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Dual Antiplatelet or Dual Antithrombotic Therapy for Secondary Prevention in High-Risk Patients with Stable Coronary Artery Disease?

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Thromb Haemost

Abstract

Antithrombotic treatment is a key component of secondary prevention following acute coronary syndromes (ACS). Although dual antiplatelet therapy is standard therapy post-ACS, duration of treatment is the subject of ongoing debate. Prolonged dual antiplatelet therapy in high-risk patients with history of myocardial infarction reduced the risk of recurrent myocardial infarction, stroke or cardiovascular death. Similarly, in patients with stable coronary artery disease, two-thirds of whom had a history of myocardial infarction, dual antithrombotic therapy with very-low-dose rivaroxaban and aspirin also resulted in improved ischaemic outcomes. In the absence of head-to-head comparison, choosing the most appropriate treatment strategy can be challenging, particularly when it comes to balancing the risks of ischaemia and bleeding. We aim to review the evidence for currently available antithrombotic treatments and provide a practical algorithm to aid the decision-making process.

Keywords

- ▶ coronary artery disease
- ▶ dual antiplatelet therapy
- ▶ dual antithrombotic therapy
- ▶ rivaroxaban
- ▶ ticagrelor

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor forms the backbone of secondary prevention following acute coronary syndromes (ACS).^{1,2} Twelve months' DAPT post-ACS is well established but evidence to support prolonged intensive therapy in high-risk patients following myocardial infarction (MI) continues to emerge. Prolonged ticagrelor-based DAPT reduced recurrent MI, stroke or cardiovascular (CV) death in patients within 1 to 3 years of having an MI in the PEGASUS-TIMI 54 trial.³ A meta-analysis that included > 33,000 patients with history of MI from multiple prolonged DAPT trials, including the PEGASUS-TIMI 54 study, also showed prolonged DAPT to result in improved major ischaemic events.⁴ Similarly, in the COMPASS trial,⁵ dual antithrombotic therapy (DATT) with an anticoagulant (very-low-dose rivaroxaban 2.5 mg twice daily) and aspirin resulted in a significant reduction in major CV events in high-risk stable

coronary artery disease (CAD) patients, two-thirds of whom had a history of MI. There was also a numerical reduction in all-cause mortality that narrowly missed the pre-specified significance threshold (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.96; $p = 0.01$; threshold p -value for significance 0.0025). Both treatment strategies resulted in increased risk of major bleeding events and, therefore, the onus is on clinicians to balance the risks of ischaemia and bleeding. Here, we will consider the evidence for and against each of these treatment strategies and provide a practical summary to aid physicians in the decision-making process.

Therapeutic Targets in Arterial Thrombosis

The role of platelets in arterial thrombosis is well established. As demonstrated in ▶Fig. 1, at the site of vascular injury, platelets adhere to collagen and von Willebrand factor and these lead to platelet activation. Two key pathways are

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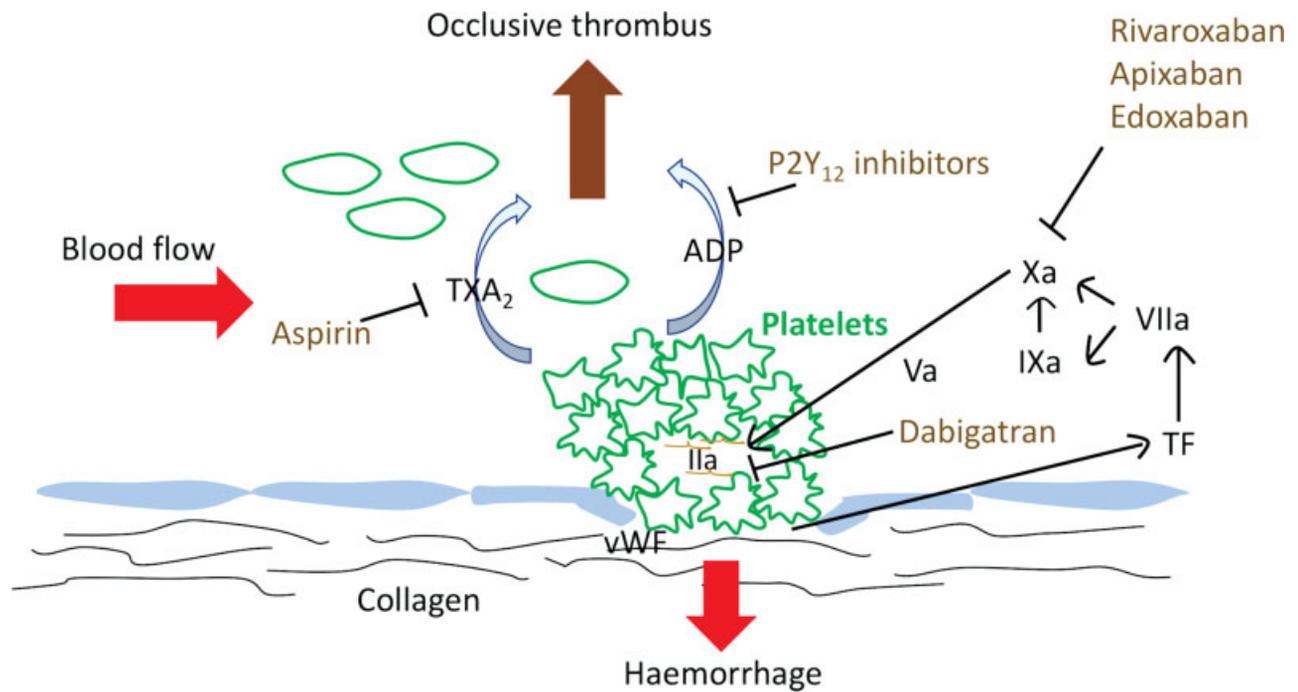


Fig. 1 Arterial thrombosis and modes of action of antithrombotic treatments. Following endothelial disruption, platelets adhere to collagen and von Willebrand factor (vWF) in the sub-endothelial matrix. Activated platelets secrete thromboxane A₂ (TxA₂), adenosine diphosphate (ADP) and also support the generation of thrombin (IIa). Endothelial disruption and plaque rupture also lead to the expression of tissue factor, triggering the coagulation cascade. Thrombin plays a more important role in stabilizing the core thrombus through fibrin generation in contrast to ADP and TxA₂, which play key roles in expansion of the platelet-rich thrombus.⁴⁰ ‘a’ denotes activated clotting factors.

implicated in amplifying this process, the thromboxane A₂ (TxA₂) and the adenosine diphosphate (ADP) P2Y₁₂ receptor pathways. Cyclooxygenase (COX) 1 is key in the production of TxA₂ while ADP is released from platelets' dense granules.⁶ Aspirin targets platelets by irreversible acetylation of COX1 enzyme and currently three oral agents inhibit platelets' P2Y₁₂ receptors either directly (ticagrelor) or through an active metabolite (clopidogrel and prasugrel). Studies of DAPT have demonstrated the pivotal roles of TxA₂ and ADP in coronary thrombosis and, in particular, stent thrombosis.⁷⁻⁹

The protein coagulation arm is also activated following vascular injury, leading to thrombin production and consequent fibrin formation. Thrombin also activates platelets through protease-activated receptors (PAR) 1 and 4¹⁰ and so anticoagulants have platelet inhibitory effects through inhibition of thrombin-induced platelet activation, either by directly inhibiting thrombin or by inhibiting thrombin generation.¹¹ However, the relative contribution of thrombin to stent thrombosis remains uncertain in comparison to the well-established roles of TxA₂ and ADP. Fibrin clots that resist lysis independently predict CV death following ACS, indicating that development of therapies to improve fibrin clot lysis may be a successful avenue in the future.¹²

Oral P2Y₁₂ Inhibitors

Multiple landmark clinical trials have established a definitive advantage for combining aspirin and a P2Y₁₂ inhibitor for approximately 12 months post-ACS.^{7-9,13} Prasugrel and ticagrelor offer more rapid, potent and consistent P2Y₁₂ inhibi-

tion compared with clopidogrel. These properties have translated into improved outcomes.^{8,9} **Table 1** summarizes the pharmacodynamics of each of these agents and provides a summary of appropriate use post-ACS.

Prolonged Dual Antiplatelet Therapy

Time-limited DAPT assumes that thrombotic risk disappears upon cessation of therapy. However, approximately 1 in 5 patients suffers a major adverse cardiovascular event (MACE) within 3 years after cessation of DAPT.¹⁴

The CHARISMA trial tested whether clopidogrel-based DAPT would reduce MACE in > 15,000 patients with multiple atherothrombotic risk factors.¹⁵ In this study, DAPT did not result in a significant reduction in ischaemic risk; however, only less than 50% of patients had documented CV disease and, among the third who had history of MI, DAPT appeared to result in improved outcomes.¹⁵

Similarly, 30 months' DAPT was tested in the DAPT study in patients undergoing percutaneous coronary intervention (PCI), the majority of whom were treated for stable CAD. In this study, prolonged clopidogrel- or prasugrel-based DAPT resulted in a reduction in MI (2.1% vs. 4.1%; $p < 0.001$).¹⁶ Concerns regarding the numerically higher rates of all-cause death in the prolonged DAPT group (2% vs. 1.5%, $p = 0.05$) and the increased risk of major bleeding (2.5% vs. 1.6%; $p = 0.001$) have limited a general adoption of such a strategy. Patients with MI appeared to accrue the greatest benefit from prolonged DAPT without an increase in all-cause death.¹⁷

Table 1 Oral P2Y₁₂ inhibitors

P2Y ₁₂ inhibitor	Pharmacodynamic properties	Appropriate indications post-ACS
Clonidogrel	Pro-drug; active metabolite irreversibly blocks platelet P2Y ₁₂ receptors. Complex pharmacokinetics leading to variable pharmacodynamic response with slow onset and offset of action. ³⁴ Genetic variants, drug interactions and unknown factors lead to poor response in up to 30% of patients ^{35,36}	<ol style="list-style-type: none"> 1. When anticoagulation is indicated in addition to DAPT (e.g. atrial fibrillation, mechanical valves) 2. In thrombolysis-treated STEMI patients 3. When the other P2Y₁₂ inhibitors are either not available or contraindicated
Prasugrel	Pro-drug; active metabolite irreversibly blocks platelet P2Y ₁₂ receptors. Efficient pharmacokinetics, starting in the intestines, leading to rapid platelet inhibition but with similar offset of action to clonidogrel ³⁷	<ol style="list-style-type: none"> 1. Only in PCI-treated ACS patients and either following angiography or if planned for primary PCI in STEMI patients 2. Should not be used in patients with history of stroke, cautioned in those ≥ 75 years of age or < 60 kg
Ticagrelor	Direct-acting drug that reversibly blocks platelet P2Y ₁₂ receptors. Similar to prasugrel, its onset of action is rapid, but, being a reversibly binding P2Y ₁₂ inhibitor, it has more rapid offset of action ³⁸	<ol style="list-style-type: none"> 1. In patients with NSTEMI and high-risk unstable angina regardless of treatment strategy. In STEMI patients planned for primary PCI 2. Should not be used in patients with history of intracranial haemorrhage or those taking strong CYP3A inducers or inhibitors 3. May be used 2 d post-thrombolysis in STEMI patients undergoing PCI³⁹

Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

More encouraging results were seen in higher-risk patients in the PEGASUS-TIMI 54 trial.³ A total of 21,162 patients within 1 to 3 years of having a MI and with additional risk factors (→**Table 2**) were randomized to placebo, ticagrelor 60 mg twice daily or ticagrelor 90 mg twice daily. Patients with a prior history of stroke or deemed to have high bleeding risk were excluded. Similar to high-dose ticagrelor, ticagrelor 60 mg twice daily reduced the MACE risk compared with placebo (7.77% vs. 9.04%, $p < 0.001$), including a non-significant numerical reduction in CV mortality in all ticagrelor-treated patients (2.9% vs. 3.39, $p = 0.06$), and the similar efficacy of the two doses of ticagrelor was explained by similarly high levels of platelet P2Y₁₂ inhibition.¹⁸ Adverse events, primarily dyspnoea and bleeding, were more common with ticagrelor resulting in higher rates of therapy discontinuation, which may have attenuated the benefits observed with ticagrelor.¹⁹ Very few patients in the trial had been exposed to ticagrelor in the past and better tolerance should be

expected if a strategy of continued treatment with aspirin and ticagrelor is adopted in those who have tolerated this combination for the initial 12 months after MI.¹⁹ Major bleeding was increased with ticagrelor (90 mg: 2.6%; 60 mg: 2.3%; placebo: 1.1%; $p < 0.001$ for each comparison with placebo). It is estimated that 42 MACE would be prevented per year for every 10,000 patients treated with ticagrelor 60 mg at the cost of 31 additional non-fatal major bleeds per year.³ Greater absolute risk reductions were seen with ticagrelor in patients with either peripheral artery disease (PAD), chronic kidney disease (CKD) or diabetes mellitus (DM) as well as those with multi-vessel versus single-vessel CAD.^{20–23}

A collaborative meta-analysis that included the sub-groups of patients with an index event of MI in thienopyridine-based DAPT studies and patients from the PEGASUS-TIMI 54 study showed that prolonged DAPT reduced MACE (6.4% vs. 7.5%, $p = 0.001$) and reduced CV death (2.3% vs. 2.6%, $p = 0.03$) with no significant increase in non-CV death.⁴

Table 2 Key inclusion criteria of PEGASUS-TIMI 54 and COMPASS trials

Inclusion criteria in the PEGASUS-TIMI 54 trial	Inclusion criteria in the COMPASS trial (CAD cohort ~90%)
MI within 1–3 years Age ≥ 50 years One additional risk factor: Age ≥ 65 years Diabetes mellitus PAD Multi-vessel CAD CKD not requiring dialysis Second previous MI (prior to index MI)	MI within 20 years or multi-vessel CAD regardless of previous revascularization Age ≥ 65 years or PAD or two additional risk factors: Current smoking Diabetes mellitus CKD—excluding eGFR < 15 mL/min Heart failure Non-lacunar ischemic stroke ≥ 1 month

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease.

Based on this evidence, the European Society of Cardiology guidelines give a class IIb recommendation to consider prolonged therapy in ACS patients who have tolerated 12 months of DAPT without bleeding complications. In high-risk patients (such as those identified in the PEGASUS-TIMI 54 trial), prolonged ticagrelor-based DAPT is preferred to thienopyridine-based DAPT.²⁴

Anticoagulant Therapy in Secondary Prevention

The notion of using anticoagulants following ACS for long-term secondary prevention is far from new. Anticoagulation with vitamin K antagonists (VKAs) following ACS significantly reduced MACE compared with placebo but at the expense of more major bleeding.²⁵ However, evidence that DAPT with aspirin and a P2Y₁₂ inhibitor was markedly superior in the prevention of stent thrombosis to a DAPT approach with aspirin and VKA,^{26,27} along with the increasing use of PCI for the management of ACS, led to preference for a DAPT strategy for ACS management.⁷ Consequently, the combination of aspirin and VKA was relegated to niche indication for ACS patients requiring anticoagulant therapy for other reasons, such as atrial fibrillation.

However, following the development of non-VKA oral anticoagulants, we learned more about the level of anticoagulation that may be needed following ACS in the DAPT era. High anticoagulation levels with apixaban (same levels needed for stroke prevention in AF) in addition to DAPT (aspirin + clopidogrel) resulted in increased risk of major bleeds, including intracranial and fatal bleeds, without a clear benefit of ischaemic risk reduction.²⁸

The novel concept of low anticoagulation levels was tested in the ATLAS ACS2-TIMI 51 trial.²⁹ Low-dose rivaroxaban (2.5 and 5 mg twice daily), in moderate-to-high-risk ACS patients, in addition to clopidogrel-based DAPT, resulted in a significant reduction in MACE (combined rivaroxaban groups 8.9% vs. placebo 10.7%, $p = 0.008$). This included a reduction in CV death with the lower dose of rivaroxaban (2.7% vs. 4.1%, $p = 0.002$). The penalty was an increase in non-surgical bleeding (rivaroxaban 2.5 mg 1.8% vs. rivaroxaban 5 mg 2.4% vs. placebo 0.6%, $p < 0.001$ for each comparison with placebo) and intracranial haemorrhage (rivaroxaban 2.5 mg 0.4% vs. rivaroxaban 5 mg 0.7% vs. placebo 0.2%).²⁹ These results became available at a time when practice favoured one of the more reliable P2Y₁₂ inhibitors to clopidogrel and this has limited adoption of a triple therapy approach.

The effects of substituting aspirin with rivaroxaban (2.5 mg twice daily) were explored in the GEMINI-ACS-1 study.³⁰ Within 10 days of ACS, 3,037 patients were randomized to either rivaroxaban or aspirin in addition to background P2Y₁₂ inhibitor therapy (clopidogrel or ticagrelor). There was no significant difference in major bleeding between rivaroxaban and aspirin. Exploratory analyses showed a trend for better ischaemic outcomes for those treated with aspirin and ticagrelor compared with other combinations. However, this study was only powered to detect a difference in bleeding endpoints and therefore

efficacy outcomes should only be interpreted as hypothesis-generating results.

In the COMPASS trial,⁵ 27,395 patients with either stable CAD (~90%) or peripheral artery disease were randomized to standard therapy with aspirin, DATT (aspirin + rivaroxaban 2.5 mg twice daily) or rivaroxaban 5mg twice daily monotherapy (► **Table 2**). Patients at high risk for bleeding, including those on DAPT or with coagulopathies, were excluded. DATT resulted in a significant reduction in MACE compared with aspirin (4.1% vs. 5.4%, respectively, $p < 0.001$), including a reduction in CV death (1.7% vs. 2.2%, $p = 0.02$) and a substantial reduction in ischaemic stroke (0.7% vs. 1.4%, $p < 0.001$). There was a penalty of increased major bleeding events with DATT compared with aspirin monotherapy (3.1% vs. 1.9%, $p < 0.001$). However, there was no significant increase in fatal or intracranial haemorrhage. Monotherapy with rivaroxaban 5 mg twice daily did not result in significantly improved ischaemic outcomes but increased major bleeding events.

Choice of Dual Therapy Strategy

The population studied in the COMPASS trial overlaps substantially with the population studied in the PEGASUS-TIMI 54 trial (► **Tables 2 and 3**). All patients in PEGASUS had history of MI (median of 1.7 years prior to randomization) and

Table 3 Baseline patient characteristic in the PEGASUS-TIMI 54 trial and the COMPASS trial

	The PEGASUS-TIMI 54 trial	The COMPASS trial
Age (mean ± SD)	65 ± 8	68 ± 8
Female	24%	22%
Smoking	17%	21.5%
Hypertension	78%	75%
Coronary artery disease	100%	90.5%
Previous MI	100%	62%
Years since MI	1.7	7.1
Peripheral artery disease	5.5%	27.2%
Diabetes mellitus	32%	38%
Chronic kidney disease	24%	23%
Previous ischaemic stroke	0%	4%
Prior CABG	NA ^a	5%
ACE I or ARB	82%	71%
Lipid lowering agent	93%	90%

Abbreviations: ACE I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass surgery; MI, myocardial infarction; SD, standard deviation.

^aIn the PEGASUS-TIMI 54 trial, patients who have had bypass surgery were excluded unless they had a myocardial infarction following bypass surgery.

approximately 60% of patients in COMPASS had previous MI (average 7.1 years). Both trials show that escalation of antithrombotic therapy in high-risk stable CAD patients leads to improved MACE rates, including numerical reductions in CV death, particularly in individuals at the highest risk. There is no head-to-head comparison between the two strategies; however, there were signals that prolonged DAPT has greater efficacy at reducing recurrent MI and stent thrombosis as opposed to greater efficacy for a DATT strategy at reducing stroke. For instance, there was no significant effect of DATT on stent thrombosis rates in COMPASS, whereas prolonged DAPT resulted in a significant reduction in stent thrombosis in the PEGASUS-TIMI 54 trial (ticagrelor 90 mg: HR, 0.30, 95% CI: 0.14–0.65; ticagrelor 60 mg: HR, 0.66, 95% CI: 0.37–1.17).³¹ The different mechanisms of action of ticagrelor and rivaroxaban make it credible that ticagrelor would be more effective at preventing occlusive coronary thrombosis, whereas rivaroxaban may be more effective at preventing cardiac thromboem-

bolism due to left atrial appendage thrombosis. Although a DATT strategy did not result in overall improved MACE rates in patients with CAD and advanced ‘unstable’ heart failure, similar signals of efficacy in stroke prevention were observed.³² There could also be differential effects of the two drugs on vascular inflammation and progression of atherosclerosis. More research is clearly needed to compare the two strategies, which will help us individualize treatments further.

In the absence of contraindications, ticagrelor is preferred to clopidogrel in ACS patients.²⁴ Among high-risk patients who tolerate ticagrelor 90 mg twice daily for a year, it seems appropriate to down-titrate to ticagrelor 60 mg twice daily, in addition to aspirin, for an additional 3 years (or as long as tolerated in the highest-risk patients). In those who have to switch antiplatelet therapy during the first year (e.g. due to dyspnoea) and have completed their intended course of DAPT, starting rivaroxaban 2.5 mg twice daily upon cessation of the P2Y₁₂ inhibitor (after 12 months of DAPT) may be considered.

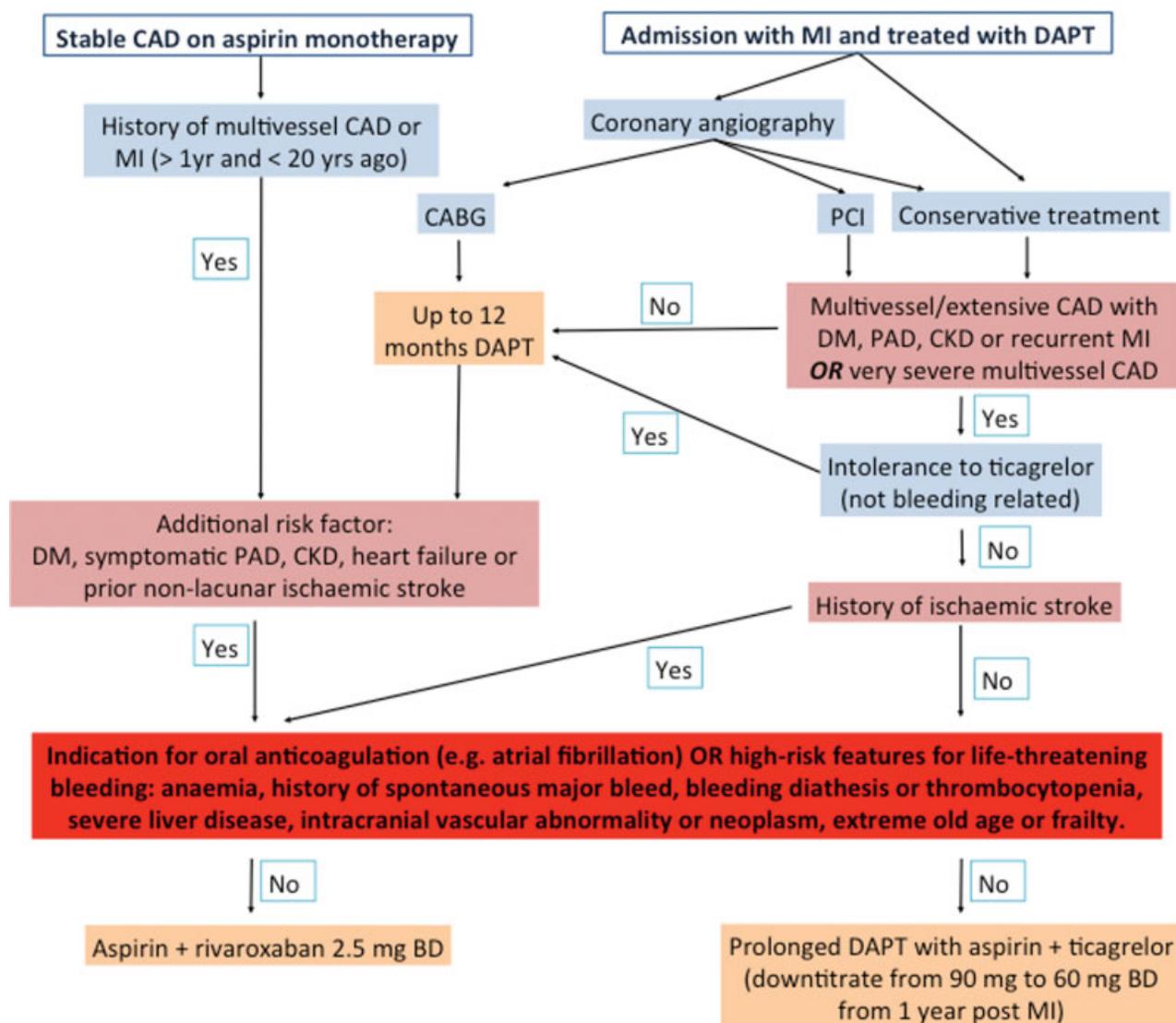


Fig. 2 Choice of antithrombotic treatment strategy in patients with coronary artery disease. CABG, coronary artery bypass surgery; CAD, coronary artery disease; CKD, chronic kidney disease (eGFR < 60 mL/min and not requiring dialysis for prolonged DAPT; eGFR < 60 mL/min and > 15 mL/min for low dose rivaroxaban); DAPT, dual antiplatelet therapy; DATT, dual antithrombotic therapy (aspirin + rivaroxaban 2.5 mg twice daily); DM, diabetes mellitus; PAD, peripheral artery disease; MI: myocardial infarction.

Treatment decisions are easier to implement at the time of presentation with ACS and become more challenging in those who have been stable on aspirin monotherapy for years. However, when encountering stable high-risk CAD patients (history of ACS with at least two risk factors such as extensive CAD, DM, PAD, CKD or recurrent MI) who are remote from their ACS event (> 1 year) and have been stable off DAPT, the addition of rivaroxaban 2.5 mg twice daily may be appropriate. ►Fig. 2 provides a decision-making algorithm to aid recommendations for antithrombotic therapy in patients with CAD, particularly those with history of MI.

The risk of bleeding should be balanced against the benefit of ischaemic risk reduction and additional therapy may be best avoided in patients at high risk of life-threatening bleeding. Tools to balance ischaemic and bleeding risk may be useful and the PRECISE-DAPT risk score was developed to aid the decision-making process.³³ This score, however, has some limitations. It was based on a study of 14,963 patients with CAD who underwent PCI (including elective patients)³³ and identified five predictors of major bleeding events (increasing age, low creatinine clearance, haemoglobin < 10 g/dL, increased baseline white cell count and history of spontaneous bleed). Although the derived risk score was validated in two other PCI-treated cohorts, the utility of the score was not studied prospectively. Furthermore, some factors included in the risk score, such as increasing age and CKD (estimated glomerular filtration rate < 60 mL/min/1.73 m²), were among the inclusion criteria of both the PEGASUS-TIMI 54 and COMPASS trials and these patients derived benefit from intensive therapy. Patients with anaemia (haemoglobin < 10 g/dL) and those with a history of spontaneous major bleeding were at greatest risk of bleeding and therefore a strategy of prolonged DAPT or DATT is best avoided in these scenarios.

Conclusion

Protection against atherothrombosis with DAPT, following ACS, is well-established and long-term ticagrelor-based DAPT, in high-risk stable patients with history of MI, has demonstrated further benefit. Consequently, prolonged DAPT may be considered in high-risk post-MI patients, with stronger consideration given to those who are at high risk of CAD-related death (e.g. extensive multi-vessel CAD) but deemed at low risk for fatal bleeding (i.e. no history of intracranial haemorrhage, stroke, bleeding diathesis or incurable gastrointestinal bleeding). The COMPASS study results provide support for the use of DATT (aspirin + rivaroxaban 2.5 mg twice daily) in stable patients with history of MI, PAD and/or multiple risk factors. Among high-risk stable patients who are not taking DAPT, DATT may be considered to reduce the risk of further ischaemic events, again with stronger consideration given to those who are at high risk of CV death and low risk of fatal bleeding.

Conflict of Interest

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