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Consensus statement

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De-escalation or abbreviation of dual antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention: a Consensus Statement from an international expert panel on coronary thrombosis

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Abstract

Conventional dual antiplatelet therapy (DAPT) for patients with acute coronary syndromes undergoing percutaneous coronary intervention comprises aspirin with a potent P2Y purinoceptor 12 ($P2Y_{12}$) inhibitor (prasugrel or ticagrelor) for 12 months. Although this approach reduces ischaemic risk, patients are exposed to a substantial risk of bleeding. Strategies to reduce bleeding include de-escalation of DAPT intensity (downgrading from potent $P2Y_{12}$ inhibitor at conventional doses to either clopidogrel or reduced-dose prasugrel) or abbreviation of DAPT duration. Either strategy requires assessment of the ischaemic and bleeding risks of each individual. De-escalation of DAPT intensity can reduce bleeding without increasing ischaemic events and can be guided by platelet function testing or genotyping. Abbreviation of DAPT duration after 1–6 months, followed by monotherapy with aspirin or a $P2Y_{12}$ inhibitor, reduces bleeding without an increase in ischaemic events in patients at high bleeding risk, particularly those without high ischaemic risk. However, these two strategies have not yet been compared in a head-to-head clinical trial. In this Consensus Statement, we summarize the evidence base for these treatment approaches, provide guidance on the assessment of ischaemic and bleeding risks, and provide consensus statements from an international panel of experts to help clinicians to optimize these DAPT approaches for individual patients to improve outcomes.

Sections

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Introduction

Antiplatelet therapy is central to the management of acute coronary syndromes (ACS) in patients undergoing percutaneous coronary intervention (PCI). The current 'standard-of-care' dual antiplatelet therapy (DAPT) for patients with ACS undergoing PCI, according to international guidelines, comprises aspirin combined with a potent P2Y purinoceptor 12 ($P2Y_{12}$) inhibitor, namely prasugrel or ticagrelor[1–6]. Although DAPT reduces the risk of ischaemic events after ACS, it substantially increases the risk of bleeding[7,8]. Increased awareness of the prognostic importance of bleeding has prompted the investigation of strategies to de-escalate DAPT and identify a strategy balancing thrombotic and bleeding risks.

The existing European and North American guidelines on the management of ST-segment elevation myocardial infarction (STEMI)[2,4], non-ST-segment elevation ACS[1,5] and PCI[3,6] only loosely cover options for antithrombotic therapy. To date, no position documents or guidelines have been published that summarize the available options for abbreviation or de-escalation of DAPT nor the evidence base supporting the various strategies. Therefore, we convened an international panel of experts to produce a Consensus Statement to guide clinicians when identifying patients who are suitable for abbreviation or de-escalation of DAPT and to improve clinical outcomes by maintaining efficacy while reducing bleeding.

In this Consensus Statement, we refer to shortening of DAPT duration (also known as abbreviation of DAPT), in which DAPT is curtailed before the standard 12 months and treatment is continued with a single antiplatelet agent, either aspirin or a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor), and to de-escalation of DAPT intensity, in which treatment is switched from conventional doses of the more potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) to either clopidogrel or reduced-dose prasugrel. We summarize the evidence base for these two approaches to treatment, provide guidance on the assessment of ischaemic and bleeding risks, and make recommendations to help clinicians to optimize these approaches to DAPT for individual patients (Box 1). We also identify current gaps in the evidence, which represent areas for future research (Box 2). Our recommendations do not apply to patients who require oral anticoagulation after ACS because they represent a very specific cohort for whom the evidence base for abbreviation or de-escalation of DAPT is not robust and different medications are required when these strategies are attempted.

Methods for consensus recommendations

We conducted a search of the literature to identify clinical trials of de-escalation of DAPT intensity or abbreviation of DAPT duration in patients with ACS treated with PCI. The PubMed, Embase and Cochrane Library databases were searched for papers published up to November 2022, with no restriction on language. Reference lists of selected papers were also checked for additional relevant papers. The authors worked on allocated sections of this Consensus Statement in pairs. All the authors reviewed all sections of the manuscript and participated in a series of 'rounds', in which the manuscript was shared with all other authors and the comments made were used to inform and evolve the manuscript in the next round. Video discussions between the authors were also conducted. All the authors judged the available evidence, leading to the consensus recommendations.

Risk of bleeding in clinical trials

In clinical trials of DAPT, the incidence of major bleeding in the 12 months after PCI among patients with ACS is 1–10% depending on the definition of 'bleeding', the type and dose of $P2Y_{12}$ inhibitor used[9–11], and the ethnicity and bleeding risk category of the patient[12,13]. In observational studies, the reported incidence of major bleeding is 2.8–11.0%[11,14]. Major bleeding in patients with ACS increases mortality by nearly threefold in the first 12 months after hospital discharge[14] and increases the adjusted hazard ratio for death or myocardial infarction (MI) at 30 days by up to fivefold, with risk increasing in proportion to the severity of the bleeding[15].

The risk of bleeding with DAPT relates not only to the combined effects of aspirin and the $P2Y_{12}$ inhibitor on haemostasis but also to the potency of the $P2Y_{12}$ inhibitor used (prasugrel and ticagrelor are more potent than clopidogrel). In a systematic review of 53 studies (36 observational studies and 17 randomized clinical trials; $n = 714{,}458$ patients with ACS) focusing on the period after discharge from hospital, the 12-month incidence of bleeding ranged from 0.2% to 37.5% in observational studies and from 0.96% to 39.4% in randomized trials, varying with the classification of bleeding used[14]. The risk of bleeding seems to be fairly consistent over time (despite being most common during the first month), whereas thrombotic risk is highest early after an ACS event[14,16,17].

In clinical trials, bruising is the most commonly reported bleeding event, followed by gastrointestinal bleeding and epistaxis, whereas intracranial bleeding is relatively rare[16]. Nuisance bleeding (Bleeding Academic Research Consortium (BARC) type 1) is very common in the first year after ACS (up to 37.5%)[18] and can lead to DAPT discontinuation, worsening quality of life, repeat hospitalization and an increased risk of subsequent serious bleeding[18]. In addition, the degree of platelet inhibition achieved by the $P2Y_{12}$ inhibitor, as measured by platelet function testing (PFT), is directly related to the risk of mild bleeding (BARC type 1 or 2)[19,20] and likelihood of DAPT discontinuation.

Clinical risk factors for bleeding

Older age (a continuum rather than a threshold age), previous bleeding and chronic kidney disease (CKD) are well-established risk factors for bleeding in patients with ACS undergoing PCI but other clinical factors also contribute (Table 1). Bleeding risk is usually based on the interaction between non-modifiable and modifiable risk factors. Multiple clinical scores have been developed to predict the risk of bleeding in patients receiving antiplatelet therapy[7,21,22]. The PRECISE-DAPT Risk Calculator was developed to predict the risk of bleeding in patients who undergo coronary stent implantation and receive subsequent DAPT[7]. The score includes five criteria (age, creatinine clearance, haemoglobin level, white blood cell count and previous spontaneous bleeding) and predicts the risk of out-of-hospital bleeding during DAPT.

In 2019, the Academic Research Consortium for High Bleeding Risk (ARC-HBR) developed a consensus definition of patients at high risk of bleeding focusing on those undergoing PCI[23]. Twenty clinical criteria were identified as major or minor, supported by published evidence. Patients were considered to be at high risk of bleeding (BARC type 3–5 bleeding, annual rate of ≥4%) if at least one major or two minor criteria were present.

Although the ARC-HBR criteria and the PRECISE-DAPT Risk Calculator can be adequately applied to real-world cohorts, several important clinical risk factors for bleeding are not covered by these scores (such as low body weight, frailty, heart failure and peripheral artery disease) and, therefore, risk of bleeding might be underestimated in these patients[24].

Box 1

Consensus Statements

Consensus Statements on the de-escalation or abbreviation of dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

1. Patients should be stratified according to individual ischaemic risk and bleeding risk.
2. Ischaemic risk is highest in the first 30 days after an ACS event.
3. Bleeding risk is highest during the first days (and particularly peri-PCI), then falls and subsequently stays constant during the period of DAPT continuation.
4. Risk factors for bleeding include age, chronic kidney disease, anaemia, thrombocytopenia, previous spontaneous bleeding, recent surgery and active malignancy.
5. Risk factors for ischaemia include age, diabetes mellitus, suboptimal cardiovascular risk factor control, polyvascular disease, complex coronary artery disease, incomplete revascularization and chronic kidney disease. In addition, technical aspects of PCI, including long lesion length, greater number of stents, two-stent bifurcation or stenting of chronic total occlusion, increase the subsequent thrombotic risk.
6. The PRECISE-DAPT and ARC-HBR scores can help to risk stratify patients for bleeding, whereas the DAPT score can help to risk stratify patients for recurrent ischaemic events.
7. Strategies available to reduce the risk of bleeding include:
   - De-escalation of DAPT intensity (either unguided or guided by platelet function testing (PFT) or genotyping).
   - Abbreviation of DAPT duration.
8. De-escalation of DAPT intensity (guided or unguided) seems to reduce bleeding without an increase in ischaemic events. However, studies have mainly been conducted on East Asian patients. De-escalation of DAPT intensity, from ticagrelor or prasugrel to clopidogrel, in non-East Asian patients has been evaluated only in two, fairly small studies, one of which used PFT to guide de-escalation.
9. Both genotype-guided and PFT-guided de-escalation of DAPT intensity, which can be started within 1 week of PCI, can reduce bleeding without an increase in thrombotic events, particularly in those without high long-term ischaemic risk.
10. Overall, abbreviation of DAPT duration reduces bleeding without an increase in ischaemic events in patients with a high risk of bleeding, particularly in those without high long-term ischaemic risk.
11. DAPT duration can be abbreviated 1–3 months after ACS, continuing with P2Y purinoceptor 12 ($P2Y_{12}$) inhibitor monotherapy, in patients with a high risk of bleeding or in those without risk factors for bleeding and without high long-term ischaemic risk.
12. DAPT duration can be abbreviated 3–6 months after ACS, continuing with aspirin monotherapy, ideally only if the patient is at high risk of bleeding.
13. In East Asian patients, reduction in the duration or intensity of DAPT after the acute phase seem to be safe strategies to reduce bleeding without an increase in ischaemic events, particularly in those at high bleeding risk or low long-term ischaemic risk.

Differences between antiplatelet agents

The differences in bleeding risk between the various oral $P2Y_{12}$ inhibitors largely reflect the extent of platelet $P2Y_{12}$ inhibition achieved. Approved regimens of prasugrel and ticagrelor achieve a higher mean level of platelet inhibition than clopidogrel[25–27] and are associated with higher rates of minor and major bleeding[9,10,28–30] (Table 2). Consistently high levels of $P2Y_{12}$ inhibition with standard doses of prasugrel (10 mg daily) and ticagrelor (90 mg twice daily) translate to similar rates of bleeding for each agent[29,31]. However, the wide interindividual pharmacodynamic response to clopidogrel is associated with variation in individual bleeding risk, such that patients with greater $P2Y_{12}$ inhibition have higher rates of bleeding[31,32]. The risk of bleeding related to surgery (either cardiac or non-cardiac) depends on the timing of $P2Y_{12}$ inhibitor cessation before surgery, the mean level of platelet $P2Y_{12}$ inhibition during treatment, and whether the inhibitory effect is reversible (ticagrelor) or irreversible (clopidogrel and prasugrel)[33].

Aspirin, even at low daily maintenance doses of ≤100 mg, achieves consistently high levels of platelet cyclooxygenase 1 inhibition, resulting in a predictable compromise between haemostasis and increased bleeding risk with standard regimens[34], either as monotherapy or as part of DAPT[30] (Table 2). However, aspirin is associated with a dose-dependent increase in the risk of gastroduodenal erosion or ulceration, which increases the risk of gastrointestinal haemorrhage beyond the risk attributable to platelet inhibition[35]. Indeed, aspirin per se is not benign from the bleeding perspective; the risk of major and intracranial bleeding with aspirin is broadly similar to that of warfarin when stratified by the HAS-BLED score in patients with atrial fibrillation[36]. The assessment and mitigation of bleeding risk in patients with atrial fibrillation and venous thromboembolism and ethnic variation in bleeding risk associated with antithrombotic drugs have been the topic of consensus documents published in the past 2 years[37,38].

Clinical risk factors for recurrent ischaemic events

Patients with ACS undergoing PCI are at risk of subsequent ischaemic events, with an incidence of nearly 5% in the first year after the index event, increasing to 15% by the fourth year[39]. The definition of high ischaemic risk has undergone several changes over time (Table 1), with the current definition based on the 2020 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation[1]. Clinical risk factors associated with recurrent ischaemic events include older age, frailty, diabetes mellitus, polyvascular disease, complex coronary artery disease and CKD[40,41] (Table 1). Technical aspects of PCI that increase ischaemic risk include implantation of at least three stents, treatment of at least three lesions, total stent length >60 mm, bifurcation with two stents implanted, history of complex revascularization (such as left main stem or chronic total occlusion) and history of stent thrombosis with antiplatelet therapy[1,42,43].

In patients with ACS undergoing PCI, definite or probable stent thrombosis occurs in 0.4–1.8% of patients in the first year[44,45] and is more frequent than in patients with chronic coronary syndromes (CCS), especially in the first 6 months[46]. The major risk with premature discontinuation of DAPT is stent thrombosis, for which mortality is 20–45%[47], being highest with acute (<24 h) and subacute (1–30 days) stent thrombosis. In a real-world registry of patients with non-ST-segment elevation ACS (patients with STEMI were excluded) receiving drug-eluting stents (DES), the incidence of stent thrombosis at 9 months was 1.3%, which is substantially higher than rates reported in major clinical trials (0.4–0.6%)[48]. Stent thrombosis occurred in 29% of patients who prematurely discontinued DAPT, with a case-fatality rate of 45%[48]. In another large registry, among patients with MI (either STEMI or non-STEMI) receiving DES, those who stopped thienopyridine therapy by 30 days had a ninefold increased risk of death over the next 11 months (7.5% versus 0.7%; $P < 0.0001$)[49]. In the PARIS registry[46], among patients with ACS, the rate of stent thrombosis increased threefold after premature cessation of DAPT. Furthermore, in a subanalysis of the Dutch ST Registry[50,51], the rate of stent thrombosis was threefold higher when clopidogrel was discontinued within the first month compared with discontinuation between 1 and 6 months. However, the findings of a systematic review and meta-analysis suggest that the increased risk of stent thrombosis with abbreviated DAPT might be attenuated with the use of second-generation DES compared with first-generation DES[52].

Balancing ischaemic and bleeding risks

The principle of balancing ischaemic risk and bleeding risk is important when reducing the intensity or duration of DAPT. Bleeding risk can be assessed using the ARC-HBR criteria[3] or the PRECISE-DAPT, CRUSADE or ACUITY risk scores[53]. However, PRECISE-DAPT is the only score validated for the selection of DAPT duration. The use of risk scores to assess bleeding risk is gaining popularity. However, risk scores for ischaemia and bleeding often have overlapping clinical features and depend on the same variables, particularly in elderly patients.

In a systematic review and meta-analysis of studies validating the DAPT score (88,563 patients undergoing PCI electively or for ACS), the DAPT score could be used to separate the risk of ischaemia from that of bleeding[54]. Patients with a DAPT score of ≥2 were at higher ischaemic risk and lower bleeding risk than patients with a DAPT score of <2, who were at higher bleeding risk and lower ischaemic risk. Therefore, application of the DAPT score could help to identify patients who might benefit from standard or prolonged DAPT. In 2022, a paper reporting on the long-term outcomes of patients enrolled in the PEGASUS-TIMI 54 trial indicated that a single factor defining increased ischaemic risk is insufficient to recommend prolonged DAPT[55]. The investigators concluded that two or more risk factors should be used to define patients who are truly at high ischaemic risk[55]. On the whole, patients with a high risk of bleeding do not derive a clear ischaemic benefit from prolonged DAPT; therefore, ischaemic risk should guide more prolonged DAPT regimens, mainly in patients without a high risk of bleeding[12,56].

Timing of ischaemic risk versus bleeding risk

The incidence of ischaemic events is highest during the first month after PCI and tends to decrease thereafter[57]. In two large registries (BleeMACS and RENAMI; 19,826 unselected patients with ACS undergoing PCI), the ischaemic risk exceeded the bleeding risk in the first 2 weeks after PCI, especially in patients with STEMI and those with incomplete revascularization[58]. Thereafter, the risk of ischaemia was generally similar to the risk of bleeding up to 1 year[58]. Data from another registry (ADAPT-DES; 19,826 patients with ACS treated with PCI) also suggest that ischaemic risk is highest in the first 30 days, especially the first 2 weeks after ACS[59]. This acute increase in ischaemic risk could be stent-related (such as stent thrombosis) due to the progression or destabilization of non-culprit lesions (such as new MI) or vascular events in other areas affected by atherosclerotic disease (such as stroke)[59].

By contrast, the risk of bleeding with DAPT, despite being relatively high in the first few days after PCI due to the use of an arterial access site and periprocedural antithrombotic therapy, does not diminish over time when antiplatelet therapy is continued[42,57]. Therefore, the net benefit of DAPT might diminish over time, depending on the clinical circumstances of the patient[57]. Hence, the rationale for de-escalation of DAPT in the setting of ACS lies in the concept that

Box 2

Evidence gaps

Gaps in the evidence on abbreviation or de-escalation of dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention.

- Clarity on specific subsets of patients with ACS who might derive the greatest net clinical benefit from DAPT de-escalation or abbreviation.
- The comparative safety and benefit of de-escalation of DAPT intensity or abbreviation of DAPT have not been compared in head-to-head randomized clinical trials.
- The clinical trial evidence base for de-escalation of DAPT intensity or abbreviated DAPT in non-East Asian patients is not as robust as in East Asian patients.
- The optimal time point after ACS (for example, 1–3 months) for abbreviation or de-escalation of DAPT intensity remains to be determined.
- Whether monotherapy, following abbreviated DAPT, should consist of aspirin or a P2Y purinoceptor 12 ($P2Y_{12}$) inhibitor is not clear.
- Guided or unguided de-escalation of DAPT intensity have not been compared in head-to-head randomized clinical trials.
- DAPT de-escalation guided by either genotyping or platelet function testing has not been compared in head-to-head randomized clinical trials.
- Whether a potent $P2Y_{12}$ inhibitor alone, from the onset of ACS, without aspirin, is non-inferior to DAPT is unknown. Pilot data using ticagrelor or prasugrel monotherapy in 70 patients with ACS suggest that this strategy might be feasible[107], and this approach is the subject of ongoing trials.
- Whether sex-related differences exist in the clinical benefit of de-escalation of DAPT intensity or abbreviation of DAPT remains to be determined.
- Tools integrating clinical and laboratory markers to optimize patient selection for DAPT de-escalation or abbreviation are needed.

ischaemic risk clusters in the first months, whereas bleeding risk remains stable and might exceed ischaemic risk beyond the first few months after ACS.

Selection of patients for DAPT abbreviation or de-escalation

Multiple strategies that vary the intensity or duration of DAPT, or both, have been investigated in an effort to mitigate bleeding risk without a trade-off in ischaemic risk (Fig. 1). The decision to abbreviate or de-escalate DAPT depends on individual clinical judgement, driven by the perceived balance between the risks of ischaemia and bleeding, adverse events, comorbidities, co-medications, and the availability of the respective drugs.

DAPT de-escalation can be tailored to the risk profile (which can be dynamic, requiring reassessment as circumstances change), PFT or genetics of a patient. Overall, many patients with ACS undergoing PCI, especially those at high risk of bleeding, could be suitable for de-escalation. Consensus-based criteria and statistical tools can assist in guiding clinical judgement and decision-making to implement this strategy. Both the ARC-HBR classification[23] and the PRECISE-DAPT score (≥25) can help to identify patients at high risk of bleeding[7,60]; however, at least one additional risk factor should be considered if age is the only underlying factor used in the PRECISE-DAPT score.

De-escalation can be either unguided, based purely on clinical judgement, or based on clinical judgement and guided either by PFT or *CYP2C19* genotyping, depending on the risk profile and availability of assays (ESC class IIb recommendation, level of evidence A)[1]. PFT allows direct determination of the degree of platelet inhibition, which can subsequently identify patients at increased thrombotic risk (high on-treatment platelet reactivity) or bleeding risk (low on-treatment platelet reactivity). This information can be used to inform the modulation of $P2Y_{12}$ therapy to achieve the desired platelet response. The benefit of genetic testing over PFT is that the results remain unchanged, whereas the results of PFT are subject to intraindividual and interindividual variability. However, genetic data should be integrated with knowledge of clinical phenotypes that impair antithrombotic efficacy such as obesity, high BMI, diabetes and kidney dysfunction. Two meta-analyses published in the past year showed that either guided or unguided DAPT de-escalation were associated with a reduction in bleeding without an increase in ischaemic events[61,62].

Table 1 | Factors that increase the risk of bleeding, ischaemic events or both

Risk variable	Bleeding risk	Ischaemic risk
Age >75 years	+	+
Chronic kidney disease: moderate (eGFR 30–59 ml/min/1.73 m^2)	+	+
Chronic kidney disease: severe (eGFR <30 ml/min/1.73 m^2)	++	+
Haemoglobin level: <11.0 g/dl	++	–
Haemoglobin level: 11.0–12.9 g/dl (men)	+	–
Haemoglobin level: 11.0–11.9 g/dl (women)	+	–
Spontaneous bleeding requiring hospitalization or transfusion within the past 6 months	++	–
Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months	+	–
Moderate or severe thrombocytopenia (platelet count <100×10^9/l)	++	–
Chronic bleeding diathesis	++	–
Liver cirrhosis with portal hypertension	++	–
Active malignancy	++	–
Previous spontaneous intracranial haemorrhage at any time or traumatic intracranial haemorrhage in the past 12 months	++	–
Moderate or severe ischaemic stroke in the past 6 months	++	++
Major surgery or trauma in the 30 days before PCI	++	–
Non-deferrable major surgery while receiving dual antiplatelet therapy	++	+
Presence of a brain arteriovenous malformation	++	–
Long-term use of oral non-steroidal anti-inflammatory drugs or steroids	+	–
Extensive and/or diffuse coronary artery disease (especially with diabetes mellitus)	–	++
At least one variable for the extent or complexity of PCI: three vessels treated, stenting of last remaining patent coronary artery, total stent length >60 mm, bifurcation with two stents implanted, use of any atherectomy device, left main stem, surgical bypass graft or chronic total occlusion as target	–	+
Previous stent thrombosis	–	+

+, indicates minor risk; ++, indicates major risk; – indicates no additional risk; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Clinical trial evidence for abbreviation of DAPT duration

The risks and benefits of ≤6-month DAPT regimens followed by aspirin monotherapy versus standard 12-month DAPT have been investigated in several studies of patients undergoing PCI with DES implantation[12,63–74] (Table 3). Among the few trials that focused on patients with ACS, substantial heterogeneity was present in the type of DES used. Some studies mandated biodegradable polymer DES and other studies mandated durable polymer DES, and a variety of drugs were eluted (biolimus, everolimus, sirolimus, tacrolimus or zotarolimus). In some studies, patients received one type of stent, whereas other studies included patients with three or more types of DES. Therefore, on the whole, we believe that the data can be extrapolated to daily clinical practice with most modern types of stent.

In the SMART DATE trial[66], 1,357 patients with ACS were assigned to the 6-month DAPT group and 1,355 to the ≥12-month DAPT group. The trial showed non-inferiority of the 6-month DAPT regimen for the composite of all-cause death, MI and stroke. However, MI occurred more frequently with 6 months of DAPT than with ≥12 months of DAPT. No significant difference in BARC type 2–5 bleeding was reported[66]. A subsequent individual patient-level analysis of 14,963 patients from eight randomized trials comparing 3–6 months of DAPT followed by aspirin with ≥12 months of DAPT showed that patients with ACS who were not at high risk of bleeding benefited from prolonged DAPT with a reduction in ischaemic events, whereas those at high risk of bleeding (PRECISE-DAPT score ≥25) did not benefit from the longer duration of DAPT irrespective of their ischaemic risk[56].

Table 2 | Bleeding risk associated with oral antiplatelet drugs

Study	Experimental drug	Comparator	Concomitant antiplatelet agent in both study groups	Risk of bleeding with experimental drug versus comparator	Incidence of major bleeding (experimental versus control)	Ref.
PLATO[a]	Ticagrelor	Clopidogrel	Aspirin	Non-CABG-related TIMI major bleeding: HR 1.25 (95% CI 1.03–1.53)	11.6% vs 11.2%; *P*=0.43	9
TRITON-TIMI 38[a]	Prasugrel	Clopidogrel	Aspirin	Non-CABG-related TIMI major bleeding: HR 1.32 (95% CI 1.03–1.68)	2.4% vs 1.8%; *P*=0.03	10
CURE[a]	Clopidogrel	Placebo	Aspirin	Major bleeding: RR 1.38 (95% CI 1.13–1.67)	3.7% vs 2.7%; *P*=0.001	28
ISAR-REACT 5[a]	Ticagrelor	Prasugrel	Aspirin	BARC type 3–5 bleeding: HR 1.12 (95% CI 0.83–1.51)	5.4% vs 4.8%; *P*=0.46	29
TWILIGHT	Aspirin	Placebo	Ticagrelor	BARC type 2, 3 or 5 bleeding: HR 1.79 (95% CI 1.47– 2.22)	7.1% vs 4.0%; *P*<0.001	30

BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft surgery; RR, relative risk; TIMI, Thrombolysis in Myocardial Infarction. [a]Bleeding risk of $P2Y_{12}$ inhibitor or placebo, when used in conjunction with aspirin.

The effectiveness and safety of abbreviated DAPT followed by $P2Y_{12}$ inhibitor (rather than aspirin) monotherapy have been compared with standard DAPT regimens in six studies (Table 3). Earlier aggregate data from direct or network meta-analyses did not conclusively quantify the risks and benefits of aspirin withdrawal in comparison with DAPT after PCI. The inclusion of events occurring during the initial DAPT phase, which was identical in both experimental and control regimens, might have biased treatment estimates towards the null, thereby underestimating the potential benefit of aspirin withdrawal.

The Single Versus Dual Antiplatelet Therapy (SIDNEY) Collaboration initially gathered individual patient data from two studies of ticagrelor monotherapy[75] and, in a second iteration, from six studies assessing either clopidogrel or ticagrelor after 1–3 months of DAPT compared with DAPT continuation[76]. The rate of the primary outcome of all-cause death, MI and stroke was similar in patients with $P2Y_{12}$ inhibitor monotherapy (mainly ticagrelor) and in patients receiving DAPT, with $P2Y_{12}$ inhibitor monotherapy meeting the criteria for non-inferiority to DAPT. The treatment effect was consistent with the use of either clopidogrel or ticagrelor and in patients with or without a high risk of bleeding or ACS. In addition, the $P2Y_{12}$ inhibitor monotherapy strategy was associated with reduced major bleeding[76].

Subsequently, in the STOPDAPT-2 ACS extension study[74], 3,008 patients with ACS undergoing PCI were randomly assigned to 1–2 months of DAPT followed by clopidogrel monotherapy or to standard DAPT, comprising aspirin and clopidogrel, for 12 months. The data were analysed in combination with the previous 1,161 patients with ACS included in the earlier STOPDAPT-2 trial[77]. Clopidogrel monotherapy after 1–2 months of DAPT did not meet the criteria for non-inferiority to conventional DAPT for net clinical benefit and was associated with a substantial increase in the rate of MI. Therefore, the use of clopidogrel monotherapy might be best reserved for patients with ACS in whom bleeding risk outweighs ischaemic risk.

In the MASTER DAPT trial[12], patients with a high risk of bleeding undergoing PCI (for either CCS or ACS) were enrolled. Among those without the need for oral anticoagulation (64% of patients), a 1-month DAPT regimen followed by antiplatelet monotherapy (either aspirin or, in two-thirds of patients, a $P2Y_{12}$ inhibitor) was compared with standard DAPT for ≥6 months. The trial demonstrated the non-inferiority of 1-month DAPT regimens, both for net adverse events and major adverse cardiac and cerebral events, together with a reduced rate of bleeding, with consistent results in patients with ACS, including those undergoing complex interventions[78,79].

Clinical trial evidence for de-escalation of DAPT intensity

Unguided de-escalation

Three randomized trials testing an unguided approach to DAPT de-escalation after ACS have been conducted[80–85] (Table 4). In the TOPIC trial[80], patients with ACS were randomly assigned to clopidogrel-based DAPT versus standard DAPT. All patients were pre-treated with either prasugrel or ticagrelor for 1 month before randomization. The primary composite end point of cardiovascular death, urgent revascularization, stroke and BARC bleeding grade ≥2 at 1 year after ACS was significantly lower in the de-escalation group than in the standard DAPT group. These findings were driven by a reduction in BARC ≥2 bleeding, whereas the incidence of ischaemic events was similar in the two groups[80].

The non-inferiority of a prasugrel dose-reduction strategy (from 10 mg to 5 mg), compared with continuation of the 10 mg dose, 1 month after ACS was tested in East Asian patients in the HOST-REDUCE-POLYTECH-ACS randomized trial[81]. The incidence of the primary end point — the rate of net adverse clinical events (all-cause death, non-fatal MI, stent thrombosis, repeat revascularization, stroke and BARC ≥2 bleeding) — was lower with the dose de-escalation strategy, driven by a reduction in minor bleeding without an increase in ischaemia[81], irrespective of PCI complexity[86].

In the TALOS-AMI study[82], an open-label, non-inferiority randomized trial, 2,697 East Asian patients were assigned to clopidogrel-based DAPT or continuation of ticagrelor-based DAPT for 1 month after ACS. The clopidogrel-based de-escalation strategy met the criteria for non-inferiority for the primary composite end point of cardiovascular death, MI, stroke or BARC ≥2 bleeding. These results were primarily driven by a reduction in BARC ≥2 bleeding events in the de-escalation group[82].

Guided de-escalation

The response of individuals to some drugs can be variable due to genetic variation and other characteristics such as body weight and the presence of comorbidities, including CKD and diabetes[87]. Of the antiplatelet drugs, only clopidogrel is subject to large interindividual variability in its antiplatelet effect partly due to polymorphism of the *CYP2C19* gene, resulting in an inadequate response to treatment in approximately 30% of patients[88]. To reduce the risk of bleeding in patients with

ACS receiving prasugrel or ticagrelor as part of DAPT, de-escalation to clopidogrel based on genetic testing could be a useful strategy.

The ABCD-GENE risk score comprises four clinical variables (age, BMI, CKD status and diabetes status) and one genetic variable (*CYP2C19* loss-of-function alleles) and can help clinicians to identify patients who are most likely to have high on-treatment platelet reactivity with clopidogrel[87]. This genotype-guided de-escalation strategy was tested in the POPular Genetics trial[85], involving 2,488 patients with STEMI undergoing primary PCI. All patients received aspirin and were randomly assigned within 48 h of PCI to a genotype-guided $P2Y_{12}$ inhibitor strategy or to a standard-of-care $P2Y_{12}$ inhibitor strategy. In the genotype-guided group, carriers of loss-of-function *CYP2C19* alleles (39%) were treated with prasugrel or ticagrelor, whereas non-carriers (61%) received clopidogrel. Genotype-guided $P2Y_{12}$ inhibitor treatment resulted in a lower rate of bleeding compared with standard treatment (9.8% versus 12.5%; HR 0.78, 95% CI 0.61–0.98; $P = 0.04$) without an increase in ischaemic events[87].

The antiplatelet effect of oral $P2Y_{12}$ inhibitors can be assessed in vitro by PFT[89]. Studies have consistently shown that patients treated with PCI and with high on-treatment platelet reactivity are at increased risk of ischaemic events, including stent thrombosis, whereas bleeding risk is higher in patients with low on-treatment platelet reactivity[89]. These observations led to the concept of a therapeutic window for platelet inhibition[32], which could enable tailoring of antiplatelet treatment, including guiding DAPT de-escalation after PCI in patients with ACS.

The TROPICAL-ACS trial[84] of 2,610 patients with ACS undergoing PCI showed that PFT-guided DAPT de-escalation met the criteria for non-inferiority, compared with standard prasugrel treatment, for a net clinical benefit end point. A similar rate of ischaemic events occurred in the two treatment groups, with a trend towards less bleeding with PFT-guided treatment. The net clinical benefit from the guided treatment approach was also seen in specific subgroups (such as younger patients)[90]. A meta-analysis (19,855 patients with ACS or CCS; 11 randomized trials and 3 observational studies) published in 2021 showed that guided (genotyping or PFT) DAPT de-escalation led to a reduction in bleeding events (risk ratio 0.81, 95% CI 0.68–0.96) compared with standard DAPT[91].

Although both genetic tests and PFT have been used in clinical trials to guide DAPT de-escalation, access to these tests is not uniform across all practice settings. Many clinicians do not have access to either test and, even when available, results might not be obtainable within a suitable time frame to guide clinical decision-making during the hospital admission for ACS. Nonetheless, reflecting the available evidence, the latest European guidelines[1,3] include a class IIb (level of evidence A) recommendation for a DAPT de-escalation strategy (including but not restricted to a PFT-guided approach), which can be considered for patients with ACS deemed unsuitable for 12 months of potent platelet inhibition.

Abbreviation versus de-escalation of DAPT

The number of patients enrolled in trials assessing the abbreviation of DAPT duration ($n = 41{,}093$) is threefold higher than the number of patients enrolled in trials assessing de-escalation of DAPT intensity ($n = 12{,}707$). Although no head-to-head comparisons of the two strategies have been performed, a network meta-analysis of 29 trials in patients with ACS undergoing PCI showed that there was no significant difference in all-cause death between abbreviated DAPT and de-escalation of DAPT intensity[92]. Abbreviated DAPT reduced the occurrence of major bleeding, whereas de-escalation of DAPT intensity reduced the rate of net adverse cardiovascular events[92]. Furthermore, although patients at high risk of bleeding have been specifically enrolled in several studies of DAPT abbreviation, the same cannot be

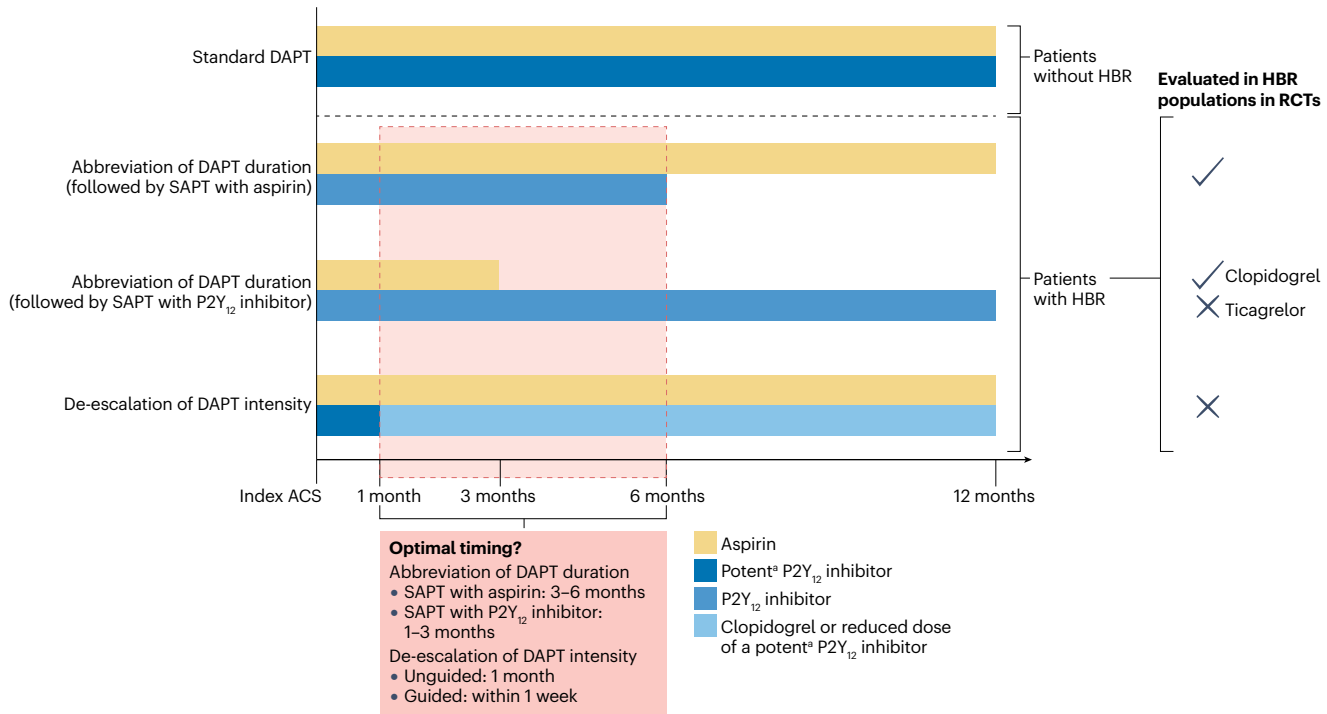

Fig. 1 | DAPT strategies to reduce bleeding risk in patients with ACS. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; $P2Y_{12}$, P2Y purinoceptor 12; RCT, randomized controlled trial; SAPT, single antiplatelet therapy. [a]Potent $P2Y_{12}$ inhibitors are prasugrel or ticagrelor.

Table 3 | Randomized clinical trials evaluating abbreviated DAPT in patients with ACS undergoing PCI

Study (year)	*n*	Treatment groups	Primary end point	Findings	Safety end point	Considerations	Ref.
Abbreviation to aspirin monotherapy							
EXCELLENT (2012)	1,443	6 months of DAPT (aspirin plus clopidogrel) vs 12 months of DAPT (aspirin plus clopidogrel)	Cardiac death, MI or ischaemia-driven target revascularization at 12 months	Abbreviated DAPT was non-inferior for the primary end point (4.8% vs 4.3%; HR 1.14, 95% CI 0.70–1.86; *P*=0.001 for non-inferiority, *P*=0.60 for superiority); numerical trend towards increased ST in the abbreviated DAPT group	No significant difference in the composite of death, MI, stroke, ST or TIMI major bleeding (3.3% vs 3.0%; HR 1.15, 95% CI 0.64–2.06; *P*=0.64) or in TIMI major bleeding (0.3% vs 0.6%; HR 0.50, 95% CI 0.09–2.73; *P*=0.64)	Open-label and non-inferiority design with wide margin; East Asian (Korean) population; lower-than-expected event rates; potent $P2Y_{12}$ inhibitors not used	63
RESET (2012)	2,117	3 months of DAPT (aspirin plus clopidogrel) vs 12 months of DAPT (aspirin plus clopidogrel)	Cardiovascular death, MI, ST, target-vessel revascularization or bleeding at 1 year	Abbreviated DAPT was non-inferior for the primary end point (4.7% vs 4.7%; difference 0%, 95% CI −2.5% to 2.5%; *P*<0.001 for non-inferiority; *P*=0.84 for superiority)	No significant difference in major bleeding (0.2% vs 0.6%; difference −0.4%, 95% CI −0.9% to 0.1%; *P*=0.16)	Open-label and non-inferiority design; East Asian (Korean) population; lower-than-expected event rates; potent $P2Y_{12}$ inhibitors not used	64
I-LOVE-IT 2 (2016)	1,829	6 months of DAPT (aspirin plus clopidogrel) vs 12 months of DAPT (aspirin plus clopidogrel)	Cardiac death, target-vessel MI or clinically indicated target-lesion revascularization at 12 months	Abbreviated DAPT was non-inferior for the primary end point (6.8% vs 5.9%; difference 0.87%, 95% CI −1.37% to 3.11%; *P*=0.0065 for non-inferiority)	No significant difference in the composite of all-cause death, all-cause MI, stroke or BARC ≥3 bleeding (7.2% vs 6.4%; *P*=0.53) or in BARC ≥3 bleeding (1.2% vs 0.7%; *P*=0.21)	Substudy, open-label and non-inferiority design; East Asian (Chinese) population; low event rates; potent $P2Y_{12}$ inhibitors not used	65
SMART DATE (2018)	2,712	6 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor) vs 12 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor)	All-cause death, MI or stroke at 18 months	Abbreviated DAPT was non-inferior for the primary end point (4.7% vs 4.2%; HR 1.13, 95% CI 0.79–1.62; *P*=0.03 for non-inferiority, *P*=0.51 for superiority); significant increase in the rate of MI with abbreviated DAPT (1.8% vs 0.8%; HR 2.41, 95% CI 1.15–5.05; *P*=0.02)	No significant difference in BARC ≥2 bleeding (2.7% vs 3.9%; HR 0.69, 95% CI 0.45–1.05; *P*=0.09)	Open-label and non-inferiority design with wide margin; East Asian (Korean) population; approximately 80% use of clopidogrel	66
DAPT STEMI (2018)	870	6 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor) vs 12 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor)	All-cause mortality, MI, any revascularization, stroke and TIMI major bleeding 18 months after randomization	Abbreviated DAPT was non-inferior for the primary end point (4.8% vs 6.6%; HR 0.73, 95% CI 0.41–1.27; *P*=0.004 for non-inferiority, *P*=0.26 for superiority)	No significant difference in TIMI major bleeding (0.2% vs 0.5%; HR 0.51, 95% CI 0.05–5.57; *P*=0.49)	Open-label and non-inferiority design; small sample size and lower-than-expected event rates; patients with STEMI and primary PCI randomized if event free at 6 months	67
OPTIMA-C (2018)	1,368	6 months of DAPT (aspirin plus clopidogrel) vs 12 months of DAPT (aspirin plus clopidogrel)	Cardiac death, MI or ischaemia-driven target-lesion revascularization at 12 months	Abbreviated DAPT was non-inferior for the primary end point (1.2% vs 0.6%; risk difference 0.6%, 95% CI −0.4% to 1.6%; *P*<0.05 for non-inferiority, *P*=0.24 for superiority)	No TIMI major bleeding events in either group	Open-label and non-inferiority design with wide margin; East Asian (Korean) population; population at very low risk; potent $P2Y_{12}$ inhibitors not used	68
REDUCE (2019)	1,496	3 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor) vs 12 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor)	All-cause mortality, MI, ST, stroke, target-vessel revascularization or BARC ≥2 bleeding at 12 months	Abbreviated DAPT was non-inferior for the primary end point (8.2% vs 8.4%; HR 0.97, 95% CI 0.68–1.39; *P*<0.001 for non-inferiority, *P*=0.80 for superiority); numerically higher rates of death and ST in the abbreviated DAPT group	No significant difference in BARC ≥2 (2.5% vs 3.0%; HR 0.83, 95% CI 0.45–1.55; *P*=0.540)	Open-label and non-inferiority design with wide margin; lower-than-expected event rates	69

Table 3 (continued) | Randomized clinical trials evaluating abbreviated DAPT in patients with ACS undergoing PCI

Study (year)	*n*	Treatment groups	Primary end point	Findings	Safety end point	Considerations	Ref.
Abbreviation to $P2Y_{12}$ monotherapy							
GLOBAL LEADERS ACS subgroup (2018)	7,487	1 month of DAPT (aspirin plus ticagrelor) followed by 23 months of ticagrelor vs 12 months of DAPT (aspirin plus ticagrelor) followed by aspirin monotherapy	All-cause mortality or non-fatal new Q-wave MI at 2 years	Abbreviated DAPT was not superior for the primary end point (3.92% vs 4.52%; HR 0.86, 95% CI 0.69–1.08; *P*=0.19)	Abbreviated DAPT reduced BARC ≥3 bleeding at 2 years (1.95% vs 2.68%; RR 0.73, 95% CI 0.54–0.98; *P*=0.037)	Open-label and subgroup analysis; lower-than-expected event rates; no central adjudication of events	70
SMART-CHOICE (2019)	2,993	3 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor) followed by 9 months of $P2Y_{12}$ monotherapy vs 12 months of DAPT (aspirin plus ticagrelor)	All-cause death, MI or stroke at 12 months	Abbreviated DAPT was non-inferior for the primary end point (2.9% vs 2.5%; risk difference 0.4%; 95% CI −∞% to 1.3%; *P*=0.007 for non-inferiority)	Abbreviated DAPT reduced BARC ≥2 bleeding (2.0% vs 3.4%; HR 0.58, 95% CI 0.36–0.92; *P*=0.02)	Open-label and non-inferiority design with wide margin; East Asian (Korean) population; patients at low risk; approximately 77% use of clopidogrel	71
TWILIGHT-ACS, 2020	4,614	3 months of DAPT (aspirin plus ticagrelor) followed by 12 months of ticagrelor vs 15 months of DAPT (aspirin plus ticagrelor)	BARC ≥2 bleeding at 12 months after randomization, key secondary end point of death from any cause, non-fatal MI or non-fatal stroke at 12 months after randomization	Abbreviated DAPT was superior for the primary end point (3.6% vs 7.6%; HR 0.47, 95% CI 0.36–0.61; *P*<0.001); no significant differences between strategies in the combined key secondary end point (4.3% vs 4.4%; HR 0.97, 95% CI 0.74–1.28; *P*=0.84)	Abbreviated DAPT reduced BARC ≥3 bleeding (0.8% vs 2.1%; HR 0.36, 95% CI 0.20–0.62; *P*<0.001)	Patients randomized if event free at 3 months after PCI; lower-than-expected rates for ischaemic events, which could bias results of the key secondary end point towards the null	72
TICO (2020)	3,056	3 months of DAPT (aspirin plus ticagrelor) followed by 9 months of ticagrelor vs 12 months of DAPT (aspirin plus ticagrelor)	Major TIMI bleeding, death, MI, ST, stroke or target-vessel revascularization at 12 months	Abbreviated DAPT was superior for the primary end point (3.9% vs 5.9%; HR 0.66, 95% CI 0.34–0.91; *P*=0.01)	Abbreviated DAPT reduced TIMI major bleeding (1.7% vs 3.0%; HR 0.56, 95% CI 0.34–0.91; *P*=0.02)	Open label; East Asian (Korean) population; lower-than-expected event rates; patients at high risk of bleeding excluded	73
MASTER DAPT (2021)	4,434	1 month of DAPT (aspirin plus $P2Y_{12}$ inhibitor) followed by SAPT vs 3–12 months of DAPT (aspirin plus $P2Y_{12}$ inhibitor)	Three primary outcomes: net adverse events (all-cause death, MI, stroke or BARC ≥3 bleeding); all-cause death, MI or stroke; and BARC ≥2 bleeding	Abbreviated DAPT was non-inferior for the primary end point of net adverse clinical events (7.5% vs 7.7%; HR 0.97, 95% CI 0.78–1.20; *P*<0.001 for non-inferiority) and for the combined end point of all-cause death, MI or stroke (6.1% vs 5.9%; HR 1.02, 95% CI 0.80–1.30; *P*<0.001 for non-inferiority)	Abbreviated DAPT reduced BARC ≥2 bleeding (6.5% vs 9.4%; HR 0.68, 95% CI 0.55–0.85; *P*<0.001 for superiority)	Open-label and non-inferiority design; patients included if at high risk of bleeding (38% with indication for oral anticoagulation); patients randomized if event free at 1 month after PCI; SAPT in abbreviated DAPT group was a $P2Y_{12}$ inhibitor in approximately 70% of patients	12
STOPDAPT-2 ACS (2022)	4,169	1–2 months of DAPT (aspirin plus clopidogrel or prasugrel 3.75 mg) followed by clopidogrel until 1 year vs 1–2 months of DAPT (aspirin plus clopidogrel or prasugrel 3.75 mg) followed by DAPT (aspirin plus clopidogrel) until 1 year	Cardiovascular death, MI, ischaemic or haemorrhagic stroke, definite ST, or major or minor bleeding at 12 months	Abbreviated DAPT did not achieve non-inferiority (3.2% vs 2.8%; HR 1.14, 95% CI 0.80–1.62; *P*=0.06 for non-inferiority); increased rates of MI with abbreviated DAPT (1.59% vs 0.85%; HR 1.91, 95% CI 1.06–3.44)	Abbreviated DAPT reduced TIMI major or minor bleeding (1.17% vs 0.54%; HR 0.46, 95% CI 0.23–0.94)	Open-label and non-inferiority design; East Asian (Japanese) population; lower-than-expected event rates	74

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; MI, myocardial infarction; $P2Y_{12}$, P2Y purinoceptor 12; PCI, percutaneous coronary intervention; RR, rate ratio; SAPT, single antiplatelet therapy; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

said about trials assessing de-escalation of DAPT intensity. Therefore, less evidence exists to support the use of DAPT intensity de-escalation in patients with a high bleeding risk.

Optimal timing of abbreviation or de-escalation

DAPT abbreviation or de-escalation strategies can be initiated at different time points. De-escalation of DAPT intensity can be instituted

Table 4 | Randomized clinical trials evaluating de-escalation of DAPT intensity in patients with ACS undergoing PCI

Study (year)	*n*	Treatment groups	Primary end point	Results	Safety end point	Considerations	Ref.
Unguided de-escalation							
TOPIC (2017)	646	Aspirin plus ticagrelor or prasugrel for 1 month followed by aspirin plus clopidogrel 75 mg once daily for 11 months vs aspirin plus ticagrelor or prasugrel for 12 months	Cardiovascular death, urgent revascularization, stroke and BARC ≥2 bleeding at 1 year	De-escalation strategy reduced the rate of the primary end point (13.4% vs 26.3%; HR 0.48, 95% CI 0.34–0.68; $P<0.01$) driven by a reduction in bleeding events; no significant differences in ischaemic end points	Reduction of BARC ≥2 bleeding with de-escalation strategy (4.0% vs 14.9%; HR 0.30, 95% CI 0.18–0.50; $P<0.01$)	Open-label and monocentric design; small sample size (limited power for non-frequent events); self-reported bleeding episodes that did not require medical attention	80
HOST-REDUCE-POLYTHEC-ACS (2020)	3,429	Aspirin plus prasugrel 10 mg once daily for 1 month followed by aspirin plus prasugrel 5 mg once daily for 11 months vs aspirin plus prasugrel 10 mg once daily for 12 months	All-cause death, non-fatal MI, ST, repeat revascularization, stroke and BARC ≥2 bleeding at 1 year	De-escalation strategy reduced the rate of the primary end point (7.2% vs 10.1%; HR 0.70, 95% CI 0.52–0.92; $P<0.001$ for non-inferiority, $P=0.012$ for equivalence) driven by a reduction in bleeding events; no significant differences in ischaemic end points	Reduction of BARC ≥2 bleeding with de-escalation strategy (2.9% vs 5.9%; HR 0.48, 95% CI 0.32–0.73; $P=0.0007$)	Open-label and non-inferiority design with wide margin; one-arm analysis of a 2×2 trial (risk of power limitation for multiple testing); East Asian (Korean) population, which present higher rates of bleeding events than Western populations	81
TALOS-AMI (2021)	2,697	Aspirin plus ticagrelor 90 mg twice daily for 1 month followed by aspirin plus clopidogrel 75 mg once daily for 11 months vs aspirin plus ticagrelor 90 mg twice daily for 12 months	Cardiovascular death, MI, stroke and BARC ≥2 bleeding from 1 to 12 months	De-escalation strategy reduced the rate of the primary end point (4.6% vs 8.2%; HR 0.55, 95% CI 0.40–0.76; $P<0.001$ for non-inferiority, $P=0.0001$ for superiority) driven by a reduction in bleeding events; no significant differences in ischaemic end points	Reduction of BARC ≥2 bleeding with de-escalation strategy (3.0% vs 5.6%; HR 0.52, 95% CI 0.35–0.77; $P=0.0012$)	Open-label and non-inferiority design with wide margin; East Asian (Korean) population, which present higher rates of bleeding events than Western populations	82
Guided de-escalation							
ANTARCTIC (2016)	877	Aspirin for 12 months plus prasugrel 5 mg once daily for 2 weeks followed by PFT-guided therapy (prasugrel 10 mg if HPR, clopidogrel 75 mg if LPR, and continuing prasugrel 5 mg if on therapeutic window) for 2 weeks followed by a second PFT-guided adjustment (prasugrel 5 mg if LPR with prasugrel 10 mg, or HPR with clopidogrel 75 mg; continuing therapy for other situations) for 11 months vs aspirin plus prasugrel 5 mg once daily for 12 months	Cardiovascular death, MI, stroke, ST, urgent revascularization and BARC ≥2 bleeding at 1 year	In older patients (age ≥75 years), the PFT-guided de-escalation strategy did not reduce the rate of the primary end point (28% vs 28%; HR 1.003, 95% CI 0.78–1.29; $P=0.98$); no significant differences in ischaemic end points	No significant difference in BARC ≥2 bleeding (20% vs 21%; HR 1.04, 95% CI 0.78–1.40; $P=0.77$)	Open-label design; small sample size (limited statistical power); incomplete monitoring in several patients	83
TROPICAL-ACS (2017)	2,610	Aspirin for 12 months plus prasugrel 10 mg once daily (or 5 mg based on age and weight) for 1 week followed by clopidogrel 75 mg for 1 week and PFT-guided maintenance therapy (continuing clopidogrel or switching back to prasugrel if HPR) for 11.5 months vs aspirin plus prasugrel 10 mg (or 5 mg based on age and weight) once daily for 12 months	Cardiovascular death, MI, stroke and BARC ≥2 bleeding at 1 year	Non-inferiority achieved with the PFT-guided de-escalation strategy for the primary end point (7% vs 9%; HR 0.81, 95% CI 0.62–1.06; $P=0.0004$ for non-inferiority, $P=0.12$ for superiority); no significant differences in ischaemic end points	No significant difference in BARC ≥2 bleeding (5% vs 6%; HR 0.82, 95% CI 0.59–1.13; $P=0.23$)	Open-label and non-inferiority design with wide margin; after de-escalation to clopidogrel, several patients were re-escalated if HPR to clopidogrel, which could have affected the risk of bleeding in that group	84

Table 4 (continued) | Randomized clinical trials evaluating de-escalation of DAPT intensity in patients with ACS undergoing PCI

Study (year)	*n*	Treatment groups	Primary end point	Results	Safety end point	Considerations	Ref.
Guided de-escalation (continued)							
POPular Genetics (2019)	2,488	Aspirin plus genotype-guided choice of $P2Y_{12}$ inhibitor (prasugrel or ticagrelor if carriers of a *CYP2C19* loss-of-function allele, clopidogrel in non-carriers) for 12 months vs aspirin plus ticagrelor or prasugrel for 12 months	Net adverse events: all-cause death, MI, definite ST, stroke or PLATO major bleeding at 1 year; safety: PLATO major or minor bleeding at 1 year	In patients undergoing primary PCI, non-inferiority achieved for the combined primary end point with genotype-guided selection of $P2Y_{12}$ inhibitor (5.1% vs 5.9%; HR 0.87, 95% CI 0.62–1.21; $P<0.001$ for non-inferiority, $P=0.40$ for superiority); no significant differences in ischaemic end points	Reduction in primary end point for bleeding with genotype-guided selection of $P2Y_{12}$ inhibitor (9.8% vs 12.5%; HR 0.78, 95% CI 0.61–0.98; $P=0.04$)	Open-label design and wide non-inferiority margin due to lower-than-anticipated incidence of the combined primary end point; initial treatment until genotyping (up to 48 h after the event) at discretion of the treating physician; choice of prasugrel or ticagrelor according to local practice	85

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; HPR, high on-treatment platelet reactivity; LPR, low on-treatment platelet reactivity; MI, myocardial infarction; $P2Y_{12}$, P2Y purinoceptor 12; PCI, percutaneous coronary intervention; PFT, platelet function testing; PLATO, PLATelet inhibition and patient Outcomes; ST, stent thrombosis.

1 week after PCI if guided by PFT or genotyping[42] and 1 month after PCI if unguided[80–82]. In most studies of DAPT abbreviation, the switch to aspirin monotherapy was made at 6 months but, in the RESET[64] and the REDUCE[69] trials, DAPT was abbreviated after 3 months and showed non-inferiority compared with 12 months of DAPT for the primary composite end point of ischaemic and bleeding events. By contrast, in most trials of DAPT abbreviated to $P2Y_{12}$ inhibitor monotherapy, the switch occurred earlier, at 1–3 months. On the basis of the available evidence, abbreviation of DAPT duration can be considered after 1–3 months if switching to monotherapy with clopidogrel or ticagrelor, or after 3–6 months if switching to aspirin monotherapy. The 2020 ESC guidelines on the treatment of patients with ACS without STEMI recommend the use of ticagrelor monotherapy after 3 months of standard DAPT as an alternative to standard 12-month DAPT[1].

As mentioned earlier, some procedural characteristics, such as double stenting of coronary bifurcations, stenting of chronic total occlusions or long lesions requiring multiple stents, are associated with an increased risk of ischaemic events[1,42,43]. In these patients, standard 12-month DAPT with prasugrel or ticagrelor, or even prolongation of antiplatelet therapy beyond 12 months, should be considered for those at low risk of bleeding, for whom low-dose ticagrelor would be the agent of choice[93]. Overall, the duration and intensity of DAPT should be tailored to the risk of ischaemia and bleeding of individual patients (Fig. 2).

DAPT abbreviation or de-escalation in specific populations

Older patients

Older patients are conventionally regarded as those aged ≥75 years and represent over one-third of the population with ACS[94,95]. These patients are at higher ischaemic and bleeding risk than younger individuals owing to increased frailty and associated comorbidities[95]. Few randomized trials have been conducted to test DAPT abbreviation or de-escalation strategies in older patients with ACS. Acute, periprocedural and long-term antithrombotic therapy in older patients was addressed in a 2023 consensus paper from the ESC Working Group on Thrombosis[96].

The GLOBAL LEADERS trial[70] compared 1 month of DAPT followed by 23 months of ticagrelor monotherapy with 12 months of DAPT followed by 12 months of aspirin monotherapy. In a prespecified analysis of older patients (aged >75 years) enrolled in this trial ($n = 2,565$), there were no significant differences between the two strategies with respect to the primary end point of all-cause death or new Q-wave MI[97]. Among the >7,000 patients with ACS enrolled in the TWILIGHT trial[30], 3 months of DAPT followed by ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, without an increased risk of death, MI or stroke. These results were confirmed when restricted to older patients (aged ≥65 years)[30]. By contrast, in the STOPDAPT-2 ACS study of >4,000 patients (29% ≥75 years), clopidogrel monotherapy after 1–2 months of DAPT did not achieve non-inferiority to 12 months of DAPT in terms of net clinical benefit, with a numerical increase in cardiovascular events[74]. No treatment interaction by age was observed.

In a prespecified analysis of the TROPICAL-ACS study, no significant differences in net clinical outcome were found between PFT-guided de-escalation (DAPT with 1 week of prasugrel followed by 1 week of clopidogrel, then maintenance therapy with clopidogrel or prasugrel) and the control group (12 months of prasugrel) in patients aged >70 years[90]. In the TALOS-AMI trial[82] of unguided de-escalation in patients with ACS, only 12% of patients were aged ≥75 years. However, the hazard ratios for the primary end point were consistent across the prespecified age subgroups (<75 years or ≥75 years), showing a significant reduction in net clinical events for the unguided de-escalation strategy[82]. Other studies of de-escalation from potent $P2Y_{12}$ inhibitors to clopidogrel have included very few older patients. An alternative strategy was assessed in the ANTARCTIC trial[83], in which older patients (aged ≥75 years) with ACS were randomly assigned to prasugrel 5 mg daily with dose or drug adjustment in the event of inadequate response (including up-titration to 10 mg or downgrading to clopidogrel according to PFT results) or oral prasugrel 5 mg daily with no monitoring. The study showed similar results with either strategy[83].

Patients with renal impairment

Renal impairment is an important risk factor for the development of complex coronary artery disease. Although patients with CKD were historically less likely to undergo coronary angiography and PCI, advances over the past two decades have led to an upward trend in the rate of interventions performed in these patients[98]. Patients with CKD tend to

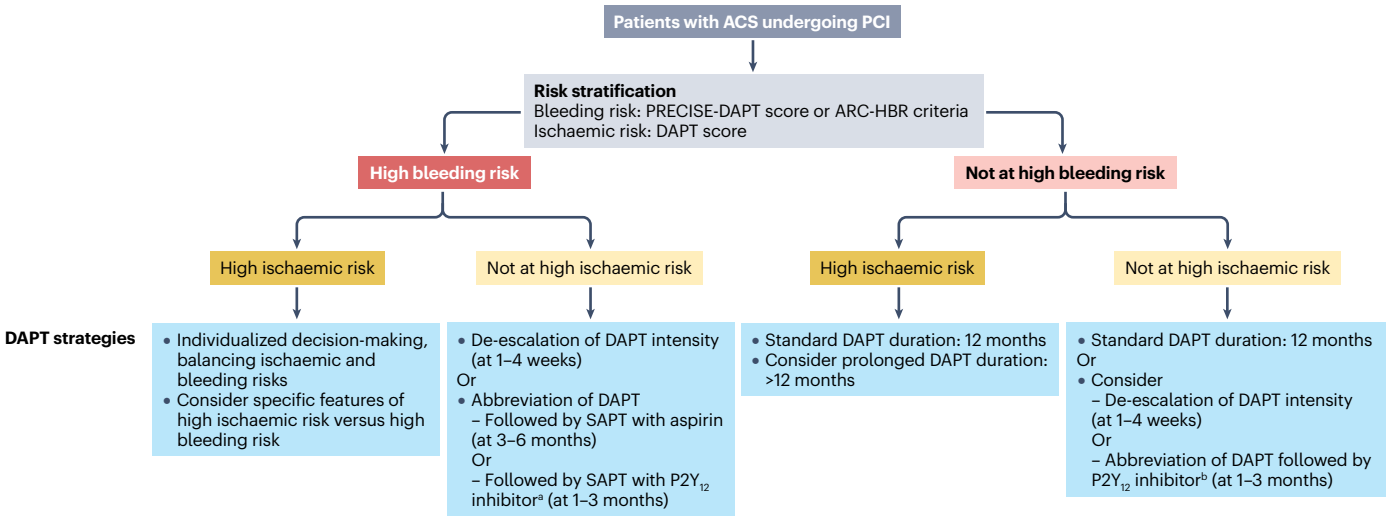

Fig. 2 | Algorithm for the selection of DAPT in patients with ACS undergoing PCI. ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium for High Bleeding Risk; DAPT, dual antiplatelet therapy; $P2Y_{12}$, P2Y purinoceptor 12; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy. [a]Clopidogrel is the most studied $P2Y_{12}$ inhibitor in this setting. [b]Ticagrelor is the most studied $P2Y_{12}$ inhibitor in this setting.

have a greater coronary calcification burden and a higher prevalence of cardiovascular risk factors, such as hypertension, hyperlipidaemia and diabetes, than those without this disease, presenting substantial challenges for PCI. Those with CKD are also at increased risk of in-hospital complications, including death and bleeding after PCI, especially if transfemoral access is used[99,100]. Importantly, CKD is a risk factor for both long-term ischaemic and bleeding events after PCI.

The ESC guidelines include baseline CKD (estimated glomerular filtration rate (eGFR) 15–59 ml/min/1.73 m^2) as a criterion for DAPT extension beyond 1 year to reduce the risk of ischaemic events[1]. However, CKD is also a major (eGFR <30 ml/min/1.73 m^2) or minor (eGFR 30–59 ml/min/1.73 m^2) criterion for abbreviation or de-escalation of DAPT according to the ARC-HBR score[1]. Trials of DAPT abbreviation[101] that provide a subgroup analysis for baseline CKD have shown the benefit of reduced DAPT duration or intensity in patients with CKD[12,30,85] as well as the safety and efficacy of this approach in those who also have a high risk of bleeding[79,102].

East Asian patients

East Asian patients are considered to be at lower ischaemic risk and higher bleeding risk (including intracranial haemorrhage) with DAPT than non-East Asian patients owing to enhanced pharmacokinetic and pharmacodynamic profiles with ticagrelor and prasugrel despite *CYP2C19* loss-of-function alleles being more frequent in those with East Asian ancestry[38]. This phenomenon is referred to as the 'East Asian paradox'. Therefore, lower-than-conventional doses of prasugrel are prescribed in some East Asian countries such as Japan and Taiwan.

Importantly, the majority of trials of de-escalation or abbreviation of DAPT have been conducted in East Asian patients[103]. A systematic review and meta-analysis published in 2023 specifically assessed the safety and effectiveness of DAPT de-escalation strategies in East Asian versus non-East Asian patients with ACS undergoing PCI[103]. The net benefit and safety of reduction in either intensity or duration of DAPT seem to be greater in East Asian than in non-East Asian patients. The 2020 (ref. 104) and 2021 (ref. 105) Asian Pacific Society of Cardiology consensus recommendations on the use of $P2Y_{12}$ antagonists in the Asia Pacific region indicate that, after a period of DAPT, use of ticagrelor monotherapy seems to be reasonable in patients with high ischaemic risk and low bleeding risk. Conversely, clopidogrel monotherapy can be used for patients with low ischaemic risk or patients with a high risk of both ischaemia and bleeding. The recommendations also support the use of abbreviated DAPT in older patients at high risk of bleeding or in patients with CKD receiving dialysis. For patients with diabetes undergoing complex PCI who are at high risk of bleeding, ticagrelor monotherapy can be considered after 3 months of DAPT[105].

Several studies have been conducted to investigate DAPT abbreviation or de-escalation strategies in East Asian populations. The TICO trial[73], conducted in South Korea, showed that 3 months of DAPT followed by ticagrelor monotherapy had clinical benefit in patients with ACS compared with 12 months of DAPT, which was mostly driven by a reduction in major bleeding. These data are supported by the findings from two other randomized clinical trials from East Asia: SMART-CHOICE[67] (Korea) and STOPDAPT-2 (ref. 102) (Japan). In these studies, compared with 12 months of DAPT, the use of $P2Y_{12}$ inhibitor monotherapy after an initial 1–3 months of DAPT was shown to reduce the risk of clinically serious bleeding in East Asian patients undergoing PCI[71,77]. The HOST-REDUCE-POLYTECH-ACS trial[86] from South Korea showed that, in patients with ACS treated with DAPT, including 10 mg prasugrel for 1 month, the subsequent reduction to 5 mg of prasugrel significantly reduced the risk of bleeding (HR 0.48, 95% CI 0.32–0.73; $P = 0.0007$) without increasing ischaemic risk (HR 0.76, 95% CI 0.40–1.45; $P = 0.40$) compared with continuation of the conventional dose of 10 mg.

The Korea Acute Myocardial Infarction Registry–National Institutes of Health study combined ischaemic and bleeding models to establish a simple clinical prediction score for the use of DAPT. Patients with a high score (≥3 points) showed an overall benefit from potent $P2Y_{12}$ inhibitor versus clopidogrel in reducing ischaemic events at 1 year without a significant increase in bleeding whereas, in patients with a low score (<3), the bleeding risk with potent $P2Y_{12}$ inhibitors exceeded the ischaemic benefit[106].

Conclusions

The duration and intensity of DAPT should be tailored to the risks of ischaemia and bleeding of individual patients. The risk of both types of event is highest in the early period following ACS, after which the bleeding risk falls and then stays constant over the duration of DAPT. Strategies to reduce the risk of bleeding include de-escalation of DAPT intensity, with dose reduction or a switch to a less-potent $P2Y_{12}$ inhibitor, or abbreviation of DAPT duration with continuation of treatment using a single antiplatelet agent. Trials have shown that de-escalation of DAPT intensity can reduce bleeding without an increase in ischaemic events in patients without high long-term ischaemic risk and can be guided by PFT or genotyping. Abbreviation of DAPT after 1–6 months reduces bleeding without an increase in ischaemic events in patients with a high risk of bleeding and without high long-term ischaemic risk. The two approaches to reducing DAPT have not been compared in head-to-head randomized trials. Our consensus statements (Box 1) should guide clinicians to tailor these approaches to DAPT abbreviation and de-escalation for individual patients to improve outcomes.

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Author contributions

The authors contributed substantially to all aspects of the article.

Competing interests

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