeprazole have the lowest.[77] However, importantly, no interaction between concomitant use of PPIs and prasugrel or ticagrelor has been observed.

Only observational studies suggested an increased risk of cardiovascular ischaemic events when PPI therapy was administered concomitantly with clopidogrel.[78] Conversely, randomized trials and propensity score-matched studies did not support such concerns.[76,79–81]

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) was a randomized, double-blind, double-dummy, placebo-controlled, phase III study of the efficacy and safety of a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg), as compared with clopidogrel alone.[79] Patients were eligible if they were 21 years of age or older and if the use of clopidogrel therapy with concomitant aspirin was anticipated for at least the next 12 months, including patients presenting with an ACS or undergoing placement of a coronary stent. Patients at high risk for gastrointestinal bleeding were excluded (i.e. those in whom the need for a PPI, an H_2-receptor antagonist, sucralfate, or misoprostol was anticipated; with pre-existing erosive oesophagitis or oesophageal or gastric variceal disease or previous non-endoscopic gastric surgery; receipt of oral anticoagulation therapy that could not be safely discontinued for the duration of the study; or recent fibrinolytic therapy). Therefore, following previous evidence of benefit from a PPI or H_2-receptor antagonist in high-risk patients treated with aspirin monotherapy, the COGENT study included patients at low risk of gastrointestinal bleeding undergoing DAPT, under the rationale that the risk of gastrointestinal bleeding is higher in patients taking aspirin and clopidogrel as compared to aspirin alone. This study was prematurely stopped with a total of 3761 patients instead of the planned 5000 due to financial reasons. The pre-specified primary gastrointestinal efficacy endpoint was the time from randomization to the first occurrence of a composite of upper gastrointestinal clinical events, which

occurred in 1.1% of patients with omeprazole and 2.9% with placebo at 180 days after randomization (HR 0.34, 95% CI 0.18–0.63; $P < 0.001$).[79]

Furthermore, there was no significant increase in the risk of cardiovascular events with concomitant use of clopidogrel and omeprazole (4.9%, 95% CI 3.4–6.4%, in the omeprazole group; and 5.7%, 95% CI 4.0–7.3%, in the placebo group; $P = 0.98$), a finding that was consistent even in high-risk subgroups and for individual endpoints. The rate of serious adverse events did not differ significantly between the two groups (10.1% with omeprazole and 9.4% with placebo, $P = 0.48$), nor did the rate of overall adverse events (41.3 and 42.8%, respectively; $P = 0.33$). Diarrhoea was reported in 3.0% of patients receiving omeprazole, as compared with 1.8% of those receiving placebo ($P = 0.01$). There were no newly diagnosed cases of osteoporosis. One case of peripheral neuropathy was reported in the placebo group.

No randomized data comparing use vs. non-use of PPI in patients taking aspirin and prasugrel or ticagrelor exist. However, the risk of gastrointestinal bleeding is higher with DAPT in the form of prasugrel[23] or ticagrelor[82] as compared to clopidogrel. The short- and long-term safety profile of PPIs has been well-established.[79] Impaired magnesium absorption with PPIs has been reported only from studies in which patients had received a PPI for at least 1 year.[83] Magnesaemia monitoring is recommended at follow-up, especially for longer than 1 year of therapy.

Type, dose of P2Y$_{12}$ inhibitor, and duration of treatment: The type and dose of P2Y$_{12}$ inhibitor are well-established according to the various settings of CAD. Previous intracranial haemorrhage or ongoing bleeds are common contraindications for prasugrel and ticagrelor, while prasugrel should be given with caution in patients ≥75 years of age or with a body weight <60 kg. Patients with previous stroke or transient ischaemic attack (TIA) may derive harm from prasugrel instead of clopidogrel.[23] Prior stroke is a marker of frailty and of subsequent risk of haemorrhagic stroke, especially during the first year thereafter. Switching from prasugrel or ticagrelor to clopidogrel is a common practice, especially in cases of minor bleeding or in patients with low platelet reactivity, a marker of major bleeding risk.[56,84,85] There are no properly powered randomized data on the long-term safety or efficacy of 'switching' patients treated for weeks or months with a P2Y$_{12}$ inhibitor to a different P2Y$_{12}$ inhibitor. Therefore, this practice is generally discouraged.

3.8 Switching between oral P2Y$_{12}$ inhibitors

Differences in the pharmacology of P2Y$_{12}$ receptor inhibitors with regard to their binding site, half-life, and speed of onset and offset of action are important factors that might lead to drug interactions when switching from one agent to another.

The transition from clopidogrel to ticagrelor is the only switch between P2Y$_{12}$ inhibitors that has been investigated in a trial powered for clinical endpoint, even if the study was not specifically designed to assess the safety and efficacy of the transition from clopidogrel to ticagrelor. In PLATO, nearly 50% of patients randomly allocated to receive ticagrelor had been pre-treated with clopidogrel, mostly given as a 300–600 mg loading dose.[20] The efficacy and safety of ticagrelor were not affected by previous clopidogrel exposure.[88] On the other hand, the TRITON-TIMI 38 trial mandated that previous exposure of patients to a P2Y$_{12}$ receptor inhibitor

Switching between oral P2Y$_{12}$ inhibitors

Recommendations	Class[a]	Level[b]
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose[c] of clopidogrel, unless contraindications to ticagrelor exist.[20]	I	B
Additional switching between oral P2Y$_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

ACS = acute coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.
[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds.

Measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.[43,44]	I	A
In patients treated with DAPT, a daily aspirin dose of 75 - 100 mg is recommended.[45–47,51,52]	I	A
A PPI in combination with DAPT[c] is recommended.[70,79,80,86,87]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.[58–60]	III	A

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PPI proton pump inhibitor.
[a]Class of recommendation.
[b]Level of evidence.
[c]While the evidence that a PPI does not increase the risk of cardiovascular events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

should be an exclusion criterion for study entry.[23] While registry data provide reassuring information with respect to the safety profile of switching from clopidogrel to prasugrel,[89–91] no randomized data exist in the setting of studies powered for clinical endpoint. Similarly, all other switching possibilities, including between prasugrel and ticagrelor or from ticagrelor/prasugrel to clopidogrel, have not been investigated with outcome data.[92–94] This practice is therefore discouraged due to a lack of safety/efficacy data. As the need to switch between $P2Y_{12}$ inhibitors may arise for clinical reasons (i.e. side effects or drug intolerance), and registry data indicate that switching is not infrequent in practice, switching algorithms based on pharmacodynamic studies are provided (*Figure 2*).

4. Dual antiplatelet therapy and percutaneous coronary intervention

An overview of all studies investigating the benefits and risks of DAPT duration beyond 1 month, largely focusing on post-PCI patients or those with prior ACS, is shown in Web addenda *Table S1 (A and B)*. An overview of recommendations endorsed by these guidelines regarding DAPT duration after PCI, as well as after CABG or in medically managed ACS patients, is provided in *Figure 3*.

4.1 Dual antiplatelet therapy after percutaneous coronary intervention for stable coronary artery disease

DAPT is not indicated in purely medically managed patients (i.e. without prior PCI) with stable CAD and no history of prior MI. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study included patients with stable vascular disease or at risk of atherothrombotic events, and showed that clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes.[95]

After PCI with stent placement, DAPT is the standard of care. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial[2] and, subsequently, other studies[96,97] established the 1-month course of DAPT after bare-metal stent (BMS). An arbitrary 12-month or more DAPT duration has been subsequently recommended based on expert opinions after first generation DES, irrespective of clinical presentation.

No dedicated study exists focusing on stable CAD patients undergoing PCI and being exposed to different DAPT durations. Hence, recommendations regarding stable CAD patients undergoing PCI derive from subgroup analyses from pertinent RCTs (*Figure 4*).[98,99]

While no RCTs investigating the use of ticagrelor or prasugrel instead of clopidogrel in stable CAD patients undergoing PCI exist, this treatment option may be considered in selected patients in whom the use of clopidogrel is unsatisfactory based on prior clinical outcomes or potentially associated with higher risk of ischaemic events that bleeding recurrences.

Three- or 6- vs. at least 12-month DAPT duration: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial compared a 6-month DAPT [acetylsalicylic acid (ASA) + clopidogrel] duration with 1-year DAPT after DES.[100] With 1443 patients randomized, the rates of target vessel failure—defined as the composite of cardiac death, MI, or ischaemia-driven target vessel revascularization—at 12 months were 4.8% in the 6-month DAPT group and 4.3% in the 12-month DAPT group ($P = 0.001$ for non-inferiority). There was a numerically lower risk of bleeding in the short DAPT arm (HR 0.50, 95% CI 0.09–2.73). There was no signal of heterogeneity for the primary study endpoint with respect to clinical presentation (i.e. stable CAD, $n = 699$ patients vs. ACS, $n = 744$ patients). The PROlonging Dual antiplatelet treatment after Grading stent-induced intimal hYperplasia (PRODIGY) trial randomized 2013 patients[101] to 6 or 24 months of DAPT (ASA + clopidogrel) and to one of four stent types (a four-by-two factorial design), including BMS and three different DES types. The 2-year incidence of all-cause death, MI, and stroke or cerebrovascular accident was 10.1% with 24-month DAPT compared with 10.0% with 6-month DAPT ($P = 0.91$). There was a lower risk of major bleeding with shorter DAPT based on both the BARC (1.9% vs. 3.4%; HR 0.56, 95% CI 0.32–0.98; $P = 0.037$) or the TIMI scale (0.6% vs. 1.6%; HR 0.38, 95% CI 0.15–0.97; $P = 0.041$). After censoring events that occurred after 12 months, while keeping the original randomization design, the risk of TIMI major bleeding was 0.5% in the short-term DAPT arm vs. 0.9% in the long-term DAPT arm (HR 0.56, 95% CI 0.19–1.66). In this trial, a total of 1465 (74.3%) patients presented with ACS whereas 505 (25.7%) had stable CAD.[99] No heterogeneity was noted with respect to the primary efficacy endpoint. There was a borderline quantitative interaction between clinical presentations and bleeding outcomes (P values for interaction = 0.056 for BARC 2, 3, or 5; $P = 0.091$ for BARC 3 or 5), suggesting a higher hazard of bleeding in the 24-month DAPT arm when compared with the 6-month arm in the stable CAD patients, which was not observed in the ACS patients.[99] Analysis of NACE—consisting of death, MI, cerebrovascular accident, or BARC 2, 3, or 5 bleeding—revealed significant harm from extended DAPT in stable CAD patients (NACE in the 24-month vs. 6-month DAPT arm: 13.3% vs. 5.6%; HR 2.5, 95% CI 1.35–4.69, $P = 0.004$; NNT for harm = 13) and no benefit in the ACS population (16.1% vs. 14.1%; HR 1.15, 95% CI 0.88–1.50; $P = 0.29$), with positive quantitative interaction testing (P value for interaction = 0.024).[99] Patients with high CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) bleeding risk score treated with 24-month DAPT experienced a threefold higher risk of major bleeding and a fivefold risk of red blood cell transfusion as compared with 6-month therapy, without clear evidence of benefit.[13]

In 2014, three additional randomized studies were published that compared 6 months of DAPT to 12 or 24 months of DAPT (ASA + clopidogrel): Is There a Life for DES After Discontinuation of Clopidogrel (ITALIC),[102] Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy (SECURITY),[103] and Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting

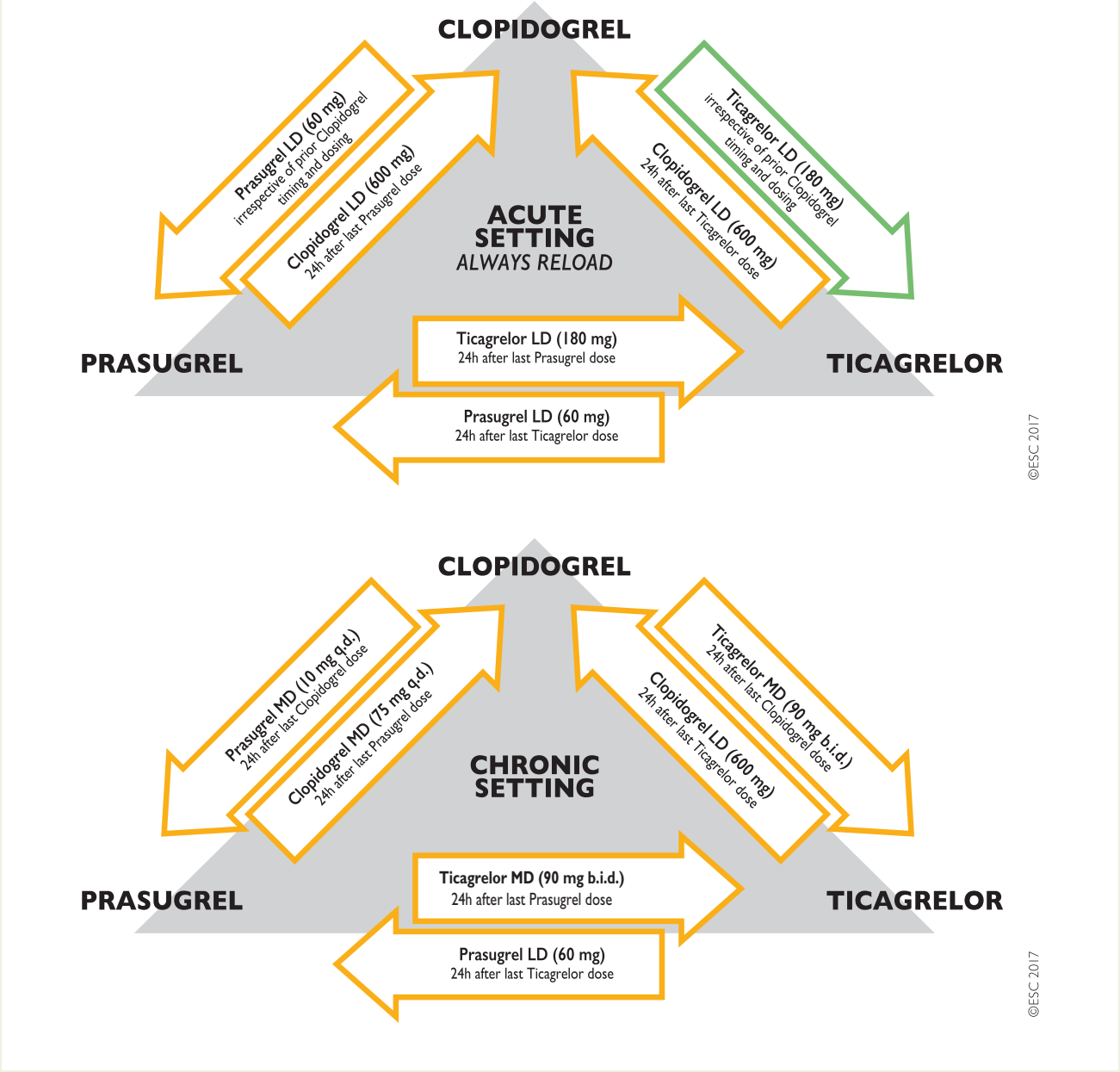


Figure 2 Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute and chronic setting. LD = loading dose; MD = maintenance dose. Colour-coding refers to the ESC Classes of Recommendations (green = Class I; orange = Class IIb). The green arrow from clopidogrel to ticagrelor highlights the only switching algorithm for which outcome data are available in patients with acute coronary syndrome. No outcome data (orange arrows) are available for all other switching algorithms. Acute setting is considered as a switching occurring during hospitalization.

Stenting (ISAR-SAFE).[104] ISAR-SAFE was the largest of these three studies, with 4005 randomized patients, and the only double-blind investigation. It confirmed that a 12-month course of DAPT did not afford any benefit over a 6-month course with respect to ischaemic endpoints. Likewise, the net clinical benefit (composite of death, MI, stent thrombosis, stroke, and TIMI major bleeding) was neutral. At subgroup analysis, there was no signal of heterogeneity with respect to the primary study endpoint among the 2394 patients who presented with stable CAD as opposed to the 1601 patients with ACS.[104] Consistent results were shown in the ITALIC and SECURITY trials. Two studies, Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation (RESET)[105] and Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice (OPTIMIZE),[106] investigated a 3-month duration of DAPT (ASA + clopidogrel). RESET randomized 2117 patients to 3- or 12-month duration of DAPT and did not show significant

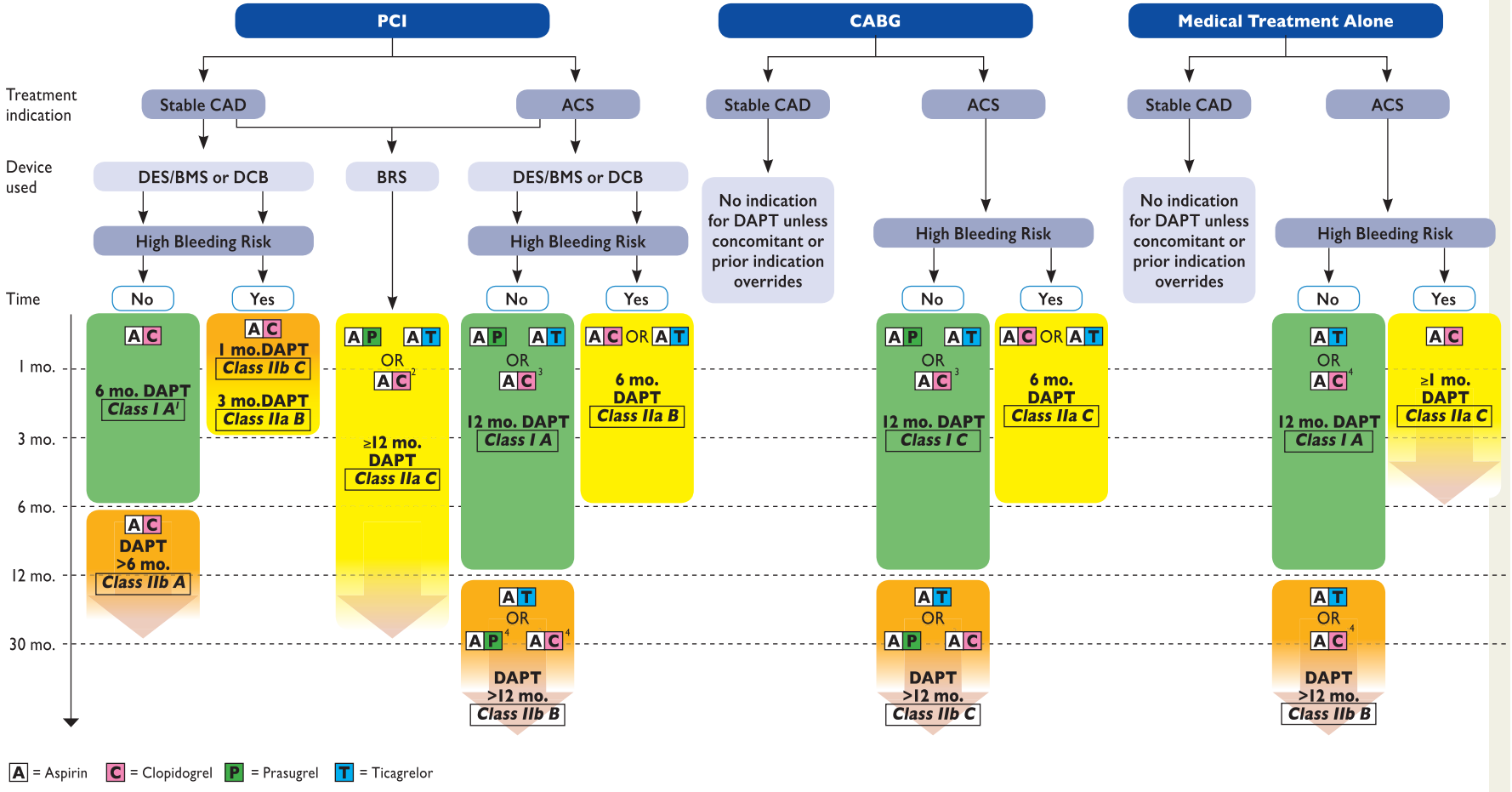


Figure 3 Algorithm for DAPT in patients with coronary artery disease. ACS = acute coronary syndrome, BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = Coronary artery bypass graft; DCB = drug-coated balloon; DES: drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD = stable coronary artery disease.
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
[1]: After PCI with DCB 6 months. DAPT should be considered (Class IIa B).
[2]: If patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
[3]: If patient is not eligible for a treatment with prasugrel or ticagrelor.
[4]: If patient is not eligible for a treatment with ticagrelor.

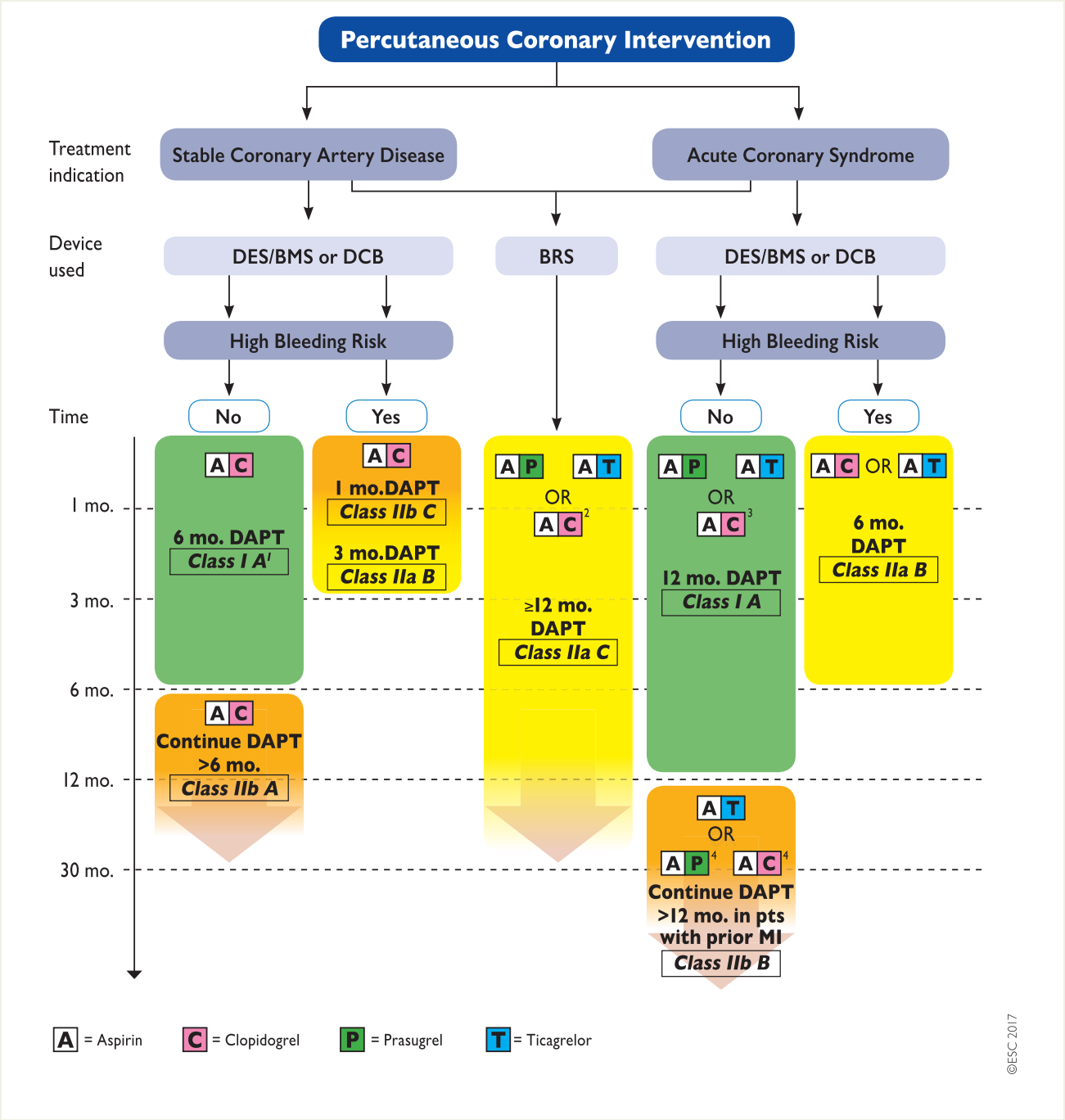


Figure 4 Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention. ACS = acute coronary syndrome; BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = coronary artery bypass graft surgery; DCB = drug-coated balloon; DES: drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD = stable coronary artery disease.
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = IIa; orange = Class IIb).
Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
[1]: After PCI with DCB 6 months. DAPT should be considered (Class IIa B).
[2]: If patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
[3]: If patient is not eligible for a treatment with prasugrel or ticagrelor.
[4]: If patient is not eligible for a treatment with ticagrelor.

harm with the shortened period (composite rates of any death, MI, or stent thrombosis 0.8% vs. 1.3%; $P = 0.48$). Similar results were achieved in OPTIMIZE with 3119 patients randomized. In this study, the 1-year incidence of MACE was 8.3% in the short-term group and 7.4% in the long-term group (HR 1.12, 95% CI 0.87–1.45). Both studies mandated the use of the Endeavor zotarolimus-eluting stent (ZES) in the 3-month DAPT arms, which is no longer available on the market. It is not clear to what extent the results of RESET and OPTIMIZE are applicable to other types of DES.

Palmerini *et al* performed a meta-analysis addressing the outcome of a ≤6-month course of DAPT vs. a 1-year course after DES.[107] The 1-year course of therapy did not confer any advantage over the shorter course of DAPT with respect to survival, stent thrombosis, or MI, but it increased the risk of major bleeding substantially. Similar results were obtained by other meta-analyses.[108,109]

Twelve-month vs. >12-month DAPT duration: Following the proposed landmark of 12 months as the standard DAPT duration after DES, the DAPT trial investigated whether further extension of DAPT might be beneficial.[110] The DAPT study enrolled patients who, at 12 months after placement of a DES, were still on DAPT and had not suffered an ischaemic or bleeding event. Patients were randomly allocated to thienopyridine or placebo for another 18 months. Aspirin was maintained throughout the study period. Thirty-month DAPT as compared with 12-month DAPT reduced the rates of stent thrombosis (0.4% vs. 1.4%; $P < 0.001$) and of major adverse cardiac and cerebrovascular events (MACCE) (4.3% vs. 5.9%; $P < 0.001$). This included a substantial reduction in the rate of MI (2.1% vs. 4.1%; $P < 0.001$); slightly more than half of this benefit could be attributed to the prevention of spontaneous MIs (see chapter 3.2). This ischaemic protection came at the cost of an increased risk of bleeding (GUSTO moderate or severe bleeding 2.5% vs. 1.6%, $P < 0.001$) and an increase in total mortality with borderline statistical significance (see section 3.3).

Of 11 648 randomized patients within the DAPT trial (9961 treated with DES and 1687 with BMS), 30.7% presented with MI.[98] The excess of mortality observed within the 30-month DAPT arm was entirely driven by fatalities, which occurred in patients without prior MI (2.1% for continued thienopyridine group vs. 1.5% for placebo; HR 1.43, 95% CI 1.02–2.00; $P = 0.04$). Yet, the interaction P value did not reach statistical significance (effect for MI vs. no MI interaction $P = 0.13$).[99]

Three independent meta-analyses, which included 5045 patients recruited within DES-Late coronary Arterial Thrombotic Events (LATE)[111] and 1259 patients from the Assessment by a Double Randomisation of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and, of Treatment Interruption Versus Continuation 1 Year After Stenting-Interruption (ARCTIC-Interruption) trial,[112] provided results consistent with a possible increase in mortality with prolonged DAPT as shown in the DAPT trial. A more recent meta-analysis of 11 RCTs that enrolled 33 051 patients who received predominantly newer-generation DES also provided weak evidence of an increased mortality rate with prolonged DAPT.[113]

Thus, if DAPT is administered for a sufficient length of time after placement of DES for stable CAD, a substantial benefit in terms of secondary prevention and reduction of stent thrombosis emerges. However, this benefit is counterbalanced by an increased risk of bleeding and by a signal for increased mortality. Thus, systematic extension of DAPT beyond six months is not justified for all patients but should be based on the individual risk profile of the patient (see section 3.5).

Impact of type of DES on duration of DAPT: The benefit of extended periods of DAPT varies with stent type. However, there are differences between first- and newer-generation DES. In PRODIGY, only patients with the paclitaxel-eluting stent benefitted from extended DAPT with a significant reduction of the risk of stent thrombosis.[114] Likewise, in DAPT, the benefit of extended DAPT was largest with patients with a paclitaxel-eluting stent and the smallest with an everolimus-eluting stent.[110,115] There also was a significant interaction between stent type and benefit of extended DAPT with respect to MACCE.[110] With an everolimus-eluting stent, the 1-year NNT for prevention of stent thrombosis was 157, whereas the 1-year NNT for harm for moderate or severe bleeding was 56.[115] In the meta-analysis by Giustino *et al*,[109] the reduction of stent thrombosis by extended DAPT was significantly reduced with new-generation stents as compared with first-generation DES, and statistical significance was lost within the new-generation subset. No such interaction was found concerning bleeding complications. Similar results were obtained in two other meta-analyses (Sharma *et al*[116] and Palmerini *et al*[117]).

Bioresorbable stents and drug-coated balloons: No dedicated studies examining the optimal duration of DAPT after implantation of a bioresorbable scaffold currently exist. In the largest randomized clinical trial investigating the treatment of patients with a poly-lactic acid-based bioresorbable scaffold, DAPT was recommended for at least 12 months.[118] However, meta-analysis has shown evidence of an approximately twofold higher rate of stent thrombosis in comparison with conventional DES, especially in the first 30 days after implantation.[119] This provides a rationale for considering more potent $P2Y_{12}$ inhibitors in these patients. In addition, some concerns have been raised regarding late stent thrombosis beyond 1 year after implantation[120,121] and a longer duration of DAPT therapy may be advocated, at least in patients at low bleeding risk. No large-scale clinical trials are available concerning magnesium-based bioresorbable scaffolds.

In patients treated with drug-coated balloons, dedicated clinical trials investigating the optimal duration of DAPT are lacking. In patients treated for in-stent restenosis, the largest randomized trials investigating drug-coated balloon therapy have recommended a treatment duration of between 3 - 12 months.[122–124] In addition, some small clinical trials, as well as larger registries, including patients with stable CAD undergoing drug-coated balloon angioplasty have recommended DAPT duration of at least 1 month.[125]

Plain old balloon angioplasty: no data on DAPT or DAPT duration exist after plain old balloon angioplasty, which is currently reserved for a small minority of patients in whom stent implantation is not feasible (e.g. small calibre vessel or extreme vessel tortuosity) or desirable (e.g. to avoid DAPT in patients referred to CABG). The institution of DAPT and its duration, if implemented, should depend on clinical profile (ischaemic vs. bleeding risks) and/or the reasons (e.g. planned surgery) for avoiding stent implantation.

Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended[c] for 6 months, irrespective of the stent type.[100,101,104,126–130]	I	A
Irrespective of the intended DAPT duration, DES[c] is the preferred treatment option.[129–132]	I	A
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months[d] should be considered.[105,106]	IIa	B
In patients with stable CAD treated with drug-coated balloon, DAPT for 6 months should be considered.[122,124,133]	IIa	B
In patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and ≤30 months may be considered.[26,107–109]	IIb	A
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month[e] may be considered.	IIb	C

BMS = bare-metal stent; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; MI = myocardial infarction; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

[a]Class of recommendation.

[b]Level of evidence.

[c]These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE mark, as detailed in Byrne *et al.*[134]

[d]The evidence supporting this recommendation comes from two studies where zotarolimus-eluting Endeavour sprint stent has been investigated in conjunction with a 3-month DAPT regimen.

[e]1-month DAPT following implantation of zotarolimus-eluting Endeavour sprint stent or Biofreedom drug-coated stent reduced risks of re-intervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration.[129,130] It is unclear if this evidence applies to other contemporary DES.

4.2 Dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome

DAPT with novel P2Y$_{12}$ inhibitors for 1 year after PCI for ACS: The evidence supporting the value of the combination of aspirin and clopidogrel in patients with ACS has been extensively reviewed in previous guidelines (NSTE-ACS), and data supporting the superiority of ticagrelor and prasugrel over clopidogrel in this setting are discussed in section 3.6.

Although both prasugrel and ticagrelor significantly increase the risk of TIMI major non-CABG related bleeds, the risk–benefit ratios were favourable with NNT for benefit of 46 and 53, respectively, and NNT for harm of 167 for both agents. These data established the 1-year course of DAPT, preferably with prasugrel or ticagrelor, for patients undergoing PCI for ACS, unless there are contraindications (*Figure 4*).

Mounting evidence for secondary prevention by intensified antiplatelet therapy: In patients presenting with ACS, the cardiovascular risk remains substantially elevated beyond the first year, even if successful revascularization has been achieved. In this setting, intensified antiplatelet therapy on top of aspirin has been shown to be an effective therapeutic strategy to prevent recurrent ischaemic events. However, the risk–benefit ratios seem less favourable than those observed in studies assessing ≤1-year DAPT duration. Relevant information has been provided by the prior MI patient subsets included in the CHARISMA[135] (*n* = 3846) and DAPT[98] (*n* = 3576) trials, which mainly compared clopidogrel with placebo on top of aspirin; by the subset of patients who underwent coronary angiography within the TRILOGY[136] trial, which compared prasugrel with clopidogrel; and by the patients with prior MI within the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P-TIMI 50)[137] (*n* = 17 779) trial, which compared vorapaxar with placebo. Taken separately, these trial results are difficult to interpret because they are based on subgroup analyses. Moreover, CHARISMA and TRILOGY had a neutral main outcome and the main results of TRA 2°P-TIMI 50 showed an unfavourable risk–benefit ratio. Therefore, a dedicated trial on prolonged DAPT for secondary prevention after ACS was needed. The PEGASUS trial filled this gap.[29]

DAPT with ticagrelor for secondary prevention after MI: PEGASUS recruited 21 162 patients with spontaneous MI 1–3 years before enrolment, who were at ≥50 years old and had at least one additional high-risk feature: age ≥65 years, diabetes mellitus, a second spontaneous MI, multivessel CAD, or chronic renal dysfunction.[29] The patients were randomly assigned to ticagrelor 90 mg *b.i.d.*, ticagrelor 60 mg *b.i.d.*, or placebo. All the patients received low-dose aspirin. Of the patients included in PEGASUS, 53% were enrolled after a STEMI and 83% were previously treated by PCI. The primary efficacy endpoint was the composite of cardiovascular death, MI, or stroke at 3 years and was 7.85% in the 90 mg arm, 7.77% in the 60 mg arm, and 9.04% in the placebo arm ($P = 0.008$ and $P = 0.004$ for the higher and lower doses, respectively, vs. placebo).[29] There was a consistent reduction in all components of the primary endpoint with ticagrelor vs. placebo, which reached statistical significance for MI with both doses of ticagrelor and for stroke with the lower dose. There was also a trend for a reduction in cardiovascular mortality. Due to a non-significant yet numerical increase in non-cardiovascular deaths in the two ticagrelor arms, the outcome was neutral with respect to all-cause death. The primary safety endpoint of TIMI major bleeding was observed more frequently with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) ($P < 0.001$ for each dose vs. placebo). The NNT for benefit for the primary endpoint was 250 for the 90 mg

dose and 238 for the 60 mg dose; the corresponding NNT for harm was 244 and 322, respectively, with the two ticagrelor doses.[29]

With the 90 mg dose, the absolute benefit in terms of the primary efficacy endpoint was in the same order as the absolute harm in terms of the primary safety endpoint, and with 60 mg the absolute benefit was only marginally larger than the absolute harm. However, the relevance of the various endpoints to the patient's overall well-being may differ and are, therefore, difficult to weigh against one another. The impact of MI and bleeding on mortality was comparable in previous studies.[11,138] A *post hoc* analysis from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial suggested that while bleeding according to BARC 2 and 3a criteria was less prognostic for death than MI, the risk of mortality was equivalent between BARC 3b bleeding and MI, and was higher following BARC 3c bleeding. Moreover, at variance with previous analyses, both MI and bleeding impacted mortality with similar time dependency.[42] In view of these consistent findings throughout multiple independent studies, both the efficacy and the safety endpoints deserve attention, as both most likely similarly impact mortality. With this background, the narrow risk–benefit ratio cautions against the universal long-term administration of ticagrelor for secondary prevention after MI, and calls for individualized treatment decisions based on ischaemic and haemorrhagic risk.

To this end, patients who continued their thienopyridine treatment without (a major) interruption (≤30 days) derived a larger benefit from extended ticagrelor intake than patients who interrupted their thienopyridine treatment for longer periods of time.[139] Depending on the actual discontinuation time frame of previous thienopyridine therapy, the HRs (95% CI) of the primary endpoint for ticagrelor (pooled doses) vs. placebo were 0.73 (0.61–0.87) for those who continued within 30 days, 0.86 (0.71–1.04) for those who interrupted for 30 days to 1 year, and 1.01 (0.80–1.27) for those who interrupted for more than 1 year (P trend for interaction < 0.001).[139] There was no significant interaction of timing with the effect of ticagrelor on bleeding risk. These findings suggest that patients who can continue their initial thienopyridine treatment are those deriving relatively greater benefit from DAPT continuation with ticagrelor. Nevertheless, even in this patient subset, the absolute increase in TIMI major bleeding associated with extended ticagrelor was similar in magnitude as compared to the absolute decrease in the composite ischaemic endpoint (i.e. 1.9 percentage point difference for both the safety and the efficacy endpoints).[139]

Patients with lower-extremities artery disease (LEAD), who are known to be at greater ischaemic risk, also derived heightened benefit from extended ticagrelor.[140] In these patients, the absolute decreases in the primary efficacy endpoint achieved by ticagrelor vs. placebo were 3.0% for the 90 mg dose and 5.2% for the 60 mg dose, whereas the increases in TIMI major bleeding were only 0.22% and 0.02%, respectively. In addition, ticagrelor was significantly associated with fewer events related to LEAD (i.e. acute limb ischaemia and peripheral revascularization procedures).

DAPT with thienopyridines (clopidogrel or prasugrel) for secondary prevention after MI: In the DAPT trial, 3567 patients had initially presented with MI.[98] A non-prespecified analysis of these patients investigated whether the benefits and risks of extended vs. standard duration of DAPT was similar among patients with or without MI. The active comparator was prasugrel in one-third of the patients with MI and clopidogrel in two-thirds of the patients.

In patients with MI, extended DAPT as compared with aspirin alone reduced stent thrombosis significantly (0.5% vs. 1.9%; P < 0.001). There also was a significant reduction of MACCE by extended DAPT (3.9% vs. 6.8%; P < 0.001). This included a major reduction in the rate of recurrent MI (2.2% vs. 5.2%; P < 0.001). On the other side, GUSTO moderate or severe bleeding was significantly increased by extended DAPT (1.9% vs. 0.8%, P = 0.005). Contrary to the main study, all-cause mortality was similar in the extended DAPT group as compared with the placebo group (1.4% vs. 1.6%; P = 0.61), even if formal interaction testing was inconclusive.

A meta-analysis on the effect of extended DAPT in patients with previous MI comprising PEGASUS and MI subgroups of studies with thienopyridines—CHARISMA, PRODIGY, and DES-LATE with clopidogrel as well as ARCTIC-Interruption and DAPT with clopidogrel or prasugrel—has been recently published.[141] Extended DAPT decreased the risk of MACCE compared with aspirin alone (6.4% vs. 7.5%; P = 0.001). There was a consistent significant reduction in each component of the primary endpoint (RR 0.85, 95% CI 0.74–0.98 for cardiovascular death; RR 0.70, 95% CI 0.55–0.88 for MI; RR 0.81, 95% CI 0.68–0.97 for stroke). This benefit was achieved at the cost of a significantly increased risk of major bleeding (1.85% vs. 1.09%; P = 0.004). Although the reduction in cardiovascular mortality associated with prolonged DAPT was significant, the absolute risk reduction was small (0.3%). In addition, there was no difference in all-cause mortality (4.0% in the extended DAPT group and 4.2% in the aspirin alone group). No significant difference between study heterogeneity was identified across the appraised endpoints. This may suggest a consistent class effect among the three $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, or prasugrel). However, caution should be used in interpreting this finding, taking into account that the PEGASUS study alone contributed ≥60% to pooled endpoint estimates and that PEGASUS was the only trial included in its totality (and as such the only properly powered study for post-MI patients), whereas *post hoc* subgroups of patients recruited in the other four investigations were pooled. In addition, when the overall included populations of the four available studies assessing DAPT for >1 year vs. 12-month therapy are pooled, an extended treatment with ticagrelor, as compared to a similar strategy with thienopyridines, exerted a more favourable effect on all-cause mortality due to a trend towards reduction of cardiovascular death and a null effect on non-cardiovascular death.[142] Finally, PEGASUS was the only trial that allowed patients who had stopped DAPT months or years before to randomly restart therapy; this likely resulted in relatively lower efficacy endpoint estimates as compared to other studies testing duration of thienopyridines where treatment was either permanently stopped or continued without treatment interruptions in between. Therefore, it is reasonable to favour ticagrelor 60 mg *b.i.d.* as the agent of choice for prolonging DAPT beyond 12 months in stabilized post-MI patients at low bleeding risk, and to reserve the use of clopidogrel (or prasugrel, the least investigated agent in this setting) as the alternative choice if ticagrelor therapy is not tolerated or feasible.

Shortening of DAPT duration in patients at high bleeding risk: There is no dedicated RCT assessing the optimal DAPT duration in patients at high bleeding risk. Moreover, many, if not all, available DAPT studies formally excluded these patients from inclusion. The Zotarolimus-eluting Endeavor sprint stent in Uncertain DES Candidates (ZEUS) and the Prospective randomized comparison of the BioFreedom biolimus A9 drug-coated stent versus the gazelle BMS in patients at high bleeding risk (LEADERS-FREE) studies recruited a selected high bleeding risk population and randomized them to BMS or drug-coated stent under a protocol-mandated DAPT duration of 1 month.[129,130] Both studies, as discussed in section 2.4, proved the superiority of the investigated DES technologies as compared to BMS despite a similarly short duration of DAPT. The trade-off between bleeding prevention and ischaemic protection of prolonging DAPT beyond 1 month in this patient subset remains unclear.

As discussed in section 4.1, two studies compared 3- vs. 12-month DAPT duration after DES. Patients were not selected based on high bleeding risk criteria and both studies included only a minority of patients presenting with acute MI (14.3 and 5.4% in the RESET and OPTIMIZE trials, respectively).[105,106] associated with an estimated increase in the risk of MI or definite/probable stent thrombosis from 1.7% to 2.4% compared with 1-year DAPT. Although this increase did not reach statistical significance (HR 1.48, 95% CI 0.98–2.22; $P = 0.059$), it has to be kept in mind that the power of this analysis was limited since the number of patients with ACS included was roughly only one-third or one-fourth of that in TRITON or PLATO, which established the superiority of intensified antiplatelet therapy over conventional 1-year DAPT with clopidogrel. Despite this limitation, it is probably fair to conclude that the ischaemic risk of shortening DAPT to 6 months after PCI in ACS is low, although not negligible. In this respect, it is also reassuring that there was no signal with respect to cardiac or all-cause death (HR 0.75, 95% CI 0.45–1.27 and HR 0.85, 95% CI 0.58–1.26, respectively). Only when DAPT duration was reduced to 3 months did the risk of MI and definite/probable stent thrombosis increase substantially (HR 2.08, 95% CI 1.10–3.93). In summary, currently available evidence suggests considering discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months, when the risk of bleeding is high.

Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).[20,23,40]	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[13,18,143]	IIa	B
In patients with ACS treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.[26,139]	IIb	A
In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.[29,115,142]	IIb	B

ACS = acute coronary syndrome; *b.i.d.* = *bis in die*; DAPT = dual antiplatelet therapy. MI = myocardial infarction; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]Defined as ≥ 50 years of age, and one or more of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance < 60 mL/min.
These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE mark, as detailed in Byrne *et al.*[134]

After an ACS, high bleeding risk status poses even greater challenges with respect to the choice of DAPT duration. The risks of shortening DAPT below 1 year have been addressed by an individual patient data meta-analysis.[143] This meta-analysis comprised six trials comparing three- or six-month DAPT with 12-month DAPT including 11 473 patients, 4758 of whom had ACS. In patients with ACS, shortening DAPT to ≤ 6 months was

4.3 Gaps in the evidence

With a marginal overall benefit-to-risk ratio of extended DAPT beyond 1 year after DES placement, tools to identify ideal candidates for long-term or even indefinite DAPT duration are critically needed. The DAPT score[15] as well as the subgroup analyses of PEGASUS[139,140,144,145] are important steps forward, but prospective validation in contemporary cohorts of newer-generation DES patients is needed.

The optimal level of platelet inhibition during the various stages of CAD remains an open question. The risk of ischaemic complication is highest immediately after PCI and then gradually declines. The same is true for patients managed for ACS, although the risk remains elevated above that of patients who never experienced an acute exacerbation for years. Thus, it is intuitive that during the chronic phase after stabilization the level of platelet inhibition may be reduced as compared with the acute phase. Until recently, there were only limited data addressing this issue from beyond the periprocedural phase to 1 year. By now, two studies addressing such a step-down concept have finished recruitment: Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial (TROPICAL-ACS) (NCT01959451) with a step-down from prasugrel to clopidogrel after the peri-interventional phase in acute MI; and GLOBAL-LEADERS (NCT01813435)[146] with a step-down from DAPT to single antiplatelet therapy with ticagrelor beyond the first month after PCI in an all-comers cohort with DES.

The risks and benefits of shortening DAPT to 3 months or even shorter is another area with limited evidence. There are only two randomized studies with a total of 5236 patients.[105,106] Both studies used the first-generation ZES that, due to its limited efficacy in suppressing neointima formation, has been largely replaced by a newer generation. Thus, in most cases with high bleeding risk, the decision to shorten DAPT below 6 months needs to rely on circumstantial evidence suggesting comparable safety of different stent types.

As outlined in section 4.1, there are no dedicated studies on the optimal duration of DAPT after the application of drug-eluting balloons or after implantation of a bioresorbable scaffold. It is also unclear whether, early after placement of a bioresorbable stent, patients may benefit from the more potent $P2Y_{12}$ inhibition achieved by prasugrel or ticagrelor as compared with the current practice of clopidogrel administration.

5. Dual antiplatelet therapy and cardiac surgery

5.1 Dual antiplatelet therapy in patients treated with coronary artery bypass surgery for stable coronary artery disease

DAPT in ACS patients significantly reduces the risk of thrombotic complications but increases the risk for both spontaneous and surgical bleeding complications.[20,23,40] The bleeding risk as well as the ischaemic benefit are further increased if ticagrelor or prasugrel are used instead of clopidogrel.[20,23] Unlike for ACS, there is currently no evidence of a survival benefit or a reduction of thromboembolic complications with DAPT in patients with stable CAD undergoing CABG. However, there is limited evidence suggesting that the use of DAPT in patients with stable CAD mitigates the risk of vein (but not arterial) graft occlusions.

5.2 Dual antiplatelet therapy in patients treated with coronary artery bypass surgery for acute coronary syndrome

Background: DAPT, as compared to aspirin monotherapy, has been proven to be beneficial in reducing ischaemic risk in ACS patients (*Figure 5*).

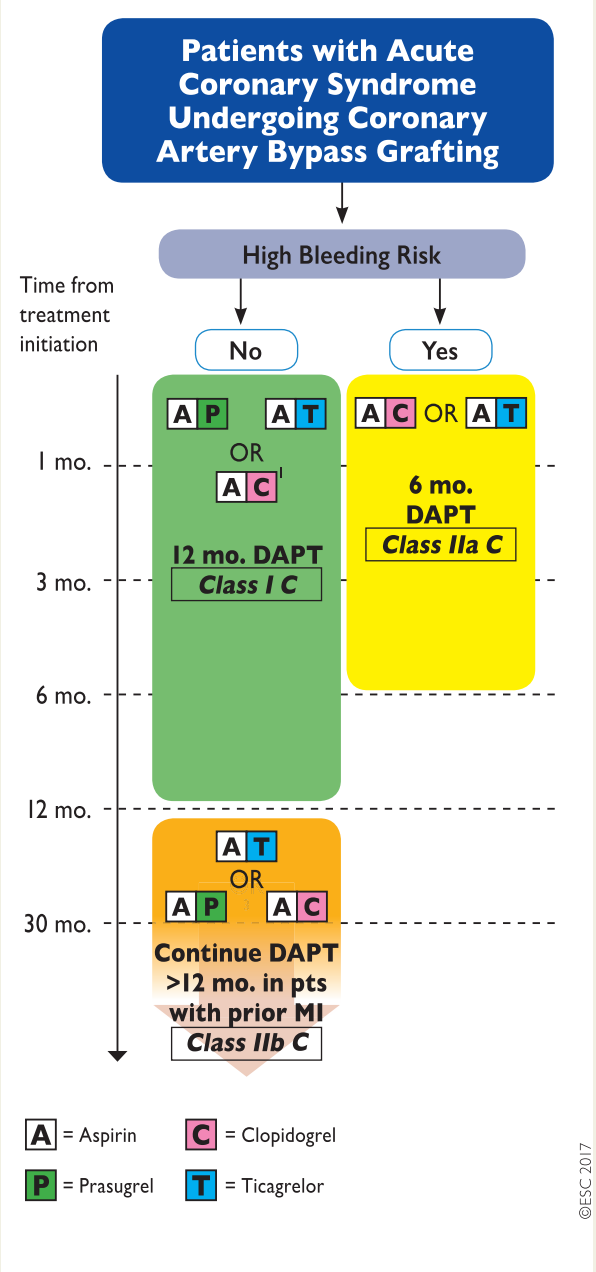


Figure 5 Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing coronary artery bypass grafting. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25). Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = IIa; orange = Class IIb). Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
1: if patient is not eligible for a treatment with prasugrel or ticagrelor.

However, there is limited evidence in patients undergoing CABG as no dedicated study exists. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the outcome in the CABG

subpopulation was consistent with the overall results of the study.[147] Further support has been presented in two meta-analyses.[148,149] In the CABG substudies of the TRITON-TIMI 38 and the PLATO trials where, respectively, prasugrel and ticagrelor were tested against clopidogrel in combination with ASA, both newer $P2Y_{12}$ inhibitors were more effective than clopidogrel in preventing fatal outcomes, with a higher risk for bleeding in the former but not the latter trial.[150,151]

Continuation of DAPT until CABG increases the risk of excessive perioperative bleeding, transfusions, and re-exploration for bleeding as shown in RCTs,[147,150,151] observational studies,[152,153] and meta-analyses.[154,155] Therefore, it is recommended that the $P2Y_{12}$ inhibitor be discontinued whenever possible before elective CABG.[156,157] Alternatively, elective operations may be postponed until the DAPT treatment period is completed. In urgent cases, most often patients with ACS, the risk of thrombotic episodes (stent thrombosis or MI) while waiting for the effect of the $P2Y_{12}$ inhibitor to cease must be weighed against the risk of perioperative bleeding complications. In extreme high-risk patients, e.g. those with recent DES implantation, bridging therapy with cangrelor or a glycoprotein IIb/IIIa blocker may be considered.[156,157]

$P2Y_{12}$ inhibitors: The safe discontinuation interval varies between the different $P2Y_{12}$ inhibitors due to variations in platelet inhibitory effect and pharmacodynamic and pharmacokinetic properties.[158] For clopidogrel, it was shown in the CABG substudy of the CURE trial that discontinuation ≥5 days before CABG did not increase the risk of bleeding complications.[147] For prasugrel, a longer time interval (7 days) is recommended due to the longer offset time compared to clopidogrel[158] and the high incidence of CABG-related bleeding complications reported in the CABG substudy of the TRITON-TIMI 38 trial.[151] In CABG patients treated pre-operatively with ticagrelor, 5 days of discontinuation was initially recommended. This recommendation was based on pharmacokinetic studies and clinical data from patients with stable CAD.[159] However, recent data from large observational studies in CABG patients challenge this recommendation.[152,153,160] In a Swedish nationwide study, CABG-related bleeding complications in patients treated with ticagrelor or clopidogrel were thoroughly investigated with respect to timing of $P2Y_{12}$ inhibitor discontinuation.[152] When either drug was discontinued according to the instructions for use (>120 h before surgery), there was no significant difference in the incidence of major bleeding complications between ticagrelor- and clopidogrel-treated patients (9% vs. 12%; unadjusted OR 0.72, 95% CI 0.51–1.02; $P = 0.065$). Within the ticagrelor group, there was no significant difference in major bleeding complications between discontinuation 72–120 h or > 120 h before surgery (OR 0.93, 95% CI 0.53–1.64; $P = 0.80$), whereas discontinuation 0–72 h before surgery was associated with a significantly higher rate of major bleeding compared with both 72–120 h (OR 5.17, 95% CI 2.89–9.27; $P < 0.0001$) and >120 h (OR 4.81, 95% CI 3.34–6.95; $P < 0.0001$). In contrast, clopidogrel-treated patients had a higher incidence of major bleeding complications when discontinued 72–120 h compared with >120 h before surgery (OR 1.71, 95% CI 1.04–2.79; $P = 0.033$). Likewise, in the clopidogrel group, discontinuation 0–72 h before surgery was associated with an increased incidence of major bleeding compared with 72–120 h (OR 1.67, 95% CI 1.02–2.73; $P = 0.042$) and >120 h (OR 2.85, 95% CI 1.98–4.10; $P < 0.0001$) (*Web Figure 2*, see Web Addenda).[152] Further support for using 3 days as the discontinuation period in ticagrelor-treated patients comes from the PLATO trial, where a discontinuation period of 24 - 72 h was recommended. In a single institution Dutch registry encompassing 705 consecutive patients who underwent isolated on-pump CABG, ticagrelor discontinuation >72 h and clopidogrel discontinuation >120 h before surgery were not associated with an increased risk of bleeding-related complications.[153]

Further evidence comes from a prospective, multicentre clinical trial performed at 15 European centres, where discontinuation of ticagrelor >2 days before surgery was not associated with increased bleeding.[160]

It is unlikely that the optimal discontinuation period for any of the $P2Y_{12}$ inhibitors will ever be tested in an RCT. As mentioned above, current guidelines recommend DAPT in all patients with ACS, independent of revascularization strategy.[34,161] This applies to patients undergoing CABG and other cardiac surgical procedures as well. Furthermore, the effect of DAPT or single antiplatelet therapy after CABG has been compared in two meta-analyses based on RCTs[148] or a combination of RCTs and observational studies.[149] In the meta-analysis based on RCTs only (which included 3717 ACS patients),[148] there were no differences in all-cause mortality in ASA + clopidogrel vs. ASA only. Conversely, all-cause mortality was significantly lower in ASA + ticagrelor and ASA + prasugrel vs. ASA + clopidogrel RCTs (RR 0.49, 95 % CI 0.33–0.71; $P = 0.0002$). There were no significant differences in occurrence of MIs, strokes, composite outcomes, or major bleeding (RR 1.31, 95 % CI 0.81–2.10, $P = 0.27$). The meta-analysis based on both RCTs and observational studies[149] included only DAPT patients treated with clopidogrel. In this analysis, in-hospital or 30-day mortality was lower with ASA + clopidogrel compared to ASA alone (RR 0.38, 95% CI 0.26–0.57; $P < 0.001$), while the risk of angina or perioperative MI was comparable (RR 0.60, 95% CI 0.31–1.14; $P = 0.12$). Long-term mortality was not reported. Patients treated with ASA + clopidogrel demonstrated a trend towards a higher incidence of major bleeding episodes as compared to patients treated with ASA alone (RR 1.17, 95% CI 1.00–1.37; $P = 0.05$). In both meta-analyses, there was large heterogeneity between the included studies regarding study drug (clopidogrel/prasugrel/ticagrelor), study design, patient inclusion (ACS vs. stable CAD, on-pump vs. off-pump surgery), study quality, and duration of follow-up. The positive effect on survival appears to be more pronounced in ACS patients and in patients treated with the second-generation $P2Y_{12}$ inhibitors ticagrelor and prasugrel. However, re-institution of DAPT after CABG may also slightly increase the risk of bleeding complications. Thus, it is recommended that DAPT is re-started as soon as it is considered safe after CABG in ACS patients, with the exception of those on anticoagulation. There is currently no scientific support for triple antithrombotic treatment after CABG. Resuming DAPT early after CABG is most likely of special importance in patients with recent stent implantation, although strong evidence is lacking. The optimal timing of resuming DAPT remains unclear, but 24 - 96 h after the operation in patients without recent stent implantation appears reasonable. One reason for not starting DAPT immediately after the operation is the considerable risk (~30%) of atrial fibrillation (AF) during the first post-operative days, which requires oral anticoagulation.[162]

Acetylsalicylic acid: A recent meta-analysis comparing pre-operative ASA administration vs. no treatment or placebo in CABG patients included 13 trials with a total of 2399 patients.[163] The meta-analysis showed that treatment with ASA reduced the risk of perioperative

MI (OR 0.56, 95% CI 0.33–0.96) but not the mortality risk (OR 1.16, 95% CI 0.42–3.22), while post-operative bleeding, red blood cell transfusions, and surgical re-explorations increased with ASA. The authors pointed out that included studies had low methodological quality. The recent Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial compared administration of ASA (100 mg) on the day of surgery vs. placebo in CABG patients.[164] The study showed no significant effect of ASA treatment on perioperative bleeding. On the other hand, ASA treatment did not reduce the incidence of thrombotic events. It should be pointed out that the study did not directly compare discontinuation vs. no discontinuation, since the included patients were only eligible for the trial if they were not using ASA pre-operatively or had stopped ASA at least 4 days before surgery. Thus, the ATACAS study does not directly apply to the ACS-CABG population and does not change current recommendations of maintaining ASA treatment during the perioperative period.

In a case-control study on 8641 CABG patients, those pre-treated with ASA were less likely to experience in-hospital mortality in univariate (OR 0.73, 95% CI 0.54–0.97) and multivariate (OR 0.55, 95% CI 0.31–0.98) analysis relative to those not exposed to ASA.[165] No significant difference was seen in the amount of chest tube drainage, transfusion of blood products, or need for re-exploration for bleeding, between patients who were or were not exposed to ASA pre-operatively.

Taken together, the evidence indicates that continuation of ASA until cardiac surgery is associated with a moderately increased risk of bleeding complications and a significant reduction in the risk of perioperative MI. If bleeding occurs during surgery, platelet transfusion has been shown to effectively counteract ASA effects.[166–168] This finding further supports the possibility of continuing ASA throughout the perisurgical period as ASA allows direct antiplatelet effect reversal if clinically indicated. The increased risk of bleeding complications if ASA and other antithrombotic drugs are not discontinued should be weighed against the potentially increased risk of thrombotic complications during the pre-operative cessation period.

Platelet function testing: Besides the variance in platelet inhibitory effects between different $P2Y_{12}$ inhibitors, there is also a large individual variation in the magnitude and duration of the antiplatelet effect.[20,159,169–171] Because of the individual variation, the use of platelet function tests may aid the optimization of the timing of surgical procedures. However, platelet function tests could also be of value to establish the grade of platelet inhibition in patients in whom the time since discontinuation is unclear, e.g. in unconscious or confused patients, and in patients with uncertain compliance to the treatment.

Treatment monitoring, using bedside tests, has been suggested as an option for guiding interruption of treatment, rather than the use of an arbitrary, specified period of time.[156,157] Pre-operative ADP-dependent platelet aggregation capacity predicts CABG-related

Dual antiplatelet therapy in patients treated with cardiac surgery with stable or unstable coronary artery disease

Recommendations	Class[a]	Level[b]
It is recommended that the heart team estimates the individual bleeding and ischaemic risks, and guides the timing of CABG as well as the antithrombotic management.	I	C
In patients on aspirin who need to undergo non-emergent cardiac surgery, it is recommended to continue aspirin at a low daily regimen throughout the perioperative period.	I	C
In patients treated with DAPT after coronary stent implantation who subsequently undergo cardiac surgery, it is recommended to resume $P2Y_{12}$ inhibitor therapy post-operatively as soon as is deemed safe so that DAPT continues until the recommended duration of therapy is completed.	I	C
In patients with ACS (NSTE-ACS or STEMI) treated with DAPT, undergoing CABG, and not requiring long-term OAC therapy, resumption of $P2Y_{12}$ inhibitor therapy as soon as is deemed safe after surgery and continuation up to 12 months is recommended.	I	C
In patients on $P2Y_{12}$ inhibitors who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, at least 5 days after clopidogrel, and at least 7 days after prasugrel should be considered.[152,153,160]	IIa	B
In CABG patients with prior MI who are at high risk of severe bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	C
Platelet function testing may be considered to guide decisions on timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors.[169,172–174]	IIb	B
In patients perceived to be at high ischaemic risk with prior MI and CABG, who have tolerated DAPT without a bleeding complication, treatment with DAPT for longer than 12 and up to 36 months may be considered.	IIb	C

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTE-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PRECISE-DAPT = PREdicting bleeding Complications in patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

bleeding complications in clopidogrel-[172–174] and ticagrelor-treated[169] ACS patients, and a strategy based on pre-operative platelet function testing, to determine the timing of CABG in clopidogrel-treated patients, led to a 50% shorter waiting time than that suggested by a simple discontinuation time-based strategy.[175] It should be pointed out that the different platelet function tests and their respective cut-off levels are not interchangeable.[176] Taken together, these results suggest that platelet function testing in ACS patients referred for CABG is of potential value to guide the timing of surgery in patients treated with $P2Y_{12}$ inhibitors. However, randomized studies with clinically relevant endpoints are lacking.

5.3 Dual antiplatelet therapy for prevention of graft occlusion

Two meta-analyses have compared graft patency in patients treated with ASA alone or ASA + clopidogrel after CABG.[149,177] The studies included in the meta-analyses comprised mainly patients with stable CAD. In a meta-analysis by Deo *et al*,[149] ASA + clopidogrel was associated with a significant reduction in saphenous vein graft occlusions (RR 0.59, 95% CI 0.43–0.82; $P = 0.02$). In the meta-analysis by Nocerino *et al*,[177] DAPT was consistently associated with a reduced occlusion rate (RR 0.63, 95% CI 0.46–0.86). DAPT proved useful in preventing vein graft occlusion (RR 0.58, 95% CI 0.42–0.83), while no clear effect was shown in arterial grafts (RR 0.85, 95% CI 0.39–1.85).[177] Weak evidence indicates that DAPT may prevent graft occlusion in patients undergoing off-pump CABG rather than on-pump CABG.[178] Given the low risk of thrombotic events after CABG in stable patients, there is insufficient evidence to generally recommend DAPT post-operatively to reduce vein graft occlusion in this surgical patient subset.

5.4 Gaps in the evidence

There are several gaps in the evidence that pertain to the use of DAPT in cardiac surgery. Clear gaps in evidence related to DAPT in cardiac surgery patients include the question of whether DAPT should be started after CABG in patients with stable CAD. Also, the exact timing of post-operative DAPT restart remains unclear, and it remains uncertain for how long the post-operative DAPT should last. Further gaps in the evidence relate to: the optimal time point for discontinuation of the different $P2Y_{12}$ inhibitors; the optimal use of platelet function testing in patients awaiting cardiac surgery; how to manage perioperative bleeding complications in cardiac surgery patients caused by DAPT; and whether and how an incomplete response or inadequate antiplatelet effect of aspirin after CABG should be addressed.

6. Dual antiplatelet therapy for patients with medically managed acute coronary syndrome

The evidence for the use of DAPT in medically managed ACS patients comes from the CHARISMA and CURE for clopidogrel,[40,95] TRILOGY for prasugrel,[24] and PLATO and PEGASUS for ticagrelor studies.[20,29] There is no evidence in favour of prasugrel treatment in patients with ACS who are medically managed, based on the negative results of the TRILOGY study and the exclusion of this patient subset in the TRITON study.[23,24] The CURE study showed a consistent benefit in ACS patients undergoing an average mean of 9 months DAPT in the form of aspirin and clopidogrel as compared to 1-month therapy in NSTE-ACS patients, irrespective of the final management strategy, including or not including coronary revascularization.[40] The post-MI subset of patients in the CHARISMA trial derived significant benefit with an NNT for benefit in the range of 100, which came at the expense of higher major bleeding, with an NNT for harm of 90.[135] While the post-MI population represents only a subset of those included in the CHARISMA study and the overall results of the trial did not show benefit of DAPT as compared to aspirin alone, it seems justifiable to give credit to this subanalysis based on the consistency of results within multiple recent studies; these studies showed that the long-term administration of an intensified antiplatelet regimen beyond 1 year of treatment reduced long-term ischaemic recurrences, even if at the cost of higher bleeding.[29,179]

Patients medically managed in the PLATO trial derived consistent benefit from ticagrelor 90 mg *b.i.d.* as compared to clopidogrel. Overall mortality was also reduced in patients treated with ticagrelor 90 mg *b.i.d.*[180]

In the PEGASUS trial, 4271 patients had no prior coronary stent implantation and they derived consistent benefits and risks from ticagrelor vs. placebo on top of aspirin compared to patients with prior stenting.

Multiple sources have shown that medically managed ACS patients are less frequently treated with a DAPT regimen as compared to patients who received PCI.[181] Current evidence, especially for ticagrelor, does not support this practice and clinicians should refrain from tailoring the implementation and/or duration of a DAPT regimen depending on prior coronary stent implantation in the current era of newer-generation DES (*Figure 6*).

A special population that warrants specific consideration comprises patients with established NSTE-ACS in whom no lumen obstruction at coronary angiography is detected. No dedicated study exists assessing the benefits and risks of DAPT in this patient subset. However, a high prevalence of ruptured plaques has been observed at intravascular imaging modalities in this population,[182] suggesting that the benefits of DAPT in preventing recurrent MI should not be withheld from these patients if the risk of bleeding does not outweigh the anticipated benefit.

The evidence in support of the DAPT treatment option in patients with STEMI conservatively managed or with prior lysis is limited to 1 month of treatment.[31,32] Yet, in consideration of the fact that the majority of these patients would undergo invasive management afterwards, and evidence that DAPT may be beneficial irrespective of whether revascularization takes place, it is reasonable to prolong DAPT further in these patients depending on the bleeding risk.

Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management.

Recommendations	Class[a]	Level[b]
In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months.[20,40]	I	A
Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischaemic benefit.[20]	I	B
In patients with medically managed ACS who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), DAPT for at least 1 month should be considered.	IIa	C
In patients with prior MI at high ischaemic risk[c] who are managed with medical therapy alone and have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg *b.i.d.* on top of aspirin for longer than 12 months and up to 36 months may be considered.[139]	IIb	B
In patients with prior MI not treated with coronary stent implantation, who have tolerated DAPT without a bleeding complication and who are not eligible for treatment with ticagrelor, continuation of clopidogrel on top of aspirin for longer than 12 months may be considered.	IIb	C
Prasugrel is not recommended in medically managed ACS patients.[24]	III	B

ACS = acute coronary syndrome; *b.i.d.* = *bis in die*; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]Defined as ≥ 50 years of age, and one or more of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance < 60 mL/min.

7. Dual antiplatelet therapy for patients with indication for oral anticoagulation

7.1 Risk stratification and strategies to improve outcome after percutaneous coronary intervention

Approximately 6–8% of patients undergoing PCI have an indication for long-term oral anticoagulants (OACs) due to various conditions such as AF, mechanical heart valves, or venous thromboembolism. Compared with oral anticoagulation therapy alone, the addition of DAPT to OAC therapy results in at least a two- to threefold increase in bleeding complications.[183–186] Therefore, these patients should be considered at high risk of bleeding, and the indication for OAC should be reassessed and treatment continued only if a compelling indication exists {e.g. paroxysmal, persistent, or permanent AF with a CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category] score ≥1 in men, ≥2 in women; mechanical heart valve; recent (i.e. 6 months) or a history of recurrent deep venous thrombosis or pulmonary embolism}. Conversely, every effort should be undertaken to implement strategies to minimize PCI-related complications in these patients (*Table 4*). In particular, the duration of triple therapy should be limited or omitted after hospital discharge (i.e. confined to the periprocedural phase with aspirin being stopped thereafter), taking into account the ischaemic (e.g. complexity of treated CAD, amount of disease left untreated, technical considerations regarding stent implantation techniques, and results) as well as the bleeding risks. While ischaemic risk scores also predict bleeding outcomes in AF,[187] suggesting considerable overlap among risk factors associated with ischaemic and bleeding outcomes, multiple bleeding risk scores,[188] including the HAS-BLED[189] [Hypertension, Abnormal renal and liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs and alcohol (1 point each)] score, have been shown to outperform $CHADS_2$ [Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)] or CHA_2DS_2-VASc in predicting bleeding risk.

Importantly, HAS-BLED draws attention to the reversible bleeding risk factors to be addressed by the responsible clinician during the follow-up. Risk is not static and, particularly for bleeding, many risk factors can be modified. Hence, a high risk of bleeding (e.g. HAS-BLED score ≥3) is not a reason to withhold OAC; instead, such patients should be 'flagged-up' for more careful review and follow-up.

More recently, the novel biomarker-based ABC [Age, Biomarkers (GDF-15, cTnT-hs, and haemoglobin), and Clinical history (previous bleeding)][190] bleeding risk score has been generated and validated in a broad AF population treated with both vitamin K antagonist (VKA) and non-vitamin K oral anticoagulants (NOACs), and has shown superior prediction capability as compared to HAS-BLED. However, similar to all other bleeding risk scores, none of these risk prediction models developed for OAC patients has been prospectively tested in the setting of prospective RCTs. Therefore, their value in improving patient outcomes remains unclear.

A comprehensive list of all risk factors that have been associated with greater bleeding risk has been previously published.[162]

In the absence of safety and efficacy data from RCTs [only 6% of patients were treated at baseline with ticagrelor or prasugrel in the Rivaroxaban and a dose-adjusted oral VKA treatment strategy in

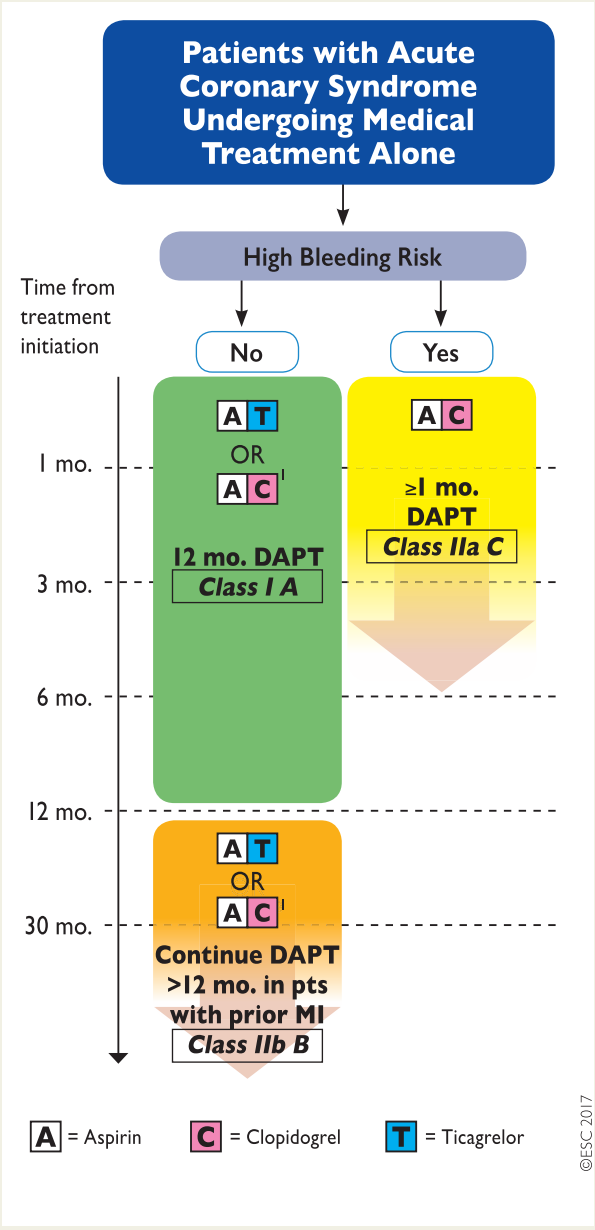


Figure 6 Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing medical management. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25). Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = IIa; orange = Class IIb). Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
1: if patient is not eligible for a treatment with ticagrelor

subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI) study[191]] and worrisome bleeding signals in registries, the use of prasugrel or ticagrelor as part of triple therapy should be avoided.[192] Gastric protection with a PPI is recommended. The dose intensity of OAC should be carefully monitored with a target international normalized ratio (INR) in the lower part of the recommended target range; in patients treated with NOACs, the lowest effective tested dose for stroke prevention should be applied and criteria for drug accumulation for each approved NOAC should be carefully assessed. Lower NOAC regimens as compared to those tested in approval studies are expected to decrease bleeding risk, but the trade-off between bleeding and ischaemic (i.e. stroke prevention) outcomes remains largely undefined. The PIONEER AF-PCI study[191] (described in detail below) tested two lower rivaroxaban doses (15 mg *o.d.* and 2.5 mg *b.i.d.*) as compared to the approved drug regimen in AF patients (20 mg *q.d.*). The Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting (REDUAL-PCI; NCT02164864) will compare two dabigatran doses (150 mg *b.i.d.* and 110 mg *b.i.d.*) vs. VKA and will provide additional insights with respect to the balance between efficacy and safety for each one. Whether there are differences according to the type of OAC (NOACs vs. VKA) or stent platform as well the duration of triple therapy is further discussed. These considerations do not pertain to medically managed patients or to patients eligible for CABG surgery in whom DAPT should be avoided on top of OAC.

Table 4 Strategies to avoid bleeding complications in patients treated with oral anticoagulant

• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
• Consider the use of NOACs instead of VKA.
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤ 100 mg daily) aspirin.
• Routine use of PPIs.

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ABC = Age, Biomarkers, Clinical history; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; NOAC = non-vitamin-K oral anticoagulant; INR = international normalized ratio; PCI = percutaneous coronary intervention; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.
[a]Apixaban 5 mg b.i.d or apixaban 2.5 mg b.i.d. if at least two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L); dabigatran 110 mg b.i.d.; edoxaban 60 mg q.d. or edoxaban 30 mg q.d. if any of the following: creatinine clearance (CrCl) of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone; rivaroxaban 20 mg q.d. or rivaroxaban 15 mg q.d. if CrCl 30–49 mL/min.

7.2 Duration of triple therapy

Cessation of aspirin after PCI while maintaining clopidogrel has been evaluated in the What is the Optimal antiplatElet and anticoagulant

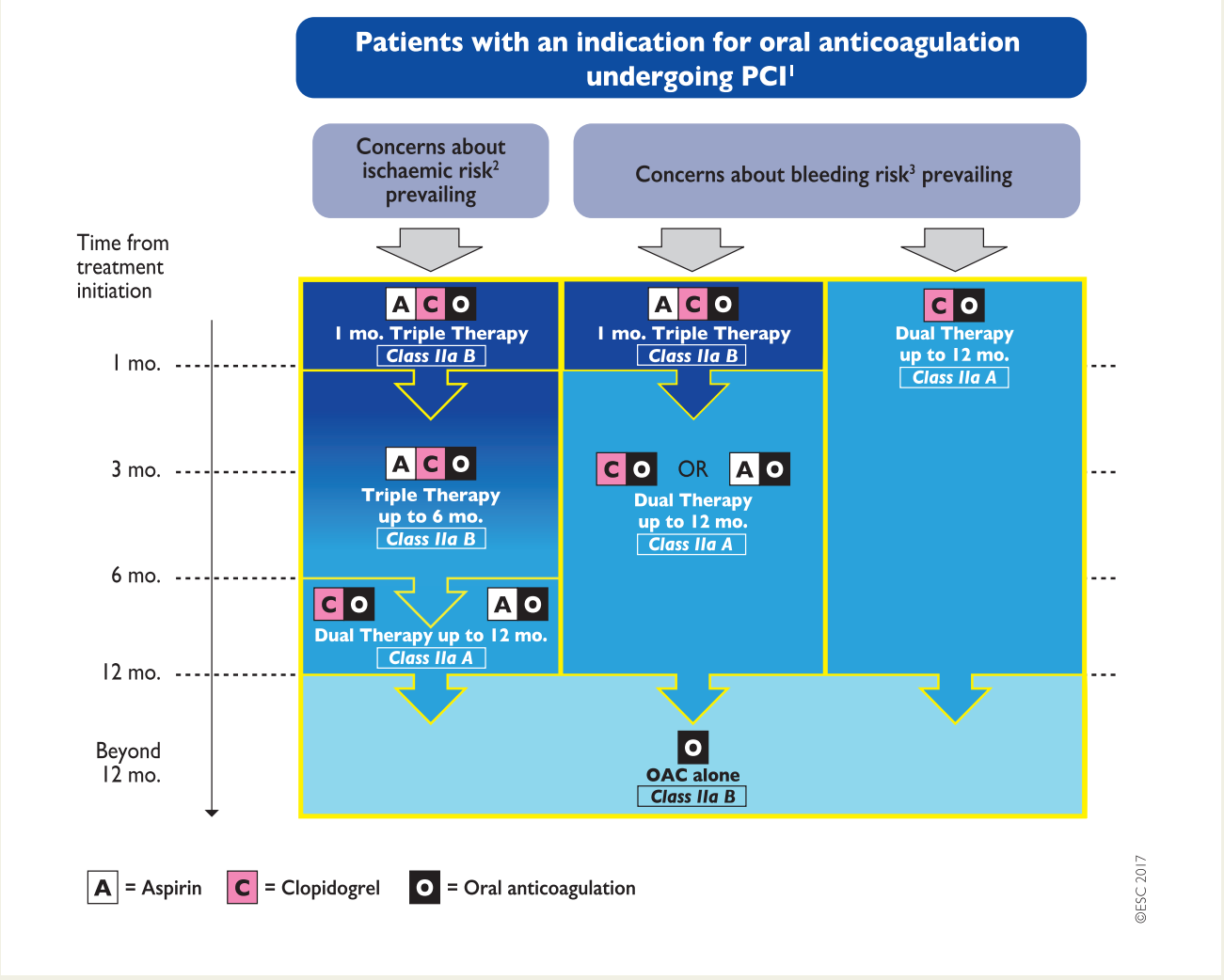


Figure 7 Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). Colour-coding refers to the number of concomitant antithrombotic medication(s). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment with a single antiplatelet agent (aspirin or clopidogrel) plus OAC.
ABC = age, biomarkers, clinical history; ACS = acute coronary syndrome; mo. = month(s); PCI = percutaneous coronary intervention.
1: Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy.
2: High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction.
3: Bleeding risk can be estimated by HAS-BLED or ABC score.

therapy in patients with OAC and coronary StenTing (WOEST) trial, which randomized 573 patients (of whom 69% of patients had AF) to dual therapy with OAC and clopidogrel (75 mg/day) or to triple therapy with OAC, clopidogrel, and aspirin 80 mg/day.[193] Treatment was continued for 1 month after BMS placement and for 1 year after DES placement (65% of patients). PCI was performed on VKA therapy in half of the patients. The primary endpoint of any TIMI bleeds assessed at 1-year follow-up was significantly reduced in the dual-therapy arm (19.5% vs. 44.9%; HR 0.36, 95% CI 0.26–0.50; $P < 0.001$), while no significant difference in major bleeding was observed. The rates of MI, stroke, target vessel revascularization, or stent thrombosis did not differ significantly, but all-cause mortality was lower in the dual-therapy group (2.5% vs. 6.4%; $P = 0.027$) at 1 year.

More recently, the PIONEER AF-PCI study randomized 2124 patients with non-valvular AF who had undergone PCI with stenting to receive, in a 1:1:1 ratio: low-dose rivaroxaban (15 mg *o.d.*) plus a $P2Y_{12}$ inhibitor (and no ASA) for 12 months; very-low-dose rivaroxaban (2.5 mg *b.i.d.*) plus DAPT for 1, 6, or 12 months; or standard therapy with a dose-adjusted VKA plus DAPT for 1, 6, or 12 months.[191] The primary safety endpoint, consisting of TIMI clinically significant bleeding, was lower in the two groups receiving rivaroxaban than in the group receiving standard therapy [16.8% in patients treated with rivaroxaban 15 mg, 18% in patients treated with rivaroxaban 2.5 mg, and 26.7% in patients treated with triple therapy (HR 0.59, 95% CI 0.47–0.76; $P < 0.001$, and HR 0.63, 95% CI 0.50–0.80; $P < 0.001$, respectively)]. It is worth mentioning that as many as 49% of patients

in both DAPT groups continued triple therapy for 12 months and no difference in major bleeding or transfusion was observed across the groups. Moreover, an INR range of 2–3 was recommended, instead of 2–2.5, which may have inflated bleeding risk in the control group. The rates of all-cause death, death from cardiovascular causes, MI, or stroke were similar in the three groups.[194] However, this study, similar to WOEST, was largely underpowered for the assessment of meaningful differences in the incidence of relevant ischaemic events such as stent thrombosis or stroke rates. Therefore, uncertainty remains regarding the comparative performance of three tested antithrombotic regimens in patients at high stroke and/or stent thrombosis risk. Procedural characteristics of coronary intervention have not been reported so far and patients with prior stroke were excluded from participation. As a result, the balance of ischaemic and bleeding risks of relatively short (i.e. 6 months or less) triple therapy duration (possibly with NOAC instead of VKA) as compared to double therapy consisting of clopidogrel and OAC remains unknown and requires a patient-by-patient decision.

Dual therapy with clopidogrel and OAC after PCI remains an appealing alternative to triple therapy given that patients exposed to OAC are at high bleeding risk, but more data, especially on efficacy and particularly in patients at high risk for stroke and/or recurrent ACS, are needed. Cessation of clopidogrel while maintaining aspirin has also been tested in the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial, where 614 patients (one-third with ACS) undergoing stenting and requiring OAC were randomly assigned to receive either 6-week or 6-month clopidogrel therapy in addition to aspirin and VKA.[195] The primary endpoint of death, MI, stent thrombosis, ischaemic stroke, or TIMI major bleeding at 9 months did not differ between the 6-week and 6-month triple therapy (9.8% vs. 8.8%; HR 1.14, 95% CI 0.68–1.91; $P = 0.63$); the same was true for the combined incidence of death, MI, stent thrombosis, and ischaemic stroke (4.0% vs. 4.3%; HR 0.93, 95% CI 0.43–2.05; $P = 0.87$). Furthermore, no difference in TIMI major bleeding (5.3% vs. 4.0%; HR 1.35, 95% CI 0.64–2.84; $P = 0.44$) was observed.

In all three studies, roughly one-third of patients presented with ACS. There was no interaction between the duration of triple therapy and clinical presentation (ACS vs. no ACS), which may reflect a real lack of increased coronary ischaemic risk in these patients or a lack of power to detect clinically meaningful differences in coronary ischaemic outcomes if these patients undergo shorter duration of DAPT regimen (i.e. 1 month[195] or immediate discontinuation of aspirin after PCI[191,193]). The rate of bleeding events peaked within the first 30 days of initiation of triple therapy and was twice as high when compared with the rate of acute coronary events including recurrent MI and stent thrombosis. These observations are consistent with the nationwide Danish registry of AF all-comers with MI, where the 90-day bleeding risk was increased on triple therapy compared with OAC plus a single antiplatelet agent (HR 1.47, 95% CI 1.04–2.08), with a consistent trend at 360 days (HR 1.36, 95% CI 0.95–1.95), without differences in ischaemic events (HR 1.15, 95% CI 0.95–1.40).[196] The same registry suggests that warfarin plus clopidogrel resulted in a non-significant reduction in major bleeds (HR 0.78, 95% CI 0.55–1.12) compared with triple therapy, with a non-significant reduction in MI or coronary death (HR 0.69, 95% CI 0.55–1.12).[197] For these reasons, duration of triple therapy should be minimized depending on bleeding and ischaemic risks (*Figure 7*; *Tables 5* and *6*).

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

Recommendations	Class[a]	Level[b]
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel, and OAC should be considered for 1 month, irrespective of the type of stent used.[195]	IIa	B
Triple therapy with aspirin, clopidogrel, and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk.[195]	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.[191,193]	IIa	A
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.[198]	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.[193,195]	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered.[c]	IIa	C
When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*[191]	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

ACS = acute coronary syndrome; AF = atrial fibrillation; *b.i.d.* = *bis in die*; CrCl = creatinine clearance; INR = international normalized ratio; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; *q.d.* = *quaque die*; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Apixaban 5 mg *b.i.d* or apixaban 2.5 mg *b.i.d.* if at least two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L); dabigatran 110 mg *b.i.d.*; edoxaban 60 mg *q.d.* or edoxaban 30 mg *q.d.* if any of the following: CrCl of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil, quinidine, or dronedarone; rivaroxaban 20 mg *q.d.* or rivaroxaban 15 mg *q.d.* if CrCl 30–49 mL/min.

Table 5 High-risk features of stent-driven recurrent ischaemic events

• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

Table 6 Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

7.3 Cessation of all antiplatelet agents

Data on the timing of cessation of any antiplatelet agents in stented patients requiring chronic OAC are scarce. In stabilized event-free patients, discontinuation of any antiplatelet agent at 1 year after stenting is encouraged in this patient population based on studies demonstrating that OACs alone are superior to aspirin post-ACS, and OAC + aspirin may not be more protective but associated with excess bleeding.[198] Dual therapy with OAC and one antiplatelet agent (aspirin or clopidogrel) may be considered beyond 1 year in patients at very high risk of coronary events as defined in *Table 5*[34] and in patients with mechanical prosthesis and atherosclerotic disease.

7.4 Type of anticoagulants

PIONEER AF-PCI is the only randomized study comparing VKAs and NOACs in patients with AF undergoing PCI for ACS or for stable CAD (i.e. patients who have an indication to receive DAPT).[191] However, in this study, two non-approved rivaroxaban regimens for AF patients were tested and a low (i.e. 15 mg *q.d.*) or very low (i.e. 2.5 mg *b.i.d.*) rivaroxaban dose in combination with a single $P2Y_{12}$ inhibitor or DAPT was compared to VKA plus DAPT, respectively. The study was underpowered for ischaemic endpoints. Therefore, no conclusion can be made on the advantages and limitations of each OAC as compared to others. However, there was an excess of stroke events in the 2.5 mg *b.i.d.* rivaroxaban arm in combination with 6-month DAPT as compared to VKA and 6-month DAPT (6 vs. 0 events; $P = 0.02$).

In the four phase III NOAC AF trials, no interactions were demonstrated between treatment effect and outcome according to prior coronary status (ACS vs. no ACS), and it is likely that the benefit of NOAC over VKA is preserved in CAD patients with AF.[199–202] At least, this was the case among patients exposed to antiplatelet therapy. There is no strong evidence for choosing one NOAC over another. Dabigatran is the only NOAC that has been tested in a phase III trial at reduced daily regimen (i.e. 110 mg *b.i.d.*) and for which non-inferiority vs. warfarin was shown.[199] Although lower doses of other NOACs (i.e. apixaban 2.5 mg *b.i.d.* or edoxaban 30 mg *o.d.*) might be considered to reduce bleeding risk, these dosages have been evaluated only in a subset of patients in the phase III trials based on prespecified dosing algorithms. Their benefit in stroke prevention in patients with a normal renal function is uncertain. Three ongoing large-scale outcome studies are evaluating combinations of NOACs or VKAs with antiplatelet therapy in AF patients undergoing stent-PCI (NCT02164864, NCT02415400, and NCT02866175). Various dose regimens of NOAC, different types of $P2Y_{12}$ inhibitors, and different exposure times are being evaluated.

7.5 Type of stent

The choice of newer-generation DES vs. BMS in patients requiring long-term anticoagulation is no longer controversial. First, data from the DAPT trial indicate a similar impact of prolonged DAPT administration irrespective of stent type (BMS vs. DES),[128] and the risk of adverse events among patients with DAPT cessation and patients undergoing non-cardiac surgery indicate no differences between BMS and DES.[17,129,203] Second, two randomized trials have demonstrated the superiority of newer-generation DES over BMS in high bleeding risk patients who cannot tolerate long-term exposure to DAPT,[130,204] such as those needing chronic OAC (section 2.2).

Altogether, both trials suggest that second-generation DES should be the default choice in patients with high bleeding risk.

8. Elective non-cardiac surgery in patients on dual antiplatelet therapy

It is estimated that 5–25% of patients with coronary stents may require non-cardiac surgery within 5 years after stent implantation.[205] Management of patients on DAPT who are referred for surgical procedures involves consideration of: (1) the risk of stent thrombosis (particularly if DAPT needs to be interrupted); (2) the consequences of delaying the surgical procedure; and (3) the increased intra- and periprocedural bleeding risk and possible consequences of such bleeding if DAPT is continued.[206–208] Given the complexity of these considerations, a multidisciplinary approach—involving interventional cardiologists, cardiologists, anaesthetists, haematologists, and surgeons—is required to determine the patient's risk for bleeding and thrombosis and to choose the best management strategy.

Surgical interventions can be divided into low-risk, intermediate-risk, and high-risk groups, with estimated 30-day cardiac event rates for cardiac death or MI of < 1%, 1–5%, and ≥5%, respectively.[205,209] A practical classification of the bleeding risk associated with each type of non-cardiac surgery has been recently proposed by the Stent After Surgery group.[210]

In surgical procedures with low bleeding risk, every effort should be taken not to discontinue DAPT perioperatively. In surgical procedures with moderate bleeding risk, patients should be maintained on aspirin while $P2Y_{12}$ inhibitor therapy should be discontinued whenever possible. More challenging decision making is to be faced among patients on DAPT who undergo high bleeding risk non-cardiac surgeries, including vascular reconstructions, complex visceral procedures, neurosurgery, and transbronchial operations.[211–213] In these cases, particular attention should be paid to timely discontinuation of $P2Y_{12}$ inhibitor therapy to minimize the off-therapy period before surgical intervention.

Discontinuation before non-cardiac surgery: To reduce the risk of bleeding and transfusion, it is recommended to postpone elective non-cardiac surgery until completion of the full course of DAPT. In most clinical situations, aspirin provides benefit that outweighs the bleeding risk and should be continued.[214,215] Possible exceptions to this recommendation include intracranial procedures, transurethral prostatectomy, intraocular procedures, and operations with extremely high bleeding risk.[157]

A higher risk of ischaemic events in the case of non-cardiac surgery has been reported after first-generation DES[203] and a higher risk for MACE has also been shown during the first weeks after non-cardiac surgery in patients with implanted stents.[203,216,217] Furthermore, surgery *per se*, irrespective of the timing of DAPT discontinuation, is associated with pro-inflammatory and pro-thrombotic effects, thereby increasing the risk of coronary thrombosis at the level of the stented vascular segment as well as throughout the coronary vasculature.[218,219] Therefore, in patients undergoing non-cardiac surgery after recent ACS or stent implantation, the benefits of early surgery for a specific pathology (e.g. malignant tumours or vascular aneurysm repair) should be balanced against the risk of cardiovascular events and the strategy should be discussed by a multidisciplinary team.

Prior recommendations with regard to duration of DAPT[220,221] and the timing of non-cardiac surgery[207,222] in patients treated with DES were based on observations of those treated with first-generation DES. Compared with first-generation DES, currently used newer-generation DES are associated with a lower risk of stent thrombosis and appear to require a shorter minimum duration of DAPT.[100,103,104,223–225] Furthermore, in the PARIS registry, interruption of DAPT grounded on physician judgment in patients undergoing surgery at any time point after PCI was not associated with an increased risk of MACE.[17]

In the absence of a surgical control group, it remains challenging to identify a clear time frame after ACS or coronary stenting where there is no additional risk or the risk is acceptably low for patients to undergo surgery. Therefore, almost all registries have attempted to identify such landmarks by looking at the time course of the surgical ischaemic risk over time in order to identify when it levels off and remains stable thereafter following an ACS or stent implantation procedure.[17] By doing so, many registries have reported that surgery-associated risk in DES-PCI-treated patients reaches a stable level after 3–6 months.[17,214,215] However, without a surgical control group, these findings are potentially influenced by the type and urgency of the surgical procedures. To overcome this limitation, two large matched cohorts of patients undergoing surgery were recently reported. Using Danish population-based registries and individual-based record linkage of Danish registries, 4303 DES-PCI-treated patients who underwent a surgical procedure within 12 months were identified and were compared with a control group of patients without established stable CAD undergoing similar surgical procedures (n = 20 232).[226] This evaluation of the comparative risk associated with surgery in DES-PCI-treated patients vs. patients without known stable CAD revealed an increased overall risk for MI and cardiac death in the patients with previous DES-PCI, owing to higher MI rates but similar mortality risk.[226] However, this difference was highly time-dependent and limited to the first month after DES-PCI.[226] These data suggest that surgery, if possible, should be delayed for at least 1 month after DES-PCI. Data for patients with coronary stents implanted in a Veterans' Administration (VA) hospital from 2000 to 2010 were also recently matched with VA Surgical Quality Improvement Program data to identify non-cardiac surgery within 24 months of stent placement.[227] Each patient with a stent(s) was matched with two surgical patients without stents on surgical characteristics and cardiac risk factors. The two groups had similar risk of adverse cardiac events during 2 years of follow-up. However, patients with stents had a higher risk of adverse cardiac events within the 30-day post-operative period.[227] The incremental risk did not vary by stent type.[227] In both studies, roughly 50% of patients underwent stenting because of ACS and no incremental risk was observed in this higher risk population as compared to stable CAD patients.

Therefore, a minimum of 1 month of DAPT should be considered, independently of the type of implanted stent (i.e. BMS or newer-generation DES), in cases when surgery cannot be delayed for a longer period; however, such surgical procedures should be performed in hospitals where catheterization laboratories are available 24/7, so as to treat patients immediately in case of perioperative thrombotic events (Figure 8). In patients at high ischaemic risk due to ACS presentation or complex coronary revascularization procedure, delaying surgery up to 6 months after index ACS or PCI may be reasonable as an additional safeguard to minimize the risk of perisurgical MI, and based on unmatched retrospective registry data if the risks of further delaying surgery are acceptable.

In patients needing surgery within a few days, it was previously recommended to withhold clopidogrel and ticagrelor for 5 days and prasugrel for 7 days prior to surgery unless there is a high risk of thrombosis.[228] However, emerging evidence, which is extensively discussed in Chapter 5, challenges such a long discontinuation period for ticagrelor before a safe surgical procedure can be undertaken (*Figure 9*).[152,153]

Although these data refer to patients undergoing cardiac surgery, it is rational to extend these findings to the non-cardiac surgery population, given the same offset kinetics and principally lower risk of bleeding in non-cardiac surgeries relative to cardiac surgery procedures (*Figure 9*). In cases where the consequences of even minor bleeding would be unacceptable (e.g. spinal surgery or other neurosurgical procedures) or the bleeding risk largely outweighs the ischaemic risk (e.g. a medium- to high-risk surgical bleeding procedure is undertaken 6 months or more after single stent implantation for stable CAD indication), $P2Y_{12}$ inhibitors may be discontinued for a

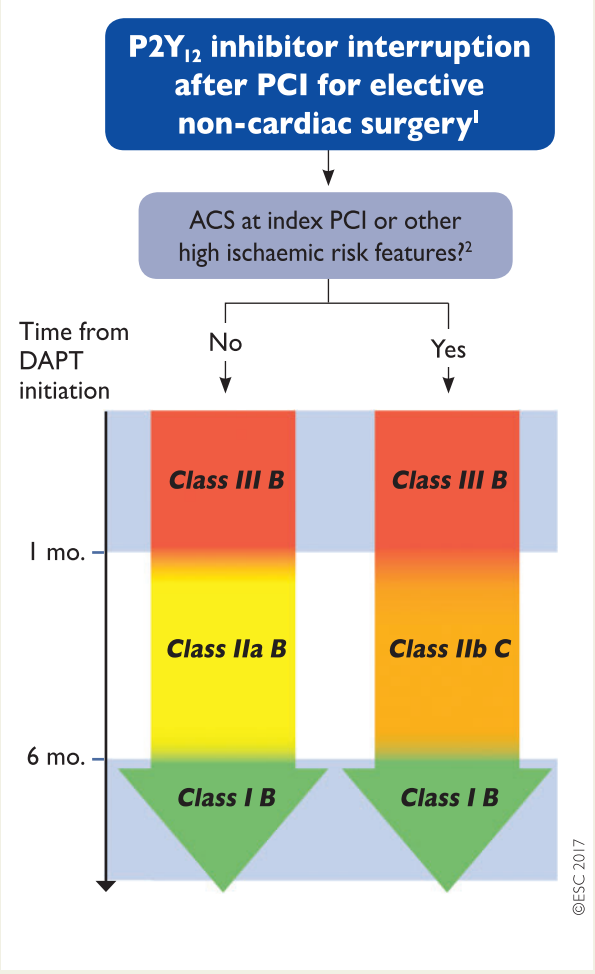


Figure 8 Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = IIa; orange = Class IIb).
ACS = acute coronary syndromes.
[1]Availability of H24 cath-lab service in place is suggested in case of major surgery within 6 months after PCI.
[2]High ischaemic risk features are presented in Table 5.

longer duration of time to ensure no residual platelet inhibition at the time of planned surgery. For patients with a very high risk of stent thrombosis, bridging therapy with intravenous, reversible glycoprotein inhibitors, such as eptifibatide or tirofiban,[229] may be considered. Cangrelor, a reversible intravenous $P2Y_{12}$ inhibitor, has been shown to provide effective platelet inhibition[230] and is an appealing alternative to glycoprotein IIb/IIIa inhibitors,[231] given the well-known role of $P2Y_{12}$ inhibition in preventing stent thrombosis and the quicker offset of action as compared to tirofiban or eptifibatide. Concomitant parenteral anticoagulation therapy in conjunction with cangrelor or reversible glycoprotein inhibitors is not recommended to minimize bleeding risk while awaiting surgical procedures.

Restart after surgery: If $P2Y_{12}$ inhibitor therapy has been stopped before a surgical procedure, therapy should be restarted as soon as possible (within 48 h), given the substantial thrombotic hazard associated with lack of platelet inhibition early after surgery in patients with recent stent implantation and/or an ACS episode (Figure 9).[232,233]

The time for restarting $P2Y_{12}$ inhibitors after surgery should ultimately be determined via a multidisciplinary discussion before surgery and traced in the patient file.

Dual antiplatelet therapy in patients undergoing elective non-cardiac surgery

Recommendations	Class[a]	Level[b]
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.[232–236]	I	B
After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period.[227]	IIa	B
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.[152,153,160]	IIa	B
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C
In patients with recent MI or other high ischaemic risk features[c] requiring DAPT, elective surgery may be postponed for up to 6 months.[17,214,215,234]	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.[229,237–239]	IIb	C
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.[203]	III	B

DAPT = dual antiplatelet therapy; MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]High ischaemic risk features are provided in Table 5.

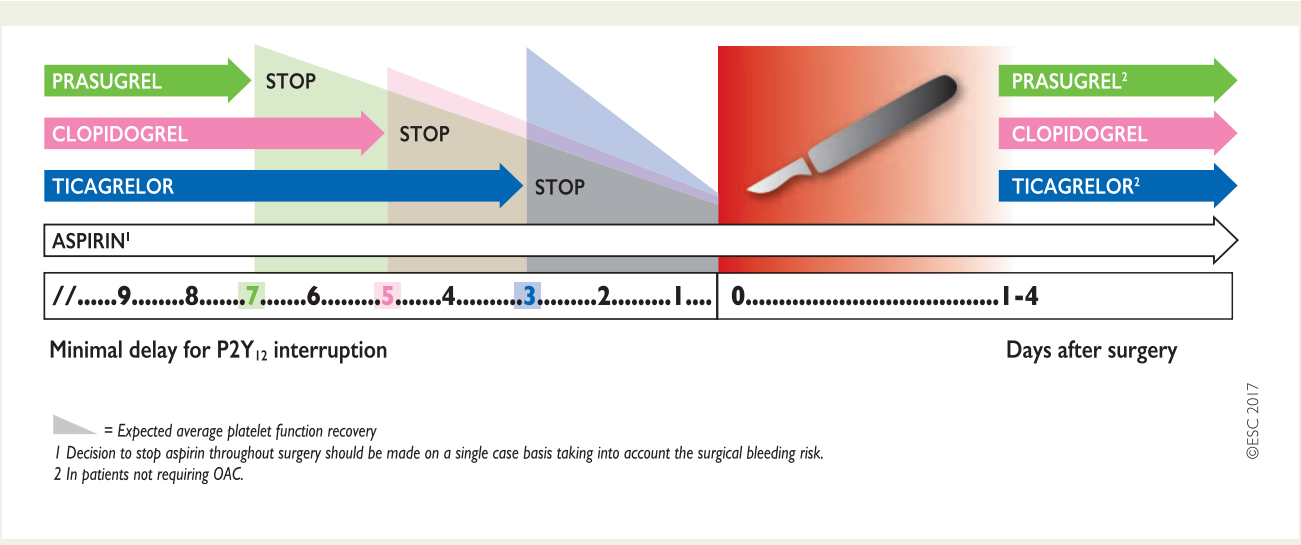


Figure 9 Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery
OAC = oral anticoagulant.

9. Gender consideration and special populations

9.1 Gender specificities

There is no convincing evidence for a gender-related difference in the efficacy and safety of currently available DAPT type or duration across studies. No single trial or pooled analysis of investigations assessing a shorter than 1 year vs. at least 1 year DAPT duration has shown heterogeneous findings across genders.[26,112,240,241] In the DAPT trial, there was a borderline quantitative interaction suggesting a lower relative treatment benefit for stent thrombosis reduction with prolonged DAPT in female as compared to male patients (P_{int} =0.04).[26] However, no such signal was apparent for MACCE (P_{int} = 0.46) or bleeding (P_{int} = 0.40) endpoints. Within the PEGASUS trial, there was no signal suggesting heterogeneity across the primary study endpoint with respect to gender (P_{int} = 0.84).[29] On the other hand, there was a positive quantitative interaction (P_{int} = 0.03) suggesting that female patients may derive a relatively greater treatment benefit with respect to stroke prevention from prolonged treatment with aspirin and ticagrelor as compared to aspirin alone. However, no such signal was evident for cardiovascular death, MI, or safety endpoints.

9.2 Diabetes mellitus

Patients with diabetes mellitus presenting with both stable and unstable CAD carry a worse prognosis in terms of short- and long-term risks of fatal and non-fatal ischaemic events, with enhanced platelet hyperactivity playing a putative causal role. In the CURE trial, patients with diabetes derived a similar treatment benefit from the addition of clopidogrel on top of aspirin as compared to patients without.[40] No signal for greater treatment benefit was apparent in TRITON-TIMI 38 in patients with diabetes as compared to those without with respect to the study primary endpoint, and a consistent lack of heterogeneity signal with respect to diabetes mellitus was observed in the PLATO trial.[20,23] Hence, there is no convincing evidence that the presence of diabetes should affect decision making with respect to the choice of $P2Y_{12}$ inhibitors.

As it related to DAPT duration, the DAPT study found a slightly lower relative risk reduction for MI endpoint in patients with diabetes as compared to those without diabetes (P_{int} = 0.02).[242] However, there was no signal for heterogeneity with respect to the concomitant presence of diabetes mellitus across all other ischaemic or safety endpoints. Finally, no difference with respect to the presence or absence of diabetes was observed for the primary efficacy endpoint in the PEGASUS study (P_{int} = 0.99).[145] Altogether, current evidence suggests that diabetes mellitus should not be the only appraised patient-specific feature when deciding upon the type or duration of DAPT.

9.3 Lower-extremities artery disease

Patients with LEAD are at heightened risk of ischaemic complications and mortality. The combination of symptomatic LEAD and CAD is associated with further heightened ischaemic risk beyond that associated with symptomatic disease in either vascular bed alone.[243] In 3096 patients with LEAD included in the CHARISMA trial, DAPT was associated with a lower rate of MI and hospitalization for ischaemic events but not the overall composite primary endpoint. There was no difference between the groups in moderate, severe, or fatal bleeding, but there was an increase in minor bleeding in the DAPT group.[244] The PEGASUS investigators recently examined a subgroup of 1143 patients with LEAD and found that patients with prior MI with LEAD had a 60% increased risk of MACE relative to patients without LEAD, even after adjusting for differences in baseline characteristics.[140] This increased ischaemic risk translated into a robust absolute risk reduction of 5.2% at 3 years with ticagrelor 60 mg *b.i.d.* compared with placebo. In the setting of this robust ischaemic risk reduction, there were significant reductions in cardiovascular and all-cause mortality. Treatment with ticagrelor vs. placebo reduced the risk of adverse limb events in addition to the benefits observed for MACE and mortality. Reductions in acute limb ischaemia have also been shown with other antiplatelet

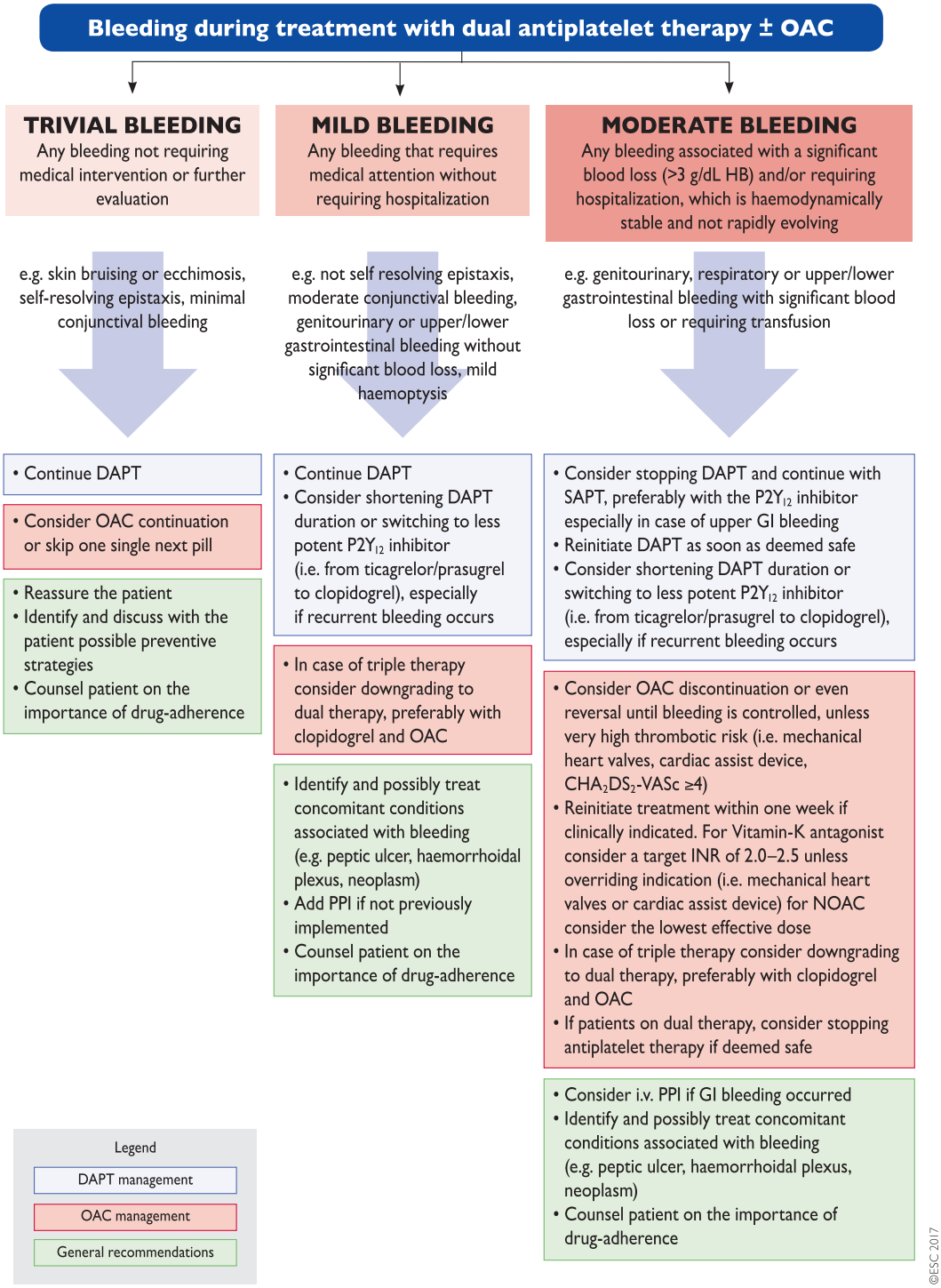


Figure 10 Practical recommendations for the management of bleeding in patients treated with dual antiplatelet therapy with or without concomitant oral anticoagulation. Practical recommendations for the management of bleeding in patients treated with dual antiplatelet therapy with or without concomitant oral anticoagulation. Blue boxes refer to management of antiplatelet therapy. Dark-red boxes refer to the management of oral anticoagulation. Light-green boxes refer to general recommendation for patients' safety.
ACS = acute coronary syndrome; CHA_2DS_2-VASc= cardiac failure, hypertension, age ≥75 (2 points), diabetes, stroke (2 points)–vascular disease, age 65–74, sex category; DAPT = dual antiplatelet therapy; GI = gastrointestinal; HB = haemoglobin; INR = international normalized ratio; i.v. = intravenous; OAC = oral anticoagulant; NOAC = non-vitamin-K antagonist; PPI = proton pump inhibitor; RBC = red blood cell; SAPT = single antiplatelet therapy.

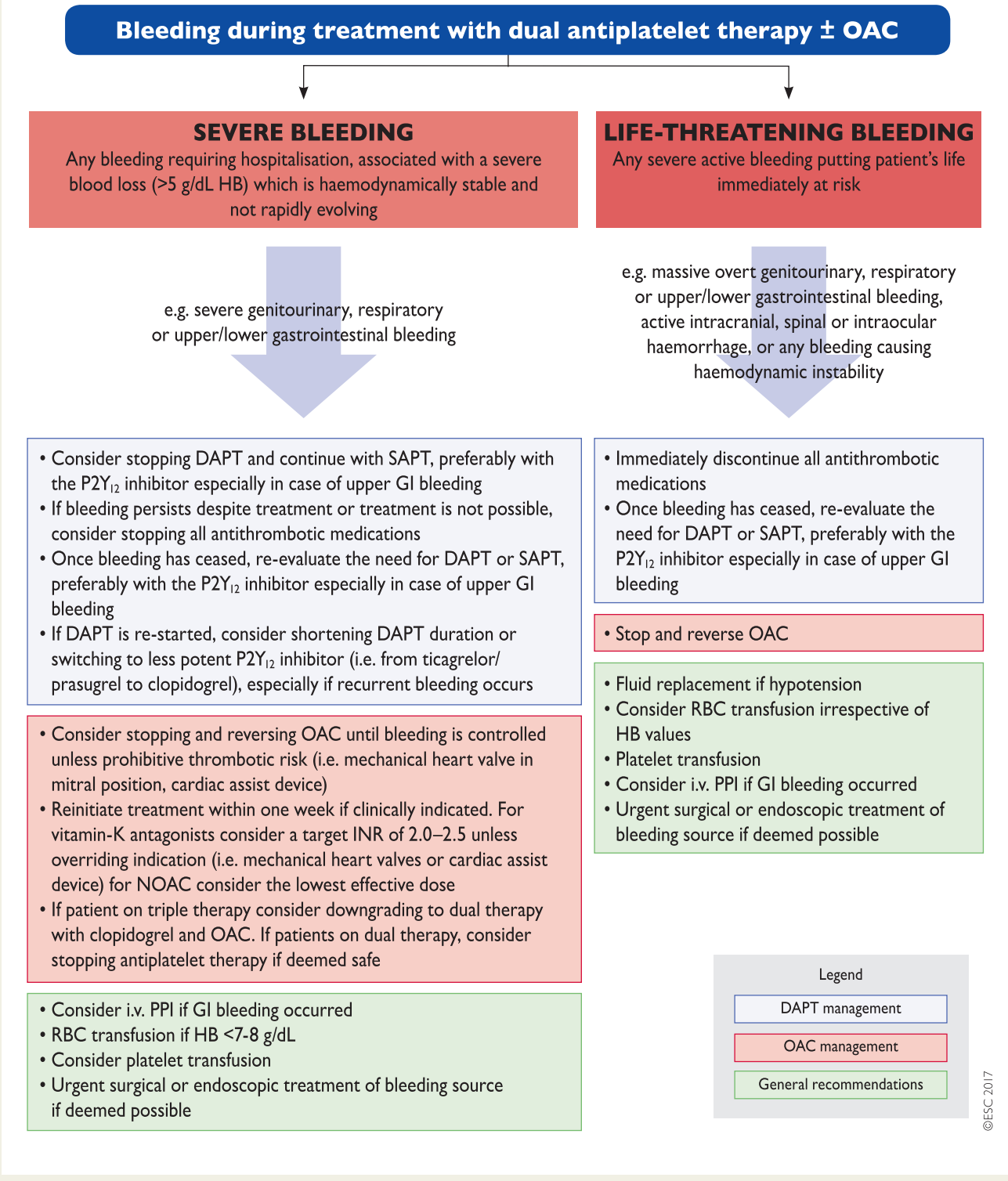


Figure 10 Continued

agents, such as vorapaxar, demonstrating that this morbidity is modifiable with potent and prolonged antithrombotic strategies.[245] In the all-comer PRODIGY trial, 246 (12.5%) patients were included with symptomatic LEAD. LEAD status was associated with a higher risk of death and ischaemic events (HR 2.80, 95% CI 2.05–3.83; $P < 0.001$).[246] Prolonged vs. short DAPT conveyed a lower risk of the primary efficacy endpoint in LEAD patients (16.1% vs. 27.3%; HR 0.54, 95% CI 0.31–0.95; $P = 0.03$) but not in patients without LEAD (9.3% vs. 7.4%; HR 1.28, 95% CI 0.92–1.77; $P = 0.14$), with positive interaction ($P = 0.01$). The risk of definite or probable stent thrombosis as well as

overall mortality was significantly lower in LEAD patients treated with prolonged DAPT as compared with those receiving short DAPT.

9.4 Complex percutaneous coronary intervention

While high PCI complexity intuitively represents a driver for favouring a prolonged over a shortened DAPT duration, the evidence regarding optimal DAPT duration based on complexity of intervention is limited. In a patient-level meta-analysis from six RCTs investigating DAPT durations after coronary stenting, including 9577 patients, complex PCI was defined as the composite of at least three stents implanted, at least three lesions treated, bifurcation with two stents implanted, total stent length >60 mm, and chronic total occlusion as target lesion.[247] Patients who underwent complex PCI had a two-fold increase of MACE (5.0% vs. 2.5%; P = 0.001). Long- and short-DAPT were defined as a DAPT duration ≥12 months and ≤6 months, respectively. Compared with short-DAPT, long-DAPT was associated with a significant reduction in MACE in the complex PCI group (4.0% vs. 6.0%; adjusted HR 0.56, 95% CI 0.35–0.89) vs. the non-complex PCI group (2.5% vs. 2.6%; adjusted HR 1.01, 95% CI 0.75–1.35; P_{int} = 0.01). The magnitude of the reduction in MACE with long-DAPT increased progressively as the degree of procedural complexity was greater. Long-DAPT was overall associated with increased risk of major bleeding, which was uniform in magnitude between groups (P_{int} = 0.15).

9.5 Dual antiplatelet therapy decision making in patients with stent thrombosis

Patients presenting with stent thrombosis represent a challenging patient population in whom no randomized clinical evidence is available to guide decision making. Observational studies have shown that the risk of stent thrombosis recurrence after the first episode of stent thrombosis is worrisome. Armstrong *et al* reported on a combined retrospective and prospective observational California registry of angiographic definite stent thrombosis at five academic hospitals from 2005 to 2013.[248] The entry criterion was the occurrence of a definite stent thrombosis, which was observed in 221 patients overall out of an unknown number of patients at risk. With the important caveat of not knowing for each stent type the exact timing of the first stent thrombosis event after the index procedure, 104 (47%) patients had received a first generation DES, 51 (23%) a BMS, and 19 (9%) a second generation DES. After a median follow-up of 3.3 years, 29 patients developed definite or probable recurrent stent thrombosis, while 19 presented angiographic definite recurrent stent thrombosis. The cumulative hazard of definite or probable recurrent stent thrombosis was 16% at 1 year and 24% at 5 years. The cumulative hazard of angiographic definite recurrent stent thrombosis was 11% at 1 year and 20% at 5 years. Taken together, these findings confirm the high risk of stent thrombosis recurrence after the first stent thrombosis. An additional piece of information, which is conveyed by this important analysis, is that the risk of recurrence is highest in the first few months after the first event and that it does not abate entirely over time. Both prasugrel and ticagrelor have been shown to be associated with a significant reduction of definite and definite or probable stent thrombosis as compared to clopidogrel.[20,23] Moreover, both studies indicated that the number of recurrent events is also significantly decreased by treatment with ticagrelor or prasugrel as compared to clopidogrel. Hence, the use of clopidogrel after stent thrombosis cannot be regarded as an effective treatment option. Considering the long-term risk of recurrence after first stent thrombosis, it may be reasonable to make every effort to maintain DAPT for a very long-term period in this highly selected high-risk patient population, if tolerated.

9.6 Patients who develop bleeding while on treatment

Patients who develop bleeding complications while on DAPT represent a challenging patient population for whom no guidance from RCTs is available.

The decision to withhold or continue DAPT in this setting largely depends on ischaemic (e.g. indication for DAPT and time from last stent insertion, if any, to bleeding) vs. recurrent/prolonged bleeding risks. A practical flow chart in order to manage this challenging population is provided in *Figure 10* and additional information on practical management can be found elsewhere.[249] As bleeding is an independent predictor of recurrent bleeding,[250] type, dose, and duration of DAPT should be reassessed in this setting.

Gender considerations and special populations

Recommendations	Class[a]	Level[b]
Similar type and duration of DAPT are recommended in male and female patients.[26,240]	I	A
It is recommended to reassess the type, dose, and duration of DAPT in patients with actionable bleeding complications while on treatment.	I	C
Similar type and duration of DAPT should be considered in patients with and without diabetes mellitus.[145,242]	IIa	B
Prolonged (i.e. >12 months[c]) DAPT duration should be considered in patients with prior stent thrombosis, especially in the absence of correctable causes (e.g. lack of adherence or correctable mechanical stent-related issues).	IIa	C
Prolonged (i.e. >12 months) DAPT duration may be considered in CAD patients with LEAD.[140,246]	IIb	B
Prolonged (i.e. >6 months) DAPT duration[d] may be considered in patients who underwent complex PCI.[247]	IIb	B

CAD = coronary artery disease; DAPT = dual antiplatelet therapy; LEAD = lower-extremities artery disease; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Possibly for as long as can be tolerated.
[d]Complex PCI defined as the composite of at least three stents implanted, at least three lesions treated, bifurcation with two stents implanted, total stent length >60 mm, and chronic total occlusion as target lesion.

10. Key messages

(1) Benefits and risks of DAPT: DAPT reduces the risk of stent thrombosis across the entire spectrum of events, from acute to very late occurrences. However, treatment with DAPT beyond 1 year after MI, or after PCI, exerts the majority of its benefit by reducing the rate of spontaneous MI. The risk of bleeding in patients on DAPT is proportionally related to its duration both within and beyond 1 year of treatment duration. Since the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on prior cardiovascular history (such as prior ACS/MI vs. stable CAD), and prediction models to estimate on-DAPT bleeding risk have been developed, an individualized approach based on ischaemic vs. bleeding risk assessment is warranted.

(2) Bleeding mitigation strategy: Every effort should be pursued to mitigate the risk of bleeding complications while the patient is on DAPT, including access site selection, modulation of modifiable risk factors for bleeding, low dose aspirin, low dose of P2Y12 inhibitor as appropriate, and routine use of PPI.

(3) $P2Y_{12}$ inhibitor selection: Clopidogrel is considered the default $P2Y_{12}$ inhibitor in patients with stable CAD treated with PCI, those with indication to concomitant oral anticoagulation, as well as in ACS patients in whom ticagrelor or prasugrel are contraindicated. Ticagrelor or prasugrel is recommended in ACS patients unless drug-specific contraindications exist.

(4) Timing of $P2Y_{12}$ inhibitor initiation: The timing of initiation of a $P2Y_{12}$ inhibitor is both drug- (i.e. ticagrelor or clopidogrel vs. prasugrel) and disease-specific (i.e. SCAD vs. ACS and type thereof).

(5) Stable CAD patients treated with PCI: Irrespective of the type of metallic stent implanted, the duration of DAPT is 1–6 month(s) depending on the bleeding risk. For patients in whom the ischaemic risk prevails over the risk of bleeding, a longer DAPT duration may be considered.

(6) Metallic stent type and DAPT duration: The need for a short DAPT regimen should no longer justify the use of BMS instead of newer-generation DES. DAPT duration in each individual patient should be guided by an individualized approach based on ischaemic vs. bleeding risk assessment and not by the stent type.

(7) Stable CAD patients treated with CABG: There is insufficient data to recommend DAPT in this patient population.

(8) ACS patients: Irrespective of the final revascularization strategy (e.g. medical therapy, PCI, or CABG), the default DAPT duration in these patients is 12 months. Six-month therapy duration should be considered in high bleeding risk patients, whereas >12-month therapy may be considered in ACS patients who have tolerated DAPT without a bleeding complication.

(9) Patients with indication for oral anticoagulation: Compared with OAC therapy alone, the addition of DAPT to OAC therapy results in at least a two- to three-fold increase in bleeding complications. Therefore, these patients should be considered at high risk of bleeding and the indication for OAC should be reassessed and treatment continued only if a compelling indication exists. The duration of triple therapy should be limited up to a maximum of 6 months or omitted after hospital discharge, taking into account the ischaemic (e.g. complexity of treated CAD, amount of disease left untreated, technical considerations regarding stent implantation techniques, and results) as well as the bleeding risk. The use of ticagrelor or prasugrel in this setting is not recommended.

(10) Patients undergoing elective non-cardiac surgery after coronary stent implantation: A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery. Scheduled surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after at least 1 month, irrespective of the stent type, if aspirin can be maintained throughout the perioperative period. If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with cangrelor, tirofiban, or eptifibatide may be considered, especially if surgery has to be performed within 1 month after stent implantation.

(11) Gender consideration and special populations: Similar type and duration of DAPT are recommended in male and female patients, as well as in patients with and without diabetes mellitus. Patients with prior stent thrombosis, especially in the absence of correctable causes, should receive prolonged DAPT. A prolonged DAPT regimen may also be considered in patients with LEAD or who have undergone complex PCI. It is recommended to reassess the type, dose, and duration of DAPT in patients with actionable bleeding complications while on treatment. In patients with active bleeding while on DAPT, the decision to stop both antiplatelet agents, especially if shortly after PCI, should be taken only if the bleeding is life-threatening and the source has not been or cannot be treated. In such a rare case scenario, the patient should be transferred to a primary PCI facility centre.

11. Evidenced-based 'to do and not to do' messages

Recommendations that are class I or III with a level of evidence A or B

Recommendations on $P2Y_{12}$ inhibitor selection and timing	Class[a]	Level[b]
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg *b.i.d.*) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.[c]	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg *o.d.*) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high risk of life-threatening bleeding or other contraindications.[c]	I	B

Continued

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, as well as in patients with STEMI.	I	A
Clopidogrel (600 mg loading dose, 75 mg *o.d.*) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.	I	A
Clopidogrel (300 mg loading dose in patients aged ≤75, 75 mg *o.d.*) is recommended on top of aspirin in STEMI patients receiving thrombolysis.	I	A
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.	III	B
Measures to minimize bleeding while on dual antiplatelet therapy		
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75 - 100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.[d]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A
Switching between oral $P2Y_{12}$ inhibitors		
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist.[c]	I	B
Dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention		
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).	I	A
Dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management		
In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months.	I	A
Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischaemic benefit.	I	B
Prasugrel is not recommended in medically managed ACS patients.	III	B
Dual antiplatelet therapy in patients undergoing elective cardiac and non-cardiac surgery		
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.	I	B
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.	III	B
Gender considerations		
Similar type and duration of DAPT are recommended in male and female patients.	I	A

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; NSTE-ACS = non-ST elevation acute coronary syndrome; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; TIA = transient ischaemic attack.

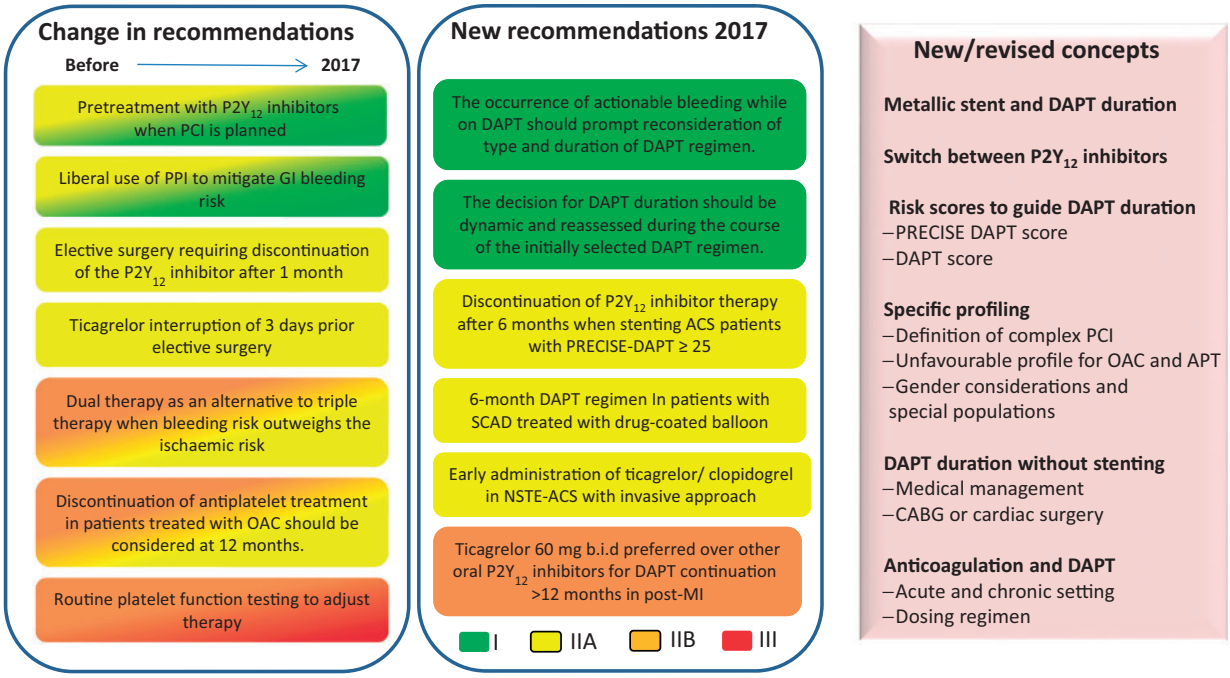
[a]Class of recommendation.

[b]Level of evidence.

[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or TIA, or ongoing bleeds; prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.

[d]While the evidence that a PPI does not increase the risk of cardiovascular events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

What is new in the 2017 ESC focussed update on DAPT?



ACS = acute coronary syndrome; APT = anti-platelet therapy; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTE= Non-st-segment elevation; OAC = oral anti-coagulant;PCI = percuatenous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; Stable CAD = stable coronary artery disease.

12. Web addenda and Clinical Cases companion document

All Web figures, Web tables, and the Clinical Cases companion document are available at the European Heart Journal online and also via the ESC Web site at: www.escardio.org/guidelines

13. Appendix

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