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REVIEW

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Pharmacotherapeutic options for coronary thrombosis treatment: where are we today?

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ABSTRACT

Introduction: Advances in pharmacotherapy for coronary thrombosis treatment and prevention have transformed the clinical outcomes of patients with coronary artery disease but increased the complexity of therapeutic decision-making. Improvements in percutaneous coronary intervention techniques and stent design have reduced the incidence of thrombotic complications, which consequently has increased the challenge of adequately powering clinical trials of novel antithrombotic strategies for efficacy outcomes. Knowledge of the pathophysiology of coronary thrombosis and the characteristics of antithrombotic drugs can help with therapeutic decisions.

Areas covered: This review covers the pathophysiology of coronary thrombosis and the mechanisms of action of drugs developed for its treatment, provides an overview of the key issues in decision-making, and highlights key areas for further work in order to guide clinicians on how to individualize risk management and address gaps in the evidence base.

Expert opinion: Individualization of antithrombotic therapy regimens has become a vital part of optimizing risk management in people with coronary thrombosis. A critical appraisal of the strengths and limitations of available drugs and the evidence supporting the use of different antithrombotic combinations is intended to provide direction to clinicians and point the way toward further improvements in pharmacotherapy for coronary thrombosis treatment and prevention.

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KEYWORDS
Anticoagulation; antiplatelet therapy; antithrombotic therapy; atrial fibrillation; bleeding; clopidogrel; percutaneous coronary intervention; ticagrelor

1. Introduction

Ischemic heart disease is the most common cause of mortality in the world [1]. Disruption of the luminal surface of an unstable coronary plaque leads to formation of thrombus within the coronary arteries and can result in acute coronary syndromes (ACS). Treatment of ACS has undergone major advances over the last three decades and often involves revascularisation strategies such as percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). However, antithrombotic therapy (ATT) continues to occupy a central role both during the acute phase and in the post-ACS maintenance phase. Since the development of aspirin in 1897 and recognition of its antiplatelet properties in the 1960s, antithrombotic therapy has undergone substantial developments and, currently, a wide array of oral, subcutaneous (sc) and intravenous (iv) medications are available for use following an ACS event [2,3].

2. Search criteria

We searched MEDLINE to identify randomized controlled trials published from inception to 27th of September 2024 in English with search terms 'Acute coronary syndrome AND antiplatelet therapy,' 'Acute coronary syndrome AND antithrombotic therapy,' 'acute coronary syndrome AND atrial fibrillation,' 'antithrombotic therapy AND PCI,' 'atrial fibrillation AND PCI,' 'fibrinolysis AND primary percutaneous coronary intervention.' Suitable articles were identified and reviewed with additional references relevant to discussion also included in this review.

3. Pathophysiology of coronary thrombosis

Atherosclerosis is a chronic inflammatory process that is characterized by the development of atherosclerotic plaques in the subendothelial intimal layer of coronary arteries [4]. Rupture or erosion of an unstable atherosclerotic plaque leads to disruption of the endothelial layer and cap of the plaque, resulting in exposure of collagen in the extracellular matrix along with release of von Willebrand factor (VWF) from the damaged endothelial cells [5]. The circulating platelets bind to exposed VWF via the glycoprotein (GP) Ib/IX complex leading to deceleration and tethering of platelets. Subsequently, GP VI and GP Ia bind with the exposed collagen, leading to activation of platelets via multiple pathways that promote release of thromboxane A_2 and ADP as well as generation of thrombin, eventually leading to activation of the GP IIb/IIIa receptors that facilitate platelet-platelet aggregation [6]. In addition, expression of tissue factor following vascular injury leads to activation of the coagulation cascade and consequent generation of thrombin, which, in addition to causing further platelet

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Article highlights

- Coronary thrombosis is a complex process driven by platelet activation and supported by production of fibrin via the coagulation cascade.
- Thrombin not only drives fibrin generation but is an important activator of platelets and so anticoagulant drugs that target thrombin generation can reduce platelet activation.
- Aspirin is a reliable inhibitor of cyclooxygenase-1-dependent platelet activation and has been a constant component of the treatment of coronary thrombosis for decades. However, this constancy is being challenged by studies supporting the use of aspirin-free regimens in some instances.
- Development of more effective oral $P2Y_{12}$ inhibitors has transformed coronary thrombosis management and the consistently high levels of platelet inhibition provided by ticagrelor and, to a lesser extent, prasugrel has allowed studies of $P2Y_{12}$ inhibitor monotherapy regimens to demonstrate improved safety without penalty after an initial period of dual antiplatelet therapy.
- The unreliable pharmacodynamic effect of clopidogrel ultimately makes it a poor choice for individualizing the management of thrombotic and bleeding risks, including in patients undergoing percutaneous coronary intervention who have an indication for oral anticoagulant therapy.
- Dual antithrombotic therapy regimens of ticagrelor or prasugrel combined with a twice-daily direct-acting oral anticoagulant (and not aspirin) show promise for providing a predictable balance of effects on thrombosis and hemostasis.
- Parenteral antithrombotic drugs are essential adjuncts in the acute management of coronary thrombosis; novel parenteral drugs and strategies continue to be explored, partly driven by delayed absorption of oral $P2Y_{12}$ inhibitors in patients treated with opiates and in cardiogenic shock.

activation, facilitates generation of fibrin [7]. This fibrin serves as the backbone of the evolving clot that ultimately results in coronary thrombosis. Occlusive thrombosis or thromboembolism in a coronary artery may manifest as ACS, which comprise of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. Platelets play an integral role in the atherothrombotic process via multiple mechanisms due to their roles in thrombosis, inflammation and neointimal proliferation [8,9]. Hence, antiplatelet therapy is fundamental in the treatment of ACS. In addition to its role in the treatment of ACS and prevention of further atherothrombotic events, antiplatelet therapy is also necessary to prevent stent thrombosis following PCI with stent implantation in the affected arteries. Antithrombotic medications currently in clinical use target the various pathways involved in platelet activation and aggregation. Figure 1 outlines the platelet activation and coagulation cascade following vascular injury.

4. Overview of antithrombotic therapies

ATT can be broadly classified into antiplatelet drugs, which prevent platelet activation and aggregation, and anticoagulant drugs, which affect various parts of the coagulation cascade ultimately affecting fibrin generation as well as thrombin-induced platelet activation. Both oral and intravenous antiplatelet and anticoagulant drugs are available and used in acute and maintenance phases of ACS treatment. A third category of drugs called fibrinolytic drugs are used in a setting of STEMI to break up the fibrin that is already generated, when timely access to primary percutaneous coronary intervention (PPCI) is not available. Table 1 and Figure 1 outline the ATT currently in clinical use.

5. Antiplatelet therapy

Antiplatelet therapies are indicated following atherothrombotic ACS events to reduce the risk of further ACS and to prevent stent thrombosis in patients that undergo PCI. Currently available antiplatelet therapies and some key characteristics are summarized in Table 2.

5.1. Aspirin

Despite being the oldest known antiplatelet drug, aspirin continues to be the cornerstone of post-ACS antiplatelet therapy. It is an O-acetyl derivative of salicylic acid that reliably inhibits cyclooxygenase-1 (COX-1) at low doses (75-100 mg daily), leading to inhibition of platelet generation of thromboxane A_2, as may be demonstrated clearly by either reduction in serum thromboxane B_2 levels or inhibition of arachidonic acid (AA)-induced platelet aggregation. Aspirin has been a constant component of various antiplatelet strategies in combination with other antithrombotic medications such as $P2Y_{12}$ inhibitors, vitamin K antagonists, and direct-acting oral anticoagulants (DOACs) as part of dual (DAT) or triple antithrombotic therapy (TAT) regimens. In addition, aspirin remains the preferred single antiplatelet therapy (SAPT) drug of choice for long-term secondary prevention after an ACS [11].

Following suspected ACS, a loading dose (LD) of 150–300 mg of aspirin is given for rapid inhibition of AA-mediated platelet aggregation, which constitutes an important component of collagen-mediated platelet aggregation. This is followed by a maintenance dose (MD) of 75–100 mg once daily (OD) [2]. Due to concerns around recovery of COX-1 activity between OD aspirin doses and recovery of platelet reactivity, alternative strategies such as low-dose twice-daily (BD) aspirin have also been studied. Parker *et al* demonstrated that a 20 mg BD regimen of aspirin provided a smoother 24-hour profile of platelet inhibition compared to a 75 mg OD regimen in patients with ACS treated with ticagrelor. However, further studies are required to assess the clinical efficacy and safety of such alternative dosing strategies.

While most guidelines recommend an aspirin-based DAT regimen for at least 12 months following ACS, there is increasing evidence to suggest that abbreviated aspirin-based DAT regimens for 1–3 months, or even as little as two weeks, followed by monotherapy with drugs such as $P2Y_{12}$ inhibitors could be a viable option with potential for reduced bleeding events [2,12–14].

5.2. $P2Y_{12}$ receptor antagonists

Although the molecular identification of the $P2Y_{12}$ receptor was first reported only after the turn of the millennium, $P2Y_{12}$ receptor antagonists have been in clinical use since the approval of ticlopidine in the 1990s [15,16]. Ticlopidine was plagued by significant side effects which led to development

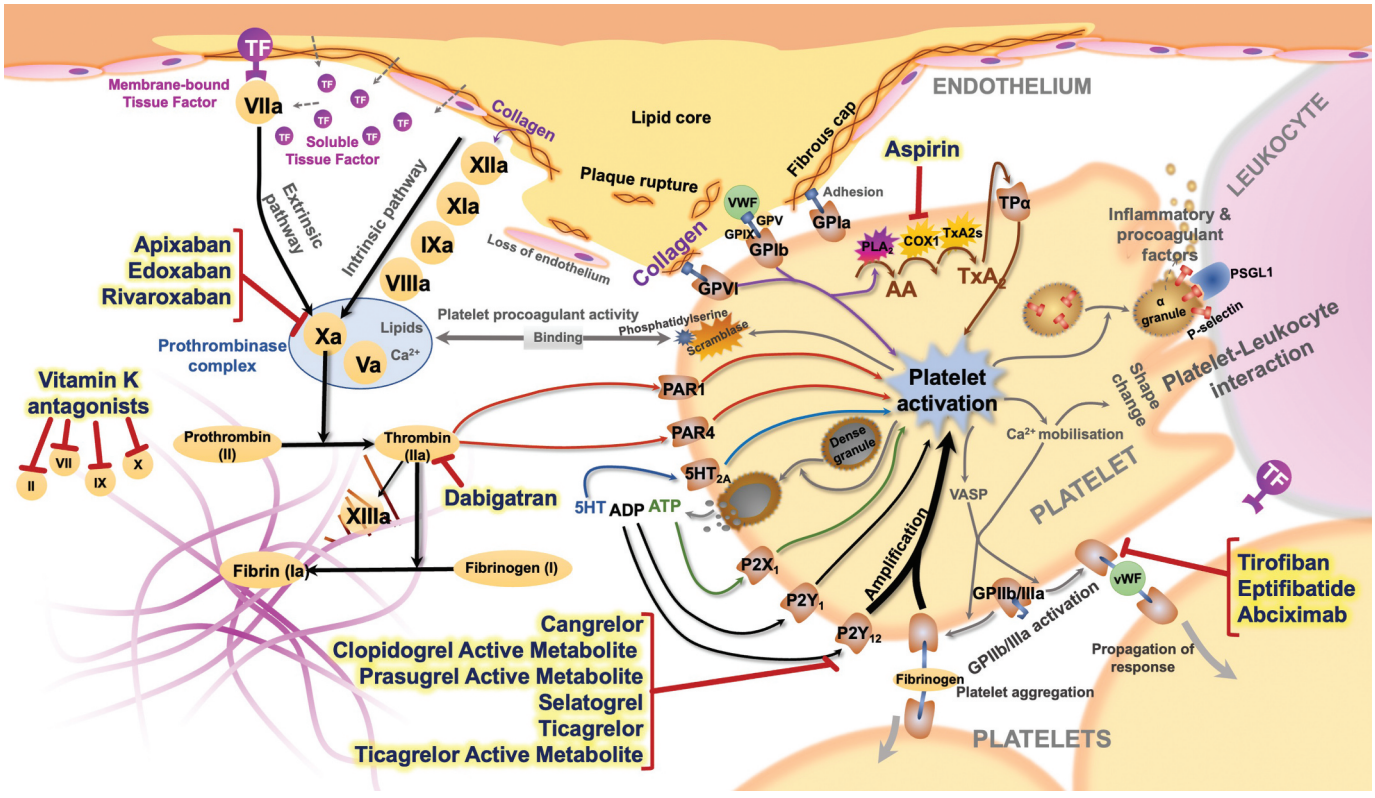

Figure 1. Pathophysiology of atherothrombosis following plaque rupture and mechanism of action of current antithrombotic drugs.

Reproduced with permission from 'New Antithrombotic Drugs in Acute Coronary Syndrome' by Zwart et al available at https://doi.org/10.3390/jcm9072059 under a CC BY 4.0 License [10]. 5HT, 5-hydroxytryptamine (serotonin); AA, arachidonic acid; ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca^{2+}, calcium; COX1, cyclo-oxygenase 1; GP, glycoprotein; IXa, activated factor IX; P2X1, platelet ATP receptor; $P2Y_1/P2Y_{12}$, platelet ADP receptors; PAR, protease-activated receptor; PLA2, phospholipase A_2; PSGL1, P-selectin glycoprotein ligand 1; TF, tissue factor; TPα, thromboxane receptor α; TXA_2, thromboxane A_2; TXA2s, thromboxane A_2 synthase; Va, activated factor V; VIIa, activated factor VII; VIIIa, activated factor VIII; VASP, vasodilator stimulated phosphoprotein; VWF, von Willebrand factor; Xa, activated factor X; XIa, activated factor XI; XIIa, activated factor XII; XIIIa, activated factor XIII.

Table 1. Antithrombotic medications currently in clinical use.

Classes of antithrombotic drugs used in acute coronary syndrome			
Antiplatelet drugs			
COX-1 inhibitors	$P2Y_{12}$ inhibitors		GP IIb/IIIa inhibitors
Aspirin	Clopidogrel Prasugrel Ticagrelor *Cangrelor*		*Tirofiban* *Eptifibatide*
Anticoagulant drugs			
Factor Xa inhibitors	Direct thrombin inhibitors	Indirect thrombin and factor Xa inhibitors	Vitamin K antagonists
Apixaban Edoxaban Rivaroxaban	Dabigatran *Bivalirudin*	*Heparin* *Enoxaparin* *Fondaparinux*	Warfarin Acenocoumarol Phenprocoumon
Fibrinolytic drugs			
Microbial plasminogen activator		Recombinant t-PA	
Streptokinase		*Alteplase* *Reteplase* *Tenecteplase*	

Parenterally administered drugs are in italics. COX-1: Cyclooxygenase – 1 inhibitor; t-PA: tissue plasminogen activator.

of other $P2Y_{12}$ inhibitors. The $P2Y_{12}$ inhibitors currently in clinical use include clopidogrel, prasugrel, ticagrelor and cangrelor.

5.2.1. Clopidogrel

Clopidogrel is an oral, thienopyridine inactive prodrug that is metabolized in the liver to an active form, which binds irreversibly to the platelet $P2Y_{12}$ receptor, inhibiting ADP-mediated platelet aggregation [16]. Clopidogrel is indicated not only in ACS but also in other vascular diseases, such as stroke and peripheral vascular disease, and remains the most widely used $P2Y_{12}$ inhibitor to date. Activation of clopidogrel in the liver is catalyzed by several cytochrome P450 (CYP) enzymes with major contribution from CYP2C19 enzyme. The

Table 2. Antiplatelet agents currently in use.

Drug	Route	Half-life	Onset	Dosing regimen
Aspirin	Oral, IV or rectal	20 mins	30–40 mins	Oral or rectal LD: 150 to 300 mg IV LD: 75 to 250 mg Oral MD: 75–100 mg OD
Clopidogrel	Oral	AM: 30–60 mins	2 h*	LD: 300–600 mg; MD: 75 mg OD LD following fibrinolysis: 300 mg
Ticagrelor	Oral	8–12 h	30 mins*	LD: 180 mg MD: 90 mg BD for 1 year after ACS and 60 mg BD beyond 1 year after MI
Prasugrel	Oral	AM distribution half-life: 30–60 mins; elimination half-life 7-16 h	30 mins*	LD: 60 mg MD: 10 mg OD or 5 mg OD if age ≥75 years or weight <60 kg
Cangrelor	IV	3 to 6 mins	2 mins	LD: Bolus 30 mg/kg MD: 4 mg/kg/min
Tirofiban	IV	2 h	3 mins	High-dose bolus regimen for PCI: CrCl ≥30 mL/min: LD 25 mg/kg over 3 mins then MD 0.15 mg/kg/min. CrCl <30 mL/min: LD 12.5 mg/kg over 3 mins then MD 0.075 mg/kg/min
Eptifibatide	IV	2.5 h	3 mins	CrCl >50 mL/min: LD 180 mg/kg bolus followed after 10 mins by second 180 mg/kg bolus then MD 2 mg/kg/min. CrCl 30–50 mL/min: LD single 180 mg/kg bolus then MD 1 mg/kg/min up to a maximum of 7.5 mg/h.

*Onset delayed by hours with concurrent opiate administration.

ACS: acute coronary syndrome; AM: active metabolite; BD: twice daily; CrCl: creatinine clearance; IV: intravenous; LD: loading dose; MI: myocardial infarction; MD: maintenance dose; OD: once daily; PCI: percutaneous coronary intervention.ACS: acute coronary syndrome; AM: active metabolite; BD: twice daily; CrCl: creatinine clearance; IV: intravenous; LD: loading dose; MI: myocardial infarction; MD: maintenance dose; OD: once daily; PCI: percutaneous coronary intervention.

CYP2C19 gene is polymorphic with wide variability in enzyme activity. Loss-of-function *CYP2C19* polymorphisms can contribute to high-on-treatment platelet reactivity during clopidogrel therapy, in addition to a wide range of other clinical factors and drug-drug interactions that contribute to this [17]. A 600-mg loading dose of clopidogrel generally has a more rapid onset of action than a 300-mg LD and may be preferred in those undergoing PCI [2].

The CURE study demonstrated the superiority of clopidogrel with aspirin compared to aspirin alone in patients with non-ST-elevation ACS (NSTEACS) [18]. However, the inconsistent effect of clopidogrel on platelet reactivity coupled with development of the more potent oral $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, with improved clinical outcomes compared to clopidogrel, meant that clopidogrel is now considered second-line to prasugrel and ticagrelor in the treatment of ACS [19,20]. Clopidogrel is primarily reserved in ACS cases where ticagrelor or prasugrel are contraindicated or as an option in patients with high bleeding risk (HBR) [2].

Evidence from studies such as CAPRIE (Clopidogrel versus aspirin in patients at risk of ischemic events) and HOST-EXAM (Harmonising Optimal Strategy for Treatment of coronary artery diseases-EXtended Antiplatelet Monotherapy) and other meta-analyses suggest that clopidogrel could be an effective alternative to aspirin as SAPT in patients with established cardiovascular disease [21–23]. As a result, clopidogrel has a class 1A recommendation for use as SAPT in patients with CCS as an alternative to aspirin in the recently published 2024 ESC guidelines [24]. Clopidogrel monotherapy after abbreviated dual antiplatelet therapy (DAPT) regimens has also been investigated in studies such as MASTER-DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen), SMART-CHOICE (Smart Angioplasty Research Team: Comparison Between $P2Y_{12}$ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) and STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) [14,25,26]. Each of these studies used different abbreviated DAPT regimens and included patients with both ACS and CCS. Although clopidogrel was found to be a viable option within these trials, the emergence of evidence in favor of ticagrelor as a potent, more consistent $P2Y_{12}$ inhibitor option for monotherapy has made ticagrelor the preferred $P2Y_{12}$ inhibitor monotherapy agent of choice during the first 12 months following ACS.

5.2.2. Ticagrelor

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine that is a reversibly-binding, noncompetitive inhibitor of the $P2Y_{12}$ receptor. It is the only available oral, reversible $P2Y_{12}$ inhibitor to date. Although an active drug, it is extensively metabolized in the liver via the CYP group of enzymes (facilitated mainly by CYP3A4) into an active metabolite that is equipotent but with longer elimination half-life [27]. Due to its metabolism by CYP3A4, it has significant interaction with strong CYP3A4 inducers or inhibitors [27]. The LD of ticagrelor is 180 mg followed by an MD of 90 mg BD. A dose of 60 mg BD is used in patients with CCS with high ischemic risk but without high bleeding risk at least 12 months after MI [28].

Following the PLATO (Platelet Inhibition and Patient Outcomes) study, ticagrelor has become the primary $P2Y_{12}$ inhibitor of choice for DAPT regimens following ACS [19]. Ticagrelor monotherapy following abbreviated DAPT regimen has garnered much interest in recent years. Studies such as TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention), TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome) and more recently, ULTIMATE-DAPT among others and individual patient-level meta-analysis have shown that ticagrelor monotherapy following 1–3 months of DAPT (aspirin + ticagrelor) in patients that underwent PCI for ACS is a viable alternative to 12 months of DAPT with improved bleeding outcomes [13,29–33]. Whilst abbreviated DAPT with

ticagrelor monotherapy could be considered in some cases, based on the results of the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction 54) trial, long-term DAPT with aspirin and ticagrelor 60 mg BD can also be considered in patients 12 months after their ACS if they have tolerated DAPT (aspirin + ticagrelor 90 mg BD) and their ischemic risk is deemed to be high without high bleeding risk [28,34].

A reversible $P2Y_{12}$ inhibitor gives rise to the potential for developing specific antidotes that could reverse its effect on platelet inhibition. Bentracimab is an intravenous monoclonal antibody that binds with ticagrelor and its active metabolite. A pre-specified interim analysis of the ongoing REVERSE-IT (Rapid and Sustained Reversal of Ticagrelor – Intervention Trial) study after enrollment of 150 patients has shown that bentracimab provides quick, sustained and effective ticagrelor reversal [35]. This can be particularly valuable in case of life-threatening bleeding in these patients or in emergency surgery. The emergence of haemadsorption devices such as Cytosorb that can remove drugs such as ticagrelor is another interesting area of ongoing research [36]. The availability of reversal agents and removal devices can potentially help offset the increased bleeding risk associated with use of potent $P2Y_{12}$ inhibitors.

5.2.3. Prasugrel

Prasugrel is a thienopyridine derivative similar to clopidogrel and acts as an irreversible $P2Y_{12}$ receptor antagonist. The prodrug requires metabolic activation via the CYP system (CYP3A and CYP2B6) to exert its antiplatelet effect and, unlike clopidogrel, is not substantially affected by *CYP2C19* polymorphisms [37]. LD of prasugrel is 60 mg followed by an MD of 10 mg OD, except for patients ≥75 years of age or with low body weight (<60 kg) in whom a reduced MD of 5 mg OD is recommended due to higher exposure to prasugrel active metabolite [2,37].

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction 38) study found prasugrel to be superior to clopidogrel, in patients with ACS that have had or are planned for PCI, in reducing ischemic events at a cost of significantly increased major bleeding with no overall mortality benefit [20]. The study noted an increased risk of adverse clinical outcomes in patients with previous stroke or transient ischemic attack and so is contraindicated in these patients.

While ticagrelor and clopidogrel have been approved for use in medically-managed ACS patients, the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study did not show any benefit with use of prasugrel compared to clopidogrel in improving cardiovascular outcomes in this population [38]. Furthermore, the ACCOAST (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) study showed that prasugrel increased bleeding risk without reducing ischemic risk when administered prior to coronary angiography [39]. Hence, use of prasugrel is not recommended prior to coronary angiography (except in STEMI planned for primary PCI) or in medically-managed ACS patients.

The choice of $P2Y_{12}$ inhibitor between prasugrel and ticagrelor has been a hotly debated topic over the recent years. The ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) study is the largest, open-label, head-to-head comparison of two antiplatelet strategies involving ticagrelor or prasugrel for cardiovascular outcomes to date [40]. Prasugrel demonstrated significantly less frequent occurrence of ischemic primary endpoints driven predominantly by reduced incidence of myocardial infarction. Despite its limitations, this led to a change in the current ESC guideline recommendations that prasugrel is to be preferred over ticagrelor in patients with ACS that undergo PCI [2]. However, unlike clopidogrel and ticagrelor, prasugrel has limited evidence to support its use as an option for $P2Y_{12}$ inhibitor monotherapy after abbreviated DAPT regimens for ACS. The STOPDAPT-3 (Short and Optimal Duration of Dual Antiplatelet Therapy-3) study failed to demonstrate superiority of prasugrel monotherapy after an abbreviated DAPT regimen for 1-month for bleeding events, with increased incidence of stent thrombosis, when compared to a standard DAPT regimen [41]. However, the study was conducted in Japan with the maintenance dose of prasugrel used being 3.75 mg OD, which results in reduced and less consistent $P2Y_{12}$ inhibition and could explain the results observed [42]. Hence, it is still uncertain whether prasugrel at standard doses would be a viable option for $P2Y_{12}$ inhibitor monotherapy. Figure 2 outlines the choice between prasugrel and ticagrelor in patients with ACS based on current evidence and guideline recommendations. The strategy of preferring prasugrel for patients undergoing PCI may not be feasible in centers where there are delays of more than 24 hours prior to coronary angiography, when pre-treatment with ticagrelor may be desirable to stabilize patients with clear-cut evidence of type I MI [43].

5.2.4. Parenteral antiplatelet drugs

Cangrelor is the only available intravenous direct, short-acting, reversible $P2Y_{12}$ inhibitor and has a rapid onset of action (2 minutes) and very short half-life (3–9 minutes). A pooled analysis of the major phase 3 studies of cangrelor, CHAMPION-PLATFORM (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), CHAMPION-PCI and CHAMPION-PHOENIX, demonstrated improved ischemic outcomes at 48 hours compared to clopidogrel at the expense of increased bleeding [44–47]. It is mainly used in settings where oral $P2Y_{12}$ inhibitor administration is not feasible. Its use is mainly limited by cost. Care must also be taken in transitioning between cangrelor and thienopyridines since cangrelor prevents the binding of thienopyridine active metabolites to the $P2Y_{12}$ receptor. Selatogrel is a novel, subcutaneous, rapid-acting reversible, potent $P2Y_{12}$ inhibitor that is currently being investigated for use as a self-administered, emergency treatment in a large, international clinical outcomes study [48–50].

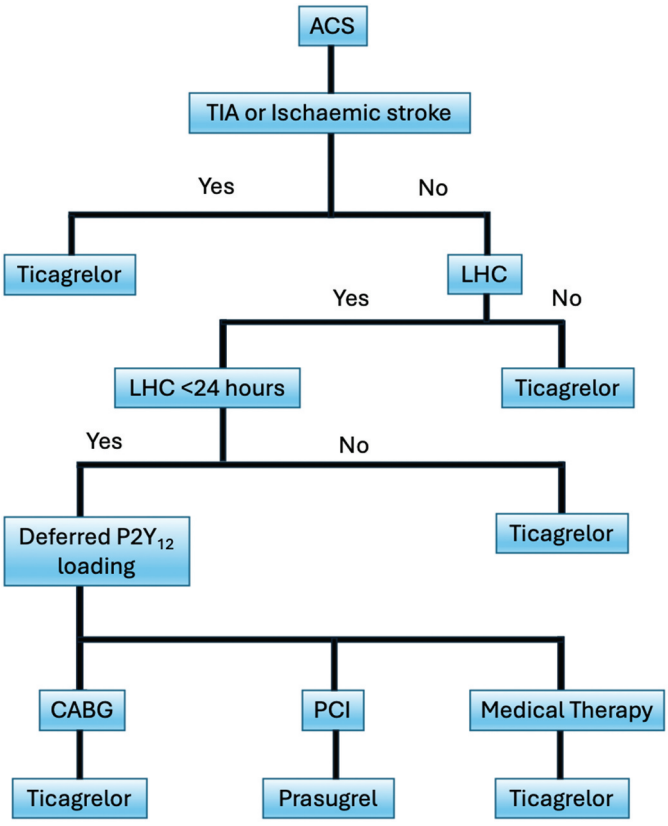

Figure 2. Selection of prasugrel versus ticagrelor in patients with acute coronary syndromes.

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; LHC, left heart catheter; $P2Y_{12}$, platelet $P2Y_{12}$ receptor antagonist; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Tirofiban, eptifibatide and abciximab competitively inhibit the GP IIb/IIIa receptors, thereby inhibiting the platelet-platelet aggregation response. A meta-analysis of trials involving GP IIb/IIIa inhibitors show reduced odds of death or MI [51]. However, these studies pre-date routine use of oral DAT strategies. Use of GP IIb/IIIa inhibitors are associated with a significantly increased risk of bleeding and there is no evidence to recommend routine use of these drugs during PCI. However, GP IIb/IIIa inhibitors are used in the event of a thrombotic complication during PCI such as no-reflow [2]. They may also reduce the risk of acute stent thrombosis in opiate-treated STEMI patients undergoing primary PCI [52]. Zalunfiban is a novel, subcutaneous, rapid-acting GP IIb/IIIa inhibitor. An ongoing study is currently evaluating the efficacy and safety of zalunfiban in a prehospital setting in patients with STEMI planned to undergo PPCI [53].

GP VI receptor antagonism has recently emergently as an area of interest. Glenzocimab is a GP VI receptor antagonist that has been shown to enhance inhibition of atherosclerotic plaque-induced platelet activation when used in addition to aspirin and ticagrelor [54]. A phase 1b/2a study in patients with acute ischemic stroke showed promise in terms of safety and potential benefit but subsequent findings in stroke have been disappointing [55]. Treatment of coronary atherothrombosis is a more promising indication and an ongoing study is currently looking into the use of this drug in patients with STEMI in reducing the size of the infarct [56].

6. Anticoagulation in acute coronary syndromes

Anticoagulation in ACS consists of both oral and parenteral anticoagulants. Parenteral anticoagulants such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and bivalirudin are predominantly used during PCI and in the acute treatment of ACS. On the other hand, oral anticoagulants such as vitamin K antagonists (VKAs) and DOACs are used, in conjunction with antiplatelet drugs, when patients with an ongoing indication for anticoagulation such as atrial fibrillation (AF) or venous thromboembolism (VTE) events suffer from an ACS, as part of maintenance therapy. Table 3 summarizes the dosing regimen of anticoagulant drugs currently in clinical use.

6.1. Parenteral anticoagulation

Parenteral anticoagulation plays a key role in treatment of coronary thrombosis and is recommended in all patients with ACS [57]. The choice of anticoagulation used often depends on the clinical presentation and patient characteristics.

UFH is a rapid-acting, reversible anticoagulant that is administered via intravenous or subcutaneous routes. It enhances the action of antithrombin, which, together with heparin, binds to several proteases, the most notable being thrombin (factor IIa) and factor Xa, thereby inactivating them [58]. This inhibits further fibrin formation and thrombin-induced platelet activation. UFH is highly heterogeneous (molecular weight from 3000 to 30,000 Daltons) with complex pharmacokinetics and, as a result, requires monitoring and titration by measuring activated partial thromboplastin time (APTT), activated clotting time (ACT) or anti-Xa levels [59,60]. Type II heparin-induced thrombocytopenia (HIT) is a serious complication associated with heparin use which results in a hypercoagulable state and life-threatening thrombotic complications [61]. Anticoagulation by heparin can be reversed by administration of protamine.

LMWHs, such as enoxaparin, dalteparin and tinzaparin, are smaller fragments of heparin with a mean molecular weight of 5000 Daltons [62]. These smaller molecules enhance the action of antithrombin, thereby promoting inactivation of factor Xa and thrombin [58]. LMWHs are less potent but have more consistent pharmacodynamic effect than UFH. Fondaparinux is a synthetic indirect factor Xa inhibitor that acts by binding to antithrombin, similar to LMWHs. These drugs do not affect APTT and can only be monitored by measuring anti-Xa levels. Bivalirudin is a fast-acting, intravenous anticoagulant used primarily during PPCI. Unlike UFH and LMWHs, it inhibits thrombin by direct binding to thrombin both within the thrombi and the thrombin in circulation [63].

UFH has been well established as the preferred anticoagulant of choice during PCI for all categories of ACS [2]. However, meta-analysis of studies comparing enoxaparin to UFH during PCI showed that enoxaparin is superior to UFH in mortality reduction and bleeding outcomes [64,65]. Other types of LMWHs have not been studied as extensively as enoxaparin and use of LMWHs other than enoxaparin, given the biochemical and pharmacological differences between the LMWHs, is not routinely recommended for PCI. A novel enoxaparin regimen of a bolus dose during PPCI followed

Table 3. Anticoagulant and fibrinolytic agents currently in use.

Drug	Route of administration/time of onset of action and half-life	Dosing regimen
Unfractionated heparin	IV/SC Half-life: 60–90 mins Onset: IV 2 mins; SC 1-2 h	ACS: IV bolus 70 U/kg followed by continuous IV infusion titrated by aPTT (60–80 seconds) During PCI: IV bolus 70 U/kg titrated by ACT measurement or supplemented to total of 100 U/kg in long procedures
Enoxaparin	IV/SC Half-life: 4–7 h Onset: IV 2 mins; SC 2–5 h	ACS: SC 1 mg/kg BD or OD if CrCl <30 mL/min. During PCI: IV bolus 0.3 mg/kg if pretreated (can be skipped if PCI is undertaken within 8 hours of last SC dose) or 0.5–0.75 mg/kg if not pretreated
Bivalirudin	IV Half-life: 25 mins Onset: 2 mins	During PPCI: Bolus of 0.75 mg/kg followed by 1.75 mg/kg/h for 4 hours after the procedure.
Fondaparinux	SC Half-life: 17–21 h Onset: 2 h	ACS (except STEMIs): 2.5 mg OD. Avoid if CrCl <20 mL/min.
Warfarin	Oral Half-life: Approx. 40 h Onset: 24 to 72 h	Dose is typically 0.5–9 mg OD, guided by target INR
Apixaban	Oral Half-life: 12 h Onset: 2–4 h	5 mg BD or 2.5 mg BD if CrCl is 15–29 mL/min or if at least two of following characteristics: age ≥80 yrs, weight ≤60 kg or serum creatinine ≥133 mmol/L
Dabigatran	Oral Half-life: 12–17 hours Onset: 0.5–2 hours	Age 18–74 years: 150 mg BD Age 75–79 years: 110–150 mg BD Age ≥80 years: 110 mg BD
Edoxaban	Oral Half-life: 10–14 h Onset: 1–2 h	60 mg OD or 30 mg OD if weight <61 kg or CrCl 15–50 mL/min
Rivaroxaban	Oral Half-life: 5–13 h Onset: 2.5–4 h	20 mg OD; 15 mg OD preferred with antiplatelet therapy. Combined with aspirin in CCS with high ischemic risk (e.g. polyvascular disease): 2.5 mg BD (when no indication for full dose anticoagulation)
Streptokinase	IV Half-life: 18 to 30 minutes	1.5 million units over 30–60 minutes
Alteplase	IV Half-life: 5 minutes	Bolus of 15 mg followed by 0.75 mg/kg over 30 minutes (up to 50 mg) then 0.5 mg/kg over 60 minutes (up to 35 mg)
Reteplase	IV Half-life: 14 minutes	Bolus of 10 units followed by a further bolus of 10 units 30 minutes later
Tenecteplase	IV Half-life: 20–25 minutes	Single bolus dose 30 mg if <60 kg 35 mg if 60 to <70 kg 40 mg if 70 to <80 kg 45 mg if 80 to <90 kg 50 mg if ≥90 kg Age ≥75 years require a half-dose bolus

BD: twice daily; ACS: acute coronary syndromes; CCS: chronic coronary syndromes; CrCl: creatinine clearance; IV: intravenous; kg: kilograms; LD: loading dose; MD: maintenance dose; mg: milligrams; OD: once daily; PCI: percutaneous coronary intervention; PPCI: primary percutaneous coronary intervention.

by a 6-hour infusion was shown to provide sustained anti-Xa activity with initial feasibility studies showing some promise in opiate-treated PPCI patients [66,67]. Further studies are needed to determine the safety and efficacy of this approach as an alternative to UFH or bivalirudin during PPCI.

Enoxaparin was also used an anticoagulant in ACS patients managed conservatively or prior to angiography [68]. However, following the OASIS-5 (Fifth Organisation to Assess Strategies in Acute Ischaemic Syndromes) study, fondaparinux was found to possess a significantly better bleeding profile compared to enoxaparin and is now the preferred anticoagulant of choice in patients admitted with NSTEACS, except for those proceeding to coronary angiography within 24 hours [69]. STEMI patients that underwent PPCI are an exception based on the results of the OASIS-6 study [70]. Anticoagulation in general is not indicated after PCI (unless there are other indications such as left ventricular thrombus or AF). In addition, crossing over between different anticoagulants should also be avoided [2].

The use of bivalirudin during PPCI has yielded conflicting results. While the HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) study demonstrated a reduction in major adverse ischemic events with heparin compared to bivalirudin, the BRIGHT-4 (BivaliRudin with prolonged high-dose Infusion durinG PPCI versus Heparin Trial 4) study, employing a bivalirudin regimen consisting of a loading dose during PPCI followed by a post-PCI high-dose infusion for 2–4 hours, demonstrated improved all-cause mortality and major bleeding outcomes, compared to heparin [71,72]. Hence, this regimen could be used as an alternative strategy to UFH in STEMI patients undergoing PPCI, especially in patients with a history of HIT.

6.2. Oral anticoagulation

Oral anticoagulants (OACs) are not routinely indicated in coronary thrombosis except when there is presence of additional conditions that mandate anticoagulation such as AF, mechanical prosthetic heart valve, or a recent VTE event. Commonly used OACs include vitamin K antagonists (VKAs) and DOACs. OACs are presumed to have some antiplatelet activity due to their effect on thrombin generation, thereby inhibiting thrombin-mediated platelet activation. However, this effect on its own does not provide adequate antiplatelet effect. Hence,

a combination of oral anticoagulant and antiplatelet drugs is often used in patients with ACS, with careful consideration for bleeding and ischemic risk. This is usually administered as DAT (OAC+$P2Y_{12}$ inhibitor) or TAT (triple antithrombotic therapy [OAC+$P2Y_{12}$ inhibitor+ aspirin]) [2].

VKAs inhibit vitamin K epoxide reductase from activating vitamin K1, which is necessary for synthesis of coagulation factors II, VII, IX, and X [73]. Warfarin is the most commonly used VKA. Since the advent of DOACs, its use has been limited to cases where DOACs cannot be used such as mechanical prosthetic valves, AF in a setting of moderate to severe mitral stenosis or consumption of medications that interact with DOACs. Monitoring of INR is required to maintain anticoagulation at therapeutic levels.

DOACs currently in clinical use include apixaban, dabigatran, edoxaban and rivaroxaban. While dabigatran works by direct inhibition of factor IIa, apixaban, edoxaban and rivaroxaban cause direct and reversible inhibition of factor Xa [74]. They are less prone to drug-drug interactions, have a wider therapeutic index and possess a better safety profile compared to warfarin and do not require regular monitoring of anticoagulant activity. Thus, they have replaced warfarin as the primary OAC of choice.

Based on the results of a network meta-analysis of major studies in patients with AF undergoing PCI such as AUGUSTUS, ENTRUST-AF PCI (Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention), PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) and WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), DOACs are preferred to VKA as the oral anticoagulant of choice following PCI, except when DOACs are contraindicated [75–80]. In most studies that compared DAT (OAC+$P2Y_{12}$ inhibitor) and TAT (OAC+ aspirin + $P2Y_{12}$ inhibitor), use of aspirin was associated with increased bleeding but the studies were not powered to assess for ischemic outcomes [76,77]. However, a meta-analysis of major trials that compared OAC-based DAT and TAT regimens showed that DAT regimens were associated with reduced bleeding complication but increased risk of myocardial infarction and stent thrombosis [81]. It is important to note that clopidogrel is the most frequently used $P2Y_{12}$ inhibitor in these studies. The wide inter-individual variability in the efficacy of clopidogrel could explain the increased risk of ischemic events observed in the absence of aspirin. This could be overcome using a potent $P2Y_{12}$ inhibitor although the effect of such a change on bleeding outcomes is currently uncertain. There are currently limited randomized data available concerning the efficacy and safety of a DAT regimen comprising of OAC and a potent $P2Y_{12}$ inhibitor, such as ticagrelor or prasugrel, and no randomized data comparing such a regimen with a TAT regimen comprising of OAC with aspirin and clopidogrel. Although a small minority of patients in the major RCTs were on TAT involving a potent $P2Y_{12}$ inhibitor, use of prasugrel or ticagrelor as part of TAT is not recommended [2]. Given the consistent platelet inhibition observed with these drugs and the efficacy of potent $P2Y_{12}$ inhibitors as part of $P2Y_{12}$ inhibitor monotherapy as observed in major trials against a DAPT regimen, the ischemic benefit from a TAT regimen consisting of OAC, aspirin and potent $P2Y_{12}$ inhibitor is likely to be outweighed by the significant bleeding risks associated with such a combination. On the other hand, a DAT regimen of apixaban with potent $P2Y_{12}$ inhibitor could offset the additional bleeding risk associated with aspirin use while overcoming the inter-individual variability seen with clopidogrel that can contribute to increased thrombotic complications [76]. A preliminary observational study encourages further study of twice-daily DOAC regimens with ticagrelor in AF patients undergoing PCI [82].

During PCI, patients already on VKA with INR > 2.5 do not require of use of parenteral anticoagulation during PCI, while the current recommendation for patients on DOACs is to use UFH or enoxaparin at lower doses during PCI [2]. Interruption of OAC with bridging using heparin or LWMH is not recommended [2]. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) study investigated the use of low-dose rivaroxaban at 2.5 mg BD in patients with established coronary artery disease in the presence of additional vascular disease and was found to improve cardiovascular outcomes at the expense of increased major bleeding events [83]. Hence, rivaroxaban 2.5 mg BD can be used as an adjunct to aspirin as long-term DAT strategy in patients with high ischemic risk but without high bleeding risk in the absence of an indication for full-dose anticoagulation. The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51) study evaluated the use of rivaroxaban 2.5 mg and 5 mg BD in addition to DAPT following ACS. The study identified a reduced risk of cardiovascular death, MI or stroke at the risk of increased major bleeding with rivaroxaban 2.5 mg BD. However, clopidogrel and ticlopidine, which has been superseded by ticagrelor and prasugrel in the treatment of ACS, were the primary $P2Y_{12}$ inhibitors used in this study. Use of rivaroxaban 2.5 mg BD with aspirin and clopidogrel in such settings should therefore be limited to cases where prasugrel or ticagrelor are not available or are contraindicated [84]. The GEMINI-ACS-1 study showed that rivaroxaban 2.5 mg BD is non-inferior to aspirin 75 mg OD in its bleeding risk profile when used as part of a DAT regimen with clopidogrel or ticagrelor to treat ACS [85]. It remains an option in cases where aspirin 75 mg is not tolerated or is contraindicated, although the ischemic outcomes of such a combination are not yet clear.

7. Determining the intensity and duration of dual antithrombotic therapy

The choice, dose, duration, escalation and de-escalation of ATT is dependent on several patient- and procedure-related factors that determine the ongoing ischemic and bleeding risks. Duration of ATT is primarily dependent on the bleeding risk. HBR is commonly assessed using the Academic Research Consortium on High Bleeding Risk (ARC-HBR) criteria or a PRECISE-DAPT score ≥ 25 [86,87]. Table 4 outlines some major

Table 4. Major randomized control trials on antithrombotic therapies for patients with established coronary artery disease.

Study characteristics and numbers	Treatment arms	Efficacy and safety endpoints	Key findings
ACCOAST [39], Montalescot et al ACS and PCI*N* = 4033	Intervention: Prasugrel 30 mg LD before coronary angiography + additional prasugrel 30 mg during procedure if PCI indicated Control: Prasugrel 60 mg LD following angiography if PCI indicated	Primary end point: Composite of CV death, MI, stroke, urgent revascularization or GP IIb/IIIa inhibitor rescue therapy Safety end point: TIMI major bleeding	Prasugrel therapy prior to coronary angiography did not improve ischemic outcomes (HR, 1.02; 95% CI 0.84 to 1.25; $p = 0.81$) but significantly increased major bleeding (HR, 1.90; 95% CI, 1.19 to 3.02; $p = 0.006$)
ATLAS ACS2-TIMI 51 [84], Mega et al ACS *N* = 15526	Intervention 1: Rivaroxaban 2.5 mg BD + aspirin + clopidogrel Intervention 2: Rivaroxaban 5 mg BD + aspirin + clopidogrel Control: Aspirin + clopidogrel	Primary end point: Composite of CV death, MI or stroke Safety end point: TIMI major bleeding not related to CABG	Rivaroxaban reduced the occurrence of primary end point (HR, 0.84; 95% CI, 0.74 to 0.96; $p = 0.008$) but increased non-CABG related to major bleeding (2.1% vs. 0.6%, $p < 0.001$) and intracranial hemorrhage (0.6% vs. 0.2%, $p = 0.009$)
ATLANTIC [88], Montalescot et alACS and PCI *N* = 1862	Intervention: Pre-hospital ticagrelor Control: In-hospital ticagrelor	Primary end points: absence of > 70% ST-segment resolution or TIMI3 flow during angiography in infarct-related artery. Safety end point: Bleeding as per PLATO, TIMI, STEEPLE, ISTH, GUSTO, BARC bleeding	Pre-hospital ticagrelor administration appeared to be safe with no increased bleeding but did not improve pre-PCI coronary perfusion (OR, 0.93; 95% CI 0.69 to 1.25; $p = 0.63$)
AUGUSTUS [76], Lopes et alACS and AF *N* = 4614	2 × 2 factorial design. Treatment group 1: $P2Y_{12}$ inhibitor + aspirin + apixaban Treatment group 2: $P2Y_{12}$ inhibitor + Aspirin + VKA Treatment group 3: $P2Y_{12}$ inhibitor + placebo + apixaban Treatment group 4: $P2Y_{12}$ inhibitor + placebo + VKA	Primary end point: ISTH major and CRNM bleeding	Clopidogrel was the most commonly used $P2Y_{12}$ inhibitor (92.6%). Primary end point occurrence in apixaban vs VKA group: 10.5% vs 14.7% (HR, 0.69; 95% CI, 0.58 to 0.81; $p < 0.001$). Primary end point occurrence in aspirin vs placebo group: 16.1% vs 9% (HR, 1.89; 95% CI, 1.59 to 2.24; $p < 0.001$) Apixaban + $P2Y_{12}$ inhibitor without aspirin seems to be the best combination for patients with AF with recent ACS or PCI.
CAPRIE [22]CCS, PVD or stroke *N* = 19185	Intervention: Clopidogrel Control: Aspirin	Primary end point: Composite of ischemic stroke, MI, or vascular death Safety end point: Severe bleeding	Clopidogrel significantly reduced primary endpoint outcomes compared to aspirin (RRR 8.7%; 95% CI 0.3–16.5%; $p = 0.043$) without increasing the bleeding risk.
CHAMPION PCI [46], Harrington et al ACS and PCI *N* = 8877	Intervention: Cangrelor Control: Clopidogrel	Primary end point: Composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours Safety endpoint: Bleeding as per the GUSTO, TIMI, ACUITY criteria	Cangrelor was not superior to clopidogrel in reducing primary endpoint (7.5% vs 7.1%; OR, 1.05; 95% CI, 0.88 to 1.24; $p = 0.59$). There was no significant increase in bleeding although the rate of bleeding was higher in cangrelor group according to the ACUITY criteria (3.6% vs 2.9%; OR, 1.26; 95% CI, 0.99 to 1.60; $p = 0.06$)
COMPASS [83], Eikelboom et al CCS or PAD or both *N* = 24824	Intervention 1: Rivaroxaban 2.5 mg BD + aspirin Intervention 2: Rivaroxaban 5 mg BD Control: Aspirin	Primary end point: Composite of CV death, stroke, or MI. Safety end point: Modified ISTH criteria for major bleeding	Rivaroxaban + aspirin group had significantly better cardiovascular outcomes compared to aspirin alone 4.1% vs 5.4%; HR, 0.76; 95% CI, 0.66 to 0.86; $p < 0.001$) but with increased bleeding risk (3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; $p < 0.001$).
CURE [18] ACS*N* = 12562	Intervention: Clopidogrel + aspirin Control: Aspirin	Primary end point: Composite of death from cardiovascular causes, non-fatal myocardial infarction or stroke	Clopidogrel has reduced rate of primary end point compared to placebo in patients with ACS on aspirin (9.3% vs 11.4%; RR, 0.80; 95% CI, 0.72 to 0.90; $p < 0.001$). STEMI patients were not included in the study.
ENTRUST-AF PCI [78] Vranckx et al AF and PCI (ACS and CCS)*N* = 1506	Intervention: Edoxaban 60 mg OD + $P2Y_{12}$ inhibitor (12 months); 30 mg OD if relevant. Control: VKA + $P2Y_{12}$ inhibitor (12 months) + aspirin (1–12 months)	Primary end point: Major or CRNM bleeding as per ISTH criteria	Clopidogrel was the default $P2Y_{12}$ inhibitor used in majority of patients (92.4%). Edoxaban was non-inferior to warfarin for primary end point outcomes (17% vs 20%; HR, 0.85; 95% CI, 0.65 to 1.05; $p_{non\text{-}inferiority} = 0.001$) but failed to achieve superiority.
HOST-EXAM [23], Koo et al PCI (ACS and CCS) in maintenance phase with SAPT*N* = 5438	Intervention: Clopidogrel 75 mg OD Control: Aspirin 75 mg OD	Primary end point: Composite of all-cause death, MI, stroke, hospital admission due to ACS, ST, BARC 3, 4 or 5 bleeding. Safety end point: BARC 3, 4 or 5 bleeding	Clopidogrel monotherapy is superior to aspirin monotherapy in the chronic maintenance period after PCI. 5·7% vs 7·7% HR 0·73; 95% CI 0·59–0·90; $p = 0·0035$). All study centers were in South Korea.
ISAR-REACT 5 [40], Schupke et al ACS and PCI*N* = 4018	Intervention: Ticagrelor + aspirin Control: Prasugrel + aspirin	Primary endpoint: Composite of death, myocardial infarction or stroke at 1 year Safety end point: BARC 3,4 or 5 bleeding	Primary end point occurred significantly more frequently in ticagrelor group compared to prasugrel group. (9.3% vs 6.9% HR, 1.36; 95% CI, 1.09 to 1.70; $p = 0.006$) with similar bleeding risk in both groups (5.4% vs 4.8% HR, 1.12; 95% CI, 0.83 to 1.51; $p = 0.46$)

(*Continued*)

Table 4. (Continued).

Study characteristics and numbers	Treatment arms	Efficacy and safety endpoints	Key findings
OASIS-5 [69], Jolly et al ACS*N* = 20,078	Intervention: Fondaparinux 2.5 mg daily OD SC Control: Enoxaparin 1 mg/kg BD SC	Primary end point: Death, MI, refractory ischemia at 9 days Safety end point: Major bleeding up to 9 days after randomization	Fondaparinux was non-inferior to enoxaparin for primary end point outcomes (5.8% vs 5.7%; HR, 1.01; 95% CI, 0.90 to 1.13). However, fondaparinux caused markedly lower bleeding than enoxaparin (2.2% vs 4.1%; HR,0.52; 95% CI, 0.44 to 0.61; $p < 0.001$)
PEGASUS-TIMI 54 [28], Bonaca et al CCS >12 months*N* = 21162	Intervention 1: Ticagrelor 90 mg BD + aspirin Intervention 2: Ticagrelor 60 mg BD + aspirin Control: Aspirin	Primary end point: Composite of CV death, MI or stroke Safety end point: TIMI major bleeding	In patients with MI more than 1 year previously, treatment with ticagrelor significantly reduced primary endpoint outcomes compared to placebo (7.85% in the ticagrelor 90 mg BD, 7.77% Ticagrelor 60 mg BD group and 9.04% in the placebo group (HR for ticagrelor 90 mg BD vs. placebo, 0.85; 95% CI, 0.75 to 0.96; $p = 0.008$; HR for ticagrelor 60 mg BD vs. placebo, 0.84; 95% CI, 0.74 to 0.95; $p = 0.004$) There was increased bleeding seen in ticagrelor groups compared to placebo (2.60% for ticagrelor 90 mg BD vs 2.30% for ticagrelor 60 mg BD vs 1.06% placebo).
PIONEER AF-PCI [79], Gibson et al AF and PCI*N* = 2124	Group 1: Rivaroxaban 15 mg + $P2Y_{12}$ inhibitor (12 months) Group 2: Rivaroxaban 2.5 mg BD + DAPT (1,6 or 12 months) Group 3: VKA + DAPT (1,6 or 12 months)	Efficacy end point: MACE (composite of CV death, MI or stroke) Safety end point: Clinically significant bleeding (composite of major bleeding or minor bleeding as per TIMI criteria or bleeding requiring medical attention)	Safety end point occurred significantly less frequently in both rivaroxaban groups (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; HR for group 1 vs. group 3, 0.59; 95% CI, 0.47 to 0.76; $p < 0.001$; HR for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; $p < 0.001$). MACE was similar in all three groups (6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; p values were nonsignificant for all comparisons)
PLATO [19], Wallentin et al ACS*N* = 18624	Intervention: Ticagrelor 90 mg BD Control: Clopidogrel 75 mg OD	Primary end point: composite of death from vascular cause, MI, or stroke Safety endpoint: Trial defined major bleeding	Ticagrelor reduced the rate of primary endpoint occurrence compared to clopidogrel (9.8% vs 11.7% HR, 0.84; 95% CI, 0.77 to 0.92; $p < 0.001$) without an increase in overall rate of major bleeding. There was an increase in non-procedure -related bleeding (4.5% vs. 3.8%, $p = 0.03$).
RE-DUAL PCI [80], Cannon et al AF and PCI*N* = 2725	Intervention 1: Dabigatran 110 mg BD + $P2Y_{12}$ inhibitor Intervention 2: Dabigatran 150 mg BD + $P2Y_{12}$ inhibitor Control: Warfarin + $P2Y_{12}$ inhibitor + aspirin (1–3 months)	Primary end point: Major or CRNM bleeding as per ISTH criteria Secondary efficacy end point: Composite of thromboembolic events (MI, stroke or systemic embolism), death or unplanned revascularisation.	Primary end point occurred significantly less frequently in Intervention 1 compared to control group (15.4% vs 26.9%; HR, 0.52; 95% CI, 0.42 to 0.63; $p < 0.001$ for noninferiority; $p < 0.001$ for superiority). Intervention 2 was non-inferior to control group. Secondary composite efficacy end point was non-inferior in the combined dabigatran group compared to control group.
TRILOGY-ACS [38], Roe et al ACS and medical therapy *N* = 7243	Intervention: Aspirin + prasugrel 10 mg OD Control: Aspirin + clopidogrel 75 mg OD	Primary end point: MACE (CV death, non-fatal MI, or non-fatal stroke) Safety end point: GUSTO severe or life-threatening bleeding.	Prasugrel-based DAPT was not superior to clopidogrel-based DAPT in primary end point outcome with similar rates of bleeding (13.9% vs 16.0% HR, 0.91; 95% CI, 0.79 to 1.05; $p = 0.21$) Patients that had undergone angiography had reduced MACE with prasugrel whereas this benefit was not seen in those that did not have coronary angiography.
TRITON-TIMI 38 [20], Wiviott et al ACS and PCI*N* = 13608	Intervention: Prasugrel 10 mg OD + aspirin Control: Clopidogrel 75 mg + aspirin	Primary end point: Composite of death from vascular causes, myocardial infarction, or stroke Safety end point: non-CABG related TIMI major bleeding	Prasugrel reduced rates of primary end point occurrence compared to clopidogrel (9.9% vs 12.1%; HR, 0.81; 95% CI, 0.73 to 0.90; $p < 0.001$) but with increased risk of major bleeding (2.4% vs 1.8%, HR, 1.32; 95% CI, 1.03 to 1.68; $p = 0.03$). There was no significant difference in mortality.

ACS:acute coronary syndrome; ACUITY: Acute catheterization and urgent intervention triage strategy; AF: atrial fibrillation; BARC: Bleeding Academic Research Consortium; BD: twice daily; CABG: coronary artery bypass graft; CCS: chronic coronary syndrome; CI: confidence interval; CRNM: clinically relevant non-major CV: cardiovascular; DAPT: dual antiplatelet therapy; GUSTO: global use of strategies to open occluded coronary arteries; ISTH: International Society on Thrombosis and Haemostasis; HR: hazard ratio; LD: loading dose; MACE: Major adverse cardiovascular events; MI: myocardial infarction; OR: Odds ratio; PCI: percutaneous coronary intervention; RRR: relative-risk reduction; STEEPLE: ST: stent thrombosis; STEMI: ST- elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; VKA: Vitamin K antagonist.

clinical trials on antithrombotic therapy in patients with established coronary artery disease that inform modern practice.

While DAPT is typically given for 12 months after an ACS, there is increasing evidence to suggest that a shortened DAPT (aspirin + ticagrelor) for 1 to 3 months followed by ticagrelor monotherapy could be a viable option with less bleeding risk [21]. This could be particularly useful in patients with HBR. Prasugrel monotherapy after shortened DAPT has limited

evidence and is currently not recommended. Table 5 outlines major clinical trials that have tested various abbreviated DAPT regimens and their key outcomes. Based on the results of the TRITON-TIMI 38 and PLATO trials, prasugrel or ticagrelor are preferred as $P2Y_{12}$ inhibitors of choice compared to clopidogrel when used as part of a standard DAPT regimen [19,20]. Clopidogrel can still be considered in cases of HBR or if potent $P2Y_{12}$ inhibitors are not available. Based on the results of the ISAR-REACT 5 study, prasugrel is recommended for use in preference to ticagrelor in ACS patients undergoing PCI. However, there are some important differences between the use of two drugs in practice that determines the choice of $P2Y_{12}$ inhibitor as outlined in Figure 2. While prasugrel is administered after delineating the coronary anatomy (except in STEMI patients undergoing PPCI), ticagrelor is given as soon as a diagnosis of ACS is made prior to coronary angiogram. The ACCOAST study demonstrated increased bleeding risk with lack of ischemic benefit with prasugrel pre-treatment [39]. This is despite a median time of only 4.4 hours from loading dose to angiogram with median time between onset of symptoms and first loading dose being 14.6 hours. Therefore, use of prasugrel prior to coronary angiography in NSTEACS patients is not routinely recommended. Based on available evidence, in NSTEACS patients, if the coronary angiogram can be performed within 24 hours of symptoms onset, loading with $P2Y_{12}$ inhibitor can be deferred until after the coronary anatomy is delineated. While prasugrel is recommended over ticagrelor in such cases, it is not known if a loading dose of ticagrelor administered after angiogram will have reduced bleeding risk compared to pre-treatment with ticagrelor. In cases where the angiogram is likely to be delayed for >24 hours, DAPT with ticagrelor (or clopidogrel if ticagrelor is contraindicated or unavailable) should be considered.

In patients requiring OAC, given the highest risk of stent thrombosis is in the first month after PCI, TAT could be considered in this time period in patients with increased ischemic risk. However, DAT with a twice-daily DOAC and ticagrelor may provide a better balance of efficacy and safety, although this requires further study. After 30 days, with progressively reducing risk of stent thrombosis but sustained risk of bleeding, the balance of risk-benefit is often in favor of avoiding bleeding and so TAT should be avoided [76]. A DAT regimen consisting of $P2Y_{12}$ inhibitor and OAC is the preferred option after 30 days. Stopping $P2Y_{12}$ inhibitor after 6 months in patients requiring long-term anticoagulation was also found to be safe compared to continuing $P2Y_{12}$ inhibitor for up to 12 months in patients with HBR [90]. In the AUGUSTUS study, the mean duration between PCI and randomization was 6 days, while in RE-DUAL PCI and ENTRUST-AF PCI studies, randomization was performed up to 5 days after PCI [76,78,80]. Consequently, patients that received DAT in these studies would mostly have had TAT prior to randomization. This is reflected in the current ESC guidelines where 1 week of TAT is recommended as default after PCI [2].

WOEST-3 and EPIDAURUS are two ongoing studies that are currently evaluating two alternative strategies involving $P2Y_{12}$ inhibitors and DOACs in patients with AF that undergo PCI [91,92].

8. Fibrinolytic therapy

Fibrinolytic therapy is indicated for STEMI patients presenting within 12 hours of onset of symptoms, when PPCI cannot be performed in a timely manner. Based on the results of studies such as DANAMI-2 and PRAGUE-2, current ESC guidelines recommend that PPCI be performed within 120 minutes of an ECG-based diagnosis of STEMI [2,93,94]. If this cannot be achieved, administration of fibrinolytics is recommended within 10 minutes of diagnosis (including pre-hospital administration of fibrinolytics if necessary) [95]. Fibrinolytics in clinical use currently include streptokinase, alteplase, reteplase, and tenecteplase. They primarily work by activating plasminogen to form plasmin which cleaves the fibrin into fibrin degradation products such as D-dimer.

Streptokinase is a microbial plasminogen activator that binds with free plasminogen to form streptokinase-plasminogen complex. This leads to conformational changes within the plasminogen leading to its activation to plasmin [96]. It was the first fibrinolytic drug to be discovered back in 1933 but remains in clinical use in parts of developing world due to its low cost compared to recombinant tissue-plasminogen activator (tPA). It is associated with high-antigenicity and allergic reactions. Consequently, it has been largely replaced by recombinant t-PAs such as alteplase, reteplase and tenecteplase. The doses of different fibrinolytics are summarized in Table 3.

Countries like the United Kingdom have developed an extensive network of centers providing 24/7 PPCI services with effective emergency ambulance services covering majority of the inhabited area. This has obviated the need for administering fibrinolytic therapies in STEMIs.

9. Conclusions

Antithrombotic treatment following coronary thrombosis has undergone significant developments over the past few decades with a multitude of options ranging from SAPT to TAT with duration of DAPT ranging from 1 month to long term. This requires careful consideration of ischemic and bleeding risks related to both the patient and the procedure, following which a personalized recommendation can be made.

10. Expert opinion

The management and prevention of coronary thrombosis has been revolutionized by the development of new antithrombotic drugs as well as marked improvements in the safety and effectiveness of PCI. Still there remains uncertainty about how to best deploy the available therapeutic options in order to optimize the balance of thrombotic and bleeding risks. Clopidogrel remains a popular option as an oral $P2Y_{12}$ inhibitor in numerous settings, but it is inevitable that it will eventually be displaced by other $P2Y_{12}$ inhibitors in acute settings and early after PCI since its pharmacodynamic effect is unreliable, even with knowledge of *CYP2C19* genotype, and this means it lacks a sound pharmacological rationale when trying to individualize management of thrombotic and bleeding

Table 5. Randomized control trials on abbreviated DAPT regimen for patients with established coronary artery disease.

Study characteristics and numbers	Treatment arms	Efficacy and safety endpoints	Key findings
GLASSY [12], Franzone et al PCI (ACS and CCS)*N* = 7585	Intervention: Ticagrelor 90 mg BD + aspirin for 1 month followed by ticagrelor monotherapy for 23 months Control: $P2Y_{12}$ inhibitors (Ticagrelor or clopidogrel) + aspirin for 12 months followed by aspirin	Primary end points: Composite of death, non-fatal MI, non-fatal stroke, urgent TVR Safety end point: BARC 3 or 5 bleeding	Ticagrelor monotherapy after 1-month DAPT was non-inferior to conventional therapy (7.14% vs 8.41%; rate ratio, 0.85; 95% CI 0.72 to 0.99 $p_{noninferiority}$ <0.001) but without any reduction in bleeding risk (rate ratio: 1.00; 95% CI: 0.75 to 1.33; $p = 0.986$).
GLOBAL LEADERS [30], Vranckx et alPCI (ACS and CCS)*N* = 15968	Intervention: Ticagrelor 90 mg BD + aspirin for 1 months followed by ticagrelor monotherapy for 23 months Control: $P2Y_{12}$ inhibitors (ticagrelor or clopidogrel) + aspirin for 12 months followed by aspirin for 12 months	Primary end point: composite of all-cause mortality or new q-wave MI Safety end point: BARC 3 or 5 bleeding	Ticagrelor monotherapy for 23 months after 1-month DAPT was not superior to conventional therapy (rate ratio 0.87; 95% CI: 0.75–1.01; $p = 0.073$).
MASTER-DAPT [25], Valgimigli et al PCI (ACS and CCS) with HBR *N* = 4579	Intervention: Abbreviated DAPT Control: Standard DAPT	Primary end point: NACE (death, MI, stroke, BARC 3 or 5 bleeding) or MACCE (death from any cause, MI, or stroke). Safety end point: BARC 2,3, or 5 bleeding	In HBR patients, abbreviated DAPT was associated with similar NACE (7.5% vs 7.7%; difference, −0.23% points; 95% CI, −1.80 to 1.33, $p < 0.001$ for non-inferiority and MACCE (6.1% vs 5.9%; difference, 0.11% points; 95% CI, −1.29 to 1.51; $p = 0.001$ for non-inferiority) but reduced bleeding rates (6.5% vs 9.4%; difference, −2.82% points; 95% CI, −4.40 to −1.24; $p < 0.001$ for superiority). Clopidogrel was the most frequently used $P2Y_{12}$ inhibitor therapy in the study. All patients had sirolimus-eluting stents.
SMART-CHOICE [26], Hahn et al PCI (ACS and CCS)*N* = 2993	Intervention: DAPT for 3 months followed by $P2Y_{12}$ inhibitor monotherapy for 12 months Control: DAPT for 12 months	Primary end point: MACCE (Cardiac death, MI, stroke, ST, or BARC 3 or 5 bleeding) Safety end point: BARC type 2 to 5	3-month DAPT followed by $P2Y_{12}$ monotherapy is non-inferior to standard DAPT with regards to MACCE (2.9% vs 2.5%; difference, 0.4%; 1-sided 95% CI, −∞% to 1.3%; $p = 0.007$ for noninferiority) but with significantly reduced rate of bleeding (2.0% vs 3.4%; HR, 0.58; 95% CI, 0.36–0.92; $p = .02$). Clopidogrel was the most frequently used $P2Y_{12}$ inhibitor (77%) in both groups. All study centers were in South Korea.
STOPDAPT-2 [14], Watanabe et al PCI (ACS and CCS)*N* = 3045	Intervention: DAPT for 1 month followed by clopidogrel monotherapy Control: DAPT for 12 months	Primary end point: CV death, MI, ischemic or hemorrhagic stroke, definite ST, TIMI major or minor bleeding at 12 months Safety end point: TIMI major or minor bleeding at 12 months	Shortened DAPT with clopidogrel was superior to standard DAPT for primary endpoint outcomes (2.36% vs 3.70%; HR, 0.64; 95% CI, 0.42–0.98; $p = 0.04$ for superiority.
TICO [89], Kim et al ACS and PCI *N* = 3056	Intervention: 3-month of DAPT followed by Ticagrelor 90 mg BD monotherapy Control: Ticagrelor-based DAPT for 12 months	Primary end point: Composite of Major bleeding, death, MI, ST, or TVR) at 12 months Safety end point: TIMI major bleeding	3-month DAPT followed by ticagrelor monotherapy significantly reduced primary endpoint outcomes compared to standard DAPT in ACS patients (3.9% vs 5.9%; HR, 0.66; 95% CI 0.48 to 0.92; $p = 0.01$).
T-PASS [31], Hong et al ACS and PCI*N* = 2850	Intervention: Ticagrelor 90 mg BD after < 1-month ticagrelor-based DAPT Control: Ticagrelor-based DAPT for 12 months	Primary end point: Composite of all-cause death, MI, definite or probable ST, stroke, BARC type 3 to 5 bleeding at 1 year.	1-month DAPT followed by ticagrelor monotherapy significantly reduced primary end point outcomes compared to 12-month DAPT (2.8% vs 5.2%; HR, 0.54; 95% CI, 0.37–0.80; $p <$ 0.001). This was primarily driven by reduced bleeding in the experimental group (1.2% vs 3.4%; HR, 0.35; 95% CI, 0.20–0.61; $p < 0.001$). All centers were in South Korea.
TWILIGHT [13], Mehran et al PCI (ACS and CCS)*N* = 7119	Intervention: 3-month DAPT followed by ticagrelor monotherapy Control: Ticagrelor + aspirin	Primary end point: Composite of death from any cause, non-fatal MI, non-fatal stroke Safety end point: BARC type 2,3,4 & 5 bleeding	3-month DAPT followed by ticagrelor monotherapy significantly reduces bleeding outcomes compared to standard DAPT (4% vs 7.1%; HR, 0.56; 95% CI, 0.45 to 0.68; $p < 0.001$) without increased risk of death, MI or stroke (3.9% in both groups, HR, 0.99; 95% CI, 0.78 to 1.25; $p < 0.001$ for non-inferiority).
ULTIMATE-DAPT [29], Zhen Ge et al ACS and PCI*N* = 3400	Intervention: Ticagrelor monotherapy after 1-month DAPT Control: Ticagrelor-based DAPT for 12 months	Primary end point: Primary superiority end point was BARC type 2,3 or 5 bleeding. Primary non-inferiority end point was MACCE (cardiac death, MI, ischemic stroke, definite ST, TVR)	Patients randomized to IVUS-ACS trial who were event-free at 1-month after PCI were recruited to this study. Ticagrelor monotherapy following 1-month DAPT was superior to 12-month DAPT regimen in reducing bleeding (2.1% vs 4.6%; HR 0.45; 95% CI, 0.30 to 0.66; p, 0.0001) and non-inferior for MACCE (3.6% vs 3.7%; HR 0.98; 95% CI 0.69 to 1.39; $p_{non\text{-}inferiority}$ <0.0001)

ACS:acute coronary syndrome; BARC: Bleeding Academic Research Consortium; BD: twice daily; CCS: chronic coronary syndrome; CI: confidence interval; CV: cardiovascular; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; HR: hazard ratio; MACCE: major adverse cardiovascular or cerebrovascular events; MACE: major adverse cardiovascular events; MI: myocardial infarction; NACE: Net adverse clinical events; PCI: percutaneous coronary intervention; ST: stent thrombosis; TVR: target vessel revascularisation; TIMI: Thrombolysis in Myocardial Infarction.

risks. Ticagrelor provides the most reliable $P2Y_{12}$ inhibition during maintenance therapy, both at the standard dose of 90 mg twice-daily and at a reduced dose of 60 mg twice-daily, and this has been well exploited in studies that have demonstrated effectiveness and reduced bleeding risk with ticagrelor monotherapy following a short period of DAPT. Ticagrelor also has the advantage of reversibility of action, which can reduce bleeding risk in patients requiring urgent major surgery; this advantage may be further enhanced in the future when an antidote such as bentracimab is available for rapidly reversing its effect in the event of serious bleeding or requirement for emergency surgery. On the other hand, some individuals cannot tolerate ticagrelor due to adverse effects associated with reversibly-binding $P2Y_{12}$ inhibitors, such as dyspnea, whereas prasugrel avoids these adverse effects and is not dissimilar in its reliability of action, particularly in the days after a loading dose. However, the irreversible action of prasugrel has confined its use to patients who either have undergone coronary angiography and are proceeding to PCI or present with STEMI and are planned for primary PCI. Consequently, judicious selection of ticagrelor or prasugrel, according to individual circumstances and tolerance, provides the greatest flexibility in optimizing antiplatelet therapy. Use of these $P2Y_{12}$ inhibitors with earlier discontinuation of aspirin, between 2 weeks and 3 months, after PCI will become more established practice as confidence and experience builds in this de-escalation strategy.

Similarly, the use of TAT after PCI is likely to become a rarity as more evidence accumulates for the use of ticagrelor or prasugrel with twice-daily DOAC regimens. Again, the use of clopidogrel in TAT regimens after PCI cannot be justified in view of its unreliability of action, meaning that high pharmacodynamic responders will be exposed to excessive bleeding risk whilst poor responders may be exposed to increased stent thrombosis risk when de-escalating early to DAT with clopidogrel. More evidence is required to support the complete avoidance of TAT after PCI, in the absence of rare indications such as acute left ventricular thrombosis with high risk of embolization or high coronary thrombus burden with slow flow and large myocardial territory at risk.

The availability of DOACs has led to much improved safety in those requiring oral anticoagulation for atrial fibrillation and some other indications in view of the hazards associated with heparinisation and dosing of VKAs. Occasionally patients have an indication for VKA such as a mechanical prosthetic heart valve or moderate/severe mitral stenosis but there is the opportunity to explore DOAC-based DAT regimens in some of these patients, particularly those with contemporary mechanical aortic valve prostheses that have a lower thrombotic risk than older prostheses or those in the mitral position. Newer classes of DOAC, such as those targeting factor XIa, may offer the opportunity for further refining the efficacy and safety of antithrombotic combinations if these newer agents can demonstrate similar efficacy to twice-daily factor Xa inhibitor regimens.

Although ticagrelor and prasugrel have rapid onset of action in stable patients, their onset of action can be delayed by many hours in opiate-treated patients and those with cardiogenic shock so parenteral options are required for addressing this. Parenteral anticoagulation is an option and many centers as well as, in some countries, pre-hospital medical services routinely administer unfractionated heparin to patients with acute MI. Indeed, such a practice is part of the justification for avoiding loading with oral $P2Y_{12}$ inhibitors until after coronary angiography in patients with suspected MI. Novel subcutaneous antiplatelet drugs, such as selatogrel and zalunfiban, are being studied in the pre-hospital setting to determine whether they can improve clinical outcomes. The ultimate goal is to provide an effective antithrombotic combination at the onset of MI in order to reduce the risk of life-threatening progression of coronary thrombosis.

For those with diagnostic features of acute coronary artery occlusion, as manifest by acute ST-elevation on the ECG, it is clear that immediate transfer for primary PCI is the best option rather than standard regimens of fibrinolytic therapy. However, this is not feasible in all patients in view of geographical or other logistic challenges and so there remains interest in the administration of fibrinolytic therapy in those facing delays to primary PCI. Novel regimens with lower risk of life-threatening bleeding may provide a better balance of benefit versus risk in the future.

In the face of so many options for antithrombotic therapy, individualization of therapy can seem a daunting task. Inevitably such complexity lends itself to the use of electronic aids and artificial intelligence that can assimilate all the characteristics associated with thrombotic and bleeding risks. We can expect further work in this area whilst also attempting to simplify antithrombotic regimens through the use of drugs that have predictable pharmacodynamic effect with little interindividual variability.

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