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STATE OF THE ART REVIEW
Interventional cardiology

Patient-tailored antithrombotic therapy following percutaneous coronary intervention

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Dual antiplatelet therapy has long been the standard of care in preventing coronary and cerebrovascular thrombotic events in patients with chronic coronary syndrome and acute coronary syndrome undergoing percutaneous coronary intervention, but choosing the optimal treatment duration and composition has become a major challenge. Numerous studies have shown that certain patients benefit from either shortened or extended treatment duration. Furthermore, trials evaluating novel antithrombotic strategies, such as $P2Y_{12}$ inhibitor monotherapy, low-dose factor Xa inhibitors on top of antiplatelet therapy, and platelet function- or genotype-guided (de-)escalation of treatment, have shown promising results. Current guidelines recommend risk stratification for tailoring treatment duration and composition. Although several risk stratification methods evaluating ischaemic and bleeding risk are available to clinicians, such as the use of risk scores, platelet function testing , and genotyping, risk stratification has not been broadly adopted in clinical practice. Multiple risk scores have been developed to determine the optimal treatment duration, but external validation studies have yielded conflicting results in terms of calibration and discrimination and there is limited evidence that their adoption improves clinical outcomes. Likewise, platelet function testing and genotyping can provide useful prognostic insights, but trials evaluating treatment strategies guided by these stratification methods have produced mixed results. This review critically appraises the currently available antithrombotic strategies and provides a viewpoint on the use of different risk stratification methods alongside clinical judgement in current clinical practice.

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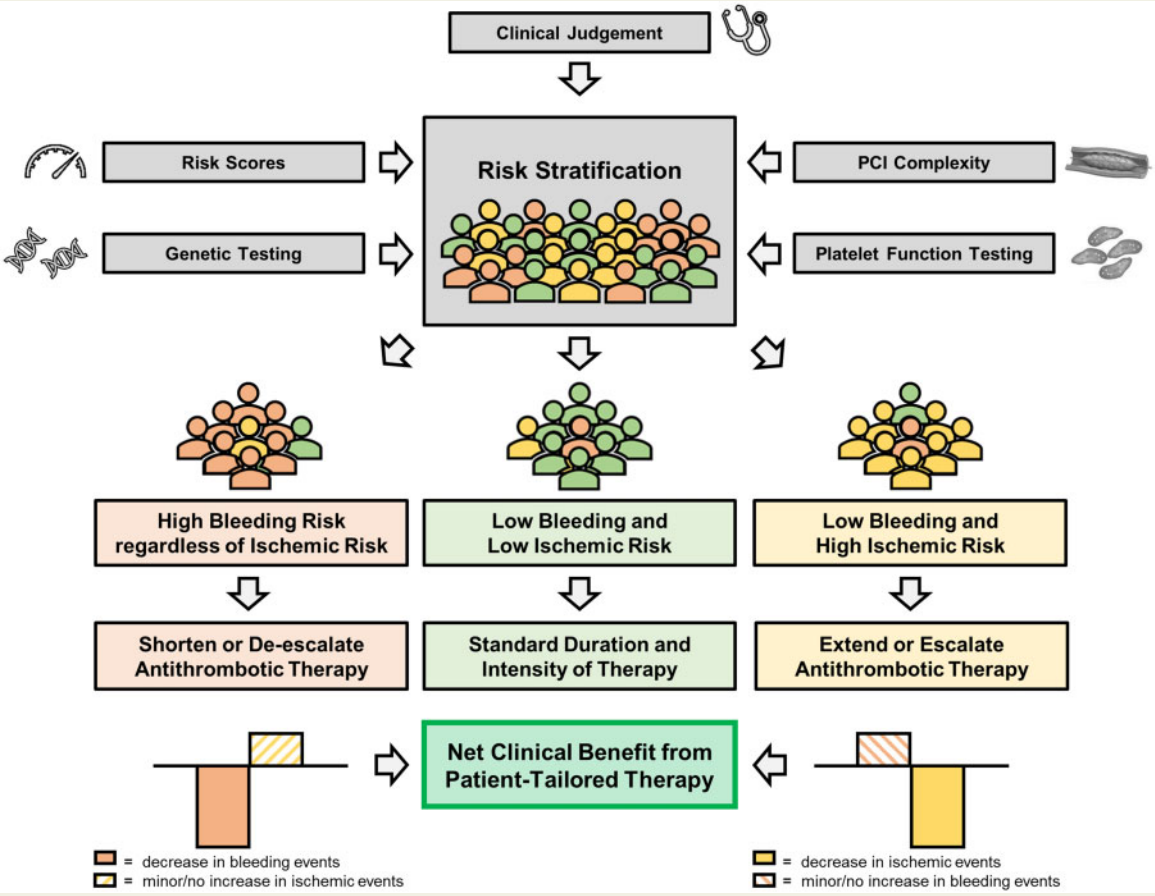
Graphical Abstract



Keywords Dual antiplatelet therapy • Patient-tailored antithrombotic therapy • Risk stratification

Introduction

Dual antiplatelet therapy (DAPT), consisting of aspirin and a $P2Y_{12}$ inhibitor, prevents stent-related and non-stent-related coronary and cerebrovascular thrombotic events and remains the standard of care following percutaneous coronary intervention (PCI) in patients with chronic coronary syndrome (CCS) and acute coronary syndrome (ACS).[1–3] Inevitably, DAPT increases bleeding complications, which are associated with significant morbidity and mortality.[4] Therefore, when determining the duration and composition of an antithrombotic regimen, physicians must carefully balance the advantages and drawbacks associated with this therapy. Historically, DAPT was recommended for at least 12 months after first-generation drug-eluting stent (DES) implantation because of concerns over late and very late stent thrombosis. However, the rates of late and very late stent thrombosis have decreased considerably with the advent of new generation DES.[5,6] In addition, some, but not all, randomized controlled trials (RCTs) have shown a reduction in bleeding complications without a signal of increased ischaemic events with a short course DAPT (3–6 months) as compared to 12 months DAPT in patients at relatively low risk of thrombotic events.[7–18] On the other hand, extending DAPT up to 3 years has been associated with a reduction in ischaemic events, with a similar increase in bleeding events, as compared to 12 months DAPT in patients treated with DES or in patients with a previous myocardial infarction (MI).[17–25] Furthermore, the field of antithrombotic therapy is rapidly evolving with novel antithrombotic strategies emerging, such as $P2Y_{12}$ inhibitor monotherapy, low-dose factor Xa inhibitors in addition to antiplatelet therapy, and platelet function- or genotype-guided de-escalation or escalation of $P2Y_{12}$ inhibition.[26–35] However, interpretation of results from RCTs investigating antithrombotic therapies is hampered by the use of composite (primary) endpoints, which combine ischaemic events [i.e. (cardiovascular) mortality, MI, and stroke] and major bleeding. The individual components of these combined endpoints can have markedly different impact on mortality, morbidity, and quality of life.[36] For example, bleeding (even major bleeding) is rarely fatal or disabling, whereas ischaemic stroke frequently results in permanent disability. Taken together, clinical decision-making regarding the optimal

duration and composition of antithrombotic therapy has become a major challenge.

Current guidelines highlight the importance of risk stratification to identify patients who benefit from either short or prolonged DAPT, or potent or less potent antithrombotic therapy as displayed in graphical abstract.[1–3] There are numerous risk stratification methods available to clinicians, such as the use of risk scores, platelet function testing (PFT) and genotyping, each with their advantages and drawbacks. This review summarizes evidence on different antithrombotic strategies after PCI, provides an overview and critical appraisal of currently available risk stratification methods, and puts into perspective the clinical need for patient-tailored antithrombotic therapy.

Short dual antiplatelet therapy followed by aspirin monotherapy

To date, 12 RCTs (Supplementary material online, *Table S1*) have evaluated short DAPT.[7–18] The vast majority of these trials demonstrated that short DAPT was non-inferior compared to standard DAPT in terms of the primary ischaemic endpoint, while some trials also showed a significant reduction in bleeding complications. In most studies, patients had a relatively low risk of recurrent ischaemia (mostly patients with CCS or low-risk ACS).[7–12,15,18] The investigated short DAPT varied from 3 to 6 months and in the majority of studies clopidogrel was used. Importantly, the SMART-DATE trial, which only included ACS patients, did show a higher risk of MI with 6 months DAPT as compared to 12 months.[13]

Several limitations of these trials should be acknowledged. Most trials used an open-label design. The majority of trials randomized patients at the time of index PCI instead of DAPT cessation thereby including early events when both groups were still using DAPT.[7–13,16–18] This may have diluted differences occurring after DAPT cessation. Some studies had lower-than-expected event rates or enrollment was prematurely discontinued, and were therefore underpowered.[9,15,18] Many trials pre-specified a wide non-inferiority margin, and in some trials, there were a large number of cross-overs between study groups, which hampers interpretation of the results.[37] Nonetheless, these studies collectively suggest that short DAPT might improve outcomes in patients with a relatively low thrombotic risk and/or high bleeding risk. Accordingly, current guidelines recommend that short DAPT should be considered in patients at high bleeding risk.[1–3]

Short dual antiplatelet therapy followed by $P2Y_{12}$ inhibitor monotherapy

In recent years, the status of aspirin as the mainstay of antithrombotic therapy has been challenged. Aspirin use is associated with an increased risk of bleeding (in particular gastrointestinal bleeding), especially in the elderly and those who concurrently use other antithrombotic agents.[38] The advent of potent $P2Y_{12}$ inhibitors, i.e. ticagrelor and prasugrel, has raised questions as to whether the additional antithrombotic benefit of aspirin outweighs the increase in bleeding complications. Especially since the antithrombotic potency of ticagrelor alone seems to be comparable to that of ticagrelor and aspirin with respect to *ex vivo* blood thrombogenicity.[39] In addition, contemporary pharmacological therapies for cardiovascular risk factors, such as hypertension, dyslipidemia, and impaired glucose metabolism, have led to reductions in an individual's cardiovascular risk.[38] These therapies were not available at the time of the pivotal studies evaluating aspirin in the setting of secondary prevention. Therefore, relative benefits of adding aspirin might translate into smaller absolute risk reductions in current clinical practice as compared to previous clinical trials.[38] Together, these observations have supported the hypothesis that $P2Y_{12}$ inhibitor monotherapy (after a short course DAPT) might be superior to standard 12 months DAPT. In fact, even complete omission of aspirin after PCI is now a topic of investigation. Recently, the ASET pilot has shown that an aspirin-free prasugrel monotherapy strategy directly following PCI was feasible in CCS patients opening the door to RCTs investigating complete aspirin omission in coronary artery disease.[40]

To date, five RCTs have investigated the efficacy and safety of aspirin discontinuation (i.e. $P2Y_{12}$ inhibitor monotherapy) after a short course of DAPT in patients undergoing PCI with new generation DES.[26–30] These trials are summarized in Supplementary material online, *Table S2*. Importantly, three of these trials were underpowered to test non-inferiority of short DAPT compared to standard DAPT with regard to ischaemic events.[28–30] Four trials applied an open-label design and randomized patients at the time of PCI (instead of at DAPT discontinuation).[27–30] In the pivotal, placebo-controlled, double-blind TWILIGHT trial, 3 months DAPT followed by ticagrelor monotherapy up to 15 months was associated with a significant reduction in BARC types 2, 3, and 5 bleeding compared to 15 months DAPT (with ticagrelor).[26] Three months DAPT followed by ticagrelor monotherapy was non-inferior to 15 months DAPT in terms of ischaemic events.[26] Importantly, 29% of patients included in TWILIGHT had CCS, for whom 6 months DAPT with clopidogrel would be standard practice. The TWILIGHT trial included patients with at least one clinical and angiographic feature associated with high ischaemic or bleeding risk, but the rate of all-cause mortality, MI, or stroke between 3 and 15 months was relatively low compared with other trials investigating high-risk PCI (3.9% in both treatment arms), suggesting that the investigated study population actually consisted of more low-risk patients. Although TWILIGHT sub-studies in high-risk groups (e.g. diabetic patients or complex PCI) have been reassuring, whether DAPT for 3 months followed by ticagrelor monotherapy actually is non-inferior to 12 months DAPT with regard to ischaemic events in true high-risk patients remains to be investigated.[41,42] In line with the results of TWILIGHT, $P2Y_{12}$ inhibitor monotherapy preceded by short DAPT (1–3 months) was associated with a lower incidence of clinically relevant bleeding compared to standard DAPT treatment without an increase in cardiovascular events after 1 year in multiple recent meta-analyses.[43–46]

Based on the available evidence, $P2Y_{12}$ inhibitor monotherapy after an initial short course DAPT should be considered as an alternative to standard DAPT in patients without high ischaemic risk undergoing PCI.[3] Ticagrelor should be the agent of choice for ACS patients, due to its superiority to clopidogrel and its predominant use in trials evaluating $P2Y_{12}$ inhibitor monotherapy.[26,27,30] For CCS patients, clopidogrel might be the preferred option, although there

are concerns of high on-treatment platelet reactivity. To address these concerns, physicians may consider PFT to assess treatment response, but this specific strategy remains to be investigated. Clopidogrel monotherapy has only been evaluated in East Asian patients, who have an unique risk profile.[28,29] Therefore, caution should be taken when extrapolating these trials results to other ethnicities. Thus far, experience with prasugrel monotherapy in the setting of $P2Y_{12}$ inhibitor monotherapy has been limited. Of note, there are currently no randomized studies available comparing $P2Y_{12}$ inhibitor monotherapy to aspirin monotherapy after a short course of DAPT and experience with $P2Y_{12}$ inhibitor monotherapy beyond 1 year after stent implantation is limited.

Extended dual antiplatelet therapy

Nine RCTs compared extended DAPT (18–48 months) with standard DAPT (6–12 months) (Supplementary material online, *Table S3*).[17–25] Most trials did not demonstrate a benefit of extended DAPT. The majority of patients enrolled in these trials had CCS and clopidogrel was used almost exclusively. Two studies randomized patients at the time of PCI or shortly thereafter, potentially diluting differences in outcome between the two groups.[17,18] Importantly, the adequately powered DAPT trial demonstrated that long DAPT (30 months) significantly reduced the risk of definite or probable stent thrombosis and major adverse cardiac events (MACE), but was also associated with an increased risk of bleeding.[22] Overall, at 30 months after index PCI, there was a trend towards increased all-cause mortality (0.5% absolute increase) with extended DAPT, explained by a statistically significant increase in non-cardiovascular mortality, mainly attributed to increased cancer related mortality. The PEGASUS-TIMI 54 trial included patients who suffered an MI 1–3 years before enrollment and had at least one additional high-risk feature (age ≥65 years, diabetes mellitus requiring medication, multiple prior MI's, multivessel disease or renal impairment). The study showed that extended DAPT with ticagrelor (median 33 months) compared to aspirin monotherapy reduced the risk of MI, stroke, and cardiovascular death combined but increased the risk of major bleeding and did not reduce all-cause mortality.[24] The absolute decrease in the primary efficacy endpoint was similar in magnitude to the increase in the primary bleeding endpoint indicating no clear benefit for the study population as a whole.

In a pre-specified subgroup of CCS patients with diabetes and previous PCI of the THEMIS trial, long-term DAPT with ticagrelor (60 mg twice daily) on top of aspirin (for a median of 3.3 years) was associated with a 1.3% absolute reduction in cardiovascular death, MI, and stroke [number needed to treat (NNT) 77], coupled with an increase in major bleeding [0.9% absolute increase, number needed to harm (NNH) 111].[47] The high NNT and similar NNH currently only support extended DAPT in diabetic patients having undergone PCI and at high ischaemic risk without high bleeding risk. Accordingly, ticagrelor has been approved by the FDA to reduce the risk of MI or stroke in high-risk patients with CCS. Importantly, in THEMIS, in patients without a previous intervention, long-term ticagrelor plus aspirin increased the rate of major bleeding (including intracranial haemorrhage) without a reduction in ischaemic events and should therefore be avoided.

A meta-analysis investigating extended DAPT in patients with prior MI showed a reduction in stent thrombosis, stroke, and MI, which translated into decreased cardiovascular mortality.[48] However, other meta-analyses including lower risk patients did not show reduced cardiovascular mortality and extended DAPT was even associated with an increased risk of non-cardiovascular and all-cause mortality.[49–51] Hence, current guidelines recommend that extended DAPT can be considered in patients with high thrombotic risk without high bleeding risk.[1–3]

Low-dose factor Xa inhibitor on top of antiplatelet therapy

Factor Xa inhibitors and other anticoagulants ultimately inhibit the formation or activation of thrombin, which plays a crucial role in both coagulation and platelet activation and may offer a synergistic benefit when added to antiplatelet therapy.[52] A strong asset of dual-pathway inhibition is that anticoagulants, like factor Xa-inhibitors, modulate a number of inflammatory pathways which may reduce their contribution to atherogenesis.[52] Oral anticoagulants have been shown to mitigate the risk of arterial thrombotic events, but because DAPT was superior to aspirin and warfarin in preventing stent thrombosis, the latter strategy was abandoned in favour of DAPT following PCI.[53] However, recently reported studies investigating (low-dose) non-vitamin K antagonist oral anticoagulants (Supplementary material online, *Table S4*) have renewed interest in combining lower anticoagulant doses with antiplatelet therapy.

In the placebo-controlled ATLAS ACS 2-TIMI 51 trial, low-dose rivaroxaban (2.5 mg twice daily) reduced the incidence of cardiovascular death, MI, and stroke in ACS patients mostly treated with aspirin and clopidogrel, at the expense of increased bleeding.[31] Subsequently, in the COMPASS trial, low-dose rivaroxaban (2.5 mg twice daily) on top of aspirin as compared to aspirin alone was associated with reduced risk of cardiovascular death, MI or stroke in patients with CCS and peripheral artery disease at moderate-high risk of ischaemic events.[32] In high-risk subgroups (e.g. patients with diabetes, moderate chronic kidney disease, and current smokers), low-dose rivaroxaban was associated with even greater absolute risk reductions. Unfortunately, pre-specified significance thresholds for cardiovascular and all-cause mortality were not met and patients on low-dose rivaroxaban on top of aspirin had more major (though not-fatal) bleeding events.[32] Interestingly, low-dose rivaroxaban and aspirin as compared to aspirin alone significantly reduced the rate of stroke by 42% (driven by a 49% relative reduction in ischaemic stroke partially offset by a numeric increase in haemorrhagic stroke), making low-dose rivaroxaban plus aspirin an important new option for stroke prevention in patients with atherosclerosis.[54]

A substantial fraction (approximately 50%) of coronary or peripheral artery disease patients encountered in daily practice seem eligible for this strategy based on an analysis in the REACH registry.[55] However, exclusion criteria like high bleeding risk, an indication for therapeutic anticoagulation or DAPT, and a history of recent stroke are common, warranting careful patient selection for this novel approach. Current guidelines now highlight low-dose rivaroxaban on

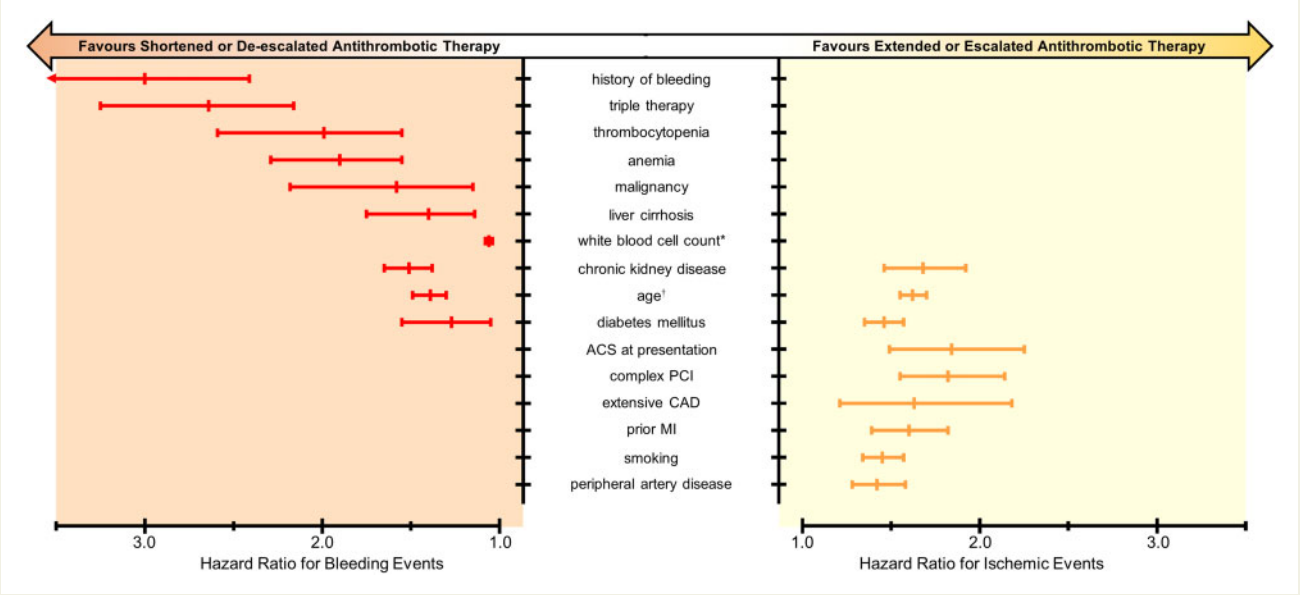


Figure 1 Clinical risk factors associated with increased risk of bleeding and/or ischaemic events. *Age per 10 years; †white blood cell count 10^3 cells/μL. ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction.

top of aspirin as an option for extended long-term secondary prevention in patients with high ischaemic risk and low bleeding risk.[3] Of note, a head-to-head comparison between low-dose rivaroxaban in addition to aspirin vs. extended DAPT for long-term secondary prevention in high-risk patients is currently lacking.

Risk stratification and risk scores

Given the benefits and risks of various DAPT durations and compositions, current guidelines recommend risk stratification to identify patients who benefit from either shortened or extended DAPT, or potent or less potent antithrombotic therapy.[1–3] Risk stratification involves determining a patient's risk of bleeding and thrombotic events, taking into account clinical, anatomical, and procedural characteristics. *Figure 1* illustrates the impact of established risk factors on thrombotic and bleeding risk by showing pooled results of previously published hazards ratios for thrombotic and bleeding events (for methodology see Supplementary material online, *Appendix S5*).

In recent years, multiple risk scores have been developed aimed at maximizing ischaemic protection and minimizing bleeding risk for individual patients by tailoring treatment duration (net clinical benefit).[56,57] Various studies, however, have questioned their calibration, predictive value, and generalizability in real-world patients. Therefore, their utility in routine clinical practice has been subject of debate.[58] Currently available risk scores developed to determine DAPT duration are summarized in Table 1. An overview of the derivation cohorts is shown in Supplementary material online, *Table S6*. The PEGASUS-TIMI 54 investigators have developed a simple patient selection algorithm incorporating both bleeding and thrombotic risk to identify patients who may benefit from long-term secondary prevention with DAPT.[59] By applying the tool in PEGASUS-TIMI 54, a patient subset at high risk of thrombotic events and low risk of bleeding was identified, who derived net clinical benefit (defined as a reduction in the composite of cardiovascular death, MI, stroke, intracranial haemorrhage, or fatal bleeding) and a reduction in all-cause mortality with extended DAPT. This promising tool, however, has not undergone the peer-review process; therefore, a detailed discussion of this tool is beyond the scope of this manuscript. The Academic Research Consortium recently proposed a consensus definition for high bleeding risk.[60] Although these criteria adequately identified patients with high bleeding risk, the criteria were not developed to tailor DAPT duration and are—like other risk scores (e.g. the PARIS risk scores), which were not specifically designed to tailor DAPT duration—therefore beyond the scope of this review. So far, risk scores have focused on determining optimal antiplatelet treatment duration, not optimal composition.

Risk scores to be used at the time of percutaneous coronary intervention

The PRECISE-DAPT score

The PRECISE-DAPT score is a five-item risk score to predict out-of-hospital bleeding after PCI (Table 1).[56] The *c*-statistic for out-of-hospital TIMI major or minor bleeding was 0.73 and 0.71 for TIMI major bleeding in the development cohort. The PRECISE-DAPT score was externally validated in PLATO and the BERN-PCI registry with good (*c*-statistic 0.70) and moderate (*c*-statistic 0.66) discrimination, respectively. In both study populations, calibration was good. Among patients with a high bleeding risk (PRECISE-DAPT score ≥25), standard DAPT was associated with no reduction in ischaemic

Table 1 Overview of risk scores developed to guide clinical decision-making surrounding optimal dual antiplatelet therapy duration

	PRECISE-DAPT score[56]	DAPT score[57]
Clinical outcome	Out-of-hospital TIMI minor or major bleeding	Out-of-hospital MI, ST, and GUSTO moderate or severe bleeding
Predictors	(1) Age (2) Kidney function (3) Hemoglobin (4) White blood cell count (5) Prior bleeding	(1) Age (2) Cigarette smoking (3) Diabetes mellitus (4) MI at presentation (5) Prior PCI or MI (6) Paclitaxel-eluting stent (7) Stent diameter <3 mm (8) CHF or LVEF <30% (9) Vein graft stent
Time of use	At time of PCI	After 12 months
Score range	0 to 100	-2 to 10
Interpretation		
Very low risk	≤10	
Low risk	11 to 17	<2
Moderate risk	18 to 24	
High risk	≥25	≥2
Clinical implications	≥25 net clinical benefit from shortened (3–6 months) DAPT	≥2 net clinical benefit from extended (30 months) DAPT
Calculator	www.precisedaptscore.nl	www.tools.acc.org/DAPTriskapp

CHF, congestive heart failure; DAPT, dual antiplatelet therapy; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

events, but a strong increase in bleeding with an NNH of 38. By contrast, standard treatment in patients without high bleeding risk (PRECISE-DAPT score <25) was associated with significant reductions in the combined ischaemic endpoint, without an increase in bleeding, with an NNT of 65. Thus, by upfront deciding on a short course of DAPT in patients at high bleeding risk, a substantial proportion of excess bleeding events might be prevented, while patients without high bleeding risk benefit from standard or extended DAPT. Noteworthy, in five out of eight RCTs included in the PRECISE-DAPT derivation cohort, exclusion criteria such as thrombocytopenia, anaemia, or history of bleeding were applied.[7–9,17,61] In the derivation cohort, the incidence of bleeding was relatively low (1.5% and 0.8% for major and minor and major bleeding events, respectively) suggesting that patients at high risk of bleeding were not included. Importantly, individual information regarding drug adherence was not available in the derivation cohort and was therefore only based on the pre-specified or randomized treatment duration at the time of PCI.[56]

External retrospective validation in other PCI cohorts showed overall moderate discrimination and adequate calibration for bleeding, but the PRECISE-DAPT score may be less suitable for elderly patients and those on concomitant oral anticoagulant therapy (Supplementary material online, *Table S7*). A 4-item PRECISE-DAPT score, without white blood cell count, has also been recently validated as a tool to identify patients who benefit from shortened DAPT.[62]

Risk scores to be used 12 months after percutaneous coronary intervention

The dual antiplatelet therapy score

The DAPT score was derived from 11 648 patients enrolled in the DAPT trial who tolerated DAPT during the first year without MACE or bleeding.[57] It is a combined ischaemic and bleeding risk score designed to predict which patients benefit from DAPT extension (up to 30 months) (Table 1). Among patients with a high score (≥2) treatment with extended DAPT (12–30 months) resulted in reductions in ischaemic events (NNT 34) without an increase in bleeding and thus in net clinical benefit. Yet, this apparent benefit disappeared when patients having received paclitaxel-eluting stents were removed from the analysis.[57] Among patients with a low score (<2) treatment with extended DAPT was associated with an increase in moderate or severe bleeding events (NNH 64), without reductions in ischaemic events. The DAPT score had good predictive value for ischaemic events (*c*-statistic 0.70) and moderate predictive value for bleeding events (*c*-statistic 0.68) in the development cohort.

The ability of the DAPT score to retrospectively identify patients who derive net clinical benefit from extended DAPT has been investigated in RCTs but none reached statistical significance in terms of absolute risk differences (Supplementary material online, *Table S8*). However, a pooled meta-analysis showed that extended DAPT reduced ischaemic events with no effect on bleeding in patients with a high DAPT score, and conversely increased bleeding without an

ischaemic benefit was seen in patients with a low DAPT score who received extended DAPT.[63]

Due to the lack of randomization, identifying patients who derive net clinical benefit from extended DAPT in registry-based validation studies is not possible, but discrimination and calibration can be assessed. In the SWEDEHEART registry, a large Swedish nationwide cohort of patients with cardiovascular disease showed that the DAPT score poorly discriminated ischaemic risk and was unable to discriminate bleeding risk.[64] In addition, the absolute risk rates for MACE followed a U-shaped pattern suggesting poor calibration of the DAPT score. However, the developers of the DAPT score argued that this might be related to the definition of MACE in SWEDEHEART, which was a composite of all-cause mortality, MI, and stroke. Older patients have a relatively low DAPT score (-1 or -2 points for those aged 65–74 or ≥75 years, respectively) and a high risk of mortality due to non-cardiovascular causes (which is not prevented by extended DAPT) explaining why MACE rates were also high in patients with a low DAPT score.[65] Furthermore, the (non-fatal) bleeding rate might have been underestimated in this cohort since events were based on administrative codes.[65] Other external validation studies of the DAPT score showed conflicting results in terms of calibration and discrimination (Supplementary material online, *Table S9*), but classic validation metrics may not be appropriate for this combined bleeding and ischaemic risk score.[65] Possible explanations for the lack of calibration and discrimination of the DAPT score in external validation studies include the fact that (i) patients with a contraindication for extended DAPT were excluded from the trial; (ii) <50% of those screened were included in the trial population, (iii) common bleeding determinants, such as previous bleeding, creatinine clearance, and anaemia, are not included in the DAPT score, and (iv) older generation stents were used, which might have inflated the risk of stent thrombosis.

Platelet function- or genotype-guided $P2Y_{12}$ inhibitor therapy

Clopidogrel and prasugrel require conversion to an active metabolite by the cytochrome P450 enzyme system. Genetic polymorphisms, especially loss-of-function mutations, have been shown to contribute to impaired conversion of clopidogrel to the active metabolite.[66] Impaired drug conversion can lead to high (on-treatment) platelet reactivity (HPR), which is common among patients on clopidogrel (~42%, reported range 7–75%), but relatively rare in prasugrel users.[67,68] HPR has consistently been associated with an increased risk of stent thrombosis and MACE.[67] Conversely, low platelet reactivity has been associated with an increased risk of bleeding.[67] Thus, PFT and genotyping might be of utility in ischaemic or haemorrhagic risk stratification and tailoring of $P2Y_{12}$ inhibitor therapy. For instance, clinicians can escalate (switch from a less potent agent, i.e. clopidogrel, to a potent agent, i.e. ticagrelor or prasugrel) or de-escalate treatment (switch from a potent agent to a less potent agent).[69] In recent years, multiple rapid (bedside) assays have become available, enabling easy implementation in routine practice.[70] Characteristics of RCTs investigating a platelet function-guided or genotype-guided escalation or de-escalation approach are given in Supplementary material online, *Tables S10 and S11*, respectively.

Unfortunately, none of the RCTs investigating platelet function-guided escalation, which mainly included CCS patients, met their respective primary endpoint. Therefore, in an updated expert consensus document, the routine use of PFT to escalate $P2Y_{12}$ inhibitor therapy in patients with HPR on clopidogrel was not recommended.[71] However, PFT-guided $P2Y_{12}$ inhibitor therapy can be considered in selected patients without high bleeding risk, in whom adequate platelet inhibition is of the utmost importance (e.g. left main stenting, last patent vessel PCI, or previous stent thrombosis).[71]

To date, two RCTs have compared PFT-guided de-escalation or dose-adjustment of $P2Y_{12}$ inhibitor therapy to standard treatment in patients with ACS.[35,72] In TROPICAL-ACS, platelet function-guided de-escalation of prasugrel to clopidogrel was non-inferior (but not superior) to standard prasugrel in terms of the primary net clinical benefit endpoint, a composite of cardiovascular death, MI, stroke, or BARC type ≥2 bleeding.[35] The rates of ischaemic events were similar in the guided vs. non-guided group (2.5% vs. 3.2%, $P = 0.12$) and there was a trend towards less bleeding in the platelet function-guided group (4.9 vs. 6.0%, $P = 0.23$), mainly driven by a reduction in minor bleedings. Of note, almost 4 out of 10 patients in the guided de-escalation group were switched back to prasugrel after 2 weeks because of HPR while on clopidogrel. Although the trial was not powered to test non-inferiority in terms of ischaemic events, the low MACE rate in the platelet function-guided group is reassuring. Therefore, PFT-guided de-escalation of $P2Y_{12}$ inhibitor therapy may be considered in specific clinical scenarios, such as high bleeding risk or a recent bleeding event.

Genotype-guided escalation or de-escalation was associated with improved outcomes in small, single, or dual centre RCTs.[73,74] In the large-scale TAILOR PCI trial, in a predominantly ACS population treated with PCI ($n = 5302$), a genotype-guided escalation strategy (ticagrelor instead of clopidogrel in carriers of CYP2C19 loss-of-function alleles) numerically, though not statistically significantly (5.9% vs. 4.0%, $P = 0.06$), reduced adverse cardiovascular events as compared to standard treatment with clopidogrel on top of aspirin in the subgroup of carriers of loss-of-function alleles ($n = 1849$).[75] A pre-specified sensitivity analysis taking into account recurrent events (not only the time to first event) did reach statistical significance and a *post hoc* analysis showed an almost 80% reduced rate of adverse events in the first 3 months, suggesting that most gain is to be made in the early high-risk period following PCI.[75] Of note, the vast majority of study population consisted of ACS patients (84%), for whom treatment with potent $P2Y_{12}$ inhibitors and not clopidogrel is the current standard of care.[1–3]

In the POPular Genetics trial, 2488 patients undergoing primary PCI were randomized open-label to genotype-guided $P2Y_{12}$ inhibition (de-escalation based on CYP2C19 genetic testing) or standard treatment with either ticagrelor or prasugrel for 12 months. Genotype-guided $P2Y_{12}$ de-escalation was non-inferior to standard treatment in terms of the primary outcome net clinical benefit, and there was a significant reduction in the primary bleeding outcome (PLATO major or minor bleeding), driven by a reduction in minor bleeding. Although the trial was not powered to test non-inferiority with regard to ischaemic events, there was no signal of increased ischaemic events in the de-escalation group.

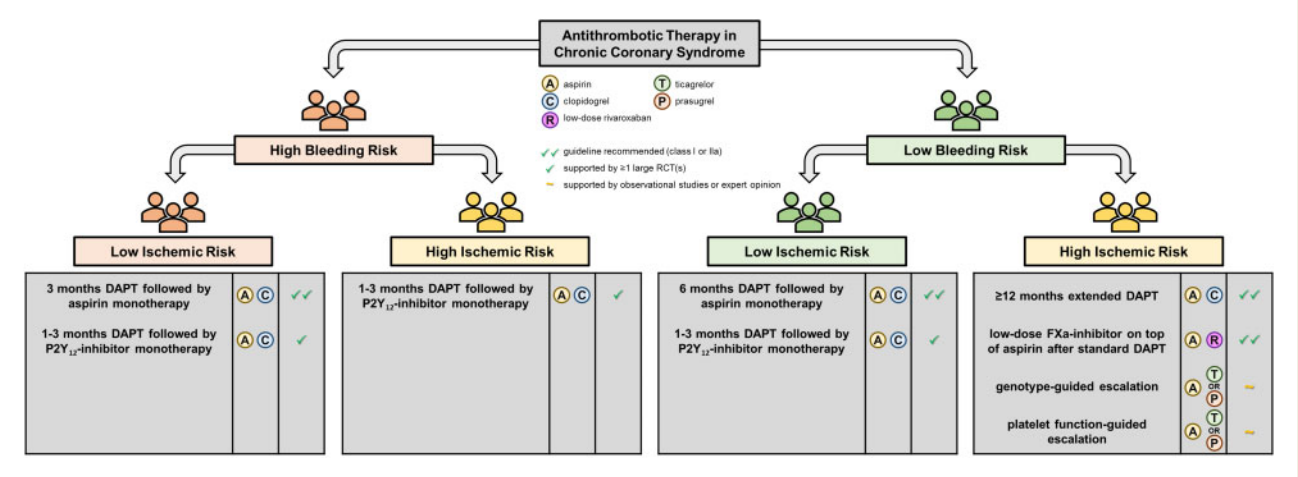


Figure 2 Patient-tailored antithrombotic strategies for chronic coronary syndrome patients. Recommendations reflect the authors' opinion. DAPT, dual antiplatelet therapy; FXa, factor Xa; RCT, randomized controlled trial.

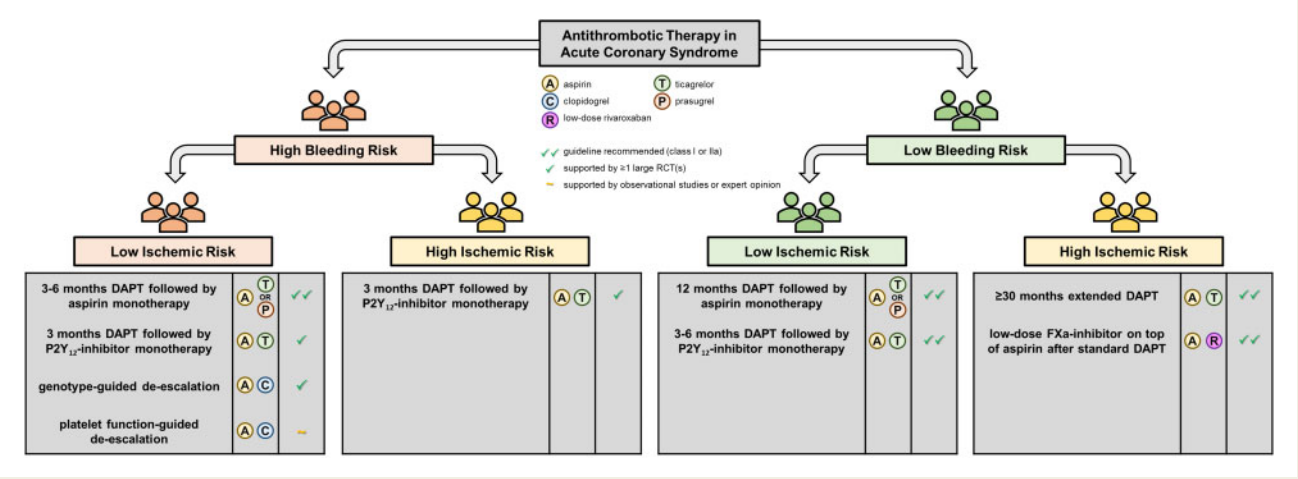


Figure 3 Patient-tailored antithrombotic strategies for acute coronary syndrome patients. Recommendations reflect the authors' opinion. DAPT, dual antiplatelet therapy; FXa, factor Xa; RCT, randomized controlled trial.

Taken together, there is some evidence supporting genotype-guided $P2Y_{12}$ inhibition, but still insufficiently for its routine adoption in clinical practice. For now, genotype-guided $P2Y_{12}$ inhibition may be considered in patients with a particular risk profile or for socioeconomic reasons. Interestingly, the recently proposed ABCD-GENE score integrates four clinical factors (age, body mass index, chronic kidney disease, and diabetes mellitus) and CYP2C19 genotype.[76] The ABCD-GENE score identifies patients with HPR on clopidogrel and those who are subsequently at increased risk for death, MI, or stroke.[76] Clinicians may consider escalating antithrombotic therapy in patients on clopidogrel with a high ABCD-GENE score, but prospective validation of this risk score is warranted.

Patient-tailored antiplatelet therapy in daily practice

Deciding for whom to shorten, extend, de-escalate, or escalate antithrombotic therapy is complex and requires collaboration between the interventional cardiologist and the treating cardiologist at the outpatient clinic. Physicians need to weigh clinical, anatomical, procedural, and laboratory aspects together with input from risk scores and in selected patients from PFT or genotyping, before choosing an antithrombotic strategy. In addition, a patient's bleeding and ischaemic risk may change over time. Treatment duration or composition dictated by risk scores or other stratification methods should therefore not be considered static and should be reassessed periodically.

Table 2 Advantages and drawbacks of risk stratification methods

	Risk scores	PFT	Genotyping
Easy to use, results rapidly available	✓✓	✓	✓
Associated with ischaemic events	✓	✓	✓
Associated with bleeding events	✓	✓	✓
Provides an overall bleeding and ischaemic risk estimate	✓	✗	✗
No need to be determined while on treatment	✓	✗	✓
Direct measure of response to therapy	✗	✓	✗
No additional healthcare costs	✓	✗	✗
Benefits established in RCTs	✗	✗	✓[a]

✓ denotes the presents of a given feature linked to the respective risk stratification method, while
✗ denotes the absence of such a feature. PFT, platelet function testing; RCT, randomized controlled trial.
[a]Genotype-guided de-escalation has been shown to reduce minor bleeding events.

Graphical abstract shows the available risk stratification tools, while *Figures 2 and 3* illustrate the subsequent treatment options for CCS and ACS patients with different risk profiles. Of the available tools, PFT and genetic testing have been most extensively investigated in RCTs. Although there is a clear biological rationale for the use of PFT or genotyping and the results of small proof-of-concept studies investigating a guided approach were promising, the robustness of the evidence, especially when considering the results of adequately powered RCTs, still does not support the routine use of PFT or genetic testing.[71] Table 2 list advantages and drawbacks associated with the different risk stratification tools. Risk scores such as the PRECISE-DAPT and DAPT scores are easy to use and free of charge, thus facilitating broad adoption in clinical practice even among non-cardiologists. To date, there have been no RCTs comparing a risk score-based approach with standard care. Currently, the FORCE-ACS study, a prospective multicentre registry study, is comparing a risk score-guided approach to standard practice in ACS patients (ClinicalTrials.gov Identifier: NCT03823547).[77] Interestingly, in this study, application of the PRECISE-DAPT and DAPT scores is combined, potentially improving the overall performance of the risk score-guided approach.

For patients with a high thrombotic risk and an acceptable bleeding risk, physicians can now choose between extending DAPT or adding low-dose rivaroxaban to aspirin. Comparing relative and absolute risk reduction from different RCTs is difficult due to variation in study populations and follow-up. Therefore, it remains to be investigated which of these two strategies is superior in terms of efficacy and safety. It is also still unknown if risk scores are able to identify patients who derive benefit from low-dose rivaroxaban in conjunction with aspirin.

Recently, two studies have underscored the importance of PCI complexity in determining DAPT duration.[78,79] These studies showed that complex PCI was an independent predictor of ischaemic events in the first year, but not beyond 12 months after PCI. In the derivation cohort of the PRECISE-DAPT score, 12–24 months DAPT was associated with significant reductions in MACE compared to 3–6 months DAPT in patients with complex lesions.[78] Conversely, in the DAPT trial, among patients without events in the first year, the benefits of extending DAPT beyond 1 year were similar regardless of PCI complexity.[79] These findings suggest that patients who have undergone complex PCI may benefit from 12 months DAPT rather than 3–6 months DAPT. Extending DAPT beyond 1 year in these patients should be based on overall thrombotic risk and not on procedural characteristics alone.

A major challenge frequently facing physicians is concurrent high bleeding and high ischaemic risk (e.g. in the PARIS registry ~40% of high bleeding risk patients also had high ischaemic risk).[80] Findings of a recent *post hoc* analysis performed in the derivation cohort of the PRECISE-DAPT score suggest that in these patients bleeding risk rather than ischaemic risk should guide decision-making regarding treatment duration.[81] This analysis found that high bleeding risk patients (i.e. PRECISE-DAPT score ≥25) with concordant high ischaemic risk (i.e. complex PCI and/or ACS at presentation) did not derive benefit from long DAPT (12–24 months) as compared to short DAPT (3–6 months) but did have excess bleeding complication.[81]

Conclusions

The future of antithrombotic therapy lies in an individualized duration and composition based on risk stratification. There are multiple risk stratification methods available to guide clinical decision-making, all with their own advantages and drawbacks. Future research will have to point out how to best stratify patients and subsequently provide them with patient-tailored therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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